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OPENING PLENARY SESSION – HALL A

OP001 HELICOBATER PYLORI ALTERS STEM CELL HOMEOSTASIS BY DIRECT COLONIZATION OF THE GASTRIC GLANDS

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INTRODUCTION: *Helicobater pylori* (*Hp*) is a bacterial pathogen that colonizes the human stomach, and is the main risk factor for gastro-duodenal ulcers and gastric cancer. *Hp* are found in close proximity to the surface of the stomach epithelium either as a free-swimming population in the gastric mucus or adhered to epithelial cells. The attached bacteria are known to alter cell signalling and behavior though different virulence factors.
AIMS & METHODS: While the effects of attachment have been studied extensively *in vitro*, we aimed to study the localization and pathological relevance of the direct interaction of bacteria with the gastric epithelum, and in particular with gastric stem cells, *in vivo*. We utilized a murine model of *Hp* infection using a mouse adapted *H*p strain PMSS1. We developed a novel technique to visualize *Hp* in mouse stomachs using 3D confocal microscopy. In addition, full thickness stomach surgical specimens were used to visualize bacteria in human stomachs. Lgr5eGFP mice were used to study the interaction of *Hp* with stem cells. Lgr5eGFPCreER RosadtTomato compound heterozygous mice were used for lineage tracing experiments.
RESULTS: We discovered that *Hp* colonize the epithelial surface deep in the gastric glands where they grow as distinct microcolonies associated with the epithelial junctions. In addition, using EdU or mitosis labeling, we find that the gland-associated *H. pylori* directly colonize the surface of progenitor cells. In addition to the data obtained in our murine model, we document gland-associated *Hp* microcolonies deep in the human gastric glands in association with the epithelial junctions and with dividing precursor cells. We hypothesized that direct colonization of precursor/stem cells may drive pathological responses. Using quantitative microscopy we mapped the distribution of bacteria in the glands of the antrum vs the corpus. We found that the location of bacteria in the glands correlates with hyperplastic and metaplastic lesions. Using Lgr5eGFP mice, we observerd a direct interaction of Hp with gastric Lgr5 expressing stem cells. Infection induced an expansion of the stem cell number. In addition, lineage tracing experiments revelaed a significantly higher number of cells being generated from Lgr5 expressing stem cell in infected animals compared to uninfected controls. The acclerated tracing tightly correlated with the bacteria in the gastric glands.
CONCLUSION: Taken together our data reveals that bacteria directly interact with progenitor and stem cells in the stomach, induce hyper-proliferation and alter the stem cell homeostasis of the colonized glands.
Disclosure of Interest: None declared

OP002 RANDOMIZED COMPARISON OF SURVEILLANCE INTERVALS AFTER COLONOSCOPIC REMOVAL OF ADENOMATOUS POLYPS: THE JAPAN POLYP STUDY

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INTRODUCTION: The National Polyp Study (NPS) Workgroup recommended an interval of at least 3 years between colonoscopic removal of all adenomatous polyps and the follow-up examination in 1993. However, the study was conducted prior to the recent studies documenting the importance of nonpolypoid colorectal neoplasms (NP-CRNs).
AIMS & METHODS: The aim of this study was to assess whether follow-up colonoscopy using high-definition colonoscope at 3 years as well as at both 1 and 3 years would detect important lesions including NP-CRNs. The Japan Polyp Study (JPS), a multicenter randomized control trial conducted at 11 participating centers was initiated in 2003. Patients were eligible if they have had two complete colonoscopies (1st-CS and 2nd-CS: interval; 1 year) with removal of all neoplastic lesions. Following this they were randomly assigned to have follow-up colonoscopy at 1 and 3 years (two-exam group) or at 3 years only (one-exam group). Index lesions (ILs) were defined as any low-grade dysplasia (LGD) ≥10mm, high-grade dysplasia (HGD) or invasive cancer. Moreover, the risk ratios (RRs) of ILs were estimated in association with age, gender, family history and endoscopic findings before randomization.
RESULTS: 3926 patients mean age 57.3 years (40-69), 2440 (62%) males with no history of FAP, HNPCC, IBD or personal history of polypectomy with unknown histology, no history of colectomy, participated in this study. Of these, 2166 patients who had 1st-CS and 2nd-CS, with removal of all adenomatous polyps were randomly assigned into two groups (1087 to two-exam and 1079 to one-exam group). The results of the non-inferiority test were significant (p=0.017 in per-protocol, p=0.001 in intention-to-treat). In per-protocol analysis (701 in two-exam vs 763 in one-exam group), the IL incidences of two groups were similar (1.7% vs 2.1%). Among all ILs, there were 6 LGD ≥10mm, 5 HGD and 1 invasive cancer in two-exam group, 9 LGD ≥10mm and 8 HGD in one-exam group, respectively. Morphologically, NP-CRNs were dominant (62%, 18/29) and most of them were classified into laterally spreading tumor non-granular (LST-NG) type; (83%, 15/18). According to the univariate analysis, the number of adenomas (≥ 5) [RR:2.84 (1.37-5.91)] and family history of colorectal cancer [RR:2.39 (1.07-5.35)] were considered as significant risk factors of ILs.
CONCLUSION: Even if NP-CRNs are considered, an interval of at least 3 years between endoscopic removal of adenomatous polyps and follow-up examination is feasible. Two complete colonoscopies before randomization provided us a lower incidence of ILs compared with NPS data (3.3%). Further investigation will be necessary to evaluate whether the detection of NP-CRNs, especially LST-NG type determines a change in the prevention of colorectal cancer.
Disclosure of Interest: T. Matsuda Financial support for research from: Grant from the Japanese Ministry of Health, Labor and Welfare, T. Fujii: None declared, Y. Sano: None declared, S.-E. Kudo: None declared, Y. Oda: None declared, K. Kaneko: None declared, K. Hotta: None declared, T. Shimoda: None declared, Y. Saito: None declared, N. Kobayashi: None declared, K. Konishi: None declared, H. Ikematsu: None declared, H. Iishi: None declared, K. Kobayashi: None declared, Y. Yamaguchi: None declared, K. Hasuda: None declared, T. Shinohara: None declared, H. Ishikawa: None declared, Y. Murakami: None declared, H. Taniguchi: None declared, S. Yoshida: None declared

OP003 LYMPHOTOXIN PROMOTES ACINAR CELL REPROGRAMMING AND ACCELERATES PRE-NEOPLASTIC CONVERSION IN KRAS INDUCED PANCREATIC TUMORIGENESIS

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INTRODUCTION: Pancreatic inflammation is a well-known risk factor for pancreatic ductal adenocarcinoma (PDAC) development in humans. PDAC initiation is linked to activating mutations in KRAS oncogene. An early event in the malignant transformation is acinar cell transdifferentiation, the formation of acinar-to-ductal metaplasia (ADM), which can give rise to pancreatic intraepithelial neoplasia (PanIN), the most common PDAC precursor. Importantly, ADM formation is also observed during pancreatitis both in humans and rodents. Despite the crucial role played by ADM in the pathophysiology of the pancreas, the regulatory mechanisms governing the dynamics of this transdifferentiation are not completely defined.
AIMS & METHODS: The aim of this study is to explore the inflammatory mechanisms promoting ADM regression and PanIN development. Therefore, we established a new genetic model (LTKP) by intercrossing the commonly used $p48^{+/Cre}$;$Kras^{+/G12D}$ (KP) model for pancreatic tumorigenesis, to a novel transgenic mouse developing spontaneous pancreatitis, due to pancreas specific Lymphotoxin (LT) overexpression. Immunohistochemistry and RT-PCR were used to obtain an inflammatory signature. *In-vitro* experiments were performed to investigate the direct role of LT in ADM development.
RESULTS: Lymphotoxin overexpression in mice harbouring a constitutively active form of Kras mutation in the pancreas (LTKP) dramatically accelerates the development of premalignant PanIN lesions compared to KP animals. Already after 6 weeks increased cell proliferation, extensive ADM and PanIN development was observed in LTKP mice. This coincides with a significant upregulation of inflammatory genes and increased ratio of active (GTP-bound) Kras. These molecular and phenotypic changes are only observed around 16 weeks in Kras animals. *In-vitro*, acinar cells isolated from LTKP mice formed significantly faster ADMs than KP cells. In contrast to wild type acinar cells, cells overexpressing Lymphotoxin, without the presence of Kras mutation could also spontaneously transdifferentiate.
CONCLUSION: Our data point towards the involvement of LTβR-signalling in the initiation of pancreatic cancer. Lymphotoxin is a critical component of spontaneous and pancreatitis-accelerated PDAC precursor formation, by (1) inducing inflammatory environment and by (2) regulating acinar cell transdifferentiation, leading to accelerated pre-malignant PanIN lesion development.
Disclosure of Interest: None declared

OP004 A RANDOMIZED CLINICAL TRIAL OF OBSERVATIONAL VERSUS ANTIBIOTIC TREATMENT FOR A FIRST EPISODE OF UNCOMPLICATED ACUTE DIVERTICULITIS

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INTRODUCTION: Do antibiotics improve the course and/or outcome of a first episode of uncomplicated acute diverticulitis? To date, most guidelines advise the use of antibiotics[1-3]. One previous randomized trial[4] has been performed but included about 40% recurrent diverticulitis, and did not change clinical practice. Whether or not antibiotics are used varies between countries and disciplines[5-7]. Importantly, use of antibiotics can lead to adverse effects and its overuse results in escalating antimicrobial resistance[8].
AIMS & METHODS: We conducted a multicenter, randomized, controlled, pragmatic, noninferiority trial (DIABOLO trial, NCT01111253) of an observational versus an antibiotic treatment strategy in patients with a CT-proven diagnosis of a first episode of acute, left-sided, uncomplicated (Hinchey 1A or 1B) diverticulitis. The primary endpoint was the time-to-recovery at 6 months as assessed by a patient diary. Main secondary endpoints were readmission rate, occurrence of complicated, recurrent and ongoing diverticulitis, need for sigmoid resection and other (non-)surgical interventions, adverse events and mortality. An intention-to-treat analysis was done.
RESULTS: In 22 centers, 528 diverticulitis patients were analyzed after randomization to an observational or antibiotic treatment strategy. In the observational arm 13% was treated on outpatient basis, and 95% did not receive antibiotics during the study period. At 6 months follow-up recovery occurred in 234 (89.3%) patients assigned to observation and in 248 (93.2%) patients assigned to antibiotics (P=0.183). Median time-to-recovery was comparable among observational and antibiotic treatment strategies (14 days [IQR, 6 to 35] vs. 12 days [IQR, 7 to 30]; P=0.291 by the Log-Rank test), with a hazard ratio for recovery of 0.910 (upper limit one-sided 95 % CI, 1.059; P=0.151). We found no significant differences between both treatment strategies for main secondary endpoints.
CONCLUSION: Observational treatment of uncomplicated acute diverticulitis, even without primary admission, does not result in an increase in time-to-recovery and readmission rate, nor in higher rates of complicated, recurrent or ongoing diverticulitis or sigmoid resection. Observational treatment is without short-term or long-term repercussions, which indicates that antibiotic treatment can safely be omitted in uncomplicated diverticulitis.
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Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 11:00-12:30
FAILED ERCP: WHAT OPTIONS DO WE HAVE? - HALL E

OP005 SENIOR DISCUSSION REDUCES MORTALITY FOLLOWING PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY: A 12-MONTH PROSPECTIVE AUDIT

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INTRODUCTION: Percutaneous transhepatic cholangiography (PTC) achieves effective biliary drainage in proximal biliary obstruction and failed ERCP but carries significant morbidity and mortality. The 2009 British Society of Interventional Radiology Audit Report recommends that post-PTC in-hospital mortality should be under 19.8%.
AIMS & METHODS: The aim of this project was to identify potential causes of high post-PTC mortality at our tertiary centre and evaluate the impact of PTC on quality of life. All patients undergoing PTC were prospectively audited in 3 consecutive four-month cycles. Quality of life pre- and 30 days post-PTC was assessed objectively based on ECOG performance status and subjectively using a visual analog scale (VAS). The Trust electronic database and patient case notes were reviewed for indication, type of intervention, post-PTC complications and mortality. Senior (consultant) level discussion between physician/surgeon and radiologist was incorporated into PTC guidelines at the start of the second cycle and made a mandatory requirement before electronic requesting for PTC in the third cycle.
RESULTS: 23 patients underwent 32 procedures in the first audit cycle. Total mortality was 30.4% with an in-hospital mortality of 21.7%. 52% of patients had single-stage stenting while 35% underwent a two-stage procedure of internal-external drainage followed by stenting at a later date. 78% of procedures were discussed at senior (consultant) level and the majority of these were performed as single-stage interventions. In the second cycle 27 patients underwent 40 procedures. 55% were single-stage stents while 33% were two-stage procedures. Senior level discussion took place for 80% of procedures. Total mortality remained high at 29.6% but in-hospital mortality decreased slightly to 18.5%. The third cycle comprised 20 patients undergoing 30 procedures, of which 45% were single-stage and 35% were two-stage. Following new electronic requesting protocols senior level discussion increased to 97%. There was a dramatic decrease in total (and in-hospital) mortality to 5%. We also found a significant improvement in subjective quality of life at 30 days post-PTC with similar rates of improvement across all 3 cycles (see table).

	Senior discussion (%)	Total Mortality (%)	In-hospital mortality (%)	VAS pre-PTC (%)	VAS post-PTC (%)
Cycle 1 (Oct '12 - Jan '13)	78	30.4	21.7	27.5	75
Cycle 2 (Feb '13 - May '13)	80	29.6	18.5	20	60
Cycle 3 (Jun '13 - Sept '13)	97	5	5	25	70

CONCLUSION: Appropriate senior level discussion before PTC improves patient selection and significantly decreases 30-day mortality. However, it did not decrease the number of two-stage interventional procedures performed in favour of single-stage stenting. Percutaneous biliary intervention also significantly improves quality of life at 30 days in appropriately selected patients and has an important role in palliation of symptoms in patients with malignant biliary obstruction.
REFERENCES
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Disclosure of Interest: None declared

OP006 CONTRIBUTION OF EARLY NEEDLE-KNIFE INFUNDIBULOTOMY IN DIFFICULT ERCP: A PROSPECTIVE STUDY

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INTRODUCTION: Difficult commun bile duct (CBD) cannulation remains a frequent problem in ERCP (approximately 10-15 % depending on the study). There are several techniques for difficult cannulation of the CBD, including precut and infudibulotomy procedures. However, the complication rate in these patient groups seems to be higher than for patients who underwent conventional sphincterotomy.
AIMS & METHODS: The aim of our study was to prospectively assess whether repetitive attempts of CBD cannulation or infundibulotomy are primarily involved in the post-ERCP complications and to evaluate the effectiveness of early infudibulotomy in difficult ERCP.
All the patients who underwent ERCP between 01/01/13 and 06/10/2013 were included in our prospective study. Patients were divided into 3 groups based on the timing of CBD cannulation before infundibulotomy (< 5 min, between 5 and 15 min and 15 min). The increase in rate of CBD cannulation with infundibulotomy, the correlation between post ERCP complications and timing of infudibulotomy have been analyzed.
RESULTS: One hundred and thirteen patients were analyzed, 43 patients with a tumor CBD obstrcution and 70 patients with gallstones. In 80 patients, the cannulation was obtained by conventional procedure (70.8%). In 30 patients, infundibulotomy was performed with total success of cannulation in 108 (95.6 %). In 5 patients the cannulation was not possible (3 patients without attempted infundibulotomy). ERCP complications included 13 cases of post-ERCP pancreatitis (PEP), 8 of them for whom the infundibulotomy was done after more than 15 min of CBD cannulation attempts. In 84.6 % of the patients with a post-ERCP pancreatitis, the cannulation time lasted more than 15 min. In the 22 patients with a cannulation that lasted more than 15 minutes, 11 PEP occurred (50 %). There was a significant correlation between the occurrence of PEP and CBD cannulation > 15 min ($p<0.001$). There was no case of perforation or relevant bleeding. Mortality was 0%. We did not observe PEP in patients with an early infundibulotomy (< 15 min).

Correlation between PEP and the timing of CBD cannulation

Table to abstract OP006

Cannulation time	ERCP without infundibulotomy (5 patients)	ERCP with infundiblotomy (8 patients)
1 to 5 min	20% (1/ 5)	0
5 to 15 min	20 % (1/ 5)	0
> 15 min	60% (3/5)	100% (8/8)

CONCLUSION: Early infundibulotomy is an efficient procedure that increases the percentage of ERCP success rate from 71% to 96%. PEP occurrence is correlated to the duration of the CBD cannulation (50% in case of pancreatitis lasting 15 min). Early infundibulotomy could avoid PEP if used early before 15 min of cannulation.
Disclosure of Interest: R. Alhameedi: no conflict, A. Di Fiore: no conflict, M. Antonietti: no conflict, P. Michel: no conflict, P. Ducrotté: no conflict, S. Lecleire: no conflict

MONDAY, OCTOBER 20, 2014 11:00–12:30

ALTERED INTESTINAL MICROBIOTA COMPOSITION IN IBS: DOES IT AFFECT CLINICAL PRACTICE? – HALL G/H

OP007 A MULTI-CENTER, RANDOMIZED, CONTROLLED, SINGLE-BLIND, COMPARATIVE TRIAL: LOW-FODMAP DIET VERSUS TRADITIONAL DIETARY ADVICE IN IBS

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INTRODUCTION: Irritable bowel syndrome (IBS) is characterized by abdominal pain or discomfort in combination with disturbed bowel habit. A diet with reduced content of fermentable short chain carbohydrates ((Fermentable Oligo-, Di-, Monosaccharides And Polyols) FODMAP) have been reported as effective in the treatment of IBS (Halmos et al Gastroenterology 2014), but proof of its superiority compared to traditional dietary advice in IBS has not yet been established.
AIMS & METHODS: The aim of the study was to compare the effects on IBS symptoms of a low-FODMAP diet and traditional dietary advice in patients with IBS. This study was performed at three Swedish hospitals and recruited adult patients diagnosed with IBS (Rome III criteria). Symptom intensity was assessed by use of the IBS Severity Scoring System (IBS-SSS) at randomization (day 0) and at the end of the four-week treatment period (day 29). An IBS-SSS score of at least 175 was needed for inclusion. Randomization (1:1) was done with the patient blinded to the identity of the dietary advice. The instructions were given in both oral and written form. A low-FODMAP diet implies specific restrictions of fermentable short chain carbohydrates. Traditional IBSs diet imply small, frequent meals, to peel and divide foods into pieces, chew thoroughly, boil food, reduce fatty and spicy foods, legumes, onions, coffee and alcohol. Carbonated beverages and sweeteners that end with –ol should be avoided. Fiber intake evenly distributed over the day. For the analysis, the patients were divided into moderate (IBS-SSS 175-300) or severe (IBS-SSS >300) symptom intensity by use of baseline data. A responder to diet treatment was defined as a reduction in IBS-SSS by at least 50 comparing day 0 with day 29.
RESULTS: Eighty-two patients completed the screening period. Eight patients were excluded due to IBS-SSS less than 175 and 9 patients did not finish the intervention period. A total of 65 patients (54 women; median age 43 years (range 19-68)) completed the full study (32 low-FODMAP, 33 traditional diet). At the end of the study 18 patients (56%) in the low-FODMAP group were responders to treatment and 17 (52%) were responders to the traditional IBS diet (p=.70). Equal response was also seen comparing patients with moderate (p=.62) and severe (p=.90) IBS. According to IBS-SSS the low-FODMAP diet reduced the symptom score from 337 (287-382) (median (25th-75th percentile)) to 231 (154-350) (p=.001), and the traditional diet reduced the symptom score from 312 (250-346) to 240 (171-296) (p<.001). The reduction in IBS-SSS was similar comparing the two groups (p=.64) and also when comparing the individual items of the IBS-SSS score; abdominal pain severity (p=.81) and frequency (p=.39), dissatisfaction with bowel habits (p=.47) and how symptoms interfered with life in general (p=.69). There was a trend for a larger reduction in abdominal distension in the traditional diet group (p=.08).
CONCLUSION: Dietary advice is efficient in reducing the gastrointestinal symptoms of IBS without any difference noted when comparing a low-FODMAP diet with traditional IBS dietary advice. Further investigations need to be done in order to find predictors of response to specific dietary regimens.
Disclosure of Interest: None declared

OP008 FASTING COLONIC VOLUME AND BREATH HYDROGEN INCREASE AFTER THE ADDITION OF A FODMAP TO THE USUAL DIET OF HEALTHY VOLUNTEERS: THE USE OF MRI TO MEASURE PHYSIOLOGICAL CHANGES IN THE GI TRACT

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INTRODUCTION: Indigestible fermentable carbohydrates, grouped as FODMAPs, have been proposed to induce gastrointestinal symptoms. Some, such as oligofructose (OF), are prebiotics and modify the microbiota. The metabolic activity of the microbiota affected transit time in a mouse model[1]. This study hypothesized that dietary supplementation with OF would shorten whole gut transit time (WGTT) and improve the capacity of the microbiota to metabolise a FODMAP challenge.
AIMS & METHODS: The study was an open-label case series. 16 healthy volunteers underwent fasting MRI to assess colonic volume[2] and the position of 5 transit markers ingested 24 hours earlier from which WGTT could be calculated[3]. Breath hydrogen (H_2) and methane (CH_4) were also measured. Subjects then consumed an inulin challenge drink (ICD): 500ml water containing 40g inulin. Inulin is fermented in the colon and known to increase H_2 and colonic volume[4]. After ICD subjects could sip water and were given a low FODMAP lunch but no other food was allowed. 8 hours post-ICD MRI was repeated. Breath measurements were repeated 4 and 8 hours post-ICD. Subjects then supplemented their usual diet with OF (gift from BENEO, Germany), 5g twice daily, for a week. Fasting and post-ICD measurements were then repeated. Dietary questionnaires were completed for the weeks preceding MRIs to assess dietary fructan intake.
RESULTS: Median [IQR] given unless stated as mean [95% C.I.]. Baseline fasting colonic volume (510ml [400-710]) and WGTT (34h [10 – 45]) were similar to previous studies of healthy volunteers. The most notable finding was that after consuming OF for a week there was a mean increase in fasting colonic volume of 94ml [12 – 177, p=0.03]. Fasting H_2 (33ppm [9–87]) increased by mean 39ppm [6 – 71, p=0.02]. No acceleration of WGTT was demonstrated: rather, transit times increased by 19h [-9 – 42] but this increase did not reach significance (p=0.09, Wilcoxon). Colonic volumes post-ICD were similar across weeks (mean 726ml [667-785]). The change from baseline was significant in week 1 but not week 2 due to the difference in fasting volumes. There was no difference between weeks 1 and 2 in H_2 at 4 or 8 hours after ICD. CH_4 did not change. Dietary fructan intake was similar in both weeks (mean <8g/ day).
CONCLUSION: OF increased fasting colonic volumes by 18%. H_2 also rose. This may reflect increased bacterial mass with increased capacity for fermentation. The suggestion that OF slows WGTT is surprising and warrants further investigation. MRI can complement research on the microbiota to describe its impact on gut physiology.
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Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 11:00–12:30

CONVENTIONAL THERAPY FOR IBD: ROOM FOR IMPROVEMENT – HALL I/K

OP009 ST10, A NOVEL ORAL FERRIC IRON, IS AN EFFECTIVE AND WELL-TOLERATED TREATMENT FOR IRON DEFICIENCY ANAEMIA IN IBD PATIENTS WHO FAIL TO RESPOND OR TOLERATE ORAL FERROUS PREPARATIONS: RESULTS FROM THE PHASE 3 STUDY PROGRAM

C. Gasche[1], Z. Tulassay[2], T. Ahmad[3], **A. Stallmach**[4,*], J. Howell[5] on behalf of The, AEGIS Study Group: ST10 in the treatment of iron deficiency anaemia in IBD.
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INTRODUCTION: Iron deficiency anemia (IDA) is common in inflammatory bowel disease (IBD). Traditional oral ferrous (Fe^{2+}) salts, are often poorly tolerated and may lead to worsening of IBD symptoms. Ferric (Fe^{3+}) iron salts are well tolerated and have less redox potential compared to ferrous salts, but are poorly absorbed due to insoluble oxide formation in the gut. ST10 is a novel Fe^{3+} iron that has been chelated with maltol. The chemistry of this product keeps it in an absorbable state through a range of pH, but readily donates the Fe to a stronger ligand i.e. the Fe transporter protein. The aim of this study was to demonstrate the efficacy of oral ST10 over placebo in the treatment of IDA in subjects with mild-to moderate IBD who have failed to respond, or been intolerant to, oral ferrous salts. The primary endpoint was change in hemoglobin (Hb) from baseline to Week 12.
AIMS & METHODS: This was a double-blind randomised controlled trial of 120 IBD subjects with IDA (Hb 9.5 - 12.0g/dL female, 9.5-13.0g/dL male; and ferritin <30µg/L). Subjects were randomised to receive oral 30mg ST10 twice a day for 12 weeks or identical placebo. At the study end all available subjects were enrolled in a 52 week open label study. In addition to routine safety monitoring subjects completed Simple Clinical Colitis Activity Index (SCCAI), Crohn's

Disease Activity Index (CDAI) and IBD Questionnaires (IBDQ) at baseline and regular intervals.

RESULTS: 128 subjects were randomised. Baseline Hb, age and gender were comparable in both groups. The pre-specified analysis plan included the first 120 subjects randomised (60 ST10, 60 Placebo; 67 CD, 53 UC). 101 (87% ST10, 82% Placebo) completed at least 12 weeks treatment. Mean Hb improved by 2.3g/dL from 10.9 to 13.2g/dL in the ST10 group and remained at 11.1g/dL in the Placebo group ($p<0.0001$, ANCOVA). There was no significant worsening in disease activity scores (SCCAI, CDAI and IBDQ) after 12 weeks of treatment with ST10 (Table). Adverse events (AEs) were recorded in 58% of ST10 and 72% of placebo subjects. Gastrointestinal (GI) AEs were observed in 38% and 40%, respectively. In the ST10 group the most common AEs were abdominal pain (10%), diarrhoea (7%), constipation (6%) and nasopharyngitis (4%). Study medication was discontinued due to related AEs in 5 ST10 and 4 Placebo subjects; these were mostly GI related.

	ST10		Placebo	
	Week 0	Week 12	Week 0	Week 12
SCCAI	1.8	2.2	1.5	2.1
CDAI	85	63	105	113
IBDQ	176	180	171	176

CONCLUSION: At 12 weeks of treatment ST10 gave a statistically significant, and clinically relevant rise in Hb of 2.3g/dL in patients with mild-to-moderate IDA and IBD who were previously unresponsive or intolerant to oral iron. Over the study period ST10 was well-tolerated (87% completing 12 weeks of treatment) and did not exacerbate Crohn's disease or ulcerative colitis symptoms. ST10 may provide an alternative to IV iron in IBD patients with IDA who fail to respond, or who are intolerant of existing oral ferrous therapies.

Disclosure of Interest: C. Gasche: None declared, Z. Tulassay: None declared, T. Ahmad: None declared, A. Stallmach: None declared, J. Howell Other: Employee

OP010 PRE-TREATMENT DIFFERENTIAL MICRORNA EXPRESSION PROFILE IN ULCERATIVE COLITIS PATIENTS ACCORDING TO THEIR RESPONSE TO CORTICOSTEROIDS

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INTRODUCTION: Corticosteroids (CS) remain the first-line treatment for moderate-to-severe active ulcerative colitis (UC). However, up to 40% of patients do not have an adequate response, an event that to date, cannot be predicted yet. microRNA (miRNA) are small non-coding RNA fragments that modulate gene expression at posttranscriptional level, thus playing a critical role in many biological processes. Little is known about the influence of miRNA in the response to CS in UC.

AIMS & METHODS: To compare the miRNA profile in rectal mucosa of patients with active UC responding and non-responding to CS.

Methods: Rectal biopsies were obtained from consecutive UC patients before starting CS therapy for a moderate-to-severe flare. Patients were grouped according to clinical response (*non-responder* = moderate or severe activity according to Montreal's classification at day 7 or need for rescue therapy before day 7; *responder* = Less than moderate activity without need for rescue therapy at day 7). miRNA were identified by means of a sequencing method *(TruSeq® SmallRNA kit from Illumina)* on those fresh-frozen rectal biopsies that reached a RNA Integrity Number (RIN) $\geq$8. Comparison of miRNA profile between groups was carried out on the miRanalyzer D.E. tool through DESeq package. Those miRNA with a fold change $\geq$ 1.5 and adjusted p-value $\leq$0.05 were further studied. Potential targets of selected miRNA were checked in *"Target Human Scan database"* (www.targetscan.org), and their impact on biological activity was searched in "GeneCodis database" (http://genecodis.cnb.csic.es).

RESULTS: 15 out of 24 tissue samples (8 responders and 7 non-responders) reached a RIN value $\geq$8 allowing miRNA sequencing. We found more than 1,300 known miRNA and about 70 new miRNA. Responders to CS had an up-regulated expression of *has-miR-5701* and *has-miR-625-3p,* and down-regulated expression of *has-miR-1246* and *has-miR-1291* as compared to non-responders. Bioanalysis using miRNA targets database showed up to 2,000 potential targets for the aforementioned miRNA, most of them involved in MAPK signalling pathways, cytoskeleton organization pathway, and cell differentiation endocytosis and autophagy mechanisms.

CONCLUSION: Patients with active UC not responding to CS show a differential mucosal miRNA expression profile before starting therapy. These findings suggest that regulation of gene expression by miRNA might play a role in the response to treatment in UC patients.

Disclosure of Interest: None declared

OP011 RAC1 POLYMORPHISMS AND THIOPURINE EFFICACY IN CHILDREN WITH INFLAMMATORY BOWEL DISEASE

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INTRODUCTION: Thiopurines are effective in approximately one third of inflammatory bowel disease (IBD) patients; predictors of response may assist in selecting the most appropriate patients for this intervention. RAC1 is a GTPase that, when activated, initiates a cascade whose effects include suppression of T-cell apoptosis. The thiopurine metabolite 6-Thio-GTP binds to and suppresses Rac-1, thereby increasing apoptosis. A genetic association has been demonstrated between two RAC1 single nucleotide polymorphisms (SNPs) and ulcerative colitis (UC) (rs10951982 and rs4720672). A different SNP (rs34932801) was recently found to be associated with poorer response to thiopurines in adult Crohn's disease (CD) patients. We aimed to determine whether these SNPs in the RAC1 gene are associated with response to thiopurines in children with IBD.

AIMS & METHODS: 59 children with IBD were enrolled to this 1-year prospective cohort study at the time of commencing thiopurines (mean age 12.7 $\pm$ 4.1 years, 37 (63%) males, median disease duration 4.5 (IQR 0.7-17.4) months, 47 (80 %) CD and 9 (15 %) UC). Response to treatment was assessed on standardized forms at 4 and 12 months thereafter. Patients receiving concomitant anti-TNF or tacrolimus were excluded. Children were genotyped for the RAC1 SNPs rs10951982 and rs4720672 using Real-time PCR TaqMan assays, and for rs34932801by direct sequencing. The primary outcome was steroid-free remission at 12 months without the need for treatment escalation.

RESULTS: Genotyping results are displayed in the table below:

SNP	Wild Type (WT) n (%)	Heterozygous n (%)	Homozygous n (%)
rs10951982	41 (69)	15 (25)	3 (5)
rs4720672	45 (76)	12 (20)	2 (3)
rs34932801	45 (90)	5 (10)	0

There was no association between genotype and disease type. Baseline PGA was similar for all genotypes except for rs4720672 homozygotes, who had a lower baseline PGA than WT ($p = 0.003$). At 12 months, 16/41 (39%) WT and 8/15 (53%) heterozygotes for rs10951982 were in remission (p=0.38), while 18/45 (40%) WT and 7/12 (58%) heterozygotes for rs4720672 were in remission (p=0.33); 22/45 (49%) WT and 2/5 (40%) heterozygotes for rs34932801 were in remission (p=1.0). All 3 homozygotes for the former 2 SNPs were in remission.

CONCLUSION: These three Rac1 SNPs of RAC1 were not found to be associated with 1-year response to thiopurines in a prospective study of pediatric IBD.

Disclosure of Interest: None declared

OP012 DIFFERENT PROFILE OF EFFICACY OF THIOPURINES IN ULCERATIVE COLITIS AND CROHN'S DISEASE

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INTRODUCTION: Azathioprine (AZT) and 6-mercaptopurine (6-MP) are effective drugs in treating ulcerative colitis (UC) and Crohn's disease (CD) as they can induce/maintain clinical remission (CR) and mucosal healing (MH) in steroid-dependent patients. Nevertheless, even if trials and meta-analyses have confirmed the efficacy of thiopurines in UC and CD, studies directly investigating a possible different profile of efficacy in UC in comparison with CD are scarce.

AIMS & METHODS: To explore the rate of CR and MH in UC patients treated by thiopurines compared to that of subjects with CD. From September 2011 to April 2014 we performed an observational longitudinal study evaluating steroid-free CR and MH in all UC and CD patients who would complete 2 years of maintenance treatment with thiopurines (AZT 2-2.5 mg/kg/day; 6-MP 1-1.5 mg/kg/day). Patients characteristics were classified according to the ECCO guidelines. CR and MH were assessed before starting treatment and 2 years later by Mayo score for UC (CR= Mayo score <2; MH= Mayo sub-score $\leq$1); CR and MH were assessed at same time-points by Crohn's disease activity index (CR=CDAI $<$ 150) and Simplified Endoscopic Score for Crohn's Disease (MH=SES-CD <2) for CD. Statistical analysis was performed using chi-square, Mann–Whitney U test and odd ratio (OR) where appropriate. To test the concordance between CR and MH in UC and CD, the Cohen's k measure was applied. Regarding the differences in outcomes for CR and MH we estimated that a total sample size of 120 patients would allow detection of a 20% difference between the 2 groups. A p value lower than 0.05 was considered significant.

RESULTS: The study included 70 patients with UC (AZT/6-MP=60/10; M/F=37/33; mean age=39 years; E1=0, E2=24, E3=46; mean baseline Mayo score=8.5) and 70 subjects with CD (AZT/6-MP=62/8; M/F= 39/31; mean age=33 years; L1=34, L2=26, L3=10; B1=54, B2=10, B3=6; mean baseline

CDAI=290) treated with thiopurines for 2 years. At the end of the study, steroid-free CR was recorded in 43 patients with UC and 37 with CD (61% vs 53%; p=0.3). MH was obtained in 38 patients with UC and 17 with CD (54% vs 25%; p<0.01; O.R.=4.5). The concordance between CR and MH was higher in UC patients than in subjects with CD (k=0.71 in UC; k=0.41 in CD).
CONCLUSION: Thiopurines are equally effective in maintaining steroid-free clinical remission in both UC and CD even if with a better profile of efficacy in UC in terms of mucosal healing. Our data confirm the higher concordance between clinical and endoscopic findings in UC compared to that observed in CD patients.
Disclosure of Interest: None declared

OP013 RANDOMIZED CONTROLLED TRIAL COMPARING THE EFFICACY OF MEASALAMINE AND ORAL STEROIDS IN PATIENTS WITH MODERATELY ACTIVE ULCERATIVE COLITIS

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INTRODUCTION: The treatment of active ulcerative colitis (UC) has been aimed at the alleviation of symptoms. However, mounting evidence suggests mucosal healing better marker of long-term outcomes.
AIMS & METHODS: To compare the efficacy of oral mesalamine with that of oral prednisolone in patients with moderately active ulcerative colitis (UC).
In this open label randomized controlled study between June 2012 and December 2013 consecutive patients of moderately active UC were randomly assigned to two treatment groups. One group (ASA) received mesalamine tablets 800mg, two tablets TID (total dosage-4.8gm/day) and the other group (CS) received prednisolone in tapering doses (40mg OD for 1 week, then 30mg for next 1 week and then 20mg for next 4 weeks). All patients were followed for 6 weeks. Mayo score, sigmoidoscopy with biopsy, and fecal calprotectin (FC) were determined at the baseline and at the end of treatment. Mucosal healing was defined as decrease in sigmoidoscopy subscore to ≤1. Clinical response was defined as a decrease of ≥3 points from the baseline Mayo score. Clinical remission was defined as achievement of Mayo score ≤2. Data was recorded in excel sheet and statistical analysis was done using SPSS v17.0
RESULTS: Twenty nine patients received mesalamine and 25 patients received steroids. Mucosal healing was achieved in 19 (65.5%) of the patients in ASA group and 17 (68%) of the patients in CS group (p=0.847). There was significant improvement in Mayo score from 8.5±1.2 to 3.5±1.7 in ASA group as well as from 8.1±1.6 to 3.1±1.8 in CS group (p=0.001). Clinical response was achieved in 26 (89.7%) patients in ASA group and 23 (92%) patients in the CS group. Clinical remission was achieved in 8 (27.6%) patients in ASA group and 12 (48%) patients in the CS group. There was no statistically significant difference between ASA and CS groups with regard to treatment response or remission. Total histopathology score in CS group decreased from 11.9±2.4 to 8.1±3 (p=0.001), but at the end of treatment total score in both ASA and CS groups was not significantly different from each other (9.7±3.4 vs 8.1±3; p=0.088). There was improvement in FC levels in both the groups (132±136.6 μg/g stool to 75.9±77.1 μg/g stool in ASA group and 165.7±116.4 μg/g stool to 115.6±83.1 μg/g stool in CS group) although the difference between paired samples could not reach a significant level (p=0.057 and p=0.136 respectively). In subgroup analysis, we observed a significant (p=0.007) improvement in FC level from 163.7±133.2 μg/g stool to 89.9±86.6 μg/g stool on follow up at 6 weeks in patients who achieved mucosal healing as compared to those who did not (p=0.783). There was significant improvement in erythrocyte sedimentation rate in ASA group; from 28.4±13.5 to 20.7±11.8 (p=0.002) as well as in CS group; from 33.5±18.8 to 21.3±13.7 (p=0.003).
CONCLUSION: Prednisolone and mesalamine are equally effective in inducing mucosal healing and clinical response in moderately severe UC. Both the drugs were associated with significant improvement in endoscopic as well as clinical activity of the disease. Mucosal healing was positively correlated with fall in FC levels.
Disclosure of Interest: None declared

OP014 CORTICOSTEROID DOSING IN PEDIATRIC ACUTE SEVERE ULCERATIVE COLITIS: A MULTICENTER PROPENSITY SCORE STUDY

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INTRODUCTION: Data to support dosing of intravenous corticosteroids (IVCS) in pediatric acute severe ulcerative colitis (ASC) are lacking and extrapolated from adult literature. We aimed to explore the optimal dosing of IVCS using a robust statistical method called propensity score analysis on the largest pediatric cohort of ASC to date.
AIMS & METHODS: 283 children treated with IVCS for ASC were included from the OSCI studies (n=227) and another 55 newly reviewed patients from Jerusalem and Liverpool, which uses high IVCS doses as part of local practice. As children were treated according to physician discretion, a simple comparison of the dosing may lead to confounding-by-indication bias. This was addressed by the propensity score method, which is the conditional probability of receiving the treatment given many pre-treatment observed covariates. By using the probability that a subject would have been treated with low dose (≤1.25mg/kg/day methylprednisolone-equivalent, max 50mg) vs. high-dose IVCS (>1.25mg/kg/d or >50mg/d) we individually matched children from both groups, thus creating a quasi-randomized trial (matching according to the nearest value of the logit of the propensity score within the determined caliper size in a blinded fashion to all outcomes). Secondary analyses utilized a high cutoff value (>2mg/kg/d or >80mg/d).
RESULTS: Of the total cohort, 208 were matched (104 in each of the high and low dose groups). The mean age was 12.1±4 years, median disease duration 2 (IQR 0-13.8) months, 47% males and mean PUCAI at admission 71±12 points, implying severe disease. The two groups were similar in important pre-treatment basic variables alluding to successful matching. Median IVCS dose was 0.84 (IQR 0.7-1.02; min 0.5) mg/kg/d in the low dose group and 1.57 (1.03-1.99; max 30.3) mg/kg/d in the high dose group. There were no significant differences in clinically relevant outcomes between the high and the low-dose groups (i.e. need for salvage therapy by discharge (35% vs 32%, respectively; P=0.77) and time to salvage therapy, rate of children achieving PUCAI<35 points by day 5 (41% vs. 43% P=0.92) and mean day-5 albumin (P=0.36), CRP (P=0.26), platelets (P=0.72) and hemoglobin (P=0.32)). The low-dose group had significantly lower mean admission-days by 3.8 days (P=0.02) and mean day-5 ESR (lower by 9mm; P=0.04). In the secondary analysis, 84 children were matched in the high-dose cutoff. Among the measured outcomes, the only different outcome was the mean admission days, which was higher by 3.67 (P=0.04) in the high dose group.
CONCLUSION: Our data suggest that IVCS doses up to 1.25mg/kg/d (max 50mg/d) are at least as effective as higher doses in ASC. These results should be considered for inclusion in clinical guidelines.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 11:00–12:30
ADVANCES IN ERCP – HALL N

OP015 BILIARY DYSPLASIA SCREENING IN PSC - THE VALUE OF BRUSH CYTOLOGY AND ERCP SCORING

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INTRODUCTION: Primary sclerosing cholangitis (PSC) is a chronic cholestatic biliary disease associated with inflammatory bowel disease (IBD). The risk for malignancies, especially cholangiocarcinoma (CCA) is elevated among PSC patients. Biliary intraepithelial neoplasia (BilIN) is the precursor of CCA.
AIMS & METHODS: We performed brush cytology (BC) for 261 consecutive patients referred for their first endoscopic retrograde cholangiography (ERCP) due to suspicion of PSC between 1st of January 2006 and 31th of October 2011. Macroscopic biliary duct changes (i.e. strictures and dilations) were graded according to the modified Amsterdam score (Ponsioen 2010). BC was graded as benign (normal or benign atypia), suspicious (cytologic dysplasia) or malignant. End points were follow up for at least two years, liver transplantation or development of CCA.
RESULTS: BC was classified as benign (93.1%), suspicious (6.1%) or malignant (0.8%). All patients with nonadvanced PSC based on ERC-scoring had benign BC, with the exception of one without known end-point. During the follow up time for at least two years (mean 4.8 years) most patients (n=249, 95.4%) reached the end point (follow up for 2 years without evidence of CCA, no biliary neoplasia in the explanted liver, BilIN, or CCA). Seven patients were diagnosed with CCA, five of them within 5 months after diagnosis of PSC. Eight out of nine patients with liver transplantation had BilIN. Two patients were diagnosed with gallbladder carcinoma. Most patients (n=232, 93.2%) who reached end-point were classified as having benign disease course. Majority of patients with BilIN or CCA were male (n=11, 73.3%), and the first BC was suspicious or malignant in eight (53.3%) of them.
CONCLUSION: In unselected patient population coming for the first time for diagnostic ERCP for PSC 7% had already a suspicion of malignancy or biliary malignancy in brush cytology. Advanced PSC and male sex were associated with biliary neoplasia.
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Disclosure of Interest: None declared

OP016 COMPARATIVE ANALYSIS OF ERCP, IDUS, EUS AND CT IN PREDICTING MALIGNANT BILE DUCT STRICTURES – RESULTS OF A TERTIARY REFERRAL CENTER WITH 234 PATIENTS

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INTRODUCTION: There are no definite guidelines for the management and diagnostics of biliary strictures of indeterminate etiology so far. Various endoscopic and radiographic imaging modalities such as endoscopic retrograde cholangio-pancreatography (ERCP), intraductal ultrasound (IDUS), endosonography (EUS) and computed tomography (CT) are available and compete with each other.

AIMS & METHODS: We aimed to evaluate the diagnostic yield of IDUS, EUS and CT in a large patient cohort of 234 scheduled for ERCP with IDUS, CT and EUS due to indeterminate strictures or filling defects of the common bile duct. Sensitivity, specificity and accuracy rates of the diagnostic procedures were calculated relating to the definite diagnoses proved by histopathology or long-term follow-up in those patients who did not undergo surgery. For each of the diagnostic measures, sensitivity, specificity and accuracy rates were calculated. In all cases, gold standard was the histopathologic staging of specimens or long-term follow-up of at least 12 months.
RESULTS: Comparison of the different diagnostic tools for detecting bile duct malignancy resulted in accuracy rates of 91% (ERCP/IDUS), 59% (ETP), 92% (IDUS+ETP), 74% (EUS) and 73% (CT), respectively. In the subgroup analysis accuracy rates (%, ERCP+IDUS/ETP/IDUS+ETP; EUS; CT) for each tumor entity were as follows: cholangiocellular carcinoma: 92/74/92/70/79; pancreatic carcinoma: 90/68/90/81/76; ampullary carcinoma: 88/90/90/76/76. The detection rate of malignancy by ERCP/IDUS was superior to ETP (91 vs. 59% $p<0.0001$), EUS (91 vs. 74% $p<0.0001$) and CT (91 vs. 73%$p<0.0001$), EUS was comparable to CT (74 vs. 73%, p=0.649). When analyzing accuracy rates with regard to localization of the bile duct stenosis the accuracy rate of EUS for proximal vs. distal stenosis was significantly higher for distal stenosis (79 vs. 57%, $p<0.0001$).
CONCLUSION: ERCP/IDUS is superior to EUS and CT in accurate diagnostics of bile duct strictures of uncertain etiology. However, multimodal diagnostics due to even better accuracy rates is recommended.
Disclosure of Interest: None declared

OP017 SMART ATLAS FOR SUPPORTING THE INTERPRETATION OF PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY (PCLE) OF BILIARY STRICTURES: FIRST CLASSIFICATION RESULTS OF A COMPUTER-AIDED DIAGNOSIS SOFTWARE BASED ON IMAGE RECOGNITION

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INTRODUCTION: pCLE enables microscopic imaging of biliary strictures, in vivo and in real time, during an ERCP procedure. Results of a multicentric study (Meining et al., GIE 2011) have shown that pCLE allows endoscopists to differentiate benign from malignant strictures in real time with high sensitivity and NPV. A computer-aided diagnosis software called Smart Atlas has been developed to assist endoscopists with the interpretation of pCLE sequences. This study aims at evaluating the performance of this software for the differentiation of benign and malignant strictures.
AIMS & METHODS: Several high quality pCLE sequences were retrospectively collected from pCLE procedures performed in multiple clinical centers. These sequences, along with their annotated final diagnosis, were used to train a classification software that uses a content-based image retrieval algorithm to predict the diagnosis of a query video based on the diagnoses of the most visually similar atlas videos. For all cases, final diagnosis was based on histology, positive tissue sampling, or one year follow-up. All evaluations were performed using leave-one-patient-out cross-validation to avoid bias. To evaluate binary classification, a receiver operating curve was generated, allowing optimization of the trade-of between false positives and negatives.
RESULTS: Among the 60 pCLE sequences collected from 30 patients, 14 were representative of healthy bile duct, 10 of inflammatory strictures and 36 of malignant strictures. The resulting receiver operating curve shows two points of interest: the first (reps. second) point has a high sensitivity of 88.9% (reps. high specificity of 91.7%), an acceptable specificity of 70.8% (reps. acceptable sensitivity of 69.4%), an accuracy of 81.7% (resp. 78.3%), a PPV of 82.1% (resp. 92.6%) and a NPV of 81.0% (resp. 66.7%). In comparison, Meining et al. reported that, for in vivo pCLE diagnosis of malignant stricture, endoscopists achieve overall sensitivity, specificity, accuracy, PPV and NPV of 98%, 67%, 81%, 71% and 97%, respectively.
CONCLUSION: These first results demonstrate that benign and malignant strictures can be automatically discriminated by the Smart Atlas software using only the image content of pCLE sequences of high quality, with an accuracy comparable to that achieved in real-time by endoscopists. The software is also able to achieve high specificity and PPV to help reduce false positives caused by inflammatory strictures. Future work will focus on improving the software to handle pCLE sequences of various quality. The resulting case-based reasoning software could be used as an educational tool to train non-expert endoscopists, but also as a second- reader tool to assist any endoscopist in real-time diagnosis of biliary strictures using pCLE.
Disclosure of Interest: None declared

OP018 ENDOSCOPIC PAPILLARY LARGE BALLOON DILATION (EPLBD) VERSUS ADDITIONAL FULL ENDOSCOPIC SPHINCTEROTOMY (EST) FOR THE ENDOSCOPIC REMOVAL OF RECURRENT LARGE BILE DUCT STONES AFTER NON-FULL EST

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INTRODUCTION: There were no reports about the comparative study between endoscopic papillary large balloon diation (EPLBD) and additional endoscopic sphincterotomy (EST) for endoscopic treatment of common bile duct stones which were recurred after endoscopic stone removal with previous non-full EST.
AIMS & METHODS: The aim of this study was to compare the safety and efficacy of EPLBD with additional EST for recurrent difficult bile duct stones after previous non-full EST.
We retrospectively reviewed the records from twelve hundred four patients who received the first ERCP for the removal of bile duct stones from August 2004 to July 2013. We enrolled a total of 89 patients who had large bile duct stones recurred after previous non-full EST, and need to receive the additional papillloplasty. The patients were classified into three groups: Group A who underwent EPLBD (group A, $n = 59$) by using 12 – 18 mm sized balloon, and group B who underwent additional full EST (group B, $n = 30$). When necessary, mechanical lithotripsy was performed. The therapeutic outcomes and complications were reviewed and compared between two groups.
RESULTS: There were no differences between two groups with regard to age, stone size, number of stones and mean procedure time. Complete stone removal was achieved in all patients, but group B had higher using rate of mechanical lithotripsy for complete removal of the large bile duct stones, compared to group A (16.9% vs. 36.7%, $P = .037$). There were no differences in procedure-related complications between two groups: pancreatitis(1.7% vs 0%, $P = .663$), Hyperamylasemia (5.1% vs 6.7%, $P = .550$) and bleeding (1.7% vs 13.3%, $P = 0.042$).
CONCLUSION: EPLBD showed results similar to those with additional full EST for removing recurrent large stone. But additional full EST group had more bleeding and increasing the need for lithotripsy, compared with EPLBD group.
Disclosure of Interest: None declared

OP019 IMPACT OF PCLE ON THE MANAGEMENT OF PATIENTS WITH INDETERMINATE BILIARY STRICTURE: RESULTS OF A LARGE MULTICENTRIC STUDY

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INTRODUCTION: Diagnosis of indeterminate biliary strictures remains a clinical problem largely due to a low sensitivity of ERCP with tissue sampling (<50%). It has been previously shown that the use of probe-based confocal laser endomicroscopy during ERCP for indeterminate biliary strictures, detects more malignant lesions, doubles sensitivity compared to that of standard tissue sampling (98% vs. 45%).
This study presents the final results of an international multicenter trial (FOCUS, NCT01392274) aiming at evaluating the impact of optical biopsy in patients with indeterminate biliary stricture using criteria for normal, inflammatory and malignant strictures.
AIMS & METHODS: Patients were enrolled at 6 international centers (2 European, 4 US) from April 2012 to September 2013 and underwent pCLE during standard ERCP. For each patient, the investigator was asked to provide a diagnosis and a patient management recommendation based on clinical data and ERCP findings before and after pCLE and again after tissue results returned. Malignancy was confirmed by positive tissue sampling at ERCP or surgery or by a deteriorating clinical course with consistent radiographs. Benign disease mandated negative histology at surgery or at least a 6 month follow period for a benign course after negative ERCP tissue sampling.
RESULTS: 107 patients presenting with an indeterminate stricture where enrolled (68 benign, 39 malignant).
Presumptive diagnosis based on clinical history and ERCP alone resulted in a sensitivity of 84.6% and a specificity of 74.3%. The addition of pCLE increased specificity up to 88.3% whereas the specificity declined to 89.7%. Finally, The addition of tissue sampling resulted in a sensitivity of 89.7% and a specificity of 87.2%. Investigators would have immediately proceed with patient management in 24 cases based on clinical history and ERCP, and in 33 cases based on clinical history, ERCP and pCLE. Out of the 33 patients, pCLE would have had a positive impact on 37% of them, a negative impact on 6% of them and would have been in accordance with the actual patient management in 57% of the patients.
CONCLUSION: pCLE is a safe and sensitive minimally invasive method for evaluating patients with indeterminate biliary stricture Our observations further suggest that the results of pCLE may have a favorable impact on patient management. In centers in which pCLE expertise is available, our results suggest a more rationalized approach to the diagnosis and management of biliary tumors.
Disclosure of Interest: None declared

OP020 ESWL FOR LARGE PANCREATIC CALCULI. A DECADES EXPERIENCE

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INTRODUCTION: ESWL is established as the standard of care for management of pancreatic ductal calculi larger than 5mm in size. We share a single tertiary care centre experience of 10 years using this technique.
AIMS & METHODS: This is a retrospective analysis of prospectively collected data at the Asian Institute of Gastroenterology Hyderabad India from February 2004 to February 2014. All patients having pain as the dominant symptom, with main pancreatic ductal calculi not amenable to standard endoscopic extraction, were subjected to lithotripsy using a 3rd generation electro magnetic lithotripter. Fragmentation was considered successful when the calculi were broken down to <3mm in size. Upto 5000 shocks were delivered per session till this result was achieved. ERCP was done within 24 - 48 hours after successful fragmentation and the main pancreatic duct was cleared following a sphincterotomy. Stents were placed as and when required.
RESULTS: A total of 2779 patients underwent ESWL during this period. A majority (69%) were under the age of 40 years and did not consume alcohol. Males accounted for 64% of patients. Single stones were seen in 24%, whereas in the rest they were multiple. The head was the commonest location of the calculi (59%). Sixty eight percent of patients needed 3 sessions or less for fragmentation. Endoscopic sphincterotomy was done in 69% of patients. Complete clearance was achieved in 79%, partial in 14% while in the rest it was unsuccessful. Complications were minimum and not life threatening. From our earlier experience short term pain relief was seen in 84% and long term relief (upto 8 years) in 60% of patients. There war significant improvement in quality of life.
CONCLUSION: ESWL should be offered as first line therapy in properly selected patients with large main pancreatic duct calculi.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 11:00-12:30

CELLULAR CROSSTALK IN PANCREATIC CANCER - HALL O

OP021 PARASYMPATHOMIMETIC AGENTS LIMIT PANCREATIC CANCER GROWTH BY SUPPRESSION OF THE P44/42 MAPK SIGNALING PATHWAY

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INTRODUCTION: The vagus nerve and parasympathetic nervous system play a major role in the regulation of pancreatic physiology and also feature a suppressive effect on acute and chronic inflammation. It is therefore conceivable that the parasympathetic nervous system may also play a role in pancreatic carcinogenesis.
AIMS & METHODS: The aim of this study was to investigate the potential effect of the parasympathetic nervous system on proliferation and invasion of pancreatic cancer (PCa) and enlighten the linked intracellular signalling pathways *in vitro* and *in vivo*. Therefore, human PCa cell lines were exposed *in vitro* to direct and indirect parasympathomimetic agents (Carbachol, Physiostigmine and Pyridostigmine) and their proliferation was quantified via the MTT proliferation assay, their invasiveness via the matrigel invasion assay, and the extent of phosphorylation of p44/42 mitogen-activated protein kinase (MAPK) was determined by immunoblotting. In an *in vivo* xenograft model, human PCa cells were injected subcutaneously into Crl:NMRI-Foxn1^{nu} nude mice and tumor area and metastasis were compared between treated and untreated groups.
RESULTS: The MTT proliferation assay showed significant dose dependent suppression of PCa cell proliferation after treatment with both direct and indirect parasympathomimetic agents. The matrigel invasion assay experiments revealed a dose dependent inhibition of PCa cell invasiveness. These results were associated with a lower intracellular phosphorylation of p44/42 MAPK and corresponded with the results obtained in the *in vivo* experiments, in which both tumor size and local invasiveness were inhibited subsequent to prophylactic and therapeutic treatment.
CONCLUSION: The systemic administration of activators of the parasympathetic nervous system restrains PCa proliferation and invasiveness via suppressing the intracellular phosphorylation of the p44/42 MAPK signalling pathway, implicating a potential novel understanding of neuro-cancer interactions and treatment of human malignancies.
Disclosure of Interest: None declared

OP022 THE PHENOMENON OF BONE MARROW DERIVED STEM CELLS MOBILIZATION IN PANCREATIC DISEASES IS PRESENT ONLY IN CANCER PATIENTS

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INTRODUCTION: Various studies indicate potential involvement of various populations of bone marrow derived stem cells (BMDSCs) into process of tissue regeneration and tumor development. Our team demonstrated recently that in patients with pancreatic cancer intensified peripheral trafficking of selected populations of BMSCs occurres (*J Cell Mol Med 2013: 17:792-9*). There is no data on this phenomenon in benign pancreatic disorders.
AIMS & METHODS: The purpose of the study was to comprehensively analyze systemic trafficking of various populations of BMSCs: mesenchymal, hematopoietic, endothelial stem/progenitor cells (MSCs, HSCs, EPCs respectively), as well as, of recently discovered population of very small embryonic/epiblast-like SCs (VSELs) in patients chronic and acute pancreatitis with comparison to pancreatic cancer patients and controls. The circulating CD133+/Lin-/CD45-/CD34+ cells enriched for HSCs, CD105+/STRO-1+/CD45- cells enriched for MSCs, CD34+/KDR+/CD31+/CD45- cells enriched for EPCs, and small CXCR4+CD34+CD133+ subsets of Lin-CD45- cells that correspond to VSELs were enumerated and sorted from blood samples derived from 16 patients with acute pancreatitis, 13 with chronic pancreatitis, 30 cancer patients and 19 healthy controls.
RESULTS: We noticed significant decrease of a number of circulating CD45(-)STRO-1(+)CD105(+) (P=0.03); CD45(-)STRO-1(+)CD105(-) (P=0.02) LIN(-)CD45(+)CD133(+) (P=0.04), and LIN(-)CD45(-)CD133(+) (P<0.04) in patients with acute pancreatitis and decrease of number of circulating LIN(-)CD45(+)CD133(+) (P=0.04); LIN(-)CD45(-)CD133(+) (P<0.04); LIN(-)CD45(+)CD34 (+) (P<0.04) in patients with chronic pancreatitis. The number of circulating CD45(-)STRO-1(+)CD105(-)(p=0,02) cells was significantly higher in patients with chronic pancreatitis than in patients with acute pancreatitis.
CONCLUSION: In contrast to heart infarction, brain stroke, skin burns and pancreatic cancer, there is no significant mobilization of the BMDSCs to the peripheral blood in patients with acute and chronic pancreatitis. Interestingly, even significant decrease of the number of circulating cells was noted. The mobilization of BMDSCs to the peripheral blood, in pancreatic disorders, seems to be connected only with pancreatic cancer.
Acknowledgment:Study financed from Ministry of Science and Higher Education Grant(402423038)
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Disclosure of Interest: None declared

OP023 INCREASING THE INFLAMMATORY COMPETENCE OF MACROPHAGES WITH IL-6 OR WITH COMBINATION OF IL-4 AND LPS RESTRAIN THE INVASION OF PANCREATIC CANCER CELLS

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INTRODUCTION: Inflammation plays a critical role in the development and progression of cancer; local inflammation in chronic pancreatitis multiplies the risk of pancreatic cancer. Recent studies suggest that pro-inflammatory type M1 macrophages work against tumour progression and anti-inflammatory M2 macrophages enhance tumour progression.
AIMS & METHODS: The aim of this study was to examine the interaction of pro-inflammatory M1 and anti-inflammatory M2 macrophages with pancreatic cancer cells.
We studied the migration rate of fluorescein stained pancreatic cancer cells (MiaPaCa-2 and HPAF-II) in Matrigel cultured alone or with GM-CSF differentiated M1 macrophages or with M-CSF differentiated M2 macrophages. We studied the changes the pancreatic cancer cells induce in the differently stimulated macrophages' cytokine expression with cytokine array. Cytokine array results are given as percentage between negative and positive control recorded on each array.
RESULTS: GM-CSF differentiated M1 macrophages increased the migration rate of primary pancreatic adenocarcinoma cell line (MiaPaCa) from 11.5μm/h $\pm$0.2 to 24.7μm/h $\pm$0.3 (p<0.001) and metastatic cell line (HPAF) from 4.0μm/h $\pm$0.2 to 19.1μm/h $\pm$0.3 (p<0.001). M-CSF differentiated macrophages M2 increased the invasion rate of MiaPaCa cells from 8.4μm/h $\pm$0.1 to 14.8μm/h

±0.1 and of HPAF from 4.5μm/h ±0.2 to 20.8μm/h ± 0.3 (p<0.001). When the cells were stimulated with IL6 or IL4+LPS, the macrophages' increasing effect on the migration rate was completely reversed in the case of primary pancreatic cancer cell line and partly reversed in the case of metastatic cancer cell line. When stimulated with IL6 (GM-CSF differentiated M1 cells) the migration rate of MiaPaCa cells was 11.7μm/h ±0.2 and of HPAF cells 13.8μm/h ±0.2. The migration rate of MiaPaCa cells co-cultured with IL4+LPS stimulated macrophages (M-CSF differentiated M2) was 8.5μm/h ±0.4 and with HPAF 8.3μm/h ±0.4.
GM-CSF differentiated M1 macrophages co-cultured with MiaPaCa cells released less inflammatory cytokines than macrophages cultured alone (TNFα from 0.64% to 0.03% ±0.30, p=0.009; IL23 from 1.14 to 0.63% ±0.15, p=0.009; INFγ from 1.30 to 0.54% ±0.26, p=0.038). Adding IL6 to GM-CSF differentiated cell culture with macrophages and MiaPaCa cells increases the expression of inflammatory cytokines IL23 (from 0.65 to 1.22% ±0.12 p=0.013), TNFα (from 0.58 to 1.34% ±0.10, p=0.007). M-CSF differentiated M2 macrophages did not secrete inflammatory cytokines but adding IL4+LPS to the cell culture with macrophages and MiaPaCa cells increased the expression of IL6 (from 0.52 to 5.03% ±2.21, p<0.001), CCL5 (from 0.58 to 23.27% ±7.65, p<0.001), TNFα (from 0.84 to 5.81% ±0.52, p<0.001) but also anti-inflammatory IL10 expression increased (from 0.31 to 1.08% ±0.10, p=0.007).
CONCLUSION: Our study shows that pancreatic cancer cells have an ability to reduce the inflammatory cytokine expression of GM-CSF differentiated pro-inflammatory M1 macrophages. This explains why both GM-CSF (M1) and M-CSF (anti-inflamatory M2) differentiated macrophages promoted the invasion of pancreatic cancer cells. IL6 and IL4+LPS activated the inflammatory cytokine expression in macrophages and this might contribute to the reversion of the macrophage induced increase of cancer cell migration rate.
Disclosure of Interest: None declared

OP024 LOSS OF ATM ACCELERATES PANCREATIC CANCER FORMATION AND EPITHELIAL-MESENCHYMAL-TRANSITION VIA AN AUTOCRINE BMP4-SIGNALLING LOOP

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INTRODUCTION: Onset and progression of pancreatic ductal adenocarcinoma (PDAC) is associated with accumulation of particular oncogenic mutations. Recent genome-wide exome sequencing studies have identified ATM mutations in independent PDAC cohorts but to date, the role of ATM in PDAC tumour biology is unclear.
AIMS & METHODS: We use a conditional PDAC mouse modell and *ex vivo* acinar cultures to delineate the role of ATM during mouse pancreatic carcinogenesis.
RESULTS: Here we report that conditional deletion of ATM in a mouse model of PDAC enhanced pancreatic cancer formation via enhanced ductal reprogramming. ATM-targeted mice had significantly shortened survival compared to controls and interestingly, loss of a single ATM allele was sufficient to induce this phenotype. Depletion of ATM gave rise to a greater number of proliferative acinar-to-ductal metaplastic (ADM) lesions and pancreatic intraepithelial neoplasias (PanIN), coupled with a pronounced fibrotic reaction. These precursor lesions in ATM-deficient mice were broadly associated with altered epithelial-to-mesenchymal transition (EMT) and a gain of tumor initiating cells. Finally, we are able to define a Bmp4-signalling loop originating within the acinar compartment, which initiates ductal programming in an autocrine manner and subsequent EMT. Notably, our mouse model recapitulates many features of more aggressive human PDAC subtypes, namely mesenchymally differentiated PDAC.
CONCLUSION: We show that ATM also acts as a tumor suppressor molecule in human PDAC, where low expression of ATM serves as an independent predictor for EMT and poor prognosis. Taken together, our data suggests an intimate link between ATM expression and pancreatic cancer progression in mice and men.
Disclosure of Interest: None declared

OP025 ANTITHETICAL NFATC1-SOX2 AND P53-MIR-200 SIGNALLING NETWORKS GOVERN PANCREATIC CANCER CELL PLASTICITY AND TUMOUR PROGRESSION

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INTRODUCTION: Pancreatic ductal adenocarcinoma (PDAC) cells undergo epithelial–mesenchymal transdifferentiation (EMT) in adaption to environmental clues, including inflammation, a process that combines tumour cell dedifferentiation with dissemination and acquisition of stemness features. However, the mechanisms coupling inflammation-induced signalling pathways with EMT and stemness remain largely unknown. We have shown that activation of the NFATc1 transcription factor promotes pancreatic cancer development and metastasis through its ability to integrate extrinsic stimuli into coordinated gene regulation.
AIMS & METHODS: To assess whether NFATc1 controls transcription of EMT genes and stemness in PDAC, particularly upon p53 inactivation. We generated mouse strains with combined pancreas-specific expression of $Kras^{G12D}$, $p53^{R172H}$ or $p53^{fl/wt}$ and NFATc using Cre-Lox technology. These mice showed a highly aggressive tumor growth (median survival of <50 or 61 days). Mouse primary tumour cells were used to identify NFATc1 targets by gene expression profiling and pathway analyses (ChIP seq, miRNA analyses and GSEA). NFATc1 mediated EMT and stemness were assessed in human and murine pancreatic cancer models using migration and spheroid assay as well as xenograft mouse models.
RESULTS: Here, we reveal the inflammation-induced transcription factor NFATc1 as a central regulator of pancreatic cancer cell plasticity. We show that NFATc1 drives EMT programming and maintains cancer cells in a stem cell-like state through Sox2-dependent transcription. Intriguingly, NFATc1-Sox2 complex mediated PDAC dedifferentiation is opposed by antithetical p53-miR200c signalling. Inactivation of the tumour suppressor pathway is essential for tumour dissemination and dedifferentiation both in genetically engineered mouse models and human PDAC.
CONCLUSION: Based on these findings, we propose a hierarchical signalling network regulating PDAC cell plasticity and suggest that molecular decisions between epithelial cell preservation and conversion into a dedifferentiated cancer stem cell-like phenotype depends on opposing levels of p53 and NFATc1 activities.
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Disclosure of Interest: None declared

OP026 NEURAL REMODELING IN PANCREATIC NEUROPATHY IS CHARACTERIZED BY NEUROTROPHIN-3-MEDIATED INCREASE IN THE PANCREATIC NOCICEPTIVE INNERVATION, DEMYELINATION AND SELECTIVE GLIAL ACTIVATION

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INTRODUCTION: Neural remodelling in pancreatic cancer (PDAC) and chronic pancreatitis (CP) is characterized by reduced sympathetic pancreas innervation among patients with severe pain. However, it remains unknown which types of nerve fibers replace sympathetic fibers in panful PDAC and in CP.
AIMS & METHODS: In the current study, we aimed to elucidate wheter the sympathetic innervation in PDAC and CP is replaced by increased nociceptive innervation and glial activation, and which molecular agents mediate this switch. For this purpose, normal human pancreas (NP, n=16), CP (n= 26) and PCa (n=25) tissues were quantitatively analyzed for the neuro-immunoreactivity of a) *nociceptive* fiber markers substance-P (SP) and calcitonin-gene-related-peptide (CGRP), b) *myelination* markers neurofilament-H (NFH) and peripheral-myelin-protein-22 (PMP22), c) *glial activation* markers $p75^{NTR}$ and glial-fibrillary-acidic-protein (GFAP) and correlated to pain, neural invasion (NI) and pancreatic neuritis. Nociceptive neurite density of dorsal-root-ganglia-(DRG)-neurons that were cultivated in human NP, CP or PDAC tissue extracts was analyzed in the presence of neutralizing antibodies against nerve-growth-factor (NGF), neurotrophin-3 (NT-3) or brain-derived-neurotrophic-factor (BDNF).
RESULTS: SP- and CGRP-containing nerve fibers were prominently increased in CP independently of the pain status. Accordingly, the neuro-immunoreactivity of NFH and PMP22 was remarkably decreased in CP and PCa. NI and pancreatic neuritis were more pronounced around nerves with decreasing SP- and CGRP-content, increasing myelination and enhanced glial activation. Cultivation of DRG neurons in CP extracts induced the sprouting of SP- and CGRP-containing neurites, which was reversed upon blockade of NT-3 within CP extracts.
CONCLUSION: Neural remodeling in CP and PDAC involves pain-independent, NT-3-mediated upregulation of nociceptive innervation, loss of myelination, and glial activation around nerves with NI and pancreatic neuritis. These alterations show that the sympathetic innervation in CP is replaced by pain-transmitting, i.e. nociceptive innervation. This switch to increased nociception, myelination and glial activity may be the determinants of the pathologic pain response in PDAC and CP.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 11:00-12:30
CLINICO-PATHOLOGICAL FEATURES OF GI CANCER - LOUNGE 5

OP027 INTERVAL GASTRIC CANCERS: PRECISE REVIEW OF PAST ENDOSCOPIC IMAGES, CLINICOPATHOLOGICAL FEATURES AND MICROSATELLITE INSTABILITY

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INTRODUCTION: There are few studies about interval gastric cancers, which are diagnosed after preceding negative upper endoscopy. Microsatellite instability (MSI), frequently observed in interval colorectal cancers, might be also a genetic feature of interval gastric cancers.
AIMS & METHODS: The aims of this study were to speculate natural history of early gastric cancer from precise review of past endoscopic images of interval gastric cancers and to elucidate clinicopathological features of internal gastric cancers. The study cohort consisted of 260 gastric cancer patients diagnosed at Sapporo Medical University Hospital. Patients who had experience of upper endoscopy within the past 10 years were stratified according to interval between past and current endoscopy. Images of past endoscopy performed at our hospital were scrutinized by two endoscopy specialists independently. Five microsatellite markers were used for MSI analysis and instability of two or more markers was defined as MSI-H.
RESULTS: Of 260 gastric cancer patients, 60 (23%) had experience of upper endoscopy within 10 years prior to the cancer diagnosis; 27 patients with endoscopy interval of 24 months or less (short interval), 19 patients with 25 to 48 months interval (intermediate) and 14 patients with 49 to 120 months interval (long interval). Rates of advanced gastric cancers (T2 or more) to all cancers were 19%, 37% and 57% for the short, the intermediate and the long interval group, respectively. For patients with over 120 months interval or without experience of endoscopy, rate of advanced gastric cancer was 51%.
High-quality images of past endoscopy performed at our hospital were available for precise review in 32 patients. Rates of advanced gastric cancers of these 32 patients were 0%, 33% and 43% for the short, the intermediate and the long interval group, respectively. At past endoscopy, existence of early (T1) gastric cancers were strongly suspected in 17 patients while there were no lesions at current cancer sites in 15 patients. Of 17 early gastric cancers observed at past endoscopy, 11 were unchanged for an average of 20.4 months (range 12-40) while 6 had grown in 43.0 months (20-64). Of 6 growing gastric cancers, 3 had grown but remained as T1 for 36.7 months while another 3 had become unresectable in 49.7 months.
Interval gastric cancers had no clinicopathological features such as age, site, macroscopic and histological type. Seven percent (3/41) of interval gastric cancers while 11% (12/106) of all other gastric cancers were MSI-H (P=0.35). All MSI-H interval gastric cancers were intramucosal (T1a) and Lauren's intestinal type.
CONCLUSION: Most early gastric cancers are unchanged for 2 years while some will become advanced or unresectable in 3 to 5 years. Endoscopy with 2-year interval might be reasonable for gastric cancer surveillance, if quality of endoscopy is warranted. MSI was not frequent in interval gastric cancers.
Disclosure of Interest: None declared

OP028 MANAGEMENTS AND CLINICAL OUTCOMES OF NON-AMPULLARY NEUROENDOCRINE TUMORS OF THE DUODENUM: A RETROSPECTIVE, MULTICENTER STUDY IN JAPAN

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INTRODUCTION: Duodenal neuroendocrine tumor (D-NET) is a rare tumor. According to the latest European Neuroendocrine Tumor Society, surgical resection is recommended for ampullary D-NET, due to the anatomical location and different growth patterns from non-ampullary D-NET (NAD-NET). In contrast, endoscopic resection (ER) is recommended for small size (< 10 mm) NAD-NET, and there is no standardized therapeutic approach for intermediate size (10 to 20mm) NAD-NET. However, it is reported that 13.2 % of small D-NET had lymph node metastases. Furthermore, there are no reports on the criteria for deciding the additional treatment after ER in NAD-NET.
AIMS & METHODS: The aim of this study was to investigate the detailed characteristics of NAD-NET for detecting risk factors for metastasis by a multicenter, retrospective study. The patients with NAD-NETs diagnosed and treated between 1992 and 2012 at 7 institutions in Japan were enrolled. The patients with follow-up period of less than 24 months, except for NAD-NET-related death, were excluded from this study. As a result, a total of 39 patients with NAD-NETs were analyzed, comprising 29 men and 10 women, with a median follow-up of 46 months. The clinical and pathological records were reviewed to investigate the therapeutic procedure, tumor size, presence of lymph node and distant metastasis, and prognosis. In addition, depth of invasion, presence of lymphatic or venous invasion, World Health Organization (WHO) grading (Ki-67 index, mitotic count per 10 high power microscopic fields), peptide products (gastrin, somatostatin, and serotonin) were re-evaluated by one pathologist who was blind to the clinical information. To identify the risk factors for metastasis, we calculated odds ratio (OR) and 95 % confidence interval (CI) of age (over 60 years), size (over 10 mm), location (bulbs), number of lesions (multiple), each peptide product, lymphatic invasion, venous invasion, and WHO grading (G2, compared to G1) by univariate analysis.
RESULTS: Thirty patients were treated with ER, and 9 were treated surgically, and all of the tumors were less than 20 mm. There were 6 lymph node metastases (15.4 %) and 2 distant metastases (5.1 %). With regard to peptide products, NAD-NETs showed immunoreactivity for gastrin, somatostatin, and serotonin in 75.7 %, 35.1 %, and 37.8 % of the cases, respectively, all of which were not significantly associated with metastasis. Two of patients with immunoreactivity for gastrin showed Zollinger-Ellison syndrome. On univariate analysis, risk factors for metastasis were lymphatic invasion (OR = 31.0; 95% CI: 3.37-282; $P = 0.002$), venous invasion (OR = 14.5; 95% CI: 1.98-106; $P = 0.009$), and G2 (OR = 10.0; 95% CI: 1.36-73.3; $P = 0.024$). Five-year overall survival was 78.9 %, and 5-year disease-specific survival was 94.7 %. In one patient with 2 mm NAD-NET which had vascular invasion and classified as G2 (Ki-67 index; 20 %), lymph node and liver metastases were confirmed 18 months after ER, resulting in death.
CONCLUSION: To our knowledge, this is the first study to demonstrate that lymphatic invasion, venous invasion, and WHO grading G2 were risk factors for metastasis in NAD-NET less than 20 mm. These pathological findings could provide useful information in considering additional treatment after ER.
Disclosure of Interest: None declared

OP029 DUODENAL POLYPOSIS OUTCOMES IN MYH-ASSOCIATED POLYPOSIS

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INTRODUCTION: MUTYH-associated polyposis (MAP) is an autosomal recessive adenomatous condition. MAP (like familial adenomatous polyposis (FAP)), predisposes to colorectal and duodenal adenoma formation. However, duodenal polyposis is less frequently seen in MAP than in FAP, occurring in up to 25% and 90%, respectively. The rationale for adopting the same upper gastrointestinal (UGI) surveillance protocol for both polyposis syndromes is questionable.
AIMS & METHODS: The aim of this study was to assess the incidence, extent and progression of duodenal adenomas in an MAP population over time and evaluate the suitability of the current FAP UGI surveillance protocol in MAP. All genetically confirmed MAP cases followed-up at a single institution were identified from a prospectively maintained registry database. Case notes, endoscopy and histology reports were analysed. The primary outcome measure was the occurrence of duodenal adenomas. Secondary outcomes included age of adenoma onset, time interval to advancing Spigelman stage, MAP mutation, polyp morphology and distribution.
RESULTS: 34 MAP patients were identified, of which 13 (38%) developed duodenal adenomas, with a median follow-up of 7.5 years (range 0-16 years). Median age at first (baseline) OGD in the adenoma group was 50 years (range 38-66) with a median age of adenoma development of 52 years (range 39-66). In 92% (12/13 cases) only 1 to 4 polyps were found. 8/13 patients had a polyp detected at their baseline OGD (median age 51 years), with the remaining 5 (with normal baseline OGDs) developing polyps over an average of 12 years subsequently. All polyps involved D2, whilst most spared D1 and the ampulla. 8/13 cases were Spigelman stage 1 at first adenoma detection, and in only 1 case did progression of Spigelman stage occur between OGDs (from stage 1 to 2, over 5 years, due to an increase in polyp size only). Stage 3 disease was seen in only 2 cases, both over 60 years and at their first OGD.
CONCLUSION: Duodenal polyposis is seen much less frequently in MAP compared to FAP patients and this study supports that finding. Adenomas had a late age of onset, although many had their 1st OGD at a late stage due to the timing of their MAP diagnosis. Duodenal polyps appear to progress slowly in MAP and it may be inappropriate to determine surveillance interval using the Spigelman staging system given the lack of polyp multiplicity and histological progression. A new protocol for MAP duodenal polyposis surveillance is therefore proposed.
Disclosure of Interest: None declared

OP030 POST COLONOSCOPY COLORECTAL CANCER (PCCRC). HOW SHOULD WE CALCULATE A RATE? IMPLICATIONS FOR QUALITY PROGRAMS

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INTRODUCTION: A significant proportion of detected colorectal cancers are found in individuals who have had a colonoscopy in the previous 36 months. These malignancies can be due to missed cancer, or cancer arising from missed or incompletely removed polyps. The rate of post-colonoscopy colorectal cancer (PCCRC) has been proposed as a key quality indicator for colonoscopy. A quality indicator should be clearly defined, reproducible over time and relevant to colonoscopists. Studies to date have calculated the rate of PCCRC as a percentage of detected colorectal cancers. This rate calculation is problematic for quality programs in that the rate may fluctuate due to changes in the incidence of detected cancers quite apart from any real improvements in colonoscopy quality. We propose that PCCRC rates be expressed relative to the number of screening colonoscopies.
AIMS & METHODS: The aim of our study was to examine the feasibility of reporting PCCRC rates relative to the number of screening colonoscopies as a denominator and to test whether meaningful comparisons can be made when rates vary due to colonoscopy quality interventions. We used service log data to identify colonoscopies carried out during the last fiscal year in a regional colorectal cancer-screening program (Edmonton, Canada). This program serves a population of 817,000 and delivers colonoscopy in 8 separate endoscopy units in response to positive FIT tests, positive family history and previous history of colonic neoplasms. A PCCRC was defined as the diagnosis of a colorectal cancer in a patient who had undergone colonoscopy in the time period of 6-36 months prior to diagnosis. We estimated the occurrence PCCRC from previous Canadian studies that observed the rate of PCCRC to be approximately 8% of detected

cancers. From this data we normalized PCCRC as a rate relative to the number of screening colonoscopies performed. We then hypothesized a colonoscopy quality intervention that would reduce the rate of PCCRC's by 50%. We calculated PCCRC rates for the region, individual endoscopy unit and individual physician to determine the granularity by which meaningful statistical comparisons could be made. Confidence intervals for proportions were constructed using a Poisson distributions for rare events.

RESULTS:

	Estimated # of PCCRC's	Screening Colonoscopies	Rate/1000 Colonoscopies	95% CI
Regional Screening Program	10	11,374	0.88	0.42-1.62
50% Reduction in PCCRC Rate	*5*	*11,374*	*0.44*	*0.14-1.03*
Single Endoscopy Unit	2	3680	0.54	0.07-1.96
Single Physician	0.4	460	0.87	0-3.56
Polish Program (6-36 Months)	33	45,000	0.73	0.50-1.03
50% Reduction in PCCRC Rate	17	45,000	0.37	0.22-0.60
Kaiser Permanente (10 year)	712	314,872	2.26	2.10-2.43
50% Reduction in PCCRC Rate	356	314,872	1.13	1.02-1.25

CONCLUSION: Expressing PCCRC as a rate relative to number of screening colonoscopies is a feasible method to provide meaningful comparisons of colonoscopy quality. However, since PCCRC is a relatively rare event relative to the number of colonoscopies performed, meaningful comparisons can only be provided for programs of more than 300,00 of colonoscopies per year. Benchmarking of PCCRC across programs requires a standard definition and calculation method.

Disclosure of Interest: None declared

OP031 GENETIC VARIANTS ASSOCIATED WITH COLORECTAL CANCER AND ADENOMA SUSCEPTIBILITY

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INTRODUCTION: Thirty common, low-penetrant genetic variants have been consistently associated with colorectal cancer (CRC) risk, but only few studies have explored the contribution of these variants in colorectal adenoma susceptibility. Age over 50 is the only identified and implemented stratification variable in population-based CRC screening programs.

AIMS & METHODS: We assessed whether genetic variants associated to adenoma susceptibility could improve selection of average-risk population for CRC. We selected 1,326 patients with high-risk adenomas (HRA) and 1,252 controls were selected from population-based CRC screening programs at 3 hospitals from Spain. We conducted a case-control association study analyzing 30 CRC susceptibility variants in order to investigate the contribution of these variants to the development of HRA. In addition, we built an individualized risk prediction model in which common genetic variants were incorporated as risk factors.

RESULTS: We found that 14 of the 30 SNPs analyzed showed a statistically significant association for HRA. We also observed that the risk of developing HRA increased with increasing number of risk alleles, with a 2.3-fold increased risk in individuals with $\geq$ 17 risk alleles. In the predictive model for HRA, ROC curves demonstrated better discrimination ability for individuals at a younger age, although with modest predictive performance.

CONCLUSION: Our results provided strong evidence that most genetic variants increase CRC risk by adenoma predisposition. The risk of developing HRA increased with multiple number of risk alleles, which may allow identifying a subgroup of individuals at a higher risk. However, there are limitations of using genetic variants associated with HRA to assess the risk at the individual level.

Disclosure of Interest: None declared

OP032 EVALUATION OF RECTAL CANCER RESPONSE TO THERAPY: ROLE OF MAGNETIC RESONANCE TUMOR REGRESSION GRADE (MR-TRG) TO PREDICT PATHOLOGICAL COMPLETE RESPONSE

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INTRODUCTION: To determine if a pathological complete response to therapy in rectal cancer can be predicted by tumor regression grade evaluated by MR (MR-TRG).

AIMS & METHODS: Thirty-seven patients, diagnosed with locally advanced rectal cancer were prospectively enrolled in the study. All patients underwent MRI on a 3 Tesla before, during and after chemoradiotherapy (CRT). All patients underwent total mesorectal excision (TME). MR-TRG was evaluated on T2-weighted fast spin-echo (FSE) multi-planar imaging. The MR-TRG was determined by the fibrosis/tumor ratio and was divided into 4 grades based on the percentage of fibrosis ($<$ 25%, $<$ 50%, $<$ 75%, 100%). Measurements were performed on all axial images including the tumor. MR-TRG evaluated on the second examination (during therapy) was correlated to the pathological finding after surgery, defined as partial response or complete response.

RESULTS: A complete pathologic response was observed only in patients (17) with MR-TRG 4 (100% fibrosis) with a negative predictive value of 100%. In lower MR-TRG groups (1, 2 and 3) a partial response was observed (20 patients).

CONCLUSION: MR-TRG 4 is a accurate predictor of complete response after CRT. When a lower MR-TRG is observed the persistence of disease should be suspected. This method, applied during therapy, may reduce the time to surgery.

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Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 11:00–12:30
SMALL BOWEL IMAGING AND ENDOSCOPIC INTERVENTIONS – LOUNGE 6

OP033 DIAGNOSTIC VALUE OF FECAL CALPROTECTIN TO DETECT SMALL BOWEL PATHOLOGY IN PATIENTS WITH PREVIOUS NEGATIVE ENDOSCOPY

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INTRODUCTION: The assessment of small bowel pathology with capsule endoscopy is laborious and costly. Therefore, the appropriate selection of patients to increase diagnostic yield is highly anticipated. Increased levels of fecal calprotectin have been measured in NSAID enteropathy and Crohn's disease of the small bowel.

AIMS & METHODS: Our aim was to examine the diagnostic value of fecal calprotectin to detect significant small bowel pathology. We performed a post-hoc analysis of a prospective cohort of 70 consecutive patients who had received capsule endoscopy (Pillcam, Given Imaging, Israel), after negative bidirectional endoscopy. Calprotectin was measured in stool samples collected within 24 hours before the investigation using an enzyme-linked immunosorbent assay (Bühlmann Laboratories, Switzerland). The presence of mucosal breaks in the small bowel (erosion, ulcer, tumor) was the primary endpoint of the study. Final diagnoses were adjudicated blinded to calprotectin values.

RESULTS: Indications for capsule endoscopy were anemia (51.4%), hematochezia (14.3%), suspected Crohn's disease (14.3%), abdominal pain (10%), suspected malignant disease (8.6%) and unexplained diarrhea (1.4%). The prevalence of mucosal breaks was 48.6% (n=34) but 4 patients had significant lesions strictly outside the small bowel and were not included in the analysis. Calprotectin testing was more often positive ($>50\mu$g/g) in patients with mucosal findings (61.4% vs. 38.6%, P=0.001) and mean calprotectin values were higher (mean$\pm$standard deviation, 305$\pm$289μg/g vs 148$\pm$228μg/g, P$<$0.001). Receiver Operating Characteristics analysis showed an area under the curve of 0.760 (95% confidence interval 0.639-0.857). At the optimal cut-off (63μg/g), fecal calprotectin had 90.0% sensitivity and 63.9% specificity to detect mucosal inflammation. This translated in a positive and negative likelihood ratio of 2.49 and 0.16, respectively, and resulted in a high negative predictive value (88.5%). The overall accuracy – (true positive test results + true negative test results)/total population – was 69.7%. In a subgroup analysis we excluded patients with gross intestinal bleeding (N=10) as this may increase fecal concentrations of calprotectin in absence of mucosal inflammation. Fecal calprotectin performed slightly better in this subset of patients (area under the curve 0.787, overall accuracy 71.4%) but the positive and negative likelihood ratios remained virtually unchanged (2.64 and 0.17, respectively).

CONCLUSION: Fecal calprotectin is a valid marker of intestinal inflammation in the small bowel and might be helpful to guide diagnostic investigations.

Disclosure of Interest: None declared

OP034 CONFOCAL LASER ENDOMICROSCOPY – A NEW METHOD FOR ENDOSCOPIC ASSESSMENT OF CROHN'S DISEASE

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INTRODUCTION: Endoscopy is crucial to evaluate the extent and severity of inflammation in patients with Crohn's disease (CD), including the response to treatment. Endoscopic remission is a predictor for extended surgery-free periods;

however, approximately 50% of patients in deep remission on biological treatment relapse within the first year after treatment cessation. Recently, confocal laser endomicroscopy (CLE) has enabled *in vivo* microscopic evaluation during endoscopy.
AIMS & METHODS: The aim of this study was to evaluate whether CLE can identify subtle lesions in CD patients, and thus delineate deep remission and contribute to better treatment algorithms. Patients with CD referred for ileocolonoscopy were included in the study using the endoscope-based CLE system (EC 3830FK; Pentax, Tokyo, Japan). CLE images, macroscopic assessment (simple endoscopic score for Crohn's disease - SES-CD), and histopathological features from biopsies obtained from the terminal ileum were registered. CLE findings in terminal ileum were analysed assessing the images for fluorescein leakage over the mucosal barrier and microerosions using the Watson Grading system, which scores endomicroscopic changes as normal (1), functional defects (2) or structural defects (3)[1]. These findings were correlated with the severity of disease (Fisher's Exact Test and two-side *t*-test). In patients with inactive CD, CLE changes were registered and correlated to treatment escalation and all surgical interventions during the follow-up period.
RESULTS: A total of 51 patients were enrolled in the study. Two patients were excluded due to indeterminate colitis. Of the 49 patients in the final study group, 38 were known with CD (19 in endoscopic remission), while 11 patients (polyp control or irritable bowel syndrome) served as controls. The mean age was 42 (18-71) years and 26 patients were female. The ileal intubation rate was 92% and CLE imaging was obtained in 86% of patients. Comparing CD patients with the control group fluorescein leakage and microerosions were seen in 50% vs. 10% (p=0.03) and 24% vs. 0 patients (p=0.09), respectively. The Watson Score was significantly higher in CD patients compared to controls (1,7 vs 1,2, p=0.02). Of note, fluorescein leakage and microerosions were also identified in patients with quiescent CD (35% and 12%, respectively) despite no macroscopically or histopathological abnormalities. Moreover, the Watson score was increased (2 or 3) in 35% of these patients. Three patients with endoscopic remission relapsed within the limited follow-up period of 34 weeks (2-69); all of them had a Watson score of 2 or 3. In contrast, all of the patients with a Watson score of 1 remained in remission.
CONCLUSION: CLE identified microscopic changes in the terminal ileum of CD patients, even in patients with otherwise quiescent disease, suggesting that this method may be a useful adjunct to routine endoscopy to predict relapse.
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Disclosure of Interest: None declared

OP035 CAN NARROW BAND IMAGING PREDICT DUODENAL HISTOLOGY IN CELIAC DISEASE? A PROSPECTIVE DOUBLE BLIND PILOT STUDY

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INTRODUCTION: Celiac disease (CD) is characterized by varying degrees of villous atrophy. Image enhancement with narrow band imaging(NBI) delineates villous patterns better than routine endoscopy. Role of NBI in delineating villous morphology of CD is sparsely reported.
AIMS & METHODS: To compare the diagnostic accuracy of NBI with histopathology in predicting the duodenal villous morphology in CD.
Amongst the 80 subjects (mean age-26.5 ±12.24 years, 35-females) included in the study, 60 were suspected to have CD (serology positive), 6 were follow up patients of CD on gluten free diet and 14 had dyspepsia with no evidence of CD on complete evaluation. CD was diagnosed on the basis of modified ESPGHAN criteria. They underwent esophagogastroduodenoscopy (EGD) along with NBI using an Olympus GIF-180 gastroscope to evaluate the villous pattern of duodenal mucosa. These images were digitally recorded for further characterization. Four duodenal biopsies were taken from second part of duodenum for histopathology. Digitally recorded images were analyzed by two experienced endoscopists and biopsy specimens by an experienced pathologist all of whom were blinded to clinical details and serological investigations. Villous patterns on NBI were classified into normal-villous pattern (NVP), distorted & blunted-villous pattern (DVP) and absent-villous pattern (AVP). NBI findings were correlated with histopathology.
RESULTS: NBI revealed AVP in 27, DVP in 27 and NVP in 26 patients. In the study group of CD (n=60), 26 had AVP, 24 had DVP and 10 had NVP on NBI, while on histopathology 27 had total villous atrophy, 20 had partial villous atrophy and 13 had no villous atrophy. 4 CD patients on gluten free diet(n=6) and the 12 dyspepsia patients (control group) had normal villous pattern on both NBI and histopathology. Significant correlation was observed between NBI and histopathological examination($p<0.001$). The overall sensitivity and specificity of NBI for delineating villous pattern were 87.03% and 84.61% and the positive and negative predictive values were 92.16 % &75% respectively.
CONCLUSION: NBI can predict villous atrophy with high sensitivity and negative predictive value in CD.
Disclosure of Interest: None declared

OP036 CLINICAL USEFULNESS OF VIRTUAL ENTEROSCOPY FOR CROHN'S DISEASE

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INTRODUCTION: The technique of virtual colonoscopy can be used to explore the colon as well as the small bowel. The clinical performance of Virtual Enteroscopy (VE) was analyzed to evaluate the safety, feasibility, and the usefulness in Crohn's disease.
AIMS & METHODS: VE was performed using the protocol reported previously1) with some modifications. The data of 130 examinations of VE performed in our hospital from November 2006 to February 2014 were reviewed, and the data of patients with Crohn's disease were analyzed.
RESULTS: Thirty-nine VEs were performed in Crohn's disease, for 27 males and 12 females. The examinations were indicated when Crohn's disease was suspected in 3, when diagnosis of Crohn's disease was made in 8, when biologic response modifier was planned or started in 4, when the disease was exacerbated in 19, and during remission in 5 cases. The mean years after the diagnosis of Crohn's disease was 10.1; mean age was 35.4 +/- 11.0 at the examination. The volume of air and intraintestinal pressure were recorded in 19 examinations for patients without previous resection of the small bowel with the indicators specially produced for this examination. The mean total volume of the injected air was 1802 +/- 784 ml, the mean maximum intraintestinal pressure was 2.45 +/- 0.67 kPa, the mean length of depicted small bowel was 472 +/- 80 cm, and whole small bowel trace was achieved in 79% of these 19 examinations. In 39 examinations, stenoses with wall thickness were found in 35. Resection of the small bowel was performed and comparisons of the findings in the VE examination and the resected sample were possible in 5 patients. The appearance of new stenoses was observed between two examinations in one patient. The cobble stone appearance was depicted and confirmed by balloon enteroscopy in one case. The ileo – sigmoid colonic fistula was depicted in one case. Balloon dilation therapy was planned according to the results of the examination and performed successfully. The mean length of the remaining small bowel was 246.5 +/- 133.9 cm in 11 patients with previous resection of the small bowel and the risk of short small bowel syndrome was assessed when re-resection was considered. In 39 examinations, vomiting and abdominal pain (requiring pain medication) were noted in 4 and 3 patients, respectively, but no additional treatments were necessary. No other complication was observed.
CONCLUSION: VE can be performed safely and examination of the whole small bowel was possible in most of the cases with Crohn's disease, despite the presence of stenosis. VE can depict characteristic findings, locate the position of the lesions, and measure the length of the small bowel objectively. VE is a powerful new tool for diagnosis, pre-treatment evaluation, and follow up for Crohn's disease.
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Disclosure of Interest: None declared

OP037 EFFECTIVENESS AND SAFETY OF ENDOSCOPIC BALLOON DILATATION FOR STRICTURES IN CROHN'S DISEASE –A MULTICENTER STUDY

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INTRODUCTION: Crohn's disease (CD) is a chronic inflammatory disease which frequently complicates by obstructive symptoms secondary to development of intestinal strictures.
AIMS & METHODS: The aim of this study was to assess effectiveness, safety of endoscopic balloon dilatation (EBD). Data of 92 EBD in 45 CD patients were retrospectively analyzed. 15.2 % of procedures were performed in upper gastrointestinal (GI) tract and 84.8% in lower GI tract. Short-term success rate was defined as the ability of endoscope to traverse the stenosis after dilatation. Long-term clinical success rate was claimed if a patient remained asymptomatic and did not require surgery or further EBD, following technical success. Prognostic factors of outcome were statistically assessed.
RESULTS: 63.04 % of strictures were de novo and 36.96% anastomotic. The mean time between diagnosis and development of strictures with symptoms was 7.26 (0-27) years. The elapsed time between diagnosis and the first balloon dilatation was 9.55 (0-35) years. 72.8 % of dilatations were successful on short-term period without serious complications. 21 (46.6 %) patients showed that EBD is effective on long-term period. Type of strictures, biological therapy before or after dilatation, immunomodulatory therapy and the time between diagnosis and first EBD did not have influence on long-term effectiveness. 7 subjects had need for surgery due to strictures after EBD.
CONCLUSION: The result of this study highlights that EBD is an effective therapy of the short strictures in CD with low complication rate. Using this endoscopic method we can avoid surgical interventions in most of the cases. The success rate is independent of the previous and current therapy, duration of the disease and the type of stenosis.
Disclosure of Interest: None declared

OP038 EFFICACY OF ENDOSCOPIC BALLOON DILATION FOR SMALL BOWEL STRICTURES IN PATIENTS WITH CROHN'S DISEASE: A NATIONWIDE, MULTI-CENTER, OPEN-LABEL, PROSPECTIVE COHORT STUDY

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INTRODUCTION: Endoscopic balloon dilation (EBD) has been known to be useful for strictures in Crohn's disease (CD) that can be approached by colonoscopy. Recently, EBD by means of balloon-assisted enteroscopy (BAE) has become a possible procedure for small bowel strictures as an alternative to surgery.
AIMS & METHODS: The efficacy and safety of this treatment remain unclear. Therefore, a nationwide, multi-center, open-label, prospective cohort study was conducted.This study was carried out prospectively within the framework of a study project undertaken by the Study Group on Intractable Diseases, the Health and Labor Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan. Subjects from twenty-three institutions were registered in this study. The study subjects were CD patients who had symptomatic small bowel strictures. Patients with strictures of the colon or in the neo-terminal ileum were excluded. Symptoms associated with small bowel strictures (abdominal pain, abdominal bloating, and nausea) were evaluated by visual analogue scale (VAS) scores before and 4 weeks after the initial EBD. A short-term success of EBD was defined as improvement of all three VAS scores. As an interim analysis, the short-term success rate and the adverse events in patients registered from Aug 2011 to Oct 2013 were analyzed.
RESULTS: One hundred and twelve patients were included in this study. EBD could not be performed in 10 patients for various reasons. Of the remaining 102 patients, VAS scores of both before and 4 weeks after EBD were available in 69 patients at the time of this analysis. The treatment outcome was therefore analyzed in those 69 patients (50 male, 19 female, disease duration: 10.7± 8.2 years). The short-term success rate was 73% (50/69). After EBD, the scope could pass through the stricture in 76% (54/69). There was not any significant difference in patients' characteristics or in the nature of stricture between successful and unsuccessful cases. Complications were encountered in two of the 69 patients (2.9%). These were all hemorrhage and the patients recovered by conservative therapy.
CONCLUSION: EBD was effective and safe for small bowel strictures in CD patients. We are going to clarify the long-term outcome of EBD in this study.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 14:00–15:30
NEW THOUGHTS ON FUNCTIONAL DYSPEPSIA – HALL B

OP039 FASTING PYLORIC PRESSURE AND COMPLIANCE IN GASTROPARESIS

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INTRODUCTION: Gastroparesis is defined by a delayed of gastric emptying associated with dyspeptic symptoms. Delayed gastric emptying may result from impairment in gastric and/or pyloric motility. To date, the role of pyloric pressure and/or compliance in gastroparesis has however been poorly investigated.
AIMS & METHODS: Fasting pyloric pressure and compliance were assessed using EndoFLIP® technique (intrapyloric balloon inflated to 40 ml) in 21 healthy volunteers (HV), 24 Gastroparetic Patients (GP; diabetic: n=3; post-surgical: n=3; idiopathic: n=16), and in 4 patients who underwent esophagectomy without pyloroplasty as positive controls. Endoflip probe was positioned without anesthesia, under videofluoroscopic control. Gastric half-emptying time (T1/2) was measured using the ^{13}C–octanoic acid breath test. Dyspeptic symptoms were recorded using a 5 point-rated scale and quality of life using gastrointestinal quality of life index (GIQLI).
RESULTS: Using Endoflip, the mean fasted pyloric compliance was 25.2±2.4 mm^2/mmHg in HV. Fasted pyloric compliance decreased both in GP (17.6±2.4 mm^2/mmHg; $p<0.05$) and patients with esophagectomy (11.2±3.7 mm^2/mmHg; $p<0.05$). By contrast, fasting pyloric pressure was not different between HV (9.6±1.0), GP (12.1±1.0 mmHg; $p>0.05$) and control (12.5±1.6 mmHg; $p>0.05$). Fasting pyloric compliance was inversely correlated with T1/2 in GP (R=-0.43; p=0.03), while fasting pyloric pressure did not (R=0.28; p=0.15). Fasting pyloric compliance was also inversely correlated with nausea, vomiting, regurgitation, gastric fullness, early satiety, and dyspeptic symptomatic score. In contrast, fasting pyloric pressure was only correlated with nausea and regurgitation. Fasting pyloric compliance, but not pressure, was correlated with the GIQLI score (R=0.31; p=0.02 and R=-0.23; p=0.10). In 8 GP with low fasting pyloric compliance (<10 mm^2/mmHg) an hydraulic dilation of the pylorus (20mm), improved fasting pyloric compliance from 7.4±0.4 to 20.1±4.9 mm^2/mmHg ($p<0.01$). Dilatation also improved the T1/2 in 6/7 patients and quality of life in 5/8 patients.
CONCLUSION: This study is the first to assess the pyloric compliance in GP. Fasting pyloric compliance seems to be decreased in GP. Fasting pyloric compliance, but not pressure, was inversely correlated with T1/2, dyspeptic symptoms and quality of life. This suggests that pyloric compliance may play a role in gastric emptying.
Disclosure of Interest: None declared

OP040 ASSOCIATION OF SERUM ADIPOCYTOKINE AND GUT HORMONE LEVELS WITH GASTRIC EMPTYING AND SYMPTOM PERCEPTION IN PATIENTS WITH FUNCTIONAL DYSPEPSIA

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INTRODUCTION: The pathogenesis of functional dyspepsia (FD) is complex and has been associated with a variety of gastrointestinal motor and sensory dysfunction. Several peptide hormones secreted by the adipose tissue and the gut play an important role in regulating food intake, gastrointestinal motility and energy balance.
AIMS & METHODS: To investigate the association of circulating adipocytokines and gut hormones with gastric emptying and symptom perception in FD patients, we conducted a case-control study in 40 FD patients (16 male and 24 female; age: 50±12) and 40 asymptomatic healthy volunteers matched for age and gender. Basic demographics, including complete anthropometric measures, were obtained. All subjects underwent a 3-h gastric emptying scintigraphy using radiolabeled oatmeal as the test meal and quantitative emptying parameters were determined. On the day of scintigraphy, dyspeptic symptoms during the preceding two weeks were evaluated using the 9-item Gastroparesis Cardinal Symptom Index. Fasting serum levels of adipocytokines (adiponectin and leptin) and gut hormones (ghrelin, obestatin and peptide YY) were assayed in all subjects with ELISA methods.
RESULTS: Anthropometric measures, including body mass index and waist circumference, were similar between the 2 groups. FD patients had significantly longer gastric half-emptying time $T_{1/2}$(57.1±19.2 vs. 48.7±8.0 min, $p<0.001$) and greater gastric retention at 1 h and 2 h (46.4±18.8 vs. 39.4±11.3, p=0.046; 11.7±10.3 vs. 7.5±4.8, p=0.023) when compared with healthy controls. Five patients with FD (12.5%) had delayed gastric emptying. FD patients had significantly lower adiponectin levels (7.6±3.4 vs. 11.4±5.0, $p<0.001$) but higher obestatin levels (4.9±1.8 vs. 3.9±0.6, p=0.003). Both adiponectin and leptin levels correlated with gastric retention at 1 h (r=0.619 and -0.582; p=0.011 and 0.018, respectively) in male but not in female FD patients. All adipocytokine and gut hormone levels were not significantly different between FD subjects with or without delayed gastric emptying. Leptin levels positively correlated with visibly larger stomach or belly after a meal (r=0.358, p=0.024) while ghrelin levels positively correlated with early satiety (r=0.364, p=0.023) and loss of appetite (r=0.353, p=0.028).
CONCLUSION: Gastric dysmotility and derangement of various circulating adipocytokines and gut hormones might participate in the heterogenous manifestations of FD patients. Further studies to elucidate the potential roles of these peptide hormones in the pathophysiology of FD and their clinical implication are warranted.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 14:00–15:30
CLINICAL CHALLENGES IN HEPATITIS C VIRUS THERAPY – HALL F1

OP041 NORMALIZATION OF LIVER-RELATED LABORATORY PARAMETERS IN HCV GENOTYPE 1-INFECTED PATIENTS WITH CIRRHOSIS AFTER TREATMENT WITH ABT-450/R/OMBITASVIR, DASABUVIR AND RIBAVIRIN

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INTRODUCTION: HCV-infected patients with cirrhosis are at increased risk for hepatocellular carcinoma and liver-related mortality, which can be significantly reduced if treated and the patient achieves a sustained virologic response. We report the changes in liver-related laboratory parameters after 12 or 24 weeks of treatment with the 3 direct-acting antiviral (3D) regimen of ABT-450/r/ombitasvir, dasabuvir, and ribavirin (RBV) among 380 treatment-naïve and peginterferon/RBV-experienced HCV genotype 1-infected patients with cirrhosis.
AIMS & METHODS: 380 patients with Child-Pugh A cirrhosis were randomized (approximately 1:1) to receive the 3D+RBV regimen for 12 or 24 weeks. Key eligibility criteria included platelet count ≥60,000 cells/mm^3, serum albumin ≥2.8 g/dL, and total bilirubin <3 mg/dL. Laboratory testing, including chemistry, hematology, and urinalysis, were conducted at each study visit during the treatment and post-treatment periods, and summarized by treatment group.
RESULTS: SVR12 was achieved in 92% and 96% of patients receiving the 12- and 24-week treatments, respectively. At the end of treatment with 3D+RBV, liver enzymes were normalized in most patients with baseline elevations regardless of treatment duration (ALT, 323/347 [93.1%]; AST, 316/360 [87.8%]; GGT, 284/307 [92.5%]). Mean liver enzyme values were normalized by Week 4. Of patients with platelet counts <LLN at baseline, counts were normalized in 28.8% of patients at the end of treatment. Activated partial thromboplastin time was normalized at the end of treatment in 47/67 (70.1%) and 46/51 (90.2%) of 12-week and 24-week 3D+RBV patients with values >ULN at baseline. Mean total bilirubin values peaked at Week 1 (predominantly indirect), subsequently decreased to the end of treatment, and normalized post-treatment.

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Parameter	12-Wk 3D+RBV			24-Wk 3D+RBV			
	Baseline	Wk12	Post-treatment Wk12	Baseline	Wk12	Wk24	Post-treatment Wk12
Alanine aminotransferase, U/L	99	24	32	100	22	19	28
Aspartate aminotransferase, U/L	88	27	33	92	26	24	29
Gamma glutamyl transferase, U/L	123	28	47	132	29	28	46
Total bilirubin, mg/L	8.5	11.5	7.1	8.8	10.2	9.7	6.5
Indirect bilirubin, mg/L	5.5	8.3	5.3	5.7	7.3	7.1	4.9
Activated partial thromboplastin time, sec	31	28	29	30	27	28	28
Platelet count, x10^3/μL	151	175	155	152	179	172	159
International normalized ratio	1.1	1.1	1.1	1.1	1.1	1.1	1.1

CONCLUSION: Treating HCV genotype 1-infected patients with the 3D+RBV regimen resulted in high SVR rates and normalization of liver-related chemistry and coagulation profile abnormalities often present in patients with cirrhosis.
Disclosure of Interest: S. Zeuzem Consultancy for: AbbVie, Achillion, BMS, Boehringer Ingelheim, Gilead, Idenix, Janssen, Merck, Novartis, Roche, Santaris, Vertex, P. Andreone Financial support for research from: Roche, Merck, Gilead, Consultancy for: Roche, Merck, Janssen Cilag, AbbVie, Boehringer Ingelheim, Gilead, BMS, S. Pol Lecture fee(s) from: GSK, Consultancy for: Sanofi, BMS, Boehringer Ingelheim, Tibotec, Janssen Cilag, Vertex, Gilead, Roche, MSD, Novartis, AbbVie, M. Bourlière Lecture fee(s) from: D, Janssen, Gilead, AbbVie, Consultancy for: BMS, Vertex, MSD, Janssen, Gilead, AbbVie, Roche, A. Castro Consultancy for: AbbVie, BMS, Janssen, Merck, Roche, M. Berenguer Consultancy for: BMS, Janssen, Roche, MSD, Novartis, AbbVie, S. Lee Financial support for research from: AbbVie, BMS, Boehringer Ingelheim, Gilead, Idenix, Janssen, Merck, Roche, Vertex, Lecture fee(s) from: BMS, Gilead, Merck, Roche, Vertex, Consultancy for: AbbVie, BMS, Boehringer Ingelheim, Gilead, Idenix, Janssen, Merck, Roche, Vertex, G. Everson Financial support for research from: AbbVie, Vertex, BMS, Merck, Roche/Genentech, Gilead/Pharmasset, GSK, Novartis, Tibotec, Janssen, Consultancy for: AbbVie, Vertex, BMS, Merck, Roche/Genentech, Gilead, GSK, Novartis, Esai, Biotest, Other: HepQuant LLC, S. Lovell Shareholder of: AbbVie, Other: AbbVie, M. Pedrosa Shareholder of: AbbVie, Other: AbbVie, R. Trinh Shareholder of: AbbVie, Other: AbbVie

OP042 CORRECTION OF VITAMIN D DEFICIENCY CORRELATED WITH SUPPRESSION OF SOLUBLE CD26 LEVELS (SCD26) AND INTERFERON-GAMMA-INDUCIBLE PROTEIN 10 (IP-10) IN PATIENTS WITH CHRONIC HEPATITIS C: A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PILOT STUDY

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INTRODUCTION: Vitamin D deficiency, serum IP-10 levels and IL28B polymorphisms are used to predicted favorable treatment outcome in chronic hepatitis C (CHC). CD26 (DPPIV) truncates the chemokine IP-10 into a shorter antagonistic form. Previous studies, this truncated IP-10 and CD26 has been shown to correlate with disease activity and also influence treatment outcome in CHC patients. We hypothesized that vitamin D supplement, which shown to improve CHC treatment response, might restore immune dysregulation in these patients through a pathway linked to the Th1/Th2 cytokines, IP-10 or CD26. The purpose of this study was to investigate the association between vitamin D supplement, IP-10 and sCD26 levels in these patients.
AIMS & METHODS: We conducted the double-blind, placebo-controlled, interventional study; CHC patients with vitamin D deficiency were assigned to receive vitamin D supplement or placebo for 6 weeks. 25-hydroxyvitamin D (25(OH)D) levels, Th1/Th2 cytokines, IP-10 and sCD26 levels were measured at baseline and at 6 weeks. Baseline characteristics were assessed.
RESULTS: A total of 80 CHC patients with vitamin D deficiency were randomized into two groups, 40 patients in each group. There were no significant differences in all baseline characteristics between two groups. At the end of study, only the mean 25(OH)D levels in vitamin D group were significantly increased from 21.07 to 48.44 ng/ml, ($p<0.001$).While no significant changes of the IP-10 levels was demonstrated in placebo group, there were significant decreasedin serum IP-10 and sCD26 in vitamin D group after 6-week of vitamin D supplement ($p< 0.05$). However, there were no significant differences in serum levels of all Th1/Th2 cytokines studied both groups.
CONCLUSION: This study demonstrated that vitamin D supplement and restoration of 25(OH)D level in CHC patients resulted in suppression of serum IP-10 and sCD26 levels without changes in systemic Th1/Th2 immune cytokines. These results connect the link and give one explanation of why vitamin D deficiency, pre-treatment high serum IP-10 levels, sCD26 level and by treatment of vitamin D deficiency could have effects on CHC treatment responses.
Disclosure of Interest: None declared

OP043 REVISITING LIVER DISEASE PROGRESSION IN HIV/HCV-COINFECTED PATIENTS: THE INFLUENCE OF VITAMIN D, INSULIN RESISTANCE, IMMUNE STATUS, IL28B AND PNPLA3

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INTRODUCTION: The importance of endocrine, metabolic, genetic and immunologic factors in the natural history of HIV/hepatitis C virus (HCV) coinfection has increasingly gained recognition.
AIMS & METHODS: We aimed to perform a comprehensive study on independent modulators of liver fibrosis progression and determinants of portal pressure considering immune status, insulin resistance (IR), serum 25-hydroxyvitamin D levels (25(OH)D), genetic variants of patatin-like phospholipase domain-containing protein 3 (PNPLA3) and interleukin 28B (IL28B) in a thoroughly documented cohort of HIV/HCV-coinfected patients.
25. OH)D deficiency (25(OH)DDEF), IR and low CD4 T-lymphocyte nadir (lowCD4NAD) were defined as 25(OH)D < 20ngxmL-1, HOMA-IR > 2 and CD4nadir < 200cellsxμL-1, respectively. Liver fibrosis progression rate (FPR) was calculated as METAVIR F units divided by the number of years since HCV-infection. Patients with a FPR > median FPR were assigned to the highFPR group.
RESULTS: Among 86 HIV/HCV, the median FPR was 0.1667unitsxyears^{-1}. While the prevalence of prior alcohol abuse, lowCD4NAD and 25(OH)DDEF was higher among highFPR patients, the prevalence of IR was comparable. The association between 25(OH)DDEF and FPR (highFPR:90%vs.lowFPR:31%;$P<0.001$) was confirmed in a subgroup of patients with METAVIR F0/F1/F2 in which 25(OH)D levels are not affected by the severity of liver disease. The distribution of IL28B C/C and PNPLA3 non-C/C was similar, while PNPLA3 G/G was exclusively observed in highFPR patients.

Patient characteristics	lowFPR n=49	highFPR n=37	P value
Prior alcohol abuse	12 (25%)	17 (46%)	0.037
25(OH)DDEF	20 (41%)	29 (78%)	<0.001
IR	27 (55%)	18 (49%)	0.553
lowCD4NAD	11 (22%)	16 (43%)	0.04
IL28B C/C	15 (31%)	14 (38%)	0.483
PNPLA3 non-C/C	21 (43%)	17 (46%)	0.775
PNPLA3 G/G	0 (0%)	4 (11)	0.031

LowCD4NAD (OR:2.947;95%CI:1.05-8.24;P = 0.034) and 25(OH)DDEF (OR:5.62;95%CI:2.05-15.38;P < 0.001) were independently associated with highFPR and showed an additive effect. Portal pressure correlated with prior alcohol abuse ($\rho = 0.447$;P < 0.001), HCV-genotype 3 ($\rho = 0.252$;P = 0.034), CD4+ nadir ($\rho = -0.288$;P = 0.015), lowCD4NAD ($\rho = 0.286$;P = 0.016) and 25(OH)D ($\rho = -0.246$;P = 0.038).
CONCLUSION: Two potentially modifiable factors, CD4+ nadir and 25(OH)D, were both independent modulators of liver fibrosis progression and determinants of portal pressure. Further studies are warranted to assess the relevance of PNPLA3 for FPR in HIV/HCV. The findings of our study suggest, that early initiation of combined antiretroviral therapy, as well as vitamin D supplementation and vitamin D receptor ligands could be of therapeutic value for the reduction liver fibrosis progression in HIV/HCV-coinfected patients.
Disclosure of Interest: None declared

OP044 MICRORNA-21 AND PTEN: A SIMPLE PREDICTIVE MODEL FOR FIBROSIS IN CHC PATIENTS

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INTRODUCTION: Down regulation of PTEN in Chronic Hepatitis C has been associated with steatosis and increase in fibrosis. Even though many predictive model have been evaluated on the basis of biochemical parameter, PTEN expression and factors affectng its expression has not been studied.
AIMS & METHODS: This study aims at finding if there is any correlation between increasing fibrosis and variables like PTEN, miR-21, HCV RNA levels, HCV genotype and other biochemical parameters and to draw a prediction model out from the dependable variables. Study consisted of 84 CHC patients whose miR-21, PTEN expression, HCV RNA levels were estimated by Real Time QPCR. All the CHC patients had undergone liver biopsy and were grouped into 3 fibrosis group, viz. 'F0' (Fibrosis score 0), 'FM'(Fibrosis 1& 2), 'FH' (Fibrosis ≥3). 76 Healthy blood donors were selected randomly and were evaluated for any history of liver disease. The PTEN and mir21a expression levels have been described in $2^{\Delta Cp}$ where $\Delta Cp = Ct_{(Household\ gene)} - Ct_{(target\ gene)}$ and so positive $2^{\Delta Cp}$ values depicts decrease in expression against the housekeeping gene concentration which is, in this case, GAPDH for RNA expression and U6 for micro RNA.
RESULTS: The average age (Mean±S.D) of CHC and control group was 42.55±11.258 and 33.42±6.293 years respectively. There was statistical significant difference in $PTEN_{(2\Delta Cp)}$ between the mean rank of control (22.93) and Cases(56.93) (U=130.5, $p<0.001$). There was statistical significant difference $miR\text{-}21_{(2\Delta Cp)}$ levels between the mean rank of control (60.09) and CHC(22.7) (U=53.5, $p<0.001$). Univariate analysis and post-Hoc test between the fibrosis group (F0,FM&FH) resulted in statistical significant difference in T.Bil FM(0.7±0.306)mg/dl & FH(1.13±.563)mg/dl (p=.014), $PTEN_{(2\Delta Cp)}$ expression FM(4.77±0.415) & FH(37.52±10.37) ($p<0.0001$), $miR21_{(2\Delta Cp)}$ expression F0(3.66±.08), FM(2.70±.50)&FH (1.48±0.09), ($p<0.0001$). Multinominal logistic regression was done to find out the predictor of increasing fibrosis with above variables and it was found that only $PTEN_{(2\Delta Cp)}$ predicted FH from FM with statistical significance (B=-1.5, $p<0.0001$). Multiple regression was carried out to predict $PTEN_{(2\Delta Cp)}$ from T.Bil and $miR21_{(2\Delta Cp)}$. These variables significantly predicted $PTEN_{(2\Delta Cp)}$, F(2,39)=46.69, $p<0.0001$, R2=0.705 and the two variables added statistically significantly to the prediction, $p<0.001$. The regression equation obtained predicted $PTEN_{(2\Delta Cp)}$=40.63-(13.85xmi21a$_{(2\Delta Cp)}$)+(10.65xT.Bil). Using this model new cut-off value of $PTEN_{(2\Delta Cp)}$ was calculated using ROC with Area under curve 0.983 and cut-off level >24.22 was found to predict advance fibrosis (Fibrosis ≥3) (sensitivity=92.86, Specificity=89.29). It had a positive predictive value (PPV) of 82.35% and negative predictive value (NPV) of 100%.
CONCLUSION: From our study we conclude that decrease in PTEN mRNA expression is significantly associated with increase in fibrosis and that there is negative correlation between PTEN expression and miR21 expression. Other than PTEN, miR21 expression levels and Total bilirubin none of the other factors significantly correlated to either PTEN, miR21 or fibrosis. Our predicitive model $_{predicted\ PTEN(2\Delta Cp)}$ using T.Bil and $miR21_{(2\Delta Cp)}$ which predicted advance fibrosis(fibrosis ≥3) with PPV and NPV of 92.86 and 89.2 respectively.
Disclosure of Interest: None declared

OP045 ANTIVIRAL TREATMENT AND RISK OF END-STAGE RENAL DISEASE IN PATIENTS WITH HEPATITIS C VIRUS INFECTION

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INTRODUCTION: Hepatitis C virus (HCV) infection can lead to renal complications and increase the risk of end-stage renal disease (ESRD).[1] It remains unknown, however, whether antiviral treatment is associated with risk reduction of ESRD in HCV-infected individuals.
AIMS & METHODS: This nationwide cohort study aimed to investigate whether antiviral treatment for HCV infection is associated with attenuation in the risk of ESRD.
We firstly screened all Taiwanese residents (n=293,480) diagnosed with hepatitis C virus infection from 1997 through 2011, based on analysis of the Taiwan National Health Insurance Research Database, which has been prospectively recording claim data of all reimbursed healthcare service in this country since 1995 Those with physical or psychiatric conditions that might contraindicate or confound antiviral treatment were excluded. A total of 12,384 eligible patients who had received pegylated interferon plus ribavirin between October 1, 2003 and December 31, 2010 were enrolled in the treated cohort, and were matched 1:2 with 24,768 untreated controls in the propensity score. Occurrence of end-stage renal disease was compared between the treated and untreated cohorts after adjustment for multiple confounders including the competing mortality.
RESULTS: During the follow-up for the years 2003 through 2011, the 8-year cumulative incidence of ESRD was significantly lower in the treated than in the untreated cohort, 0.15% (95% confidence interval [CI], 0.04-0.26%) versus 1.32% (95% CI, 1.01-1.64%; $p<0.001$). Multivariate-adjusted analyses confirmed the association between antiviral therapy and a lower risk of end-stage renal failure (adjusted hazard ratio [HR], 0.15; 95% confidence interval [CI], 0.07-0.31), whereas diabetes mellitus (adjusted HR, 20.85; 95% CI, 12.67-34.29), male gender (adjusted HR, 1.79; 95% CI, 1.16-2.75), hypertension (adjusted HR, 1.54; 95% CI, 1.04-2.28), and management in a local community hospital (adjusted HR, 1.99; 95% CI, 1.18-3.36) were associated with excessive risks. Intriguingly, the risk was not attenuated in patients receiving incomplete therapy shorter than 16 weeks.
CONCLUSION: Antiviral treatment for HCV is associated with risk reduction in ESRD. These findings suggest the extrahepatic effectiveness of treating HCV infection in improving renal outcome.
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Disclosure of Interest: None declared

OP046 MANAGEMENT OF HAEMOGLOBIN DECREASE IN PATIENTS TREATED WITH ABT-450/RITONAVIR/OMBITASVIR AND DASABUVIR WITH OR WITHOUT RIBAVIRIN IN HCV GENOTYPE 1-INFECTED PATIENTS

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INTRODUCTION: Ribavirin (RBV), which may be associated with anaemia, is commonly prescribed with direct-acting antivirals for treatment of hepatitis C virus (HCV) infection. The randomized phase 3 PEARL trials evaluated the safety and efficacy of the "3D" regimen of ABT-450/ritonavir/ombitasvir (formerly ABT-267) and dasabuvir (formerly ABT-333) with or without RBV in HCV genotype 1b-infected treatment-experienced (PEARL-II) or treatment-naïve (PEARL-III) patients, and in genotype 1a-infected treatment-naïve (PEARL-IV) patients.
AIMS & METHODS: The management of decreased haemoglobin was determined using data from the 910 patients enrolled in PEARL-II (n=186), PEARL-III (n=419), and PEARL-IV (n=305) trials. In each trial, HCV genotype 1-infected patients were randomized to 12 weeks of treatment with the 3D regimen + RBV (co-formulated ABT-450/r/ombitasvir [150mg/100mg/25mg QD] and dasabuvir [250mg BID] with weight-based RBV [1000 or 1200 mg daily divided BID]), or 3D+placebo for RBV (PEARL-III and -IV) or 3D without RBV (PEARL-II). Haemoglobin was assessed at baseline and throughout treatment and follow-up periods. Decreases from baseline in haemoglobin during the treatment period and patient outcomes are reported.
RESULTS: Among patients with normal baseline haemoglobin values, on-treatment grade 2 haemoglobin decrease (8 to ≤10 g/dL) occurred in 23 patients (5.7%) receiving 3D+RBV; grade 3 decrease (6.5 to ≤8 g/dL) occurred in 2 patients (0.5%). No patients receiving 3D without RBV experienced grade 2 or greater haemoglobin decrease while on treatment (Table). There were no grade 4 haemoglobin decreases (<6.5 g/dL). RBV dose was reduced in 23 patients (5.7%) to manage anaemia or haemoglobin decrease, and all patients with RBV dose modification achieved SVR12. Mean haemoglobin values decreased by the second week of treatment, and returned to near-baseline by 4 weeks post-treatment. 1 patient (0.1%) received a blood transfusion for haemoglobin <8 g/dL. No erythropoietin use was required. No patient discontinued the study due to decreased haemoglobin.

	3D+RBV N=401 n (%)	3D N=509 n (%)
Haemoglobin decrease (n)		
LLN to 10 g/dL (Grade 1)	209 (52.1)	34 (6.7)
≤10 to 8 g/dL (Grade 2)	23 (5.7)	0
≤8 to 6.5 g/dL (Grade 3)	2 (0.5)	0
<6.5 g/dL (Grade 4)	0	0
RBV dose modification due	23 (5.7)	0
to haemoglobin decrease or anaemia		
Study drug interruption due	1 (0.2)	0
to haemoglobin decrease or anaemia		
Discontinuation due to	0	0
haemoglobin decrease or anaemia		

CONCLUSION: The 3D regimen was well tolerated with and without RBV. Clinically significant decreases in haemoglobin were uncommon. Haemoglobin levels <10 g/dL were managed successfully with RBV dose modification, without impact on treatment response.
Disclosure of Interest: M. Diago Financial support for research from: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Roche,

MSD, Novartis, Vertex, Lecture fee(s) from: MSD, Roche, Janssen, BMS, Gilead Sciences, P. Andreone Financial support for research from: Roche, Merck, and Gilead Sciences, Consultancy for: Roche, Merck, Janssen Cilag, AbbVie, Boehringer Ingelheim, Gilead Sciences, and BMS, D. Forton Financial support for research from: Roche, Gilead, Consultancy for: Abbvie, Roche, BMS, Merck, Boehringer Ingelheim, Gilead, Janssen, H. Reesink Financial support for research from: AbbVie, BMS, Boehringer Ingelheim, Gilead Sciences, Janssen-Cilag, Merck, PRA-International, Roche, and Santaris, Consultancy for: AbbVie, Astex, BMS, Gilead Sciences, GSK, Janssen-Cilag, Merck, PRA-International, Roche, Tibotec, R-Pharm, and Regulus, V. Rustgi Financial support for research from: Abbvie, Gilead, BMS, Lecture fee(s) from: Gilead, Genentech, Janssen, Consultancy for: Abbvie, Gilead, Janssen, D. Bernstein Financial support for research from: AbbVie, BMS, Gilead, Janssen, Vertex, Merck, Genentech, Lecture fee(s) from: AbbVie, Gilead, Janssen, Vertex, Merck, Consultancy for: AbbVie, Gilead, Janssen, Vertex, Merck, T. Sepe Financial support for research from: AbbVie, J. Vierling Financial support for research from: Abbvie, Biotest, BMS, Gilead, Janssen, Vertex, Merck, Genentech, Genfit, Hyperion, Intercept, Ocera, Sundise, Consultancy for: Abbvie, Boerhinger-Ingelheim, BMS, Gilead, Janssen, Merck, Hyperion, Intercept, Sundise, W. King: None declared, Y. Hu Shareholder of: AbbVie, Other: AbbVie, J. Enejosa Shareholder of: AbbVie, Other: AbbVie, D. Cohen Shareholder of: AbbVie, Other: AbbVie, Y. Luo Shareholder of: AbbVie, Other: AbbVie, M. Pedrosa Shareholder of: AbbVie, Other: AbbVie, P. Ferenci Financial support for research from: Roche, Lecture fee(s) from: Roche, MSD, BMS, Gilead, Abbvie, Böhringer Ingelheim, Idenix, Janssen, Consultancy for: Roche, MSD, BMS, Gilead, Abbvie, Böhringer Ingelheim, Idenix, Janssen

MONDAY, OCTOBER 20, 2014 14:00–15:30

NEW IMAGING TECHNIQUES IN COLONOSCOPY – HALL F2

OP047 NARROW BAND IMAGING MAGNIFICATION FOR THE DIAGNOSIS OF COLORECTAL NEOPLASTIC LESIONS

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INTRODUCTION: Narrow Band Imaging (NBI) magnification has been recognized as a time-saving and convenient tool for the differentiation between neoplastic and nonneoplastic colorectal lesions. The aim of this study was to clarify the clinical efficacy of NBI magnification for the diagnosis of colorectal neoplastic lesions, compared to chromoendoscopic magnification.
AIMS & METHODS: The subjects of this prospective study were 569 colorectal lesions, examined by an expert endoscopist with 12-year experience in magnifying diagnosis. Endoscopic diagnosis was examined on the basis of Sano's classification with NBI and Kudo's classification with chromoendoscopic magnification; capillary pattern (CP) type II, and IIIL or IV pit pattern were defined as indicators of tubular adenoma (TA), CP type IIIA and IIIs or VI (low-grade) pit pattern as intramucosal or submucosal slightly invasive cancer (M-SM-S), and CP type IIIB and VI (high-grade) or VN pit pattern as submucosal massively invasive cancer (SM-M). Additionally, both inter- and intraobserver agreement were evaluated using kappa statistics among 150 lesions (50 lesions each in TA, M-SM-S and SM-M) between the expert and three observers, that were endoscopists with 10-, 2- and 1-year experience respectively in magnifying diagnosis.
RESULTS: 569 lesions included 180 TA, 277 M-SM-S and 112 SM-M. Sensitivity, specificity and accuracy for TA were 98.5%, 75.9% and 81.9% with NBI and 93.3% (N.S), 87.4% ($p<0.01$) and 89.5% ($p<0.01$) with chromoendoscopic magnification. Similarly, those for M-SM-S were 64.3%, 84.9% and 81.9% with NBI and 82.3% ($p<0.01$), 83.2% (N.S) and 82.8% ($p<0.01$) with chromoendoscopic magnification, and those for SM-M were 69.6%, 98.9% and 89.8% with NBI and 81.3% ($p<0.05$), 98.9% (N.S) and 95.4% (N.S) with chromoendoscopic magnification. Additionally, among the lesions less than 10mm, accuracy with NBI magnification for TA was comparable to that with chromoendoscopic magnification (93.0% and 94.8%, N.S). Interobserver agreement of NBI magnification varied according to the year of experience, with similar result to chromoendoscopic magnification (kappa value of 0.73, 0.54 and 0.45 with NBI and 0.64, 0.57 and 0.53 with chromoendoscopic magnification), whereas intraobserver agreement was similar among three observers in both two modalities (0.76-0.77 and 0.71-0.84, respectively). Concordance rates of CP type II and IIIB between the expert and observers, didn't significantly differ respectively among the three (87.0%, 79.6% and 68.5% with CP type II and 76.5%, 94.1% and 88.2% with CP type IIIB), although those of CP type IIIA significantly decreased according to the year of experience (83.9%, 59.7% and 48.4%, $p<0.01$). Moreover, overestimated diagnosis with NBI magnification increased according to the fewer experience (6.0%, 19.0% and 35.3%, $p<0.01$), while underestimated diagnosis tended to be higher according to the year of experience (18.8%, 16.7% and 12.5%, respectively).
CONCLUSION: NBI magnification would have the clinical benefits for the diagnosis of colorectal neoplastic lesions, although sensitivity for early colorectal cancer was low compared to chromoendoscopic magnification. Moreover, NBI magnification has good concordance rate of intraoberver agreement, but it would take years of experience to achieve good diagnostic skill even in NBI magnification.
Disclosure of Interest: None declared

OP048 NOVEL 3D IMAGE OF COLON NEOPLASM MUCOSAL TISSUES USING MULTIPHOTON MICROSCOPY

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INTRODUCTION: During recent years, multiphoton microscopy became one of the most important optical imaging techniques for in vivo basic research. Multiphoton microscopy (MPM) can allow a detailed 3D structure analysis of tissue and can be used for the early diagnosis of dysplastic mucosal lesion.
AIMS & METHODS: The aim of this study was to make the gastrointestinal mucosa 3D structure using DNA probe of multiphoton microscopy and to compare normal mucosa with adenoma and adenocarcinoma tissues. This study was a single center study during Jury to September 2013. We obtained normal, adenoma and adenocarcinoma colon tissue samples by biopsy or endoscopic mucosal resection during colonoscopy from 7 patients. Then the tissues were placed in sterile specimen bottles containing PBS(phosphate buffer solution). Multiphoton images were collected using a DM IRE2 Microscope (Leica Microsystems GmbH, Wetzlar, Germany).
RESULTS: Total 7 Patient was composed of 4 adenoma and 7 adenocarcinoma. Among them, 4 patients were diagnosed adenoma and adenocarcinoma at the same time. We were able to get 3D structural images at depths of 90-140 μm. Normal tissue had a defined texture, whereas adenoma and cancer tissue was amorphous. And cancer tissues increased nucleus/cytoplasm ratio compared to normal mucosa.
CONCLUSION: Colon mucosa 3D structure analysis using multiphoton microscopy can be successfully used to determine colon mucosa architecture and may help to diagnose early colon cancer together with histopathologic examination.
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Disclosure of Interest: None declared

OP049 FEASIBILITY STUDY FOR THE EVALUATION OF MORPHOPATOLOGICAL PATTERN OF NEOANGIOGENESIS IN HUMAN COLORECTAL CANCER USING CONFOCAL LASER ENDOMICROSCOPY AND TARGETED ANTI- CD105 ANTIBODIES

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INTRODUCTION: Confocal Laser Endomicroscopy (CLE) is an imaging technique for gastrointestinal endoscopy providing in vivo microscopy at subcellular resolution. An important question in validating tumor angiogenesis is what proportion of the tumor vascular network is represented by pre-existing parent tissue vessels or newly formed vessels. CD105 (endoglin) represents a proliferation-associated endothelial cell adhesion molecule. In contrast to pan-endothelial markers, such as CD31, CD105 is preferentially expressed in activated endothelial cells that participate in neovascularization.
AIMS & METHODS: The aim of the study was to evaluate neoangiogenesis and vessel density in colorectal cancer patients by using two fluorescently labeled antibodies on fresh biopsy samples imaged with CLE. We evaluated CD105 and CD31 expression from samples of five patients with primary colon adenocarcinoma, using a dedicated endomicroscopy system (EC-3870 CIFK, Pentax, Japan). Image J (National Institutes of Health, USA) software was used to obtain the Z projection of the confocal serial images from each biopsy sample previously combined into stacks. Vascular density and vessel diameters were measured within two 50x475 mm rectangular regions of interest centered in the middle of each image in the horizontal and vertical direction. The results were averaged over all the patients and were expressed as the mean± standard error.
RESULTS: The use of CD105-antibody was found to be suitable for the detection of blood vessels only in colorectal cancer. Whereas anti-CD31 antibodies stained blood vessels in both normal and pathologic colon equally, CD105 expression was observed primarily in malignant lesions, with little or no expression in the vessels of the normal mucosa (252.63±195.6 vessels/mm3 in only two patients). We could measure the average diameter of anti-CD105 antibodies stained vessels of 11.22±0.8 μm in tumor tissue, counting 2812.61±147.3 vessels/mm3. When using anti-CD31 antibodies, the average diameter of vessels in the normal sample was 6.22±0.3 μm and the vessel density was 3199.98±478.5 vessels/mm3, while in the tumor sample we obtained an average diameter of 10.38 ± 0.4 μm and a vessel density of 4816.81± 620.7vessels/ mm3. Thus,

there were more vessels stained with CD31 than by CD105 ($p < 0.05$). The results were also confirmed by immunohistochemistry.
CONCLUSION: Specific imaging and quantification of tumor microvessels is feasible using CLE examination and CD 105 immunostaining of samples. CD 105 is a more specific marker for tumour angiogenesis, as compared to commonly used panendothelial markers. The combination of CD 105 staining with CLE analysis could provide a more reliable evaluation of the angiogenetic status of patients with colorectal cancer.
Disclosure of Interest: None declared

OP050 CLINICAL PATHOLOGY AND MOLECULAR BIOLOGY FOR MIXED SERRATED LESIONS DIAGNOSED IN MAGNIFYING ENDOSCOPY

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INTRODUCTION: We have previously reported that a novel surface microstructure Type II-Open pit patterns (Type II-O), which is highly specific to SSA/P with BRAF mutation and CpG island methylator phenotype (CIMP) (1). SSA/P with cytological dysplasia has been established in the field of serrated lesions in the fourth edition of the WHO classification of tumors of the digestive system. Progression of SSA/Ps to cytological dysplasia was suggested to be associated with additional morphological changes, including the tumor-like pits (similar to Type III, IV and V pits in Kudo's classification), but the clinical findings are still not clear.
AIMS & METHODS: We examined the characteristics of clinical pathology and molecular biology of the mixed serrated lesions in which conventional Type II pits, Type II-O pits and tumor-like pits coexisted in magnifying endoscopy. From April 2009 to September 2013, 54 patients (56 mixed serrated lesions) were enrolled in this study. Surface microstructures were analyzed using magnifying endoscopy. A gastrointestinal pathologist who was blinded to the clinical and molecular information evaluated histological findings for all lesions. Biopsy specimens were obtained for each respective pit pattern for the extraction of genomic DNA. Mutation in BRAF and KRAS was examined by pyrosequencing. Methylation of p16, MLH1 and MINT1, -2, -12 and -31 was analyzed using bisulfite pyrosequencing. Tumors were defined as CIMP-positive when methylation was detected in three or more loci of the five markers (MINT1, -2, -12, -31 and *p16*). The baseline characteristics, the histological findings, and the molecular analyses in the mixed serrated legions were assessed.
RESULTS: Endoscopic characteristics of these lesions were Type II + Type IV 1, Type II + Type IV with serration 24, Type II-O + Type IV 3, Type II + Type IV with serration 21, Type II-O + Type V 7. Histopathological results of these lesions were SSA/P alone 3, traditional serrated adenoma (TSA) alone 28, SSA/P+TSA 8, SSA/P with cytological dysplasia 10 and SSA/P + adenocarcinoma 7. All Type II-O plus Type IV lesions showed SSA/P with cytological dysplasia histology, and both the Type II-O subcomponents and the Type IV subcomponents showed *BRAF* mutation and CIMP-positive. By contrast, majority of the serrated lesions (76%) presenting with Type IV with serration were traditional serrated adenoma (TSA) with BRAF mutation and CIMP-negative. These results suggest that serrated lesions with Type IV pit and Type IV with serration appear to develop through distinct tumorigenic pathways. All lesions presenting with Type II-O + Type V pits were SSA/P + adenocarcinoma with BRAF mutation and CIMP-positive. MLH1 methylation and MSI was observed only in portions with a Type V pit pattern.
CONCLUSION: Our results may provide a model that variation in surface microstructure and molecular alterations are directly linked each other. Analysis based on magnified endoscopy may have an importance in understanding the developmental progress of serrated lesions.
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Disclosure of Interest: None declared

OP051 AN INVESTIGATION INTO THE DIAGNOSIS OF INVASION DEPTH IN COLORECTAL TUMORS BY MORPHOLOGICAL TYPE USING MAGNIFYING AND ULTRA-HIGH MAGNIFYING ENDOSCOPY

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INTRODUCTION: Pit pattern diagnosis used for endoscopic diagnosis of invasion depth colorectal tumors has high diagnostic accuracy. However, there is a tendency toward disparities in diagnostic accuracy depending upon the morphological type of the tumor.
AIMS & METHODS: The aim of this study was to investigate the diagnostic characteristics of magnifying and ultra-high magnifying endoscopy by morphological type of colorectal lesions and evaluated the diagnostic differences and clinical applicability of the technique. We investigated 292 lesions [129 protruding lesions, 47 laterally spreading tumors-granular (LST-G), and 116 LST-non-granular (NG) ≥10 mm] that could be observed under magnification and under ultra-high magnification using endocytoscopy in patients treated at our facility between May 2005 and March 2013. Pit pattern classifications of III and IV were considered as tubular adenoma (TA), V_I slight pit pattern was considered as carcinoma with intramucosal to submucosal shallow invasive carcinoma (M/SM-s), and V_I highly disorganized and V_N pit patterns were considered as carcinoma with submucosal deep invasion (SM-d). Using the EC classification with endocytoscopy, EC2 was considered as TA, EC3a was considered as M/SM-s, and EC3b was considered as SM-d. We investigated the diagnostic accuracy of each of these classifications.
RESULTS: The diagnostic accuracies using pit pattern classification and EC classification for all lesions were 83.6% and 85.8%, respectively. Diagnostic accuracy by morphological type under magnification using the former was 86.1%, 78.7%, and 79.3% for protruding lesions, LST-G, and LST-NG, respectively, whereas that using the latter was 80.6%, 83.0%, and 90.5%, respectively. There was no significant difference of diagnostic accuracies between each morphological type using pit pattern classification, whereas the diagnostic accuracy using EC classification for LST-NG was significantly higher than that for protruding lesions (90.5% vs 80.6%, $p < 0.05$). We also compared the diagnostic accuracies of each classification for LST-NG. The results (pit pattern classification, EC classification) were 79.3% and 90.5%, respectively, so these results indicate that, for LST-NG, the diagnostic accuracy of EC classification was significantly higher ($p < 0.01$).
CONCLUSION: This study showed that there was a difference in diagnostic accuracy by morphological type when performing endocytoscopy on colorectal tumors. EC diagnosis was significantly more useful for LST-NG lesions than for protruding lesions, and the diagnostic accuracy was higher than that of pit pattern diagnosis.
Disclosure of Interest: None declared

OP052 THREE-DIMENSIONAL ENDOSCOPIC MEASUREMENT SYSTEM THAT EXPLOITS GRID-BASED ACTIVE STEREO FOR PRECISE MEASUREMENT OF GASTROINTESTINAL MUCOSAL LESIONS

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INTRODUCTION: Endoscopy is essential for clinical diagnosis and treatment of gastrointestinal (GI) disorders and for gastroenterological research. A major disadvantage, however, is that the size of a lesion cannot be determined precisely by endoscopic visual estimation. Although several techniques for precise endoscopic measurement have been proposed, none have been applied clinically because of costs or inaccuracies. We have proposed a 3-dimensional (3D) reconstruction method called "active stereo." Active stereo measurement is based on a mono/multi-projector, mono-/multi-camera system. An image of patterned light projected onto a target object is obtained, and the 3D shape of the object is reconstructed by analysing the distribution of the light pattern in the image.[1)] We have also developed an endoscopic system that allows 3D measurement based on active stereo techniques and projection of a static pattern.
AIMS & METHODS: The aim of this study was to evaluate the accuracy of our 3D endoscopic system, which exploits grid-based active stereo techniques. We evaluated the system as applied to 17 sites, each between two points marked on GI mucosa. Lesions were examined with the use of a video endoscopy system (EG-590WR; Fujifilm Medical Co. Ltd., Japan) and a micro-pattern projection catheter. Study samples were 1 esophageal cancer, 2 gastric cancers, and 2 colonic tumor specimens obtained by endoscopic resection at our institution. We evaluated the characteristics of error (E = degree of under- or over-estimation: E = average value of (measured value – true value)/true value), the magnitude of error (|E| = absolute degree of error: |E| = average value of |measured value – true value|/true value), and correlation between the true value (actual measurement) and the measured value (active stereo endoscopy system measurement).
RESULTS: E was −2.22% [−6.62, 2.22] (mean [95% CI(%)]), and |E| was 6.78% [3.96, 9.60]. Strong positive correlation was found between the true value and the value measured by the active stereo endoscopy system ($r = 0.99$: 99% CI [0.97, 1.00]; $P < 0.01$).
CONCLUSION: Our newly developed 3D endoscopic system provided for successful measurement of lesions in GI mucosa. Further development of our system will allow for accurate, real-time measurement of GI lesions in vivo. With attachment of a micro-pattern projector to a normal, unaltered endoscope, it is possible to measure the 3D shapes of target surfaces. This work was supported in part by NEXT program No.LR030 in Japan.
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Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 14:00–15:30
LATE BREAKING DIGESTIVE ONCOLOGY ABSTRACTS – HALL I/K

OP052-LB1 METAL OR PLASTIC STENTS FOR PREOPERATIVE BILIARY DRAINAGE IN RESECTABLE PERIAMPULLARY CANCER: PROSPECTIVE MULTICENTER STUDY

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INTRODUCTION: A recent randomised controlled multicenter trial (RCT) found a higher complication rate after preoperative biliary drainage (PBD) as compared to direct pancreatoduodenctomy in jaundiced patients with resectable pancreatic tumors, which might be related to the plastic endoprotheses used. However, PBD is still frequently indicated due to logistic hurdles and neoadjuvant therapy. Aim of this study was to compare the complication rates after PBD with metal stents to plastic stents.
AIMS & METHODS: A prospective cohort of patients with obstructive jaundice due to a periampullary or pancreatic tumor who were scheduled to undergo PBD before resection was added to the study cohort of the earlier RCT. PBD with a metal stent was performed in jaundiced patients when early surgery was not appropriate. The multidisciplinary setting and inclusion criteria were identical to the criteria reported in the RCT. Metal stent and plastic stent groups were compared for the primary outcome, PBD-related complications. A three-group comparison with early surgery patients was performed to compare overall complications.
RESULTS: A total of 53 patients underwent drainage with a metal stent and were compared with the plastic stent group (n=102). Patients' characteristics did not differ. PBD related complications rates were 24% in the metal stent group compared to 46% in the plastic stent group (relative risk (RR) of the plastic stent use 1.9, lower limit 90% confidence interval (CI) 1.2, P=0.006). Specific stent related complications (occlusion and exchange) were 6% in the metal stent group compared to 31% in the plastic stent group (P=0.001). RR of plastic stent use 5 (lower limit 90% CI 1.9). In the three-group comparison overall complication rates for the metal stent, plastic stent and early surgery groups were resp. 51% vs. 74% vs. 39% ($p<0.001$) (metal vs. early surgery: $p=0.09$).
CONCLUSION: Metal stents are superior to plastic stent for selective PBD in jaundiced patients. Although early pancreatoduodenectomy is still the preferred treatment of choice in jaundiced patients, metal stent should be used when PBD is indicated.
Disclosure of Interest: None declared

OP052-LB2 FEATURES PREDICTING MALIGNANCY IN BRANCH DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM OF THE PANCREAS

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INTRODUCTION: The aim of this study was to determine the features predicting malignancy and analyze their diagnosis value in a large single-center cohort that includes resected branch duct Intraductal Papillary Mucinous Neoplasm (BD-IPMN) histologically proven.
AIMS & METHODS: This study included all consecutive patients who underwent surgical pancreatic resection with final pathological diagnosis of BD-IPMN by histological examination between 2006 and 2014. Neoplasms were classified as malignant if high grade dysplasia (HGD) or invasive carcinoma was found. Medical and radiological records were retrospectively reviewed, with a special focus on features that predict malignancy according to 2012 Sendai guidelines. Endoscopic ultrasound (EUS) was also considered.
RESULTS: 120 patients (65 males, 55 females, mean age: 57.75 years) were included. 53 patients had at least one acute pancreatitis (AP).
Of the 120 patients, 89 (74.1%) had at least one surgical indication, 23 underwent surgery for relief of symptoms, 5 because of their family history of pancreatic cancer, 3 because of multifocality. 36 patients had a malignant tumor. Within those 89 patients (Sendai positive), 34 had a malignant tumor (sensitivity: 94.4%, specificity: 34.5%). Among the 31 Sendai-negative patients, 29 (93.5%) had a benign tumor and only 2 harbored HGD. Patients with malignant neoplasms had significantly more indications for resection than those with low or moderate dysplasia (2.06 +/- 0.98 vs. 0.99 +/- 0.95, $P < 0.001$).
The univariate and multivariate analysis clarified the significant factors associated with malignancy, these being the obstructive jaundice (p=0.002), mural nodule (MN) (median diameter: 10mm) (p=0.005), thickened/enhancing walls (p=0.019), the main pancreatic duct (MPD) from 5 to 9mm (p=0.004). Age, family history of pancreatic cancer, AP, mutifocality and cyst size $\geq$ 30mm were not statistically associated with malignancy.

Table to abstract OP052-LB2

Analysis of predictive features of malignancy in BD-IPMN

	N°	Sensitivity	Specificity	PPV	NPV
Obstructive jaundice	5	13.9%	100%	100%	73%
Thickened/enhancing walls	27	36.1%	83.3%	48.1%	75.3%
Ø MPD 5-9 mm	44	59.4%	69.9%	43.2%	81.7%
Mural nodule (MN)	17	27.8%	91.7%	58.8%	74.8%
MN in EUS	17	25%	90.5%	52.9%	73.8%

CONCLUSION: Sendai guidelines increased surgical indications due to high sensitivity and low specificity. The 61.8% of the patients with surgical indications in our study harbored low or moderate dysplasia.
Disclosure of Interest: None declared

OP052-LB3 PREOPERATIVE BILIARY DRAINAGE IN PERIHILAR CHOLANGIOCARCINOMA: IDENTIFYING PATIENTS THAT BENEFIT FROM IMMEDIATE PERCUTANEOUS INSTEAD OF ENDOSCOPIC DRAINAGE

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INTRODUCTION: Preoperative biliary drainage in perihilar cholangiocarcinoma is mostly initiated with endoscopic biliary drainage (EBD), but additional percutaneous transhepatic biliary drainage (PTBD) is frequently required to establish optimal biliary drainage prior to surgery. This study aimed to develop and validate a simple prediction model that identifies patients likely to require pre-operative PTBD.
AIMS & METHODS: Two databases from specialty centers were used (Europe and USA), and patients that underwent (attempted) EBD with plastic stents prior to surgery for presumed perihilar cholangiocarcinoma between 2001-2013 were included. A prediction model was derived from the European population based on variables uniformly available prior to biliary drainage. Performance of the risk model was assessed for discrimination and calibration in the validation population (USA).
RESULTS: 108 patients of 288 patients (38%) required additional PTBD prior to surgery. Incremental risk factors of the need for pre-operative PTBD included bile duct obstruction at the left, right, or bilateral segmental level as assessed on preoperative CT and/or MRI, and a pre-drainage total bilirubin level above 150 µmol/L. The prediction model identified three subgroups: Patients with a predicted low risk of 7%, a moderate risk of 40%, and high risk of 62% of the need for pre-operative PTBD. The high risk group consisted of patients with obstruction at the level of the right or bilateral segmental bile ducts in combination with a total bilirubin above 150 µmol/L. The prediction model had good discrimination (area under the curve 0.74) and adeqaute calibration in the external validation dataset.
CONCLUSION: Patients with perihilar cholangiocarcinoma likely to need additional PTBD after initial attempt at endoscopic stent placement can be identified using the predictive model described. These patients should be treated with initial PTBD instead of initial EBD, thereby potentially reducing the number of preoperative biliary drainage procedures and associated complications.
Disclosure of Interest: None declared

OP052-LB4 INTERVAL CANCERS USING A FAECAL IMMUNOCHEMICAL TEST FOR HAEMOGLOBIN WHEN COLONOSCOPY CAPACITY IS LIMITED

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INTRODUCTION: Introduction of faecal immunochemical tests for haemoglobin (FIT) for colorectal cancer (CRC) screening poses considerable challenges for countries with limited colonoscopy capacity. To secure low positivity rates, high faecal haemoglobin concentration (f-Hb) cut-offs must be used. This decreases sensitivity, particularly for adenoma. Interval cancers (IC) are an important consideration but little examined for FIT-based programmes. We assessed IC using an 80 µg Hb/g faeces cut-off in an established screening programme.
AIMS & METHODS: A single estimate of f-Hb using quantitative automated immunoturbidimetry (OC-Sensor, Eiken, Japan) was obtained for 30894 participants aged 50-75 who took part in a six-month evaluation of FIT as a first-line test within the Scottish Bowel Screening Programme. 754 participants with f-Hb $\geq$ 80 µg Hb/g were referred for colonoscopy. IC, defined as CRC diagnosed

within two years of a negative screening test result, or the time to next invitation, were identified from the Cancer Registry.
RESULTS: We identified 31 IC and 30 screen-detected CRC, giving an IC rate of 50.8%. IC rate was 46.9% for men and 55.2% for women. CRC site distribution did not differ between IC and screen-detected CRC, but IC were later stage (Dukes' C or D): 46.7% and 37.0%, respectively. Of the 31 IC, 23 had f-Hb <10 µg Hb/g, the lower limit of quantitation. Of these 23, 6 had undetectable f-Hb. Lowering the f-Hb cut-off to 10 µg Hb/g would increase positivity rate from 2.4% to 9.4%, colonoscopy demand from 754 to 2137, and reduce the IC rate to 37.7%.
CONCLUSION: Our results provide unique insight into IC rates using FIT in a screening programme with limited colonoscopy capacity. Our IC rate was similar to the ca. 50% commonly reported with guaiac faecal occult blood tests, but much higher than the 14.4% IC rate with f-Hb cut-off of 20 µg Hb/g[1]. Thus, a high f-Hb cut-off limits the improved sensitivity of FIT. The more advanced stage distribution of IC highlights the need for improved CRC detection with screening. However, with 19.4% of IC having undetectable f-Hb, some cancers would always be missed, even with significant lowering of the f-Hb cut-off. With more CRC missed in women than in men, it appears that women may be disadvantaged by the use of one f-Hb cut-off for all and we propose better individualized use of FIT in CRC screening.
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Disclosure of Interest: J. Digby: None declared, C. Fraser Consultancy for: Immunostics Inc, Other: Alpha Labs Ltd, F. Carey: None declared, J. Lang: None declared, R. Steele: None declared

OP052-LB5 ASSOCIATION OF THE 3'UTR HLA-G +3187A/G POLYMORPHISM WITH RELAPSE AND SURVIVAL IN COLORECTAL CANCER PATIENTS IN ADJUVANT REGIMEN. A MULTICENTER STUDY

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INTRODUCTION: HLA-G is involved in cancer immune tolerance. HLA-G expression is linked to 3'UTR regulation. To date, the prognostic value of 3'UTR HLA-G SNPs has never been explored in colorectal cancer (CRC) in the adjuvant chemotherapy (ADJ-CT) regimen.
AIMS & METHODS: To quantify in CRC patients the association between SNPs, alleles and haplotypes of HLA-G 3' UTR region with disease free survival (DFS) and OS. 274 CRC patients (stage II-III) after primary surgery were included in 2 independent cohorts: 1) the discovery set (N=124); 2) the validation set (N=150). All patients received fluoropyrimidines (FL) as ADJ-CT; of them, 164 received FL plus oxaliplatin. 3'UTR of the HLA-G gene was amplified by PCR from genomic DNA. 9SNPs: 14bp INDEL, +3003T/C, +3010G/C, +3027C/A, +3035C/T, +3142C/G, +3187A/G, +3196C/G, +3227G/A, were analysed by direct sequencing. UTR haplotypes frequencies were determined by PHASE method. We evaluated data by means of Cox models. Multivariate Hazard ratios (HRs) and 95% CIs of DFS and OS were computed adjusting for age, sex, stadium and type of ADJ-CT. Data validation was performed between the 2 cohorts.
RESULTS: Relapses were 79/274 and deaths were 45/274. Mean follow-up time was 67.2 months (range: 4.6-186.3). The association between DFS and 3'UTR +3187G/G genotype was statistically significant (HR=2.2; 95%CI:1.1-4.6). The +3187A/G SNP was also significantly associated to DFS under a recessive genetic model (HR=2.1; 95%CI:1.1-4.3). 20 haplotypes were identified (6 novel); 8 with frequencies $>1\%$ (93% of total): UTR-2(33%), UTR-1(24%), UTR-3(13%), UTR-4(12%), UTR-7 (5%), UTR-5(3%), UTR-18(2%) and UTR-15(1%). The 3'UTR-1 in homozygous state was significantly associated to DFS (HR=2.2;95%CI:1.0-4.5). OS was directly associated to these variants but not statistically significant. HR heterogeneity tests across the two cohorts, were not significant for +3187A/G and 3'UTR1/UTR1 (i.e. p=0.24 for DFS and p=0.61 for OS).
CONCLUSION: For the first time, the 3'UTR of the HLA-G gene was explored in CRC patients. Analyses showed that 3'UTR +3187A/G and 3'UTR-1, which includes +3187G allele, were associated to an unfavourable DFS and OS. +3187A allele was related to a decreased *HLA-G* expression, while +3187G allele and UTR-1 haplotype were associated to higher soluble HLA-G levels. Next analyses will explore, at germinal level, the 3'UTR HLA-G region novel prognostic role to better manage CRC patients in FL based ADJ treatment.
Disclosure of Interest: None declared

OP052-LB6 ADJUVANT CHEMOTHERAPY FOLLOWING COLORECTAL CANCER RESECTION - WHAT TIMEFRAME CONSTITUTES A DELAY AND HOW DOES THIS IMPACT OVERALL SURVIVAL?

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INTRODUCTION: The ideal timing of adjuvant chemotherapy in colorectal cancer surgery and the impact of its delay has been extensively studied. However there has been no real consensus on a specific timeframe.
AIMS & METHODS: Elective colorectal cancer resections between April 1997 and March 2012 were collated from prospectively recorded Hospital Episode Statistics in England. Reoperation rates and time to adjuvant chemotherapy were ascertained and their impacts on overall survival were analysed utilising multivariate logistic regression and survival statistics. Patients who received adjuvant chemotherapy were grouped depending on their timing of initiation into 4-week cohorts. These groups were then compared to assess the impact of increasing adjuvant chemotherapy delay, on overall survival.
RESULTS: 210,581 individuals underwent colorectal cancer resection. 40,479 (19.2%) received chemotherapy within 24 weeks of surgery. Patients receiving adjuvant chemotherapy in the first month were taken as a reference and each subsequent month of patients was compared to it sequentially.

Overall Survival

Timing of adjuvant chemotherapy initiation	Hazard Ratio (95% CI)	Sig.
0-4 weeks	Ref	
5-8 weeks	0.81 (0.75-0.87)	<0.001
9-12 weeks	0.92 (0.85-0.99)	0.028
13-16 weeks	1.10 (1.01-1.19)	0.029
17-20 weeks	1.35 (1.23-1.48)	<0.001
21-24 weeks	1.31 (1.18-1.45)	<0.001

33,435 (82.6%) of the 40479 patients received it within 12 weeks. Adjuvant chemotherapy beyond 12 weeks resulted in poorer survival, compared to within 12 [Hazard Ratio (HR) 1.39, 95% CI 1.34-1.44, $p<0.001$]. Reoperation was an independent predictor of adjuvant chemotherapy delay (HR 2.22, CI 1.98-2.48, $p<0.001$). Patients who avoided a reoperation and received timely adjuvant chemotherapy demonstrated the greatest median survival [no delay + no reoperation = 90 months (m); no delay + reoperation = 75m, delay + no reoperation = 50m, delay + reoperation = 50m, Log rank p value <0.001)].
CONCLUSION: Twelve weeks may be an appropriate 'cut-off' for timely initiation of adjuvant chemotherapy and with such a delay adversely impacting colorectal cancer patients' overall survival. Reoperation is a significant cause of delayed adjuvant chemotherapy. Efforts to prevent complications necessitating reoperation and to improve access to chemotherapy services will improve survival in this patient group.
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Disclosure of Interest: None declared

OP052-LB7 ADM RECEPTOR WAS RELATED WITH THE METASTASIS OF COLORECTAL CANCERS THROUGH WNT AND NO PATHWAYS

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INTRODUCTION: ADM is significantly overexpressed in human colorectal cancer (CRC) samples with a mutant KRAS oncogene and it can promote cell invasion. ADM acts as a peptide ligand that activates receptors including the adrenomedullin receptor (ADMR, also known as L1-R) and the calcitonin-receptor-like-receptor (CRLR). However, the role of ADM receptors remains unknown.
AIMS & METHODS: We first detected the expression of ADM, ADMR and CRLR in human colon tissues by immunohistochemistry and correlated the expression levels with clinicopathological features. The expression of ADMR and CRLR was interfered by lentivirus and their effects on the proliferation, cell cycle, apoptosis, migration and invasion were evaluated by MTS, flow cytometry and transwell assays, respectively. We screened the downstream targets related with the metastasis-related signaling pathways of ADMR and CRLR in CRC by metastasis Gene-expression Array and validated the results by PCR.
RESULTS: The expression level of ADM and CRLR were statistically higher in CRC tissues than those in adjacent tumor-free tissues ($p<0.01$). The expression of ADMR and CRLR mRNA was correlated with lymph node metastasis of colon cancer ($p<0.01$). ADMR or CRLR shRNA-transfected RKO and HT-29 cells inhibit the cell viability and induced a significant increase in early and total apoptosis of RKO and HT-29 cells. In addition, dual interference with ADMR and CRLR significantly inhibited cell migration and invasion in RKO

and HT-29 cells ($p<0.01$). Exogenous ADM administration (50nmol/L) can promote cell migration and invasions, and these effects were blocked with silencing of ADMR and CRLR. cDNA microarray and qPCR validation analysis showed that APC, EGF, PIK3CA, PIK3CB and DVL1 were up-regulated, while NOS2 is down-regulated by silencing of ADMR and CRLR.
CONCLUSION: High expression of ADM and its receptors- ADMR and CRLR was associated with lymph node metastasis. Silencing expression of ADMR and CRLR significantly inhibited proliferation, impaired migration and invasion of colon cancer cells, which might be mediated through Wnt and NO signaling pathways.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 14:00–15:30
NEW IMAGING TOOLS FOR IBD – HALL N

OP053 DEVELOPMENT AND INITIAL VALIDATION OF A UNIQUE SCORE FOR IN VIVO DIFFERENTIATION OF ULCERATIVE COLITIS AND CROHN'S DISEASE FEATURING CONFOCAL LASER ENDOMICROSCOPY

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INTRODUCTION: Confocal Laser Endomicroscopy (CLE) allows on demand *in vivo* characterization of architectural and cellular tissue details during endoscopy. Recent evidences have shown that CLE can detect Crohn's disease (CD) and ulcerative colitis (UC) associated histological changes *in vivo*.
AIMS & METHODS: We prospectively assessed the efficacy of CLE for *in vivo* differentiation of IBD by developing a unique CLE scoring system based on histopathological hallmarks of colonic IBD involvement. Consecutive patients with a well-established diagnosis of UC and CD and no disease reclassification during the last three years underwent colonoscopy with biopsies and blind fluoresceine-aided confocal imaging. Analysis of contingency tables was performed using the Fisher's Exact test, thereby considering significant a two-sided P value <0.05.
RESULTS: Seventy-nine patients were prospectively included (40 CD, 39 UC). In CD, CLE showed significantly more often discontinuous inflammation (90% vs. 5%), focal cryptitis (75% vs. 13%) and discontinuous crypt architectural abnormality (90% vs. 5%). Conversely, UC was associated with severe, widespread crypt distortion (87% vs. 17%), decreased crypt density (79% vs. 22%) and frankly, irregular surface (90% vs. 17%). Significant differences were not seen for heavy, diffuse lamina propria cell increase or mucin preservation. Granulomas were not visible in any case. Based on these findings, we developed a scoring system for *in vivo* IBD differentiation based on endomicroscopic assessment (IDEA). Compared to the historical clinical diagnosis and histopathology, the IDEA score revealed excellent validity measures in both UC and CD subjects (sensitivity 97% and 90%, specificity 90% and 97%, positive predictive value 91% and 97%, negative predictive value 97% and 91%, accuracy 94% for both).
CONCLUSION: CLE enables *in vivo* characterization of most microscopic tissue features and inflammatory changes of tissue and cellular characteristics conventionally used by standard histopathology both to confirm diagnosis and to distinguish UC from CD. However, according to the penetration depths of CLE, submucosal details or granulomas are not visible. The new scoring system "*IDEA*" allows for on demand *in vivo* differential diagnosis of UC and CD with high accuracy.
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OP054 THE NOVEL PILLCAM CROHN'S DISEASE CAPSULE DEMONSTRATES SIMILAR DIAGNOSTIC YIELD AS ILEOCOLONOSCOPY IN PATIENTS WITH ACTIVE CROHN'S DISEASE - A PROSPECTIVE MULTICENTER INTERNATIONAL COHORT STUDY

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INTRODUCTION: Mucosal lesions in Crohn's disease (CD) can be found throughout the GI tract. While an endoscopist may visualize to D3 with EGD and from anus to terminal ileum with ileocolonoscopy (IC), visualization of the entire small bowel (SB) is challenging. The novel PillCamCD is designed to examine the entire GI tract. This study compares the diagnostic yield of PillCamCD to IC.
AIMS & METHODS: In 8 centers, the PillCamCD capsule (Given Imaging, Yoqneam, Israel) was prospectively compared to IC in a cohort of patients with known CD presenting with objective signs and symptoms of active disease. Patients underwent patency capsule testing if they did not have recent radiographic evidence of small bowel patency. Subjects underwent standardized bowel prep. Ingestion of PillCamCD was followed by IC the same or following day per investigator discretion. RAPID videos were reviewed by one of three central readers. Mucosal lesions identified during PillCamCD and IC were analyzed by type and location. A priori, "Active CD" was defined as the presence of aphthae, ulcerations, inflammatory stricture or bleeding. Other lesions were defined "Non-active CD". Localization was to SB, ileum, cecum, ascending, transverse, descending, sigmoid or rectum. Each segment was reported as "Active disease likely" or "Active disease NOT likely".
RESULTS: Total of 114 subjects screened; 76 enrolled. Screen failures were due to lack of evidence of inflammation or failure to pass the patency capsule. Of 76 subjects, 66 were included in the efficacy analysis (mean age 37yrs, 67% F). The majority of exclusions was due to capsule retention in the SB or stomach. Forty-six of 66 (70%) had "Active CD likely" by IC. PillCamCD identified 43 (94%) similarly. There was no significant difference between PillCamCD and IC for classifying subjects as having active CD ($p= 0.43$). Fifty-five subjects (83%) were identified with "Active CD likely" by PillCamCD including 12 identified by PillCamCD only. The proximal SB was evaluated only by PillCamCD; however, 5 of 12 were found to have lesions in the TI as defined by the last 10 minutes of the SB portion of the study. Thirty subjects (46%) were identified with "Active CD likely" in the SB. There was no significant difference between PillCamCD and IC in classifying segments as having "Active CD likely" ($p\leq0.09$). There were three (3%) adverse events: 1 bowel obstruction due to CD capsule retention, 1 abdominal pain due to prep, 1 episode of fever, nausea, vomiting, abdominal pain and bloating (without obstruction) related to the patency capsule.
CONCLUSION: As compared to IC, the novel PillCamCD capsule was equally effective in identifying active CD in the colon and TI in patients with signs and symptoms of active CD, identified more overall patients with active CD, and provides the advantage of imaging the entire small bowel and colon in a single procedure.
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OP055 CONFOCAL LASER ENDOMICROSCOPY PREDICTS RELEVANT CLINICAL OUTCOMES IN CROHN'S DISEASE: A PROSPECTIVE, OBSERVATIONAL, FOLLOW-UP STUDY

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INTRODUCTION: Assessment of prognostic factors in Crohn's disease (CD) patients is crucial for early intervention and "treat to target" strategies [1]. Confocal Laser Endomicroscopy (CLE) enables on demand *in vivo* characterization of architectural changes during endoscopy [2].
AIMS & METHODS: Here, we prospectively evaluated the value of CLE, endoscopic index of severity (CDEIS) and serum C-reactive protein (CRP) for prediction of clinical outcomes in CD. Consecutive CD patients undergoing colonoscopy with fluoresceine-aided confocal imaging were enrolled in a blind, observational, follow-up study. Consistent with previous reports [2], CLE analysis focused on two highly reproducible architectural microscopic tissue changes referred as histological hallmarks of acute inflammation in CD: focal cryptitis and discontinuous crypt architectural abnormality.
RESULTS: Thirty-two CD patients were included (14 men; median age/range 37/18-60 years; mean distance from diagnosis 11 years). Baseline CRP was ≥5 mg/L in 46% and CDEIS ≥3 in 73% of patients. Mean follow-up period was 2.5 years (range=6-48 months). Focal cryptitis and discontinuous crypt architectural abnormality were observed in 63% of patients. This finding showed a weak correlation with CDEIS (P=0.068, RR=1.6) and no correlation with CRP (P=0.4, RR=1.6). Focal cryptitis and discontinuous crypt architectural abnormality were significantly associated with an increased risk of medical treatment escalation with biologics, immunosuppressant or systemic steroids within 6 months (P=0.045, RR=2.0), showing 75% sensitivity and 70% specificity. This finding was also confirmed at 12 month follow up (P=0.012, RR=2.1; sensitivity=76%, specificity=78%). Patients with positive CLE findings developed significantly more transmural complications such as stenosis or perianal disease during the first 12 months (P=0.023, RR=6.0; sensitivity=91%, specificity=52%). Conversely, basal CDEIS ≥3 was only associated with treatment escalation at month 12th (P=0.022, RR=2.27; sensibility=85%, specificity=37%). CRP was not correlated with prognostic clinical outcomes.

CONCLUSION: *In vivo* characterization of CD-related signs of acute inflammation by means of CLE showed moderate correlation with CDEIS but not with CRP. CLE appeared as a good predictor of relevant clinical outcomes such as treatment escalation and transmural complications, performing better than CRP and CDEIS. This finding was substantial in the short term but disappeared after one year follow up. Therefore, endomicroscopic assessment of acute mucosal inflammation appears to be a promising prognostic tool, which may allow early risk stratification of strong clinical outcomes with high sensitivity and moderate to good specificity, thereby potentially improving the timing of treatment strategies targeting mucosal inflammation in CD.

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Disclosure of Interest: G. E. Tontini Financial support for research from: Italian Group for the study of IBD (IG-IBD), J. Mudter: None declared, M. Vieth: None declared, R. Atreya: None declared, C. Günther: None declared, M. Vecchi: None declared, M. Neurath: None declared, H. Neumann: None declared

OP056 MR ENTEROCOLONOGRAPHY CAN IDENTIFY PATIENTS WHO NEED ADDITIONAL TREATMENT BY PREDICTING RECURRENCE, HOSPITALIZATION AND SURGERY OF CROHN'S DISEASE PATIENTS IN REMISSION

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INTRODUCTION: Crohn's disease (CD) is a lifelong chronic inflammatory bowel disease. Evaluating the extension and severity of the disease is critical to determine appropriate therapeutic strategies in patients with CD. MR enterography (MRE) can investigate not only intraluminal changes, but also extraluminal abnormalities without ionizing radiation and anesthesia, which makes it appropriate for frequent examinations in CD patients. We developed novel magnetic resonance enterocolonography (MREC) for simultaneously evaluating both small and large bowel lesions in patients with CD and recently we reported its excellent correlation with endoscopy. However, there are few reports about predictability of CD recurrence by MRE. The aim of this study was to evaluate the capability of MREC for prediction of recurrence, hospitalization, and surgery among CD patients in clinical remission.
AIMS & METHODS: A total of 284 patients with established CD were prospectively examined by MREC between July 2009 and February 2014. Among them, 213 patients were in clinical remission (Crohn's Disease Activity Index (CDAI) $\leq$150). Patients underwent ileocolonoscopy (ICS) after MREC on the same day. MREC score (0-60) was defined by modifying SES-CD. Presence and size of ulcers, extent of ulcerated surface, extent of affected surface and presence of narrowings were scored (0-3) in each segment of small and large intestine. MREC score, simplified endoscopic activity score for Crohn's disease (SES-CD), CDAI and CRP was evaluated. The patients were followed up for a maximum of 58 months unless clinical recurrence occurred earlier.
RESULTS: 126 patients (59.2%) in clinical remission had active lesion on MREC (MREC score $\geqq$2; reflecting active disease). Over a median follow up of 12 months (3-58), 81 patients recurred, 57 needed hospitalization and 49 had operation. Patients who had active lesion on MREC more often experienced recurrence than those who didn't (88.9% vs 11.1%. $p<0.001$). Higher SES-CD, higher CDAI and higher CRP at baseline also predicted clinical recurrence. But only active lesion on MREC was a predictor for both hospitalization (37.3% vs 11.5%, $p<0.001$) and operation (32.5% vs 9.2%, $p<0.001$). Even in 152 patients in remission with negative CRP, the detection of active lesion on MREC significantly predicted clinical recurrence (52.6% vs 10.5%, $p<0.001$), hospitalization (40.8% vs 11.8%, $p<0.001$) and operation (35.5% vs 10.5%, $p<0.001$).
CONCLUSION: This prospective study suggested that MR enterocolonography is useful for predicting recurrence of Crohn's disease and identifying patients who need additional treatment.

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Disclosure of Interest: None declared

OP057 MAGNETIC RESONANCE ENTEROCOLONOGRAPHY CAN DETECT SMALL INTESTINAL ACTIVE LESIONS IN CROHN'S DISEASE; COMPARISON WITH BALLOON ENTEROSCOPY

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INTRODUCTION: To assess active lesions such as ulcers or aphtha is important in Crohn's disease (CD). Magnetic resonance (MR) enterography is a recommended imaging technique for detecting intestinal involvement in Crohn's disease (CD). However, the diagnostic accuracy of MR enterograpy has not been compared directly what that of enteroscopy of the jejunum and proximal ileum. In addition, there is no widely accepted endoscopic or MR scoring system for the entire small intestine in CD. We evaluated the usefulness of MR enterocolonography (MREC) by comparing its findings with those from balloon-assisted enteroscopy.
AIMS & METHODS: MREC and enteroscopy were performed within 3 days on 100 patients. The segmentation and assessment of the endoscopic findings were defined based on modified SES-CD, and those of MREC findings were defined based on modified MaRIA score as well. Physicians and radiologists were blinded to results from other studies. Findings from MREC were directly compared with those from enteroscopy; the sensitivity and specificity with which MREC detected CD active lesions were assessed. Additionally, we are evaluating the correlation between modified SES-CD and MaRIA scores.
RESULTS: The scope was passed in retrograde fashion and reached the proximal ileum in 98 patients (98.0 %), the jejunum in 40 patients (40.0 %), and the entire intestine in 11 patients (11.0 %). In the assessment of CD active lesions, MREC detected ulcerative lesions and all mucosal lesions in the small intestine with 82.4% sensitivity and 67.5% sensitivity, respectively; specificity values were 87.6% and 94.8%, respectively. Modified MaRIA scores correlated with modified SES-CD in the terminal ileum ($r = 0.75$), but did not in the jejunum and proximal ileum ($r = 0.48$).
CONCLUSION: MREC is useful for detecting active lesions in deep small intestine. Evaluation of active lesions is important to determine medical treatment. Suitable imaging approaches should be selected to assess CD lesions in deep small intestine. Alternatively, it is needed to develop the new scoring system of enteroscopy or MR for the entire small intestine in CD.
Disclosure of Interest: None declared

OP058 LOOKING BEYOND MUCOSAL HEALING: EFFECT OF BIOLOGIC THERAPY ON TRANSMURAL HEALING EVALUATED BY ULTRASOUND IN PEDIATRIC CROHN'S DISEASE

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INTRODUCTION: Therapeutic goals for Crohn's disease (CD) have evolved from a mere control of symptoms to the concept of deep remission (DR), including clinical and biomarker remission and mucosal healing (MH). Biologic therapy with anti-TNFα is effective in achieving MH. Yet, CD is a transmural disease, characterized by a progressive bowel damage leading to complications.
AIMS & METHODS: This is the first pediatric study prospectively evaluating the efficacy of anti-TNF therapy in inducing clinical remission, MH and TH in ileal CD. Pediatric patients (pts) with ileal CD starting biological therapy with Infliximab or Adalimumab were prospectively enrolled. All pts were naïve to biologics. Clinical activity (Pediatric Crohn's Disease Activity Index, PCDAI), laboratory tests (CRP, ESR), endoscopic activity (simple endoscopic score, SES-CD) and transmural disease assessed by small intestine contrast ultrasonography (SICUS) were evaluated before starting (T0) and after 9-12 months of therapy (T1). Complete MH was defined as a SES-CD of 0-1, partial MH as 50% decrease vs T0. At US the evaluated parameters were: extension of disease (cm), bowel wall thickness >3 mm (BWT), BW vascularity (BWV), stratification of the BW (BWS), presence of stricture, fistulae and abscess. Wilcoxon signed rank test was used for pair comparison (T1–T0).
RESULTS:

	T0	T1	p value
PCDAI	33.77 $\pm$18.20	13.10 $\pm$12.86	<0.0001
Ileal SES-CD	6.6 $\pm$3.6)	2 $\pm$ 2.3	<0.001
PCR (µg/l)	30609 $\pm$24539	8744 $\pm$16330	<0.001
ESR (mm/h)	69 $\pm$35	35 $\pm$ 26	<0.0001
BWT (mm)	5.98 $\pm$1.67	4.31 $\pm$ 1.71	<0.0001
Extension of ileal disease (cm)	13.63 $\pm$ 5.78	9.08 $\pm$ 5.74	<0.0001

26 pts (mean age 13.3 $\pm$ 4, 16 males) were included. The mean PCDAI, ileal SES-CD, CRP, ESR, BWT and disease extension values significantly decreased at T1 (table; mean SD $\pm$ values). Increased BWV was present in 80% of pts at T0 and in 24% at T1 ($p<0.0001$). In pts with complete and partial MH the extension of disease and the mean BWT at US were significantly reduced at T1 ($p<0.02$); in pts without endoscopic response the US parameters didn't change significantly, despite clinical response. Presence of strictures and BWS didn't modify during therapy in any group.
CONCLUSION: Biologics are effective in inducing clinical and laboratory remission and in achieving MH in pediatric CD. Transmural inflammation significantly improves during therapy, however when a substantial bowel damage (stricture) is present, the effect on TH might be poorer. Further studies are needed to evaluate the impact of TH on the long term outcome of CD.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 14:00–15:30
IMAGING IN PANCREATIC CANCER: STILL A CHALLENGE – HALL O

OP059 PROSPECTIVE MULTICENTER RANDOMIZED CONTROLLED TRIAL OF HISTOLOGICAL DIAGNOSTIC YIELD COMPARING 25G EUS-FNA NEEDLES WITH AND WITHOUT A CORE TRAP IN SOLID PANCREATIC MASSES: ANALYSIS OF FACTORS AFFECTING TISSUE ACQUISITION AND DIAGNOSTIC ACCURACY

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INTRODUCTION: We have reported that a prospective multicenter randomized controlled trial indicated that the novel EUS-FNA 25G needle with a core trap by a single pass offers significantly higher tissue acquisition rate and the definite histological diagnosis rate of solid pancreatic tumors compared with the 25G standard needle (DDW May 3, 2014).
AIMS & METHODS: The aim of the present study was to assess factors affecting the tissue acquisition and diagnostic rates for both needles. Consecutive patients with pancreatic solid masses presenting to 8 referral centers for EUS-FNA from April 2013 to Sept 2013 were prospectively recruited. All patients were randomized to EUS-FNA performed with either the novel 25G EchoTip® ProCore™ (PrC) with a core trap and the standard 25G EchoTip® Ultra™ (Ult). Only a single pass was performed. The whole specimen was inserted into a formalin bottle and processed for histological analysis. All tissue samples were brought to one facility where experienced pathologists reviewed them. All samples were divided into three groups based on quality (rich, moderate, and poor cellularity). The tissue acquisition and diagnostic rates were assessed for different access routes and compared between the needles. Also, the diagnostic rates in three groups with different sample quality were compared.
RESULTS: A total of 214 patients were enrolled with 106 patients in the PrC and 108 in the Ult. The tissue acquisition rate for histological analysis was significantly higher in the PrC than the Ult (90.6% vs. 79.6%; p=0.025). The definite histological diagnosis achieved by the PrC was significantly higher than the Ult (81.1% vs. 69.4%; p=0.048). The samples of the PrC showed significantly superior quality than the Ult (rich: moderate: poor = 38: 29: 39cases in the PrC vs. 21: 28: 59cases in the Ult; p=0.003). In terms of tissue-sampling, the tissue acquisition rate of the PrC (46/50 cases; 92.0%) was significantly higher than that of the Ult (33/43 cases; 76.7%) in transduodenal EUS-FNA (p=0.04), although these values did not differ significantly in transgastric EUS-FNA. Overall sensitivity, specificity, and accuracy in pathological diagnosis of malignancy were 100%, 100%, and 100%, for rich group, 90%, 100%, and 92.5% for moderate group, 83%, 100%, and 84% for poor group respectively. The sensitivity and accuracy were significantly higher in rich group than moderate group (p =0.027, p =0.028) and significantly higher in rich group than poor group (p=0.003, p=0.002).
CONCLUSION: The novel EUS-FNA 25G needle with a core trap by a single pass offers significantly better sample quality for histological diagnosis of solid pancreatic tumors compared with the 25G standard needle, especially in transduodenal access. The high quality of EUS-FNA sample allows increasing accuracy for histological diagnosis.
Disclosure of Interest: None declared

OP060 USEFULNESS OF CONTRAST-ENHANCED ENDOSCOPIC ULTRASONOGRAPHY FOR DIFFERENTIAL DIAGNOSIS OF PANCEATIC SOLID LESIONS: A SINGLE-CENTER PROSPECTIVE STUDY

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INTRODUCTION: Recently, contrast-enhanced endoscopic ultrasonography (CE-EUS) has become available in the diagnosis of pancreatic lesions.
AIMS & METHODS: The aim of this study was to investigate the accuracy of CE-EUS in differentiating pancreatic ductal carcinoma from other lesions. Between, February 2009 and July 2013, we prospectively evaluated 147 patients with pancreatic solid lesions. After intravenous injection of a contrast agent (Sonazoid®), CE-EUS was performed using a radial-type endoscope. Pancreatic solid lesions were classified into three vascular patterns (hypervascular, isovascular, and hypovascular) on the basis of CE-EUS imaging, and these patterns were compared to the histological diagnosis.
RESULTS: The lesions were diagnosed as ductal carcinoma (n=109), acinor cell carcinoma (n=2), inflammatory mass (n=11), neuroendocrine tumor (NET) (n=8), autoimmune pancreatitis (AIP) (n=9), invasive intraductal papillary mucinous neoplasm (IPMN) (n=5), metastatic lesion (n=2; lung cancer 1, melanoma 1) or intraductal tubular tumor (ITT) (n=1) by operation, EUS-FNA, biopsy of liver metastasis, or international consensus diagnostic criteria for AIP. 104 of 109 ductal carcinomas were hypovascular patterns (95%), 8 of 9 AIPs were isovascular patterns (89%). 6 of 8 NETs were hypervascular patterns (75%). 8 of 11 inflammatory masses were isovascular patterns (73%). 3 of 5 invasive IPMNs were hypovascular patterns (60%). All 2 acinor carcinomas were isovascular patterns (100%). A hypovascular pattern, determined by CE-EUS, was calculated to diagnose ductal carcinoma with sensitivity and accuracy of 95% and 89%, respectively.
CONCLUSION: CE-EUS was useful for characterization of pancreatic solid masses with high sensitivity and accuracy.
Disclosure of Interest: None declared

OP061 LIQUID BIOPSY BASED ON CIRCULATING TUMOUR CELLS (CTC) DETECTION IS A DIAGNOSTIC AND PROGNOSTIC MARKER IN PATIENTS WITH PANCREATIC SOLID TUMOURS

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INTRODUCTION: The pancreatic cytology by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is considered as the standard procedure for the diagnostic of pancreatic tumour. We recently showed that detection of circulating tumour cells (CTC) had a diagnostic accuracy of 70% for pancreatic adenocarcinoma *(Am J Gastroenterol 2013;108:152-155)*. The aim of the study was to evaluate both diagnostic and prognostic impact of CTC detection in an extended series of patients referred for a EUS-FNA for a pancreatic solid tumour.
AIMS & METHODS: It was a single center study including all consecutive patients referred from 01/2011 to 07/2013 for a EUS-FNA procedure in a context of pancreatic solid mass. EUS-FNA was performed with a 22 gauge needle and analysed by two pathologists. A 10 ml peripheral blood sample was collected in each patient before the EUS-FNA procedure. Samples were filtered using the ScreencellsCyto method®, stained with Giemsa and analyzed by a cytologist blinded to clinical data and FNA results. The CTC detection was positive according to the presence of the following parameters: nuclear diameter > 7m, anisocytosis, membrane irregularities, presence of a large nucleolus.
RESULTS: A total of 69 patients were included. Amon them, 57 (83%) have a confirmed pancreatic tumours corresponding to 47 primitive adenocarcinoma, 4 others primitive tumours and 6 metastatic lesions. The sensitivity and the specificity of EUS-FNA was 83% and 100%, respectively. CTC were positive in 36/69 (52%) patients. The sensitivity and specificity of CTC was respectively 64.4% and 73.3% in patients with pancreatic cancer and 64.1% and 81.8% in patients with all types of cancer. The presence of CTC was significantly associated with the diagnosis of cancer (p=0.01) and with the presence of distant metastases (p=0.004). In contrast, tumour size, arterial involvement and CA19-9 serum level were not associated with CTC. The 18 months survival rate was significantly lower in patients with positive CTC as compared to those without detectable CTC (33 vs 44%, p=0.03).
CONCLUSION: Ours results highlighted that liquid biopsy based on circulating tumour cells (CTC) detection may be a diagnostic and prognostic marker in patients with pancreatic solid tumours.
REFERENCES
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Disclosure of Interest: None declared

OP062 EUS AND MRI AS SCREENING TOOLS FOR PANCREATIC CANCER: A COMPARATIVE PROSPECTIVE BLINDED ANALYSIS OF THEIR EFFECTIVENESS

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INTRODUCTION: Previous studies suggest that endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) are promising tests to detect asymptomatic, non-invasive precursor lesions and early stage pancreatic cancer (PC) in high-risk individuals (HRI). However, most studies were not performed in a blinded fashion. Therefore, it is still unclear which screening technique is to be preferred. We aimed to compare the effectiveness of EUS and MRI in a prospective blinded fashion in their ability to detect clinical relevant lesions in individuals at high risk for developing pancreatic cancer.
AIMS & METHODS: In the interim-analysis of this ongoing Dutch multicenter prospective study, the results of 139 asymptomatic HRI undergoing first time screening by EUS and MRI are described. HRI (>10% life time risk of PC) were defined as (1) mutation carriers of pancreatic cancer prone gene mutations and

(2) first-degree relatives of patients with familial pancreatic cancer. Clinical relevant lesions included all solid lesion, MB-IPMNs, and all cystic lesions ≥10mm and/or with malignant features. Results were compared in a blinded, independent fashion.
RESULTS: Clinical relevant lesions were detected by either EUS and/or MRI in 9 out of 139 HRI (6%). Within these 9 HRI, a total of 11 clinical relevant lesions were detected: 2 solid lesions and 9 cysts ≥10 mm. Both solid lesions were detected by EUS only, one 11 mm and one 7 mm lesion, which, after resection, proved to be a stage I adenocarcinoma and multifocal PanIN-2 lesions. Of the 10 cysts ≥10 mm, 6 were detected by both EUS and MRI and 3 were detected by MRI only. There was a slight agreement between EUS and MRI for the detection of clinical relevant lesions with a Kappa-value of -0.279 (55% agreement) and a good agreement between EUS and MRI for the location (Kappa 1.000, agreement 100%) and size of detected lesions (Spearman's rho 0.638).
CONCLUSION: EUS and/or MRI showed clinical relevant pancreatic lesions in 6% of high risk individuals. There was a slight agreement between EUS and MRI on detection of lesions was, however, on location and size a good to perfect agreement. EUS and MRI seem rather complementary of each other than corresponding: contrary to EUS, MRI proved very sensitive for cystic lesions, however, MRI might have some important limitations with regard to the timely detection of (small) solid lesions.
Disclosure of Interest: None declared

OP063 NEEDLE BASED CONFOCAL LASER ENDOMICROSCOPY (NCLE) FOR THE DIAGNOSIS OF PANCREATIC MASSES: CORRELATION BETWEEN PCLE AND HISTOLOGICAL CRITERIA (CONTACT STUDY)

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INTRODUCTION: Needle-based Confocal Laser Endomicroscopy (nCLE) is an imaging technique, which enables microscopic observation of solid organs, *in vivo* and in real-time, during an EUS FNA procedure. The CONTACT study (Clinical evaluation Of NCLE in The lymph nodes Along with masses and Cystic Tumors of the pancreas) aims at building an image atlas, and define interpretation criteria for nCLE images in the pancreatic masses.
AIMS & METHODS: 3 centres in France (7 investigators) took part in this prospective study.
34 patients with a pancreatic mass of unknown nature were included prospectively during the study (June 2012 to March 2013). There were 17 men, and 18 women, mean age 66 years, (range: 32-87 years old). The localization of the pancreatic masses was: head (17 cases), body (12 cases), tail (6 cases). Mean size was 30mm (+/- 9mm). The puncture of the mass was done in all cases with a 19G puncture needle with the nCLE probe preloaded. After examination of the track of the puncture by nCLE, aspiration was done in the same track to compare images and histological results. No complication occurred during the nCLE procedure or the puncture. A definitive histological diagnosis was obtained in 30/34 patients: adenocarcinoma (21 cases), fibrous stroma adenocarcinoma (1 case), neuroendocrine tumor (4 cases), pseudopapillary tumor (1), chronic pancreatitis (3 – diagnosis confirmed by a one year follow-up)).
Preliminary characteristic descriptive criteria were previously described [1].
To go further, nCLE sequences were re-visualized by two gastro-enterologists and two pathologists to compare, for each type of lesion, their findings to the pathology specimen.
RESULTS: During this review, normal pancreas shows an aspect of coffee beans corresponding to the histological structure of acinis.
Adenocarcinomas showed dark cells aggregates with pseudo-glandular aspects and straight hyperdense elements more or less thick. These criteria correlate with the histological structure of those tumors which are characterized by tumoral glands, surrounded by fibrosis in case of fibrous stroma tumor.
Neuroendocrine tumors showed a dense network of small vessels on a dark background, which fits with the histological structure based on cord of cells surrounded by vessels and by fibrosis in case of fibrosis area.
Chronic pancreatitis showed residual acinis, which corresponds to the pancreatic regression.
CONCLUSION: This preliminary classification of nCLE images obtained in pancreatic masses could help in the differentiation of adenocarcinomas and neuroendocrine tumors, and between malignant tumors from normal pancreatic tissue. nCLE could therefore facilitate the diagnosis of these lesions, by bringing *in vivo* microscopic information, in real-time.
REFERENCES
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Disclosure of Interest: None declared

OP064 DETECTION OF KRAS GENE MUTATION BY LIQUID BIOPSY IN PATIENTS WITH PANCREATIC CANCER

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INTRODUCTION: Circulating nucleic acids in plasma or serum have been considered to be a candidate for noninvasive cancer diagnosis which is called "liquid biopsy". However, conventional mutation detection assays have not been sufficiently sensitive, specific, nor quantitative for the clinical use, because the number of circulating tumor cells and serum free DNA with somatic mutations are very low compared to those of wild type. Newly developed technologies on digital PCR such as droplet digital PCR (ddPCR) and next generation sequence (NGS) have provided new insight to this area. The methods dramatically improve the detection rate of rare mutations and are able to quantify the mutant fraction among normal DNA molecules.
AIMS & METHODS: This study was designed to estimate the clinical utilities of genetic analysis for circulating DNA in serum with pancreatic cancer by droplet digital PCR (ddPCR) (QX200, Biorad). We compared KRAS mutation detected in endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) biopsy tissue DNA and in circulating serum DNA in 75 patients with pancreatic cancer admitted in our institute between January 2008 and December 2010. Codon12 KRAS mutations were examined by ddPCR to detect circulating serum DNA with rare mutations and compared with survival.
RESULTS: Median age of the patients were 66 years old. Two patients, 5 patients, and 68 patients were diagnosed as stage I/II, III and stage IV, respectively. KRAS mutations were detected in 74.7% (56/75) of the EUS-FNA tissue samples. The frequencies of the mutations at GTT, GAT, CGT, GCT, AGT and TGT in codon12 were 28/56 (50%), 22/56 (39.3%), 6/56 (10.7%), 0/56 (0%), 0/56 (0%) and 0/56 (0%), respectively. On the other hand, the rate of KRAS mutations in circulating serum DNA was 68% (51/75). The mutations at GTT, GAT and CGT in codon12 were 30/51 (58.8%), 29/51 (56.8%) and 4/51 (7.8%), respectively. Although the mutations detected in EUS-FNA samples were not completely matched to those in serum DNA, the frequencies of mutations were very similar between them (N.S.). Interestingly 12/75 (16%) circulating DNA showed multiple mutations at GTT, GAT and/or CGT, whereas EUS-FNA revealed only one kind of KRAS mutation. Survival was not different by KRAS mutations at GTT, GAT, CGT, GCT, AGT and TGT in EUS-FNA tissue DNA, but it was shorter in patients with KRAS mutation at GTT compared to others in circulating serum DNA analysis ($P < 0.01$).
CONCLUSION: Analysis of circulating DNA in serum is a new useful procedure to detect genetic mutations in pancreatic cancer. This method is simple and noninvasive, and may have great potential as a new strategy for the diagnosis of pancreatic cancer as well as to predict patients' survival. The findings in this study warrant further verification in other populations.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 14:00–15:30
CLINICAL AND MOLECULAR FACTORS IN OESOPHAGO-GASTRIC CANCER OUTCOMES – LOUNGE 5

OP065 SURVIVAL AFTER PATHOLOGIC COMPLETE RESPONSE IN PATIENTS WITH CANCER OF THE ESOPHAGUS OR GASTRO-ESOPHAGEAL JUNCTION

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INTRODUCTION: The preferred curative strategy for esophageal cancer patients with locally advanced tumors, but without distant metastases consists of esophagectomy with preceding chemo(radio)therapy (CRT). In 10-40% of patients who are neoadjuvantly treated, there is absence of viable tumor at the time of surgery (pathologic complete response (pCR)). The aim of the present study was to define the outcome of patients with a pCR and identify predictive factors for survival in this group.
AIMS & METHODS: Between March 1994 and September 2013 all consecutive patients with cancer of the esophagus or gastroesophageal junction who underwent esophageal resection after neoadjuvant chemo (radio) therapy were included in the present study. Multivariate Cox regression analysis was carried out to identify independent prognostic factors.
RESULTS: Of the 463 included patients, 86 (19%) patients had a pCR (pyT0N0M0R0) (54 men, 32 women, median age: 63yrs (range 33-82 years)). 48 (56%) patients had an adenocarcinoma. Eight (9%) patients underwent neoadjuvant chemotherapy and 78 (91%) underwent neoadjuvant chemoradiation therapy. During follow-up, 25 (29%) patients developed recurrent disease. Nineteen (76%) patients developed haematogenous metastases, 6 developed lymphatic metastases (of which 3 patients with a distant lymphatic location). 5-year disease free survival was 61%, 5-year overall survival was 58%. Cox regression analysis revealed no prognostic factor for any of the tested variables (sex, age, histologic subtype, tumor location, type of neoadjuvant therapy, cTNM stage).
CONCLUSION: Patients with a pathologic complete response have a relatively good survival. However, one third of these patients developed recurrent disease. Thus far it is unclear how these patients can be identified.
Disclosure of Interest: None declared

OP066 TUMOR MICROENVIRONMENT IN ESOPHAGEAL ADENOCARCINOMA: CD80 EXPRESSION PEAKS IN EARLY STAGES, IT IS ENHANCED BY NEOADJUVANT THERAPY AND IT IS AN ACCURATE PREDICTOR OF SURVIVAL

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INTRODUCTION: Esophageal adenocarcinoma (EAC) is an increasingly common cancer with a poor prognosis. EAC microenvironment is characterized by lack of cytokines with anti-cancer effect and by high expression of immunosuppressive factors. The aim of the study is to characterize the antigen presenting cells (APC) and lymphocyte function in EAC investigating their relationship with stage, response to neoadjuvant therapy and prognosis.
AIMS & METHODS: Mucosa samples from cancer and from healthy esophagus were obtained during esophagectomy from 64 patients affected by EAC. Frozen samples were analysed with Real Time qPCR for costimulatory molecules (Cd80, Cd86), and lymphocytes activation (Cd38, Cd69) genes expression. Immunohistochemistry for CD8 and NK cells cytolytic activity (CD107a) of tumor infiltrating lymphocytes and for CD80 was performed. Flow cytometry for epithelial cells (Cytokeratine+Cd80+ and Cytokeratine+HLA-ABC) acting as APC and activated (CD8+Cd28+ and CD8+CD38+) tumor infiltrating lymphocyte (TIL) was performed. Non parametrical statistics, survival analysis and ROC curve analysis were used.
RESULTS: In normal mucosa a lower level of epithelial cells expressing HLA-ABC compared to neoplastic tissue was observed (p=0.02) but the rate of CD80+epithelial cells was similar (p=0.61) and well as the rate of activated CD8 lymphocytes. In normal mucosa, a significant upregulation of Cd80 mRNA expression in patients who underwent neoadjuvant therapy compared to that from patients who had no neoadjuvant therapy was observed (p=0.02). Immunohistochemistry showed a high level of CD80 expression in normal mucosa of patients with stage I EAC compared to stage III and to yT0N0 (p=0.02). A similar peak was observed in CD38 mRNA levels (p=0.02). Patients with CD80+ normal mucosa survived significantly longer than CD80- patients (p=0.02) while the stage distribution of the two groups was equivalent (p=0.69). CD80 expression in normal mucosa had a great accuracy in predicting cancer-related deaths (AUC=0.87 (95% CI=0,68-0,96): p=0.001).
CONCLUSION: In EAC, tumor cells expressed more HLA-ABC but their CD80 expression was similar to normal tissue levels confirming an impaired APC function in cancer tissue. Neoadjuvant therapy seemed to induce a high expression of CD80 in healthy mucosa suggesting an APC activation. CD80 expression was highest in stage-1 EAC and this peak expression corresponded to a peak in lymphocyte activation. Finally, CD80 expression in normal mucosa resulted an accurate predictor of postoperative survival suggesting its possible role as a biomarker in EAC management.
Disclosure of Interest: None declared

OP067 TRANSCRIPTIONAL FACTORS FOR EPITHELIAL-MESENCHYMAL TRANSITION ARE ASSOCIATED WITH PATHOGENESIS OF CARCINOSARCOMA OF THE ESOPHAGUS: WITH EVIDENCE OF MONOCLONAL ORIGIN BY TP53 MUTATIONAL ANALYSIS

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INTRODUCTION: Carcinosarcoma of the esophagus is a rare malignant neoplasm composed of both carcinomatous and sarcomatous elements. The histogenesis of sarcomatous and carcinomatous components of the tumor has not been elucidated. Epithelial-mesenchymal transition (EMT) is the conversion of cells with an epithelial phenotype into cells with a highly motile fibroblastoid or mesenchymal phenotype[1]. It is unclear whether EMT is involved in sarcomatous differentiation in carcinosarcoma of the esophagus.
AIMS & METHODS: We carried out immunohistochemistry for Slug, Twist, ZEB1 and ZEB2, genes associated with EMT[1], in 14 cases of carcinosarcoma of the esophagus to assess whether there is evidence of expression of these genes. We also performed immunohistochemical analysis for E-cadherin, whose loss of expression is considered as the key step of EMT[1]. The staining of Slug, Twist, ZEB1, ZEB2 and E-cadherin was scored as follows: -, 0% of positive cells; +, 1-10%; ++, 11-50%; +++, 51-80%; ++++, >80%. To verify the neoplastic nature of sarcomatous components, we examined monoclonality between carcinomatous and sarcomatous components comparing *TP53* mutation status and p53 expression of both areas by DNA sequencing and p53 immunohistochemistry, respectively.
RESULTS: Nuclear ZEB1 was significantly more widely expressed in the sarcomatous component ($P < 0.0001$). Twelve cases showed ZEB1 expression in > 80% neoplastic cells in the sarcomatous component. In contrast, neoplastic cells in carcinomatous components were negative in these 12 cases. Nuclear Twist was also significantly more widely expressed in the sarcomatous component ($P = 0.0256$). Membranous E-cadherin was significantly more widely expressed in the carcinomatous component in all cases ($P < 0.001$), and neoplastic cells in the sarcomatous component were largely negative. Nuclear Slug and ZEB2 expression showed no significant difference between carcinomatous and sarcomatous components ($P = 0.1379$, $P = 0.1292$, respectively). *TP53* mutation analysis was carried out in 13 cases. Seven cases had mutations in both carcinomatous and sarcomatous components and the mutations patterns were identical. One case had mutation only in sarcomatous components. p53 immunohistochemical study was carried out for all 14 cases. Immunohistochemistry detected moderate to strong p53 expression in 6 cases, and the sarcomatoid and epithelial tumor components showed almost concordant p53 expression patterns and intensities, except one case that had mutations only in sarcomatous components. Of these 6 cases, 4 cases harbored *TP53* mutations.
CONCLUSION: We found that ZEB1 and Twist were significantly widely expressed in the sarcomatous component, and the expression of E-cadherin in the sarcomatous area was lost. We also detected identical *TP53* mutation patterns and nuclear p53 immunohistochemical staining in both carcinomatous and sarcomatous components. These findings suggest that this uncommon tumor has a monoclonal origin and support the hypothesis that EMT may play an important role in the pathogenesis of carcinosarcoma of the esophagus, mainly through ZEB1 and Twist expression.
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Disclosure of Interest: None declared

OP068 THE THERAPEUTIC EFFECT OF IRREVERSIBLE ELECTROPORATION ACCORDING TO TISSUE PROPERTIES OF UPPER GASTROINTESTINAL TRACT: GENE EXPRESSION SIGNATURE ANALYSIS

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INTRODUCTION: Irreversible electroporation (IRE) is a promising novel technique for the ablation of tumors. IRE has an advantage over other ablation techniques in its mechanism to remove undesired cells by affecting the cell membrane without thermally destroying blood vessels, nerves and the surrounding tissues. This therapeutic modality has been considered to apply to Barrett's dysplasia or epithelial neoplasm of upper gastrointestinal tract instead of previous radiofrequency ablation. Recently, we have validated the effectiveness of IRE tissue ablation on stomach, but there was no study about treatment effect of IRE according to tissue property in upper gastrointestinal tract. Our purpose was to study effectiveness of IRE according to tissue properties in rat stomach.
AIMS & METHODS: The Sprague-Dawley rats were used throughout this study. IRE ablation was applied in upper stomach (squamous cell epithelium) and lower stomach (columnar cell epithelium) with same energy parameters. The energy delivered for each ablation was 50/100 pulses of 1KV/cm ~ 3KV/cm. All samples for histologic analysis and tunnel assay were got at 0hrs, 10hrs, 24hrs and 72hrs after IRE. And we used DNA microarrays to measure the expression levels of large numbers of genes in rat stomach according to different electrical energy. And we measured several apoptotic gene expression using real time RT-PCR.
RESULTS: All animals survived for their designated times. H-E staining showed extensive cell death area, which were proved by a pyknotic nucleus and eosinophilic cytoplasm near absence of cell at 10 hours after IRE ablation in upper (squamous cell epithelium) and lower (columnar cell epithelium) gastric tissue. We confirmed apoptotic cell death by Tunnel assay. The number of significantly up-regulated apoptotic genes was higher in 2KV, 100 pulse and 10hr than that of other electrical energy groups. The significantly up-regulated genes related to apoptosis after IRE ablation in all IRE setting were s100a8/9, Ccl2, Timp1. Aif1, Lcn2, hspb1 genes, but caspase-related genes were down-regulated in all condition.
CONCLUSION: This study showed that IRE ablated stomach tissue through cellular apoptosis. And the degree of apoptosis after IRE ablation was tissue and electric energy specific in gastrointestinal tract. This study suggests the potentiality of IRE application in the treatment of not only gastric neoplasm but also esophageal neoplasm including dysplasia of Barrett's esophagus without metastasis.
Disclosure of Interest: None declared

OP069 THE RELEVANCE OF THE LOCATION OF INVOLVED NODES IN PATIENTS WITH CANCER OF THE DISTAL ESOPHAGUS OR GASTRO-ESOPHAGEAL JUNCTION

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INTRODUCTION: Truncal node metastases as well as lymphatic dissemination in the proximal field (subcarinal, paratracheal and aortopulmonary window lymph nodes) after neoadjuvant chemoradiation therapy does not alter the TNM classification. The incidence and impact of these relatively distant lymph node metastases on long-term survival remains unclear. Therefore the aim of the present study is to identify the incidence and prognostic significance of the location of lymph node metastasis in patients who underwent neoadjuvant chemoradiation therapy followed by a transthoracic esophagectomy (TTE).
AIMS & METHODS: Between March 1994 and September 2013 a total of 286 consecutive patients with cancer of the mid-to-distal esophagus or gastroesophageal junction (GEJ) who underwent potentially curative esophageal resection after neoadjuvant chemoradiation therapy were included.
RESULTS: The majority of patients was male (219 patients, 76.6%) and had an adenocarcinoma (208 patients, 72.7%). The tumor was located in the mid-esophagus in 53 (18.5%), in the distal esophagus in 210 (73.4%) and at the GEJ /

cardia in 23 (8.0%) patients. 279 (97.6%) patients underwent a radical (R0) resection. 112 (39.2%) patients had a complete or near complete pathologic response (tumor regression grade 1 or 2). 110 (38.5%) patients had nodal metastases in the marked resection specimen. 63 (22.0%) patients were classified as N1, 33 (11.5%) patients as N2 and 14 (4.8%) patients as N3. Of the patients with tumorpositive lymph nodes, 40 (36.4%) patients had metastases localized in locoregional nodes, 35 (31.8%) patients had localisation of metastases in at least one truncal node, 14 (12.7%) patients had positive nodes in the proximal field and 5 (4.5%) patients had positive truncal nodes as well as positive proximal lymph nodes. Median disease free-survival was 90.3 months for N0 patients, 65.7 months for patients with nodal metastases limited to locoregional nodes, 18.8 months for patients with truncal nodes, 15.4 months for patients with lymph node in the proximal field and 10.1 months if nodes were positive in both the truncal and the proximal field. In multivariate analysis yN stage as well as location of lymph nodes were independently associated with a worse survival.
CONCLUSION: The present study demonstrated that the location of positive nodes after neoadjuvant chemoradiation therapy harbors important prognostic information.
Disclosure of Interest: None declared

OP070 ADIPOSE TISSUE PROMOTES PROLIFERATION, DIFFERENTIATION AND INVASION OF ESOPHAGEAL SQUAMOUS CELL CARCINOMA IN VITRO

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INTRODUCTION: Esophageal squamous cell carcinoma (ESCC) develops within squamous epithelial layer, and progressively invades into submucosal to subadventitial layers. Given that abundant adipose tissue exists in the subadventitia, adipose tissue seems critical for the progression of ESCC. However, their interaction is unknown.
AIMS & METHODS: We aimed to address an interaction between ESCC and adipose tissue *in vitro*. ESCC cells (well and poorly differentiated types, EC-GI-10 and TE-9, respectively) were cultured on rat or human subcutaneous adipose tissue-embedded or -nonembedded collagen gel. Culture assembly was analyzed by electron microscopy, immunohistochemistry, Western blotting, ELISA and small interfering RNA (siRNA) transfection, in terms of cell survival, growth, differentiation and invasion.
RESULTS: Adipose tissue promoted the expression of the growth markers, Ki-67 antigen and bromodeoxyuridine (at 24 h-labeling) in the cancer cell types, whereas it inhibited that of the apoptosis marker, cleaved caspase-3. Adipose tissue promoted the basal and superficial expression of the differentiation markers, p63 and involucrin, respectively, within the epithelial layer formed by cancer cell types. Adipose tissue accelerated the invasion of cancer cell types into the gel, together with increased expression of filamin A, laminin-5 and membrane type 1-matrix metalloproteinase (MT1-MMP), and with decreased display of E-cadherin. Adipose tissue promoted the expression of mitogen-activated protein kinase (MAPK: pERK1/2) and phosphoinositide 3-kinase-AKT (PI3K-AKT: pAKT1/2/3, p4E-BP1 and pS6) pathways, and insulin-like growth factor-1 receptor (IGF-1R) in the cell types, while it decreased that of human epidermal growth factor receptor 2 (HER2). Cancer cell types in turn decreased IGF-1, adiponection, leptin and registin production in adipose tissue. IGF-1 (10 nM) promoted the growth of cancer cell types, while IGF-1R inhibitor (picropodophyllin, 1 μM) enhanced the apoptosis. Finally, IGF-1R siRNA-transfected EC-GI-10 cells did not replicated the adipose tissue-induced phenomena above.
CONCLUSION: The data suggest, first, that adipose tissue may influence the progression of ESCC with the increased growth/invasion and the decreased apoptosis through MAPK, PI3K-AKT and IGF-1R up-regulation, although adipose tissue seems to induce the differentiation of the cancer cells; second, that adipose tissue may adversely affect the HER2-targeted therapy; and third, that the cancer cells may affect adipokine production of adipose tissue. Collectively, we conclude that adipose tissue may be involved in the progression of ESCC under adipose tissue-cancer cell interaction.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 14:00–15:30
OBESITY AND THE GUT – LOUNGE 6

OP071 ACCELERATED INTESTINAL GLUCOSE ABSORPTION IN MORBID OBESITY – RELATIONSHIP TO GLUCOSE TRANSPORTERS, INCRETIN HORMONES AND GLYCAEMIA

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INTRODUCTION: Glucose absorption in the small intestine is mediated by sodium dependent glucose co-transporter 1 (SGLT-1) and glucose transporter-2 (GLUT2), and is potentially linked to sweet taste receptor (STR) signaling and incretin hormone secretion. Both glucose absorption and expression of SGLT-1 are increased in obese rats, but human data are lacking.
AIMS & METHODS: This study aimed to examine intestinal glucose absorption in morbidly obese humans, and its relationship to glycemia, incretin responses, and expression of SGLT-1, GLUT2, and STR.
Methods: 17 non-diabetic, morbidly obese subjects (5M:12F; 45 ± 3yrs, BMI: 48 ± 4kg/m2) and 11 lean controls (10M:1F; 44 ± 6yrs, BMI: 25 ± 1kg/m2) underwent endoscopic duodenal biopsies immediately prior to intraduodenal (ID) glucose infusion (30g glucose over 30 min, with 3g 3-O-methylglucose (3-OMG) to assess glucose absorption). Blood glucose and plasma concentrations of 3-OMG, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), insulin, and glucagon were measured over 270 min. Absolute expression of duodenal SGLT-1, GLUT2 and STR transcripts was quantified by PCR.
RESULTS: The rise in plasma 3-OMG ($P<0.001$) and blood glucose ($P<0.0001$) were greater in obese than lean subjects. Plasma 3-OMG was directly correlated with blood glucose ($r=0.78$, $P<0.01$). After ID glucose, plasma GIP ($P<0.001$), glucagon ($P<0.001$), and insulin ($P<0.001$) were higher, but GLP-1 ($P<0.001$) was less, in the obese than in the lean. Expression of SGLT-1 ($P=0.035$), but not GLUT2 or T1R2, was higher in the obese than lean subjects, and was related to peak plasma 3-OMG ($r=0.60$, $P=0.01$), GIP ($r=0.67$, $P=0.003$) and insulin ($r=0.58$, $P=0.02$).
CONCLUSION: In morbid obesity, proximal intestine glucose absorption is accelerated and related to increased SGLT-1 expression, leading to an incretin profile that promotes hyperinsulinemia and hyperglycemia. These findings are consistent with the concept that accelerated glucose absorption in the proximal gut underlie the *foregut theory* of obesity and type 2 diabetes.
Disclosure of Interest: None declared

OP072 IMPACT OF A 2-WEEK VERY LOW CALORIE DIET (VLCD) ON GLUCOSE SENSING, ABSORPTION, TRANSPORTERS, INCRETIN HORMONES AND GLYCEMIA IN MORBIDLY OBESE HUMANS

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INTRODUCTION: Glucose absorption is accelerated in the proximal intestine of morbidly obese humans, which is associated with increased expression of sodium dependent glucose co-transporter 1 (SGLT1), an altered incretin profile, hyperinsulinemia and hyperglycemia (Nguyen et al. DDW 2014).
AIMS & METHODS: This study aimed to examine the effects of energy restriction on glucose absorption, expression of intestinal glucose transporters and sweet taste receptors (STR), incretin hormone responses and glycemia in the morbidly obese.
14 morbidly obese subjects (BMI: 46±3kg/m2) were studied before and after a 2-week VLCD (750kcal/day). On each occasion, endoscopic duodenal biopsies were collected before and after a 30-min duodenal glucose infusion (30g glucose with 3g 3-O-methylglucose (3-OMG)). Measurements of blood glucose, plasma 3-OMG, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), insulin, and absolute expression of SGLT-1, GLUT2 and STR (T1R2) transcripts obtained.
RESULTS: Fasting expression of T1R2 (-54±22%, $P=0.03$), SGLT1 (-30±7%, $P=0.004$) and GLUT2 (-50±15%, $P=0.008$) were markedly reduced after 2 weeks VLCD, which were associated with reductions in fasting blood glucose (-0.5±0.1mmol/L, $P=0.02$), insulin, GIP and GLP-1, body weight (-5.6±0.5kg, $P<0.001$), and HbA1c (-0.32±0.08%, $P=0.001$). Although intra-duodenal glucose had no impact on T1R2, SGLT1 and GLUT2 expression prior to VLCD, it increased the expression of T1R2 (45±30%, $P=0.03$) and GLUT2 (57±14%, $P=0.003$) after 2-wk VLCD. The blood glucose ($P=0.002$) and plasma insulin ($P=0.002$) responses to intra-duodenal glucose were all reduced after VLCD, while plasma 3-OMG and GLP-1 concentrations were unchanged. The peak plasma 3-OMG (at ~60min), however, was higher after VLCD (0.57±0.04 vs. 0.51±0.04mmol/L; $P=0.05$) and was associated with a small elevation of plasma GIP ($P=0.03$) at 60 to 90 min after glucose stimulation.
CONCLUSION: In morbid obesity, both fasting and glucose-stimulated expression of intestinal STR and glucose transporters are modulated by short-term VLCD. Further studies with inhibitors of STR and glucose transporters are warranted to determine whether the changes in STR and GTs expression, rather than the associated weight loss, are responsible for the observed glycemic and incretin responses.
Disclosure of Interest: None declared

OP073 EFFECTS OF VERTICAL SLEEVE GASTRECTOMY (VSG) AND CALORIC RESTRICTION BY DIET ON GLUCOSE METABOLISM IN OBESE PATIENTS WITH TYPE 2 DIABETES

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INTRODUCTION: Vertical sleeve gastrectomy (VSG) effectively induces weight loss and ameliorates hyperglycemia making it a successful treatment option for obese diabetic patients. However, the exact mechanisms underlying its efficacy and a direct comparison with a dietary intervention to mimic these effects are elusive. Hence, we thought to compare the regulation of glucose metabolism before and after a hypolcaloric diet (HD) or VSG in morbidly obese patients with type 2 diabetes.
AIMS & METHODS: Obese diabetic subjects were studied before as well as 3 months after VSG (N 9, BMI 54.2 kg/m^2, HbA1c 7.0%) or a HD (14, 45.6 kg/m^2, 6.7%). During each visit a hyperinsulinemic euglycemic clamp to determine

insulin sensitivity as well as a hyperglycemic clamp 100 mg/dl above basal glucose was performed. After 120 min of stable hyperglycemia 50 ml of a liquid meal with 13C-acetate was consumed while constant hyperglycemia was maintained. This allowed determining insulin in response to glucose during fasting as well as in a postprandial state. Furthermore, postprandial changes in gut hormones, gastric emptying and the incretin effect (greater insulin secretion in response to intestinally delivered glucose over iv-glucose) were determined. Additionally, sensations of satiety, fullness, gastric distension and nausea were recorded by a visual analogue scale (VAS).
RESULTS: Change in BMI, absolute weight loss and %>weight loss was significantly more pronounced in the VSG-group than after HD (18.9±1.0% vs. 8.8±0.5%, $p<0.001$). While the relative reduction of fasting glucose was greater in the VSG-group (150±13 to 100±8 mg/dl vs. 132±6 to 114±6 mg/dl, $p<0.05$) absolute values did not differ 3 months after the intervention. Similarly, insulin resistance and insulin secretion in response to iv-glucose improved markedly in both cohorts but were not significantly different after diet or VSG. However, after the meal insulin secretion was significantly more pronounced (4.7±0.9 vs. 2.2±0.2-fold increase over fasting, $p>0.01$) in the VSG group than after diet. Furthermore, the incretin effect (71±7 vs. 48±6%, $p<0.05$) was significantly greater 3 months after VSG compared with diet alone. This was associated with significantly higher postprandial levels of incretin hormones, more rapid gastric emptying and greater satiety in the operated subjects.
CONCLUSION: These results suggest that HD in the short term results in a number of beneficial effects on glucose metabolism similar to VSG, particularly in the fasting state (insulin resistance, glucose stimulated insulin secretion, fasting glucose). However, in the postprandial state VSG mediates additional metabolic effects that cannot be mimicked by caloric restriction per se. Particularly the faster rate of gastric emptying and the higher levels of anorexigenic gut hormones as well as the more pronounced insulin response seem to be responsible for the favorable and more durable effects of bariatric surgery compared to dietary interventions.
Disclosure of Interest: None declared

OP074 IMPAIRED GLUCOSE REGULATION IN OBESE SUBJECTS: THE LINK TO HYPERINSULINEMIA IN OBESIY?

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INTRODUCTION: An important clinical finding in obesity is insulin resistance. The potential influence of gastric emptying on the incretin effect mediated by GIP and GLP-1 has not been defined. In healthy subjects, the incretin effect during an oral glucose tolerance test increases with the size of glucose load, resulting in similar glucose excursions independently of the glucose loads. Whether patients with obesity are able to regulate their incretin effect through gastric emptying is unknown.
AIMS & METHODS: A total of 24 non-diabetic obese (12 male and 12 female, BMI $\geq$ 30 kg/m^2) and 24 lean control (12 male and 12 female, BMI between 18.5 and 25.0 kg/m^2) subjects were included. The study was conducted as a randomized, double-blind, parallel-group trial. Subjects received intragastric infusions of different glucose concentrations (10g, 25g and 75g glucose). The test solutions were labelled with ^{13}C-sodium acetate for determination of gastric emptying rates. Plasma samples were collected for insulin, glucose, glucagon, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP) and peptide tyrosine tyrosine (PYY) analysis.
RESULTS: Obese subjects had significantly higher fasting insulin ($P<0.001$) and glucose ($P=0.005$) levels resulting in a markedly higher HOMA index ($P<0.001$). Patients with obesity exhibited higher peak plasma glucose and insulin levels in response to increasing oral glucose loads, whereas no differences in peak plasma glucose values among control subjects were observed. Fasting as well as postprandial glucagon levels were significantly above the levels of the lean control group ($P<0.001$, respectively). In the obese group, a trend for decreased secretion of GLP-1 and PYY was observed after 75g glucose. Equal and progressively delayed gastric emptying due to the increasing loads was found in both groups, but gastric emptying rates of the different glucose loads were significantly delayed in obese subjects ($P\leq0.001$, respectively) compared to healthy controls.
CONCLUSION: In healthy subjects, glucose metabolism is largely determined by gastric emptying rates. Patients with obesity are characterized by impaired gastric emptying with consecutive changes in glucose regulatory hormone secretions, which may contribute to the exaggerated glucose excursions after oral ingestion of glucose in these patients. We conclude that these changes are important pathophysiological steps in the development of metabolic syndrome in obesity.
Disclosure of Interest: None declared

OP075 BITTER TASTE RECEPTOR T2R38 EXPRESSION IN THE COLON OF OVERWEIGHT/OBESE AND LEAN SUBJECTS

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INTRODUCTION: The sense of taste is important to evaluate the quality of nutrients and distinguish between safe and dangerous food prior to ingestion. in particular, bitter taste has evolved as a warning mechanism against toxic or harmful chemicals. Transcripts for bitter taste receptors (T2Rs) and their signaling molecules are distributed to the mucosa of the mammalian gastrointestinal (GI) tract including humans and are expressed by enteroendocrine cells (EECs). Intraluminal bitter tastants actiate vagal afferent neurons, induce avoidance and affect feeding behavior and gastric emptying. Bitter tastants also induce release of cholecystokinin (CCK) and glucagon like peptide 1 (GLP1) from EECs, peptides that are involved in GI chemosensing. We have shown that T2R subtypes are differentially regulated in the mouse GI tract by diet manipulation and that T2R138 expression is upregulated by long-term high fat diet, which is known to alter the gut microflora and is associtated with chronic low grade inflammation.
AIMS & METHODS: Test whether T2R38 expression is altered in the mucosa of overweight or obese healthy subjects compared to lean subjects and to characterize the cell types expressing T2R38 in human colonic mucosa.
Methods: Colonic mucosal biopsies were obtained during screening sigmoidoscopy from 30 volunteers: 15 overweight to obese (OW/OB) (8 males and 7 females; 20-55 year-old; mean BMI 32±0.7 kg/m^2) and 15 normal weight (NW) (7 males and 8 females; 22-55 year-old; mean BMI 20±0.5) subjects. Biopsies were processed for quantitative qRT-PCR using Taqman Gene expression assays with hT2R38 and 18S RNA as the reference gene, and immunohistochemistry. For double immunolabeling, the following antibodies were used: rabbit anti-T2R38 (1:2,000), goat anti-chromogranin (CgA, 1:600, a generalized marker for EECs), mouse anti- GLP-1 (1:1,000), mouse anti-CCK (1:1,000), and guinea pig anti-peptide YY (PYY, 1:600).
RESULTS: The levels of hT2R38 mRNA in the mucosa of OW/OB subjects were markedly increased compared to those in the mucosa of NW subjects (4.20±0.9 vs. 1.68±0.5, respectively, $P<0.05$). T2R38 immunoreactivity (-IR) was localized to EECs as shown by their labeling with CgA. T2R38-IR cells coexpressed CCK-, GLP1- or PYY-IR. The number of T2R38/CgA cells in the OW/OB group was significantly increased compared to lean controls (124.5±15.9 vs. 55.88±8.0 in 3.36 mm^2, respectively) ($P<0.006$). There was an increase in T2R38/GLP1 and T2R38/CCK cells in OW/OB vs. NW subjects (51±14.2 vs. 24.6±3.9, and 34.0±6.4 vs. 19.6±6.5, respectively) whereas there was no difference in the number of T2R38/PYY cells in OW/OB vs. NW subjects (8.6±2.1 vs. 9.2±4.8).
CONCLUSION: T2R38 upregulation observed in overweight / obese subjects might be due to changes in luminal content including alteration of microbiome that has been associated with obesity. This is consistent with the proposal that T2R38 is activated by food-born toxins and quorum-sensing molecules released by bacteria to initiate a protective response, which could involve the release of gut hormones such as GLP1, CCK and PYY.
Disclosure of Interest: None declared

OP076 STABLE GENOMIC INTEGRANT OF E. COLI NISSLE 1917 (ECN) AS NATURAL ALTERNATIVE TO ALLEVIATE SUCROSE INDUCED METABOLIC EFFECT

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INTRODUCTION: Implementation of probiotics in the field of therapies is sustaining in the market since decades. Against the various drug based treatments available in the market, probiotics proves to be significantly safe and efficient towards the most commonly prevailing clinical outcomes. Risk factors are relatively high in metabolic diseases associated with sugar consumption. These metabolic effects can be attributed to hypertension, hypertriglyceridemia oxidative stress and many more. EcN has been promising probiotic with unique characteristics *i.e.* antimicrobial activity, lack of endotoximia.
AIMS & METHODS: To achieve stable expression of Vitreoscilla Hemoglobin (*vgb*), Green fluorescent protein (*gfp*), pyrroloquinoline quinone (*pqq*) and inulosucrase (*inuJ*) in EcN for alleviating metabolic effect induced by dietary sucrose. Stable genomic integration was carried out by Tn7 mediated integration system. Male Charles foster rat weighing 180-220 grams were fed with 20% sucrose in drinking water for 70 days. Modified EcN was given 10^{9}CFU/per week. Antioxidant enzyme activity, serum insulin, serum and hepatic lipid profile, short chain fatty acid (SCFA) analysis and liver oil red O staining was used to assess metabolic syndrome. Expression of FAS, ACOx and Mitochondrial to nuclear DNA ratio was quantified in liver by real time PCR.
RESULTS: Genomic integrants of EcN:: *vgb-gfp-pqq-inuJ* were confirmed by loss of ampicillin resistance and PCR. PQQ quantification, formation of red colour in Tris buffered media and growth on sucrose was monitored to check the functionality of *inuj-pqq* gene. Rat fed with 20% sucrose in drinking water developed clinical characteristics of metabolic syndrome including increased plasma glucose, triglycerides and oxidative stress (Blood and Hepatic) in comparison to control group. In addition, they showed increased liver lipid accumulation, compared to chow fed controls. mRNA expression of FAS was found to be significantly increased and ACOx was decreased in sucrose fed rats without probiotic supplementation. EcN:: *vgb-gfp-pqq-inuJ* administration restored clinical characteristics of metabolic syndrome to almost normal levels. In addition, EcN:: *vgb-gfp-pqq-inuJ* showed significant increase in colonic SCFA (Acetic acid, propionic acid and butyric acid) on comparison with all other groups.
CONCLUSION: Modified probiotic EcN:: *vgb-gfp-pqq-inuJ* can suppressed dietary sucrose induced metabolic effects, therefore, may provide an natural alternative for dietary sucrose induced metabolic syndrome.
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Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 15:45–17:15
HOT TOPICS FROM LATIN AMERICA – HALL F1

OP077 INTRAGASTRIC BALLOON IN PREPARATION FOR BARIATRIC SURGERY PATIENTS

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INTRODUCTION: It is well established that the loss of at least 10% of initial weight or 25% of overweight in pre-bariatric surgery significantly improves the comorbidities of morbid obese patients.
The use of pharmacotherapy can promote mild weight loss, but carries a greater risk to the patient for possible side effects of many medications. High failure rates (between 90 and 98%) have been reported in the literature.
With the high rates of failure of less invasive therapies using new techniques in the preparation of these patients is necessary. A considerable option is the use of the intragastric balloon (BIG).
AIMS & METHODS: The aim of this study is to evaluate the weight loss induced by gastric balloon preoperative bariatric surgery.
Retrospective study of patients from clinics in Sao Paulo and Belo Horizonte. All patients were evaluated with greater than 45 kg / m^2 who chose to put the BIG weight loss prior to bariatric surgery between January 2008 to December 2013 and remained with the BIG BMI at certain time (6 months). Of the 38 patients, 19 (76.32%) were female and 9 male (23.68%). All participants were over 18 years old.
RESULTS: The mean initial weight of these patients was 143kg (+25.70), and initial BMI was 50.52 kg / m^2 (+7.86). After removal of the BIG average final weight was 111.2 kg (+17.5), with the final BMI of 42.49 kg / m^2 (+6.68). The weight loss during the treatment period, on average, was 25.3 kg (+12.7), which represented 17.4% (+00,6) of initial weight. Thus we found a loss of 31.86% (+9.65) of the initial excess weight and a final BMI of 42.49 kg / m^2 (+6.68) after six months of using BIG. The values in parentheses correspond to the standard deviation.
CONCLUSION: We observed that there was an average weight loss of 25.3 kg and 31.86% overweight, considerably reducing the BMI of the patients. The reduction of at least 10% of the initial or 25% overweight weight was achieved in 100% of patients. Thus we conclude that the BIG is an excellent therapeutic option for weight loss for morbidly obese patients undergoing bariatric surgery.
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Disclosure of Interest: None declared

OP078 PENTAX RETROVIEW™ COLONOSCOPE FOR THE EVALUATION OF COLON MUCOSA IN FORWARD AND RETROVIEWING: A SAFETY AND FEASIBILITY PILOT STUDY

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INTRODUCTION: Colonoscopy is the gold standard for inspection of the colon, but it offers incomplete visualization of the proximal aspects of colonic haustral folds, flexures or valves. Recent studies indicate that retroflexing in the right colon or the use of retrograde viewing devices can provide a more thorough examination, with improvements in polyp detection reported. However, limitations as: absence of high definition (HD) vision, use of a second equipment and no therapeutic possibility is reported. A new colonoscope RetroView (RV) (PENTAX Medical) with a 4 cm retroflexed radius and 3.2 mm working channel may allow withdrawal from the cecum to rectum in segmental retroflexion and provide therapeutic access.
AIMS & METHODS: To test the feasibility and safety of segmental retroflexion with the RV colonoscope throughout the entire colon.
Methods: In this single centre, one operator, prospective study, the RV colonoscope was advanced to the cecum in the forward view in all enrolled patients, after approval by the ethics committee and signing of an informed consent. Withdrawal colonoscopy was performed in retroflexion until the hepatic flexure, at which point the distal tip was straightened and readvanced to the cecum and withdrawn in forward view through the hepatic flexure. RV was again retroflexed and the withdrawal pattern was repeated by segment (transverse, left, sigmoid and rectum). Data was collected on cecal intubation rate, segmental retroflexion success, total procedure time, time to cecum, total withdrawal time, lesions detected in retroflexion, biopsy/therapeutics performed while retroflexed and adverse events.
RESULTS: Forty-eight consecutive screening, surveillance or diagnostic patients underwent colonoscopy {64% (31/48) female with mean age of 55}. Cecal intubation was achieved in 48/48 pts (100%). Retroflexed withdrawal success: right colon 47/48 (98%), transverse colon 48/48 (100%), left colon 48/48 (100%), sigmoid colon 39/48 (81%), rectum 48/48 (100%). Total mean procedure time was 16.5 mins and mean withdrawal time was 9.81mins. 31% more lesions (3 ulcers, 12 polyps, 9 diverticules, 2 erosions, 6 vascular ectasia, 1 papiloma and 1 hemorrhoid) were seen in retroflexion that were not seen in forward view, including 67% (6/9) more adenomas: 2 in right colon (10mm, 10mm) and 4 in transverse colon (7mm,10mm,10mm, 15mm). Therapeutics, including biopsy, endoscopic mucosal resection and argon plasma coagulation were performed successfully (100%) in retroflexed position in all attempted patients. Adverse event post-procedure (abdominal pain) was observed in 1/48 cases (2%).
CONCLUSION: In this single centre, single operator study, segmental retroflexion with the RetroView throughout the colon was safe, allowed performance of retroflexed biospies/therapeutics, increased the number of lesions found by 31% and the number of adenomas by 67% compared to forward view alone.
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Disclosure of Interest: C. Robles-Medranda Consultancy for: Pentax Medical, MaunaKea technologies, M. Soria: None declared, A. Oropeza: None declared, F. Abarca: None declared, F. Abarca Rendon: None declared, J. Ospina: None declared, G. Bravo: None declared, C. Robles-Jara: None declared, H. Pitanga Lukashok: None declared

MONDAY, OCTOBER 20, 2014 15:45–17:15
NEW DIAGNOSTIC MODALITIES IN UPPER GI ENDOSCOPY – HALL G/H

OP079 NARROW-BAND IMAGING AND MAGNIFYING ENDOSCOPY IN PATIENTS WITH DYSPHAGIA AND FOOD IMPACTION. PREVALENCE OF EOSINOPHILIC ESOPHAGITIS/ESOPHAGEAL EOSINOPHILIA AND LYMPHOCYTIC ESOPHAGITIS

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INTRODUCTION: Eosinophilic esophagitis (EoE) is a chronic inflammatory dysfunction characterized by eosinophilic infiltration in the esophageal epithelium. Lymphocytic esophagitis (LyE) is an independent entity expressing intraepithelial lymphocytes infiltration. Endoscopy plays a vital role in the diagnostic process since esophageal biopsies are required for diagnosis. Several conventional endoscopic features in EoE have been reported, however they are not specific for EoE and can be observed in other esophageal disorders. Very few studies report on endoscopic findings in LyE. Magnifying NBI endoscopy (NBI-ME) is able to highlight the esophageal mucosa and have widely used for esophageal early neoplasm. This study aimed to clarify the prevalence of EoE including esophageal eosinophilia(EEo) and LyE in the patient with dysphagia, and to assess endoscopic and NBI-ME features.
AIMS & METHODS: Adult patients with dysphagia and/or food impaction in the esophagus underwent EGD with magnifying NBI between August 2011 and November 2013. Biopsies were collected in proximal, middle and distal esophagus besides the antrum and duodenum. Based on previous reports, four endoscopic findings were identified as valuables of EoE/EEo (EoE group) and LyE (LyE group): mucosal rings, linear furrows, white exudates, and narrow- caliber/stenosis. Meanwhile NBI –ME features used were: (1) beige color of the mucosa, (2) increased and dot-shaped congested IPCLs, and (3) invisibility of submucosal vessels which were established in our previous report (Tanaka, Endoscopy, 2013). Endoscopic findings were compared with the histological diagnosis.
RESULTS: A total of 114 patients with dysphagia and/or food impaction underwent gastroscopy with biopsies. Of these 95 patients were studied with NBI-ME. Eighteen patients (19%) of 95 were histologically diagnosed as the EoE/EEo (definite EoE; 6), nineteen as LyE (20%) and twenty (21%) as GERD. In conventional endoscopy, mucosal rings, linear furrows, white exudates, and narrow-caliber/stenosis were seen in 14, 14, 11, 8 patients in the EoE group; 8,9,4,5 in the LyE group and 3,2,0,4 patients in the GERD groups. With NBI-ME, beige color, increased IPCL, invisibility of submucosal vessels were observed in all 18 patients in the EoE group, 12, 13,10 in the LyE group and 3,7 and none patients in the GERD group. With conventional endoscopy, at least 1 finding was seen in 16 patients (89%) in the EoE group, 14 (74%) in the LyE group and in 8 (40%) in the GERD group.Regarding NBI-ME, all patients in the EoE group, 13 (68%) in the LyE group and none in the GERD group had all three findings. The EoE and the LyE group patients with these all three findings are significantly higher than the GERD group ($p < 0.0001$, $p < 0.0001$).
CONCLUSION: Esophageal biopsies showing eosinophilia or severe lymphocytic infiltration(EoE/EEo or LyE) are common findings in patients with dysphagia or food impaction. Conventional endoscopy might assist the diagnosis of EoE/EEo and LyE when one of four findings is observed, however, they can be found in GERD. A combination of three NBI features was found in all patients with EoE/EEo and in the majority of LyE. NBI-ME was more reliable than conventional endoscopy in predicting endoscopic EoE/Eeo/LyE diagnosis before pathological assessment.
Disclosure of Interest: None declared

OP080 WHITE GLOBE APPEARANCE: A NOVEL FINDING USEFUL FOR CORRECT DIAGNOSIS OF EARLY GASTRIC CANCER BY MAGNIFYING NARROW-BAND IMAGING

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INTRODUCTION: We previously reported that magnifying endoscopy with narrow-band imaging (M-NBI) is useful for the correct diagnosis of gastric mucosal lesions [1]. However, differential diagnosis between low-grade adenoma (LGA) and high-grade dysplasia (HGD)/early cancer (EC) is sometimes difficult even with M-NBI. We recently noticed the unique finding of a small white lesion with a globular shape (< 1 mm), present underneath the gastric cancerous epithelium, during M-NBI examination. Conversely, this finding was rarely detected in noncancerous lesions. We termed this finding the "white globe appearance (WGA)." However, the nature of this finding and its clinical significance were unclear.
AIMS & METHODS: The aims of this study were to: (1) investigate the histological nature of the WGA, and (2) determine whether the WGA is a useful marker in the differential diagnosis between LGA and HGD/EC. (1) Two EC specimens in which the WGA was detected by M-NBI and that were resected by endoscopic submucosal dissection (ESD) were prepared for histopathological investigation. Before resection, we placed a marking beside the WGA using electrocoagulation under M-NBI. We then resected the lesion by ESD. After extending the specimen on a board, we placed two pins on the specimen with reference to the electrocoagulation mark to create a section identical to the WGA. (2) We retrospectively reviewed the M-NBI findings of 111 consecutive patients with gastric LGA, HGD, and EC that were resected by ESD from July 2013 to January 2014. We determined the prevalence of the WGA in HGD/EC, LGA, and non-neoplastic background mucosa (BM).
RESULTS: (1) By careful histological investigation, the WGA visualised by M-NBI was proven to be identical to the histological presence of intraglandular necrotic debris (IND) within markedly dilated neoplastic glands. (2) The prevalence of the WGA in HGD/EC, LGA, and BM was 21.7% (20/92), 0% (0/19), and 0% (0/111), respectively. Accordingly, the WGA was evident in HGD/EC lesions, but not in LGA or BM ($P < 0.001$, Fisher's exact test). The sensitivity, specificity, positive predictive value, and negative predictive value for differential diagnosis between HGD/EC and LGA according to the presence of the WGA were 21.7%, 100%, 100%, and 20.9%, respectively.
CONCLUSION: Because IND with dilated neoplastic glands is a possible histological marker specific for HGD/EC but not for LGA [2], we suggest that the presence of the WGA could be a novel marker for differential diagnosis between HGD/EC and LGA. We have started a prospective study to verify this hypothesis (UMIN 000013650).
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Disclosure of Interest: None declared

OP081 A NOVEL SYSTEM OF HYPOXIA IMAGING ENDOSCOPY EQUIPPED WITH LASER LIGHT SOURCE

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INTRODUCTION: Recent endoscopy has evolved into image-enhanced endoscopy (IEE), such as Narrow Band Imaging and Blue Laser Imaging. IEE focused on increasing abnormal microvessels in the surface of early cancers. It is difficult to recognize biological change, function, and metabolism in cancer by observing the morphological features of the microvessels. In contrast, hypoxia is one of the functional characteristics in cancer, with strong association to the biological features. Therefore, hypoxia imaging was innovated to visualize directly the biological and functional changes in cancer.
AIMS & METHODS: The aim of this prospective study is to evaluate the visualization of human early cancers in hypoxia imaging endoscopy. In endoscopic equipment, we utilized a difference of absorption between oxy- and deoxyhemoglobin in visible light wavelength. The signals converted from laser light were calculated in oxygen saturation (StO_2) by processor. Hypoxia imaging was obtained in real-time, displaying two types of StO_2 images. One was a pseudocolor image showing StO_2 levels as different hues, and the other was an overlay image that overlapped low StO_2 levels in blue on a white light illumination image of background mucosa. In the first in human clinical trial (UMIN: 000004983), patients who had been confirmed to have pharyngeal, esophageal, gastric, or colorectal neoplasia by previous endoscopy were enrolled. To compare histologic findings to hypoxia imaging, all patients received endoscopic resection immediately after conventional and hypoxia imaging endoscopy. We determined the corresponding areas of neoplasia and non-neoplasia in the endoscopic images and obtained StO_2 levels from the StO_2 map.
RESULTS: Forty patients with neoplastic lesions in the pharynx, esophagus, stomach and colorectum were analysed. The hypoxic area was completely corresponded to the portion of early cancer. Furthermore, 8 colorectal adenomas with histological low-grade atypia were also detected as hypoxia, ranging from 3 to 10 mm in diameter. All esophageal cancers including 2 Barrett's cancers were detected in hypoxia images. Median StO_2 differences between neoplastic and non-neoplastic areas in the pharynx, esophagus, stomach and colorectum were -15.4%, -14.5%, -5.1% and -21.5%, respectively. Significant differences of StO_2 levels were seen in the esophagus ($p=0.0078$, $n=8$) and colorectum ($p=0.0001$, $n=14$), but not in the stomach ($p=0.9341$, $n=15$) or pharynx ($p=0.2500$, $n=3$). Furthermore, sensitivity of neoplasia, defined as the proportion having correctly detected neoplasia, in the pharynx, esophagus, stomach, and colorectum was 67%, 100%, 33% and 86%, respectively.
CONCLUSION: Hypoxia imaging with the laser endoscope enables us to visualize spatial and temporal information of hypoxic conditions in human tumors. Hypoxia imaging illustrates a novel aspect of cancer biology as a potential biomarker and can be widely utilized in cancer diagnosis.
Disclosure of Interest: None declared

OP082 SMART ATLAS FOR SUPPORTING THE INTERPRETATION OF PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY (PCLE) OF GASTRIC LESIONS: FIRST CLASSIFICATION RESULTS OF A COMPUTER-AIDED DIAGNOSIS SOFTWARE BASED ON IMAGE RECOGNITION

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INTRODUCTION: pCLE enables microscopic imaging of gastrointestinal mucosal lesions, *in vivo* and in real time, during an endoscopy procedure. Recent studies have demonstrated that pCLE enables accurate diagnosis of superficial gastric neoplasia. In parallel, a computer-aided diagnosis software called Smart Atlas has been developed to assist endoscopists with the interpretation of pCLE sequences. This study aims at evaluating the performance of this software for the classification of gastric lesions into four pathological classes: healthy stomach, gastric intestinal metaplasia (GIM), dysplasia, and cancer.
AIMS & METHODS: Several pCLE video sequences were retrospectively collected from pCLE procedures performed in multiple clinical centers. These sequences, along with their annotated final diagnosis, were used to train a classification software that uses a content-based image retrieval algorithm to predict the diagnosis of a query video based on the diagnoses of the most visually similar atlas videos. For all cases, final diagnosis was based on histological analysis of corresponding tissue sampling. All evaluations were performed using leave-one-patient-out cross-validation to avoid bias. A confusion matrix was established to evaluate 4-class classification, and a receiver operating curve was generated to evaluate the binary classification between non-neoplasia (healthy stomach, GIM) and neoplasia (dysplasia, cancer).
RESULTS: Among the 40 pCLE video sequences collected from 30 patients, 14 were annotated with healthy stomach, 13 with GIM, 6 with dysplasia, and 7 with cancer. For the differentiation of non-neoplasia and neoplasia, the results maximizing the accuracy show an accuracy of 92.5%, a sensitivity of 92.3%, a specificity of 92.6%, a PPV of 85.7% and a NPV of 96.2%. The 4-class classification results show an average accuracy of 75% and per-class accuracies of 90% for healthy stomach, 82.5% for gastric intestinal metaplasia, 85% for dysplasia and 92.5% for cancer. In comparison, Bok at al. reported in GIE 2013 that, for real-time in vivo pCLE diagnosis of superficial gastric neoplasia, endoscopists achieve overall accuracy, sensitivity and specificity of 90.7%, 90.6% and 90.9%, respectively.
CONCLUSION: These first results demonstrate that gastric lesions can be automatically classified into four pathological classes by the Smart Atlas software based on the image content of pCLE video sequences only. The high accuracy, sensitivity and specificity results achieved by the software for differentiating non-neoplasia and neoplasia are comparable to those achieved by endoscopists. The case-based reasoning software could thus be used as an educational tool to train non-expert endoscopists, but also as a second-reader tool to assist any endoscopist in real-time diagnosis of gastric diseases using pCLE.
Disclosure of Interest: None declared

OP083 NEEDLE-BASED CONFOCAL LASER ENDOMICROSCOPY (NCLE) FOR THE DIAGNOSIS OF LYMPH NODES: CORRELATION BETWEEN PCLE AND HISTOLOGICAL CRITERIA (CONTACT STUDY)

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INTRODUCTION: Needle-based Confocal Laser Endomicroscopy (nCLE) is an imaging technique, which enables microscopic observation of solid organs, *in vivo* and in real-time, during an EUS-FNA procedure. The CONTACT study (Clinical evaluation Of NCLE in The lymph nodes Along with masses and Cystic Tumors of the pancreas) aims at building an image atlas, and define interpretation criteria for nCLE images in the lymph nodes, within the frame of cancer staging.

AIMS & METHODS: 3 centres in France (7 investigators) took part in this prospective study. Patients with a suspicious lymph node ≥ 1 cm proposed for a EUSFNA, were included. In case of multiple lymph nodes, only one of them could be imaged. The puncture was done with a 19G puncture needle with the nCLE probe preloaded. After examination of the track of the puncture by nCLE, aspiration was done in the same track to compare images and histological results. 17 patients with suspicious lymph node were included over 8 months (August 2012 to March 2013). There were 14 men, and 3 women, mean age 59 years old, (extreme: 35-69 years old). The localization of the lymph nodes were: mediastinal (6 cases), celiac (6 cases), intra-abdominal (3 cases), hepatic hilum (1 case) and hepatic pedicule (n=1). All had a size superior to 10mm.
No complication occured during the nCLE procedure or the puncture. A definitive histological diagnosis was obtained in 14/17 patients. It was the following: 7 malignant (metastasis of primary cancer: pancreas, stomach, lung, kidney, prostate and lymphoma), 7 benign (according to a one year follow-up).
Preliminary characteristic descriptive criteria were previously described [1]. To go further, nCLE sequences were re-visualized by two gastro-enterologists and two pathologists in order to compare, for each type of lesion, their findings to the pathology specimen.
RESULTS: During this review, all benign or inflammatory lymph nodes showed one sign: a reticular background, which corresponds to the histological structure of lymphocytes.
Tumoral lymph nodes presented dark clumps or aggregates of dark cells, tumoral glands and some times only a grey background which could histologically correponds to necrosis.
Finally, all a few criteria could be observed in all cases: white bands (blood vessels), macrophages, fat cells (bubbles), and thin straight bands over a regular dark aggregate which corresponds to fibrosis in the capsula of the lymph node.
CONCLUSION: This preliminary classification of nCLE images obtained in lymph nodes could help in the differentiation of malignant and benign lymph nodes. nCLE could therefore facilitate the diagnosis of these lesions, by bringing *in vivo* microscopic information, in real-time.
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Disclosure of Interest: None declared

OP084 A RETROSPECTIVE AUDIT OF THE EFFECTIVE USE OF ENDOSCOPIC UPPER GASTROINTESTINAL HISTOPATHOLOGY

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INTRODUCTION: Histological assessment is an important tool for the endoscopist and remains the gold standard for the diagnosis of many conditions affecting the gastrointestinal (GI) tract. GI biopsies cost approximately £60[1] (€73) to process and create considerable histopathology workload. With the growing demand for diagnostic oesophagogastroduodenoscopy (OGD), recently published guidance to clarify the appropriate indications for endoscopic biopsy and histological evaluation is welcomed[2].
AIMS & METHODS: We retrospectively audited our unit's use of endoscopic biopsy against the new guidelines[2]. Our aim was to highlight methods of reducing the histopathology workload and validate the guideline against local UK hospital practice. Using an endoscopy auditing tool (Unisoft) we identified all OGDs where a biopsy was taken over a 6 month period (1st July – 31st Dec 2013). Reviewing the endoscopy report we compared the stated indication for biopsy to the guideline. The procedural details were cross-referenced with the pathology database to identify relevant histology results.
RESULTS: During the study period 1439 OGDs were performed and a biopsy was taken during 655 (45.5%) procedures. Nurse endoscopists performed 190 OGDs, trainees 137 and consultants 328. In the study population 53.9% of patients were female with a median age of 55 (IQR 40-68).
Approximately two thirds (435/655) of OGDs had biopsies taken in accordance within the stated criteria. The most common indications for biopsy were identification of coeliac disease (46.4%) and mucosal lesions suspicious of neoplasia (23.6%). Indications for biopsy were missing in 12.2% (80/655) of endoscopy reports. In 21.4% (140/655) of OGD's biopsies were taken outside criteria. Indications in this group included uncomplicated inflammation (100/140), checking Helicobacter pylori status in patients on proton pump inhibitors, surveillance of premalignant conditions e.g. intestinal metaplasia (IM) and abnormal imaging findings with normal endoscopic appearance.
Histopathologic assessment of biopsies taken outside guideline criteria demonstrated pathology that could potentially change management in 25.7% of cases (36/140): 20 cases of *H. pylori*; 14 of IM; 1 of possible inflammatory bowel disease; 1 new neuroendocrine nodule.
In total 3531 individual biopsies were taken, which equates to approximately £211,860. The estimated number of biopsies taken without a stated indication or indications outside the criteria is 954, generating a cost of £57,240 over 6 months. There were no recorded complications related to biopsy retrieval during the study period.
CONCLUSION: The new guidelines give a timely reminder of the financial implications of routine histology. By adopting biopsy policies, endoscopy departments can make significant savings of time and money to ensure effective use of healthcare resources. We have demonstrated that stringent application of the guidelines may miss certain pathology. However the uncertain implications of IM and the availability of other methods of identifying *H. pylori* mean their identification by biopsy are of debatable clinical importance[1]. We would recommend adapting the current guidance to develop unit specific policies applicable to local practice.
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Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 15:45–17:15
LATE BREAKING CLINICAL TRIALS IN DIGESTIVE DISEASES – HALL I/K

OP084-LB1 TIMING OF CHOLECYSTECTOMY AFTER MILD BILIARY PANCREATITIS: A RANDOMISED CONTROLLED MULTICENTER TRIAL

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INTRODUCTION: In mild biliary pancreatitis, international guidelines advise cholecystectomy during index-admission or within four weeks after discharge to prevent recurrent biliary disease. However, high quality evidence for the optimal timing of cholecystectomy is limited and in daily practice the waiting period for cholecystectomy often exceeds 6 weeks.
AIMS & METHODS: We conducted a randomised trial to investigate whether cholecystectomy during primary admission can reduce the number of readmissions for biliary events compared to postponed cholecystectomy. All adult patients admitted with a first episode of mild biliary pancreatitis (i.e. the absence of necrotizing pancreatitis, fluid collections or organ failure) were assessed for eligibility. Patients were randomised before discharge for either laparoscopic cholecystectomy within 72 hours ('early') or after 25 to 30 days ('interval'). Primary endpoint was a composite of mortality or readmission for biliary events (i.e. recurrent pancreatitis, biliary colics, cholecystitis or choledocholithiasis needing endoscopic retrograde cholangiopancreatography [ERCP]). Secondary endpoints included patient reported biliary colics at home, safety of cholecystectomy expressed by technical difficulty, need for conversion, perioperative complications and length of hospital stay. The trial protocol has been published1.
RESULTS: In 23 Dutch hospitals 265 patients with mild biliary pancreatitis were enrolled. 129 Patients were randomised for early cholecystectomy and 136 for interval cholecystectomy. Baseline characteristics were similar between groups. Median time from randomisation to cholecystectomy was 1 day (interquartile range [IQR] 1 to 2) in the early *vs.* 27 days (IQR 26 to 29) in the interval group. The primary endpoint occurred less often in the early group (5% *vs.* 17%; risk ratio 0.28; 95% confidence interval [CI] 0.12-0.66; $p = 0.002$). The incidence of recurrent biliary pancreatitis was lower in the early group (2% *vs.* 9%; RR 0.27; 95% CI 0.08-0.92; $p = 0.03$). 51% of the patients in the interval group reported colics during the waiting period. Need for ERCP, readmissions for colics, difficulty of cholecystectomy, number of conversions, perioperative complications, and length of hospital stay did not differ between groups.
CONCLUSION: This trial provides solid evidence that cholecystectomy should be performed during the initial admission for mild biliary pancreatitis, as this prevents readmissions for recurrent biliary events, including recurrent biliary pancreatitis, without increased risk of complications.
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Disclosure of Interest: None declared

OP084-LB2 COMPARATIVE CLINICAL EFFECTIVENESS OF INFLIXIMAB AND CICLOSPORIN FOR ACUTE SEVERE ULCERATIVE COLITIS: EARLY RESULTS FROM THE CONSTRUCT TRIAL

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INTRODUCTION: The relative clinical effectiveness and cost-effectiveness of infliximab (IFX) and ciclosporin (CsA) in the treatment of steroid-resistant, acute severe ulcerative colitis are not known. In 2012 GETAID reported no significant difference in efficacy, colectomy rates or adverse events in 115 patients 3 months after treatment.
AIMS & METHODS: Between May 2010 and March 2014, we conducted a multi-centre, pragmatic, randomised trial in 52 sites across the United Kingdom. This mixed methods study addressed clinical and cost-effectiveness, patient and professional views, and will monitor long-term outcomes using routinely collected data. Two hundred and seventy patients with acute severe colitis who failed to respond to intravenous (iv) hydrocortisone over 2 to 5 days consented to randomised treatment with IFX or CsA. IFX was given as Remicade® in 5mg/kg iv infusions over two hours, at baseline and 2 and 6 weeks after the first infusion, in accordance with local prescribing guidelines. Participants randomised to CsA received it as Sandimmun® by continuous infusion of 2 mg/kg/day. Intravenous treatment continued for up to 7 days if successful. Participants responding to iv CsA were changed to twice-daily oral doses delivering 5.5 mg/kg/day, adjusted to achieve trough CsA concentrations of 100–200 ng/ml. Depending upon recruitment date, participants were followed up for 1 to 3 years. The primary outcome was quality-adjusted survival (QAS), measured by the area under the curve of scores from the Crohn's & Colitis Questionnaire (CCQ), a modification of the UKIBDQ validated for use by patients in both

acute and community settings. It was completed by patients at baseline, 3 and 6 months after randomisation, and then at 6-monthly intervals.
RESULTS: There was no significant difference between age, gender, ethnicity, family history, smoking status, Mayo score on sigmoidoscopy, or quality of life scores of the 135 patients in each group at baseline. No difference in QAS (IFX mean 614.6 days; sd 229.8; CsA 626.0 days; sd 226.8), or QAS per day, was found between the two groups. There was no significant difference in mean CCQ or EQ-5D scores over time; colectomy rates (IFX 53; CsA 63); time to colectomy; mortality (IFX 3; CsA nil); or serious adverse reactions (IFX 12; CsA 11, including 3 and 1 malignancies respectively).
CONCLUSION: There is no difference between the two drugs in clinical effectiveness. This conclusion highlights the importance of the other elements of this mixed methods study.
Disclosure of Interest: None declared

OP084-LB3 BETTER LIVING THROUGH ALGORITHMS: MACHINE LEARNING ALGORITHMS TO IDENTIFY ADEQUATE IMMUNOSUPPRESSION AND PREDICT IMPORTANT CLINICAL OUTCOMES ARE SUPERIOR TO THIOPURINE METABOLITE CHEMISTRY

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INTRODUCTION: Optimizing thiopurine therapy for IBD has proven difficult. Current methods using 6-thioguanine nucleotide (6-TGN) metabolites have failed in two published RCTs, and have never been used to predict biologic remission (BR).
AIMS & METHODS: (1) Develop a machine learning algorithm (MLA) using lab values and age to identify patients in biologic remission (thus adequate immunosuppression [IS]) on thiopurines, and (2) determine whether achieving lab patterns predictive of IS resulted in fewer clinical events (steroid prescriptions, hospitalizations, and surgeries) per year. Data from 1082 IBD patients (3269 observations) on thiopurines were used to build the MLA with lab values from the CBC and chemistry panel as predictors. Biologic Remission was defined by the absence of objective measures of inflammation on scan, scope, biopsy, or serum/fecal tests. The MLA was built in a 70% training set and tested on a 30% test set. IS was defined as a lab pattern predictive of BR as identified by the MLA. Clinical event rates per year of follow-up were compared in those with sustained predicted IS vs. those without predicted IS.
RESULTS: A MLA to differentiate patients with BR from non-responders produced an AuROC curve of 0.79 (95% CI, 0.78-0.81) in the 30% test set. This is dramatically superior to 6-TGN measurement, which had an AuROC of 0.49 for BR (95% CI, 0.44-0.54). In patients with sustained predicted IS, the mean total number of clinical events per year was 1.52 compared to 4.69 in those who did not achieve predicted IS (p=0.0000000002). Reductions in the individual endpoints of steroid prescriptions/year (-1.63, p=1.2E-9) hospitalizations/year (-1.05, p=2.0E-6), and surgeries /year (-0.19, p=0.065) were seen with sustained predicted IS. Therapeutic interventions changed 32 subjects from sustained lack of IS to sustained predicted IS, largely through dose increases and splitting dosing to bid. In these subjects, the mean number of steroid prescriptions decreased by 2.4/year, hospitalizations by 1.5/year, and surgeries by 0.5/year. Total events decreased by a mean of 4.3/year after achieving sustained predicted IS.
CONCLUSION: This MLA can predict adequate IS in IBD patients on thiopurines. Sustained predicted IS is associated with significant clinical benefits, including decreased steroid prescriptions, hospitalizations, and surgeries. Therapeutic interventions can induce sustained predicted IS and clinical benefits in patients on inadequate thiopurine monotherapy.
Disclosure of Interest: P. Higgins Other: My employer, the University of Michigan, holds the patent on this algorithm, K. Sauder: None declared, A. Patel: None declared, Y. Zhang: None declared, J. Zhu: None declared, U. Balis: None declared, A. Waljee: None declared

OP084-LB4 OBJECTIVE EFFECTIVENESS, SATISFACTORY RELIEF, AND COMPLIANCE DURING LOW-FODMAP AND GLUTEN-FREE DIETS IN IBS PATIENTS ARE NOT RELATED TO PSYCHOPATHOLOGICAL STATUS. A DOUBLE-BLIND RANDOMIZED CONTROLLED CLINICAL STUDY

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INTRODUCTION: Low-FODMAP diets are suggested as effective interventions for IBS. Many IBS patients eliminate gluten from their diet, reporting benefit. Some IBS patients are affected by non-celiac gluten sensitivity. Gluten amount is undeniably reduced in low-FODMAP diets. It is not known to what extent the benefits of low-FODMAP diets are due to low FODMAPs per se or gluten reduction. It is also unclear whether patients' psychopathology modulates these benefits.
AIMS & METHODS: The aims were to: 1) assess in 60 IBS patients (F=37, age range=21-67 yrs), the effectiveness on abdominal bloating and pain of 3 diets, low FODMAP and gluten-free (FOD-GF), low-FODMAP and normal-gluten (FOD-NG), normal-FODMAP and normal-gluten (balanced control diet); evaluate if satisfactory relief and compliance differed between the 3 groups and were influenced by psychopathology. At enrollment, patients filled out the Symptom Checklist-90-Revised (SCL-90-R) to assess psychological features, a visual analogue scale (VAS), ranging 0-100, to rate the subjective intensity of bloating, and a 2-week diary card registering their habitual diet to calculate the objective frequency of abdominal bloating/pain. After diary completion, they were blindly assigned to one of the three 4-week diets. During the last 2 weeks they filled out a 2nd diary card and then rerated the intensity of bloating, plus satisfactory relief and compliance, by using a VAS. Paired t-test measured intragroup differences of IBS symptoms, pre- and post-diet, one-way ANOVA with Tukey post-hoc test intergroup differences. Pearson's r was used for correlations.
RESULTS: Age, gender, IBS subtype, SCL-90-R scores, and satisfactory relief did not differ between the 3 groups, compliance was lower in the FOD-GF group (p=0.041). After the diets, FOD-GF and FOD-NG groups showed improved intensity of abdominal bloating and frequency of abdominal bloating/pain (p-values from 0.001 to 0.008 in the former group and equal to 0.000 in the latter), while controls only slightly improved. Intensity of bloating and frequency of abdominal bloating/pain were comparable in the 3 groups pre-diet (p=0.217), but differed post-diet (p=0.000). A greater improvement of IBS symptoms in the 2 test diet groups vs. the control group, and a trend favoring the FOD-NG group vs. the FOD-GF group were found. No correlation was found between SCL-90-R scores, objective benefits, satisfactory relief, and compliance.
CONCLUSION: IBS patients have considerable benefit from restricting FODMAPs in the diet. Gluten avoidance in addition to a FODMAP restricted diet does not seem to add any significant benefit and affects negatively compliance. A modified balanced diet benefits patients in terms of satisfactory relief, irrespectively of FODMAP or gluten content. Psychopathology does not influence clinical improvement, satisfactory relief, or compliance during the diets.
Disclosure of Interest: None declared

OP084-LB5 EFFECTS OF THE GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONIST, EXENATIDE, ON SMALL INTESTINAL MOTILITY, FLOW, AND GLUCOSE ABSORPTION IN HEALTHY SUBJECTS AND IN TYPE 2 DIABETES

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INTRODUCTION: The GLP-1 receptor agonist, exenatide (Ex) reduces postprandial blood glucose in type 2 diabetes in part by slowing gastric emptying. However, its impact on small intestinal function is unknown.
AIMS & METHODS: Our aim was to determine the acute effects of intravenous (IV) Ex on duodenal motility, flow events, and glucose absorption, following intraduodenal (ID) glucose infusion. 10 healthy subjects (HS) (mean age (±SE) 37±5yrs; BMI 27.4±1.7 kg/m^2) and 10 patients with diet-controlled type 2 diabetes (DM) (60.4±2.3 yrs; BMI 29.1±1.5 kg/m^2) were studied twice in random order. After an overnight fast, a catheter was positioned with 6 manometry side-holes, 7 impedance electrode pairs, and an infusion port in the duodenum. Ex (7.5mg) or saline control was given IV from T= -30 to 240min. ID glucose was infused from T=0 to 60min at 3kcal/min, together with 5g 3-O-methylglucose (3-OMG). Blood was sampled frequently for blood glucose and serum 3-OMG concentrations (an index of glucose absorption). Symptoms were monitored using 100mm visual analogue scales.
RESULTS:

T = 0 to 240 min	Exenatide	Control	P
HS - Peak blood glucose (mmol/L)	7.9 ± 4	10.7 ± 0.5	<0.001
DM- Peak blood glucose (mmol/L)	11.5 ± 0.7	13.4 ± 0.7	<0.05
HS – Number of duodenal pressure waves	577 ± 98	2088 ± 282	<0.001
DM - Number of duodenal pressure waves	781±149	1976 ± 446	<0.05
HS – Number of antegrade flow events	55 ± 12	114 ± 15	<0.05
DM – Number of antegrade flow events	36 ± 8	105 ± 10	<0.001
HS - Serum 3-OMG AUC (mmolL^{-}1.min)	68.3± 3.4	101.5±6.7	<0.005
DM - Serum 3-OMG AUC (mmolL^{-}1.min)	81.0 ± 6.1	128.7 ± 10.3	<0.001
HS + DM – Peak nausea score (%)	32.3±7.7	7±2.5	<0.005

Blood glucose (T=0 to 240min) was lower during Ex than control in both HS and DM. During the same period, there were fewer duodenal pressure waves with Ex than control in both groups, as well as fewer antegrade flow events. 3-OMG absorption (area under the curve) was markedly less with Ex than control, in HS and DM. Peak nausea scores were higher with Ex than control in both groups. However, 10 subjects without any nausea still had suppression of duodenal pressure waves (678 ± 137 vs 1963± 467; P<0.05) and flow (58 ± 9 vs 106± 6; P<0.001).
CONCLUSION: IV Ex acutely suppresses duodenal motility and flow events, and slows small intestinal absorption of glucose, in both health and type 2 diabetes, suggesting that changes in small intestinal motor function, and thereby glucose absorption, contribute to the lowering of postprandial glycaemia by GLP-1 receptor agonists.
Disclosure of Interest: S. S. Thazhath: None declared, C. Marathe: None declared, T. Wu: None declared, J. Chang: None declared, J. Khoo: None declared, P. Kuo: None declared, H. Checklin: None declared, M. Bound: None declared, A. Russo: None declared, R. S. Rigda: None declared, K. L. Jones: None declared, M. Horowitz: None declared, C. K. Rayner Financial Support from: This research was conducted with support from the Investigator-Sponsored Study Program of AstraZeneca

OP084-LB6 THE COMPARATIVE STUDY OF SPLIT-DOSE OF POLYETHYLENE GLYCOL (PEG) BETWEEN LOW VOLUME PEG PLUS ASCORBIC ACID FOCUSING ON THE BOWEL CLEANSING EFFICACY, PATIENTS' AFFINITY TO PREPARATION SOLUTION AND MUCOSAL INJURY: A PROSPECTIVE RANDOMIZED TRIAL

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INTRODUCTION: Adequate bowel cleansing is essential for a high-quality, effective, and safe colonoscopy. The aims of this study were to compare the efficacy and patients' affinity to preparation solution and mucosal injury of split dose of polyethylene glycol (PEG) solution with low volume PEG plus ascorbic acid for outpatients who underwent scheduled colonoscopy.
AIMS & METHODS: Overall, 160 patients were enrolled for split-dose of PEG and 159 for the low volume PEG plus ascorbic acid, respectively. The bowel cleansing efficacy of preparation was rated according to the Ottawa bowel preparation scale and patients' affinity to preparation solution was assessed using a questionnaire. All mucosal abnormalities observed during colonoscopy were noted and biopsied. These biopsy specimens were reviewed by pathologists.
RESULTS: Of the 319 patients, 308(96%) ingested more than 75% of the bowel preparation. There was no significant difference between the two groups for the mean total score using the Ottawa bowel preparation scale ($P = 0.376$). Significantly greater residual colonic fluid was observed in the low volume PEG plus ascorbic acid group (0.81 ± 0.54) than in the split-dose PEG group (0.66 ± 0.62) ($P = 0.023$). There was significant difference in the Ottawa bowel preparation score for the middle colon (split-dose PEG vs. low volume PEG plus ascorbic acid: 1.19 ± 0.94 vs. 1.42 ± 0.73; $P = 0.014$). In patients' preference and acceptance, low volume PEG plus ascorbic acid group showed better results ($P = 0.001$). The overall incidence of adverse events was not significantly different between the two groups (69/160 [43.1%], 69/159 [43.4%], $P = 0.972$); however, the split-dose PEG group tended to have less headache and dizziness ($P = 0.056$). Endoscopically, mucosal lesions, possibly associated with two preparation regimen, were observed in total 11 patients (split-dose PEG: 5, low volume PEG plus ascorbic acid: 6, respectively). Mucosal ulceration occurred in 1 patient taking split-dose PEG compared with 2 patients receiving low volume PEG plus ascorbic acid.
CONCLUSION: Low volume PEG solution plus ascorbic acid, compared with split-dose PEG, was associated with more residual fluid, but showed equivalent colon cleansing efficacy and resulted in more patient preference, and acceptance. There was no significant difference in mucosal injury.
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Disclosure of Interest: None declared

OP084-LB7 EFFICACY AND TOLERABILITY OF LOW VOLUME POLYETHYLENE GLYCOL PLUS ASCORBIC ACID VERSUS SODIUM PICOSULFATE + MAGNESIUM CITRATE: A PROSPECTIVE RANDOMIZED TRIAL

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INTRODUCTION: Colonoscopy is the standard method for the evaluation of mucosa of large intestine. High quality bowel preparation is essential for improving patient's compliance and the detection rate of colorectal lesions in screening colonoscopy. Recently, a new Polyethylene glycol (PEG)-based solution has became available. It combines PEG with a high dose of ascorbic acid (PEG + Asc, Coolprep®, Taejoon, Korea). Also, sodium picosulfate with magnesium oxide and citric acid (MC-SP, Picolight®, Pharmbio, Korea) is a commonly prescribed hyperosmolar bowel preparation in Korea.
AIMS & METHODS: The aim of this study is to compare the efficacy, tolerability, and safety of this new 2L PEG + Asc with MC-SP. Patients were enrolled from the endoscopy unit at the Kangdong sacred heart hospital, Seoul, Korea, between Feb 2014 and June 2014. Adult ambulatory outpatients scheduled for elective colonoscopy were randomized to receive 2L PEG + Asc (Coolprep®), or MC-SP (Picolight®). Before colonoscopy, patients were asked to complete a questionnaire regarding the acceptability, the tolerability, and side effects of the preparation. Six experienced endoscopists, who were blinded to the randomization and the study group of the patients, rated the quality of bowel cleansing by using Ottawa bowel preparation scale immediately after colonoscopy.
RESULTS: A total number of 223 consecutive individuals were randomly assigned to receive either 2L PEG + Asc solution (n=109) or MC-SP solution (n=114). Baseline and demographic characteristics were not different between both groups. Comparing PEG + Asc and MC-SP, there were no differences in overall quality of bowel cleansing (p=0.806). However, when dividing individual bowel segments, MC-SP was superior to the PEG + Asc in right colon segment (p=0.03). Side effects during preparation, such as nausea, vomiting, abdominal pain, abdominal bloating and dizziness, were less frequent in MC-SP group (p=0.031). Overall satisfaction of patients was superior in MC-SP group ($p < 0.001$) and more patients had an intention to do next colonoscopy with same bowel preparation method in MC-SP group (p=0.001).
CONCLUSION: Our study suggest that MC-SP provided significantly better cleansing in the right colon, and showed better acceptability and tolerability profile to that achieved with 2L PEG + Asc solution. However, for overall quality of bowel cleansing, both solutions showed similar level of effectiveness.
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Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 15:45–17:15
IBD: NEW THERAPEUTICS FOR SPECIFIC TARGETS – HALL L/M

OP085 INDUCTION OF MUCOSAL LIPOCALIN 2 IS A KEY REGULATORY EVENT IN IBD THAT SHAPES MICROBIAL COMMUNITIES TO CURB INFLAMMATION AND PREVENT COLITIS-ASSOCIATED CANCER

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INTRODUCTION: Lipocalin−2 (Lcn2), a member of the lipocalin family, constitutes an innate immune molecule involved in antimicrobial immunity and iron metabolism. Lcn2 is up−regulated during inflammatory bowel diseases (IBD). Its functional contribution to mucosal immunity remains unknown.
AIMS & METHODS: Aim of this study was to decipher the functional role of Lcn2 in IBD. For this purpose we generated mice double−deficient in IL10 and Lcn2. Severity and course of colitis were measured by clinical, histological, and biochemical parameters. Microbial communities were assessed by culture-independent analyses of bacterial 16S rRNA genes in fecal samples and complemented by bacterial FISH. Relevant findings were amended by additional functional experiments in vitro and in vivo.
RESULTS: We show that deficiency of Lcn2 resulted in exacerbated colitis and spontaneous emergence of proximal colonic tumours in IL-10−deficient mice. Colitis and tumourigenesis were dependent on microbial signals and responsive to antibiotics and IL-6−deletion. Lcn2−deficiency was associated with alterations in the composition of gut microbial communities and loss of spatial segregation. Colito− and tumourigenic properties were transmissible by cross−fostering and co−housing. Lcn2−induced dysbiosis fostered the bloom of pathobionts such as Alistipes and Robinsoniella species able to mimic observed changes when gavaged.
CONCLUSION: Our results suggest a pivotal role of inflammation-induced Lcn2 as a key guard against colonic inflammation and carcinogenicity in IBD through its microbiota−modulating properties.
Disclosure of Interest: None declared

OP086 EPITHELIAL IL-23R SIGNALING LICENSES PROTECTIVE IL-22 RESPONSES IN INTESTINAL INFLAMMATION

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INTRODUCTION: The identification of the *IL23R* as a genetic risk factor in inflammatory bowel disease (IBD) has highlighted the role of IL-23 signaling in the intestinal immune response. However, the impact of IL-23 on the immune regulation is ambigious. Whereas IL-23 induced Th-17 polarization contributes to pathogenesis of IBD[5], IL-23 induced IL-22 in Thy-1$^+$ innate lymphoid cells is indispensable in the innate immune response to bacterial pathogens and experimental colitis. This study aimed to describe the role of the Il23R in the intestinal epithelium.
AIMS & METHODS: Conditional knockout of the Il23R in the intestinal epithelium was established by crossing VillinCre mice with Il23Rfl/fl mice, resulting in IL23R$^{IEC\text{-}KO}$ or IL23R^{fl}.
For chronic colitis induction, mice were supplied with 2% of DSS dissolved in drinking water for 5 days followed by 5 days of regular drinking water with total 3 cycle repetitions.
Diseased intestines were subjected to gene expression analysis was performed using custom made TaqMan probes and post-mortem histopathological analysis. Lumina faeces were subjected to pyrosequencing of bacterial DNA and sequences with at least 97% similarity were clustered in to species level operational taxonomical units (OTUs).
RESULTS: Here we show that *IL23R* is expressed in intestinal epithelial cells and profoundly affects the intestinal immune defense. *IL23R*$^{IEC\text{-}KO}$ mice produce less antimicrobial peptides, have a disturbed colonic microflora and succumb to experimental colitis. *IL23R*$^{IEC\text{-}KO}$ intestinal lamina propria cells contain less immune cells and produce less IL-22 in response to IL-23 or Flagellin stimulation. Lastly, we could show, that IL-22 therapy fully restores epithelial immune defense in *IL23R*$^{IEC\text{-}KO}$.
CONCLUSION: These data contribute to the understanding of the IL-23 axis in primary immune response and describes a so far unknown role of IL23R signaling in the intestinal epithelium.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 15:45–17:15
IMMUNOPATHOGENESIS OF PANCREATITIS AND HEPATITIS – HALL R

OP087 AUTOIMMUNE PANCREATITIS – EXPLORING DISEASE PATHOPHYSIOLOGY AND NOVEL, STEROID SPARING THERAPEUTIC INTERVENTIONS

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INTRODUCTION: Autoimmune pancreatitis (AIP) is a recently identified, rare form of chronic pancreatitis, which has become a new evolving field in gastroenterology. Currently, the treatment options, especially the long-term management for AIP are limited. The only therapy that has been established and accepted so far is corticosteroids, but the relapse rate is significant (15-60%). We previously demonstrated that acinar specific Lymphotoxin expression in mice (*Tg*(Ela1-Lta, b)) induces autoimmunity with features reminiscent of human AIP. This includes formation of tertiary lymphoid organs, increased serum IgGs, anti-nuclear antibodies and immune-complex glomerulonephritis. In this model we have previously shown that in contrast to corticosteroids, which only diminished inflammation, inhibition of Lymphotoxin beta receptor signaling (LTβR-Ig) also abrogated autoimmunity.
AIMS & METHODS: The aim of the study is to investigate the effectiveness of LTβR pathway inhibition compared to the depletion of specific subset of immune cells (B-cells and CD4$^+$ T-cells), which are suggested to play a pathological role in AIP development. Therefore, *Tg*(Ela1-Lta, b) mice with established AIP were treated with anti-CD20 mAb (Rituximab), anti-CD4 mAb in order to deplete B- and CD4$^+$ T-cells respectively and with LTβR-Ig fusion protein. Histology, autoantibody production, cytokine and chemokine expression, TLO integrity and other organ involvement (in kidneys) were tested, and compared to LTβR-Ig treatment. Furthermore, macrophage and T helper cell polarization was evaluated upon different treatments.
RESULTS: LTβR-Ig and anti-CD20 treatment led to a significant decrease in autoantibody production, inflammatory cell infiltration in the pancreas and reduced extrapancreatic manifestation in the kidneys. The molecular mechanism of this beneficial effect possibly involves the down regulation of Stat3 and non-canonical NF-κb activation. Additionally, in contrast to anti-CD20 and anti-CD4 treatments, blocking LTβR-signaling reverted acinar cell proliferation and acinar-to-ductal metaplasia formation and also disrupted the formation of TLOs. Anti-CD4 treatment resulted in reduced Th1 and Th2 polarization; however this did not ameliorate AIP.
CONCLUSION: In this unique genetic mouse model of AIP, we demonstrate that therapy with LTβR-Ig and anti-CD20 antibody is superior to CD4$^+$ T-cell depletion. With these targeted therapies we reveal novel anti-inflammatory and anti-autoimmune mechanisms. Assessing numerous parameters associated with AIP pathogenesis, LTβR-Ig achieved the greatest improvements. Therefore, inhibition of the LTβR-signaling pathway could become an alternative or supplementary approach for AIP treatment.
Disclosure of Interest: None declared

OP088 NEUTROPHIL EXTRACELLULAR TRAPS TRIGGER TRYPSIN ACTIVATION, PATHOLOGICAL INFLAMMATION AND TISSUE DAMAGE IN SEVERE ACUTE PANCREATITIS

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INTRODUCTION: Neutrophils play a pivotal role in local and systemic complications of acute pancreatitis (AP), but the mechanisms regulating neutrophil-induced tissue damage in the inflamed pancreas is not fully understood. Recently, neutrophil extracellular traps (NETs) have been demonstrated to contribute to organ dysfunction in both infective and non-infective diseases. In the present study, we investigated for the first time the potential role of NETs in AP.
AIMS & METHODS: AP was induced in male C57BL/6 mice by infusion of taurocholate into the pancreatic duct. Extracellular DNA was stained by Sytox green and NET formation was quantified by confocal microscopy and cell-free DNA in plasma. Pancreatic levels of chemokines and histone 3 and 4 as well as cytokines and chemokines in plasma were determined by ELISA. Neutrophil expression of Mac-1 was determined by flow cytometry. To analyze the impact of NET formation in AP, NET depletion was induced by DNAse I administration. In separate experiments, signal transducer and activator of transcription-3 (STAT-3) phophorylation and trypsin activation were analysed in isolated acinar cells exposed to NETs and histone 3 and 4.
RESULTS: Taurocholate challenge evoked formation of NET in the pancreas and increased cell-free DNA in plasma. Formation of macrophage inflammatory protein-2 (CXCL2), neutrophil infiltration and tissue damage in the inflamed pancreas and lung were significantly attenuated by DNAse I treatment. Moreover, DNAse I administration markedly reduced levels of blood amylase, CXCL2, interleukin-6 and high-mobility groups protein 1 as well as macrophage-1 antigen expression on circulating neutrophils in mice with pancreatitis. NETs and histones triggered trypsin formation and activation of STAT-3 in isolated acinar cells. Pre-incubation of NETs with polysialic acid abolished NET-induced activation of trypsin in acinar cells, suggesting that histones are responsible for a great part of NET-induced trypsin activation.
CONCLUSION: This study demonstrates for the first time wide-spread NET formation in AP. We found that NET formation regulates local and remote organ inflammation and damage in AP. These novel findings provide new insights in the pathophysiology of pancreatitis and indicate that targeting NETs might be an effective way to ameliorate tissue damage severe AP.
Disclosure of Interest: None declared

OP089 EARLY INTRAACINAR EVENTS AND IMMUNE RESPONSE IN ALCOHOLIC ACUTE PANCREATITIS IN HUMANS

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INTRODUCTION: Acute pancreatitis (AP) continues to be a challenging problem without specific solution. 20-25% of patients with AP develop severe disease. Systemic inflammatory response syndrome (SIRS) and associated multiorgan dysfunction (MODS) is responsible for early mortality. It is prudent to understand the early pathogenesis of AP and the associated immune responses, so that effective focused treatment modalities can be developed. Even though pathogenesis of AP has been studied extensively in murine experimental models, data are lacking for AP in humans.
AIMS & METHODS: In this study we evaluate the early intraacinar events and acinar-immune interactions in alcoholic AP in humans.
Normal pancreatic tissues were obtained from samples of Whipple's surgery for symptomatic benign biliary and periampullary pathology and pancreatic resection for pancreatic cystic lesions. Pancreatic slices and acini were prepared, treated with 50mM fatty acid ethyl esters/FAEE (alcohol metabolites) and incubated for different time intervals. Acinar injury was evaluated by trypsin and cathepsin B activation, H&E staining and transmission electron microscopy. McDonald & Ellis and Kawabata methods were used to evaluate for trypsin and cathepsin B activity respectively. Subcellular fractionation was performed to evaluate intraacinar redistribution of zymogen and lysosomal compartments. IHC and western blotting was used to evaluate the type of cell injury. Flow cytometry was performed to evaluate cytokine release by stimulated acinar cells and peripheral blood mononuclear cells (PBMCs) exposed to conditioned medium from stimulated acinar cells.
In order to validate our experimental findings, we evaluated cytokine expression from PBMCs isolated from patients with AP (n=43) at different time points and studied the association with clinical severity.
RESULTS: FAEE induced acinar injury was evidenced by a 15- and 10-fold elevation of trypsin and cathepsin B activity within 30mins of exposure. This was corroborated with histologic evidence of acinar injury. Subcellular fractionation demonstrated redistribution of cathepsin to zymogen-enriched compartment after 30mins exposure. There was a time dependent secretion of predominantly IL-6 and IL-8 by the FAEE treated acini from 2hrs onwards which peaked at 18hrs (median values of 1052.18 pg/mL and 3933.99pg/mL respectively). A robust secretion of the cytokines IL-6, IL-8, IL-1b, IL-10 and TNF-a (median values of 13583.77 pg/mL, 1462.97 pg/mL, 4875.32 pg/mL, 1858 pg/mL and 1121.71 pg/mL respectively) was observed from PBMCs exposed to conditioned media from FAEE treated acini. Interestingly, there was no secretion of IL-10 and TNF-a by the FAEE treated acinar tissue.
PBMCs from patients with alcoholic AP showed a significant increase in IL-6 and IL-8 secretion from the first week to the second week compared to non-alcoholic AP. This was significantly associated with disease severity (persistent organ failure).
CONCLUSION: Alcoholic AP in humans is characterized by early autophagy and redistribution of cathepsin B, which possibly causes intraacinar trypsinogen activation to active trypsin. There is also early secretion of pro-inflammatory cytokines by the treated acini that causes activation of circulating monocytes to further produce cytokines and initiate SIRS.
Disclosure of Interest: R. Talukdar Financial support for research from: Wellcome-DBT India Alliance, A. Jakampudi: None declared, R. Jangala: None declared, P. Pelluri: None declared, C. Ramji: None declared, M. S: None declared, G. Rao: None declared, D. Reddy: None declared

OP090 RESVERATROL IMPROVES THE PATHOGENESIS OF NONALCOHOLIC STEATOHEPATITIS THROUGH INHIBITION OF ENDOTOXIN-INDUCED LIVER INFLAMATION AND FIBROSIS

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INTRODUCTION: Nonalcoholic fatty liver disease (NAFL) morbidity rate in Asia Pacific region is close to 12–24%, while in Western countries is about 20–30% and NAFLD can progress to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma. In spite of its high prevalence, up till now here is no proven effective treatment for NAFLD. Although gut-derived endotoxin (ET), such as lipopolysaccharide (LPS), plays a key role in the pathogenesis of nonalcoholic steatohepatitis (NASH), detailed mechanisms of this pathogenesis becomes clear. We previously reported that overexpression of CD14 via activation of leptin-STAT3 signaling in Kupffer cells induced hyper-inflammatory response to low-dose ET, resulting in progression from simple steatosis to steatohepatitis with liver fibrosis. Therefore, we hypothesized that inhibition of leptin-STAT3 signaling in Kupffer cells may lead to attenuate the progression of steatohepatitis via inhibition of CD14 expression.
AIMS & METHODS: The aim of this study was to investigate whether the resveratrol which is known to inhibit activation of STAT3, improves the pathogenesis of steatosis or steatohepatitis in murine model. Eight-week-old male

C57BL/6J mice were randomly distributed into 3 groups of 10 animals each: a high fat diet group (HF), HF supplemented with 2mg/kg resveratrol daily (HFR2), and HF supplemented with 20mg/kg resveratrol daily (HFR20). After 12 weeks of dietary treatment, the rats were euthanized and relevant tissues were prepared for subsequent analysis. In this study, E. coli-derived LPS (0.25 mg/kg) was used.
A) We investigated whether the resveratrol attenuates HFD-induced steatosis.
B) We investigated whether the resveratrol attenuates ET-induced liver damage via inhibition of response to ET.
C) We investigated whether the resveratrol improves the pathogenesis of long-term exposed ET-induced steatohepatitis with liver fibrosis.
RESULTS: Resveratrol prevented the high fat–induced steatosis assessed by semiquantitative grading, which furthermore corresponded with a complete normalization of the hepatic triglyceride content ($P < .001$), despite no change in total body fat, and hepatic SREBP1c expression was significantly decreased as compared with HF. HFR showed significant inhibition of hepatic CD14 expression through suppression of STAT3 activity in Kupffer cells, following inhibition of a single low-dose LPS-induced liver damage. Moreover, long-term low-dose LPS-induced liver fibrosis in HFR is significantly decreased as compared with HF.
CONCLUSION: These data indicated that the resveratrol improves not only the pathogenesis of steatosis thorough inhibition of lipogenesis but also steatohepatitis through inhibition of endotoxin-induced liver damage via suppression of STAT3-CD14 signaling in Kupffer cells. The resveratrol may have application for the treatment of NAFLD
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Disclosure of Interest: None declared

OP091 GUT-DERIVED LYMPHOCYTES MIGRATE TO THE LIVER IN A MOUSE MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE

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INTRODUCTION: An intimate immunological relationship between the gut and liver has been demonstrated, but the role of gut-derived lymphocytes in the progression of non-alcoholic fatty liver disease (NAFLD) remains unknown. We investigated the migration of gut-derived lymphocytes to the liver in a mouse model of NAFLD.
AIMS & METHODS: The mice were fed a high-fat diet for 12 weeks to induce NAFLD model. Control mice were fed a normal-fat diet. Lymphocytes from the spleen, bone marrow, thymus and mesenteric lymph nodes (MLN) of NAFLD mice were intravenously injected into NAFLD and control mice for near-infrared scanning. The percent of the lymphocyte subsets were analysised by flow cytometry. The chemotactic index of MLN cells of NAFLD and control mice was analyzed by chemotaxis assays.
RESULTS: The fraction of activated CD4+T cell($CD4+CD44^{high}CD62^{low}$) in MLN was significantly increased in NAFLD mice. Meanwhile, the control memory CD4+T cells and CD8+T cells($CD4+CD44^{high}CD62L^{high}$ and $CD8+CD44^{high}CD62L^{high}$), B cells increased in liver of NAFLD mice. Additionally, the fraction of CD4 effector T cells (Th1 and Th17) increased significantly in the liver, MLN and blood of NAFLD mice. The adoptive transfer model showed that MLN cells from the NAFLD donor mice predominately accumulated in the liver in both NAFLD and control recipient mice. Compared to control recipient mice, NAFLD recipient mice accumulated much more MLN cells from NAFLD donor mice in their livers. Whereas only a few lymphocytes from the spleen, bone marrow and thymus of the NAFLD donor mice migrated to the liver. Moreover, MLN cells from NAFLD mice induced liver injury in both NAFLD and control recipient mice, as reflected by elevated levels of serum ALT and AST after adoptive transfer. After the injection of MLN cells from NAFLD donor mice, the percent of activted CD4+T cells, activated CD8+T cells and B cells increased in liver. The CCL5 mRNA expression increased significantly in liver of NAFLD mice. Meanwhile, the CCL5 receptor CCR3 expression increased in CD4+T cell subsets, CD8+T cell subsets and CD19+B cells in the MLN cells of NAFLD mice. Blocking the CCL5 with the CCL5 antibody inhibited the migration of the MLN cells of NAFLD mice migration to liver.
CONCLUSION: Our study provides evidence that gut-derived lymphocytes from NAFLD mice have a strong propensity to migrate to the liver and induce liver injury and that fatty liver promotes the migration of gut-derived lymphocytes. Meanwhile, the gut-derived lymphocytes promoted CD4+T cells and CD8+T cells activation in liver of NAFLD mice. The propensity for the migration of gut-derived lymphocytes to the liver was associated with the mechanism of the upregulation of CCL5 in liver and CCL5 receptor CCR3 in gut-derived lymphocytes.
Disclosure of Interest: None declared

OP092 SIGNIFICANCE OF SELECTED BIOMARKERS OF INFLAMMATION, ANGIOGENESIS AND ADIPOKINES IN THE NON-INVASIVE ASSESSMENT OF PATIENTS WITH ALCOHOLIC LIVER DISEASE

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INTRODUCTION: Alcohol abuse is a major cause of liver disease in Europe. The idea of using serum biomarkers for early risk stratification and decision making in patients with alcoholic liver disease (ALD) seems an attractive alternative to invasive diagnostic methods (eg. liver biopsy, endoscopy) used in the current clinical practice.
AIMS & METHODS: Determination of serum profile of selected biomarkers of three different processes showing synergism in the pathogenesis of ALD i.e. inflammation, angiogenesis and adipose tissue secretion (adipokines). Two new subsets of T helper cells: Th17 and Treg, vascular endothelial growth factor (VEGF), angiopoietin 1, 2 (Ang1, Ang2), as well as total adiponectin (Acrp30), leptin and resistin were investigated. 147 pts (40 females, 107 males) with ALD were prospectively recruited and compared with 30 healthy controls (HC). They were divided into subgroups based on their: 1. gender, 2. severity of liver dysfunction according to the Child-Turcotte-Pugh and MELD scores; and 3. the presence of ALD complications at the time of hospital admission (i.e. ascites, hepatic encephalopathy, esophageal varices, cholestasis, renal dysfunction and death). In order to confirm alcohol misuse the AUDIT-C questionnaire was used. A FACSCalibur flow cytometer (Becton Dickinson, USA) with CellQuest software was used to identify T cell phenotype. CD3+CD4+IL17+ cells were considered Th17 and CD4+CD25+FOXP3+ Tregs. They were expressed as the percentage of all CD3+CD4+ and CD4+CD25+ lymphocytes, respectively. Serum levels of angiogenic biomarkers and adipokines were assessed using immunoenzymatic ELISA tests. Multivariable logistic regression was applied in order to select independent predictors of advanced liver dysfunction and the disease complications.
RESULTS: Twelve of 147 pts died within the 90-day follow up. The alteration of the Th17/Treg balance was observed in the most severely ill patients. Frequency of Th17 cells was an independent predictor of mortality in the study group. Significantly higher plasma concentrations of Ang2 and VEGF, as well as Acrp30 and resistin in comparison with HC were found. Increased Ang2 concentrations turned out to be an independent predictor of severe liver dysfunction (MELD score ≥ 20) and the development of ascites, encephalopathy, renal dysfunction, and death. Also Acrp30 concentrations revealed an independent association with the severity of liver dysfunction and the development of ascites and hepatic encephalopathy.
CONCLUSION: High frequency of Th17 cells, as well as Ang2 and Acrp30 concentrations revealed the best individual predictive value for ALD complications. The predictive power of complex statistical models which included several parameters from different pathways in the pathogenesis of ALD occurred to be superior to either biomarker alone.
Disclosure of Interest: None declared

OP093 RESCUE FROM EXPERIMENTAL ALCOHOLIC STEATOHEPATITIS BY A PEPDUCIN-BASED BLOCKADE OF INTERLEUKIN-8 RECEPTORS

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INTRODUCTION: Alcoholic steatohepatitis (ASH), exhibiting short-term mortality rates as high as 40%, is characterised by hepatic neutrophil infiltration and peripheral blood neutrophilia. It is thought to evolve from an initial inflammatory response to end products of ethanol catabolism and ethanol-induced break-down of the enteric barrier with consecutive bacteraemia and entotoxinaemia. Interleukin-8-induced signalling through CXCR1/2 G protein coupled receptors (GPCRs) is critical for the recruitment and activation of neutrophils at sites of inflammation. We have previously shown that pepducins, short consciously designed lipopeptides, modulate GPCRs by interfering with the receptor's activation of G-proteins.
AIMS & METHODS: Pepducins were synthesised by standard fMOC and tested in a murine model of ASH. Mice were fed a liquid high fat (Lieber DeCarli) diet for 5 weeks, followed by parenteral administration of endotoxin. Liver/body weight ratio, histological hepatic inflammation, and neutrophil myeloperoxidase were measured.
RESULTS: We demonstrate that experimental ASH is driven by CXCR1/2-dependent activation of neutrophils. CXCR1/2-specific pepducins protected from histological inflammation, weight loss and mortality associated with experimental ASH. Importantly, pepducins were effective even when administration was commenced late in established experimental ASH. Neutrophil infiltration and lipid accumulation in hepatocytes were significantly reduced by CXCR1/2 pepducin treatment. Hepatocyte cell lines were shown to secrete interleukin-8 upon ethanol stimulation, and CXCR1/2 pepducins blocked chemoattraction of neutrophils toward hepatocyte supernatants.
CONCLUSION: Experimental ASH remarkably closely phenocopies human ASH, which represents a major unmet therapeutic need. These data establish a key role for CXCR1/2 signalling and hepatic neutrophil recruitment in the pathogenesis of ASH. CXCR1/2 pepducins might therefore represent a pharmacological approach that merits exploration in a clinical trial in ASH. Pepducins directed against another GPCR are currently studied in a phase I clinical trial.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 15:45–17:15
PROGRESS IN GASTRIC AND DUODENAL ENDOTHERAPY – HALL N

OP094 LONG TERM FOLLOW-UP OF UPPER GI NEOPLASIA TREATED BY ENDOSCOPIC RESECTION

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INTRODUCTION: Endoscopic mucosal resection (EMR), or mucosectomy technique, developed by Japanese endoscopists consists of resecting flat and polypoid neoplasms of the mucosa. Its a relatively simple technique and carries a low morbidity. It represents an important advance for endoscopists in both technical and cancer areas. Is based on the concept that endoscopy provides visualization and acess to the mucosa, the innermost lining of the gastrointestinal tract. EMR presents also the advantage of obtaining a complete specimen for histologic analysis, allowing to know whether the resection has been complete laterally, in depth and the level of tumor invasion. Provides the opportunity to preserve organs' anatomy and physiology avoiding surgery and long term hospital stay.
AIMS & METHODS: The aims of the study were to measure the success rate of achiving complete resection and the complication rate of EMR in a single center. A retrospective analysis was done among 137 EMRs procedures conducted in our endoscopic department between December 1997 and March 2014. The procedure was done either with dual-channel gastroscope Fujinom and cap or bandligation with regular scope. EUS was performed in the majority of patients with high frequence miniprobes or radial Fujinom System scope. In patients with high-grade dysplasia (HGD) and intramucosal cancer who were treated by EMR, careful follow-up and additional therapy to treat residual or recurrent cancer was done.
RESULTS: 81 of 137 patientes were men. The average age was 68 +/- 9 years.EMR was done in outpatient basis and the patients were discharged after 4 hours in the recovering area. Twenty-five of 137 lesions were esophageal squamous cell carcinoma (18.2%), nineteen HGD and esophageal adenocarcinoma (13.8%), forty-eight gastric adenocarcinoma (35%), thirteen duodenal adenocarcinoma (9.4%) and the remaining thirty-two (23%) benign lesions. Of the 137 patients treated by EMR during a mean follow-up of 49.8 months, only 6 patients with HGD and intramucosal cancer presented recurrent lesions (5.7%). 95.1% curative resection was achieved in patients with m1, m2 and reaching m3 disease. *En-bloc* resection was possible initially in 91.2%. Minor bleeding was present in 17 patients (12.4%), controlled endoscopically with clips. Prophylatic clips were used in 22 patients (16%). One large perforation was treated by surgical repair.
CONCLUSION: EMR is well suited for superficial esophageal, gastric and duodenal cancer treatment with very little risk of complication and low recurrence rate, as shown in our long-term retrospective study. However in cases when lateral margins and depth of invasion of the specimen are not clear of neoplastic changes (mainly in peace-meal resections), the patients should have careful follow-up.
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Disclosure of Interest: None declared

OP095 FEASIBILITY AND SAFETY OF ENDOSCOPY-ASSISTED LAPAROSCOPIC FULL-THICKNESS RESECTION FOR SUPERFICIAL DUODENAL NEOPLASMS

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INTRODUCTION: Superficial duodenal neoplasms (SDNs) are a challenging target in the digestive tract. Endoscopic resection is technically difficult and surgical approach is difficult to decide the borderline of the lesion precisely. We invent the new approach to remove SDNs that involves a combination of endoscopic and laparascopic technics: endoscopy-assisted laparoscopic full-thickness resection (EALFTR).
AIMS & METHODS: The aim of this study was to investigate the results of a single center experience and assess the validity of EALFTR for SDNs. Between January 2011 and March 2014, 64 patients with nonamupllary duodenal neoplasm without familial polyposis syndrome were included in this study. All cases were assessed for their age, sex, location, en-bloc resection rate, R0 resection rate, lesion size, sample size, procedure time, length of hospital stay after EALFTR, complication, and histopathological report. EALFTR procedure: Under general anesthesia, the duodenum was first mobilized laparoscopically under endoscopic guidance. Then the tumor location was confirmed by endoscopy. The peripheral margin was marked around the tumor endoscopically and each marking was perforated intentionally using a needle knife in the coagulation mode under laparoscopic observation. Subsequently, the sero-muscular layer was laparoscopically dissected along the marking circumferentially using an ultrasonically activated device. After sero-muscular layer incision, submucosa-mucosal layer was dissected along sero-muscular layer incision with ultrasonically activated device. The closure of the defect in the duodenal wall was performed by the laparoscopic hand-suturing technique.
RESULTS: 64 patients (50 males and 14 females, mean age 62.7) were treated by EALFTR. In 2 patients, because 2 lesions were located quite closely, we resected them at the same time. 37 lesions were located at the second portion, 24 at the bulb and 5 at the third portion of the duodenum. En-bloc and R0 resection was achieved for 97.0 % (64/66), too. The mean resected lesion size was 12.0 mm, and the mean resected specimen size was 26.0 mm. The mean procedure time was 136 minutes. The mean length of hospital stay after EALFTR was 13.1 days. Anastomotic leakage occurred in three patients and anastomotic stenosis occurred in three patients postoperatively, but all cases recovered conservatively. Histopathological examination confirmed that 31 were adenomas, 17 adenocarcinomas, 13 neuroendcrine tumors and 5 hyperplastic polyps.
CONCLUSION: EALFTR enables successful en bloc, R0 resection, and full-thickness excision was achieved with an adequate surgical margin in all patients without severe complications. We believe that in treatment of SDNs this method can be a feasible, safe, and minimally invasive treatment option for superficial nonampullary duodenum tumors.
Disclosure of Interest: None declared

OP096 HEMOSTATIC SECOND-LOOK ENDOSCOPY IS USEFUL FOR PREVENTING DELAYED BLEEDING AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) IN EARLY GASTRIC CANCERS

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INTRODUCTION: Endoscopic submucosal dissection (ESD) has been now standard therapy for early gastric cancers. Although safety of the ESD procedure has been substantiated, complications such as perforation and bleeding are still serious problems. Second-look endoscopy for the purpose of hemostasis is routinely performed to prevent post-ESD bleeding in most hospitals, though there is little solid evidence to support this practice. A few reports suggested that second-look endoscopy after gastric ESD contributed little to preventing delayed bleeding. However, these results contradicted our experience. Hemostatic second-look endoscopy is considered to reduce delayed bleeding when it would be appropriately performed according to Forrest classification. The aim of the present study was to verify whether a second-look endoscopy after ESD is effective for the prevention of delayed bleeding and to investigate the clinicopathological features of delayed bleeding after hemostatic second-look endoscopy to identify specific lesions that may require third-look endoscopy.
AIMS & METHODS: Subjects were 186 consecutive patients (142 males and44 females; mean age, 71.0 years) who underwent ESD for gastric cancers between January 2006 and December 2013. Properly preventative coagulation for all exposed vessels on the artificial ulcer with hemostatic forceps was performed routinely at the end of ESD procedure. The vessel types on artificial post-ESD ulcers were evaluated by Forrest classification at the next day after ESD. Ia, Ib or IIa of Forrest classification were essentially required with endoscopic hemostasis. On the other hand IIb or III of Forrest classification were not performed with endoscopic hemostasis.
RESULTS: Patients with hemodialysis significantly harbored Ia, Ib or IIa of Forrest classification at second-look endoscopy. However, there were no significant differences in patient-related factors (age, gender, and use of anticoagulants and antiplatelet drugs) and tumor related factors (tumor location, histological type, depth, size of the resected specimen, and operation time) between Ia, Ib or IIa and IIb or III of Forrest classification. None of 136 patients with IIb or III of Forrest classification at second-look endoscopy had delayed bleeding during hospitalization. In 50 patients with Ia, Ib or IIa of Forrest classification at second-look endoscopy, there was only one patient (2%) with delayed bleeding which required hemostatic third-look endoscopy. The patient underwent hemodialysis and took an antiplatelet drug. The rate of bleeding after appropriately hemostatic second-look endoscopy was 0.5% (1 of 186 patients). The rate in our study was extremely low compared with previous reports in which second-look endoscopy was not performed.
CONCLUSION: Appropriately hemostatic second-look endoscopy for early gastric cancers removed by ESD was useful for preventing delayed bleeding. Precise hemostasis based on Forrest classification at second-look endoscopy may exceedingly reduce delayed bleeding. Third-look endoscopy was not required when appropriate hemostasis at second-look endoscopy was performed.
Disclosure of Interest: None declared

OP097 ENDOSCOPIC TISSUE SHIELDING METHOD WITH POLYGLYCOLIC ACID SHEETS AND FIBRIN GLUE DECREASES THE RISK OF BLEEDING AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION OF GASTRIC NEOPLASMS

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INTRODUCTION: Prevention of bleeding after endoscopic submucosal dissection (ESD) for gastric neoplasms is still an important problem, but there have been no preventive measures other than proton pump inhibitor use and preventive coagulation of visible vessels on the artificial ulcer after ESD.
AIMS & METHODS: We aimed to evaluate the efficacy and safety of the tissue shielding method with polyglycolic acid (PGA) sheets and fibrin glue for preventing bleeding after gastric ESD. This is a non-randomized historical controlled study. We defined high-risk patients for post-ESD bleeding as follows: 1) those who took antithrombotic drugs regularly; or 2) those who were expected to undergo large mucosal resection ($\geq$ 40mm). We enrolled patients who were scheduled to undergo gastric ESD and had above-mentioned risk factors from July 2013 as the study group (Group A). We placed PGA sheets on the mucosal defect and fixed with fibrin glue in the study group. Between January and July 2013, before the first enrolment of a study patient, 126 gastric neoplasms in 101 consecutive patients were treated with ESD. From this cohort, we extracted high-risk patients as the historical control group (Group B). We set the post-ESD bleeding rate as the primary endpoint to compare both groups.
RESULTS: From July 2013 to February 2014, 45 ESD-induced ulcers in 41 high-risk patients for bleeding were enrolled in the study group. In the historical control group, 41 ESD-induced ulcers in 37 patients were extracted. The baseline characteristics were not significantly different between the two groups: sex (A: male 41/female 4, B: male 34/female 7; $P = 0.256$); age (A: 73.6 $\pm$ 7.5 yrs, B: 74.8 $\pm$ 7.0 yrs; $P = 0.482$); antithrombotic drug use (A: 29 lesions, 66.4%, B: 23 lesions, 56.1%; $P = 0.429$); Heparin bridging therapy (A: 7 lesions, 15.6%, B: 3 lesions, 7.3%; $P = 0.319$); and the diameter of resected specimens (A: 40.1 $\pm$ 12.4 mm, B: 43.9 $\pm$ 15.1 mm; $P = 0.206$). Neither intraoperative perforation or delayed perforation occurred in the two groups. Post-ESD bleeding occurred at a rate of 6.7% in the study group (3 lesions), and 22.0% in the historical control group (9 lesions). There was a significant difference in the post-ESD bleeding rate between the two groups ($P = 0.041$). In the study group, post-ESD bleeding occurred only in heparin bridging therapy. In the study group, the procedural time for applying PGA sheets and fibrin glue was 20.4 $\pm$ 9.5 min.
CONCLUSION: The endoscopic tissue shielding method with PGA sheets and fibrin glue appears to be promising for the prevention of post-ESD bleeding.
Disclosure of Interest: Y. Tsuji: none, M. Fujishiro Financial support for research from: Astellas Pharmaceutical, Takeda Pharmaceutical, Zeria Pharmaceutical, Otsuka Pharmaceutical, Astrazeneca Pharmaceutical, Dainihon-Sumitomo Pharmaceutical, Taiho Pharmaceutical, Ajinomoto Pharmaceutical, and, Eisai for his department outside the submitted work, Lecture fee(s) from: Olympus Medical Systems, HOYA Pentax, Eisai, MSD, Daiichi-Sankyo Pharmaceutical, Astrazeneca Pharmaceutical, Aska Pharmaceutical, Taisho-Toyama Pharmaceutical, Otsuka Pharmaceutical, Zeria Pharmaceutical, Takeda Pharmaceutical, Astellas Pharmaceutical, Seikagaku Corp., Johnson & Johnson, Ajinomoto Pharmaceutical, Amco, Novartis Pharmaceutical, Boston Scientific, and, Boehringer-Ingelheim, outside the submitted work, Other: non-financial support from HOYA Pentax, Olympus Medical Systems, and, Fujifilm for his department, Y. Sakaguchi: none, C. Minatsuki: none, I. Asada-Hirayama: none, K. Niimi: none, S. Mochizuki: none, S. Ono: none, S. Kosdashima: none, N. Yamamichi: none, K. Koike: none

OP098 LONG-TERM SURVEILLANCE AND TREATMENT OUTCOMES OF METACHRONOUS GASTRIC CANCER AFTER CURATIVE ENDOSCOPIC SUBMUCOSAL DISSECTION

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INTRODUCTION: Endoscopic submucosal dissection (ESD) allows patients with early gastric cancer (EGC) to preserve their stomach and contributes to better quality of life compared with surgery. However, the incidence of metachronous gastric cancer (MGC) after ESD is higher than that after gastrectomy. The long-term treatment outcomes of MGC after curative ESD are poorly understood.
AIMS & METHODS: This study aimed to evaluate long-term surveillance and treatment outcomes of MGC after curative ESD. Among 1537 consecutive patients with initial EGC who achieved curative resection by ESD between 1999 and 2006, 1526 patients who were followed up were included in this study. 11 patients who underwent scheduled surgery for synchronous esophageal or gastric cancer just after ESD were excluded. They were generally followed up by annual or biannual upper gastrointestinal endoscopy to check for MGC. This study assessed treatment outcomes of MGC, 5-year and 10-year disease specific survival (DFS). Curability of ESD was assessed based on Japanese Gastric Cancer Treatment Guideline 2010[1)].
RESULTS: Of 1526 patients, 334 MGCs were found in 238 patients during a median follow up period of 82.2 months (5 year follow-up: 90.6%). 5- and 7-year cumulative incidence of MGC on surveillance endoscopy were 10.0% and 16.4%, respectively. 296 MGCs in 215 patients were treated with endoscopic resection (Upper/Middle/Lower=62/125/109, Differentiated (D)-type/Undifferentiated (UD)-type/Special/13/2, median tumor size 10 mm (1-50), intramucosa: M/minute submucosa ($<500\mu$m): SM1/deeper submucosa ($\geq 500\mu$m): SM2=270/15/11, ESD/strip biopsy=294/2). En bloc resection, R0 resection and curative resection were 99.3% (294), 94.3% (279) and 88.8% (263), respectively. 183 patients were determined to have curative resection and 32 patients had non-curative resection. Of 183 patients with curative resection, one died of initial EGC with local recurrence and distant metastasis (9.1 years after initial ESD) but none died of MGC. 14 of 32 patients with non-curative resection underwent additional surgery and 18 patients were followed up (the cause of non-curative resection in 10 patients was only positive margin). Of 32 patients with non-curative resection, one patient who underwent additional surgery and one who was followed up died of MGC (2.7 and 4.6 years after initial ESD). 25 MGCs in 14 patients were treated surgically (Upper/Middle/Lower=8/7/10, D-type/UD-type=17/8, median tumor size: 25.0 mm (1-108), M/SM1/SM2/advanced=16/0/4/5). Two of 14 patients died of MGC (6.2 and 7.2 years after initial ESD). 3 patients with 3 clinically unresectable MGCs received palliative chemotherapy and died of MGC (over 5 years after initial ESD). The remaining 10 lesions in 6 patients were observed without any intervention due to high age or co-morbidity but none died of MGC. 5-year and 10-year DFS in 238 patients with MGC was 99.2% and 92.5%, respectively. Both of 5-year and 10-year DFS in 1288 patients without MGC were 100%.
CONCLUSION: Careful surveillance should be utilized for early detection of MGC not only for 5 years but also beyond 5 years after curative gastric ESD.
REFERENCES
1) Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; 14: 113–123.
Disclosure of Interest: None declared

OP099 INTERIM RESULTS OF A MULTI-CENTER, PROSPECTIVE, CONTROLLED TRIAL OF THE DUODENAL-JEJUNAL BYPASS LINER FOR THE TREATMENT OF TYPE 2 DIABETES IN OBESE PATIENTS: ARE THERE ANY FACTORS PREDICTING A SUB-OPTIMAL EFFECT?

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INTRODUCTION: The global increase in obesity incidence results in an increase of type 2 diabetes mellitus (T2DM) incidence. Surgical treatment has proven to be effective, however it carries a high risk of complications. The duodenal-jejunal bypass liner (Endobarrier®, GI Dynamics, DJBL) is an endoscopic implant that mimics the intestinal bypass portion of the Roux-en-Y gastric bypass. It results in weight loss and improvements in glucose control in obese patients with T2DM.
AIMS & METHODS: This is an interim report of an ongoing three years study. The aim of this prospective, controlled, multicentre study is to determine the effectiveness of DJBL and to identify clinical factors associated with a suboptimal outcome of DJBL.
RESULTS: Forty four subjects (24 with an implant, 20 controls) were included in the study. The groups were comparable with respect to age, gender, BMI (mean 37.7 vs. 38.1 kg/m2), T2DM duration (7.2 vs. 8.3 years), HbA1c level (8.8 % vs 8.1 %) and T2DM treatment. In the stent group, all devices were successfully implanted. Only three devices had to be explanted prior to the end of the 6 months study period (bleeding, dislocation and need for ERCP because of choledocholithiasis). The mean procedure time was 21.2 minutes for an implantation and 35.5 minutes for an explantation. At six months there was significantly greater weight loss (27% vs. 9%) and significantly improved HbA1c % (2.3 vs. 1.1) in the device group. T2DM medicinal treatment could be reduced in more device subjects than controls. There was no serious adverse event. Mild abdominal pain and nausea after implantation were experienced by 75% of patients during first 14 days after implantation, 40% of patients during the first month and 11% of patients after one month. Lower initial BMI, distal position of the anchor and lower body height were identified as negative prognostic factors for pain.
CONCLUSION: The DJBL is safe when implanted for 6 months, and results in significant weight loss and HbA1c reduction. This suggests that this novel device is a candidate for the primary therapy of morbid obesity and type 2 diabetes. Lower initial BMI, distal position of the anchor and lower body height could be negative prognostic factor for pain.
Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 15:45-17:15
CHANGING LANDSCAPE OF *H. PYLORI* INFECTION - HALL O

OP100 INTERGENERATIONAL CHANGE IN HELICOBACTER PYLORI COLONIZATION IN CHILDREN LIVING IN A MULTI-ETHNIC WESTERN POPULATION

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INTRODUCTION: *Helicobacter pylori (H. pylori)* colonization rates in childhood have declined in Western populations, but it is unknown whether this trend is similar in children of non-Western ethnic backgrounds, who are born in a Western country. Insight into colonization and transmission of *H. pylori* could improve approaches to assessing *H. pylori*-related diseases.
AIMS & METHODS: We aimed to identify *H. pylori* status in mothers and their children, and to determine both mother-to-child transmission and factors associated with loss of *H. pylori* in one generation. Antibodies against *H. pylori* and cytotoxin-associated gene A (CagA) were measured in mothers and children participating in a population-based prospective cohort study in Rotterdam, the Netherlands. Information on demographics, maternal and child's characteristics was collected using questionnaires. Logistic regression analysis was used to assess factors associated with loss of *H. pylori,* including the following: gender, ethnicity, mother's educational level, delivery mode, breastfeeding, number of older siblings, day-care attendance, and cumulative antibiotic exposures.
RESULTS: *H. pylori* and CagA status were determined in 3,185 mothers and their children. In mothers (mean age of 30.5 ±5.0 years), the overall *H. pylori* colonization rate was 42%, compared to 10% ($p<0.001$) in their children (mean age of 6.2 ±0.5 years). An *H. pylori*-positive mother was associated with an *H. pylori*-positive child (OR 3.22; 95% CI 2.52-4.12). Overall, the *H. pylori* prevalence decreased 76% comparing mothers and their children. A significant and consistent decline in both *H. pylori*$^{+}$CagA^{-} and *H. pylori*$^{+}$CagA^{+}-strains was observed across all nine ethnic groups studied. Multivariate analysis of the loss of *H. pylori* in children with an *H. pylori*-positive mother (n = 1,328) revealed male gender (OR 1.64; 95% CI 1.21-2.23), higher maternal education level (OR 1.78; 95% CI 1.15-2.76), and no older siblings (OR 1.37; 95% CI 1.01-1.88) independently associated with an *H. pylori*-negative child.
CONCLUSION: We identified a large decline in *H. pylori* colonization rate in children living in a European city. The observed drop was uniform across all ethnic groups, implying the importance of environmental factors in *H. pylori* transmission in modern cities, independent of ethnicity.
Disclosure of Interest: None declared

OP101 HELICOBACTER PYLORI COLONIZATION, RESPIRATORY OUTCOMES AND ECZEMA IN SCHOOL-AGE CHILDREN

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INTRODUCTION: The declined *Helicobacter pylori (H. pylori)* prevalence in Western countries is suggested to be associated with the simultaneous increases in childhood asthma and allergic diseases. Bacterial exposure during childhood may be protective for asthma and atopy.
AIMS & METHODS: We aimed to examine the association between children's *H. pylori* colonization and asthma or related diseases. This study was embedded in The Generation R Study, a population-based prospective multi-ethnic cohort study among children, followed from early pregnancy onwards. We measured anti-*H. pylori* and anti-CagA-IgG antibodies in serum of children obtained at age of 6 years. Also at age 6 years, asthma-related outcomes including ever wheezing, physician-diagnosed asthma, and eczema were obtained by questionnaires. Data analyses were performed in the total cohort as well as in different ethnic groups (Western *vs.* non-Western). Multivariate logistic regression analyses were adjusted for maternal educational level, history of asthma and atopy, smoking during pregnancy, and parity, and for child's gender, ethnicity, gestational age at birth, birth weight, breastfeeding habits, day-care attendance, pet keeping, and lower respiratory tract infections.
RESULTS: In total 3,838 children (mean age 6.1 ± SD 0.5) were available for these analyses. Of those, 328 (9%) were *H. pylori*-positive, of whom 100 (30%) were CagA-positive. Univariate analyses revealed the following results of comparison between *H. pylori*-positive versus negative children: ever wheezing [63.3% vs. 56.0% (p=0.07)], physician-diagnosed asthma [11.2% vs. 6.6% (p=0.01)], and eczema [27.0% vs. 22.2% (p=0.07)]. In multivariate analyses *H. pylori*-positivity was associated with physician-diagnosed asthma (odds ratio (OR) 1.63; 95% CI 1.02-2.61), but not with ever wheezing (OR 1.02; 95% CI 0.85-1.23) or eczema (OR 1.06; 95% CI 0.79-1.41). A significant interaction between *H. pylori* and ethnicity was found for wheezing ($p<0.001$) and eczema (p=0.006). Analyses stratified according to ethnicity showed that *H. pylori*-positivity was inversely associated with ever wheezing (OR 0.66; 95% CI 0.48-0.91), and eczema (OR 0.64; 95% CI 0.41-1.00) in children of non-Western ethnicity (n= 1,155), but not in children of Western ethnicity (n= 2,683). This negative association was mainly explained by the CagA-positive strains.
CONCLUSION: *H. pylori* colonization is negatively associated with both wheezing and eczema in children of non-Western ethnicity, with the strongest inverse effect found for CagA-positive strains. In contrast, in all children *H. pylori*-colonization was positively associated with physician-diagnosed asthma to the age of 6 years. Trends in the Western and non-Western children appear opposite.
Disclosure of Interest: None declared

OP103 META-ANALYSIS OF SEQUENTIAL VS. STANDARD TRIPLE THERAPY FOR HELICOBACTER PYLORI ERADICATION: FINAL RESULTS OF A COCHRANE SYSTEMATIC REVIEW

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INTRODUCTION: Sequential therapy (SEQ) has been suggested as a new first-line treatment option to replace the standard triple therapy (STT), where eradication rates have declined to unacceptable levels.
AIMS & METHODS: To conduct a meta-analysis of studies comparing SEQ vs. STT for *H. pylori* eradication.
Selection of studies: randomized controlled trials comparing SEQ (10 days) and STT (at least 7 days) for the eradication of *H. pylori*. *Search strategy:* bibliographical searches in electronic databases, and manual search of abstracts from Congresses, were conducted up to November 2013. *Data synthesis:* intention-to-treat eradication rate.
RESULTS: We included 33 randomized controlled studies with a total of 9,750 patients (4,542 in SEQ and 5,208 in STT). The overall analysis showed that SEQ was significantly more effective than STT (84% vs. 74% in the intention-to-treat analysis; OR=2.07; 95%C.I.=1.64-2.61; $p<0.001$). Results were highly heterogeneous (I^2=77%) and 11 studies were unable to demonstrate differences between therapies. Subgroup analyses suggested that patients with clarithromycin resistance and/or taking esomeprazole-rabeprazole could benefit more from the SEQ. However there were no differences when STT lasted 14 days. Although, overall, mean eradication rate with SEQ was over 80%, a tendency towards lower efficacy with this regimen was observed in the more recent studies [weighted linear regression per year -0.02 (-2% per year) in SEQ vs. -0.005 (-0.5% per year) in STT], and in studies performed outside Italy (OR 1.57 vs. 4.09).
CONCLUSION: The meta-analysis demonstrated that SEQ is more effective than STT lasting less than 14 days. Nevertheless, the apparent advantage of sequential treatment seems to be decreasing over time; therefore further and continuous assessment is needed before a generalized change in all settings is recommended for first line *H. pylori* treatment.
Disclosure of Interest: None declared

OP104 THE EFFICACY OF PROBIOTICS AS ADJUVANT TREATMENT IN ERADICATING HELICOBACTER PYLORI BY STANDARD TRIPLE THERAPY: A RANDOMIZED CONTROLLED TRIAL

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INTRODUCTION: The current report of the European Helicobacter Study Group considers probiotics as an adjuvant treatment in reducing side effects during the standard *Helicobacter pylori* eradication therapy. The primary objective in the study is determination of efficacy of probiotic preparation as a supportive therapy in eradication of *H. pylori*.
AIMS & METHODS: The study was multicenter, prospective, randomized, placebo controlled, and double-blind. The enrolment of subjects into the trial was conducted in 121 general practitioners' offices, in different regions in Croatia from September 2009 until June 2012. The study was reported according to the CONSORT guidelines and was registered at www.clinicaltrials.gov (NCT01969331).The initial diagnosis of *H. pylori* infection was established using rapid urease test, stool antigen, or urea breath test. The subjects first filled out a specially designed questionnaire in order to assess the severity of the 10 symptoms which can be related to eradication therapy to be monitored during the trial. Each subject then received 28 capsules of probiotic preparation or matching placebo capsules, which they were supposed to take over the following 14 days, twice a day, at least two hours prior to or after the antibiotic therapy administration.
RESULTS: A total of 804 patients were enrolled in the trial, of which 650(80.85%) were included in the analysis. The results show a significantly larger share of cured subjects in the probiotic arm versus the placebo arm (87.38% vs. 72.55%; $p<0.001$). Additionally, odds ratio, absolute and relative risk reductions as well as number needed to treat all point strongly in favour of probiotic arm. Overall, at baseline the average value of intensity for all 10 symptoms was 1.17 for subjects on probiotic and 1.07 for subjects on placebo ($p<0.001$). At follow-up visit 15 days after the start of the trial, the intensity of the same symptoms that were monitored at enrolment was again evaluated.

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Outcome Measure	ProCore (n)	FNA (n)	Procore Pooled Estimate: mean % (95% CI)	FNA Pooled Estimate: mean % (95% CI)	Pooled RR (95%CI)	p-value
Diagnostic Adequacy: All Masses	742	745	82.7 (74.2-89.8)	79.3 (70.4-87.0)	1.06 (0.97-1.16)	0.221
Diagnostic Adequacy: Pancreatic Masses	317	324	84.8 (70.4-95.0)	88.5 (80.1-94.9)	0.98 (0.85-1.12)	0.721
Diagnostic Accuracy: All Masses	421	474	84.9 (76.1-92.0)	79.3 (71.8-85.9)	1.06 (0.99-1.14)	0.083
Diagnostic Accuracy: Pancreatic Masses	225	277	88.4 (82.4-93.3)	79.9 (73.6-85.5)	1.12 (0.99-1.26)	0.067
Histology: All Masses	104	108	66.8 (49.7-81.9)	68.7 (54.5-81.3)	1.02 (0.85-1.22)	0.864
Histology: Pancreatic Masses	66	70	75.4 (60.2-87.8)	75.2 (63.2-85.5)	1.03 (0.84-1.26)	0.756
Mean no. of passes for diagnosis: All Masses	209	209	-	-	SMD -0.90 (-1.80 - 0.005)	0.051

Overall, the average intensity value for all 10 symptoms was 0.55 for subjects on probiotic and 0.76 for subjects on placebo ($p<0.001$).
CONCLUSION: Adding probiotics to the standard triple therapy for *H. pylori* eradication significantly contributes to treatment efficacy and distinctly decreases the adverse effects of therapy and the symptoms of the underlying disease.
Disclosure of Interest: G. Hauser Financial support for research from: Company sponsored trial, Consultancy for: principal investigator served as consultant, N. Salkić: None declared, K. Vukelic Other: emploee of the company, V. Vrbanovic Other: emploee of the company, D. Stimac: None declared

OP105 PAN-EUROPEAN REGISTRY ON *H. PYLORI* MANAGEMENT: INTERIM ANALYSIS OF 5,000 PATIENTS

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INTRODUCTION: Due to the diversity of *H. pylori* strains, resistances and geographical particularities, the most efficient management strategy is still to be found.
AIMS & METHODS: To systematically register the clinical practice of European gastroenterologists regarding *H. pylori* infection and treatment (31 countries and 250 recruiting investigators)
A Local Coordinator was selected from each Country with more than 10 *H. pylori* REFERENCES on PubMed. Each Coordinator selected a representative group of recruiting investigators from its country (250 so far). An electronic clinical research file was created to systematically register all adult patients infected with *H. pylori*. Variables included: Patient's demographics, previous eradication attempts, prescribed eradication treatment, adverse events, and outcomes (cure rates, compliance, follow up, etc.).
RESULTS: Up to now, 5,000 patients have been included, and 3,333 have finished follow up. 58% females. 87% Caucasian. Mean age was 57 years. 4.3% had drug allergies (77% to penicillin). 53% of indications were dyspepsia. 23% had gastroduodenal ulcer. 70% were diagnosed using endoscopy based methods. 78% were naïve, 16% second-line, 4.8% third-line, 1.2% fourth-line, and 0.5% fifth-line. Culture was performed in 15%, of which 57% showed antibacterial resistance (40% to nitroimidazoles, 32% clarithromycin, 17% quinolones, 0.8% amoxicillin and 0.9% tetracycline). 63% of prescriptions were triple regimens (PPI + 2 antibiotics), 12% non-bismuth concomitant quadruple, 14% sequential, and 6.9% bismuth quadruple. 53% of patients had adverse events (13% metallic taste, 12% diarrhea, and 11% nausea) although they were mostly mild (65%) and lasted an average of 6.8 days, causing treatment discontinuation in 4.2% of cases. Overall eradication rate was 80%, and only 64% of eradication failures were retreated. The most common prescribed treatments for first (triple therapy with clarithromycin and amoxicillin) and second line (triple therapy with amoxicillin and levofloxacin) achieved suboptimal eradication rates: 76% and 78% respectively.
CONCLUSION: *H. pylori* management by gastroenterologists in Europe is extremely diverse. It is important to notice that the achieved eradication rates are clearly suboptimal, especially with the use of the commonly recommended standard triple therapy (76%). Continuation of this registry and deeper evaluation of its data may offer valuable information to improve *H. pylori* management.
Disclosure of Interest: None declared

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MINIMALLY INVASIVE INTERVENTIONS IN THE PANCREAS – LOUNGE 5

OP106 ENDOSCOPIC ULTRASOUND-GUIDED TISSUE ACQUISITION: META-ANALYSIS COMPARING THE PROCORE AND STANDARD FINE NEEDLE ASPIRATION NEEDLES

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INTRODUCTION: To overcome the limitations associated with cytology, a ProCore biopsy platform has been developed in 19, 22 and 25G sizes. However, individual studies comparing the ProCore and FNA needles have yielded varying conclusions.
AIMS & METHODS: This meta-analysis was conducted to compare the performance of the ProCore and standard FNA needles when performing EUS-guided tissue acquisition. All published manuscripts and presented abstracts (International Scientific Meetings) that compared the ProCore and FNA needles were analyzed. Excluded were non-comparative and technical feasibility studies. Main outcome measures: Compare the rates of diagnostic adequacy, diagnostic accuracy, histological core tissue procurement and mean number of passes to diagnosis when sampling all solid organ lesions and solid pancreatic masses.
RESULTS: A total of 21 studies involving 1617 patients met inclusion criteria. There was significant heterogeneity in study design and end points. Study outcomes are shown in the Table. There was no significant difference in diagnostic adequacy/accuracy, histological core tissue procurement or mean number of passes to diagnosis between both cohorts. Subgroup analysis did not reveal any difference between the 19, 22/25G needles for any of the outcome measures.
CONCLUSION: Current data does not demonstrate a significant difference in performance between the ProCore and standard FNA needles for establishing a diagnosis with fewer no. of passes, for yielding a better cytological aspirate or histological core tissue. Therefore, the choice of a needle should be based on endosonographer preference and needle costs.
Disclosure of Interest: None declared

OP107 SMART ATLAS FOR SUPPORTING THE INTERPRETATION OF NEEDLE-BASED CONFOCAL LASER ENDOMICROSCOPY (NCLE) OF PANCREATIC CYSTS: FIRST CLASSIFICATION RESULTS OF A COMPUTER-AIDED DIAGNOSIS SOFTWARE BASED ON IMAGE RECOGNITION

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INTRODUCTION: nCLE enables microscopic imaging of pancreatic cysts, in vivo and in real time, during an EUS-FNA procedure. Differentiating branch duct-type Intraductal Papillary Mucinous Neoplasm (IPMN) and Serous Cystadenoma (SCA) of the pancreas can be difficult, especially in case of a solitary lesion without clear communication with the pancreatic duct. Recent studies (Konda et al., Endoscopy 2013; Napoleon et al., DDW 2013) have identified reliable nCLE descriptive features (superficial vascular network in SCA; finger- like projections in IPMN), allowing endoscopists to discriminate between SCA and IPMN. In parallel, a computer-aided diagnosis software called Smart Atlas has been developed to assist endoscopists with the interpretation of nCLE video sequences. This study aims at evaluating the performance of this software for the differentiation of SCA and IPMN cases.
AIMS & METHODS: Several nCLE sequences, of proven SCA or IPMN, were retrospectively collected from nCLE procedures performed in multiple clinical centers. These video sequences, along with their annotated final diagnosis, were used to train a classification software that uses a content-based image retrieval algorithm to predict the diagnosis of a query video based on the diagnoses of the most visually similar atlas videos. All evaluations were performed using leave-one-patient-out cross-validation to avoid bias. To reduce the number of unnecessary surgeries with high morbidity rates, false positives were minimized on a receiver operating curve.
RESULTS: 29 nCLE video sequences were collected from 18 patients, with one lesion per patient (12 SCA, 6 IMPN), leading to 22 sequences annotated with SCA and 7 sequences annotated with IPMN. The classification results maximizing the specificity for an acceptable sensitivity show a specificity of 95.5% for a sensitivity of 85.7%, an accuracy of 93.1%, a PPV of 85.7% and a NPV of 95.5%, with only one false positive and one false negative. In comparison, Napoleon et al. reported that the performance achieved by a consensus of investigators on retrospective data to differentiate SCA from all other types of lesions reaches a specificity of 100% for a sensitivity of 62.5%.
CONCLUSION: These first results demonstrate that the Smart Atlas software is able to differentiate SCA and IPMN cases using only the image content of nCLE sequences, with very high specificity and rather high sensitivity. Besides, the case-based reasoning software can detect relevant video content and provide diagnostic confidence levels. It could thus be used as an educational tool to train non-expert endoscopists, but also as a second-reader tool to assist any user in real-time diagnosis of pancreatic cysts using nCLE. Future software improvements will leverage a larger sample size, various types of cysts and clinical metadata.
Disclosure of Interest: None declared

OP108 A PROSPECTIVE RANDOMIZED CROSS-OVER STUDY OF THE DIFFERENCE IN DIAGNOSTIC YIELD BETWEEN EUSFNA NEEDLES WITH AND WITHOUT A SIDE PORT IN PANCREATIC MASSES

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INTRODUCTION: Currently two needles with similar designs, apart from absence and presence of side port, are available from Olympus Corporation (Tokyo, Japan) for EUS-guided fine needle aspiration (FNA). These are EZ-Shot 2 and EZ-Shot 2 with side port. The theoretical basis for introduction of the side port was to facilitate the process of FNA and increase diagnostic yield but this advantage remained unproven.
AIMS & METHODS: This pilot study aimed to determine the difference in diagnostic yield between EZ-Shot 2 and EZ-Shot 2 with side port in patients with pancreatic masses. This was a pilot multicenter prospective randomized cross-over study involving 3 referral centers in Korea, Singapore and Taiwan. Patients referred for EUSFNA of pancreatic masses were recruited. Four EUSFNA passes were performed per patient. Patients were randomized to one needle for the first 2 passes, followed by the other needle for the next 2 passes. Rapid on-site cytopathological assessment was not performed. A pathologist blinded to the needle that was used assessed each individual needle pass for cellularity and morphology. The diagnostic yield between both needles was compared. The reference standard was based on composite of cytology, histology and clinical course.
RESULTS: A total of 30 patients were recruited (mean age 66 year; 53% female) with total of 120 needle passes. The sites of lesions were 15/30 at pancreatic head, 7/30 at pancreatic neck/body and 8/30 at pancreatic tail. The final diagnoses were pancreatic adenocarcinoma (24/30), neuroendocrine tumor (2/30), cholangiocarcinoma (1/30), pancreatitis related pseudotumour (2/30) and serous cystadenoma (1/30). Mean size of mass was 3.5 cm (range: 1.2 – 6.3). Comparison of the 2 needles for cellularity adequacy: first pass: EZ Shot 2 vs. EZ Shot 2 with side port: 26/30 (86.7%) vs. 25/3 (83.3%) ($p = 0.718$): 2nd pass: EZ Shot 2 vs. EZ Shot 2 with side port: 25/30 (3.3%) vs. 26/30 (86.7%) ($p = 0.718$). Comparison of the 2 needles for diagnostic accuracy: first pass: EZ Shot 2 vs. EZ Shot 2 with side port: 22/30 (73.3%) vs. 23/30 (76.7%) ($p = 0.766$); combined 2 passes: EZ Shot 2 vs. EZ Shot 2 with side port: 26/30 (86.7%) vs. 26/30 (86.7%) ($p = 1.0$). When the 4 passes for each lesion were assessed together adequate cellularity was obtained in all cases and the correct diagnosis was obtained in 24/24 cases of pancreatic adenocarcinoma, 2/2 neuroendocrine tumor, 2/2 pseudotumor, 1/1 serous cystadenoma and 0/1 case of cholangiocarcinoma. There were no EUSFNA related complications.
CONCLUSION: For EUSFNA of pancreatic masses, there were no statistically significant differences in adequacy of cellularity or diagnostic accuracy between FNA needles with or without side port. After 4 passes, adequate cellularity was obtained in all cases and the correct diagnosis was achieved in 96% of cases.
Disclosure of Interest: None declared

OP109 CRITICAL ASSESSMENT OF THE CHOICE OF ENDOPROSTHESIS FOR TRANSMURAL DRAINAGE OF PANCREATIC FLUID COLLECTIONS

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INTRODUCTION: With increased application of endoscopic techniques for the management of pancreatic fluid collections (PFCs), metal stents are being used more frequently for transmural drainage despite the lack of data.
AIMS & METHODS: A systematic review and meta-analysis were conducted to compare the performance of metal and plastic stents when undertaking endoscopic transmural drainage of PFCs.
MEDLINE and EMBASE were searched to identify all published manuscripts that evaluated metal stents for endoscopic transmural drainage of PFCs. Additionally, all published studies from the same period involving plastic stent placement for the same indication that included >50 patients were also identified. A random effects model was used. Main Outcome Measures: Compare the rates of treatment success, complications and recurrence between patients undergoing metal versus plastic stent placement for endoscopic transmural drainage of PFCs.
RESULTS: A total of 12 studies consisting of 725 patients met inclusion criteria. The overall treatment success was marginally higher for patients treated with plastic than metal stents (Table) as the proportion of success for plastic stents (89.7%) was more than the 95% confidence interval (CI) for metal stents (72.6-88.7%). Also, subgroup analysis revealed that the treatment success rates were higher when pseudocysts were drained using plastic (96.3% [95% CI 91.8-98.4%]) than metal stents (82.0% [95% CI 71.8-89.1%]) as there was no overlap of 95% CI between the cohorts. There was however, no difference in the rates of treatment success for walled-off pancreatic necrosis (WOPN). Additionally, there was no difference in the rates of complications or recurrence between plastic and metal stents as evident by the considerable overlap of 95% CIs.

	Metal stents (n=94)	Plastic stents (n=631)
Treatment success: % (95% CI)		
All PFC types	82.1 (72.6 - 88.7)	89.7 (78.9 - 95.3)
Pseudocysts only	82.0 (71.8 - 89.1)	96.3 (91.8 - 98.4)
WOPN only	75.1 (39.2 - 93.4)	74.9 (56.9 - 87.1)
Complications: % (95% CI)		
All PFC types	17.9 (10.7 - 28.3)	15.7 (9.4 - 25.1)
Pseudocysts only	17.1 (9.6 - 28.5)	9.8 (2.9 - 27.9)
WOPN only	20.6 (6.0 - 51.3)	17.0 (12.0 - 23.6)
Recurrence: % (95% CI)		
All PFC types	9.3 (4.1 - 15.9)	9.1 (5.1 – 15.6)
Pseudocysts only	9.2 (3.9 - 20.5)	9.7 (3.7 - 23.0)
WOPN only	10.0 (0.6 - 67.4)	8.3 (3.3 - 19.5)

CONCLUSION: Current evidence does NOT support the routine placement of metal stents for transmural drainage of PFCs, particularly pseudocysts. Large, multicenter, randomized trials are needed to justify the use of metal stents for PFC drainage.
Disclosure of Interest: None declared

OP110 LAPAROSCOPIC VERSUS OPEN DISTAL PANCREATECTOMY FOR BENIGN AND MALIGNANT DISEASE: A MULTICENTER RETROSPECTIVE MATCHED-COHORT STUDY

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INTRODUCTION: Recent cohort studies from expert centers suggest that laparoscopic distal pancreatectomy (LDP) is superior to open distal pancreatectomy (ODP). Introduction of LDP, however, has been slow, possibly because of unclear external validity of these data. Data on the use, outcomes and attitude regarding LDP on a national level are lacking.
AIMS & METHODS: This study aimed to determine the extent of LDP in the Netherlands and to assess the attitude of Dutch pancreatic surgeons regarding this procedure. Adults who underwent LDP or ODP in one of the 17 Dutch medium-high volume centers between January 2005 and September 2013 were analyzed retrospectively. Patients were excluded if DP was not the primary procedure or if too little data were available. Every LDP patient was matched to an ODP patient based on sex, age, ASA score, indication for surgery and tumor size. Primary endpoint were clinically relevant complications (Clavien-Dindo score >2). Analyses were by intention-to-treat. A questionnaire regarding attitudes towards LDP was sent to all 30 Dutch pancreatic surgeons.
RESULTS: Of 633 included patients, 64 (10%) underwent LDP and 569 (90%) ODP. 128 patients were excluded, 124 because DP was not the primary procedure and 4 because too little data were available. 63 LDP patients were matched adequately to 63 ODP patients, such that baseline characteristics were comparable. Clinically relevant complications occurred less after LDP than after ODP (14% vs. 30%, *P=0.03*). Conversion occurred in 33% of LDPs. LDP was associated with 375ml less intra-operative blood loss (*P=0.04*) and 2 days shorter postoperative stay (*P=0.01*). No significant differences were seen regarding operating time, fistula, gastroparesis, bleeding, infection, ICU admittance and total duration of hospitalization. The questionnaire (90% response) showed that 85% of Dutch pancreatic surgeons wanted to participate in LDP-training and 96% in a randomized trial.
CONCLUSION: LDP seems to be safe in the Netherlands in this relative small group of selected patients despite the high conversion rate. A nationwide training scheme for LDP (LAELAPS) has been developed.
Disclosure of Interest: None declared

OP111 ENDOSCOPIC TREATMENT OF CHRONIC PANCREATITIS IN CHILDREN: LONG TERM FOLLOW UP

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INTRODUCTION: Chronic pancreatitis (CP) in children is a rare disease and experience of ERCP in children with CP is limited.
AIMS & METHODS: All pediatric patients (<18 yrs) with CP who underwent ERCP from Oct 1992 to Feb 2013 were retrospectively identified from a prospective database at a tertiary care referral center. Indications, findings, treatment modalities, adverse events/outcomes were recorded. Data on long term follow-up were analyzed. Safety and efficacy on treatment were also evaluated.
RESULTS: During the study period 125 children underwent ERCP for biliopancreatic disorders. Of these, 35 (28%) children (16 boys, mean age 11.6 yrs [range 2.5-17]) underwent ERCP for painful CP and were included in the study. Indications to ERCP were recurrent bouts of pancreatitis and pain. Mean symptoms duration before ERCP was 2.4 yrs (range 0.1 to 14 yrs). Gene mutations for CP had 17 (48.5%) children while 8 (22.8%) had pancreatic calcifications (X-ray/CT/US). Data were missing regarding the number of patients that underwent MRCP before ERCP. On ERCP, normal main pancreatic duct (MPD) anatomy was found in 19 (54.3%) children, while pancreas divisum and dominant dorsal duct anatomy had 10 (28.6%) and 6 (17.1%) respectively. On first ERCP, 21 children had major papilla pancreatic endoscopic sphincterotomy (ES), while minor papilla ES was done in 9 (5 had both major and minor papilla ES). Of these, 3 underwent also Extracorporeal Shock-Wave Lithotripsy on pancreatic stones. Stones and plugs were extracted and in 17 cases. Dominant MPD stricture was found in 5 children, and plastic stents were placed. ERCP-related complications during the first treatment (bleeding/pancreatitis) occurred in 2 children (5.7%) and were managed conservatively. Mean follow-up of the 35 patients was 8 yrs (range 0.7-21). Fourteen (40%) children had only one ERCP and were pain-free during 7.3 yrs (range 0.7-17) of follow-up, while 21 (60%) had recurrence of pain after a mean of 3.8 yrs (range 0.1-20.4) and underwent additional ERCPs (total of 68 re-interventions [range 1-13; 3.2/patient]). On re-interventions, 9 patients had dominant MPD stricture and were treated with plastic stents placement. These were pain-free on last follow-up (5.8 yrs [range 0.3-14.8]) after stent removal. Sixteen children had stricture on the site of ES and had re-ES and/or pneumatic dilation. Plugs were extracted in 17 children during re-interventions. One boy had post re-ES bleeding that was managed endoscopically and there were two cholecystitis managed conservatively. After the last re-intervention these children were pain-free for mean 3.6 yrs [range 0.3-5.6]). The number of re-interventions was higher in female children ($p < 0.01$), and in those with less than 8 yrs of age ($p < 0.01$). Pain recurrences were not related to MPD anatomy or the presence of gene mutations (p=0.2 and p=0.3 respectively).
CONCLUSION: ERCP in pediatric patients with chronic pancreatitis is a safe and effective procedure. In more than one third of cases only one ERCP can be resolutive. Like already described (1), our series confirms the need for repeated ERCPs for pain recurrences, that can be managed endoscopically without major complications.

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Disclosure of Interest: None declared

MONDAY, OCTOBER 20, 2014 15:45–17:15
CIRRHOSIS AND NON-INVASIVE DIAGNOSIS OF FIBROSIS – LOUNGE 6

OP112 PROTON PUMP INHIBITOR INTAKE IS NEITHER ASSOCIATED WITH THE DEVELOPMENT OF SPONTANEOUS BACTERIAL PERITONITIS OR OTHER INFECTIONS NOR WITH MORTALITY IN PATIENTS WITH CIRRHOSIS AND ASCITES

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INTRODUCTION: Conflicting results have been reported on the association between proton pump inhibitor (PPI) intake and spontaneous bacterial peritonitis (SBP) development in patients with cirrhosis and ascites.
AIMS & METHODS: The aim of this study was to assess the impact of PPI intake on the development of SBP or other infections, as well as mortality, in a thoroughly documented cohort with a particularly high prevalence of PPI intake. We performed a retrospective analysis of data from 607 consecutive patients with cirrhosis who had their first paracentesis at the Medical University of Vienna from 2006 through 2011. Cox models were calculated to investigate the effect of PPI intake on the incidence of SBP or other infections, as well as transplant-free survival. All models were adjusted for age, hepatocellular carcinoma (HCC), previous variceal bleeding, varices and model of end-stage liver disease (MELD) score.
RESULTS: PPI intake was very common (86%). At the first paracentesis, mean age was lower (PPI:57.1 ±11.7 vs. no-PPI:60.2 ±12.1; P=0.02), while median MELD score was higher (PPI:18 (10.3) vs. no-PPI:15.2 (7.7); P=0.037) among patients with PPI intake. While the proportion of patients with HCC was higher among patients without PPI intake (PPI:22% vs. no-PPI:37%; P=0.003), previous variceal bleeding (PPI:20% vs. no-PPI:10%; P=0.038) and varices (PPI:75% vs. no-PPI:60%; P=0.003) were more frequently observed in the PPI group. Similar differences were observed in the subgroups of patients without SBP and patients without SBP or other infections at the first paracentesis.
The proportion of patients with SBP at the first paracentesis was comparable between PPI (19%) and no-PPI (17%; P=0.691) patients. After adjusting for potential confounding factors, PPI intake was not associated with SBP incidence (HR:1.33; 95%CI:0.6-2.96; P=0.486), or incidence of SBP or other infections (HR:1.36; 95%CI:0.67-2.77; P=0.389).
Moreover, PPI intake had no impact on transplant-free survival, neither in the overall cohort (HR:0.973, 95%CI:0.719-1.317; P=0.859), nor in the subgroups of patients without SBP (HR:1.01, 95%CI:0.72-1.42; P=0.971) and without SBP or other infections at the first paracentesis (HR:0.944, 95%CI:0.668-1.334; P=0.742).
CONCLUSION: Previous studies reporting an association between PPI intake and SBP incidence were based on cohorts with a substantially lower proportion of patients on PPI treatment, suggesting indications for PPI administration were followed more rigorously. In our cohort with a particularly high prevalence of PPI intake, we observed no association between PPI intake and SBP or other infections, as well as mortality. Thus, the underlying disease and other unknown factors, rather than PPI treatment per se may predispose for complications in patients with cirrhosis and ascites.
Disclosure of Interest: None declared

OP113 PORTAL VEIN THROMBOSIS NATURAL COURSE AND SURVIVAL IN CIRRHOTIC PATIENTS

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INTRODUCTION: Portal vein thrombosis (PVT) has a high incidence in patients with liver cirrhosis, frequently in its advanced stages, and determines a poor prognosis of hepatic disease.
AIMS & METHODS: The aim of this study was to evaluate long-term outcome of patients with portal vein thrombosis and liver cirrhosis. We conducted a prospective cohort study including all adult patients referred to a tertiary center between January 2011 and December 2013 with non-malignant PVT and liver cirrhosis. We excluded patients who received anticoagulant treatment, patients with malignant disease including hepatocellular carcinoma, known thrombofilia, those with portal cavernoma. All patients were evaluated by Doppler abdominal ultrasound and computed tomography. Portal vein thrombosis group was compared with a control group consisting in cirrhotic patients comparable in terms of liver disease severity.
RESULTS: A total of 62 patients (51.6 % female) were included, with a median age at PVT-diagnosis of 59.02 years (range 29–80). Study group included 32 patients diagnosed with PVT, 22 of them with partial PVT. The control group consisted in 30 cirrhotic patients with comparable baseline characteristics as the study group. Median follow-up was 21.69 months (range 4–31). There was no

difference regarding hepatic decompensation rate at 6 and 18 months between patients with PVT and control group groups (19% *vs.* 20%, *P*=0.821 and 54% *vs.* 51%, *P*=0.755, respectively). The survival rate at 6 months was 81.3% in PVT group *vs.* 84.7% (*P*=0.067) in control group, and 63.1% *vs.* 61.7% (*P*=0.122) at 18 months, respectively. Multivariate analysis showed that total PVT was the independent predictor of hepatic decompensation [hazard ratio (HR) 1.56; 95% confidence interval (CI): 1.14-6.67, *P*=0,032] with no influence on survival rate.
CONCLUSION: There was no difference regarding decompensation and survival rates between cirrhotic patients with or without PVT and similar stage of liver disease. Total portal vein thrombosis negatively influence hepatic decompensation rate.
Disclosure of Interest: None declared

OP114 PATIENT UNDERSTANDING OF LIVER CIRRHOSIS: IMPROVEMENT THROUGH USE OF AN EDUCATIONAL SCREENCAST

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INTRODUCTION: Working in partnership with patients and their families is essential in modern healthcare. For this partnership to be effective, patients must have sufficient understanding of their condition. Patient understanding may be limited due to restricted time for counselling in clinic and the variable quality of available educational resources. To our knowledge, patient understanding of cirrhosis and its complications has not been previously studied.
AIMS & METHODS: We aim to assess the baseline knowledge of a cohort of patients with liver cirrhosis and to test the effectiveness of a condition-specific screencast. This is a narrated video that presents relevant and evidence-based information about liver cirrhosis, supported by on-screen text, diagrams and animations.
The study has been approved by our local research and development department as a study designed for service quality improvement. Patients attending the outpatient clinic aged 18 years or over with liver cirrhosis and on a surveillance programme for hepatocellular carcinoma were eligible to participate. Those who were not aware they had liver cirrhosis and patients who had hepatic encephalopathy were not eligible to participate.
Participants completed a baseline questionnaire assessing their knowledge of the management and complications of cirrhosis. They were then invited to watch a 12-minute-long screencast, which was developed in collaboration with patient groups and liver specialists. The screen-cast describes the definition, causes, management and complications of cirrhosis. Patients were invited to complete a new copy of the original questionnaire immediately after watching and once again at least one month (range 1-6 months) after watching the screen-cast. Participants completed the interval questionnaire and submitted it by post or online.
RESULTS: Sixty-three patients were approached. Eight were not eligible to participate and six declined. Forty-nine patients were assessed (M=31, F = 18) with a median age of 56 and median follow-up period of three years. Participants achieved a total score of 29.1% on the baseline questionnaire. This increased to 67.9% after watching the screencast ($P<0.001$). Thirty-four patients completed the follow-up questionnaire after an interval period. They achieved a total score of 64.7%, an increase of 35.6% compared to baseline ($P<0.001$). Between baseline and interval follow-up, knowledge of the reason for having regular ultrasounds improved by 22.2%, regular endoscopies by 41.3%, bone-density scans by 53.3%, being prescribed laxatives by 73.3%, risk of bleeding by 51.1%, liability to develop encephalopathy by 66.1%, knowledge of complications (e.g. muscle wasting and impaired clotting) by 12.9% and knowledge of liver functions by 27.2%.
CONCLUSION: Participating patients had been seen previously in a liver clinic where information about cirrhosis is regularly delivered by healthcare professionals and where information leaflets are readily available. Despite this, baseline understanding was poor. Delivering information by video led to a significant increase in patients' knowledge about their condition. This was present both immediately and following an interval period. We therefore present an effective way to empower patients with accurate, up-to-date and retainable information, which could be easily translated to several other chronic disease conditions.
Disclosure of Interest: None declared

OP115 ASSESSMENT OF PORTAL HYPERTENSION USING PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY (P-CLE)

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INTRODUCTION: There has been recent increasing interest in the early detection of portal hypertension (PHT) in an attempt to prevent the morbidity of late-stage cirrhosis, stratify disease severity and modify outcomes in potentially-reversible conditions like NAFLD and alcoholic hepatitis.
AIMS & METHODS: To evaluate as a proof-of-concept the relationship of novel quantitative endomicroscopic microvascular and morphological features to clinical markers of PHT.
Methods: In an IRB-sanctioned study, we enrolled subjects with and without PHT scheduled for a medically-indicated upper endoscopy at VA Boston. Upon IV injection of 300 mg sodium fluorescein, real-time pCLE and video microangiography were performed. The microvasculature was best visualized in the duodenum where villi were imaged using a GastroFlex-UHD™ mini-probe (Mauna Kea Technologies, Atlanta, GA), providing 1000x magnification, a 20 μm optical slice thickness, 1μm lateral resolution, and a 240μm field of view. Digital videos were then analyzed off-line in a blinded manner for vessel and epithelial morphometry using image processing algorithms.
RESULTS: To date, pCLE images have been analyzed from 15 control and 16 PHT patients. Average vessel diameter (AVD) and branching (AVB) were measured in 249 regions of interest from control vs. 301 regions from PHT subjects. Average columnar cell height (ACCH) within the villus epithelial stripe was measured in 219 control vs. 197 PHT regions. Spearman correlations of 0.87 (95%CI, 0.74,0.93; $p=8.3\times10^{-11}$), 0.42 (95%CI, 0.09,0.67; p=0.01), and 0.71 (95%CI, 0.48,0.85; $p=3.8\times10^{-6}$) were obtained for AVD, AVB, and ACCH, respectively, when compared to the severity of portal gastropathy, and of 0.88 (95%CI, 0.76,0.94; $p=1.99\times10^{-11}$), 0.41 (95%CI, 0.07,0.66; p=0.02), and of 0.66 (95%CI, 0.41,0.82; $p=3.1\times10^{-5}$), respectively, when compared to the grade of esophageal varices. In addition, AVD, AVB, and ACCH correlated with spleen size with a Pearson correlation of 0.72 (95%CI, 0.49,0.85; $p=2.6\times10^{-6}$), 0.20 (95%CI, -0.15,0.51; p=0.26), and 0.56 (95%CI, 0.27,0.76; $p=6.2\times10^{-4}$), respectively, and correlated with platelet count with a correlation of -0.69 (95%CI, -0.84,-0.45; $p=8.7\times10^{-6}$), -0.30 (95%CI, -0.58,0.05; p=0.09), and -0.40 (95%CI, -0.65,-0.07; p=0.02), respectively.
CONCLUSION: PHT is associated with endoscopically-inapparent microvascular dilatation and altered epithelial cell volume/morphology revealed *in vivo* by pCLE. Analysis shows that quantitative pCLE markers correlate with surrogate clinical markers of PHT. Additional studies will seek to define the correlation between microscopic portal hypertensive vascular patterns, epithelial cell volume, and the hepatic venous pressure gradient. Quantitative pCLE of the duodenum may reveal subclinical PHT and serve as a novel and early biomarker of liver disease and its complications.
Disclosure of Interest: None declared

OP116 LIVER STIFFNESS AND CONTROLLED ATTENUATION PARAMETER FOR ASSESSMENT OF FIBROSIS AND STEATOSIS IN CHILDREN WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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INTRODUCTION: Liver stiffness measurement (LSM) by FibroScan® (FS) was previously shown to be a valuable method in detection of liver fibrosis in adults with chronic liver diseases as HCV and non-alcoholic fatty liver disease (NAFLD). The Controlled Attenuation Parameter (CAP) available on FS allows simultaneous assessment of the degree of liver steatosis. This method seems especially promising for children with liver diseases in whom indications to perform liver biopsy are limited.
AIMS & METHODS: Aim of the study was to evaluate LSM and CAP in children with NAFLD and compare these results to healthy controls. We also assessed their relationship to non-invasive parameters describing the degree of obesity, liver function and lipid metabolism.
We investigated 38 overweight/obese children aged 14y (11.4-15.8) [median (Q1-Q3)] with NAFLD diagnosed by presence of liver steatosis on ultrasound and increased ALT activity and 18 healthy controls aged 12y (6.7-15.2). NAFLD patients underwent detailed investigation including risk factors associated with metabolic syndrome. In children with NAFLD we performed MRI of the lumbar region to assess subcutaneous (SAT) and visceral adipose tissue (VAT). VAT area and SAT area at the L2-L3 and L4-L5 interspaces and total VAT and SAT volumes were determined by manual examination using image analysis software. Correlations were tested by Spearman rank test.
RESULTS: NAFLD patients had significantly increased LSM compared to controls [5.35 (4.70-6.4) vs. 4.2 (3.6-4.4) kPa] and there was a marked difference in CAP [264.5 (243-304) vs 187 (112-217) dB/m]; $p<0.05$.
LSM correlated with all fat tissue compartments measured by MRI and HDL cholesterol (r=(-0.4)). CAP significantly correlated with waist circumference (r=0.51), extraperitoneal visceral adipose tissue (r=0.37), subcutaneous subfascial fat tissue (r=0.38) and serum levels of ALT (r=0.57), AST (r=0.42) and GGTP (r=0.5).
CONCLUSION: 1. LSM and CAP using Fibroscan® are easily applicable to children with NAFLD.
2. Liver stiffness and steatosis using LSM and CAP are significantly higher in NAFLD patients when compared to healthy controls.
3. Liver fat content measured by CAP correlates significantly with liver function tests and adipose visceral tissue in the extraperitoneal compartment as well as subcutaneous adipose tissue. LSM is correlated to fat tissue in all compartments but does not correlate with liver function tests.
Disclosure of Interest: None declared

OP117 ELASTOGRAPHIC ASSESSMENT OF LIVER STIFFNESS IN CHILDREN

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INTRODUCTION: Non-invasive techniques for liver fibrosis assessment were developed for adult patients and recent researches tested their accuracy in children. There is a trend towards elastography replacing liver biopsy in the evaluation of liver fibrosis among children with chronic diffuse liver diseases.
AIMS & METHODS: To investigate the feasibility of liver stiffness (LS) measurement in children with chronic diffuse hepatopathies by means of Acoustic Radiation Force Impulse Elastography (ARFI) and Shear Wave Elastography (SWE), compared to transient elastography (TE) as reference method. 54 children aged 4-18 years with different chronic hepatopathies (HBV, HCV infections, autoimmune hepatitis, nonalcoholic steato-hepatitis, Wilson disease) were enrolled. All children were examined by means of TE using FibroScan.10 valid TE measurements were performed under fasting conditions and the median value was calculated. ARFI was performed with Siemens Acuson S2000 Virtual Touch ultrasound system. We calculated the mean value of 10 valid measurements for each patient. SWE was performed with an Aixplorer ultrasound system (SuperSonic Imagine). We calculated the mean value of 5 valid measurements for each patient. All measurements were performed in the right liver lobe, in the same session. In all patients, transaminases levels didn't overcome 3 times upper normal limit values.
RESULTS: 54 children with an average age of 8.4 years (± 2.5) were included and had a successful measurement rate of 94,4%(51/54). Valid measurements were defined as a median value of LS measurements with a success rate(SR) ≥60% and an interquartile range interval(IQR) < 30%. Mean values were as follows: FibroScan: 7.36 ±1.3 kPa; ARFI: 1.46 ± 0.12 m/s; SWE: 6.33 ± 2.1 kPa. Accuracy of ARFI for detecting F=1 was 85.71%, for F=2 was 90.47 %, for F=3 was 80.95% and for F=4 was 88%. Accuracy of SWE for detecting F=1 was 88%, for F=2 was 92.85%, for F=3 was 91% and for F=4 was 95.23%. We found a significant correlation between FibroScan and SWE (r=0.64, p=0.001). Analysis of the whole lot of patients with valid measurements didn't show significant correlation between FibroScan and ARFI (r=0.24, p=0.14). SWE didn't correlate with ARFI values (r=0.18, p=0.28). We analyzed separately the subgroup of patients with valid measurements but less satisfactory technical parameters (SR between 60% > 70% and/or IQR=30%). There was no significant correlation between LS measurements by means of FibroScan and ARFI (r=-0.26, p=0.52). However, in the same subgroup FibroScan correlated significantly with SWE (r = 0.67, p=0.05). In the subgroup of children in whom the quality parameters for LS measurements were fulfilled with SR between 70% and 100% and IQR < 30%, there was a significant correlation between FibroScan and ARFI (r=0.58, p=0.01) and FibroScan and SWE (r=0.90, p=0.01).
CONCLUSION: SWE based on supersonic share imaging is a new technique designed to overcome some of the disadvantages of other elastographic techniques. Overall, it seems to correlate better with FibroScan compared to ARFI in children. Excluding patients with less satisfactory technical parameters (SR=60% > 70% and/or IQR=30%), we obtained significant correlations between all 3 elastographic techniques. Both SWE and ARFI are non-invasive techniques feasible to perform in children along with FibroScan.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
THERAPY UPDATE: GORD – HALL D

OP118 RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF BIOFEEDBACK FOR THE TREATMENT OF RUMINATION

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INTRODUCTION: In a previous study we showed that rumination is produced by an unperceived, somatic response to food ingestion and developed an original biofeedback technique for the treatment of rumination based on EMG-guided control of abdomino-thoracic muscular activity.
AIMS & METHODS: Our aim was to demonstrate the superiority of biofeedback versus placebo for the treatment of rumination. Twenty-four patients (16 women, 8 men; 16-82 yrs age range) who fulfilled the Rome criteria for rumination were recruited and randomly allocated to biofeedback and placebo treatment. Abdomino-thoracic muscle activity after a challenge meal was recorded by EMG and the signal was displayed on a monitor and front in the patients: in the biofeedback group, patients were instructed to control muscle activity, whereas in the placebo group patients were administered 120 mg symethicone. In each patient 3 sessions were performed over a 10-day period. Physiological (muscular activity by EMG) and clinical outcomes (number of rumination events by questionnaires administered daily for 10 days) were measured before and after treatment. Data of 16 patients who already completely the study (8 per group) were analyzed and mean ±SE calculated.
RESULTS: Patients on biofeedback, but not on placebo, effectively learned to reduce intercostal activity (by 46±7 % vs 1±7 % on placebo; $P < .001$) and anterior wall muscle activity (by 50±4 % vs 1±4 % on placebo; $P < .001$). Biofeedback was followed by a reduction of rumination activity (73±8 % decrease of regurgitation episodes/day vs -2±18 % on placebo; $P=015$).
CONCLUSION: Rumination can be effectively corrected by biofeedback-guided control of abdomino-thoracic muscular activity
Disclosure of Interest: F. Azpiroz Financial support for research from: Danone, Given, Beneo, Shire, Consultancy for: Danone, E. Barba: None declared, M. Mego: None declared, A. Accarino: None declared, J. Malagelada: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
UPDATE ON THE MANAGEMENT OF ACUTE PANCREATITIS – HALL B

OP119 VALIDATION AND COMPARISON OF THE NEW SEVERITY CLASSIFICATION SYSTEMS FOR SEVERITY OF ACUTE PANCREATITIS WITH OLD ATLANTA CLASSIFICATION

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INTRODUCTION: Two new classification systems for the severity of acute pancreatitis (AP) have been proposed recently, the determinant based classification (DBC) and revised Atlanta classification (RAC). We aimed to validate and compare these classification systems with original Atlanta classification (OAC).
AIMS & METHODS: Our aim was to validate and compare the DBC and RAC with original Atlanta classification (OAC).
469 adult patients with AP admitted to a tertiary care center from January 2009-June 2013 were included in the study. The new classification systems were validated and compared in terms of outcomes (need for interventions, total hospital and intensive care unit (ICU) stay and mortality).
RESULTS: The mean age of patients was 39.9±13.4 years (331 males) with the commonest etiology being alcohol (161, 34.3%) followed by gall stones (125, 26.6%). There were 119 (25.4%) patients with mild and 250 (74.6%) patients with severe AP as per OAC. Pancreatic necrosis was present in 66.1% and infected pancreatic necrosis in 23.1% patients. 126 (26.9%) patients underwent interventions (endoscopic n= 49, 10.4%, radiological n=95, 20.2% and surgical n=47, 10%). 93 (19.8%) patients died. As per DBC, 97(20.7%), 172 (36.7%), 152 (32.4%), and 48(10.2%) patients were determined to have mild, moderate, severe, and critical AP, respectively. As per RAC, 119 (25.4%), 160 (34.1%), and 190 patients (40.3%) were determined to have mild, moderately severe, and severe AP, respectively. Higher grades of severity were associated with worse outcomes in DBC, RAC and OAC.
Predictive accuracies were evaluated using area under the receiver operator characteristics curve (AUROC) and Somer's D co-efficient. The DBC, RAC and OAC were comparable in predicting the need for interventions (AUROC 0.53, 0.55, 0.54, p=0.36) and length of hospital stay (Somer's D, 0.27, 0.26, 0.23, p=0.41). However, both DBC and RAC had comparable but better accuracy than OAC in predicting need for ICU admission (AUROC 0.73 for both vs. 0.62 for OAC, $P < 0.001$), length of ICU stay (Somer's D, 0.35 for both vs. 0.24 for OAC, $p < 0.001$) and mortality (AUROC 0.78 for both vs. 0.61 for OAC, $p < 0.001$).
CONCLUSION: Determinant based classification and revised Atlanta classification categorize patients into subgroups that reflect clinical outcomes. Both have comparable and higher predictive accuracy than old Atlanta classification for need for ICU admission, length of ICU stay and mortality.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
COLORECTAL CANCER SCREENING: THE FUTURE – HALL C

OP120 POSITIVE PREDICTIVE VALUE OF FLEXIBLE SIGMOIDOSCOPY SCREENING FOR PROXIMALLY LOCATED COLON LESIONS

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INTRODUCTION: In the UK flexible sigmoidoscopy screening (FSS) is offered at the age of 55. During sigmoidoscopy, if one of the following criteria is met, the participant is referred for colonoscopy: detection of a polyp in left colon >10mm; 3 or more adenomas; adenoma with villous or tubulovillous component; adenoma with high-grade neoplasia (dysplasia); or 20 or more hyperplastic polyps > 3 mm above the distal rectum. It is of importance to estimate which lesions in the proximal colon (proximal to the splenic flexure) are left undetected by FSS.
AIMS & METHODS: We aimed to evaluate the positive and negative predictive value (PPV & NPV) of FSS for proximally located colorectal lesions using a model screening population.
In a previous Dutch screening colonoscopy trial (COCOS-trial), 1426 asymptomatic persons between 50-75 years of age underwent primary colonoscopy. We evaluated which participants (based on the distally located findings that would have been identified during a screening sigmoidoscopy) would have met the criteria for referral for colonoscopy. We also evaluated which participants had relevant lesions in the proximal colon (defined as carcinoma, any adenoma, any sessile serrated adenoma/polyp, or a hyperplastic polyp > 10 mm). We calculated the PPV and the NPV of FSS for lesions in the proximal colon.

RESULTS: If participants of the Dutch primary colonoscopy screening trial had been screened by sigmoidoscopy, 117 of 1426 (8.2%) would have been referred for colonoscopy. In 59% of the referred participants, no relevant lesions would have been detected in the proximal colon (Table 1). In 81.3% of 1309 participants that would not have been referred, no relevant lesions would have been missed in the proximal colon. However, in 18.7% a relevant lesion would have been missed; 1.5%advanced neoplasia, and 16.6% tubular adenomas with low-grade dysplasia. The PPV of FSS for the detection of relevant lesions in the proximal colon is 41% and the NPV is 81%, with an accuracy of 78%.
Table 1.Lesions detected in the proximal colon

	Total number of colonoscopies 1426	Would not have been referred for colonoscopy = 1309 (91.8%)	Would have been referred for colonoscopy = 117 (8.2%)
Findings proximal colon	2 (0.1%)	2 (0.2%)	0
Carcinoma			
Tubular & tubulovillous	8 (0.6%)	4 (0.3%)	4 (3.4%)
adenomas HGD any size			
Tubulovillous adenoma	11 (0.7%)	8 (0.6%)	3 (2.6%)
LGD any size			
Tubular adenomas	224 (15.8%)	189 (14.4%)	35 (29.9%)
LGD any size			
Sessile serrated lesions	48 (3.4%)	42 (3.2%)	6 (5.1%)
any size and/or hyperplastic			
polyps > 10 mm			
No findings	1133 (79.4%)	1064 (81.3%)	69 (59%)

CONCLUSION: This descriptive study evaluating the accuracy of FSS for predicting proximal lesions showed a PPV of 41% and a NPV of 81%. However, of the missed relevant lesions only 1.5% had advanced dysplasia. A limitation of our study is that the age of the participants in the primary colonoscopy screening trial was 50-75 years old, whereas FSS participants are invited at the age of 55. Larger studies are needed to further describe the yield of FSS.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
CHALLENGES IN COELIAC DISEASE AND GLUTEN-RELATED DISORDERS – HALL F1

OP121 BIOMARKER DISCOVERY THROUGH A PEPTIDE MICROARRAY MASS MANUFACTURING IN THE CELIAC DISEASE

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INTRODUCTION: Celiac disease (CD) while triggered by a reaction to gluten has features of an autoimmune disease with antibodies directed against tissue transglutaminase (TTg). The B-cell reaction is directed at both the autoantigen tTG and gliadin peptides especially those that have been deamidated by TTg. However, the precise epitopes recognized by individual patients varies and little is known about antibody recognition of the TTg-gliadin complexes.
AIMS & METHODS: Our aims were to identify the optimal peptide sequences of deamidated gliadin peptides (DGPs) combined with and without TTg that are most predictive of celiac disease using high-density in situ synthesis in combinatorial analysis. We also explored the epitope recognition in patients with likely undiagnosed celiac disease in the community. Methods: 2 sets of serum were used (biopsy proven untreated CD (n=48) with controls (n=50) as a training cohort and undiagnosed celiac disease (n=306) with age-and gender- matched controls for a validation cohort). Undiagnosed CD patients were confirmed by the serology CD test. A 2-stage process was utilized for the biomarker discovery. In the 1st stage high-density microarrays with systemically native deamidated gliadin and tissue transglutaminase, 12-mer overlapping sequences and 3-mer subsequences were paired. Then synthetic DGPs were synthesized with combining other different 3-mer subsequences, random 3-mer, and 6-mer. ROC curves were constructed for each peptide. A matrix of subsequences and the highest percentage of sequences showing IgG and IgA antibody response among all positive samples were then filtered out using a novel algorithm; then we combined the sequences from both TTg and DGPs to generate the peptides with the highest accuracy.
RESULTS: Two distinct consensus native DGPs sets (IgG or IgA) were identified for discriminating CD in the training cohort, exhibiting 80% sensitivity and 85% specificity in peptide set 1, 86% sensitivity and 89% specificity in peptide set 2. Two synthetic DGPs sets, which were synthesized by combining other different 3-mer subsequences of the native DGPs, random 3-mers, and 6-mers subsequences, showed much higher sensitivities (IgG=97% or Ig A=99%) and specificities (IgG=98% or IgA=100%) in the training cohort. Two synthetic peptides sets was further tested in a validation cohort and showed a high accuracy for undiagnosed CD with roughly two distinct groups by the antibody binding intensity. The cross-validated area under the curve of a Receiver Operating Characteristic (ROC) curve using deamidated sequences for predicting undiagnosed CD was 0.99. While TTg peptides sequences were not sensitive nor specific to identify the undiagnosed CD, the combining peptides sequences of DGPs and transglutaminase were both highly sensitive (98.9 %) and highly specific (100 %).
CONCLUSION: Combining subsequences in a specific order shows a high degree of specificity and sensitivity for celiac disease. Specially, the combination of transglutaminase and deamidated gliadin seems likely to be a high-fidelity test with a high degree of accuracy. This method also may provide insight into the shift in epitope recognition as patient's progress from undiagnosed to symptomatic disease
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
MANAGEMENT OF COMPLICATED CROHN'S DISEASE – HALL F2

OP122 EFFICACY OF ADALIMUMAB IN PATIENTS WITH CROHN'S DISEASE AND SYMPTOMATIC SMALL BOWEL STRICTURE: A MULTICENTRE, PROSPECTIVE, OBSERVATIONAL COHORT STUDY

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INTRODUCTION: Efficacy and safety of anti-TNF therapy in patients with Crohn's disease (CD) and intestinal strictures is poorly known. The aim of this study was to identify predictive factors of adalimumab (ADA) failure in patients with CD and symptomatic small bowel stricture (SSBS). (ClinicalTrials.gov No.NCT01183403).
AIMS & METHODS: We performed a multicentre, prospective, observational cohort study in patients with CD and a SSBS (defined by a CD obstructive score (CDOS) ≥ 3 on a scale from 0 to 6, evaluated over the 8 previous weeks). Patients with a contraindication to ADA or who were exposed to an anti-TNF therapy within the last 12 months were excluded. ADA was administered subcutaneously as following: 160 mg at W0, 80 mg at W2, and then 40 mg every 2 weeks. MR enterography was performed at baseline and at W24. The primary endpoint was ADA failure at W24, as defined by at least one of the following criteria during the study period: a) use of an prohibited treatment (corticosteroids after the 8th week following inclusion, artificial nutrition, other anti-TNF); b) endoscopic dilatation; c) bowel surgery including stricturoplasty; d) severe adverse effect leading to ADA discontinuation; d) loss to follow-up. Secondary endpoints included CDOS and MR items evolution from W0 to W24. Predictive factors were searched using univariate and multivariate logistic regression analyses. We computed that a minimum of 80 patients would provide a 80% power to detect a relative risk of failure of 2.0 to 4.0, according to a prevalence of patients at high risk of failure of 25 to 75%.
RESULTS: From January 2010 to December 2012, 118 patients from 20 GETAID centers were included. After exclusion of 21 non evaluable patients, 97 (53W; median age: 36 yrs [inter-quartile range (IQR): 29-49]; median duration of obstructive symptoms: 3.6 months [IQR: 1.2-11.2]) were analysed. At W24, 35/97 (36%) patients experienced failure of ADA including 10 who needed surgical bowel resection. CDOS values at baseline and at W24 (n=86) were 5.0 and 3.0 (IQR 1-5), respectively. Prognostic factors including demographic data, characteristics of CD and MR items are currently analysed. At the end of follow-up period (median duration: 71 weeks [IQR 50-123]), failure was observed in 51 (53 %) patients.
CONCLUSION: In a large prospective cohort of CD patients suffering from SSBS, ADA failure was observed in 36% of patients at W24 and in approximately 50% at 18 months. Analysis of prognostic factors, including MR enterography items, will help to select CD patients with symptomatic stricture who could benefit from anti TNF.
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Nachury: None declared, H. Brixi-Benmansour: None declared, A. Bourreille: None declared, L. Picon: None declared, A. Bourrier: None declared, M. Allez: None declared, L. Peyrin-Biroullet: None declared, J. Moreau: None declared, G. Savoye: None declared, M. Fumery: None declared, S. Nancey: None declared, X. Roblin: None declared, R. Altwegg: None declared, G. Bouguen: None declared, G. Bommelaer: None declared, E. Louis: None declared, J. Mary: None declared, F. Carbonnel: None declared

OP123 GROWTH PATTERN IN PEDIATRIC CROHN DISEASE IS RELATED TO INFLAMMATORY STATUS BUT NOT TO DURATION OF STEROID THERAPY

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INTRODUCTION: Growth failure is the main complication of pediatric-onset Crohn disease (CD). The respective role of disease activity and steroid therapy in growth faltering is still a matter of debate.
AIMS & METHODS: The aim of the present study was to investigate whether the growth pattern of children with CD was correlated with the evolution of inflammatory status during the disease course, whatever the cumulative duration of steroid therapy. 107 patients (63 boys and 44 girls) from the inflammatory bowel diseases cohort in Nothern France (EPIMAD registry), with a diagnosis of CD made <17 years of age, followed in the University Children's Hospital of Lille during ≥ 2 years and for whom ≥ 2 height measures were available during follow-up, were identified between 1998 and 2010. Height, C-reactive protein (CRP), orosomucoid and duration of steroid therapy were collected at each visit. Growth velocity was compared to the evolution of inflammatory status during follow-up in a longitudinal multivariate analysis using a mixed model.
RESULTS: Median age at CD diagnosis was 11.7 years (Q1-Q3: 9.8-13.5). According to the Paris classification, location of CD at diagnosis and at maximal follow-up was respectively as follows: L3 (70%; 86%); L2 (16%; 5%); L1 (14%; 9%); L4a (39%; 52%); L4b (11%; 22%). Behaviour at diagnosis and at maximal follow-up was respectively as follows: B1 (90%; 62%); B2 (7%; 28%); B3 (3%; 10%). Mean Height (H)/Age (A) Z-score at diagnosis was 0.1 ± 1.3. Growth failure (H/A Z-score <-2) was present in seven (8%) patients at diagnosis and in five (5%) at maximal follow-up (median: 4.9 years; Q1-Q3: 3.8-6.4). Among the 75 patients who had reached their final height at maximal follow-up, mean H/A Z-score was 0.1 ± 1.2. Twenty (29%) patients had a final height that was at least 4 cm below their targeted height. Growth velocity was not influenced by the cumulative duration of steroid therapy (median: 7.1 months; Q1-Q3: 4.9-12.5), but was negatively correlated with the evolution of CRP (coefficient of the equation of regression (e) = –0.16; $p<0.0001$) and orosomucoid (e = –0.60; $p<0.0001$) during follow-up.
CONCLUSION: CD children with uncontrolled inflammatory status have a lower growth velocity, regardless of cumulative duration of steroid therapy. The inflammatory status should be kept as close to normal as possible in pediatric-onset CD patients in order to optimize their growth pattern.
Disclosure of Interest: None declared

OP124 DUAL ENERGY COMPUTERIZED TOMOGRAPHY (DE-CT) – A NOVEL DECISION MAKING TOOL IN PREDICTING THE NEED FOR SURGERY IN PATIENTS WITH CROHN'S DISEASE AND OBSTRUCTING INTESTINAL LESIONS

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INTRODUCTION: Intestinal strictures are common in patients with Crohn's (CD) disease and may result in intestinal obstruction. Current available imaging studies can usually identify and locate the stricture, but can not reliably differentiate the patients who will require surgery from those who will respond to medical therapy. Dual Energy computerized tomography (DE-CT) uses two energy sources using high and low tube voltage, thus creating two data sets. Dedicated software creates overlay of the low and high energy images, in which enhancement of tissues with iodine can be better appreciated and quantified compared to standard CT. We hypothesize that dual energy can better visualize the iodine uptake in bowl wall as a marker of inflammation within intestinal lesions, and may help in identifying the patients who will or will not require surgery.
AIMS & METHODS: To evaluate the efficacy of DE-CT studies in predicting need for surgery within 3 months.
Patients with known CD undergoing abdominal CT for possible obstructive presentation prospectively underwent a DE-CT using intravenous iodinated contrast material, and were followed for 3 months for an outcome of surgery. The DE-CT was interpreted by a radiologist blinded to the clinical outcome, and the attending physicians of the patients were blinded to the interpretation of the DE-CT. DE-CT parameters assessed at the intestinal lesions included the degree of enhancement in overlay images (Hounsfield Units-HU) and Iodine content (mg/ml)
RESULTS: The study group included 25 patients, (mean age 38.3 years; F/M ratio of 12/13); 3 patients were treated with steroids (1 over 20mg), 5 with thiopurines and 4 with anti-TNF agents. Of the 25 studies 19 were performed from the emergency department. A total of 39 intestinal lesions were demonstrated (1-3 per patient) and 26 had pre-stenotic dilatation. Location of the lesions was classified as small intestinal, terminal ileum or colonic (30, 9 and 10 respectively). Mean degree of enhancement in overlay images was 33.97 ± 12.09 HU and the mean iodine content was 1.85 ± 0.99 mg/ml.
A total of 6 patients (9 lesions) underwent surgery, within a mean of 5.4 weeks from the CT study.
Using cut-off values of less than 2 mg/ml iodine content and less than 30 HU measured on the overlay as predictors for requiring surgery in 3 months achieved negative predictive value (NPV) 0.84 and 0.88 respectively.
CONCLUSION: DE-CT can be performed in patients with CD and suspected obstructive symptoms, and is valuable in evaluating the severity of intestinal inflammation, with a negative predictive value of 88% for identifying patients which will not require surgery. This study marks DE-CT as valuable decision making tool in managing patients with Crohn's disease, useful also in acute settings.
DISCLOSURE: This abstract has been accepted for presentation at DDW 2014.
Disclosure of Interest: T. Adar Financial support for research from: Synageva, Lecture fee(s) from: Shire, Consultancy for: Janssen, Other: Boston scientific, Immune Pharma, R. Biron: None declared, A. Shitrit: None declared, D. Wenrower: None declared, R. Cytter: None declared, I. Halpern: None declared, E. Goldin Consultancy for: Immune Pharma, Bioline Rx Ltd, N. Bogot: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
OPTIMISING LESION DETECTION IN COLONOSCOPY – HALL G/H

OP125 COMPARISON OF IMPACT OF REINFORCED EDUCATION BETWEEN TELEPHONE AND SHORT MESSAGE SERVICE ON THE QUALITY OF BOWEL PREPARATION: A PROSPECTIVE, COLONOSCOPIST-BLINDED, RANDOMIZED, CONTROLLED STUDY

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INTRODUCTION: High-quality bowel preparation is essential for a successful colonoscopy.
AIMS & METHODS: This study aimed to compare the impact of reinforced education between telephone and short message service on the quality of bowel preparation. A prospective, endoscopist-blinded, randomized, controlled study was conducted at a tertiary hospital. All subjects received regular instructions on the day of their colonoscopy appointment. Reinforced group was provided with additional education for reminding by telephone (TRE) or short message service (SMS) a day before colonoscopy. The primary outcome was the quality of the bowel preparation according to the Boston Bowel Preparation Scale (BBPS). The secondary outcomes included polyp detection rate (PDR), patients' compliance and subjective feelings.
RESULTS: 390 subjects were included in the study (TRE 126, SMS 127, control 137). Mean scores of BBPS were 7.09 ± 1.15, 6.76 ± 1.29, and 6.31 ± 1.43 in TRE, SMS and control group, respectively ($p<0.001$). Rates of poor preparation (BBPS <5) were 0.8%, 5.5%, and 13.1% in TRE, SMS and control groups, respectively ($p<0.001$). PDRs of TRE (48.4%) and SMS (44.9%) were higher than that of control group (32.8%) ($p=0.026$). Fewer subjects in reinforced education groups showed a high anxiety before colonoscopy ($p=0.013$). Reinforced education group had a high level of compliance with preparation instructions compared with control ($p=0.019$). Willingness to repeat bowel preparation was observed by 92.1%, 89.0%, and 81.8% of TRE, SMS, and control group, respectively ($p=0.034$). Multivariate analysis revealed that TRE (OR, 15.63, $p=0.009$), $>80\%$ amount of purgative ingestion (OR, 5.75, $p=0.003$) and interval of preparation to colonoscopy time $<$ 6 hrs (OR, 3.981, $p=0.003$) were independent factors associated with adequate bowel preparation.
CONCLUSION: Reinforced education with telephone and SMS few days before colonoscopy improves quality of bowel preparation, PDR, patients' compliance and subjective feelings. TRE is more effective for preparation of colonoscopy than SMS in healthy screening subjects.
Disclosure of Interest: None declared

OP126 PRACTICE, INDICATION AND PREDICTIVE FACTORS OF SECOND LOOK COLONOSCOPY IN A SCREENING POPULATION

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INTRODUCTION: Screening programs for colorectal cancer (CRC) are implemented worldwide. European guidelines recommend fecal immunochemical testing for primary screening followed by colonoscopy in case of a positive fecal immunochemical test (FIT, e.g. iFOBT). Although there are many studies focusing on the quality aspects of colonoscopy, no information is currently available on the practice of second look colonoscopies in a screening setting. These colonoscopies are a substantial burden for patients and the health care system. This is the first study to evaluate the number, indications and predictive indicators of second look colonoscopies following a screening colonoscopy.

AIMS & METHODS: We prospectively registered all colonoscopies performed in average risk subjects, aged 50-74 years, who were approached for a maximum of three rounds of FIT screening. A second look colonoscopy was defined as any colonoscopy performed following a screening colonoscopy within one year.
RESULTS: A total of 1216 patients with a positive FIT underwent colonoscopy (57.4% male, median age 63 years (IQR 57-68 years), median fecal Hb level 142 ng/ml (IQR 77-426 ng/ml)). Unadjusted cecal intubation rate was 96% and the overall adenoma detection rate was 55%. A total of 97 (8.0%) patients underwent a second look colonoscopy within one year, with a median time between the index colonoscopy of 61 days (IQR 35-99 days). Twenty-four patients (2.0%) underwent more than one second look colonoscopy (range 2-9). The most frequently reported reasons for a second look colonoscopy were assessment of completeness of removal of a neoplastic lesion (41.2%), need for further polypectomy (30.9%), and poor bowel preparation (15.5%). In multivariate analysis, the level of fecal hemoglobin was the only significant predictor for the need of a second look colonoscopy.
CONCLUSION: In this population-based screening program using FIT, a second look colonoscopy was performed in 8% of the patients within one year. In two thirds of the patients a second look colonoscopy was performed for control of completeness of removal of a neoplastic lesion or for polypectomy. A higher fecal hemoglobin level was the only independent predictor in identifying patients at risk for a second look colonoscopy and complex polypectomy.
Disclosure of Interest: None declared

OP127 DYNAMIC POSITION CHANGE INCREASE ADENOMA DETECTION DURING COLONOSCOPE WITHDRAWAL: A RANDOMIZED CONTROLLED MULTICENTER TRIAL

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INTRODUCTION: Adequate luminal distention is essential to maximize adenoma detection during colonoscope withdrawal. There was an only single operator study reporting dynamic position change improves luminal distension and has the potential to improve adenoma detection rate.
AIMS & METHODS: We designed a randomized, controlled multicenter trial to verify the effect of dynamic position change in colonic adenoma detection. Patients aged 45 to 80 years who underwent colonoscopy for the first time were included. In position change group, position changes during colonoscope withdrawal were as follows: cecum, ascending colon, and hepatic flexure: left lateral position; transverse colon: supine position; splenic flexure, descending colon, sigmoid colon and rectum: right lateral position. In control group, examination was performed entirely in left lateral position during colonoscope withdrawl. The primary outcome measure was the proportion of patients with $\geq$1 adenoma detected from transverse colon to rectum, namely, in the segments in which the patient position was different from left lateral.
RESULTS: A total 1000 patients were randomized to position change group (500 patients) and control group (500 patients). At least 1 adenoma was detected in 33% of patients in colon areas in which the patient position differed from left lateral (from transverse colon to rectum) compared with 24% examined with the patient in the left lateral position alone (P=0.005). Most of the apparent improvement in adenoma detection appeared to occur through supine positioning for examination of the transverse colon (21% and 14% in the position change group and contol group, respectively, P=0.003). The mean number of adenoma was 0.8 $\pm$ 1.4 (standard deviation) in position change group and 0.4 $\pm$ 0.8 in control group from transverse colon to rectum ($p = 0.019$).
CONCLUSION: Dynamic position change during colonoscope withdrawal increased adenoma detection rate.
Disclosure of Interest: None declared

OP128 G-EYE COLONOSCOPY SIGNIFICANTLY IMPROVES ADENOMA DETECTION RATES – INITIAL RESULTS OF A MULTICENTER PROSPECTIVE COHORT STUDY

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INTRODUCTION: The adenoma detection rate (ADR) is an important quality marker of colonoscopy. Higher ADR lead to reduced interval cancers and missed adenomas.
The G-EYE^{TM} endoscope (Smart Medical Systems, Ra'anana, Israel), is a newly developed system which combines a forward viewing HD endoscope with an integral, reusable and reprocessable balloon at its bending section. Following cecal intubation, the endoscope is withdrawn with the balloon inflated thereby straightening colonic folds, reducing bowel slippage and centering the optic of the endoscope in the middle of the lumen. Aim of the study was to compare the ADR of standard colonoscopy with G-EYE colonoscopy (with balloon partially inflated) at nine European centers.
AIMS & METHODS: From May 2013 to February 2014, patients (age $>$50) with indication for regular screening or surveillance were included and assigned to either conventional colonoscopy or G-EYE^{TM} colonoscopy. The G-EYE^{TM} endoscope was based on the same instrument as the conventional HD-colonoscope (3890i Series, Pentax Medical, Japan).
RESULTS: 222 patients are included, 117 patients underwent conventional colonoscopy and 105 patients underwent G-EYE^{TM} colonoscopy. Conventional colonoscopy detected in average 0.36 adenomas per patient. G-EYE^{TM} colonoscopy detected an average of 0.63 adenomas per patient, 75% higher than the conventional colonoscopy (Table 1). Reported ADR was 23.5% in the conventional colonoscopy group and 35.4% in the G-EYE group. Compared with conventional colonoscopy, G-EYE^{TM} colonoscopy increased ADR by 50%. Mean withdrawal times were 7:07±1:29 minutes and 7:05±1:44 minutes for standard colonoscopy and G-EYE^{TM} colonoscopy, respectively. Cecal intubation was accomplished in all patients and no adverse events were reported in either group.
Table 1 Results summary

	SC	G-EYE
Number of Patients	117	105
Adenoma per patient	0.36	0.63
Adenoma detection rate	23.5%	35.4%
Withdrawal time	7:07±1:29 minutes	7:05±1:44 minutes
Adverse Events	None	None

CONCLUSION: The distal balloon of the G-EYE colonoscope which is moderately inflated during withdrawal is highly effective for straightening colonic folds and identifying polyps and adenomas in a regular screening population. The use of the balloon was safe (no adverse events). This multicenter work reports a significant increase in adenoma detection rates by using the G-EYE^{TM} colonoscope compared to standard HD-colonoscopy. The results of this ongoing prospective cohort study will be reported at UEGW 2014.
Disclosure of Interest: Z. Halpern Consultancy for: Consultant to Smart Medical Systems Ltd., S. Ishaq: None declared, H. Neumann: None declared, M. Dobosz: None declared, E. Viale: None declared, A. Hoffman: None declared, J. Hendel: None declared, H. Senturk: None declared, H. Jacob: None declared, R. Kiesslich: None declared

OP129 G-EYE ADVANCED COLONOSCOPY FOR INCREASED POLYP DETECTION RATE - RANDOMIZED TANDEM STUDY WITH DIFFERENT ENDOSCOPIST

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INTRODUCTION: An apparently leading cause of missed polyps during colonoscopy is attributed to polyps that are located behind haustral folds in the colon, and are therefore hidden from the conventional, forward-viewing endoscope optics. The new G-Eye system is a balloon-colonoscope (*NaviAidTM G-EYE, Smart Medical Systems, Israel*), comprising a standard colonoscope having a re-processable, permanently integrated balloon at its distal tip.
AIMS & METHODS: Patients referred to colonoscopy, were randomized into two groups. Group A underwent Standard Colonoscopy (SC) followed by Balloon Colonoscopy (BC); group B underwent BC followed by SC. During the BC, the endoscope is inserted with the balloon deflated till the cecum. Then, the balloon is inflated to intermediate pressure and the balloon-colonoscope is withdrawn, thus straightening intestinal folds, smoothening colon topography and improving colon visibility. All polyps detected were removed. For the first time in this randomized, tandem study the endoscopists changed after each withdrawal and were blinded to the results of the first withdrawal. Also the degree of expertise was changing after each withdrawal (expert vs. trainee).
RESULTS: 45 patients were enrolled, randomized into two groups having similar baseline properties.23 patients underwent SC followed by BC and 22 underwent BC followed by SC. In Group A, SC detected a total of 25 polyps, and the following second pass BC detected 23 additional polyps, yielding 92.0% additional detection, the polyp miss-rate of the standard colonoscopy was 48%. In group B, BC detected 35 polyps, and the following SC detected 8 additional polyps, implying a BC miss- rate of 18.6%. The polyp miss-rate of the BC was significantly lower than the SC polyp miss-rate, fisher exact test $p<0.05$. BC additional detection over SC was 100% for adenomas and BC ratio of adenoma additional detection to miss rate, relative to SC was 5.988. BC detected more flat and small polyps ($<$5mm) than SC. For comparison, average procedure time of Standard Colonoscopy and Ballon Colonoscopy was similar. No adverse event occurred.
CONCLUSION: Balloon-colonoscopy is safe, easy to use and exhibits substantial increase in polyp detection rate, and presents significant reduction in miss rate during colonoscopy. For the first time a tandem study was conducted with changing endoscopists after each withrawal to decrease the bias to a minimum.
Disclosure of Interest: None declared

OP130 ENDOCUFF-ASSISTED COLONOSCOPY SIGNIFICANTLY INCREASES THE ADENOMA DETECTION RATE: A RANDOMIZED CONTROLLED MULTICENTER TRIAL WITH 652 PATIENTS

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INTRODUCTION: Screening colonoscopy for colorectal cancer has proven to reduce mortality rates. Recently the Endocuff (EC), an attachment to the distal tip of the colonoscope, was introduced. The aim of our study was to further compare Endocuff (EC)-assisted colonoscopies with standard colonoscopies (SC) for the detection of colonic polyps.
AIMS & METHODS: This study is a randomized prospective multicenter trial. The study was conducted at three tertiary care centers. Participants: 652 patients (320 males, mean age 64±15 years) for colon adenoma screening purposes were included. All patients underwent SC with or without the use of Endocuff. Overall polyp detection rate, the number of colonic polyps and the polyp distribution in the colon were measured. Difference in recognition of polyps with or without the use of Endocuff was assessed. Statistical analysis was applied. This study has been supported by the HELIOS Research Center (No HRC003053).
RESULTS: Total colonoscopy was performed in almost all patients (98.5 with EC, 99.1% without EC). The mean cleanliness score of each group did not differ significantly (EC: 1.36 vs. SC: 1.41, p=0.282). A total of 765 polyps in the patient cohort could be detected (EC:464 vs. SC: 301 polyps). Overall, we found significant differences in the polyp detection rate and overall number of polyps detected per patient. In the EC group, the number of polyps detected per patient was 59% higher (1.45±2.42 vs. 0.91±2.21, $p<0.0001$). The polyp detection rate in patients increased by 15.5% with the use of EC (55.4% vs. 39.9%, $p<0.0001$). For polyp detection, superiority by use of EC could be observed in the sigmoid region ($p<0.0001$) and caecum (p=0.008) for polyps < 1cm in diameter. In the EC group, the adenoma detection rate significantly increased by 66% (EC: 0.90±2.19 vs. SC: 0.54±1.34, p=0.014). No major complications occurred attributable to EC. The withdrawal time did not differ significantly between the two groups (p=0.603).
CONCLUSION: The use of the EC is feasible and safe with a significantly higher adenoma detection rate in the coecum and sigmoid. The Endocuff system has the potential to improve the accuracy of screening colonoscopies.
Disclosure of Interest: None declared

OP131 INTERVAL COLORECTAL CANCER AFTER COLONOSCOPY; TIME FOR NATIONAL REPORTING SYSTEMS?

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INTRODUCTION: Colonoscopy is known to prevent colorectal cancer by resection of adenomatous polyps. An interval colorectal cancer has been defined as one diagnosed 6-36 months after an index colonoscopy[1]. It follows that interval cancer is surrogate measure of quality in colonoscopy. Poor bowel preparation, incomplete colonoscopy, poor management of particularly sessile and right sided polyps and short withdrawal time have been identified as contributory factors[2]. We sought to indentify a regional rate of interval colorectal cancer as an auditable quality outcome in centres performing a total of 7150 colonoscopies during 2013.
AIMS & METHODS: All colorectal cancer cases presenting to the Royal United Hospital (RUH) Bath and the Great Western Hospital Swindon (GWH) United Kingdom, were indentified for the year 2013. The local endoscopy databases were interrogated for flexible sigmoidosopy or colonoscopy performed in the preceding 3 years.
RESULTS: 331 cases of colorectal cancer were indentified and managed at RUH and 152 at GWH. Of these 7 patients (2%) had undergone colonoscopy within the preceding 3 years at RUH and 10 (7%) at GWH. The average period from index procedure until cancer diagnosis was 15 months at RUH and 16 months at GWH. At RUH 6 of the 7 interval cancers could potentially be related to poor quality of the index endoscopic procedure; at GWH this was 7 out of the 10 interval cancers. The table below details the potential attributable reasons for interval cancer at the index procedure.

Factor at index procedure likely to explain interval cancer	GWH	RUH
Poor bowel preparation	1	2
Inadequate management of right sided colonic polyps	5	2
Inadequate surveillance interval	0	1
Incomplete procedure	1	1
No feature identified	3	1
Total interval cancers diagnosed in 2013	10	7
Total cancers diagnosed in 2013	152	331

CONCLUSION: From these data it is evident that the quality of colonoscopy, both regionally and nationally, is vital in terms of preventing colorectal cancer and should be audited routinely. While the rate regionally is comparable to published series of interval cancer[3], we have undertaken review of these procedures to improve practice; focus has been on careful review of right sided and sessile lesions at both centres, ensuring that completion procedures are adequate and a review of the local bowel preparation guidelines at RUH. It is vital that this small but significant miss-rate is considered in managing patients presenting with persistent symptoms despite normal endoscopy. It could be argued that patients should be consented appropriately. We suggest that a nationally defined interval cancer rate should be recorded routinely as part of local audit within the UK GRS system.
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Disclosure of Interest: None declared

OP132 LEADERSHIP IN TRAINING TO IMPROVE ADENOMA DETECTION RATE IN SCREENING COLONOSCOPY: A NATIONWIDE RANDOMIZED TRIAL

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INTRODUCTION: Suboptimal adenoma detection at colonoscopy is associated with increased risk of interval colorectal cancer. It is uncertain how to improve adenoma detection skills.
AIMS & METHODS: We compared the effect of teaching leadership in training versus feedback-only on colonoscopy quality in a nationwide randomized trial. Forty colonoscopy screening centres with suboptimal performance in the Polish colorectal cancer screening program (centre leader adenoma detection rate ≤25% during pre-intervention period January to December 2011) were randomized to either a train-the-colonoscopy leaders (TCL) program (pre-training assessment, hands-on-training courses, post-training feedback) or feedback only (individual performance quality indicators). Colonoscopies performed June to December 2012 (after intervention) were used to calculate changes in quality measures at leaders and screening centers level. Primary outcome was change in leaders' adenoma detection rate. Mixed effect models using odds ratios (OR) and 95% confidence intervals (95%CI) were computed.
RESULTS: The study included 17,341 colonoscopies performed by 40 colonoscopy leaders, of which 38 completed the study (19 in each group). Mean adenoma detection rate of screening centre leaders improved by 8.2% (17.4% - 25.6%) in the TCL group, compared to 1.1% (18.5% - 19.6%) in the feedback group. In mixed effect models, the TCL group had larger improvements in adenoma detection rate (OR1.61; 95%CI1.29 to 2.01; $p<0.001$), proximal adenoma detection rate (OR1.58; 95% CI1.19 to 2.11; $p<0.001$), and non-polypoid lesion detection rate (OR2.78; 95%CI 1.53 to 5.05; p=0.001). Moreover, in the TCL group non-polypoid lesion detection rate improved significantly at the screening centre level (OR 1.85; 95% CI 1.19 to 2.86; p=0.006).
CONCLUSION: Teaching colonoscopy leaders in training improved important quality outcome measures in screening colonoscopy. This may translate into a reduced interval cancer risk after screening colonoscopy. ClinicalTrials.gov, NCT01667198.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
OLD AND NEW BIOMARKERS IN IBD – HALL I/K

OP134 LEVELS OF FECAL CALPROTECTIN ARE ASSOCIATED WITH THE SEVERITY OF POSTOPERATIVE ENDOSCOPIC RECURRENCE IN PATIENTS WITH CROHN'S DISEASE

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INTRODUCTION: Despite surgery in Crohn's disease (CD) being almost unavoidable, disease endoscopic recurrence is common and its presence during the first year after surgery is predictive of subsequent clinical recurrence. Fecal calprotectin (fCal) represents the most studied and widely used marker of gut inflammation associated with a strong correlation with the severity of endoscopic lesions in CD. We analyzed the relationships between levels of fCal and the presence and severity of postoperative endoscopic recurrence in a cohort of CD patients after ileo-colonic resection.
AIMS & METHODS: Blood and Fecal samples were collected in 114 CD patients with a past history of ileocolonic resection followed by an ileo-colonic anastomosis. A routine ileocolonoscopy was performed in all of them to detect

endoscopic disease recurrence, according to the Rutgeerts score (graded as ≥ i2). CRP and fCal were measured and the respective performance and usefulness of both surrogate markers with respect to the presence and severity of postoperative endoscopic disease recurrence were assessed by computing correlations, sensitivity, specificity and predictive values at adjusted cutoffs and also tests operating characteristics.
RESULTS: A moderate (i2) and a severe (≥ i3) endoscopic recurrence was observed in 18 and 36 patients, respectively. FCal concentrations differed significantly in patients experiencing evidences for endoscopic recurrence when compared with those in endoscopic remission (mean ± SEM 484.3 ± 71 μg/g *vs* 118 ± 17 μg/g; p<0.0001). The area under the ROC curve (AUROC) to discriminate between patients in endoscopic remission and recurrence was 0.85 for fCal and lower 0.70 for CRP. The best cutoff point for fCal to distinguish between endoscopic remission and recurrence after surgery was 100 μg/g, as determined by the ROC curve and its sensitivity, specificity, positive and negative predictive values as well as overall accuracy were 93 %, 57 %, 66 %, 89 % and 74 %, respectively. In our cohort, fCal concentrations lower than 100 μg/g would allow with a high accuracy to avoid colonoscopy in almost 31 % of patients.
CONCLUSION: Measurement of fCal concentrations may be a promising and useful tool for monitoring CD patients after ileocolonic resection. Patients with a concentration of fCal below 100 μg/g are highly likely to be exempt of endoscopic recurrence and therefore fCal measurement in CD patients who had undergone surgery would get some help in making decision for colonoscopy.
Disclosure of Interest: None declared

OP135 PROGNOSTIC VALUE OF COMPLETE REMISSION IN PATIENTS WITH MUCOSAL HEALING IN ULCERATIVE COLITIS

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INTRODUCTION: The presence of endoscopic remission (ER) in patients with ulcerative colitis (UC) predicts better outcome with fewer relapses and colectomy rates. However, there is scarce data on the additive prognostic value of histological and biological activity among patients with both clinical and endoscopic remission (complete remission).
AIMS & METHODS: To assess the prognostic value of histological and biological activity in UC patients with clinical and endoscopic remission.
METHODS: Prospective observational study including 77 UC patients in clinical and endoscopic remission from 2 referral centres. Clinical remission was defined as clinical Mayo score<3 and no blood in the stools. Biological activity was assessed with C-reactive protein haemoglobin and albumin levels, and by leukocyte, and platelet counts. ER was defined as a Mayo endoscopic subscore (MES) of 0-1. Histological activity was assessed according to Geboes score (GS). Histological activity was defined as GS≥3.1 (neutrophils in the epithelium). Patients were followed up after the endoscopy for 12 months. Clinical relapse (CR) was defined as a clinical Mayo score ≥3. Univariate and multivariate analyses were performed to assess predictors of CR.
RESULTS: Baseline characteristics are summarized in **Table 1**. During follow up, 21 patients relapsed (9/27 patients with MES grade 1 and 12/50 with MES grade 0; *P*=0.38), but no colectomies occurred. A GS≥3.1 was present more often in patients with MES 1 than in patients with MES 0 (48 vs. 14%; *P*=0.002). CR was more frequent among patients with GS≥3.1 (43 vs. 20%; *P*=0.034). After adjusting for endoscopic activity, a GS≥3.1 remained as an independent risk factor for CR (OR 3.1 (95% CI 1.03-9.09), *P*=0.043). Patients with basal plasmacytosis presented numerically more CR, but differences were not statistically significant (19 vs. 11%; *P*=0.45). None of the demographic and biological variables included were predictive for CR (**Table 1**).

Baseline characteristics	All patients (n=77)	No relapsers (n=56)	Relapsers (n=21)	P
Female (%)	27 (35)	21 (38)	6 (28)	0.47
Median (IQR) age (years)	51 (41-60)	51 (42-58)	50 (37-66)	0.86
Median (IQR) disease	11 (6-18)	12 (9-20)	8 (2-15)	0.06
duration (years)				
Montreal classification(%):	13/39/25(17/51/32)	7/29/20(13/52/35)	4/13/4(19/62/19)	0.75
E1/E2/E3				
C reactive protein (mg/L):	1.2 (0.9-2.7)	1.2 (0.7-2.5)	1.5 (1-3.6)	0.09
median(IQR)				
Hemoglobin (g/dL):median(IQR)	14.2 (13.2-15.4)	14.5 (13.2-14.5)	14.1 (13.3-15.6)	0.89
WBC (10**9/L): (IQR)	5.9 (5-7.9)	6.0 (4.9-8)	5.7 (5.1-6.9)	0.62
Platelets (10**9/L):median(IQR)	241 (211-295)	249 (212-300)	232 (209-263)	0.37
Albumin (g/L):median(IQR)	46 (43-47)	46 (42-47)	46 (44-47)	0.66

CONCLUSION: In a prospective cohort, histological activity defined as GS ≥3.1 predicts CR at 1 year among patients with both clinical and endoscopic remission.
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OP136 PROFILING OF SERUM MICRORNA IDENTIFIES NOVEL BIOMARKERS OF FIBROSTENOSING CROHN'S DISEASE

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INTRODUCTION: Fibrostenosing Crohn's disease (CD) leads to stricture formation and bowel obstruction and is the main indication for surgery. A stricturing phenotype is associated with increased healthcare costs, increased morbidity and a worse quality of life. It is often difficult to differentiate inflammation from fibrosis using currently available imaging modalities, and no investigation can predict the future risk of stricture formation. The development of non-invasive biomarkers of fibrostenosing CD would represent a significant clinical advance. MicroRNAs (miRNAs) inhibit protein translation and thereby co-ordinate gene expression networks. MiRNAs are also present in the circulation, where they are resistant to degradation and can act as accurate biomarkers of disease. Our lab has recently demonstrated through targeted assays that the expression of the miR-29 family is reduced in the mucosa overlying stricture and in the serum of patients with a stricturing phenotype (SCD). These data suggest that miRNAs may act as biomarkers of SCD (Nijhuis et al 2014).
AIMS & METHODS: In this study we aimed to explore the potential of serum miRNAs as biomarkers of fibrostenosing CD. Profiling of RNA isolated from serum was performed by qPCR array and used to identify miRNAs associated with SCD (n=6) relative to inflammatory CD (n=11) and healthy controls (n=5). Differentially expressed miRNAs were subsequently validated by single qPCR assay in an independent cohort of CD patients (SCD n=35; inflammatory n=26; and penetrating n=19) and healthy controls (n=10).
RESULTS: A supervised modeling approach indicated that the SCD patients had a unique serum miRNA signature. In this model miR-19a-3p and 19b-3p contributed most strongly to the separation of SCD patients and inflammatory CD patients; changes in miR-29a-3p and 29c-3p also contributed, albeit to a lesser extent. Subsequent qPCR validation in an independent cohort demonstrated a significant reduction in miR-19a-3p and 19b-3p in SCD patients relative to inflammatory and penetrating CD groups (i.e. non-stricturing CD). In this cohort, stepwise linear regression confirmed that the association of the miRNAs with SCD was not affected by confounding factors, e.g. age, smoking status, disease duration etc. Levels of miR-19a-3p and 19b-3p also remained low in SCD patients following surgical resection.
CONCLUSION: We have demonstrated that miR-19a-3p and 19b-3p in serum are novel predictors of fibrostenosing CD. SCD was associated with low levels of miR-19a-3p and 19b-3p. The levels remained low in SCD patients after surgical resection indicating that miR-19a-3p and 19b-3p are markers of an SCD phenotype, and not merely the presence of stricture at the time of sampling. A longitudinal study is required to determine whether a reduction in serum miR-19 levels predates the development of stricture.
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Disclosure of Interest: None declared

OP137 CD62L (L-SELECTIN) SHEDDING FOR ASSESSMENT OF FUNCTIONAL BLOCKADE OF TNF-ALPHA IN ANTI-TNF TREATED INFLAMMATORY BOWEL DISEASE PATIENTS: CLINICAL FEASIBILITY AND PERSPECTIVES

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INTRODUCTION: Tumor necrosis factor (TNF) inhibition is central to the therapy of inflammatory bowel diseases (IBD). However, the durability and efficacy of this blockade hasn't been well studied and a better understanding is crucial for the prognosis of long-term treatment and decision making in case of loss of response (LOR) to these costly anti-TNF agents. Besides the presence of antibodies against the drug and serum trough levels additional tests to predict LOR are needed.
AIMS & METHODS: Consecutive IBD Patients receiving anti-TNF therapy (infliximab (IFX) or adalimumab) from Bern University Hospital were identified

and followed prospectively. Patient whole blood was stimulated with a dose-titration of either human TNF or the TLR agonist lipopolysaccharide (LPS) followed by flow cytometry. Median fluorescence intensity of CD62L on the surface of granulocytes was quantified by surface staining with fluorochrome conjugated antibodies against CD33 and CD62L. Logistic curves of these data permit the calculation of EC50 or the concentration of TNF required to induce a 50% shedding of surface CD62L [Patuto *et al,* DDW 2011]. The change in EC50 following the anti-TNF agent infusion, was used to predict the in vivo response to the anti-TNF agent. This predicted response was correlated to the clinical evolution of the patients in order to analyze the ability of this test to identify LOR.

RESULTS: We collected prospective clinical data and 2 blood samples, before and after anti-TNF agent administration, on 33 IBD patients, 25 Crohn's disease and 8 ulcerative colitis patients (45% females) between June 2012 and November 2013. The assay showed a functional blockade (PFR) for 22 patients (17 CD and 5 UC) whereas 11 (8 CD and 3 UC) had no functional response (NR). Selected clinical characteristics between predicted PFR and NR are compared below (Table). Among the 22 Patients with PRF, only 1 patient was a clinical non responders (LOR to IFX), based on clinical prospective evaluation by IBD gastroenterologists (PJ, FS and AJM), and among the 11 predicted NR, 3 had no clinical LOR. Sensitivity of this test was 95% and specificity 73% and AUC adjusted for age and gender was 0.81. During follow up (median 10 months, range 3-15) 8 "hard" outcomes occurred (3 medic. flares, 4 resections and 1 new fistula) 2 in the PFR and 6 in the NR group (25% vs. 75%; $p<0.01$).

	Predicted responders (N=22)	Predicted non responders (N=11)	p value
Age (years +/-SD)	34.8 (+/-11)	31 (+/- 11)	0.35
Clinical LOR: No/partial/complete	68%/27%/1%	27%/27%/46%	0.01
Perianal	41%	12%	0.15
Dis. Dur. start IFX (years +/-SD)	6.9 (+/- 6)	3.6 (+/- 4)	0.07
interval reduction needed	23%	73%	< 0.01
Smokers	33%	36%	0.684

CONCLUSION: CD62L (L-Selectin) shedding is the first validated test of functional blockade of TNF alpha in anti-TNF treated IBD patients and will be a useful tool to guide medical decision on the use of anti-TNF agents. Prospective comparative studies with antibodies against the drug and trough levels are ongoing.

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OP138 THE NEW FECAL MARKER MATRIX METALLOPROTEASE-9 IS MORE SENSITIVE FOR DIAGNOSING ULCERATIVE COLITIS AND POUCHITIS AND FOR DIFFERENTIATING THEM FROM CROHN'S DISEASE THAN FECAL CALPROTECTIN

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INTRODUCTION: Inflammatory biomarkers that correlate with enteric inflammation would be beneficial for monitoring the course of disease and targeting treatment in patients with inflammatory bowel disease (IBD). Only limited data are available about the diagnostic accuracy of fecal matrix metalloprotease (MMP)-9 in IBD.

AIMS & METHODS: The aims of our prospective study was to assess the diagnostic accuracy of fecal MMP-9 in patients with active Crohn's disease (CD), ulcerative colitis (UC) and pouchitis assessed by clinical, endoscopic and histological scores and to compare the diagnostic accuracy of fecal MMP-9 and fecal calprotectin (CP) in IBD. Stool and blood samples were collected in 50 CD, 54 UC and 34 ileal pouch-anal anastomosis patients before control endoscopy. Biopsies were taken for histology. The activities of CD, UC and pouchitis were defined with the use of clinical, endoscopic and histological activity scores (CDAI, partial Mayo score, PDAI, SES-CD, Mayo endoscopic subscore, D'Haens and Riley score). Fecal CP and MMP-9 levels were quantified by use of enzyme-linked immunosorbent assay.

RESULTS: Active CD, UC and pouchitis was detected in 38%, 54% and 29% of the patients. Significant correlation was revealed between fecal CP and the clinical activities of CD and UC, and between fecal CP and the endoscopic activity of UC and pouchitis. No correlation was found between fecal CP and the other examined activity scores in CD, UC and pouchitis. Fecal MMP-9 did not correlate with any of the activity indices of CD, however strong association was shown between fecal MMP-9 and clinical, endoscopic and histological activities of both UC and pouchitis.

CONCLUSION: This is the first study assessing the diagnostic accuracy of MMP-9 in different types of IBD. Our results showed that fecal MMP-9 has an exclusively high specificity in the detection of active UC and pouchitis. These non-invasive methods help assessing intestinal inflammation and also differentiating between CD and UC.

Disclosure of Interest: None declared

OP139 FC GAMMA RECEPTOR MUTATIONS FOR PREDICTION OF SUSTAINED CLINICAL REMISSION AFTER INFLIXIMAB DISCONTINUATION IN CROHN'S DISEASE PATIENTS

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INTRODUCTION: Genetic markers, as compared to serologic markers, could theoretically be superior for predicting inflammatory bowel disease (IBD) outcomes as genes are not affected by disease activity and are stable over time. Genetic polymorphisms of Fc gamma receptors (FcγR) may affect the efficacy of immunoglobulin (Ig)-based therapies by influencing the affinity of Ig to the receptors. We therefore hypothesized that these could facilitate prediction of sustained remission after anti-TNF discontinuation in IBD.

AIMS & METHODS: We aimed to investigate if polymorphisms in the *FcγRIIa*, *FcγRIIIa* and *FcγRIIIb* genes are predictive of sustained clinical remission (SCR) after infliximab (IFX) cessation for clinical remission in Crohn's disease (CD) patients. In this single-center retrospective study, 100 CD patients who discontinued IFX for clinical remission (luminal CD, n=57) were identified from an electronic database. The majority of patients (n=84) continued on immunomodulators. SCR was defined as maintained disease remission without the need to re-introduce medical therapy (biologicals, corticosteroids, thiopurines or methotrexate) or surgery until the end of follow up. The functional polymorphisms 131H/R in FcγRIIa (n=84), 158V/F in FcγRIIIa (n=91) and NA1/NA2 in FcγRIIIb (n=87) were analyzed by PCR-RFLP / TaqMan.

RESULTS: With a median follow up of 9.7 (IQR 8-11.5) years, 52/100 patients had SCR. Univariate (Log-Rank) analysis revealed no significant association of the investigated polymorphisms with either SCR or relapse after IFX discontinuation for clinical remission. Nevertheless, individual analysis of patients with luminal CD interestingly showed that NA2/NA2 homozygosity in FcγRIIIb was associated with increased risk for relapse (HR:2.4, 95%CI:1.1-5.3, p=0.021). Multiple COX regression analysis identified NA2/NA2 homozygosity as an independent variable predicting relapse after IFX cessation (HR:2.3, 95%CI:1.03-5.1, p=0.043).

CONCLUSION: We identified that FcγRIIIb NA2/NA2 homozygosity is an independent factor predicting relapse in patients with luminal CD who discontinue IFX for clinical remission. The lack of NA1 variant, which shows a higher affinity for IgG1 and probably leads to a more efficient downstream effects (antibody-dependent cellular cytotoxicity), may therefore predispose to relapse after IFX cessation in patients with luminal CD. Of note, NA1/NA1 homozygosity was previously found to be associated with higher biological response to IFX in IBD patients.[1]

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OP140 PHARMACOLOGICAL INTERVENTION BASED ON FECAL CALPROTECTIN LEVELS IN PATIENTS WITH ULCERATIVE COLITIS AT HIGH RISK OF A RELAPSE: A PROSPECTIVE, RANDOMIZED, CONTROLLED STUDY

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INTRODUCTION: Pharmacological treatment of ulcerative colitis (UC) is traditionally divided into treatment of active disease and treatment to maintain remission. Recently, targeted therapy for patients at increased risk of a flare, using biomarkers to detect subclinical disease activity, has been proposed.
The objective of this study was to assess if fecal calprotectin (FC), as a marker for inflammatory activity, can be used to guide medical intervention, to maintain remission in patients with UC.

AIMS & METHODS: In this open-label, prospective, controlled study, 91 adult patients with UC in clinical remission, and under treatment with an oral 5-ASA agent, were randomized to either an intervention group (n=51) or a control group (n=40). All patients had at least one flare within one year prior to the

inclusion. Patients on corticosteroids or anti-TNF therapy at inclusion were excluded. A stool sample for analysis of FC was delivered monthly during 18 months. A FC value of > 300 µg/g was set as cut-off for intervention. Provided that a second stool sample, delivered within a week, confirmed a FC value above the cut-off level, a dose escalation of the 5-ASA agent was performed in the intervention group. Accordingly, the dosages of Asacol® (mesalazine), Pentasa® (mesalazine), or Colazid® (balsalazide) were increased to 4.8 g, 4.0 g and 6.75 g, respectively. This dose was maintained until the FC value was < 200 µg/g, but for at least 3 months. No action was taken in the control group until clinical signs of a relapse were recorded. The primary end-point was the number of patients to have relapsed at month 18. Secondary end-points were time to relapse and the need for corticosteroids.
RESULTS: Eighteen (35.3 %) patients in the intervention group suffered at least one relapse over the 18-month period, compared with 20 (50.0 %) of those in the control group (p=0.231). The time to first relapse was 14.2 ± 5.9 vs 12.1 ± 6.9 (mean ± SD) months in the two groups, respectively (p=0.125). Dose escalation due to a FC value above the cut-off level was accomplished in 28 (54.9 %) patients in the intervention group. In the control group, 28 patients (70.0 %) had at least one FC value > 300 µg/g. In all, 8 (28.6 %) and 16 (57.1%) of these patients with a FC > 300 µg/g experienced a relapse, in the intervention and control groups, respectively (p < 0.05). In all, 9 and 6 patients in the intervention group and 6 and 5 patients in the control group were treated with oral and topical corticosteroids during a flare, respectively (NS).
CONCLUSION: In this trial with UC patients at high risk of disease relapse, we found no significant difference in relapse rates between the patients with targeted therapy based on FC levels and the patients in the control group. However, among the patients with active intervention due to a FC above the cut-off level, the relapse rate was significantly lower as compared to the patients in the control group with a FC value > 300 µg/g. Thus, our results indicate, that FC-levels might be used to identify patients with UC at risk for an imminent disease flare before symptoms develop, and that dose escalation of a 5-ASA agent is a therapeutic option for these patients.
Disclosure of Interest: None declared

OP141 STOOL TESTS CAN POTENTIALLY RULE OUT SIGNIFICANT BOWEL DISEASE IN SYMPTOMATIC PATIENTS IN PRIMARY CARE

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INTRODUCTION: Assessment of colorectal symptoms in primary care is difficult as they are poor predictors of underlying pathology. Patients presenting with new symptoms are frequently referred for colonoscopy, which is the gold standard for detection of significant bowel disease (SBD; colorectal cancer (CRC), high risk adenoma (HRA, defined as ≥ 3 or any ≥ 1 cm) and inflammatory bowel disease (IBD)). When symptomatic patients are brought to colonoscopy, yield of SBD is low, with local audit revealing CRC yield of only 2%. Faecal immunochemical tests for haemoglobin (FIT) are established in colorectal cancer screening, as faecal calprotectin (CPT) tests are in IBD clinics. We aimed to test their performance in primary care as a means to reduce unnecessary colonoscopy.
AIMS & METHODS: Over a six-month period, general practitioners (GPs) in one health board in Scotland were prompted when referring patients with colorectal symptoms to the Colorectal Service to obtain single samples of faeces for each stool test (OC-Sensor FIT and BÜHLMANN Calprotectin ELISA). Patients referred to endoscopy were appointed within six weeks of referral. Clinical outcomes were collected for all patients completing the tests and undergoing endoscopy. Analysis of test performance for identification of SBD was performed.
RESULTS: To date, 1000 patients have participated and analysis is ongoing. At present, a total of 569 patients (52.7% female, median age 64 years (range: 16-90, IQR: 52-73) have completed both stool tests and had clinical outcomes available. CRC was detected in 24 patients, 36 had HRA and 32 cases of IBD were diagnosed. FIT at the manufacturer's recommended cut-off concentration of 50ng/ml or above was present in 25.2% of referrals and at this cut-off, positive predictive value (PPV) for SBD would be 43.0%, negative predictive value (NPV) 92.9%, sensitivity 67.0% and specificity 82.8%; no CRC cases were below 50ng/ml but 48.6% patients with HRA and 40.6% of IBD cases were below this cut-off. The CPT test at the manufacturer's recommended cut-off concentration of 50µg/ml or above was present in 60.0% of referrals and would give a PPV 19.9%, NPV 90.5%, sensitivity 75.9% and specificity 42.9%, however two cases of CRC had a reading of below 50µg/ml along with 39.2% of HRA and 17.2% of IBD cases. Further results will be available once analysis is complete.
CONCLUSION: If we use FIT at a 50ng/ml cut-off concentration in primary care it would potentially reduce referrals by around 75% whilst affording GPs confidence that CRC in negative patients is highly unlikely, with no CRC cases were present below this concentration in our cohort. The CPT test did not perform as well, but combining the tests is an option to reduce missed cases of HRA and IBD; however, this would produce many more referrals and false positives. If we are setting an arbitrary cut-off concentration for FIT of 50 ng/ml, we would have to accept that a number of HRA would be missed and we would have to balance the risk of not referring patients with these lesions against the risks associated with unnecessary colonoscopy. Using FIT in primary care may help target colonoscopy more appropriately when patients present with colorectal symptoms.
Disclosure of Interest: None declared

OP142 FECAL CALPROTECTIN AFTER ILEOCAECAL RESECTION FOR CROHN'S DISEASE: CORRELATION WITH RUTGEERTS SCORE

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INTRODUCTION: Crohn's Disease (CD) has a high frequency of recurrence after ileocaecal resection. Ileocolonoscopy remains the gold standard method to assess postoperative recurrence. The severity of endoscopic findings in the anastomotic area according to Rutgeerts score is considered to reflect the subsequent clinical course. However ileocolonoscopy is an invasive method and suboptimal when a dynamic evaluation of the inflammatory process is desired. Fecal calprotectin (FC) has been shown to correlate with findings at ileocolonoscopy in CD. However few studies and with few patients have evaluated the accuracy of FC in predicting postoperative recurrence in CD. Currently the role of this biomarker in this specific scenario of postoperative recurrence is largely unknown.
AIMS & METHODS: The aim of this study was to assess the correlation between the concentration of fecal calprotectin and endoscopic findings one year after ileocaecal resection for Crohn's Disease.
Prospective cohort study. Adult patients with CD that performed ileocaecal resection between September 2011 and December 31, 2013 were considered for inclusion. Variables analyzed: age, sex, Montreal classification, smoking habits, concentration of FC one year after surgery, ileocolonoscopy findings one year after ileocaecal ressection according with Rutgeerts score. The sensitivity and specifity of FC was assessed using endoscopic findings as gold standard. Endoscopic recurrence was considered if the Rutgeerts score was ≥ i2. A ROC curve was performed to assess the best cut-off value for FC.
RESULTS: 22 patients were included. 48% males; 36% smokers. Endoscopic findings one year after ileocaecal resection according to Rutgeerts score was: i0 (n=9), i1 (n=4); i2 (n=2); i3 (n=2) and i4 (n=5). Average fecal calprotectin concentration one year after surgery was 149.12 ug/g [minimum 10, maximum 562] in i0 group; 751.7 ug/g [minimum 81, maximum 1888] in the i1 group; 181 ug/g [minimum 157, maximum 205] in the i2 group; 424 ug/g [minimum 55, maximum 793] in the i3 group and 529.8 ug/g [minimum 33, maximum 1117] in the i4 group. In this study the concentration of fecal calprotectin was not statistically different between the group with endoscopic remission and the group with endoscopic recurrence (p=0.31). However, all patients with fecal calprotectin concentration > 570ug/g had endoscopic recurrence. Some patients (n=4) with endoscopic recurrence had FC < 200ug/g. The sensibility and specificity of FC was calculated using 5 cut-offs. The best cut- off for a 67% sensitivity and 81% specificity was > 200ug/g. Thus, a value greater than 200ug/g of FC 1 year after surgery shows a strong correlation with the presence of endoscopic recurrence of CD, although we have observed a high number of patients with endoscopic recurrence with values below this cut -off.
CONCLUSION: Fecal calprotectin is a biomarker that, according to this study, has a high specificity but moderate sensitivity for predicting postoperative recurrence in CD. All patients with FC > 570ug/g had endoscopic recurrence. Studies with a larger number of patients are needed to better define the role of calprotectin in this scenario.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
IMPLICATIONS OF MOLECULAR PATHOGENESIS ON ENDOSCOPIC THERAPY FOR BARRETT'S OESOPHAGUS – HALL L/M

OP143 A FISH BIOMARKER PANEL FOR THE PREDICTION OF HIGH-GRADE DYSPLASIA AND ADENOCARCINOMA IN NON-DYSPLASTIC BARRETT'S ESOPHAGUS; RESULTS FROM A LONG-TERM PROSPECTIVE COHORT STUDY

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INTRODUCTION: Barrett's esophagus (BE) with no dysplasia is associated with a risk as low as 0.1% per year of developing esophageal adenocarcinoma (EAC). Predictive biomarkers would be of great clinical value in facilitating more cost-effective surveillance. Due to the low progression rate of non-dysplastic BE, biomarker studies require long-term follow-up as well as a robust sample size and are therefore scarce.
AIMS & METHODS: We conducted a prospective multicenter cohort study in a community-based setting of Barrett patients with no dysplasia to determine genetic predictors of progression. All patients were enrolled in an endoscopic surveillance program. Genetic abnormalities were detected on endoscopic cytology brushes by fluorescence in situ hybridization (FISH) using a probe-set including probes for P16, P53, Her-2/neu, 20q, and MYC, and the chromosomal centromeric probes 7 and 17 to detect aneuploidy. All markers were dichotomized into normal/abnormal based on cut-off values determined using ROC curves. Endpoints were progression to high-grade dysplasia (HGD) or EAC.
RESULTS: A total of 428 patients were included in the study (345 males; age 59 ± 12 y.o.; BE length 3 cm, IQR 2-6) Median follow-up was 45 months (IQR 35 – 72). There were 22 patients (5%) with histologic progression after review by 2 expert pathologists; 13 cases of HGD and 9 cases of EAC. Univariable analysis revealed that P16, and aneuploidy were significantly associated with progression, as well as the clinical variables age and maximum Barrett segment length (M). The remaining markers showed a non-significant tendency towards increased odds of progression. Patients who tested positive for P16 and/or aneuploidy were designated as marker-positive. Kaplan-Meier analysis revealed that there

was a significant difference in time to progression between the two groups (Log-rank P=0.009; Figure 1). The overall rate of progression to HGD/EAC was 1.09% per patient-year. Marker-positive patients had a higher annual risk to progress to HGD/EAC (1.85%) than marker-negative patients (0.58%) (P=0.015). In a multivariate proportional hazards model, controlling for M and age, a positive FISH result was a significant predictor of histological progression to HGD/EAC (HR 3.23; 95% CI 1.32-7.95).
CONCLUSION: A FISH panel assessing aneuploidy and P16, can be used as a decision making tool to stratify non–dysplastic Barrett patients into low- and high-risk disease categories to improve the efficacy of surveillance programs.
Disclosure of Interest: M. Timmer Other: The FISH probes used in this study were donated by Abbott Molecular., C. T. Lau: None declared, W. Rosmolen: None declared, S. Meijer: None declared, M. Dijkgraaf: None declared, P. Fockens: None declared, J. Bergman: None declared, K. Krishnadath: None declared

OP144 PERSISTENT HUMAN PAPILLOMAVIRUS INFECTION AND P53 OVEREXPRESSION ARE ASSOCIATED WITH TREATMENT FAILURE AFTER ENDOSCOPIC ABLATION OF BARRETT'S OESOPHAGUS

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INTRODUCTION: Recently, we reported that transcriptionally active high-risk HPV was strongly associated with Barrett's dysplasia (BD) and oesophageal adenocarcinoma (OAC) suggesting a potential role in oesophageal carcinogenesis.[1] Moreover, increasing viral load and integration status was significantly associated with disease severity along the Barrett's metaplasia-BD-OAC pathway.[2]
AIMS & METHODS: Thus, HPV and p53 (a good predictor of dysplasia progression in Barrett's oesophagus) clearance was examined in relation to treatment outcome after endoscopic ablation of BD/OAC. Forty patients with BD/neoplasia undergoing RFA+/-EMR were included in the study. Pre/post-treatment biopsies obtained from the lesion/neo-squamous epithelium were analysed for HPV DNA (nested PCR), viral transcriptional markers (E6/E7mRNA and p16INK4A) and p53.
RESULTS: Post-ablation, 34/40 subjects achieved complete eradication of dysplasia and 24 reverted to squamous epithelium and 10 to intestinal metaplasia. Pre-ablation, 15 patients were positive for transcriptionally active hr-HPV. 13/15 patients cleared HPV and transcriptional markers after a median of 6.7 months (range 4 to 23.1). All but one who cleared the virus eliminated dysplasia/OAC whereas 2 who continued to have detectable HPV oncogene activity had persistent dysplasia ($p<0.05$). A single patient with biologically active HPV and high-grade dysplasia at pre-ablation, cleared the virus post-treatment and subsequently developed persistent p53 positivity with progression to cancer. Of thirteen p53 positive patients pre-ablation, 2 had non-biologically active HPV. 10/13 patients cleared p53 overexpression after a median of 6.7 months (range 3 to 36.4) becoming disease free, whilst 3/13 with persistent p53 mutation continued to have detectable dysplasia at the end of the investigation (p=0.004). 12/40 patients negative for both HPV & p53 at pre-ablation eradicated dysplasia/neoplasia. All patients with persistent/progressive dysplasia/neoplasia at the end of the study (6/40) had either detectable biologically active hr-HPV (n=2) or over-expression of p53 (n=4). Only 1/10 patients with intestinal metaplasia (post-treatment) had persistent laboratory abnormality (p53 over-expression) at the end of the investigation. 0/24 individuals who reverted to squamous epithelium had any detectable transcriptionally active hr-HPV or p53 mutation. There were no cases of recurrence.
CONCLUSION: Most HPV infected BD/OAC patients cleared the infection with endotherapy. Persistence/progression of dysplasia/neoplasia after endoscopic ablation of BO was associated with the presence of either HPV oncogenic activity (viral persistence) or p53 overexpression.
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Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30
RISK FACTORS AND MANAGEMENT OF UPPER GI BLEEDING – HALL N

OP145 DERIVATION AND VALIDATION OF A PROGNOSTIC SCORE IN OVER 12,000 PATIENTS WITH ACUTE UPPER GASTROINTESTINAL BLEEDING

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INTRODUCTION: Upper gastrointestinal bleeding (UGIB) is a common medical emergency worldwide. Early risk assessment is an essential part of management to help identify appropriate support and timely endoscopy for high risk patients as well as early discharge for low risk patients. The Rockall and Glasgow-Blatchford (GBS) scores are the most commonly utilised indices, with the former a better prediction tool for mortality and the latter for identification of low risk patients.
AIMS & METHODS: We aimed to derive and validate a new risk score which combines features of both the Rockall and GBS scores to create a single scale which could better identify low risk patients, as well as higher risk patients requiring intervention (therapeutic endoscopy, surgery/embolisation) and at risk of adverse outcome (mortality, rebleeding). Variables were selected for inclusion in the model based upon widespread association with outcomes plus clinical judgement. The new score was derived using three large observational data-sets (UK audit, Canadian RUGBE and REASON studies) and ranged on a scale from 0-20. The score was then validated in two independent data-sets (a UK randomised trial and an Australian database). Receiver operating characteristics were used to compare the performance of the new score with the Rockall and GBS scores, as well as quantifying the number of patients with events (therapeutic endoscopy, mortality, rebleeding, and surgery) at a score of ≤ 3 in comparison to the GBS.
RESULTS: Variables in the new score were age, blood pressure, pulse, haematemsesis, melaena, syncope, haemoglobin, urea, liver disease and malignancy. The score was derived in 10639 cases of UGIB and validated in 1606 cases. The new score was superior to the GBS in predicting mortality (AUROC 0.77 vs. 0.74; P=0.05), had a higher AUROC for surgery/radiological embolisation (0.72 vs. 0.70; P=0.51), and was identical for rebleeding (AUROC 0.68 vs. 0.68); it performed less well than the GBS for predicting therapeutic endoscopy (AUROC 0.77 vs. 0.78; P=0.05). The new score was superior to the Rockall score in predicting need for therapeutic endoscopy (AUROC 0.77 vs. 0.66; <0.01), transfusion (AUROC 0.90 vs. 0.75; $P<0.01$), rebleeding (AUROC 0.68 vs. 0.64; P=0.09), surgery/embolisation (AUROC 0.72 vs. 0.72; P=0.01); it had a lower AUROC than the Rockall score for mortality (0.77 vs. 0.79, P=0.43). Using a threshold of ≤ 3 for the new score, fewer patients experienced all of the clinical endpoints of need for therapeutic endoscopy [2.3% (10/437) vs. 3.3% (20/600)], rebleeding [2.3% (10/436)] vs. 2.7% (16/597)], mortality [0.5% (2/437) vs. 1.3% (8/600)] or surgery [0.5% (2/437) vs. 0.7% (4/600)] in comparison to patients with a GBS score of ≤ 3.
CONCLUSION: We have successfully derived and externally validated a novel risk score for UGIB which can be used to triage both low and high risk patients with UGIB. It performs better than the Rockall score for all outcomes apart from mortality and better than GBS in predicting mortality and need for surgery/embolisation. It also performs more favourably than the GBS in identifying low risk patients with a score of ≤ 3. The study was performed in a large sample size across three continents, enhancing the generalisability of the results. Further validation of the score is now warranted.
Disclosure of Interest: None declared

OP146 A MODEL TO ASSESS THE RISK FOR ASA/NSAID-RELATED ULCER BLEEDING FOR THE INDIVIDUAL PATIENT BASED ON THE NUMBER OF RISK FACTORS

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INTRODUCTION: Aspirin/NSAID related peptic ulcer bleeding occurs in 1-3% of patients and with a mortality rate of 10-15%. A number of risk factors are well established, but the incidence rate for the individual patient with a given set of risk factors is unknown. The aim of this study was to develop a model that could predict the incidence rate of UGB in users of ASA/NSAID based on the presence of well-defined risk factors for the individual patient.
AIMS & METHODS: The model was developed on data from a case-control study. Cases were all diagnosed with upper gastrointestinal bleeding (UGB) from 1995-2006. Controls were sampled from the source population by use of a risk-set technique. All cases and controls were characterized in terms of factors known to affect the risk of UGB. By use of census data, we inflated the control group, so that their composition accurately reflected the age and gender distribution of the source population.
The incidence rate of UGB was calculated among 80-89 year old women, who were users of NSAID, but not corticosteroids, ASA or SSRI and had no ulcer history. This constituted the largest subgroup and could thus be used as reference. We used multivariate logistic regression and included first-order interactions which could be meaningfully interpreted.
RESULTS: Number of cases was 1388. The adjusted incidence rate ratios (IRR) for each risk factor was found with the reference: woman aged 80-89 and in NSAID-treatment.incidence UGB: 12.1/1000 patient-year.

OP146

	Adjusted incidence rate ratio	95% Confidence intervals		Adjusted incidence rate ratio	95% Confidence intervals
Male	1.23	1.11-1.38	Warfarin-treatment	2.56	1.98-3.28
Age 60 år	0.10	0.08-0.12	ADP-inhibitor (clopidogrel)	5.47	3.88-7.72
60-69 år	0.27	0.23-0.32	Dipyridemol	1.29	1.02-1.61
71-79	0.47	0.42-0.54	Corticosteroids	1.84	1.56-2.17
80-89	1.0	Reference group	SSRI	1.80	1.53-2.10
90 år	1.35	1.10-1.65	Prior ulcer	2.67	2.18-3.27
Low dose ASA-alone	0.55	0.48-0.62	Interactions: age < 60 years* Aspirin and NSAID	4.83	2.41-9.67
ASA and NSAID	2.13	1.80-2.50	Interaction: age < 60 years * Aspirin alone	2.82	1.82-4.36

An example: Male (1.23) aged 85 (1.0) in warfarin-treatment (2.56). corticosteroids (1.84) and SSRI (1.80). 1.23*1.0*2.56*1.84*1.80*12.1= 125.74 risk/1000 pers /year.
CONCLUSION: This model allows an estimate of the incidence rate for UGB for each patient group based on the individual pattern of risk factors. Further studies are needed to confirm the validity of the model.
Disclosure of Interest: None declared

OP147 RISK FACTORS FOR EARLY AND DELAYED POST-OPERATIVE BLEEDING AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION OF GASTRIC NEOPLASMS

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INTRODUCTION: Endoscopic submucosal dissection (ESD) has been widely recongnized as the optimal treatment for gastric neoplasms. Safety of gastric ESD has been almost established, post-operative bleeding is sill the main concern affecting the safety, effectiveness, and outcome of the procedure.
AIMS & METHODS: Our aim of this study was to identify risk factors for post-operative bleeding after gastric ESD, and to evaluate the relevance between such risk factors and the time of post-operative bleeding.
There were 413 patients with 425 gastric neoplasms consecutively treated by ESD from June 2005 to March 2014. Demographic and clinical parameters associated with post-operative bleeding were investigated. 83 patients (20.0%) were receiving antithrombotic agents, and they were assessed separately by the methods of how to use such agents during ESD procedure. Post-operative bleeding that occurred during the first 5 postoperative days was defined as early post-operative bleeding, whereas subsequent bleeding was defined as delayed post-operative bleeding.
RESULTS: Overall post-operative bleeding rate was 4.8%. In multivariate analysis, intravenous heparin replacement (HR), chronic kidney disease (CKD) undergoing hemodialysis, and a specimen size of ≥ 40 mm were predictive factors for post-operative bleeding (odds ratio 5.77, 95 % CI: 1.67-19.96, odds ratio 33.86, 95 % CI: 4.72-242.74, and odds ratio 3.70, 95 % CI: 1.09-12.52, respectively). A specimen size of ≥ 40 mm was a predictive factor for early post-operative bleeding (odds ratio 6.08, 95 % CI: 1.74-21.27), and HR and CKD undergoing hemodialysis are risk factors for delayed one (odds ratio 12.23, 95 % CI: 2.63-56.77 and odds ratio 28.35, 95 % CI: 4.67-172.11, respectively).
CONCLUSION: Large size of specimen is a risk factor for early post-operative bleeding, and intravenous HR and CKD undergoing hemodialysis are risk factors for delayed one. Patients with one or more risk factors should be watched carefully allowing for the timing of post-operative bleeding after ESD.
Disclosure of Interest: None declared

OP148 VALIDATION OF A NEW BEDSIDE PROGNOSTIC SCORE (AIMS65) IN UPPER GASTROINTESTINAL BLEED

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INTRODUCTION: There are various risk stratification scores available for predicting outcome in upper gastrointestinal (GI) bleed. However they are cumbersome and sometimes require endoscopic evaluation and therefore are rarely applied for early risk stratification.
AIMS & METHODS: To prospectively evaluate the newly proposed early bedside score, AIMS65 (A-albumin, I-INR, M-Mental status, S –Systolic Blood pressure), in patients with acute upper GI bleed admitted to our tertiary care hospital
251 consecutive patients presenting with acute upper GI bleed, from January 2012 to December 2012, were included in the study. The AIMS65 scores were calculated by allotting 1 points each for albumin (A) <30g/l, INR (I) >1.5, alteration in mental status (M), systolic blood pressure (S) ≤90mmHg and age ≥ 65 years. The risk stratification was completed within 24 hours of hospital admission. Patients were managed as per standard protocol and outcomes were evaluated.
RESULTS: The mean age of study group was 52.4 years with 193 males. The etiology for upper GI bleed was duodenal ulcer in 74 (29.6%), gastric ulcer in 38 (15.2%) and esophageal varices in 32 (12.8%) patients. 51 patients (20.3%) required intensive care unit (ICU) admission. The mean hospital and ICU stay were 10.6±16.9 and 4.6±5.4 days respectively. The overall mortality was 10.3% (n=26).
The mortality in those with AIMS65 scores of 0,1,2,3 and 4 were 3%, 7.8%, 20%, 36% and 40% respectively. The mortality was significantly higher in those with score ≥3 (37.1%) as compared to those with score <3 (6%), p<0.001. The predictive accuracy for mortality with a score ≥3 was high (area under the receiver operator characteristics curve = 0.70, 95% CI= 0.57-0.82). The mean hospital stay (21.5±31.1 versus 9.0±12.8 days, p=0.040) and ICU stay (5.1± 6.1 versus 3.5±3.6 days, p=0.042) were significantly higher in patients with scores ≥3 as compared to those with <3.
CONCLUSION: AIMS65 is a simple, accurate, non endoscopic risk score that can be applied early (within 24 hours of hospital admission) in patients with acute upper GI bleeding. AIMS65 score ≥3 predicts high in-hospital mortality and increased duration of hospital and ICU stay.
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OP150 USE OF GASTROPROTECTIVE AGENTS AND RISK OF DABIGATRAN ASSOCIATED GASTROINTESTINAL BLEEDING: A POPULATION-BASED RETROSPECTIVE COHORT STUDY

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INTRODUCTION: Dabigatran, a direct thrombin inhibitor, is the first new oral anticoagulant available as an alternative to warfarin. Despite its convenience and superiority over warfarin in the prevention of stroke and thromboembolism, recent studies suggested an increase risk of gastrointestinal bleeding (GIB) in patients treated with dabigatran when compared to warfarin. These data were however largely derived from clinical trials in selected patient population.
AIMS & METHODS: This study determined the risk of dabigatran associated GIB and the role of gastroprotective agents, including proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs), in preventing dabigatran related GIB in a population-based retrospective cohort study. Data were extracted from the central database of the Hong Kong Hospital Authority, which is the provider of all public medical services to a 7 million population. We identified all patients who were newly prescribed with dabigatran between Jan 2010 and Dec 2013. The primary endpoint is the onset of clinical GIB. Multivariate analysis was used to characterize the risk of GIB after adjusting for baseline patient's characteristics, medical illnesses and concurrent medications.
RESULTS: 5,041 patients, who were newly prescribed dabigatran, were included in the analysis. Among them, 222 (4.4%) patients developed GIB with a median time to bleeding of 97 (IQR 262) days. Patients who were aged ≥75 years (OR 1.83; 95% CI, 1.36 to 2.47), had prior ischemic stroke, transient ischemic attack or systemic embolic events (OR 1.62; 1.19 to 2.2), and a prior history of peptic ulcer or GIB (OR 2.48; 1.81 to 3.39) were found to have higher risks of GIB. Concurrent use of gastroprotective agents (OR 0.61; 0.44-0.84; log rank test P = 0.018) or statin (OR: 0.58; 0.43-0.78) reduced the likelihood of GIB. Subcategory analysis showed that the use of either PPIs (OR 0.70; 0.51-0.98) or H2RAs (OR 0.67; 0.50-0.90) significantly lowered the bleeding risk. The risk reduction by gastroprotective agents was significant only in patients with prior history of ulcers or GIB (OR 0.24; 0.14 to 0.43) but not in patients with no prior history (OR 0.83; 0.56 to 1.21).
CONCLUSION: The risk of GIB associated with dabigatran use in real life clinical settings is 4.4%. The use of gastroprotective agents significantly reduced the risk of dabigatran related GIB, particularly in high-risk patients with prior history of peptic ulcer or GIB.
Disclosure of Interest: W. Lau: None declared, E. Chan: None declared, I. Wong: None declared, Y. He: None declared, T. Tong: None declared, W.-K. Leung Lecture fee(s) from: Takeda, Ferring, Consultancy for: Janssen.

OP151 ENDOSCOPIC TREATMENT OF UPPER GASTROINTESTINAL BLEEDING WITH A NOVEL HEMOSTATIC POWDER: RESULTS FROM A MULTICENTER PROSPECTIVE REGISTRY PERFORMED IN ROUTINE PRACTICE (THE 'GRAPHE' REGISTRY)

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INTRODUCTION: In recent pilot studies, the use of a hemostatic powder showed promising results to treat gastrointestinal bleeding. However, few data exist in routine practice with this new method.
AIMS & METHODS: The aims of registry were to determine 1) the feasibility of the application of the hemostatic powder in routine clinical practice, and 2) its effectiveness in the short and medium term in different clinical situations. We performed a prospective multicenter study in 17 centers, with 46 endoscopists. All patients receiving the hemostatic powder (Hémospray™, Cook Medical, USA) were included. The hemostatic powder was sprayed endoscopically onto the bleeding site using a catheter passed through the operative channel of the endoscope. The quantity of powder was administered at the discretion of the endoscopist based on clinical efficacy. The following parameters were analyzed: demographic characteristics, type of exteriorization (hematemesis, melena, hematochezia), type of bleeding lesion, use of hemostatic powder as a first-line treatment or a rescue therapy (i.e. after failure of conventional treatment) and ease of use of the hemostatic powder as well as the main outcomes parameters, which were: firstly, the immediate efficacy defined by hemostasis achieved at the end of the endoscopic procedure, and secondly the absence of clinical recurrence eight days after the procedure.
RESULTS: Ninety-six patients (69M/27F) aged 70 ± 14 years were included in the study between June 2013 and April 2014. Patients were hospitalized for hematemesis (n = 34), melena (n = 54) or hematochezia (n = 11). Initial hypotension was noted in 28 patients. At endoscopy, an active bleeding was noted in 88/96 (91%) cases, either pulsatile (14.6%) or oozing (85.4%). The location of bleeding was esophageal (n = 14), gastric (n = 31) or duodenal (n = 50). The bleeding lesion was identified in 89/96 (92.7%) cases. These lesions were 31 tumors (32%), 43 ulcers (45%), 8 bleeding margins following endoscopic mucosal resection (8%) and 14 (15%) others bleeding lesions. The duration of the endoscopic procedure (including both the diagnostic and therapeutic steps) was 32 ± 23 minutes. Application of the hemostatic powder was found to be very easy, easy, moderately easy or difficult in respectively 39%, 50%, 5% and 6% of cases. This treatment was used as a first-line treatment in 51.6% of cases and as a rescue therapy in 48.4% of cases. The immediate efficacy rate was 93.6%. No recurrence of bleeding was noted in 74% of cases.
CONCLUSION: Our multicenter data obtained in routine practice conditions suggest the good feasibility and effectiveness of the hemostatic powder applied endoscopically for gastrointestinal bleeding, even after failure of conventional methods.
Disclosure of Interest: None declared

OP152 RESTRICTIVE VERSUS LIBERAL BLOOD TRANSFUSION FOR ACUTE UPPER GASTROINTESTINAL BLEEDING (TRIGGER): PRAGMATIC, CLUSTER RANDOMISED, FEASIBILITY TRIAL

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INTRODUCTION: Transfusion thresholds for upper gastrointestinal bleeding (UGIB) are controversial. Observational studies suggest associations between liberal red blood cell (RBC) transfusion and adverse outcome, and a recent trial reported increased mortality following liberal transfusion.
AIMS & METHODS: Pragmatic cluster randomised trial to evaluate the feasibility and safety of implementing a restrictive (transfusion when haemoglobin (Hb) <8gdL) versus liberal (transfusion when Hb <10g/dL) RBC transfusion policy for UGIB. Hospitals were randomised to a policy which was implemented through a multi-faceted educational intervention targeting all staff caring for patients with UGIB. All adult patients were eligible to participate, regardless of co-morbidity; the only exclusion criterion was exsanguinating haemorrhage. Feasibility and exploratory clinical outcomes were recorded up to day 28.
RESULTS: 936 patients were enrolled in six hospitals (three restrictive, three liberal). Although there were some baseline imbalances, Rockall and Blatchford risk scores were identical between policies. Protocol adherence was 96% in the restrictive policy *vs* 83% in the liberal policy (difference 14%, 95% CI 7 to 21%). In patients with Hb < 120 g/L, Hb at discharge was lower for the restrictive policy (difference -0.7; 95% CI -1.4 to 0.0; p=0.05). For the restrictive policy fewer patients received RBCs (difference -13%, 95% CI -35 to 11%) with on average 08 (-19 to 03) fewer RBC units transfused. Clinical outcomes were better in the restrictive policy: 28-day further bleeding, 5% restrictive *vs* 9% liberal (difference -37%, 95% CI -122 to 48%); 28-day mortality, 5% restrictive *vs* 7% liberal (difference -1.3%, 95% CI -8.0 to 5.5%).; serious adverse events, 18% restrictive *vs* 22% liberal (difference -4.9%, 95% CI -22.6 to 12.8%). In the subgroup with IHD, there was a large observed difference for mortality (12% restrictive arm (n=6) vs. 3% liberal arm (n=2); interaction P=0.11).
CONCLUSION: Adherence to both policies was high, resulting in a reduction in RBC transfusion and separation in the degree of anaemia and RBC exposure. There was a trend towards improved safety in the restrictive policy, apart from the increased mortality observed in patients with IHD. We have demonstrated that a large-scale cluster randomised trial is feasible and is now warranted to determine the effectiveness of implementing restrictive RBC transfusion for all patients with AUGIB.
Disclosure of Interest: None declared

OP153 A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF HIGH-DOSE REBAMIPIDE FOR LOW-DOSE ASPIRIN-INDUCED MODERATE TO SEVERE SMALL INTESTINAL DAMAGE IN CHRONIC ASPIRIN USERS

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INTRODUCTION: Recent studies using capsule endoscopy have shown that prevalence of small intestinal damage in patients taking low-dose aspirin (LDA) is high. Although some drugs have been shown to be effective in treating LDA-induced small intestinal damage, patients with mild damage which was thought to be clinically insignificant have not been excluded and not a few patients with such damage have been enrolled in most studies. Furthermore, few randomized, double-blind, placebo-controlled trials to evaluate the efficacy of drugs in the treatment of the LDA-induced damage have been reported.
AIMS & METHODS: We conducted a multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy of high-dose of rebamipide, which is a gastro-protective drug with various actions including enhancement of prostaglandin synthesis, for the healing of LDA-induced moderate to severe small intestinal damage. Methods: Patients received 100 mg enteric-coated aspirin daily for more than 3 months for primary or secondary prevention of cardiovascular and cerebrovascular disease, and were found to have more than 3 mucosal breaks (i.e., erosions or ulcers) in the small intestine by capsule endoscopy were enrolled, whereas patients who had less than 3 mucosal breaks (mild damage) were excluded. Since we used inactive placebo, patients with overt gastrointestinal bleeding were also excluded. Eligible patients were assigned to receive either rebamipide 300 mg three times daily or placebo for 8 weeks with an allocation ratio of 2:1. Then capsule endoscopy was performed again to investigate the treatment effects on the damage. The primary endpoint was change in the numbers of mucosal breaks in 8 weeks. Secondary endpoints included complete healing of small intestinal mucosal breaks and improvement of the severity of the damage (from the damage of more than 3 mucosal breaks to the damage of less than 3 mucosal damages or complete healing).
RESULTS: A total of 43 patients were enrolled between February 2011 and January 2014 and were randomly assigned to rebamipide group (n=29) or placebo group (n=14). Five patients were excluded because of cessation of LDA therapy (n=2), incomplete visualization at the second capsule endoscopy (n=1), patient's intention to withdraw from the trial (n=1), and development of overt gastrointestinal bleeding (n=1). Remaining 38 patients (rebamipide group; n=25, placebo group; n=13) completed the study. After 8 week's treatment, rebamipide significantly decreased the number of mucosal breaks (p=0.046), whereas placebo did not. Although the difference was not significant (p=0.13), the rate of complete healing of mucosal breaks in rebamipide group (32%, 8 of 25) had a tendency to be high, compared with placebo group (7.7%, 1 of 13). The rate of improvement of severity of the damage in rebamipide group (63%, 17 of 25) was significantly higher than that in placebo group (23.1%, 3 of 13, p=0.016). Triple dose of rebamipide was well-tolerated.
CONCLUSION: High-dose rebamipide is effective in the treatment for LDA-induced moderate to severe enteropathy.
Disclosure of Interest: O. Handa: None declared, T. Watanabe: None declared, T. Tanigawa: None declared, M. Shiba: None declared, T. Takeuchi: None declared, Y. Sakata: None declared, Y. Naito Financial support for research from: Takeda Pharmaceutical Co. Ltd, Otsuka Pharmaceutical Co. Ltd, Eisai Co. Ltd, K. Higuchi Financial support for research from: Otuka Pharmaceutical, Lecture fee(s) from: Otuka Pharmaceutical, K. Fujimoto: None declared, T. Yoshikawa: None declared, T. Arakawa: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30

GASTRIC CANCER: NEW INSIGHTS INTO PATHOGENESIS AND MANAGEMENT – LOUNGE 5

OP154 *H. PYLORI* INFECTION ALTERS HUMAN GASTRIC MICROBIOTA AND BACTERIAL DIVERSITY

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INTRODUCTION: *H. pylori* (HP) is classified by the World Health Organization as a type I carcinogen. However, the distribution and significance of other bacteria in the human stomach remain poorly characterized.
AIMS & METHODS: This study aims to characterize the gastric microbiota in individuals with and without HP infections; and determine the changes in microbiota after HP eradication. Endoscopic gastric biopsies were obtained from the antrum and corpus of informed consent patients. Patients should have no ulcer or tumor found on gastroscopy. HP infection status was determined by rapid urease test and histology exam. Bacterial DNA was extracted and sequenced on next generation sequencing platform (454 pyrosequencing), targeting the V3 and V4 regions of bacterial 16S rRNA genes. Operational taxonomic unit (OTU) clustering, diversity indexes calculation, taxonomic classification, PCoA and statistical analyses were performed after quality control and raw sequence processing. Hierarchical clustering based on weighted UniFrac distance of samples using Ward's algorithm was implemented.
RESULTS: A cohort of 27 patients was studied including 13 HP infected patients, among which 3 had repeated endoscopic biopsy after receiving antibiotics for HP eradication. In total, 494 non-singleton OTUs were identified from 165,651 high-quality sequencing reads. 27 OTUs accounted for over 90% of all sequencing reads, which belong to three phyla of *Proteobacteria* (5 OTUs), *Firmicutes* (16 OTUs) and *Actinobacteria* (6 OTUs). Hierarchical clustering presents two cluster groups: first group contains mostly HP negative samples (n=37) while the second group exclusively comprises HP positive samples only (n=16). The phylum *Fusobacteria* was only found in the first group of predominantly HP negative samples. The first group has markedly greater microbial species diversity with an average Shannon diversity index of 4.08 (SD 0.50) comparing to 1.95 (SD 0.46) of the second group ($p < 0.01$); the species richness estimator Chao 1 index is also distinctly greater in the first group ($S_{Chao\ 1} = 61.71$, SD 19.21) than that of the HP positive group ($S_{Chao\ 1} = 35.66$, SD 14.19) ($p < 0.01$). Consistent with the Chao 1 index, 227 and 58 OTUs specifically appeared in the first and second group, respectively. The average Shannon diversity index increases from 2.42 (SD 0.97) to 4.37 (SD 0.35) ($p < 0.01$) after antibiotics treatment for HP. Besides the increase in diversity and species richness, two genera *Corynebacterium* ($p = 0.03$) and *Haemophilus* ($p = 0.03$) were significantly enriched in the post treatment samples. Clustering analysis however shows minimal correlation between microbiota composition and the anatomical site of the biopsy or patient's age.
CONCLUSION: *H. pylori* colonization of the stomach results in alteration in gastric microbiota and reduction in bacterial diversity. The changes in gastric microenvironment by HP may contribute to gastric carcinogenesis that deserves further investigations.
Disclosure of Interest: None declared

OP155 INCOMPLETE TYPE OF INTESTINAL METAPLASIA HAS THE HIGHEST RISK TO PROGRESS TO GASTRIC CANCER: RESULTS OF THE SPANISH FOLLOW-UP MULTICENTER STUDY

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INTRODUCTION: In high or moderate risk population, periodic surveillance of patients at risk of progression from gastric precursor lesions (PL) to gastric cancer (GC) is recommended, as it represents the most effective strategy for reducing the burden of GC. The incomplete type of intestinal metaplasia (IM) may be considered as the best candidate, but more research is needed to confirm it, and to identify other markers of progression.
AIMS & METHODS: 1)To evaluate the risk of progression to GC in patients with PL and 2)To assess the effect of virulence factors of *H. pylori* infection, the effect of polimorphisms of candidate genes, and the effect of epigenetic variants. Results regarding the first aim are described in this presentation.
A multicenter follow-up study was carried-out including 649 patients, diagnosed with PL between 1995 and 2004, in 9 participating hospitals from Spain, which repeated the endoscopy and biopsy (following the Sidney protocol) during 2011-2013. Fresh gastric mucosa, a sample of saliva, and a questionnaire on medical information and habits of life were collected. DNA from paraffin blocks of recruitment biopsy was used for analysis of *H. pylori* by PCR, and for the analysis of methylation patterns by the Infinium 450 K methylation arrays. Based on morphology, IM was sub-classified as complete (small intestinal type, CIM) and incomplete (colonic type, IIM). Analysis was done using Cox proportional hazards risk (HR) models.
RESULTS: At baseline, 24% of patients had atrophic gastritis, 38% CIM, 34% IIM, and 4% dysplasia. The mean of follow-up was 12 ys. 24 patients (3.7%) developed a gastric adenocarcinoma during follow-up. The incidence rate of GC was 2.76 and 5.76 per 1,000 person-years, for those with CIM and IIM respectively. The HR of progression to CG was 6.4 (95%CI 0.8-49.6) and 2.4 (0.3-19.8) for those with IIM and CIM at baseline, compared with those with chronic atrophic gastritis, after adjusting for sex, age, family history of GC and use of NSAIDs.
CONCLUSION: Patients with IIM have the highest risk of progression to GC.
Disclosure of Interest: None declared

OP156 ZIPPER-INTERACTING PROTEIN KINASE INDUCES EPITHELIAL-MESENCHYMAL TRANSITION IN GASTRIC CANCER CELL THROUGH AKT-BETA CATENIN SIGNALING

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INTRODUCTION: Zipper-interacting Protein Kinase (ZIPK) belongs to the death-associated protein kinase family [1]. In accordance with its cell death promoting activity, some evidences suggest that ZIPK functions as a tumor suppressor[2]. However, the DAPK family exhibits anti-apoptotic activity under certain conditions. ZIPK is described as a novel co-activator of the AR and provide a growth advantage to prostate cancer cells [3]. ZIPK induces Wnt/β-catenin - mediated gene expression and cell growth in human colon carcinoma cells [4]. In the current study, both in vitro and in vivo assays have been used to characterize the function of ZIPK. The possible molecular mechanism of ZIPK in cancer cell growth and metastasis has been emphasized.
AIMS & METHODS: ZIPK was stably expressed in BGC-823 cells using lentiviral vector. Foci formation and soft agar assays were performed to detect cell growth, and cell proliferation was tested by XTT as well. Cell migration and invasion were investigated by wound healing and transwell invasion experiments. For in vivo tumorigenicity and metastatic assays, subcutaneous and intravenous injections were done in the 4- to 5-week old nude mice. EMT markers and AKT-GSK3β signaling were detected by western blot. ZIPK and AKTp308 were tested by immunohistochemistry in primary gastric cancers and matched metastatic lymph nodes, the patient survival time was also analyzed.
RESULTS: ZIPK could markedly increase BGC-832 cell proliferation, colony formation, migration and invasion in vitro. The nude mouse tumor growth curves showed that tumors induced by ZIPK-transfected cells grew much more rapidly. A significantly larger number of metastatic nodules were found at the surface of the lungs of mice injected with the *ZIPK*- BGC823 cells. Through western blot, we found that ZIPK increased expression of β-catenin and vimentin, and decreased the levels of E-cadherin. In addition, the expression levels of Snail and Slug, were dramatically elevated by ZIPK expression. The expression of pAkt was increased when ZIPK was overexpressed. However, the phosphorylation of GSK-3β was not changed. These results suggested that ZIPK plays a key role in regulation of EMT through AKT/β-catenin. Consistent with our finding in gastric cancer cells, co-expression of ZIPK and phosphorylated AKT in metastatic lymph nodes predicted unfavorable outcome in gastric cancer patients.
CONCLUSION: ZIPK promoted cell growth, migration and tumor formation in nude mice. ZIPK enhanced AKT activity, inducing EMT and promoting tumor invasion and metastasis.
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Disclosure of Interest: None declared

OP157 HELICOBACTER PYLORI-RELATED LONG NONCODING RNA (LNCRNA) DOWN-REGULATED EXPRESSION (DREG) INHIBITS GASTRIC CANCER PROLIFERATION AND METASTASIS BY TARGETING MUC2

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INTRODUCTION: Gastric cancer is one of the most frequent malignancies in East Asian countries [1]. Despite efforts in multiple fields, there has been little success in improving the disease-free survival rate of patients [2]. *H. pylori* has infected more than 50% of the total population and has been recognized as type I carcinogen of gastric cancer [3]. A significantly association has been identified in the relationship between *H. pylori* infection and gastric cancer but the underlying mechanism was still unclear
AIMS & METHODS: Long non-coding RNAs (lncRNAs) have been shown to have critical regulatory roles in cancer biology. In this study, we investigated whether *H. pylori* infection could promote gastric cancer by regulating the expression of lncRNAs. Differentially expressed lncRNAs between *H. pylori* positive and negative tissues were identified by microarray and validated using quantitative real-time polymerase chain reaction.
RESULTS: Our results indicated that *H. pylori* positive tissues have a specific profile of lncRNAs. Cell biological assays in combination with small interfering RNA-mediated knockdown or lentivirus vector-mediated over-expression were performed in order to probe the functional relevance of these lncRNAs. We identified an lncRNA, AF147447 (termed as Dreg), down-regulated expression by *H. pylori* infection, which can inhibit gastric cancer growth and invasion in vitro, act as a tumor suppressor in the development of *H. pylori* induced gastric cancer. LncRNA-Dreg could combine with the oncogene MUC2 and repress its expression. We also found that Dreg was regulated by transcription factor E2F1 by RNA immunoprecipatation and RNA pull down assays. These findings support a role of lncRNA- Dreg in tumor suppression.
CONCLUSION: This discovery contributes to a better understanding of the importance of the deregulated lncRNAs by *H. pylori* in gastric cancer and provides a rationale for the potential development of lncRNA-based targeted approaches for the treatment of *H. pylori*-related gastric cancer.
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Disclosure of Interest: None declared

OP158 MICRORNA-18A PROMOTES CELL PROLIFERATION BY TARGETING IRF2 IN HUMAN GASTRIC CANCER AND PREDICTS POOR SURVIVAL IN GASTRIC CANCER PATIENTS

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INTRODUCTION: MicroRNAs (miRNAs) are regulatory factors which are believed to play a crucial role in oncogenesis. Gastric carcinoma is one of the most common malignancies and the second most lethal cancer worldwide. In this study, we assessed the value of miR-18a in predicting outcome after curative resection in gastric cancer (GC) patients and defined the oncogenic significance and function of miR-18a.
AIMS & METHODS: We analyzed miR-18a expression in 90 clinicopathologically characterized GC tissues by in situ hybridization, and 53 gastric juice samples (24 GC patients, 14 healthy controls, and 16 gastric ulcer patients) by quantitative RT-PCR. The prognostic significance was assessed using Kaplan-Meier survival estimates and log-rank tests. Biological roles of miR-18a were also explored in vivo. The interferon regulatory factor 2 (IRF2) were validated as targets of miR-18a by luciferase assay, quantitative RT-PCR, and western blot. The expression of IRF2 in the same 90 GC cases was also analyzed by immunohistochemistry.
RESULTS: In this study, we found that overexpressed intratumoral miR-18a was associated with poor survival rate ($P < 0.001$), and was an independent prognostic factor for overall survival rate ($P < 0.001$) in the GC patients. High expression of miR-18a was also found in the gastric juice of GC patients. Forced expression of miR-18a remarkably enhanced cell proliferation, migration, and invasion in GC cells, while inhibition of miR-18a by inhibitor caused the opposite effects. Bioinformatics analysis identified the IRF2 as a potential miR-18a target. Further studies confirmed the miR-18a suppressed the expression of IRF2 by directly binding to is 3'-untranslated region. Moreover, miR-18a expression levels correlated inversely with IRF2 in human GC tissues. Western blot showed that forced expression of miR-18a in GC cells could not only down-regulate the expression of IRF2, but also inhibit the expression of P53, suggesting that IRF2 might play as a tumor suppressor by regulating P53 signaling in GC.
CONCLUSION: Taken together, these results demonstrated that miRNA-18a promoted cell proliferation by targeting IRF-2 in human GC and predicted poor survival in GC patients.
Disclosure of Interest: None declared

OP159 EFFECTS OF ALDH2-GENOTYPE, PPI-TREATMENT AND L-CYSTEINE ON THE LEVELS OF CARCINOGENIC ACETALDEHYDE IN GASTRIC JUICE AND SALIVA AFTER INTRAGASTRIC ALCOHOL ADMINISTRATION

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INTRODUCTION: Acetaldehyde (ACH) associated with alcoholic beverages is Group 1 carcinogen to humans (IARC/WHO). Aldehyde dehydrogenase (ALDH2), a major ACH eliminating enzyme, is genetically deficient in 30-50% of Eastern Asians. In alcohol drinkers ALDH2-deficiency is well known risk factor for upper digestive tract cancers. Presence of alcohol in systemic blood circulation of ALDH2-deficient subjects results in significantly elevated salivary ACH levels. This provides strong evidence for the causal relationship between local ethanol-derived ACH and oral, pharyngeal and esophageal cancers. Alcohol and ALDH2-deficiency are established risk factors also for stomach cancer. Normal human gastric mucosa expresses three alcohol dehydrogenase (ADH) isozymes and low K_m ALDH2-enzyme activity. High-K_m and high-V_{max} ADH4 plays a key role in the gastric first pass metabolism of ethanol to ACH at high intragastric ethanol concentrations during the first 1 – 2 hours after alcohol intake. ADH-containing oral microbes, colonizing hypochlorhydric stomach, contribute significantly to local intragastric production of ACH. However, the combined role of ALDH2-genotype, PPI-induced achlorhydria and ACH eliminating L-cysteine in the regulation of ACH levels in gastric juice and saliva is not yet known.
AIMS & METHODS: To assess the effect of ALDH2-genotype, achlorhydria produced by PPI-treatment and slowly L-cysteine releasing capsule on the levels of ACH in gastric juice and saliva following an intra-gastric infusion of ethanol. 15. ALDH2-active and 10 ALDH2-deficient *H. pylori* negative healthy volunteers were included in the study. Through a nasogastric tube 15% ethanol (0.5g/kg) was infused into the stomach. 5ml of gastric aspirate and 1-2 ml of saliva were collected at 30-min intervals up to 120 min. The first two samplings were done before and after 7-day administration of proton pump inhibitor (PPI, rabeprazole 10mg b.i.d.) (experiment 1 and 2). After 3 more days on PPI, sampling of gastric juice and saliva was repeated with 200mg of slowly L-cysteine releasing capsule administered before ethanol infusion (experiment 3).
RESULTS: After intragastric infusion of alcohol ALDH2-deficiency resulted in mean 5.6-fold increase in gastric juice ACH and mean 2.1-fold increase in salivary ACH compared to the subjects with normal ALDH2-enzyme ($p < 0.0001$ for both). In ALDH2-active subjects PPI-treatment increased gastric juice ACH to 3.3.-fold ($p < 0.0001$), but had no effect on salivary ACH. L-cysteine eliminated effectively gastric juice ACH both in PPI-treated ALDH2-active and ALDH2-deficient subjects (mean 75% and 60%, $p < 0.0001$ and < 0.0031, respectively).
CONCLUSION: Alcohol-induced marked increase in gastric juice ACH in ALDH2-deficient subjects provides strong evidence for the local carcinogenic action of ACH in gastric carcinogenesis. Nondependent changes in gastric juice and salivary ACH levels caused by PPI-treatment and intragastric L-cysteine indicate that gastric juice ACH level is locally regulated by gastric mucosal ADH- and ALDH2-enzymes and by oral microbes colonizing acid free or achlorhydric stomach.
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OP160 MIR-21, MIR-223 AND MIR-155 ARE NOVEL MUCOSAL BIOMARKERS FOR HIGH-RISK GASTRITIS

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INTRODUCTION: Gastric carcinogenesis is a multifactorial *H.pylori*-triggered dynamic process that goes through a cascade of preneoplastic conditions. Identification of biomarkers predictive for gastric cancer development may help to improve current screening and surveillance programs.
AIMS & METHODS: In this study, we systematically characterized expression of miR-21, miR-155 and miR-223, microRNAs that are frequently deregulated in gastric cancers (GC), with regard to preneoplastic precursor conditions in gastric mucosa, *H. pylori* infection and gastric region. In a prospective study, 80 patients (normal (N), chronic gastritis (CG), atrophic gastritis ± intestinal metaplasia (AG) and GC) underwent upper GI endoscopy and *H.pylori* status, mucosal inflammation, atrophic or malignant changes were systematically evaluated according to the updated Sydney classification. Biopsies were assessed from corpus, antrum and in case of gastric tumor also from the tumor (T-GC) and near the tumor (NT-GC). Expression of miR-21, miR-223 and miR-155 was analyzed by qRT-PCR from total RNA. Normalization was performed using RNU6b. Potential diagnostic utility was tested using a simple miRNA expression score.
RESULTS: All three studied miRNAs are differentially expressed in normal gastric mucosa compared to tumor, especially for miR-21 and miR-223. Remarkably, miRNA expression pattern was different between normal gastric corpus and antrum mucosa ($p < 0.001$) and therefore, further analyses were performed for different localizations independently. In correlation with Correás cascade of mucosal alterations, we observed gradual increase in miR-155, miR-

223 expression in corpus mucosa and increase of all 3 miRNAs in antrum from N to CG to AG ($p<0.001$). In GC patients, adjusted non-tumorous corpus and antrum mucosa showed increased miRNA expression compared to subjects with normal mucosa, although, we also observed heterogeneous and miRNA-specific expression pattern between different regions including non-tumorous and tumorous tissues. *H.pylori* infection was associated with increased miR-155 and miR-223 expression both in corpus and antrum, and slight increase of miR-21 expression in antrum. Lastly, using calculated summary score of three miRNAs, we were able to distinguish atrophic gastritis from normal mucosa with area under the curve (AUC) = 0.90 (95% CI 0.8±1.0) for corpus and AUC = 0.98 (95% CI 0.96±1.01) for antrum.

CONCLUSION: Gastric cancer-associated miRNAs are differentially expressed in preneoplastic gastric mucosa and surrounding mucosa of GC patients. Gradual increase in miRNA expression correlates with Correás cascade of preneoplastic alterations and *H.pylori*, suggesting miRNAs as diagnostic and potential predictive biomarkers. However, regional differences in miRNA expression pattern within the stomach need to be considered in future studies.

Disclosure of Interest: None declared

OP161 HIGH LEVELS OF RELM-ALPHA CORRELATE WITH POOR PROGNOSIS AND PROMOTE METASTASIS IN GASTRIC CANCER

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INTRODUCTION: Accumulating evidence indicates that Resistin-like molecule–α (RELM-α) is involved in the angiogenesis of endothelial cells and inducing of vascular of remodeling, while the clinical significance of RELM-α in gastric cancer is poorly understood and the exact role of RELM-α in gastric cancer remains obscure.

AIMS & METHODS: The aim of this study is to evaluate the expression of RELM-α and its clinical significance in gastric cancer, to investigated its effective mechanism in order to the new therapeutic target. In the present study, expression levels of RELM-α in 96 gastric carcinoma tissues, adjacent normal tissue, and 2 types of gastric cancer cell lines were quantified by immunohistochemical staining or Western blot, and the relationship between RELM-α expression and cliniopathological characteristics of cancer was explored. To investigate the potential role of RELM-α in gastric cancer cell biological behavior, the study performed cell proliferation, migration and invasion assays in two gastric cancer cell lines (SGC7901 and MKN45), and the study tested whether knockdown of RELM-α modulates vascular endothelial growth factor (VEGF) expression by small interference RNA in cancer lines, and dissected the possible signaling pathways that link RELM-α to VCAM-1 up-regulation by western blot, and further explored its effect on NF-κB activation by EMSA method.

RESULTS: 65 (67.7%) tested positive for RELM-α expression, mainly in the cytoplasm of gastric cancer mucosa. Contrasting sharply with the strongly RELM-α-positive tumors, adjacent normal tissue and cell lines was negative or weakly positive expression ($P < 0.01$). Higher expression levels of RELM-α were associated with more advanced stage ($P < 0.01$). Additionally, the expression of RELM-α was significantly correlated with lymph node metastasis and tumor size but had no correlation with the patient's prognosis. The knockdown expression of RELM-α by SiRNA treatment could significantly inhibited cell migration and invasion ability in SGC7901 and MKN45 gastric cancer cells compared with control cell lines ($P < 0.01$). However, the knockdown expression of RELM-α also significantly blocked NF-κB activation and attenuated VEGF production in two cancer lines.

CONCLUSION: The data demonstrated that RELM-α is a novel biomarker for metastasis in patients with gastric cancer. The study identified that up-regulation of RELM-α may regulate the proliferation, invasion and migration of gastric cancer cells, its mechanism was involved into VEGF up-regulation induced by RELM-α promotes tissue angiogenesis by NF-κB signaling pathway activation.

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Disclosure of Interest: None declared

OP162 THE CLINICAL UTILITY OF SERUM HER2 IN GASTRIC CANCER

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INTRODUCTION: Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) are the current mainstays of diagnosis of tissue HER2 status in gastric cancer. In contrast to breast cancer, however, HER2 expression in gastric cancer occasionally demonstrates intratumoral heterogeneity, raising concern about false-negative cases. Serum HER2, concentrations of the HER2 extracellular domain (ECD) shed into the bloodstream, evaluates a different aspect of HER2 status but has not been well studied in gastric cancer.

AIMS & METHODS: To elucidate the clinical utility of serum HER2 in gastric cancer, we performed a prospective multicenter study (SHERLOCK trial, UMIN 000009773). Patients with gastric or gastro-oesophageal junction cancer of all stages were recruited. Pretreatment serum HER2 level was measured using chemiluminescense immunoassay (CLIA), and tissue HER2 status was assessed by IHC and FISH for IHC 2+ cases at central laboratory. For stage IV cases, tissue HER2 status was firstly assessed by various anti-HER2 antibodies at local laboratories of each hospital, then reevaluated using two antibodies (Dako HercepTest II and SV2-61γ) and FISH at central laboratory in a blinded manner.

RESULTS: From June 2011 to July 2013, a total of 224 patients were enrolled from 14 centers. Both tissue HER2 status and serum HER2 level were successfully determined in 194 patients (stage I: 103, stage II: 11, stage III: 16, stage IV: 64). Tissue HER2 was positive in 42 patients (21.6%) and HER2 positive rate was higher in an advanced stage. Serum HER2 level ranged from 4.5 to 148.0 ng/ml (median 10.3 ng/ml), and significantly correlated with tissue HER2 status ($p=0.0058$). With a cut-off level of 16.5 ng/ml determined by receiver operating characteristics (ROC) analysis, sensitivity, specificity, positive predictive value and negative predictive value of serum HER2 were 26.2%, 95.4%, 61.1% and 82.4%, respectively.

Among 64 stage IV patients, tissue HER2 results from both local and central laboratories were available in 56 patients. Local laboratories initially diagnosed 18 cases as tissue HER2-positive and 38 as negative. Serum HER2 levels were elevated (>16.5ng/ml) not only in 9 of 18 tissue HER2-positive cases but also in 7 of 38 tissue HER2-negative cases. Reevaluation of tissue by central laboratory had identified 4 false-negative cases among 38 initially judged as HER2-negative. Of these 4 cases, 2 demonstrated extremely high serum HER2 level (61.2 and 53.3 ng/ml). Consequently, serum HER2 thus rescued 2 false-negative cases out of 4.

CONCLUSION: Serum HER2 level was correlated with tissue HER2 status in gastric cancer. Although the low sensitivity is a drawback, serum HER2 might be useful to salvage tissue HER2 false-negative patients who will benefit from anti-HER2 treatment.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 8:30–10:30

HOT TOPICS IN CHOLESTATIC AND PANCREATIC DISEASES – LOUNGE 6

OP163 INTRAHEPATIC CHOLESTASIS OF PREGNANCY AND RISK OF AUTOIMMUNE, CARDIOVASCULAR AND MALIGNANT DISEASES: A POPULATION-BASED COHORT STUDY OF 125,281 SWEDISH WOMEN

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INTRODUCTION: Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease in pregnancy and closely associated with prevalent and future hepatobiliary diseases. In addition, ICP bears an almost 3-times higher risk of gestational diabetes and preeclampsia.

AIMS & METHODS: We now aimed to find possible associations between ICP and autoimmune, cardiovascular and major malignant diseases. We analyzed data of women with births between 1973 and 2009 and registered in the Swedish Medical Birth Register. By linkage with the Swedish Patient Register, we identified 11,388 women with ICP who were matched to 113,893 women without this diagnosis. Diagnoses of autoimmune, cardiovascular and major malignant diseases (breast, uterus, lung, colorectal, hepatobiliary) were obtained from the Patient Register. Main outcome measures were hazard ratios (HRs) for later disease in women with ICP at <1 year, 1-5 years, >5 years after delivery. Risk estimates were calculated through Cox regression and logistic regression analysis.

RESULTS: Women with ICP were more often diagnosed with later autoimmune disease (HR 1.25; 95% CI 1.16 - 1.35; $p<0.0001$). The risk was specifically increased for diabetes mellitus (HR 1.46; CI 1.25 - 1.71), thyroid disease (HR 1.26; CI 1.11-1.23), Crohn's disease (HR 1.55; CI 1.14-2.11), psoriasis (HR 1.23; CI 1.04-1.46) and inflammatory polyarthropathias (HR 1.32; CI 1.10-1.56), as compared to women without ICP. Women with ICP were also at increased risk for liver (HR 3.51; CI 1.64-7.58) and biliary (HR 2.49; CI 1.19-5.21) malignancies. The risk of cardiovascular disease was not increased.

CONCLUSION: Women with ICP have increased risk to be later diagnosed with autoimmune diseases, in particular diabetes mellitus. This however, was not reflected by increased risk of cardiovascular diseases. The close association of ICP with hepatobiliary diseases also comprises increased risk of liver and biliary tree cancers.

Disclosure of Interest: None declared

OP164 PAEDIATRIC ONSET PRIMARY SCLEROSING CHOLANGITIS IN FINLAND: CLINICAL COURSE AND PROGNOSIS

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INTRODUCTION: Natural history of paediatric onset primary sclerosing cholangitis (PSC) and PSC/autoimmune hepatitis (PSC/AIH) overlap syndrome is poorly known[1].
AIMS & METHODS: Aim of this retrospective observational cohort study was to evaluate the clinical course and prognosis of patients with a paediatric onset PSC-PSC/AIH over a long follow-up. Between 1993-2011, 41 paediatric ($\leq$ 18 years) PSC and PSC/AIH patients (pts) referred to Helsinki University Central Hospital, comprised the study group. The diagnosis was confirmed in all pts reviewing clinical, pathological and radiological data at the disease onset and in the end of the follow-up (31st December 2013). All ERC images (endoscopic retrograde cholangiography) were re-reviewed by 2 experienced endoscopists. All liver biopsies were also re-reviewed by one experienced pathologist. PSC was defined when typical biliary duct changes were present (i.e., strictures and dilations); PSC/AIH when pts met both the diagnostic criteria for PSC and AIH (e.g., interface hepatitis and ANA/SMA antibodies). Timing of ERC follow-up was decided according to (i) severity of cholangiography changes and (ii) presence of dysplasia (Dys) or aneuploidy (Ane) on brush cytological samples.
RESULTS: In the final analysis 37 pts (Median age: 16 years; range: 5-18. Male: 24; 65%) were included. Median follow-up was 9 years; range: 2-20. PSC/AIH overlap syndrome was present in 12/37 (32%). Concomitant inflammatory bowel disease was associated in 28/37 (75%), mostly ulcerative colitis (25/28; 89%). Autoimmune diseases were present in 6/37 (16%). The insidious onset (none or slight symptoms) was the most common presentation (20/37; 54%). Number of patients with liver lab tests elevation at disease onset and in the end of follow-up is shown in Table 1. All the pts underwent ERC at diagnosis; 29/37 (78%) at the end of follow-up (Table 1). Liver biopsy was performed in 34/37 (92%) at diagnosis. All patients were managed with UDCA and immunosuppression. Four pts (11%) underwent LTx (2 for severe Dys and Ane, 1 for Budd-Chiari syndrome, 1 for acute liver failure and 1 for suspicion of malignancy due to persistent elevation of Ca19-9 and CEA); no pts had disease recurrence on the graft during a mean follow up of 3 years (SD $\pm$ 2.9). None of the pts developed cholangiocarcinoma and all are still alive.
TABLE 1

	AT DIAGNOSIS (%)	AT THE END OF FOLLOW-UP (%)
ALT	30/37 (81%)*	11/37 (30%)*
AST	27/37 (73%)*	8/37 (22%)*
GGT	30/37 (81%)*	14/37 (38%)*
ALP	21/37 (57%)*	16/37 (43%)*
BILIARY CHANGES		
- INTRA-HEPATIC	26/37 (70%)	18/29 (62%)
-INTRA AND EXTRA HEPATIC	11/37 (30%)	11/29 (38%)

CONCLUSION: This retrospective observational cohort study showed a better prognosis of PSC and PSC/AIH with a paediatric onset compared to previous published. The careful endoscopic follow-up conducted in these patients could prevent complications.
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Disclosure of Interest: None declared

OP165 EVIDENCE OF A NORTH SOUTH GRADIENT IN THE OCCURRENCE OF PRIMARY BILIARY CIRRHOSIS IN THE UK USING TWO DECADES OF NATIONAL DATA

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INTRODUCTION: Previous studies of the occurrence of Primary Biliary Cirrhosis (PBC) have been small and regional, but in combination they suggest a north south gradient in incidence in the UK, and elsewhere geospatial clustering.[1-4] This raises the possibility of specific environmental factors related to geographical location leading to PBC occurrence. However few studies have been truly national or population based. We have therefore assessed the patterns in occurrence of PBC across the whole of the UK over 2 decades.
AIMS & METHODS: Patients with Primary Biliary Cirrhosis (PBC) were identified in the Clinical Practice Research Datalink between 1990 and 2010 using specific Read codes for PBC. Incidence rates and prevalence were calculated by age group, sex, year, socio-economic status and region of residence. Incidence rate ratios (IRR) adjusted for these variables were then calculated with Poisson regression.
RESULTS: 1390 incident cases of PBC were identified from the CPRD. 88% of cases were women with the highest incidence in those aged over 70 years of age. Between 1990 and 2010 the overall incidence rate of PBC increased from 1.2/100,000 (95% CI, 0.6–2.1) in 1990 to 2.9/100,000 ((95% CI, 2.4-3.7) in 2010, with an adjusted 2-fold increase (IRR 1.9 (95% CI, 1.1-3.5)). There was a clear north south gradient in PBC incidence that persisting after adjusting for socioeconomic differences (table, $p = 0.001$ for a trend). When time trends were stratified by region there was a significant increase in incidence in the north of England ($p < 0.02$) that was not reflected elsewhere in the country. We did not find an association between PBC incidence with socioeconomic status (likelihood ratio test, $p = 0.3$). Prevalence of PBC followed a similar pattern to incidence across the country and over time.
Table .Average incidence rates for Primary Biliary Cirrhosis (1990-2010, per 100,000 person years) and the corresponding incidence rate ratios adjusted for age group, sex, year, and socio-economic status.

Regions (Aggregated)	Incidence	95% CI	IRR	95% CI
Scotland and Northern Ireland	4.8	(4.2–5.3)	2.8	(2.6-2.9)
Northern England and Yorkshire	2.8	(2.5-3.2)	1.8	(1.7-1.9)
Mid England and Wales	2.0	(1.8-2.4)	1.1	(1.1-1.2)
Southern England and London	1.8	(1.6-2.0)	1.0	-

CONCLUSION: We found that across a 20 year period there was a 2-fold increase in the incidence of PBC in the UK with large regional variations. The greatest increases were seen in the north of England with small rises elsewhere. Although geographical differences raise the possibility that specific environmental exposures are responsible, the lack of association with socioeconomic status makes some of the suggested culprits, smoking and living conditions, less probable.[3] The most likely reasons for these variations were therefore differences in ascertainment of disease.
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Disclosure of Interest: None declared

OP166 THE CLINICAL SIGNIFICANCE OF SPHINCTER OF ODDI INSUFFICIENCY AFTER CHOLECYSTECTOMY

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INTRODUCTION: It's usual to expect organic obstacles of bile flow in patients with postcholecystectomical abdominal pain and dyspeptic disorders but more often it must be distinguished from sphincter of Oddi functional disorders.
AIMS & METHODS: To evaluate the clinical significance of the loss of sphincter of Oddi's closing contraction function in patients after cholecystectomy.
The study included 100 patients after cholecystectomy (17 men, 83 women, aged 17-72 yrs), excluding those who had signs of cholestasis. Two groups were identified: 1st - 86 patients after cholecystectomy; 2nd - 14 patients after cholecystectomy combined with papillotomy, in whom we assumed that the sphincter of Oddi's closing contraction function was lost.
Clinical manifestations, biochemical blood tests, the results of X-ray and endoscopic studies were evaluated. Patients underwent hepatobiliary scintigraphy (HBSG) using radionuclide tracer 99 m Tc-HIDA within 90 minutes, with fatty meal ingestion on the 45th minute. The function of the common bile duct (CBD) and the duodenum was measured. Specific «time-activity» histogram were made, time-to-peak CBD activity (TP CBD), half time of excretion (T½ CBD), latent period of CBD (T lat CBD), duodenal appearance time (DAT), half time of excretion of the duodenum (T½ duodenum), degree of duodeno-gastric reflux (DGR) were calculated.
RESULTS: According to HBSG in 20 (23.2%) patients of the 1st group the appearance of radionuclide tracer small portions in the duodenum (DAT) was recorded at 27.7±10.2 minute (min), and the intensive removal from time-to-peak CBD activity started immediately after fatty meal ingestion at 45.9±1.8 min, with T½ CBD 27.7±13.9 min, which corresponds to normal. In 66 (76.8%) patients of the 1st group DAT was registered already in 18.6±6.0 min and the choledoch started to empty before the fatty meal ingestion, TP CBD was determined on 32.9±6.8 min and T½ CBD – on 26.4±10.8 min. These indicators were regarded as the sphincter of Oddi insufficiency. In all cases of the 2nd group a premature start (TP CBD 30.4±0.8 min) and rapid emptying of the CBD (CBD T½ 27.5±11.2 min) were observed, with the appearance of the radionuclide tracer in duodenum at 17.6±0.8 min. These figures were identical to those in patients with sphincter of Oddi failure in the 1st group, but differed from those with normal sphincter of Oddi function ($p < 0.05$). TP CBD correlated with T½ duodenum ($r=0.57$, $p<0.001$) and degree of DGR ($r=0.74$, $p<0.01$). DGR degree was associated with belching bitter complaints ($r=0.36$, $p<0.01$), heartburn ($r=0.24$, $p=0.025$). X-ray duodenum antistalsis was accompanied by reflux into the stomach ($r=0.73$, $p<0.01$) and endoscopic data of antral gastritis and esophagitis ($r=0.39$, $p<0.048$). Diarrhea was observed in 73% patients of the 1st group with the sphincter of Oddi insufficiency and 86% - after papillotomy versus 10% of normal bile flow ($p < 0.01$). Diarrhea rate correlated with TP CBD($r= -0.43$, $p<0.01$).
CONCLUSION: Sphincter of Oddi insufficiency develops in 77% cases after cholecystectomy and becomes most clinical significant in patients with duodenum dyskinesia. The relationship of functional disorders of biliary tract and the duodenum should be taken into account while choosing therapeutic management, complementing therapy with regulating intestinal motility.
Disclosure of Interest: None declared

OP167 INTERSTITIAL CAJAL-LIKE CELLS/TELOCYTES AND GALLBLADDER AUTONOMIC NERVOUS SYSTEM INTERPLAY IN THE PATHOGENESIS OF CHOLELITHIASIS

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INTRODUCTION: The major mechanisms of gallstone formation include biliary cholesterol hypersecretion, supersaturation and crystallization, mucus hypersecretion, gel formation and bile stasis. Gallbladder hypomotility seems to be a key event that triggers the precipitation of cholesterol microcrystals from supersaturated lithogenic bile. Recently, we reported a significant decrease in interstitial Cajal-like cell (ICLC) density in gallbladders of patients with cholelithiasis. Such cells in the gallbladder were strongly influenced by lithogenic bile. ICLCs, as well as the autonomic neurons located within gallbladder muscularis propria are considered as predominant regulatory cells of gallbladder motility.
AIMS & METHODS: The purpose of the current study was to determine the influence of lithogenic bile on gallbladder autonomic neurons, in relationship to ICLCs. Gallbladder specimens were collected from 20 patients (8 males and 12 females) who underwent elective laparoscopic cholecystectomy for symptomatic gallstone disease. The control gallstone-free group consisted of 20 consecutive patients (9 males and 11 females) who received elective treatment for pancreatic head tumors. ICLCs were visualized in paraffin sections of gallbladders with double immunofluorescence using primary antibodies against c-Kit (anti-CD117) and anti-mast cell tryptase. The telocytes were stained with anti-CD34 antibody and assessed simultaneously. Autonomic neurons within the gallbladder wall were visualized by immunohistochemistry using anti-PGP9.5, anti-ChAT and anti-NOS antibodies and assessed semi-quantitatively. Cholesterol, phospholipid and bile acid concentrations were measured in bile samples obtained by needle aspiration from the gallbladder during surgery.
RESULTS: The number of ICLCs in the gallbladder wall was significantly lower in the study group than in the control group (3.2 ± 1.5 vs. 6.6 ± 1.8 cell/area of view in the muscularis propria, $P < 0.001$) and correlated with a significant increase in the cholesterol saturation index, so did the telocytes count. The glycocholic and taurocholic acid levels were significantly elevated in the control subjects compared with the study group. Numerous PGP9.5 – positive neural fibers were present, including some neuron bodies. Only sparse cholinergic (ChAT-positive) as well as nitrergic (NOS-positive) neurons were found. The cumulative neurons count was slightly decreased in patients with gallstones.
CONCLUSION: These results suggest that bile composition plays an important role in the reduction of ICLC and autonomic neurons density in the gallbladder, and this might lead to the gallbladder dysmotility in patients with cholelithiasis.
Disclosure of Interest: None declared

OP168 SMALL FIBERS PERIPHERAL NEUROPATHY IN WILSON DISEASE: AN IN VIVO DOCUMENTATION BY CORNEAL CONFOCAL MICROSCOPY

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INTRODUCTION: Wilson disease (WD) is a rare inherited autosomal recessive disorder of copper metabolism whose hallmarks are: liver damage, neuropsychiatric symptoms and Kayser-Fleischer (KF) corneal ring. The presence of KF ring correlates with central nervous system (CNS) involvement, being detectable in nearly 100% of subjects with CNS involvement, and in about 50% of those with hepatic and pre-symptomatic WD. Corneal confocal microscopy (CCM) is a fast reliable and repeatable technique to analyze the human cornea in vivo, allowing a high magnification imaging of different corneal structures, including corneal nerves.
AIMS & METHODS: We aimed to investigate central corneal changes and to assess the parameters of corneal subbasal nerve plexus (CSNP) in patients affected by Wilson disease (WD), using corneal confocal microscopy (CCM). Twenty-four patients affected by WD and 24 healthy control subjects were enrolled in this cross-sectional comparative study. One eye of each subject was examined to quantify different corneal parameters, by means of non invasive corneal confocal microscopy. Mean cell diameter and mean cell density of the epithelium; number of fibers (NF), nerve fiber length density (NFLD), number of branchings (NBr), number of beadings (NBe) and fiber tortuosity (FT) of the subbasal nerve plexus; mean cell density of keratocytes of the anterior, medium and posterior stroma and mean cell density, polimegatism and pleomorphism of the endothelium were analyzed.
RESULTS: WD induced significant alterations in both corneal subbasal nerve plexus, and corneal epithelium. All the parameters of the subbasal nerve plexus were altered in WD: NFLD ($P < 0.0001$), NF ($P=0.001$), NBe ($P=0.025$) and NBr ($P < 0.0001$) were significantly lower, whereas FT ($P < 0.0001$) was significantly higher in WD subjects compared to controls, documenting, for the first time, a (corneal) peripheral nerve damage in WD. The decrease of major CSNP parameters confirms the damage (and death) of a significant number of small nerve fibers, whereas the increase of FT is a sign of tentative nerve regeneration. Mean epithelial cell diameter ($P < 0.0001$) and mean epithelial cell density ($P < 0.0001$) resulted significantly higher and lower compared to controls, respectively. No significant difference in corneal stroma and endothelium were observed.
CONCLUSION: CCM showed significant corneal changes in subbasal nerve plexus, with secondary corneal epithelium changes in WD, demonstrating the presence of small fibers peripheral neuropathy in these patients. CCM may contribute to diagnose and monitor the peripheral nervous system involvement in WD. Further larger studies needed to confirm these findings.
Disclosure of Interest: None declared

OP169 PANCREATIC ENZYME REPLACEMENT THERAPY IN PANCREATIC CANCER – ARE WE GETTING IT RIGHT?

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INTRODUCTION: Pancreatic cancer (PC) is the 10th most common cancer in the UK, accounting for 8500 all new cases per year. PC is unique compared to other cancers, as weight loss and malabsorption are present in 80%–90% of patients at the time of diagnosis. Pancreatic enzyme replacement therapy (PERT) in the form of enteric coated pancreatin microspheres is recommended in pancreatic cancer patients with these symptoms to prevent weight loss and malnutrition and improve quality of life. Given that the probability of pancreatic exocrine insufficiency is high in PC, PERT is recommended without the use of formal diagnostic tests. The optimal dose of pancreatic enzyme replacement therapy is 40-50000 lipase units per main meal with half that dose for each snack.
AIMS & METHODS: The aim of this study was to evaluate the use of PERT in pancreatic cancer and to ascertain if patients were being prescribed the recommended dose. A single centre retrospective analysis of patients diagnosed with PC in a large North London district general hospital was performed. The database of all patients diagnosed with PC since 2010 was obtained from the local upper gastrointestinal cancer multidisciplinary team records. 149 patients were identified but 32 excluded from the study due to poor documentation in the records leading to insufficient information surrounding enzyme supplementation and dosages. Information was collected from electronic patient records on the patients' symptoms, evidence of PERT and the dose prescribed.
RESULTS: Symptoms of pancreatic enzyme insufficiency (weight loss and/or steatorrhoea) were recorded in 72/117 (61.5%) of patients included in this study. Only 14 out of the 117 (8%) patients included in this study were prescribed PERT. The table below shows the enzyme formulation and dosages used.

Pancreatic enzyme formulation	Dose (units)	Number of patients
Creon®	50 000 three times/day (TDS)	1
	40 000 TDS	1
	30 000 TDS	1
	25 000 TDS	4
	10 000 TDS	4
	Not documented	2
Creon® Micro	Not documented	1

CONCLUSION: In our study we demonstrate that the majority of patients (92%) with PC are not prescribed PERT despite the presence of symptoms indicating pancreatic enzyme insufficiency. Of the 14 patients prescribed PERT, only 2 patients were treated with the recommended dose. This study highlights the missed opportunity to reduce symptoms and improve quality of life in PC patients with simple PERT. Increased awareness of the availability of this simple treatment amongst those treating patients with PC is required.
Disclosure of Interest: None declared

OP170 FAST TRACK RECOVERY REDUCES COMPLICATIONS AND COSTS AFTER PANCREATICODUODENECTOMY

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INTRODUCTION: Enhanced recovery after surgery is multimodal, evidence based approach to optimize the patient outcome. Enhanced recovery after surgery (ERAS) or fast track programmes were developed and described by Kehlet et al. more than 10 years ago for colorectal surgical patients. Pancreaticoduodenectomy (PD) is a very complex operation with a high morbidity rate and long post-operative hospital stay.
AIMS & METHODS: The aim of this study was to evaluate the safety and clinical outcome of a fast track programme after PD. 100 pancreaticoduodenectomies were prospectively followed at Skåne University Hospital Lund, Sweden. 50 patients were evaluated before adopting the perioperative routine changes (preFastTrack) and 50 patients after (FastTrack). The postoperative care was challenged and changes were made according to the basic ERAS concept. A programme was adopted that standardized the care and automated certain functions. Changes made include; preoperative nutrition, secondary antibiotic prophylaxis, standardized withdrawal of nasogastric tubes and abdominal drains. Patients were also put on a standardized pain relief scheme. Patients were thoroughly informed preoperatively regarding the proposed care and discharge criteria. Data regarding demographics, symptoms, blood, operations and postoperative course was prospectively and continuously registered.
RESULTS: There was no difference between the groups regarding background data on age, sex, symptoms, histopathological diagnosis and TNM stage. 30 days-mortality was zero in both groups.
Complications were decreased in the Fast Track group with delayed gastric emptying (DGE) significantly decreased (Table 1). Patients with complications (55% vs 34%) and severity of complications according to Clavien-Dindo was significantly reduced ($p=0.013$ and $p=0.0.001$ respectively).

Table 1.
Table to abstract OP170

	Pre Fast Track	Fast Track	P-value
Wound infection	12 (24%)	7 (14%)	0.067
Seroma	3 (6%)	1 (2%)	0.096
'Postoperative bleeding ¤	2 (4%)	2 (4%)	1.0
Pancreatic fistula ¤	14 (28%)	11 (22%)	0.288
Serious complications *	5 (10%)	6 (12%)	1.0
Delayed Gastric Emptying *	25 (48%)	11 (22%)	**0.029**

CONCLUSION: The result of this study shows it is feasible to perform an enhanced recovery even after a major operation such as the pancreatodudodenectomy without increasing mortality or morbidity. The shorter hospital stay and less frequent use of radiology decrease the in-hospital cost significantly with almost 25%.
Disclosure of Interest: None declared

OP171 ELEVATED ALKALINE PHOSPHATASE IS AN INDEPENDENT PREDICTOR OF GOOD RESPONSE DURING SOMATOSTATIN ANALOGUE THERAPY: A MULTI-CENTER POOLED ANALYSIS ON INDIVIDUAL PATIENT DATA

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INTRODUCTION: Somatostatin analogues (SA) reduce liver volumes in patients with polycystic liver disease. However, polycystic liver disease patients show a great variety in treatment responses, which makes it difficult to predict which patients will respond to SA therapy.
AIMS & METHODS: Our aim was to identify specific patient, disease or treatment characteristics that predict good response to SA in polycystic liver disease. We pooled the individual patient data of 4 trials (NCT00771888, NCT00426153, NCT01157858, NCT01354405) that evaluated the effect of long-acting SAs (120 mg lanreotide or 40 mg octreotide) for 6-12 months in polycystic liver disease patients and had liver volume as a primary outcome. We performed univariate and multivariate logistic regression analysis with preselected patient, disease and drug characteristics to identify predictors of good-response. Good-response was defined as a reduction of 120 ml in liver volume, as this was associated with a clinical response[1]. All analyses were adjusted for center and baseline liver volume.
RESULTS: We included 153 polycystic liver disease patients (86% female, mean age 50 years, median liver volume 4974 ml) from 3 international centers that were treated with octreotide (n=70) or lanreotide (n=83). Median reduction in liver volume was 4% (range -32 to +10%), and 57% patients achieved a good response during therapy. Multivariate logistic regression revealed that elevated alkaline phosphatase (ALP) (odds ratio 2.61, 95% confidence interval 1.17 – 5.83, $p = 0.019$) as a predictor of good response during SA therapy, independent of baseline liver volume. Renal function, elevated bilirubin, duration of therapy (6 versus 12 months) and SA type (octreotide or lanreotide) did not affect the probability for a response. Elevated ALP remained an independent predictor for response when it was defined as percent change in liver volume instead of absolute change. Our model, including ALP, performed well in differentiating patients with and without good response during SA therapy (AUC 0.72, $p < 0.001$).
CONCLUSION: Elevated ALP is an independent predictor for good response during SA therapy in polycystic liver disease, and could possibly serve as a marker to select patients for initiating therapy.
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Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 11:00-12:30
INFLAMMATION AND CELL DEATH IN GI DISORDERS – HALL R

OP172 ADIPOSE TISSUE REGULATORY LYMPHOCYTES MISMATCH WITH ANTHROPOMETRIC PARAMETERS IS ASSOCIATED WITH INSULIN RESISTANCE IN OBESE PATIENTS

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INTRODUCTION: Insulin resistance is associated with obesity. The mechanism for why some obese patients develop insulin resistance (IR) while others retain normal IR is unknown, and may be multifactorial. Adipose tissue is recognized as an inflammatory active organ, harboring several types of regulatory lymphocytes, which may be involved in the development of IR.
AIMS & METHODS: To identify different adipose tissue regulatory lymphocytes population patterns in obese patients with and without insulin resistance. Peripheral blood samples and intra-operative visceral adipose tissue biopsies were taken from consenting patients undergoing elective abdominal surgery. Patients were divided into normal, moderate and high IR according to their homeostatic model assessment (HOMA score).
Flow cytometry (FACS) was used to identify CD4+CD25+FOXP3+ regulatory lymphocytes (Tregs) and CD4+IL17+ (TH17) cells from both the peripheral blood and visceral adipose tissue, which were then compared with anthropometric parameters.
RESULTS: Intra-operative biopsies and blood samples were collected from 28 patients. 16 patients had normal IR (HOMA score <3) and 9 patients had moderate IR (HOMA score 3-5). 3 patients had high HOMA score and were excluded from final analysis because of a small group size.
Mean age and body mass index (BMI) of the normal and moderate IR groups were 44.5 and 38.5 years (NS) and 39.5 and 41.6 kg/m^2 (NS).
In patients with normal IR, Tregs positively correlated both BMI and waist circumference [$r = 0.6$ ($p=0.01$) and 0.66 ($p<0.01$), respectively). However in patients with moderate IR, the correlation between Tregs and BMI was lost, and the correlation to waist circumference was actually reversed and became negative [$r = -0.86$ ($p<0.01$)]. No significant difference was demonstrated in waist circumference (122 and 127.6 cm in normal and moderate IR groups).
Similarly, a positive correlation between the adipose tissue Treg/TH17 ratio and the BMI and waist circumference which was demonstrated in normal IR patients [$r = 0.59$ ($p<0.05$) and 0.74 ($pp<0.01$) respectively] was lost in the moderate IR group.
CONCLUSION: In this study we identify two opposite distribution patterns for adipose tissue Tregs, differentiating obese patients according to their insulin resistance status.
Combined analysis of anthropometric parameters with adipose tissue Tregs may offer a new insight into the pathogenesis of insulin resistance in obese patients, and may mark adipose tissue Tregs as potential therapeutic targets.
Disclosure of Interest: T. Adar Financial support for research from: Synageva, Lecture fee(s) from: Shire, Consultancy for: Janssen, Other: Boston Scientific, Immune Pharma, R. Spira: None declared, S. Shteingart: None declared, A. Ben-Ya'acov: None declared, S. Shmorak: None declared, A. Jarjoui: None declared, G. Kalak: None declared, S. Abu-Khalaf: None declared, M. Yisraeli: None declared, A. Shitrit: None declared, M. Mahamid: None declared, E. Broide: None declared, E. Goldin Consultancy for: Immune Pharma, Bioline Rx Ltd

OP173 HELICOBACTER PYLORI INFECTION CAUSES INSULIN RESISTANCE THROUGH C-JUN/MIR-203/SOCS3 PATHWAY

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INTRODUCTION: Epidemiological studies indicate that patients with chronic Helicobacter pylori (*H. pylori*) infection have an increased risk of developing type 2 diabetes mellitus (1, 2), but the underlying mechanism remain largely unknown.
AIMS & METHODS: This study aims to investigate whether *H. pylori* infection contributes to the development of insulin resistance, as well as the underlying mechanism both in vivo and in vitro.
RESULTS: We found that average fasting glucose levels were increased in patients and mice with *H. pylori* infection. Diabetic mice with *H. pylori* infection showed impaired glucose and insulin tolerance and hyperinsulinemia. Furthermore, *H. pylori* infection impairs insulin signaling in primary hepatocytes. *H. pylori* infection can upregulate suppressors of cytokine signaling (SOCS)-3, a well-known insulin signaling inhibitor by down-regulating miR-203. SOCS-3 over-expression interfered with insulin signaling proteins and knockdown of SOCS-3 alleviates *H. pylori*-induced impairment of insulin signaling. We also identified c-Jun, a transcription factor which affect gene expression, could induced by *H. pylori* infection and suppress miR-203 expression.
CONCLUSION: Our results demonstrated that *H. pylori* infection could induce hepatic insulin resistance by c-Jun/miR-203/SOCS3 signaling pathway and provide possible implications toward resolving insulin resistance.
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Disclosure of Interest: None declared

OP174 A UBIQUITIN-MODIFYING ENZYME A20 CONTROLS THE DYNAMICS OF AUTOPHAGY

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INTRODUCTION: Crohn's disease is a chronic inflammatory disease, mainly affecting the gastrointestinal tract. Genome wide association studies identified autophagy related genes as conferring susceptibility to Crohn's disease. We have also reported that A20 (Tnfaip3), a ubiquitin-modifying enzyme, is a Crohn's disease susceptibility gene. A20 is critical for preventing inflammation in vivo. A20 may play important roles in human autoimmune diseases and Crohn's disease. However, the physiological role of A20 in T cells is not fully understood.
AIMS & METHODS: In this research, we analyze A20's potential function in T cells, and demonstrate how important A20 is for autophagy regulation and inflammation.

To analysis the function of A20 and autophagy in vivo, we generated mice lacking A20 and ATG5 specifically in T cells by breeding A20FL and ATG5FL mice with CD4-Cre transgenic mice. Single-cell suspensions were prepared from thymus, spleen, and peripheral lymph nodes of mice, and were analyzed by flow cytometry and immunoblotting. To determine whether A20 regulates autophagy in T cells, A20 deficient naïve CD4 T cells were purified from spleens and lymph nodes. Cells were stimulated with anti-CD3 plus anti-CD28 in vitro. Live cells were analyzed by immunohistochemistry using LC3 antibody (LC3 is generally considered as a marker of autophagosome). Images were acquired on a confocal laser microscope.

RESULTS: A20 and ATG5 double deficient (DKO) mice were obtained in Mendelian numbers and developed normally. Enlarged spleen and lymph node were observed in DKO mice. Surprisingly, the absolute number of peripheral T cells was significantly reduced in DKO mice as compared to control mice. Moreover, both B cells and myeloid cells were expanded in DKO mice. These data indicate that T cell lineage deletion of A20 and ATG5 perturbs lymphoid homeostasis. The immunohistochemistry analysis of naïve CD4 T cells revealed that the LC3 punctae formation was reduced in A20 deficient cells after stimulation. To understand the biochemical mechanisms by which A20 may regulate autophagy, we studied CD4 T cells in vitro and found the target of A20 in autophagy signaling. Thus, A20 regulates induction of autophagy in naïve CD4 T cells.

CONCLUSION: Our studies demonstrate that A20 regulates autophagy, and provide new insights into how Crohn's disease susceptibility genes in T cells regulate inflammation.

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Disclosure of Interest: None declared

OP175 PREVENTION OF GENOTOXICITY AND PROTUMORAL EFFECT MEDIATED BY COLIBACTIN-PRODUCING BACTERIA

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INTRODUCTION: Colorectal cancers are frequently colonized by *Escherichia coli* producing the toxin called colibactin. Those bacteria induce DNA damage in host cells, exhibit protumoral activities and increase the number of tumors in colorectal cancer mouse model.

AIMS & METHODS: Our objectives were to identify drug-like molecules that prevent the toxic effects mediated by colibactin-producing bacteria. Using a structural approach, we selected putative ligand of the ClbP enzyme, which is involved in the synthesis of colibactin. The activity of compounds was evaluated *in vitro* and *in vivo* using intestinal epithelial cells and a colorectal cancer mouse model.

RESULTS: Crystallography revealed that two drug-like molecules were able to bind the active site of ClbP. These compounds suppressed both *in vitro* and *in vivo* the genotoxic activity of colibactin-producing *E. coli*. In addition, they prevented cellular proliferation, as well as tumourigenesis mediated by those bacteria in mouse.

CONCLUSION: These demonstrate that targeting colibactin production controls genotoxicity and protumoral effects mediated by this toxin.

Disclosure of Interest: None declared

OP176 DEOXYCHOLIC ACID INDUCES MIR-21/PDCD4-DEPENDENT CYTOTOXICITY BY HAMPERING NF-KB SURVIVAL SIGNALLING IN PRIMARY RAT HEPATOCYTES

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INTRODUCTION: Toxic bile acids have been implicated in the development of several liver diseases, including non-alcoholic fatty liver disease (NAFLD). In particular, deoxycholic acid (DCA) is increased in the liver of NAFLD patients, correlating with disease progression.We have recently shown that microRNA-21 (miR-21) is decreased in response to DCA in primary rat hepatocytes.

AIMS & METHODS: Our aim was to describe the mechanisms by which DCA modulates miR-21-dependent pathways and whether these contribute to DCA-induced cytotoxicity. Primary rat hepatocytes were treated with 25-200 μM DCA for 24 h. Cell death, viability and caspase-3 activity were measured by the ApoTox-Glo™ Triplex Assay and the presence of apoptotic nuclei confirmed by Hoechst staining. miR-21 expression was measured by qRT-PCR. Programmed cell death 4 (PDCD4), a miR-21 pro-apoptotic target, was evaluated by both immunoblotting and after transfecting cells with a specific luciferase plasmid, containing the miR-21 3-UTR-binding fragment of the PDCD4 mRNA. NF-κB, IκB and active caspase-2 levels were also measured by immunoblotting. NF-κB activation was evaluated using a specific luciferase assay and by analysing NF-κB subcellular localization. In functional studies, miR-21, PDCD4, caspase-2 and NF-κB were modulated using both genetic and pharmacologic modulators. Finally, reactive oxygen species (ROS) levels were determined by using the fluorescent probe 2',7'-dichlorodihydrofluorescein diacetate.

RESULTS: Our results show that the miR-21/PDCD4 pathway is modulated by DCA in a dose-dependent manner, with a concomitant decrease in cell viability and an increase in cell death, apoptotic nuclei, caspase-2/-3 activation and ROS production. Importantly, miR-21 overexpression and either PDCD4 or caspase-2 silencing counteracted DCA-induced apoptosis. Furthermore, NF-κB activity was decreased in a similar pattern to miR-21 expression after incubation of hepatocytes with DCA. In fact, NF-κB inhibition, using a selective chemical inhibitor (BAY 11-7085), potentiated the effects of DCA impacting on the miR-21/PDCD4 pathway, further decreasing miR-21, while increasing PDCD4 expression levels and apoptosis. In agreement, NF-κB overexpression had opposite effects.

CONCLUSION: In conclusion, the miR-21/PDCD4/apoptosis axis is modulated by DCA in a dose-dependent manner. Mechanistically, DCA targets miR-21 *via* inhibition of NF-κB activity, likely as a downstream result of caspase-2 engagement in response to DCA-induced ROS production. A better understanding of the network of signalling mechanisms activated by toxic bile acid species may allow the development of new therapeutic tools to treat bile acid-associated liver pathologies. (Supported by PTDC/SAU-ORG/111930/2009, PTDC/BIM-MEC/0873/2012, SFRH/BD/88212/2012 and SFRH/BD/91119/2012 from FCT, Portugal)

Disclosure of Interest: None declared

OP177 ROLE OF NECROPTOSIS IN MURINE MODELS OF BILE ACID TOXICITY

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INTRODUCTION: Cholestasis is a common pathological condition caused by disruption of bile flow, resulting in retention of bile acids in serum and in liver, with a concomitant toxic response in hepatocytes. Accumulating evidence suggests that regulated necrosis or necroptosis may be involved in hepatocyte injury during cholestasis, through unclear signalling pathways.

AIMS & METHODS: Thus, we aimed to evaluate the role of necroptosis in hepatocytes exposed to toxic bile acids and in animal models of bile acid toxicity. Bile duct ligation (BDL) was performed in male C57BL/6 mice to induce cholestasis and secondary fibrosis. Serum and livers were collected 3, 7 and 14 days after BDL. To further explore the role of toxic bile acids in necroptosis activation, deoxycholic acid (DCA; 250 mg/Kg/day, oral gavage, 5 days) was administered to male Wistar rats. Necroptotic markers were evaluated in liver tissue and serum. HepG2 cells and primary rat hepatocytes were incubated with glycochenodeoxycholic acid (GCDCA; 200 μM) or DCA (400 μM), in the presence or absence of pan-caspase inhibitor, zVAD-fmk (50 μM), and/or necroptosis inhibitor, necrostatin-1 (100 μM), or ursodeoxycholic acid (UDCA; 100 μM).

RESULTS: Our results showed that BDL-operated mice displayed a strong increase of serum transaminases, alkaline phosphatase and bilirubin. Histological analysis revealed that BDL resulted in bile duct hyperplasia, multifocal necrosis and fibrosis. Moreover, BDL increased liver proinflammatory cytokines. Similarly, DCA induced hepatocellular necrosis and inflammatory cell infiltration in rat liver, with a concomitant increase of liver proinflammatory cytokines and serum transaminases. Serum markers of necroptosis, namely high mobility group box 1 (HMGB1) and cyclophilin A, were increased in both animal models. Further biochemical pathway analysis in the liver of BDL and DCA animals, namely receptor interacting protein 3 (RIP3) expression, confirmed the role of necroptosis in pathogenesis. Finally, DCA and GCDCA were strong inducers of apoptosis in both HepG2 cells and rat hepatocytes. In HepG2 cells, bile acid-induced cell death was completely abolished by zVAD-fmk. On the contrary, DCA and GCDCA induced caspase-3-independent cell death, inhibited by necrostatin-1, representing necroptosis of primary rat hepatocytes. UDCA was also effective at modulating necroptosis.

CONCLUSION: In conclusion, necroptosis is involved in liver injury induced by toxic bile acids both *in vitro* and *in vivo*. As such, necroptosis may play a role in the pathogenesis of cholestatic liver disease and should be regarded as a potential therapeutic target. (Supported by FCT, Portugal; PTDC/SAU-ORG/119842/2010, HMSP-ICT/0018/2011, SFRH/BD/91119/2012 and SFRH/BD/88212/2012).

Disclosure of Interest: None declared

OP178 STUDY THE ROLE OF MIR-223 IN COLITIS ASSOCIATED CARCINOGENESIS

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INTRODUCTION: MicroRNAs are short non-coding single-stranded RNAs that modulate gene expression by destabilizing mRNA and/or inhibiting translation. They are also implicated in many pathophysiological processes, including inflammation and cancer. Patients diagnosed with inflammatory bowel disease (IBD) have an increased risk of developing a colorectal cancer. Inflammatory conditions are increasingly being acknowledged to contribute to tumor formation; however, there is a limited understanding of the mechanisms that are involved in the transition from intestinal inflammation to cancer. Myeloid derived suppressor cells (MDSC) represent immature heterogenous cells that are recruited from bone marrow under inflammatory conditions and in cancer. These cells have immunosuppressive properties contributing to the inhibition of anti-tumor immunity. However, the molecular mechanisms responsible for MDSC expansion remain elusive. Recent studies revealed that miRNA could be involved in the expansion of MDSC.
miR-223 is the main miRNA linked to myeloid development, and its role in myeloid cell proliferation and differentiation has been extensively studied both in vitro and in vivo. In a recent work in our laboratory, we identified miR-223 as one of the main miRNA showing strong upregulation in mouse colons during tumor formation. Cell sorting enabled us to confirm high expression of miR-223 in infiltrating myeloid cells (CD45+ CD11b+ Gr-1+) as compared to colonocytes, but also in the blood and spleen as compared to other immune cells (CD45+ CD11b – Gr-1 –).
AIMS & METHODS: We used the well-established Azoxymethane (AOM)/Dextran Sulfate Sodium (DSS) mouse model of colitis-associated cancer in order to characterize miR-223 expression in the different myeloid cell subpopulations, during tumor development and to determine whether inhibition of miR-223 activity or its overexpression by means of a lentiviral vector strategy can affect the recruitment of myeloid cells and carcinogenesis.
RESULTS: Flow cytometry and cell sorting revealed 4 myeloid subpopulations in spleen and blood of AOM/DSS-treated mice. Using real-time QPCR, we found that one monocytic subpopulation and the granulocytic cells are the main sources of miR-223 in mouse spleen and blood during periods preceding tumor development. We generated lentiviral vectors to specifically overexpress miR-223 or inhibit its activity by expressing miR-223 Target sequences (miR-223T). We verified that intravenous injection of the miR-223 expressing lentivirus in mice resulted in an increase of circulating miR-223 that persisted for at least 3 weeks. We are currently assessing whether this lentivirus based strategy affects MDSC recruitment and subsequent tumor development.
CONCLUSION: miR-223 may contribute to myeloid cell recruitment, differentiation and function during colon tumor development. Our lentiviral vectors represent valuable tools to investigate its role in mouse models of colorectal cancer.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 11:00–12:30
TOWARDS BETTER UNDERSTANDING OF IBD PATHOGENESIS – HALL N

OP179 SYNDECAN-4 IS A KEY REGULATOR OF INTESTINAL EPITHELIAL REGENERATION AND INFLAMMATION

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INTRODUCTION: Syndecan(Sdc)4 is a transmembrane protein with receptor function and was found to modulate wound healing and inflammation, e.g. in the skin. However, the role of Sdc4 in intestinal epithelial wound healing/regeneration and inflammation has not been investigated yet. The aim of this study was to evaluate the impact of Sdc4 deficiency on intestinal epithelial wound healing *in vitro* and *in vivo* as well as to evaluate its potential impact on experimental colitis.
AIMS & METHODS: *In vitro*, impact of Sdc4 on intestinal epithelial wound healing was evaluated by scratch assays in WT human T84 and murine colon-26 cells as well as after blockade of Sdc4 by siRNA or anti-Sdc4 antibody administration (n=6). *In vivo*, epithelial wounds were mechanically generated using a biopsy forceps during colonoscopy of $Sdc4^{-/-}$ and WT mice (n=5/group). Monitoring of wound closure was performed by daily endoscopic examination. To evaluate the susceptibility of $Sdc4^{-/-}$ mice to intestinal inflammation, experimental colitis was induced by DSS (n=6/group). The course of colitis was assessed by weight loss, colon length, histological damage as well as immunohistochemical staining for F4/80, Gr1 and CD20. Finally, intestinal barrier function as reflected by mucosal permeability was determined by mucosal uptake of Evans Blue and immunohistochemical analysis of tight junction proteins composition including Cl-1, Cl-3, Cl-5 and ZO-1.
RESULTS: *In vitro*, administration of anti-Sdc4 antibody or siRNA targeting Sdc4 resulted in significantly delayed wound closure compared to WT cells (wound closure at day 7: 61%±4,3 vs. 88%±3.7; $P<0.05$). Similarly, *in vivo*, colonic epithelial wound healing in $Sdc4^{-/-}$ mice was significantly impaired (wound closure at day 6: 62%±2.3 vs. 98.1%±3.1, $P<0.05$).
After induction of DSS-colitis, $sdc4^{-/-}$ mice lost significantly more body weight compared to WT animals (day 8: 24.8%±1.9 vs. 9.2%±3.1; $P=0.008$). Furthermore, colonic inflammatory damage in $Sdc4^{-/-}$ mice was dramatically increased as reflected by increased colonic shortening (63.3 mm±2.4 vs. 74.8 mm±2.3; $P=0.01$), increased histological damage (Dieleman Score: 16AU±3.7 vs. 3.4AU±0.2; $P=0.016$) as well as enhanced mucosal infiltrate of macrophages and neutrophils. Additionally, aggravated damage of intestinal barrier function in $Sdc4^{-/-}$ animals was indicated by significantly reduced Cl-1, Cl-3 and ZO-1 expression and increased Evans blue uptake compared to WT mice (extinction: 4.3±0.03 vs. 2.7±0.07; $P<0.01$). Notably, Evans Blue uptake and tight junction protein expression was not altered in healthy $Sdc4^{-/-}$ compared to WT mice.
CONCLUSION: Loss of Syndecan-4 significantly impaired intestinal epithelial wound healing *in vivo* and *in vitro* and resulted in a markedly aggravated course of experimental colitis. Future studies are needed to elucidate the potential therapeutic effects of Syndecan-4 in inflammatory bowel disease.
Disclosure of Interest: None declared

OP180 RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (RAGE): A NEW FRONTIER IN INTESTINAL FIBROSIS

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INTRODUCTION: Intestinal fibrosis is a common and severe complication of inflammatory bowel disease (IBD) characterized by excessive deposition of extracellular matrix components (ECM) and for which efficient and well-tolerated therapies are currently lacking. Inflamed colonic mucosa of patients with active IBD show a significant increase in expression of the receptor for advanced glycation end products (RAGE), a member of the immunoglobulin superfamily of cell surface receptors, able to regulate chronic inflammation by activating the NF-kB pathway and inducing inflammatory and oxidative stress. In addition, a growing body of evidences in kidney, liver and lung fibrosis shows how the increased myofibroblast activation and numbers and the consequent ECM accumulation are regulated by RAGE. All these data may place this receptor among the most innovative and promising targets for new antifibrotic therapies in IBD
AIMS & METHODS: We propose to investigate the involvement of RAGE in the development of the DSS-induced intestinal fibrosis in mice. Chronic colitis and fibrosis were induced in C57BL/6 wild type (WT) and RAGE null mice by administration of 2.5% (w/v) dextran sulfate sodium (DSS) in drinking water for 5 days followed by 7 days of water, for three cycles. Three days after the last cycle of treatment, the entire colon was rapidly excised and scored for the assessment of macroscopic lesion, including dilation, thickness and adhesion, on a 0-3 scale by an investigator naïve to the experimental conditions. The sum of the scores of colonic lesions was expressed as total macroscopic score. Tissue specimens, collected from distal colon, were subject to Hematoxylin/Eosin staining, to assess the degree of inflammation, and Picrosirius red staining was performed to assess collagen deposition. Thus, a total microscopic score was calculated evaluating presence of ulceration, inflammatory degree, depth of lesions and fibrotic degree. mRNA expression of the main profibrotic mediator, *Tgf-β1*, and the expression of ECM components, mainly collagen types I-III (*Col1A1* gene) and fibronectin (*Fn-1* gene), were evaluated by quantitative RT-PCR
RESULTS: Compared to WT mice, DSS-treated C57/Bl6 RAGE null mice showed a significant 29% decrease of the colon weight/length ratio ($p<0.0001$), an indicator of wall thickening. A total macroscopic score of 6 ± 0.92 was assessed in colons recovered from DSS-treated WT mice, but in mice devoid of RAGE, the appearance of the macroscopic lesions was significantly reduced, 1.43 ± 0.54 ($p<0.0001$, n=15). DSS-treated RAGE null mice showed also a significant 49% decrease of total microscopic score compared to WT mice. mRNA *Tgf-β1* expression was significantly increased 3.4 fold by the DSS administration in WT mice colon, whereas it was unchanged in RAGE null mice compared to mice receiving only tap water. *Col1A1* and *Fn-1* genes were upregulated in DSS-treated WT mice (5.52 folds, p= 0.137 and 53 folds, p= 0.0016, respectively). Lack of RAGE decreased 3.17 folds (p= 0.0341) *Col1A1* expression and totally prevents the *Fn-1* upregulation induced by DSS treatment
CONCLUSION: The potential profibrotic role of RAGE in IBD could both shed light into the complex and dynamic fibrogenic processes in IBD and pave the way for new anti-fibrotic agents and approaches in this disease.
Disclosure of Interest: None declared

OP181 ENHANCED NOD2-DRIVEN IMMUNITY TO ENTERIC BACTERIAL INFECTION IN NLRP12-DEFICIENT MICE

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INTRODUCTION: The Nucleotide-binding oligomerization domain protein 12 (Nlrp12) is thought to negatively regulate inflammatory response to intracellular bacteria, but its role on the growth and colonization by extracellular bacteria remains largely undefined. In this study, we aim to investigate the role of Nlrp12 in bacterial-driven colitis using *Citrobacter rodentium* as an infection model for attaching and effacing infections.
AIMS & METHODS: Age and sex-matched wild-type, Nlrp12 -/-, Nod2 -/-, and Nlrp12-/-Nod2-/- mice were orally inoculated with ~1 × 109 CFU of either *C. rodentium* strain DBS100 or kanamycin (Kn)-resistant *C. rodentium* strain DBS120 for non-invasive monitoring of bacterial growth in vivo. Lamina propria

mononuclear cell influx to the site of the infection was examined by FACS analysis before and one week after infection. Gene expression profiling was determined in the caecum of non-infected and infected wild-type and Nlrp12-/- mice. Vali dation of gene expression changes was performed by qRT-PCR analysis on RNAs isolated from either the caecum, the colon, the intestinal epithelial cells and the lamina propria mononuclear cells.
RESULTS: An enhanced inflammatory response was found to correlate with improved clearance of *C. rodentium* in the early phase of the infection of Nlrp12-deficient mice. Mechanistically, the colonic mucosa of Nlrp12-deficient mice showed spontaneous signs of colitis which was improved in the absence of the major Crohn's disease predisposing Nod2 gene. The protective immune response in Nlrp12-deficient mice was primarily restricted to the intestinal epithelium and corroborated with enhanced recruitment of monocyte-derived dendritic cells.
CONCLUSION: Overall, our results suggest that Nlrp12 repress Nod2-mediated host defense against enteric bacterial infection, which may have contributed to a selective advantage of Nlrp12 variants. Exploitation of the Nlrp12-coupled inflammasome represents a novel gene-for-gene model of pathogen evolution alongside host immunity.
Disclosure of Interest: None declared

OP182 STAT6 DEFICIENCY IMPAIRS M2 MACROPHAGE POLARIZATION AND DELAYS WOUND HEALING IN A MURINE MODEL OF COLITIS

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INTRODUCTION: Inflammatory Bowel Disease (IBD) is a chronic disorder of the intestinal tract caused by a deregulated mucosal immune response and epithelial barrier disruption. These changes are mainly produced by an alteration of the cytokine production. STAT6 has diverse biological functions within immune system and is a critical mediator of cytokine signalling. It has been shown that STAT6 promotes *in vitro* polarization towards M2 macrophages. We aim to evaluate the role of STAT6 in M2 polarization *in vivo* and to determine its relevance on wound healing in a murine model of colitis.
AIMS & METHODS: Peritoneal macrophages were isolated from wild type (WT) and STAT6-/- balb/c mice by an injection of 10ml DMEM in the peritoneal cavity, RNA was extracted and gene expression of M1 markers (*iNOS, IL-6* and *Cd11c*) and M2 markers (*Arg1*, *Ym1*, and *Fizz1*) was analyzed by qPCR. Colitis was induced in WT and STAT6-/- balb/c mice by an intrarectal injection of 17.5 mg TNBS/100g mice dissolved in EtOH 40% (day 0). Mice were weighted diary (results are expressed as percentage vs the weigth at day 0) and were sacrificed on day 2, 4 and 6 after TNBS administration. The colon length was measured and the histology was evaluated according to Wallace Score (1-10). Vehicle mice received an intrarectal injection of 40% ethanol.
RESULTS: Analysis of the expression of M1- and M2-markers in peritoneal macrophages reveal that macrophages isolated from knock-out mice exhibited higher expression levels (fold induction) of *iNOS* (4.1±1.1), *IL-6* (5.8±1.0) and *Cd11c* (5.7±0.6) than macrophages from WT mice. In contrast, in macrophages from knock-out mice the expression of *Arg1* (0.42±0.12), *Ym1* (0.32±0.04) and *Fizz-1* (0.54±0.19) was reduced compared with WT mice. In STAT6 knockout mice either the body weight or the histological score were similar to that observed in WT mice, and these parameters were not significantly altered at any time analyzed. TNBS administration induced, 2 days later, a peak reduction in body weight in both WT mice (91.3±1.9%) and STAT6 knockout (87.7±1.8%). Three days after TNBS administration, the body weight started to recover in WT mice (97.6±1.6%) and it was completely recovered at day 4 (99.1±1.0%) and day 6 (101.7±1.8%). In contrast, in knockout mice the body weight recover was slower (87.2±2.7% at day 3, 90.8±2.2% at day 4 and 96.2±1.7% at day 6) and differ significantly ($P<0.05$) than that observed in WT mice. In a similar manner, TNBS administration induced intestinal damage that peaked 2 days later and was similar between WT mice (6.5±0.6) and knockout mice (6.4±0.5). However, significant differences in damage were observed at day 4 and day 6 between WT mice (4.6±0.5 and 3.1±0.4, respectively) and knockout animals (6.9±0.5 and 4.4±0.7, respectively). Finally, TNBS induced a significant reduction at day 2 in the colon length in both WT and knockout mice, compared with the respective vehicle. However, at day 4 only knockout animals still maintained a reduced colon length.
CONCLUSION: STAT6 deficiency delays wound healing in a murine model of colitis which may be related to an impaired M2 macrophage polarization.
Disclosure of Interest: None declared

OP183 GPR84, A NOVEL TARGET FOR THE DEVELOPMENT OF THERAPIES FOR IBD

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INTRODUCTION: Among the GPCRs demonstrated to be activated by FFAs, GPR84 is less characterized and suggested not to play a role in energy homeostasis. It is liganded by medium chain fatty acids, has a restricted expression profile (mainly immune cells as macrophages and polymorphonuclear leukocytes (PMN)) and is upregulated under inflammatory conditions. In addition, a GPR84 agonist is described to mediate PMN and macrophage activation and migration. In view of these data, we set out at developing GPR84 inhibitors to confirm the pro-inflammatory role of GPR84 *in vitro* and *in vivo*. Several series of GPR84 inhibitors were developed and shown to inhibit immune cell migration. As the infiltration of immune cells to the inflamed intestinal tissue is a hallmark of inflammatory bowel diseases (IBD), we further tested the capacity of these compounds at reducing disease severity in an IBD model.
AIMS & METHODS: Activity of GPR84 antagonists was measured in a GTPgS assay using membranes of HEK293 cells expressing GPR84 and the di-indolyl methane agonist of GPR84. The capacity of GPR84 antagonists to inhibit the GPR84 agonist (Embelin)-induced neutrophil chemotaxis was assessed in primary cells using the Transwell system. This assay was also used to test the activity on ortholog receptors using primary neutrophil from different species. *In vivo* efficacy was evaluated in the well-validated mouse chronic dextran sodium sulphate (DSS)-induced colitis model for IBD using disease activity index score, histology lesion score and neutrophil infiltration score as readouts.
RESULTS: Several series of GPR84 inhibitors were developed with potencies at the target in GTPgS assay down to low nM levels and clear SAR. The series displayed strong developability properties and PK, with GLPG1205 as lead compound. GPR84 inhibitors were shown to inhibit GPR84 agonist-driven neutrophil and macrophage migration *in vitro*, with an IC_{50} matching their potency at GPR84. GPR84 antagonism also modulated rat macrophage biology, as GPR84 antagonists specifically inhibit Embelin-induced macrophage migration. The impact of GPR84 inhibitors on the migration of neutrophils from different species was assessed to confirm activity at orthologs and support the proposed development path towards the clinic. GPR84 gene expression level was found increased in DSS colon versus intact colon. In the DSS model, GLPG1205 dose-dependently hampered the development of the disease, by reducing the disease activity index, to a similar level as sulphasalazine and cyclosporine. The histological score for colon lesion, neutrophil influx as well as MPO content was substantially reduced by GLPG1205 oral administration, providing hints forthe mode of action of GPR84 inhibition in IBD.
CONCLUSION: GLPG1205 is characterized as a potent and selective antagonist of GPR84 with strong developability properties. It demonstrates good *in vitro* activity in primary neutrophil assays, as well as pronounced *in vivo* activity in the mouse chronic DSS model. These studies support GPR84 antagonism as novel mode-of-action for the treatment of IBD and the progression of GLPG1205 towards the clinic.
Disclosure of Interest: S. Dupont Other: employee, F. Labéguère Other: employee, R. Blanqué Other: employee, S. de Vos Other: employee, P. Clément-Lacroix Other: employee, L. Nelles Other: employee, A. Hagers Other: employee, C. Cottereaux Other: employee, D. Merciris Other: employee, M.-C. Ceccotti Other: employee, C. Belleville Da Costa Other: employee, S. Fletcher Other: employee, R. Brys Other: employee

OP184 SILENCING OF PROLYL HYDROXYLASE 1 IN INTESTINAL MICROVASCULAR ENDOTHELIAL CELLS PREVENTS INFLAMMATION-INDUCED ENDOTHELIAL DYSFUNCTION AND DAMPENS MURINE COLITIS

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INTRODUCTION: Active inflammatory bowel disease (IBD) is characterized by extensive mucosal angiogenesis. However, these newly formed blood vessels are likely dysfunctional, as they are unable to resolve the inflammation-induced mucosal hypoxia. Prolyl hydroxylases (PHD1-3) are oxygen sensing enzymes that are actively involved in tumoral vascular dysfunction. We previously showed that the expression of PHD1, but not PHD2 and 3, is increased in inflamed biopsies of IBD patients.
AIMS & METHODS: The aim was to characterize endothelial dysfunction in IBD patients and to investigate the role of PHD1, 2 and 3 in the vascular endothelium during experimental colitis. The expression of endothelial dysfunction markers was analyzed by qRT-PCR in inflamed and non-inflamed colonic biopsies from IBD patients and compared to samples from healthy controls and infectious colitis patients. Human colonic microvascular endothelial cells (freshly isolated from resection specimens) and mouse endothelial cells were subjected to TNF to mimic inflammatory angiogenesis. The expression of endothelial dysfunction markers and PHD isoforms was analyzed. We then generated endothelial specific PHD1, PHD2 and PHD3 knock-out mice and subjected these mice to dextran sulfate sodium (DSS)-induced colitis, after which they were assessed for histological inflammation. Colonic vascular leakage was quantified using dynamic contrast-enhanced T1-weighted micro-MRI.
RESULTS: Inflamed colonic biopsies from both UC and CD patients showed a significant up-regulation of the endothelial dysfunction markers ICAM-1, VCAM-1, vWF and VEGFR-2 (all $p<0.0001$). Moreover, these markers all displayed a strong positive correlation with PHD1 (r=0.667, r=0.792, r=0.731 and r=0.747 respectively) and TNF (r=0.908, r=0.881, r=0.806 and r=0.860). Endothelial cells showed a significant up-regulation of PHD1 ($p<0.01$) in response to TNF. In accordance, $PHD1^{-/-}$ cko mice had significantly less weight loss ($p<0.0001$), reduced colon shortening ($p<0.01$) and a lower histological inflammation score ($p<0.001$) during DSS-induced colitis, when compared to the littermate controls. Furthermore, the $PHD1^{-/-}$ cko mice showed significantly less vascular leakage ($p<0.05$) and a significant down-regulation of the endothelial dysfunction markers ICAM-1, VCAM-1, vWF and VEGFR-2 (all $p<0.05$) in their colonic lysates. Pharmacological hydroxylase inhibition in mouse endothelial cells significantly reduced the expression of ICAM-1, VCAM-1 and the inflammatory marker CXCL2 (all $p<0.05$) in response to TNF.

Genetic inhibition of endothelial specific PHD2 and PHD3 had no effect on the course of DSS-colitis.
CONCLUSION: Our findings characterize a dysfunctional endothelial phenotype in IBD and show that selective silencing of PHD1 in microvascular colonic endothelial cells is sufficient to restore endothelial function and to dampen experimental colitis.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 11:00–12:30
NOVEL ENDOSCOPIC INTERVENTIONS IN THE OESOPHAGUS – HALL O

OP185 EFFICACY AND SAFETY OF HYBRID-APC FOR THE ABLATION OF BARRETT'S ESOPHAGUS: RESULTS OF THE PILOT SERIES

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INTRODUCTION: The widely used methods for the ablation of Barrett's esophagus (BE) are radiofrequency ablation and argon-plasma coagulation (APC). However, these methods lead to stricture formation in 5-15% of patients. The question arises whether submucosal fluid injection prior to thermal ablation may lower the risk of stricture formation.
AIMS & METHODS: The aim of the present study was to evaluate the efficacy and safety of the new technique of Hybrid-APC for BE ablation. Patients who had a residual Barrett's segment of at least 1 cm after endoscopic resection of early Barrett's neoplasia underwent thermal ablation of BE by Hybrid-APC. During Hybrid-APC, submucosal injection of sodium chloride 0.9% was carried out using an ErbeJet probe (Erbe Elektromedizin, Tuebingen, Germany). Check-up upper GI endoscopy was carried out 3 months after macroscopically complete ablation including biopsies from the Neo-Z-line and the former BE segment. Potential stricture formation was recorded.
RESULTS: A total of 60 patients were included into the study during a 2-yr interval. 55 patients were male (92%), 5 female (8%). The mean age was 62±9 Jahre (42-79). The LSBE:SSBE ratio was 41:19. 10/60 patients were excluded from the study. In 5 of these 10 patients, poor mucosal healing after ablation had been observed, and the patients could not be treated according to the study protocol. In 48 of the remaining 50 patients (96%), macroscopically complete Barrett's ablation was achieved after a mean of 4±2 APC sessions (range 1-10). In ITT analysis, macroscopic ablation success was 80% (48/60). The 2 other patients had ablation rates of >95%. In 48/50 patients, the biopsy protocol was complete. Freedom from BE was histopathologically observed in 39/48 patients (78%). In 6% of patients, buried glands without intraepithelial neoplasia were detected in the area of the neosquamous epithelium. There was no treatment-related stricture.
CONCLUSION: According to this pilot series, Hybrid-APC was effective and safe during BE ablation. There was no treatment-related stricture. Further studies are required to confirm the present results.
Disclosure of Interest: None declared

OP186 IS A COMPLETE REMISSION OF INTESTINAL METAPLASIA A SUITABLE ENDPOINT IN PATIENTS UNDERGOING RADIOFREQUENCY ABLATION (RFA)? LONG-TERM RESULTS OF RFA TREATMENT IN 67 CONSECUTIVE PATIENTS

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INTRODUCTION: Radiofrequency ablation (RFA) in combination with endoscopic resection (ER) is a method of choice for treatment of early esophageal neoplasia. Complete remission of intestinal metaplasia (CR-IM) and complete remission of dysplasia (CR-D) are commonly used as the endpoints of successful treatment. The relevance of CR-IM (in patients with macroscopically normal neo-Z-line) has recently been challenged.
AIMS & METHODS: The aim of this prospective, single center study was to assess the long-term efficacy of RFA. Main outcome measurements were complete remission of intestinal metaplasia (CR-IM) or dysplasia (CR-D) in patients with/without a complete macroscopic eradication of Barrett's esophagus and recurrence rate of IM and dysplasia. Conover one-way analysis was used to calculate the risk factors for recurrence of IM.
RESULTS: The study involved 67 consecutive patients (mean age 62, range 20-86; 60 males and 7 females) undergoing endoscopic treatment for esophageal neoplasia in our center during 1/2009-4/2014. Sixty-five patients were diagnosed with Barrett's esophagus related neoplasia, the remaining 2 patients had squamous neoplasia. The median follow-up was 30 months (range 4-64). In 20 patients (30%), RFA was a single treatment modality while in 47 patients (70%), RFA was combined with endoscopic resection or dissection of a visible lesion. The indications for endoscopic treatment were as follows: early adenocarcinoma (EAC): 25 (37,3%), early squamous carcinoma (ESC): 2 (3%), high-grade dysplasia (HGD): 22 (32,8%), low-grade dysplasia (LGD): 18 (26,9%).
A total of 125 RFA treatment sessions were performed (38x with HALO 360, 86x with HALO 90 and once with HALO 60).
CR-IM and CR-D were achieved in 66% (95% CI 36-70%) and 94,5% (95% CI 93-99%), respectively. In a majority of patients without CR-IM (83%), the neo-Z-line was normal without macroscopically visible islands or tongues of metaplastic mucosa.
During the follow-up, there were 10 recurrences of IM at the level of neo-Z-line (out of 35 patients with BE with the follow-up of at least 18 months after finishing the treatment; 28,6%). In 9 of these patients, the neo-Z-line was macroscopically normal. LGD (within the Z-line) recurred in 2 patients (3,8%). HGD and/or carcinoma have not recurred. The risk factors for recurrence of IM were male sex, younger age and diagnosis of cancer. We did not detect burried glands beneath the new neosquamous epithelium in any patient.
CONCLUSION: Treatment of BE with RFA results in CR-D and CR-IM in a high proportion of patients with a low recurrence rate. A majority of patients without CR-IM or with a recurrence of IM have macroscopically normal neo-Z-line. CR-IM and a recurrence of IM might not be clinically relevant endpoints in patients with macroscopically normal neo-Z-line after RFA.
Disclosure of Interest: None declared

OP187 PREVENTION OF POST-ESD ESOPHAGEAL STRICTURE USING ENDOSCOPIC TRANSPLANTATION OF TISSUE-ENGINEERED AUTOLOGOUS ORAL MUCOSAL EPITHELIAL CELL SHEETS AT THE END OF ROUND TRIP TRANSPORTATION BETWEEN TOKYO AND NAGASAKI

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INTRODUCTION: Endoscopic submucosal dissection (ESD) is a treatment of choice for superficial esophageal neoplasms. However, largely extended esophageal ESD requires multiple balloon dilations due to postoperative luminal stricture. Endoscopic transplantation of tissue-engineered autologous oral mucosal epithelial cell sheets offers a treatment of choice for management of post-ESD stricture.
AIMS & METHODS: We investigated the safety and efficacy of endoscopic transplantation of tissue-engineered autologous oral mucosal epithelial cell sheets following the transportation of 1200 km between Tokyo and Nagasaki in the clinical settings of large esophageal ESD. For this aim, we collected specimens of oral mucosal tissue and sufficient serum from 7 patients themselves with superficial esophageal squamous cell carcinoma in Nagasaki University Hospital, and the samples were transferred into Institute of Advanced Biomedical Engineering and Science, Tokyo via air. Then, epithelial cell sheets were fabricated ex vivo by culturing isolated cells for 16 days on temperature-responsive cell culture surfaces nourished using auto-sera. Again, the cell sheets were transferred into Nagasaki which is distant from Tokyo with 1200 km by airplane. After a reduction in temperature, these sheets were endoscopically transplanted directly onto the ulcer surfaces of patients who had just undergone esophageal ESD on the day. All patients were monitored by endoscopy once a week until epithelialization was complete. Untra-magnification endoscopy employing Endocyte (Olympus) was performed after 4 weeks.
RESULTS: Autologous cell sheets were successfully grown despite the transportation of 1200 km-distance in each case and were transplanted to ulcer surfaces. Complete re-epithelialization occurred within a median time of 4 weeks. Endocytoscopic observation under approximate 400-fold magnification revealed that almost normal squamous epithelial cells were grown over each transplanted area more than 4 weeks after transplantation. The nuclei of cells showed nominal abnormality in size and configuration. Notably, this transplantation substantially reduced sessions of endoscopic balloon dilation or even nullified in 4 cases. There were no adverse events in association with cell sheet transplantation.
CONCLUSION: Endoscopic transplantation of autologous oral mucosal epithelial cell sheets promotes re-epithelialization of the esophagus after ESD, preventing post-operative luminal stricture. This study paves the way for clinical application and dissemination of cell sheet engineering for the intractable stenosis diseases and provides new possibilities in the field of regenerative medicine.
Disclosure of Interest: H. Isomoto: None declared, N. Yamaguchi: None declared, H. Fukuda: None declared, K. Nakao: None declared, S. Kobayashi: None declared, K. Kanetaka: None declared, Y. Sakai: None declared, S. Eguchi: None declared, N. Kanai: None declared, T. Ohki: None declared, M. Yamato: None declared, T. Okano Financial support for research from: Teruo Okano is a founder and director of the board of CellSeed Inc., a cell sheet regenerative medicine company in Japan, licensing technologies and patents from Tokyo Women's Medical University related to this presentation. The presentator is also a stake holder of the company listed at JASDAQ (Code: JQG 7776).

OP188 EFFICACY OF PROPHYLACTIC STEROID ADMINISTRATION FOR STRICTURES AFTER ENDOSCOPIC RESECTION FOR LARGE SUPERFICIAL ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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INTRODUCTION: Esophageal stricture is a major problem after endoscopic resection (ER) for large superficial esophageal squamous cell carcinomas (SESCC). Steroid administration is reported as a prophylactic treatment for strictures, however, it is uncertain regarding steroid administration technique and esophageal circumference of mucosal defect after ER. We evaluated the

efficacy of prophylactic administration of steroids in patients with large SESCC receiving endoscopic resection.
AIMS & METHODS: Between 2009 and 2013, 951 consecutive SESCC patients underwent ER in our institution. Eligibility criteria showed as follows: 1) a mucosal defect after ER for a solitary lesion was 3/4ths or more circumference of the esophageal lumen, and 2) follow-up periods of 3 months or longer. In December 2009, steroid (triamcinolone acetonide 50 mg) injections into ulcer bed after ER were introduced for the patients with 3/4ths and larger mucosal defects. Furthermore, from November 2012, we commenced oral steroid administration (30 mg daily, tapered gradually for 8 weeks) in addition to the local injections in case of the mucosal defect of 7/8ths and larger the circumference after resection. The mucosal defect circumference in all cases was retrospectively estimated by independent endoscopists in endoscopic pictures taken immediately after ER. We defined as an esophageal stricture in case the endoscope could not pass through the stricture, and then endoscopic balloon dilation (EBD) was required. All patients were classified into 3 groups according to the width of the mucosal defect (group A: 3/4<=, <7/8; group B: 7/8<=, subentire circumference; group C: completely entire circumference), and the frequency of esophageal strictures and the efficacy of individual prophylactic therapies were compared among 3 groups. This study was approved by an institutional review board in our institution.
RESULTS: Of 951 patients, 121 patients (104 men, 17 women; median age 69 years, range 46–85) were eligible. Endoscopic submucosal dissection and endoscopic mucosal resection were performed in 112 and 9 patients, respectively. There were 49 patients in group A (no treatment: 37%, local injection of steroid: 55%, oral steroid: 8%); 45 in group B (13%, 64%, 22%), and 27 in group C (11%, 26%, 63%), respectively. The frequencies of stricture after ER of group A, B, and C were 22%, 53% (vs group A, $p = 0.0027$), and 85% (vs group B, $p = 0.0098$), respectively. A significant efficacy of the prophylactic steroid administration was not found in group A. However, oral steroids were effective in group B, since there was a significantly lower stricture rate (no treatment: 100%, local: 59%, oral: 10% (vs local; $p = 0.011$)). Conversely, a higher stricture rate was found in group C regardless of prophylactic treatment (no treatment: 100%, local: 100%, oral: 77%).
CONCLUSION: The stricture rate after ER for SESCC increased in the larger mucosal defect circumference. Oral steroid administration was most effective to prevent strictures when the mucosal defect was from 7/8ths to subentire circumference. However, the efficacy of steroid treatments was limited in cases of completely entire circumference and stricture formation remains a major problem to be resolved.
Disclosure of Interest: None declared

OP189 MANAGEMENT OF ACUTE VARICEAL BLEEDING USING HEMOSTATIC POWDER

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INTRODUCTION: The treatment of acute variceal bleeding (AVB) includes restrictive transfusion, vaso-active drugs, antibiotics and endoscopic therapy. Early endoscopic treatment is recommended, however it is not always possible in daily practice mainly due to the lack of treatment capabilities available in every center in an emergency setting. A hemostatic powder (Hemospray ®) has recently been introduced for management of non variceal upper GI bleeding and was shown effective in preliminary studies for managing peptic ulcer bleeding, cancer related bleeding or temporizing uncontrollable bleeding in severe situations.
AIMS & METHODS: A bi-centric prospective trial to evaluate the effectiveness of hemospray application for emergency control of AVB. (Clinical-Trials.gov under number NCT01783899). In addition to routine medical treatment, emergency endoscopy was performed confirming acute variceal bleeding, identification of a bleeding site was assessed; esophageal, gastric or duodenal varices, then hemostatic powder was administered diffusely covering the mucosa over the bleeding varices in order to obtain immediate endoscopic hemostasis. Clinical surveillance was performed to every patient with second endoscopy and definitive therapy the next day.
RESULTS: Thirty eight patients with suspected acute variceal bleeding were included. 8 were excluded because bleeding was not variceal. Endoscopy was performed under sedation without endotracheal intubation, bleeding site was from esophageal varices in 83.4%, from gastric varices in 10% and from duodenal varices in 6.6 % and the bleeding was active at the time of endoscopy in 43.4 %. Primary endoscopic hemostasis was observed in all patients after Hemospray application. Clinical hemostasis was achieved in 29/30 (96.7%) patients. One patient experienced hematemesis 6 hours after Hemospray application and was treated by emergency band ligation. No mortality was reported for all those patients over 30 days follow-up.
CONCLUSION: Hemospray application appears to be safe and easy technique to control, at least temporally, AVB in this series. Further studies, preferably randomized controlled trials are required to determine its role and effectiveness in acute variceal bleeding and its potential impact on patients outcome.
Disclosure of Interest: None declared

OP190 EVOLVING ENDOSCOPIC MANAGEMENT OPTIONS FOR SYMPTOMATIC STENOSIS POST-LAPAROSCOPIC SLEEVE GASTRECTOMY FOR MORBID OBESITY: EXPERIENCE AT A LARGE BARIATRIC SURGERY UNIT IN NEW ZEALAND

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INTRODUCTION: Symptomatic stenosis is an increasingly recognized complication following laparoscopic sleeve gastrectomy (LSG) to treat obesity with a reported prevalence between 0.1 to 3.9%. Common findings are stricture and twisting at the incisura of the stomach remnant resulting in functional obstruction.This study aimed to determine the prevalence and management options for symptomatic stenosis (SS) after LSG.
AIMS & METHODS: All cases referred for management of symptomatic stenosis after LSG were recorded between May 2008 and June 2013. Patients were followed up until resolution of the symptoms and up to 1 year following resolution. A total of 857 morbidly obese patients underwent LSG at Counties Health in the study timeframe. Methods of management included Balloon dilatation with CRE Balloons 12-20 mm size, Rigiflex Achalasia Balloon dilators 30-35 mm size and use of removable fully covered self expanding metal stents. The area of deformity at and near the stricture was noted as short (<3cm) and long (>3 cm). Peustow metal guidewire was used to facilitate the passage of the rigiflex balloons to the area of the sleeve requiring dilatation.
RESULTS: Symptomatic stenosis developed in 26 (3.03%) of these patients. Eleven (42%) were males and 15 (58%) females with a mean age of 45.3 ± 9 years and a mean body mass index of 46.5 ± 8.1 kg/m^2. Four (15.4%) patients had SS following stent placement for sleeve leaks. The remaining 22 (84.6%) patients showed fixed stenosis at the incisura angularis on barium swallow. Endoscopic treatment was initiated with standard CRE balloon dilators ranging between 12-20 mm in diameter in the majority of patients (n=19, 73%). The mean number of dilatations was 1.6. Nine (34.6%) patients required only one dilatation with CRE Balloon. Out of patients who required more than one dilatation (n=11, 42.3%) only 1 (3.84%) was successfully treated with <20mm dilators. All of these had long (>3 cm) segment of stricture and deformity. Seven (78%) of the Non-responders (All long segment strictures) (n=9, 35%) were trialled with 30mm achalasia dilators and 2 (22%) with metal stents with 100% success. Achalasia balloon dilatation (30 mm) was attempted as primary treatment in 7(27%) patients with long segment strictures at the incisura successfully in 5(71%) success and 2(29%) of these required metal stents. In total 5(19.2%) patients were sucessfully treated with metal stents. No adverse events were recorded amongst any patients treated endoscopically and none needed surgical intervention.
CONCLUSION: Endoscopic techniques of dilatation are safe and effective for management of SS post LSG. The use of 30 mm achalasia balloon dilators was also found to be safe and effective in patients who failed standard dilators. Encouraged by our results, we now inititate dilatation therapy with 30mm achalasia balloon for those with SS post LSG
Disclosure of Interest: R. Ogra Other: Member Australia New Zealand Medical Advisory board for Boston Scientific corporation, P. geogry: None declared

TUESDAY, OCTOBER 21, 2014 11:00–12:30
UPPER GI MOTILITY DISEASES: MECHANISMS, DIAGNOSTICS AND NEW TREATMENT OPTIONS – LOUNGE 5

OP191 HIGH RESOLUTION MANOMETRY IMPROVES THE DIAGNOSIS OF ESOPHAGEAL MOTILITY DISORDERS IN PATIENTS WITH DYSPHAGIA: RESULTS OF A RANDOMIZED MULTICENTER TRIAL

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Motility Disorders	None	Achalasia	EGJ obstruction	Hypertensive disorders	Hypotensive disorders	UES disorders	Non classified
Immediate diagnosis (N = 245)							
CM, n (%)	64 (52)	15 (12)	6 (5)	9 (7)	9 (7)	0 (0)	19 (16)
HRM, n (%)	35 (28)*	32 (26)*	9 (7)	6 (5)	33 (27)*	4 (3)	4 (3)*
6 months (N = 218)							
CM, n (%)	57 (52)	18 (17)	8 (7)	9 (8)	7 (6)	2 (2)	8 (7)
HRM, n (%)	31 (28)*	29 (27)	9 (8)	6 (6)	28 (26)*	3 (3)	3 (3)

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INTRODUCTION: High resolution manometry (HRM) may facilitate the diagnosis of esophageal motility disorders compared to conventional manometry (CM).
AIMS & METHODS: Our aim was to compare HRM to CM in patients with dysphagia in a randomized multicenter trial. Patients with dysphagia and normal upper endoscopy were randomized to be investigated with either HRM or CM in 6 centers. Dysphagia severity was assessed using the Sydney swallow score. Duration of both procedure and interpretation were recorded. Esophageal motility disorders were diagnosed using the Castell and Spechler classification for CM and the Chicago classification for HRM. Patients were followed up 6 months after manometry. Results of immediate diagnosis and after 6-months follow up were compared between the 2 groups (CM and HRM), using Student t-test or Mann-Whitney test for quantitative parameters and using chi-square or Fisher exact test for qualitative parameters.
RESULTS: 245 patients (99 males, mean age 58 years, range 19-94) were analyzed: 122 were randomized in the CM group and 123 in the HRM group. Patients in the CM group were significantly older than in the HRM group (61 vs 56 years, p=0.02); gender and dysphagia severity were not significantly different. Procedure duration and data analysis were significantly shorter with HRM compared to CM (12±6 minutes vs 19±11 and 6±4 minutes vs 9±9 respectively, $p<0.01$). Immediately after manometry, a motility disorder was more frequently identified with HRM than with CM (97% vs 84%, $p< 0.01$) (Table). This difference remained significant after adjustment for age. Dysphagia tended to be more severe in patients with normal CM compared to those with normal HRM (Sydney score /1700= 490±278 vs 403±308, p=0.07). Six months follow up data were available in 109 patients in each group. The initial diagnosis was confirmed in 83% of patients in the CM group versus 90% in the HRM group (p=0.12). Nine out of 15 patients initially with non-classified disorder in CM presented finally achalasia (n=2), EGJ outflow obstruction (n=2), hypotensive disorders (n = 1), hypertensive disorders (n=2) and UES disorders (n=2) while the 2 patients initially non classified with HRM had achalasia and EGJ outflow obstruction.
CONCLUSION: This is the first randomized trial demonstrating that HRM might be superior to CM regarding diagnostic yield for achalasia and esophageal motility disorders. Six months outcome data tended to show that HRM might diagnose esophageal motility disorders sooner than CM.
Disclosure of Interest: S. Roman Lecture fee(s) from: Given Imaging, Consultancy for: Given Imaging, L. Huot: None declared, F. Zerbib: None declared, S. Bruley des Varannes: None declared, G. Gourcerol: None declared, A. Roux: None declared, B. Coffin: None declared, A. Roppert: None declared, F. Mion: None declared

OP192 MOTILITY PATTERNS IN RESPONSE TO A RAPID DRINK CHALLENGE TEST DISCRIMINATE BETWEEN DIFFERENT MOTILITY DISORDERS

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INTRODUCTION: We have previously shown that a rapid drink challenge test during high resolution manometry can detect motor disturbances not detected by standard manometry. However, the specific motility patterns in response to this test are not characterized.
AIMS & METHODS: To characterize specific motor patterns in response to a rapid drink challenge test in patients with esophageal motility disorders.
A rapid drink challenge test (rapid drink of 200 ml water in sitting position) was performed in 29 healthy controls (17 F, 12 M, age range 18-68 yrs) and 275 patients with esophageal motility disorders (170 F, 105 M, age range 12-88 yrs): 65 weak peristalsis, 20 aperistalsis, 28 hypercontractile esophagus, 27 esophageal spasm, 33 non-treated achalasia and 100 normal manometry. During the test we evaluated the pressure responses of the esophageal body at isobaric contour 20 mmHg and pressure gradient across the EGJ.
RESULTS: Healthy controls had an almost complete lack of pressure activity during the drink test (0.2±0.8 pressurizations of 2±1 sec duration) resulting in a 1±4% of swallowing time with pressure > 20 mmHg and a pressure gradient across EGJ of -2.2±3.2 mmHg. Pressure responses in patients showed 3 distinct patterns: Patients with weak peristalsis and aperistalsis alike showed similar responses as healthy controls: 0.6±1.0 pressurizations of 0.7±0.6 sec duration resulting in 1±3 % of time with pressure > 20 mmHg, and a pressure gradient across UEG -0.6±3.0 mmHg (pooled data, NS vs health for all; *hypopressive or normal pattern*). Patients with hypercontractil esophagus and esophageal spasm had an increment in the number and time of pressurisations above 20 mmHg (2.5±3.0 pressurizations resulting in 8±10 % of time with pressure > 20 mmHg, and a pressure gradient across UEG 4.4±9.0 mmHg ($p<0.05$ vs health for all; *non-obstructive hyperpressive pattern*). Finally, patients with non-treated achalasia developed the greatest pressurizations of the esophageal body (7.8±5.5 pressurisations with 41±30% of time pressure > 20 mmHg, and a pressure gradient across UEG 16±13 mmHg ($p<0.05$ vs all; *prolonged hyperpressive or obstructive pattern*). Using ROC-curve analysis the cut-off values that could discriminate between the hypopressive or normal pattern from the hyperpressive patterns are: less than 1 pressurization (sens 80%, sp 75%), <1% of time over 20 mmHg (sens 60%, sp 90%) and pressure gradient across EGJ <1 mmHg (sens 72%, sp 80%). The prolonged hyperpressive or obstructive pattern is characterized by more than 3 pressurizations (sens 70%, sp 75%), > 6% of time over 20 mmHg (sens 90%, sp 50%) and a pressure gradient > 9 mmHg (sens 80%, sp 75%). Using these patterns, we found that 64 % of patients with esophageal symptoms and normal manometry had a normal pattern in response to the drink challenge test, 27 % had a non-obstructive hyperpressive pattern, and 9 % had a prolonged obstructive hyperpressive pattern.
CONCLUSION: Different patterns of responses to a rapid drink challenge test could be used to identify specific motility disorders in patients with esophageal symptoms and unclear or normal esophageal manometry.
Disclosure of Interest: None declared

OP193 CHAGAS DISEASE IN EUROPE: ESOPHAGEAL MOTILITY DISORDERS IN INFECTED IMMIGRANTS IN A NON-ENDEMIC EUROPEAN AREA

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INTRODUCTION: Immigration-related new diseases suppose a new and growing challenge for health care services in Europe. Following Latin American migration, Chagas disease has inevitably appeared in Europe and other countries where the parasite involved, *Trypanosoma cruzi*, is not vectorially-transmitted. Up to 30% of infected patients develop severe cardiologic or digestive disease. The typical esophageal involvement consists in an achalasia-like magaesophagus which is commonly diagnosed by barium x-ray examination. However, in the last years more sensitive tools to study esophageal motility disorders, like high resolution manometry, have been available. The main objective of this study was to determine the prevalence and characteristics of esophageal motility disorders in immigrants infected with *Trypanosoma cruzi,* studied with high resolution esophageal manometry (HRM).
AIMS & METHODS: A cross-sectional study was carried out from April 2010 to December 2013. All newly-diagnosed cases of chronic Chagas infection referring any upper digestive symptom underwent a protocolized clinical evaluation and complementary tests including barium x-ray examination and HRM. The protocol and interpretation of the HRM results was conducted according to the Chicago classification (J Clin Gastroenterol 2008).
RESULTS: We included 62 patients (47 women, 15 men; age range 26-63 yrs) most of whom were Bolivian natives (97%). The referred symptoms were dysphagia (43%), chest pain (40 %), heartburn (85 %), and regurgitation (56 %). Only 7 patients (11 %) had an alteration on barium examination, 6 patients had a slow transit with minor retention of contrast, and 1 had a small-moderate increase in calibre of the esophageal body. By contrast, 47 (76 %) of patients showed an alteration in esophageal manometry, mainly peristaltic dysfunction (30 %), hypotensive lower esophageal sphincter (32 %) or both (32%). Only one patient had esophageal aperistalsis, and none patient had the typical achalasia-like motility pattern. Dysphagia was the only symptom statistically related to presence the esophageal motility abnormalities (p=0.021) and regurgitation showed a trend (p=0.082). Likewise, esophageal motor abnormalities correlated with the presence of an alteration in electrocardiomyography (p=0.05). Furthermore, HRM abnormalities were observed as a unique pathological finding among 26% of individuals.
CONCLUSION: Esophageal motor disorders in infected immigrants with Chagas disease in Europe are common, and are mainly characterized by a peristaltic dysfunction with hypocontractility. The typical achalasia-like megaesophagus is unusual in this specific group of infected patients.
These results suggest that HRM should be the gold-standard for the study of esophageal involvement in this group of patients.
Disclosure of Interest: None declared

OP194 THE BITTER TASTE RECEPTOR AGONIST QUININE HYDROCHLORIDE ALTERS INTRAGASTRIC PRESSURE PROFILES DURING NUTRIENT DRINK TEST IN HEALTHY VOLUNTEERS

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INTRODUCTION: Bitter taste receptors are expressed in the stomach and the duodenum but their function is unclear.
AIMS & METHODS: We assessed the effects of a potent bitter tastant, quinine hydrochloride (QHCl) on intragastric pressure (IGP, a measure of gastric accommodation) and satiation in response to a liquid meal.
We conducted a single-blind crossover trial in 12 healthy volunteers (6 female; mean age 35.1±3.5 yrs; mean BMI 23.8±0.5) given intragastrically 10 μmol/kg (0.1mL/kg) of a 100 mM QHCl solution or placebo in random order on separate occasions at least 1 week apart. First, both a standard high-resolution manometry (HRM) catheter and a 4mm feeding catheter were positioned intra-gastrically via the nose with location confirmed by detection of the lower esophageal sphincter (LES) and/or fluoroscopy. After an adjustment period, QHCl or placebo was administered through the feeding catheter. After 30 min, nutrient drink (ND; 30% fat, 42% carbohydrate, 28% protein) was infused into the stomach at 60mL/min until maximum satiation, at which point it was stopped. Satiation (scored on 0-5 scale) was assessed every minute. IGP was measured as average pressure over 5 channels in the proximal stomach at least 1cm below the LES, with 5-minute baseline measured 5 minutes before ND start. Outcomes were compared with paired t-test. All data are expressed as mean±SEM.
RESULTS: Baseline IGP prior to ND infusion was similar between QHCl and placebo (-0.2±0.7 mmHg placebo vs 0.5±1.2 mmHg QHCl). During the

intragastric nutrient drink infusions, the IGP decreased initially and gradually increased thereafter both in placebo and QHCl. The nadir intragastric pressure during nutrient drink infusion was significantly lower after QHCl administration compared to placebo (-7.2±1.0 mmHg vs -3.4±1.2 mmHg after placebo and QHCl, respectively; p=0.03). The average IGP drop during the nutrient drink infusion was significantly reduced after QHCl treatment (4.7±0.7 mmHg vs. 1.4±1.1 mmHg after placebo and QHCl, respectively; p=0.01). Moreover, the total area under the IGP curve during nutrient infusion was significantly smaller after QHCl (66.8±11.6 mmHg*min for placebo vs 13.9±12.2 mmHg*min for QHCl, p=0.006), consistent with attenuation of the gastric accommodation response. At maximum satiation, the volume of ND ingested (805.1±81.7 ml vs 692.6±69.9 ml, placebo and QHCl respectively, p=0.08) and the duration of the nutrient infusion (13.4±1.4 min vs 11.5±1.2 min, for placebo and QHCl respectively, p=0.08) tended to be lower after QHCl. No adverse effects were noted after either agent.

CONCLUSION: The potent bitter tastant QHCl inhibits gastric accommodation to a meal independently of taste receptor stimulation on the tongue. This is associated with a tendency for decreased nutrient volume tolerance in healthy volunteers. The mechanism involved in this action, and its application in the treatment of obesity, warrant further study.

Disclosure of Interest: None declared

OP195 THE EFFECT OF PRUCALOPRIDE ON GASTRIC ACCOMMODATION IN HEALTHY VOLUNTEERS

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INTRODUCTION: Functional dyspepsia Postprandial Distress Syndrome (FD-PDS), one of the most common functional disorders, is characterised by meal-related symptoms such as early satiation and postprandial fullness. Disturbances of gastric motor function have been implicated the pathogenesis of PDS symptoms, and hence, motility modifying agents are considered for the treatment of PDS. Prucalopride (Resolor®), a highly selective 5-TH_4 receptor agonist which stimulates gastrointestinal motility throughout the GI tract, is currently approved for the treatment of chronic constipation.

AIMS & METHODS: The objective of this study was to evaluate the effect of prucalopride on gastric sensorimotor function in healthy volunteers (HV). A total of 10 HV (50% females) underwent 2 barostat studies with administration of placebo or prucalopride 2 mg in a blinded cross-over fashion. Isobaric distentions with stepwise increments of 2 mm Hg starting from minimal distending pressure and scoring of intensities of gastric sensations (0-6: pain) were used to determine gastric compliance and sensitivity. Gastric accommodation was quantified as the difference (delta) in intra-balloon volume 30 min before and 60 min after ingestion of 200 ml of a nutrient drink (ND) (1.5 kcal mL(-1)). On 2 separate days, the intragastric pressure (IGP) response to intragastric infusion of ND (60 ml min(-1)) was studied by high resolution manometry (HRM) of the stomach. Before and during intragastric infusion, HV scored satiation on a graded scale (0-5: maximal satiation). Throughout the studies, HVs scored their epigastric symptoms on visual analogue scales (0-100: bothersome sensation) every 5 minutes.

RESULTS: Prucalopride did not affect proximal stomach compliance. However, fasting sensitivity to isobaric balloon distention was significantly enhanced by prucalopride. The mean sensitivity curve slope after placebo treatment was 0.6±0.1 mmHg(-1) and the mean slope after resolor treatment was 0.9±0.1 mmHg(-1) (P=0.001). Moreover, the gastric accommodation was significantly increased after treatment with resolor (Delta placebo: 55.4±36.3 mL and delta resolor: 166.9±32.2 mL; P=0.002). During the barostat study, HVs reported significantly higher ratings for symptoms of nausea and belching after prucalopride ($P<0.05$), and vomiting was induced after the meal in 50% of the HVs (all females). The drop in IGP during nutrient-drink infusion was not affected by prucalopride treatment (placebo:-4.6±0.9 vs. prucalopride:-4.0±0.9 mmHg; $p>0.05$). The nutrient tolerance (placebo: 618±68 ml; prucalopride: 654±80 ml; $P>0.05$) and the epigastric symptom scores were not affected by prucalopride.

CONCLUSION: This study shows that prucalopride increases sensitivity to gastric distention. Barostat and IGP show seemingly differential effects on gastric accommodation. However, it seems that prucalopride enhances responses to gastric distention and sensitizes to gastric distention-induced nausea, which may be accompanied by enhanced gastric relaxatory responses. This interpretation is supported by the lack of an effect on nutrient volume tolerance.

Disclosure of Interest: None declared

OP196 IMPAIRED VASOACTIVE INTESTINAL PEPTIDE PATHWAY IN HUMAN GASTRIC ANTRUM IN OBESITY

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INTRODUCTION: Biological pathway-based genome-wide association analysis identified a relevant role of Vasoactive Intestinal Peptide (VIP) pathway for obesity. VIP is a neuropeptide that elicits a broad spectrum of biological functions, including anti-inflammatory and relaxant actions. According to the tissue, VIP interacts with VPAC1 and VPAC2 receptors coupled to the cAMP signaling pathways and with Natriuretic Peptide Clearance Receptor (NPR-C) coupled via endothelial nitric oxide synthase (eNOS), to the cGMP-pathway. In inflammatory conditions a switch from VPAC2 to VPAC1 expression has reported as well as a decrease in eNOS expression.

AIMS & METHODS: Aim of the study was to investigate VIP actions in obesity in terms of biological effects, receptor subtypes expression and related signalling pathways in human gastric antrum, whose relaxation is predominantly VIP-related. Smooth muscle cells (SMC) and strips were isolated separately from human gastric antrum obtained from 13 normoglycemic-normocholesterolemic morbid obese patients ($40.9<BMI<52.0$ Kg/m2; $37<age<45$ years) submitted to sleeve gastrectomy and 7 patients submitted to gastrectomy for gastric cancer (control: $19.0<BMI<25.0$ Kg/m2; $56<age<75$ years). qPCR analysis was performed for mRNA encoding for VPAC1, VPAC2, NPR-C, e-NOS and inflammatory cytokines. On muscle strips and cells relaxant effects were tested on maximal cholecystokinin (1nM)-induced contraction for VIP (1μM), the adenylate cyclase activator forskolin (FSK,10 mM), the guanylate cyclase activator sodium nitroprusside (SNP,1μM) and the 2nd messengers cAMP and cGMP (0.1 mM). Data are expressed as mean±SE, $p<0.05$ considered significant.

RESULTS: In obese SMC the mRNA encoding for VPAC2 was significantly decreased in comparison to control: (VPAC2: 3.6±0.6 vs 6.3±0.8) while the expression of VPAC1 lacking in control SMC, was detected (6.37±1.81). The expression of NPR-C receptor, was slightly reduced in obese SMC (8.7±0.4) in comparison to control (10.8±2.2) whereas mRNA expression encoding for eNOS was not detected, while was present in control (6.6±0.4). Finally, the mRNA encoding for inflammatory cytokines was increased in obese in comparison to control SMC (TNFα: 4.93±1.2 and 4.00±0.4; COX2 4.63±0.63 and 1.10±0.1 respectively). In obese antrum, VIP-induced relaxation resulted almost abolished both on muscle strips (13.8±5.2%) and SMC (14.5±7.3%) in comparison to control (strips:78.1±7.4; SMC:75.6±0.9%). No differences between obese and control SMC were observed in relaxation induced by FSK (52.9±5.0 and 53.5±4.2% respectively) as well as that induced by SNP (38.1±4.44 and 37.0±5.5% respectively). The 2 cyclase activators induced also similar relaxation in obese muscle strips. Likewise, no differences were observed in obese and control SMC in response to cAMP (59.1±7.1 and 50.3±8.2% respectively) as well as in response to cGMP.

CONCLUSION: The present study confirms a VIP pathway alteration in obesity reflected by an impaired relaxant transmembrane signaling caused by a reduction in expression of VPAC2 receptors and coupled molecules.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 11:00–12:30

PEPTIC ULCER DISEASE: RISK FACTORS AND TREATMENT – LOUNGE 6

OP198 LONG-TERM EXPOSURE TO PARTICULATE MATTER AIR POLLUTION AND HOSPITAL ADMISSIONS FOR PEPTIC ULCER DISEASE

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INTRODUCTION: Air pollution is a major health hazard and leading cause of death, particularly in developing countries. Among various pollutants, particulate matter (PM) is of much clinical relevance. Specifically, $PM_{2.5}$ is an airborne particle with aerodynamic diameter less than 2.5 μm that is linked to cardiovascular and respiratory illnesses. Little, however, is known about the effect of $PM_{2.5}$ on the gastrointestinal system.

AIMS & METHODS: We investigated the association between long-term exposures to $PM_{2.5}$ and hospital admissions for peptic ulcer diseases (PUD) in a large cohort of older persons in Hong Kong. Subjects aged 65 or older, have enrolled voluntarily in the Government Elderly Health Centres between 1998 and 2001. All subjects had medical, socio-demographic, lifestyle and anthropometric data recorded during an interview at baseline. The annual mean exposures to $PM_{2.5}$ at individuals' residence were estimated by regressing of $PM_{2.5}$ concentrations from monitoring site measurements against heights of individual's residence and satellite data through linkage with their address details. All hospital admission records of the subjects up to year 2010 were retrieved from the central electronic database of the Hospital Authority. We used Cox regression to model the hazard ratios (HR) of hospitalization due to PUD (including subcategories of gastric and duodenal ulcers) per 10μg/m^3 increase of $PM_{2.5}$ after adjustment for individual, ecological and environmental covariates. Sensitivity analyses were performed by adjusting for or excluding baseline hospitalizations for ischemic heart disease, stroke, chronic obstructive pulmonary disease and diabetes mellitus.

RESULTS: A total of 60,273 subjects with complete baseline information were included in the Cox model. Among them, 1,991 (3.3%) were hospitalized for PUD during the 10-year study period. We found that $PM_{2.5}$ concentration, age, male gender, high BMI, smoking habits, low education level and underlying medical diseases were all associated with PUD hospitalizations and they were all mutually adjusted for in the analyses. The adjusted HR for PUD hospitalization per 10μg/m^3 of $PM_{2.5}$ was 1.18 (95% CI, 1.02 - 1.36). Sensitivity analyses yielded similar HRs for the association between $PM_{2.5}$ and PUD (1.18; 1.02 - 1.35 and 1.18; 1.00 - 1.36, respectively). Subcategory analysis showed that the associations with $PM_{2.5}$ were significant with gastric ulcers (HR 1.28; 1.08 – 1.52) but not with duodenal ulcers (HR 0.98; 0.79 – 1.21). There was no association between $PM_{2.5}$

concentration and hospitalization for other GI diseases including reflux esophagitis and gastroenteritis.
CONCLUSION: Long-term exposures to $PM_{2.5}$ are associated with PUD hospitalization in this older Hong Kong population. Long term exposure to fine particulate air pollutants may be a new risk factor of gastric ulcer development.
Disclosure of Interest: H.-K. Lai: None declared, C.-M. Wong: None declared, H. Tsang: None declared, T.-Q. Thach: None declared, G. Thomas: None declared, K. P. Chan: None declared, R. Lee: None declared, J. Ayres: None declared, T.-H. Lam: None declared, W.-K. Leung Lecture fee(s) from: Ferring, Takeda, Consultancy for: Janssen

OP199 LONG-TERM PREVENTION OF RECURRENCE OF PEPTIC ULCERS BY RABEPRAZOLE IN PATIENTS TAKING LOW-DOSE ASPIRIN – A PHASE 2/3, RANDOMIZED, PARALLEL-GROUP, MULTICENTER, EXTENSION STUDY

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INTRODUCTION: In a recent randomized, double-blind, 24-week study with patients receiving low dose aspirin (LDA) for cardiovascular and cerebrovascular protection, we demonstrated that both rabeprazole 10 mg and 5 mg once daily were significantly more efficacious in preventing ulcer recurrence than teprenone (geranylgeranylacetone: active control, mucosal protective agent, 50 mg three times a day). However, once LDA treatment is begun as a routine clinical care, treatment will continue on a semi-permanent basis. So we planned a long-term administration study, extending the treatment period by additional 28 - 52 weeks (the maximum total duration of treatment of 76 weeks) (ClinicalTrials.gov Identifier: NCT01398410).
AIMS & METHODS: Eligible patients for the extension trial had an endoscopically confirmed history of peptic ulcers, were receiving long-term LDA (81 mg/day or 100 mg/day) therapy for cardio- and cerebro-vascular protection, and were confirmed to have no recurrence of peptic ulcers by endoscopy at the end of 24-week double-blind phase. The patients allocated to the rabeprazole 10 mg group and the rabeprazole 5 mg group in the double-blind phase were maintained on the same doses of rabeprazole in the 28 - 52-week extension phase: that is, patients were treated with rabeprazole for the maximum period of 76 weeks (76-week rabeprazole 10- and 5-mg groups). The patients allocated to the teprenone group in the double-blind phase were randomized to take rabeprazole 10 mg or rabeprazole 5 mg at the ratio of 1:1 in the 28 - 52-week extension phase (52-week rabeprazole 10- and 5-mg groups). The presence or absence of ulcer recurrence was determined by the endoscopy central review panel.
RESULTS: 301 subjects (rabeprazole 10 mg, n=151; rabeprazole 5 mg, n=150) in the 76-week rabeprazole groups and 91 subjects (rabeprazole 10 mg, n=47; rabeprazole 5 mg, n=44) in the 52-week rabeprazole groups constituted the full analysis set. The cumulative recurrence rates of peptic ulcers in the 76-week rabeprazole 10- and 5-mg groups were 2.2% and 3.7%, respectively (Kaplan-Meier estimates). Furthermore, very low cumulative recurrence rates were also observed in the subgroup over 70 years of age (1.4% and 2.8%, respectively), in the subgroup with *H. pylori* negative (1.5% and 5.6%, respectively), and in the subgroup with a history of bleeding ulcers (0% and 0%). Recurrent peptic ulcers were not observed in the 52-week rabeprazole 10- or 5-mg groups. No bleeding ulcers were reported in all subjects during the extension phase. Incidence of gastroduodenal damage, reflux esophagitis, and dyspeptic symptoms were also inhibited by both rabeprazole 10- and 5-mg treatments. Rabeprazole was well-tolerated at both doses, and no clinically significant safety findings, including cardiovascular events, emerged.
CONCLUSION: Rabeprazole 10 mg and 5 mg once daily prevent the recurrence of peptic ulcers in patients with long-term LDA therapy, and are well-tolerated.
Disclosure of Interest: N. Tsuruoka: None declared, R. Iwakiri: None declared, K. Higuchi Financial support for research from: Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., Lecture fee(s) from: Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., M. Kato Financial support for research from: Eisai Co., Ltd., Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Company, Ltd., AstraZeneca and Astellas Pharma Inc., Lecture fee(s) from: Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., Takeda Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co., Ltd. and AstraZeneca, M. Fujishiro Financial support for research from: Dainippon Sumitomo Pharma Co., Ltd., Lecture fee(s) from: Eisai Co., Ltd., Y. Kinoshita Financial support for research from: Eisai Co., Ltd., Lecture fee(s) from: Eisai Co., Ltd., T. Watanabe Financial support for research from: Eisai Co., Ltd., T. Takeuchi: None declared, N. Sugisaki Other: Employee of Eisai Co., Ltd., S. Ichikawa Other: Employee of Eisai Co., Ltd., Y. Okada: None declared, H. Ogawa Financial support for research from: AstraZeneca, Astellas Pharma Inc., Bayer Holding Ltd., Boehringer Ingelheim, Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Company, Ltd., Eisai Co., Ltd, Kowa Company, Ltd., Mitsubishi Tanabe Pharma Corporation, MSD K.K., Novartis Pharma K.K., Otsuka Pharmaceutical Co. Ltd., Shionogi & Co., Ltd. and Takeda Pharmaceutical Co. Ltd., Lecture fee(s) from: Pfizer Japan Inc. and Sanofi K.K., Consultancy for: Eli Lilly Japan K.K, Novartis Pharma K.K., Pfizer Japan Inc. and Takeda Pharmaceutical Co. Ltd., T. Arakawa Consultancy for: Eisai Co., Ltd, and Otsuka Pharmaceutical Co. Ltd., K. Fujimoto Consultancy for: Eisai Co., Ltd.

OP200 EFFECTS OF PRO-GLY-PRO AND N-ACETYL-PRO-GLY-PRO ON ACETIC ACID-INDUCED ULCER FORMATION IN RATS AND CYTOKINES RELEASE FROM RAT GASTRIC EPITHELIAL CELLS

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INTRODUCTION: The Glyprolines peptide family includes the simplest proline-containing peptides: Pro-Gly, Gly-Pro, Pro-Gly-Pro, Hyp-Gly, Gly-Hyp, cycloPro-Gly and etc. Glyprolines are generated during synthesis and catabolism of collagen. Glyprolines have a broad spectrum of biological activity including protective and therapeutic anti-ulcer effects.
AIMS & METHODS: In our research we studied the influence of PGP and N-acetyl-PGP on acetic acid-induced ulcer formation/healing and the release of cytokines *in vivo* and *in vitro*.
Chronic gastric ulcers in male Wistar rats were induced experimentally according to method Okabe [1]. *In vivo:* single intranasal administration of PGP and N-acetyl-PGP was administrated in a dose of 3.7 μmol/kg during 1-3 days and 4-6 days after ulceration. Estimation of ulcer area and histomorphological study were carried out on the 4th and 7th after ulcerogenesis. All stomachs were homogenized for cytokines evaluation. *In vitro:* rat gastric surface epithelial cells were isolated and inoculated in a 1.5×10^6 cells/dish [2]. Peptides were added in volume 20 μl/dish in concentration 10^{-3}- 10^{-5} M. RT-PCR, Real time PCR and ELISA were used for quantative and qualitive analyzes of cytokines.
RESULTS: A maximal ulcer area had developed on the 4th day after application of acetic acid to gastric serous mucosa. PGP and N-acetyl-PGP significantly reduce ulcers by 76.4 % and 86.4 %; respectively, compared to the control group. Antiulcer effects of peptides on the 7th day were equal to 76.41 % and 65.9%, respectively, vs the control group. *In vivo* experiments we have detected cytokines GRO/CINC-1, IL-12a, IL-17a, TGFα and TGFβ. Expression of GRO/CINC-1, TGFα and TGFβ was increased in the control group in comparison with the intact rats. Glyprolines suppressed GRO/CINC-1 ($p<0,05$) on the 4th and 7th days, TGFβ expression was only on the 4th day. *In vitro* experiments the rat gastric surface epithelial cells can secrete GRO/CINC-1, TGFα and TGFβ. We have found no effect of the peptides at the different concentrations on expression and production of GRO/CINC-1 in intact rats and rats after ulceration.
CONCLUSION: 1) Intranasal administration of PGP and N-acetyl-PGP significantly inhibits the development of acetic ulcers and enhances their healing.
2) Cytokines gene expression GRO/CINC-1, TGFα, TGFβ, IL-12a, IL-17a was identified in stomach tissue.
3) The rat gastric surface epithelial cells secrete GRO/CINC-1, TGFα and TGFβ.
4) Acetic acid-induced ulceration increases expression of GRO/CINC-1, TGFα and TGFβ, but epithelial cells do not have changes of expression of these cytokines.
5) One of the mechanisms of anti-ulcer action PGP and N-acetyl-PGP *in vivo* can be caused by the suppression of proinflammatory cytokines expression GRO/CINC-1, TGF α and TGFβ.
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2. Tani S, Okuda M, Morishige R, et al. Gastric mucin secretion from cultured rat epithelial cells. *Biol Pharm Bull* 1997; 20: 482-485.
Disclosure of Interest: None declared

OP201 SEQUENTIAL AND CONCOMITANT TREATMENTS IN H. PYLORI ERADICATION: A NETWORK META-ANALYSIS

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INTRODUCTION: Conventional meta-analyses comparing non-bismuth quadruple sequential (SEQ) and concomitant (CON) regimens in *H. pylori* eradication have been unable to demonstrate differences on treatment efficacy. Network meta-analyses combining pooled data from direct comparisons and comparisons with a common control treatment (standard triple therapy, STT) may provide more complete and consistent information for the selection of the most effective treatment.
AIMS & METHODS: To perform a network meta-analysis of randomized trials comparing SEQ vs. CON treatment, or with STT as common comparator.
Selection of studies: randomized clinical trials comparing CON vs. SEQ, or comparing them with STT. Studies with different treatment arm lengths were excluded. *Search strategy:* bibliographical searches in electronic databases, and manual search of abstracts from Congresses, were conducted up to May 2013. *Data synthesis:* intention-to-treat eradication rate. *Outcome:* Odds Ratio (OR) pooled using random effects model.

RESULTS: 26 trials were included: 13 SEQ vs. STT (3,648 patients), 8 CON vs. STT (1,230 patients) and 5 CON vs. SEQ (966 patients). Only the SEQ vs. STT comparison was heterogeneous (I^2=62%). Direct comparisons showed significantly lower eradication efficacy of STT than SEQ (OR=1.74; 95%CI=1.27-2.38) and CON (OR=2.57; 95%CI=1.85-3.58) treatments. Direct CON vs. SEQ meta-analysis showed significantly better results for CON than for SEQ treatment (OR=1.47; 95%CI=1.02-2.12). Indirect comparison obtained similar results: OR=1.48 (95%CI=0.98-2.36). Network meta-analysis (combining the results from direct and indirect comparisons) demonstrated that CON regimen was significantly more effective than SEQ (OR=1.47; 95%CI=1.06-2.05) and that results were consistent. Number needed to treat was 11.
CONCLUSION: The results from this network meta-analysis demonstrate that non-bismuth quadruple concomitant treatment offers consistent and significantly better cure rates than sequential treatment in the eradication of *H. pylori*.
Disclosure of Interest: None declared

OP202 SEQUENTIAL THERAPY ACHIEVES HIGH ERADICATION RATES IN TREATMENT NAÏVE PATIENTS HARBOURING MULTI-DRUG RESISTANT STRAINS OF H PYLORI

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INTRODUCTION: Sequential therapy has been shown to achieve acceptably high eradication rates also in those patients harbouring *H. pylori* resistant strains.
AIMS & METHODS: To prospectively assess the efficacy of Sequential therapy in eradicating H pylori in treatment naive patients with multi-drug resistant strains. Between 2010 and 2014, consecutive patients undergoing upper endoscopy were evaluated. Each patient had a ^{13}C-UBT, and during endoscopy 2 biopsies each from the antrum, angulus, and corpus were obtained to perform histology. Further biopsies from antrum were also taken to perform ultrafast urease test and to carry out culture and antimicrobial sensitivity by Epsilometer test (Etest). According to new EUCAST 2012 the following MIC breakpoints were used to evaluate resistance: > 0.5, >8 and 1 microgram/ml for clarithromycin (Cla), metronidazole (Met) and levofloxacin (Lev), respectively. Patients were considered infected if culture alone or histology and ultrafast urease test were positive. All received standard Sequential therapy. Four to six weeks after the end of the treatment, eradication was assessed by ^{13}C-UBT.
RESULTS: So far, 908 *H. pylori* infected patients have been enrolled. Follow up is now available in 887 and eradication was achieved in 844 patients (95.1%; 95% CI: 93.8-97); 90.4% in clarithromycin, 92.9 in metronidazole, and 94.4% in levofloxacin resistant strains (single or combined). Eradication rates according to antibiotic resistance patterns are provided in the Table.

Resistance	Total cases	Cases followed-up	Eradication rate (%)
Cla (single)	77	75	94.6
Metro (single)	87	83	97.5
Levo (single)	49	49	95.9
Cla & Metro	155	137	88.3
Cla & Levo	106	97	91.5
Metro & Levo	128	121	94.5
Cla & Metro & Levo	84	77	91.4

CONCLUSION: Sequential therapy is able to overcome the problem of multi-resistant strains in a large proportion of patients. Sequential therapy may be the optimal treatment for patients suspected of having multi-drug resistant strains especially if clarithromycin is involved.
Disclosure of Interest: G. Fiorini: None declared, N. Vakil Consultancy for: Astra Zeneca, Takeda, Shareholder of: Meridian Diagnostic, Orexo, V. Castelli: None declared, I. M. Saracino: None declared, C. Zaccaro: None declared, C. Ricci: None declared, A. Zullo: None declared, L. Gatta: None declared, D. Vaira: None declared

TUESDAY, OCTOBER 21, 2014 14:00-15:30
NEW DRUGS IN IBD - HALL C

OP203 MONGERSEN, AN ORAL SMAD7 ANTISENSE OLIGONUCLEOTIDE, IN ACTIVE CROHN'S DISEASE

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INTRODUCTION: Crohn's disease (CD)-related inflammation is characterized by defective activity of the immunosuppressive cytokine transforming growth factor (TGF)-β1, due to high Smad7 (an inhibitor of TGF-β1) signalling. The effects of an oral, topically active Smad7 antisense oligonucleotide, Mongersen, were evaluated in a phase II study in patients with active CD.
AIMS & METHODS: In a double-blind, placebo-controlled trial, the efficacy of Mongersen as induction therapy was evaluated in steroid-dependent or steroid-resistant patients (utilizing ECCO consensus definition) with active CD (CD activity index [CDAI] score 220-400). Patients were randomized to Mongersen 10, 40 or 160 mg/day or placebo for 2 weeks. The primary outcomes were clinical remission (CDAI score $<$150 at Day 15 and maintained for $\geq$2 weeks) and safety. Secondary endpoints included clinical response (CDAI score reduction of 100 points) at Day 28.
RESULTS: Clinical remission was achieved by significantly greater proportions of patients receiving Mongersen 40 (55.0%) and 160 mg/day (65.1%) compared with placebo (9.5%; $p<0.0001$ for both). No significant difference in clinical remission was seen for 10 mg/day (12.2%) vs. placebo. The rate of clinical response was significantly greater among patients receiving 10 (36.6%), 40 (57.5%) or 160 mg/day (72.1%) of Mongersen vs. placebo (16.7%; p=0.039, p=0.0001 and $p<0.0001$, respectively). The rates of adverse events (AEs) and serious AEs (SAEs) were similar across groups. Nine SAEs occurred in 6 patients (placebo, n=1; Mongersen 10 mg, n=3; 40 mg, n=1; 160 mg, n=1). Most SAEs consisted of hospital admissions for CD-associated complications or symptoms, and included: pyrexia and cough (placebo); abdominal pain (n=2), CD worsening and pyrexia (Mongersen 10 mg); seton placement for perianal fistula and surgery for hemorrhoid thrombosis (Mongersen 40 mg); and thermal burn (Mongersen 160 mg).
CONCLUSION: Induction therapy with orally administered, topically active Mongersen for CD was well tolerated; toxicities previously reported with systemically active antisense agents were not observed. Mongersen treatment resulted in significant improvements in clinical remission and response rates within 4 weeks of initiation of treatment (EUDRACT NUMBER 2011-002640-27).
Disclosure of Interest: G. Monteleone Other: Giovanni Monteleone reports being holder of a patent for the use of Smad7 antisense, M. Neurath: None declared, S. Ardizzone: None declared, A. Sabatino: None declared, M. Fantini: None declared, F. Castiglione: None declared, M. Scribano: None declared, A. Armuzzi: None declared, F. Caprioli: None declared, G. Sturniolo: None declared, F. Rogai: None declared, M. Vecchi: None declared, R. Atreya: None declared, F. Bossa: None declared, S. Onali: None declared, M. Fichera: None declared, G. Corazza: None declared, L. Biancone: None declared, V. Savarino: None declared, R. Pica: None declared, A. Orlando: None declared, F. Pallone: None declared

OP204 AVX-470, AN ORALLY DELIVERED ANTI-TNF ANTIBODY FOR TREATMENT OF ACUTE ULCERATIVE COLITIS: RESULTS OF A FIRST-IN-HUMAN TRIAL

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INTRODUCTION: AVX-470 is an oral, enteric-coated, polyclonal bovine-derived anti-TNF antibody in development for treatment of IBD. AVX-470 is delivered orally to neutralize TNF locally in the gastrointestinal tract, minimizing potential for systemic exposure. This was a double-blind, placebo-controlled, first-in-human trial designed to assess the safety, pharmacokinetics, immunogenicity, and early efficacy of 4 weeks of AVX-470 administration in patients with acute ulcerative colitis (UC).
AIMS & METHODS: 36 patients were randomized 3:1 to receive active drug or placebo in 3 ascending dose cohorts (AVX-470 0.2g/d, 1.6g/d, or 3.5g/d) over 4 weeks. Symptomatic patients with Mayo Score between 5 and 12 and Mayo endoscopic subscore of 2 or greater 15 cm from the anal verge were eligible for participation. Concomitant use of 5-ASA, corticosteroid ($\leq$ 20mg prednisone), and immunosuppressive agents, and prior use of a systemically administered anti-TNF antibody with secondary failure, were permitted. Pancolonoscopies were scored centrally by Mayo and UCEIS (Ulcerative Colitis Index of Severity)

scales. The primary endpoint was safety (adverse events (AEs)). Secondary endpoints included pharmacokinetics (bovine Ig in serum, tissue, and stool); immunogenicity (human anti-bovine antibodies (HABA) in serum); and efficacy (clinical and endoscopic response and remission by Mayo Score).
RESULTS: 36 patients received treatment with AVX-470 0.2g/d (n=8), 1.6g/d (n=12), 3.5g/d (n=7) or placebo (n=9). 50% of patients had pancolitis on entry; 66.7% of patients had prior or concomitant use of corticosteroids, and 41.7% and 33.3% had failed use of immunosuppressive or anti-TNF agents, respectively. 33 patients completed treatment; there were no AE-related dropouts. The incidence of AEs was similar across treatment groups, and no allergic reactions or opportunistic infections were reported. Bovine Ig with TNF binding capacity was detected in stool, while levels of TNF-specific antibody in serum remained 1000-fold lower than concentrations associated with the activity of systemic TNF therapies. Mucosal bovine Ig penetration was demonstrated in all colonic segments. Reduction in tissue TNF levels was noted at 3.5 g/d. AVX-470 therapy did not induce serum HABA. 28% patients across all AVX-470 doses achieved clinical response compared to 14.3% on placebo, with clinical and endoscopic remissions at higher doses. Dose-related improvement in total Mayo Score (-2.1 vs. -1.4) and CRP (-7.2 vs. -0.7) were observed at higher dose (3.5g/d vs. placebo). A linear gradient was observed in the magnitude of endoscopic improvement, with a 1.5-point improvement in UCEIS score (8-pt scale) at 3.5g/d compared to placebo in the proximal colon and lesser improvement distally.
CONCLUSION: AVX-470 appeared to be safe and well tolerated in this first-in-human trial of UC patients, with efficacy trends at the highest dose group and a linear gradient of response on endoscopy from proximal to distal colon after only 4 weeks of treatment. This is the first study to suggest the benefit of an orally delivered locally active agent in a moderate-severe UC population. Future studies are planned to assess the effects of higher dose and longer duration of treatment on disease activity.
Disclosure of Interest: M. S. Harris Consultancy for: Avaxia Biologics, Rhythm Pharmaceuticals, Theravance, Symbiomix, Biomedical Systems, ZS Pharma, Drais Pharmaceuticals, Shareholder of: Ocera Therapeutics, D. Hartman Shareholder of: Avaxia Biologics, Other: Avaxia Biologics, S. Spence Consultancy for: Avaxia Biologics, S. Kennedy: None declared, T. Ptak: None declared, R. Pruitt: None declared, S. Vermeire Financial support for research from: Abbott Laboratories, Merck Sharp and Dohme, UCB, Consultancy for: Merck Sharpe and Dohme, Abbott Laboratories, UCB, Ferring, Chiesi, Pfizer, Shire, B. Fox Shareholder of: Avaxia Biologics, Directorship(s) for: Avaxia Biologics, Other: Avaxia Biologics

OP205 LONG-TERM EFFICACY OF VEDOLIZUMAB THERAPY FOR CROHN'S DISEASE

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INTRODUCTION: The efficacy and safety of the anti–$\alpha_4\beta_7$ integrin monoclonal antibody vedolizumab (VDZ) were evaluated in the 52-week GEMINI 2 study of patients with Crohn's disease (CD).[1] The long-term efficacy of VDZ 300 mg administered every 4 weeks to patients who completed GEMINI 2 and enrolled in an open-label extension study (GEMINI LTS; ClinicalTrials.gov No. NCT00790933; EudraCT No. 2008-002784-14) is described here.
AIMS & METHODS: The double-blind, randomized, placebo (PBO)-controlled GEMINI 2 study of patients with CD involved an induction trial (weeks 0-6) and a maintenance trial (weeks 6-52). Patients who completed the study and those who withdrew early were eligible for enrollment in GEMINI LTS, with VDZ administered every 4 weeks. For the subgroup of patients who completed GEMINI 2, clinical remission (Harvey-Bradshaw Index [HBI] score $\leq$4 points) and response (decrease in HBI score of $\geq$3 points from baseline) were assessed and are reported here for weeks 52, 80, and 104. Prespecified analyses were performed at each time point for the efficacy population (all GEMINI 2 patients who received any amount of study drug in GEMINI LTS).
RESULTS: Of 814 patients treated with VDZ in GEMINI 2, 295 completed week 52 assessments and entered into GEMINI LTS. Clinical remission outcomes at weeks 52, 80, and 104 are shown in the Table. Proportions of GEMINI 2 completers who had clinical remission (week 52, 57%; week 104, 61%) and of those who had a clinical response (week 52, 81%; week 104, 74%) were maintained from weeks 52 to 104. Among completers with previous tumor necrosis factor (TNF) antagonist failure, clinical remission was seen in 51% of patients and clinical response in 70% of patients at week 104. Of VDZ-treated TNF antagonist–naive completers, 69% were in clinical remission and 77% had a clinical response at week 104. Long-term VDZ safety data have been previously described.[2]
Table to abstract OP205

	GEMINI 2 Completers (VDZ Combined) Efficacy Population		
	All Patients (n=295)	TNF Antagonist Naïve (n=159)	Previous TNF Antagonist Failure (n=136)
Clinical Remission (HBI score $\leq$4 points)			
Wk 52	167 (57)	97 (61)	70 (52)
Wk 80	190 (64)	114 (72)	76 (56)
Wk 104	179 (61)	110 (69)	69 (51)

Data are No. of patients (%). Study wk refers to time since start of GEMINI 2.

CONCLUSION: The efficacy of VDZ observed in GEMINI 2 was maintained over the course of an additional 52 weeks in GEMINI LTS, regardless of TNF antagonist exposure prior to GEMINI 2.

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2. Colombel JF, et al. *Poster presented at: American College of Gastroenterology Annual Scientific Meeting*, San Diego, CA, 11-16 October 2013.

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OP206 LONG-TERM EFFICACY OF VEDOLIZUMAB THERAPY FOR ULCERATIVE COLITIS

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INTRODUCTION: Vedolizumab (VDZ) is an anti–$\alpha_4\beta_7$ integrin monoclonal antibody with demonstrated efficacy and safety in the 52-week GEMINI 1 study of patients with moderately to severely active ulcerative colitis.[1] Eligible patients from GEMINI 1 could enroll in an ongoing, long-term, open-label extension study (GEMINI LTS; ClinicalTrials.gov No. NCT00790933; EudraCT No. 2008-002784-14). Here, we describe the long-term efficacy of VDZ in patients who completed GEMINI 1 and enrolled in GEMINI LTS.
AIMS & METHODS: The double-blind, randomized, placebo (PBO)-controlled GEMINI 1 study consisted of induction (weeks 0-6) and maintenance (weeks 6-52) phases. Patients who completed GEMINI 1 (n=344) and those who withdrew early (n=313) could enroll in GEMINI LTS, wherein open-label VDZ was administered every 4 weeks. The following efficacy end points were assessed and are reported here for GEMINI 1 completers: clinical remission (partial Mayo Clinic [pMC] score $\leq$2 with no individual subscore $>$1) and clinical response (decrease in pMC score of $\geq$2 and $\geq$25% from baseline and decrease in rectal bleeding subscore of $\geq$1 from baseline or absolute rectal bleeding subscore $\leq$1). Two analyses are presented, 1 prespecified analysis involving the efficacy population (EP; GEMINI 1 completers who received any amount of study drug in GEMINI LTS) and a post hoc analysis involving observed cases (OC; EP patients who had baseline and $\geq$1 postbaseline measurement) at each time point.
RESULTS: Efficacy outcomes at weeks 52, 80, and 104 for the EP and OC are shown in the Table. Proportions of GEMINI 1 completers who had clinical remission and those who had clinical response were maintained from weeks 52 to 104. The efficacy of VDZ from GEMINI 1 was maintained during GEMINI LTS. Of patients with previous tumor necrosis factor (TNF) antagonist failure, 65.3% (EP) and 79.5% (OC) had clinical remission and 79.6% (EP) and 89.7% (OC) had a clinical response at week 104; 76.7% (EP) and 85.7% (OC) of TNF antagonist–naive patients had clinical remission and 82.8% (EP) and 92.5% (OC) had a clinical response at week 104. Long-term safety data for VDZ have been previously described.[2]

	GEMINI 1 Completers (VDZ Combined)		
		Observed Cases	
	Efficacy Population No. (%) of Patients n=275[a]	No. (%) of Patients	n
Clinical Remission			
Wk 52	181 (65.8)	181 (72.4)	250
Wk 80	212 (77.1)	212 (83.8)	253
Wk 104	200 (72.7)	200 (83.7)	239
Clinical Response			
Wk 52	216 (78.5)	216 (86.4)	250
Wk 80	234 (85.1)	234 (92.5)	253
Wk 104	219 (79.6)	219 (91.6)	239

CONCLUSION: The efficacy of VDZ observed in GEMINI 1 was maintained for an additional 52 weeks in GEMINI LTS, regardless of previous TNF antagonist exposure.

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2. Colombel JF, et al. *Poster presented at: American College of Gastroenterology Annual Scientific Meeting*, San Diego, CA, 11-16 October 2013.

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OP207 EFFECTS OF INCREASED VEDOLIZUMAB DOSING FREQUENCY ON DISEASE ACTIVITY IN ULCERATIVE COLITIS AND CROHN'S DISEASE

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INTRODUCTION: Efficacy and safety of vedolizumab (VDZ) in patients with ulcerative colitis (UC) and Crohn's disease (CD) were established in the GEMINI (GEM) 1 (Feagan BG, et al. *N Engl J Med*.2013;369 (8):699-710) and 2 (Sandborn WJ, et al. *N Engl J Med*.2013;369(8):711-21) trials, respectively. To investigate whether increased VDZ dosing frequency benefits patients who lost response to VDZ every 8 wks (Q8W) during GEM 1 or 2, disease activity was assessed when these patients received VDZ every 4 wks (Q4W) in an open-label, long-term extension study (GEM LTS; EudraCT No. 2008-002784-14).

AIMS & METHODS: The randomized placebo-controlled GEM 1 and 2 studies included a 6-wk induction phase and a 46-wk maintenance phase. Data from patients who responded to VDZ 300 mg induction therapy but later discontinued for lack of efficacy on VDZ 300 mg Q8W maintenance therapy and who enrolled in GEM LTS (to receive VDZ 300 mg Q4W) were analyzed. Mean partial Mayo Clinic (pMC) scores (UC) and mean Harvey-Bradshaw Index (HBI) scores (CD) were calculated. For patients who discontinued from GEM 1 and 2, average wk 52 VDZ concentrations were predicted to standardize pharmacokinetic data at the same time point relative to study entry (Rosario M, et al. Presented at: 9th Congress of the ECCO; Feb 20-22, 2014; Copenhagen). These values were compared with predicted VDZ concentrations in those who completed GEM 1 or 2.

RESULTS: Among those who received VDZ Q8W in GEM 1 (n=122) or GEM 2 (n=154), 32 patients (26%) from GEM 1 and 57 (37%) from GEM 2 discontinued for lack of efficacy. Mean disease activity scores for these patients improved after transition to VDZ Q4W dosing in GEM LTS (Table). AE profiles were generally similar for the VDZ Q8W and Q4W regimens in GEM 1 and 2.

Study Time Point	n	Mean (SD) Score Baselinea	On Study	Change From Baselinea Mean (SD)	95% CI
pMC score for UC	32	5.9 (1.7)	2.6 (1.6)	−3.3 (1.7)	−3.9, −2.7
GEMINI 1	9	6.2 (1.6)	4.3 (3.2)	−1.9 (3.6)	−4.6, 0.9
Wk 6	31	5.9 (1.7)	5.8 (1.8)	−0.1 (1.6)	−0.7, 0.5
Wk 26	19	5.9 (1.6)	2.4 (1.7)	−3.5 (2.1)	−4.5, −2.5
GEMINI LTS	16	5.8 (1.6)	1.8 (1.7)	−4.0 (2.4)	−5.3, −2.7
Wk 0					
Wk 28					
Wk 52					
HBI score for CD	56	11.4 (3.0)	6.4 (3.1)	−5.0 (3.3)	−5.9, −4.1
GEMINI 2	19	11.4 (2.2)	8.5 (4.1)	−2.9 (4.7)	−5.2, −0.6
Wk 6	57	11.5 (3.0)	10.1 (4.1)	−1.4 (4.3)	−2.5, −0.2
Wk 26	40	11.3 (2.7)	6.0 (3.4)	−5.3 (3.7)	−6.5, −4.1
GEMINI LTS	30	11.1 (2.4)	4.1 (3.0)	−7.0 (3.4)	−8.2, −5.7
Wk 0					
Wk 28					
Wk 52					

Consistent with the findings above, median predicted average wk 52 VDZ concentrations in patients on VDZ Q8W were higher for those who completed the studies (GEM 1: 36.9 mcg/mL, n=75; GEM 2: 39.5 mcg/mL, n=74) than for those who discontinued (GEM 1: 30.5 mcg/mL, n=32; GEM 2: 32.7 mcg/mL, n=57).

CONCLUSION: Patients who lost response to VDZ Q8W had improvements in mean disease activity scores with an increase in VDZ dosing frequency to Q4W without an apparent accompanying increased risk for AEs. Although uncontrolled, these data provide insight regarding possible utility of VDZ Q4W dosing.

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OP208 HOW LONG SHOULD GOLIMUMAB TREATMENT BE CONTINUED IN PATIENTS WITH ULCERATIVE COLITIS WHO DO NOT RESPOND TO INITIAL INDUCTION THERAPY?

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INTRODUCTION: To determine an appropriate time to discontinue golimumab (GLM) maintenance therapy for ulcerative colitis (UC) in patients (pts) who do not respond to initial induction treatment.

AIMS & METHODS: The PURSUIT study enrolled pts with moderate to severe, active UC (Mayo scores 6–12 inclusive; endoscopic subscore >2) with inadequate response or intolerance to conventional UC therapy. Pts were randomized to receive at wk 0/2 either placebo (PBO)/PBO, GLM 200mg/100mg, or GLM 400mg/200mg. Pts who were not in clinical response (≥30% and ≥3 points Mayo score decrease from wk 0 with a rectal bleeding subscore of 0/1 or decrease ≥1) after 6-wk induction received GLM 100mg every 4 wk. Partial Mayo response (improvement ≥3 from wk 0) and remission (score ≤2) without endoscopy were evaluated through wk 22. There was no control group; all nonresponders received GLM. Pts who had a prohibited medication change, ostomy or colectomy, dose adjustment, missing partial Mayo scores, or discontinued for lack of efficacy were considered nonresponders.

RESULTS: Among GLM induction nonresponders (N=398, 7 pts excluded due to site misconduct), further GLM therapy resulted in additional pts achieving response/remission (table; data from induction responders are shown for comparison). At wk 10 of GLM exposure, 11.8% of induction nonresponders had achieved partial Mayo remission, and 23.1% had achieved partial Mayo response. At wk 14, 15.6% achieved remission; 28.1% achieved response. Although the proportion of pts who achieved remission/response increased beyond wk 14, the incremental benefit was minimal. While adverse events (AEs) were reported with a slightly greater frequency during the first months of maintenance treatment, the majority of pts did not report an AE during continued treatment.

Table. Partial Mayo Response/Remission With Continued GLM Treatment
Table to abstract OP208

	Induction Nonresponders (N=398)		Induction Responders (50 and 100mg dose groups) (N=302)	
Wk of GLM exposure	**Partial Mayo remission, n (%)**	**Partial Mayo response, n (%)**	**Partial Mayo remission, n (%)**	**Partial Mayo response, n (%)**
Wk 6[a]	7 (1.8)	14 (3.5)	205 (67.9)	234 (77.5)
Wk 10	47 (11.8)	92 (23.1)	190 (62.9)	232 (76.8)
Wk 14	62 (15.6)	112 (28.1)	186 (61.6)	206 (68.2)
Wk 18	77 (19.4)	129 (32.4)	181 (59.9)	201 (66.6)
Wk 22	84 (21.1)	129 (32.4)	172 (57.0)	186 (61.6)

CONCLUSION: Among patients who were nonresponders after initial GLM induction, 15.6% achieved partial Mayo score remission, and 28.1% achieved response by wk 14. Continued therapy may not be useful in patients who show no evidence of therapeutic benefit after 12–14 wks of GLM treatment. (Financial support for this study was provided by Janssen Research & Development, LLC., Spring House, PA, USA.)
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TUESDAY, OCTOBER 21, 2014 14:00-15:30
IBD: DYSPLASIA AND CANCER - HALL I/K

OP209 RARITY OF ADENOMATOUS POLYPS IN ULCERATIVE COLITIS: IMPLICATIONS FOR COLONIC CARCINOGENESIS

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INTRODUCTION: Despite ample research on dysplasia-carcinoma risk in ulcerative colitis (UC) there are scant data on sporadic adenomas' risk in this population.
AIMS & METHODS: The aim of this study was to investigate the prevalence of sporadic colon adenoma in UC patients in order to gain insight of possible role of chronic immune-driven inflammation on adenoma development. For this purpose, the number and histology of all polyps detected at colonoscopies of UC patients during 2006-2012 were compared to controls undergoing screening colonoscopy. The analysis was deliberately restricted to patients who were over 50 years-old at the time of the index colonoscopy to reinforce the validity of the comparison to screening colonoscopy controls. However, to exclude a potential bais, an additional analysis was performed including all prior colonoscopies undergone by the UC group. A third group comprising of Crohn's disease patients was also evaluated to dissect the role of colonic IBD versus ileal IBD on sporadic adenoma rate.
RESULTS: 206 UC patients and 624 controls (mean age 61.7±8.7 versus 60.8±6.1, respectively, P=0.15) were included. Adenomatous polyps were detected in only 13/206 UC colonoscopies compared to 162/624 colonoscopies of controls (6.3% vs. 25.9% respectively, OR 0.19, 95%CI 0.1-0.34, p<0.0001). When also considering all prior colonoscopies performed over 7.7±4.6 years of follow-up (mean 4.1±2.9 colonoscopies/patient, range 1-15, total 832 colonoscopies), the risk of ever finding an adenoma in UC patients was still significantly lower compared to controls (14.1% vs.25.9% respectively, OR 0.47, 95%CI 0.3-0.72, p=0.0005). On multi-variate analysis, the incidence of adenomas was positively associated with advanced age (OR 1.07/year, 95%CI 1.04-1.09, P<0.0001) and with male gender (OR1.54, 95%CI 1.02-2.3, p=0.04) and negatively associated with having UC (OR 0.16, 95%CI 0.09-0.30, P<0.0001). Among 115 Crohn's patients >50 years old, the rate of ever-adenomas in Crohn's ileitis patients and controls was similar (p=0.8), whereas patients with Crohn's disease involving the colon had significantly lower rate of adenomas compared to controls (3.9% vs. 25.9%, p=0.002).
CONCLUSION: Patients with UC or colonic Crohn's disease seldom develop sporadic adenomatous polyps. These data provide novel insight into possible mechanisms restricting the adenoma-carcinoma sequence and suggest organ-specific immune activation may confer protection against development of colonic adenomas.
Disclosure of Interest: S. Ben-Horin Consultancy for: Abbott, Janssen, Takeda & Schering-Plough, Z. Izhaki: None declared, O. Haj-Natur: None declared, S. Segev: None declared, R. Eliakim Consultancy for: Abbott, Janssen & Schering-Plough, B. Avidan: None declared

OP210 CHARACTERIZATION OF INCIDENT CASES OF CANCER IN INFLAMMATORY BOWEL DISEASE PATIENTS: RELATION WITH IMMUNOMODULATORY TREATMENTS AND DISEASE PHENOTYPE IN A PROSPECTIVE MULTICENTER MATCHED-PAIR IG-IBD STUDY

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INTRODUCTION: Concern exists about cancer risk using thiopurines (IMM) and/or anti-TNFs in Inflammatory Bowel Disease (IBD).
AIMS & METHODS: In a prospective, multicenter, case-control study, we aimed to characterize incident cases of cancer in IBD. The role played by clinical characteristics of IBD *vs* IMM and/or anti-TNFs use in determining the frequency of cancer was also investigated. From Jan 2012 to April 2014, characteristics of all incident cases of cancer in IBD patients (pts) referring to 15 centers were recorded. In each center, each IBD pt developing cancer (IBD-K) was matched with 2 IBD pts with no cancer (IBD-C) for: IBD type (CD/UC), gender, age (±5yrs). Data reported as median (range):chi-squared, Fisher exact, Student *t* test, univariate analysis as appropriate.
RESULTS: The study included 106 IBD-K and 212 IBD-C. Cancer occurred in 106 IBD-K (54M, age 59 [16-85];2 cancers in 8 pts).The frequency of cancer was higher in CD (CD-K)(n=61;57%) *vs* UC (UC-K)(n=45;43%; p=0.03). IBD-C included 212 pts (110M, age 57[15-83]). IBD duration was comparable between IBD-K and IBD-C (yrs:12[1-54] *vs* 12.5[10-50]. Cancers included: GI tract (n=42;40%;colorectal, CCR 24%), genitourinary (n=26;25%), skin (n=9;8%), lung (n=9;8%), breast (n=9;8%), hematologic cancers (n=7;7%:5NHL/1HL,5%;1 leukemia (0.9%), others (4%). Cancers involved: GI tract (n=42; 18 CD/28UC; CCR n=26: 7CD/19UC; ileal carcinoma 6CD/0UC), genitourinary tract (n=26:15CD/11UC; cervix 5CD/0UC), skin (n=9; 6CD/3UC;CD:3 melanoma [2 noIMM/anti-TNFs;1 IMM], 3 NMSC [2IMM+anti-TNFs,1IMM]; UC: 1 melanoma,1 Kaposi [no IMM/anti-TNFs both];lung (n=9;5CD/4UC), breast (n=9;6CD/3UC), lymphoma (n=6; 5NHL/1HL, 6CD, 6M, [2 IMM+anti-TNFs, 1 IMM, 2 no IMM/anti-TNFs], others (n=5). Cancer-related death: 10/106 (9.4%) pts. GI cancers were more frequent in UC (53%) *vs* CD (29%; p=0.02), lymphoma and ileal carcinoma in CD *vs* UC (9.8% vs 0%; p=0.03both). The frequency of any cancer was higher in pancolitis (59%) *vs* distal (30%; p=0.01), subtotal UC (11%; p=0.0001), with no differences between stricturing, fistulizing, inflammatory CD (39% vs 27% vs 34%; p=ns). IMM and anti-TNFs were used in a comparable proportion of IBD-K and IBD-C pts (IMM 39% *vs* 45%; Anti-TNFs 28% *vs* 35%;p=ns both).
CONCLUSION: In a prospective multicenter match-pair study, incident cases of cancer were more frequent in CD *vs* UC, with a high frequency of GI and genitourinary cancers in IBD. CCR was more frequent in UC, lymphoma and ileal carcinoma in CD. CD phenotype and UC extent may influence the frequency of any cancer, while IMM and/or anti-TNFs the frequency of specific cancer histotypes (lymphoma, skin cancer).
Disclosure of Interest: None declared

OP211 SERRATED POLYPS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD): ENDOSCOPIC CHARACTERISTICS DIFFER FROM SERRATED POLYPS IN NO-IBD POPULATION

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INTRODUCTION: Serrated polyps (SP) include hyperplastic polyp (HP), sessile serrated adenoma (SSA) and traditionnal serrated adenoma (TSA). Endoscopic characteristics of these lesions are well-known in general population, but whether they have specific aspect in patients with inflammatory bowel disease (IBD) is unknown.
AIMS & METHODS: To compare endoscopic characteristics of SP between IBD and non-IBD patients. Prospectively, 229 patients were included. A chromoendoscopy with indigo carmin (0.2%) was performed (H180, Olympus, Japan) under sedation. All the lesions were described according to Paris classification; the size (mm), localization and histology were reported.
RESULTS: 154 IBD patients (77 men, 53 ± 13.5 yrs, mean ± SD) and 75 non-IBD patients (38 men, 58 ± 15 yrs) were included. We detailed for each group the characteristics of HP and SSA polyps which are summarized on table1. No patient presented TSA. A total of 349 SP were detected by chromoendoscopy: 195 in 56% (42/75) of patients in non-IBD and 154 in 13.6% (21/154) of IBD patients. Among patients with SP, the HP polyps were more frequent in non-IBD group (26/42, 62% vs 11/21, 52.3%, NS) and presented the same macroscopic aspect (IIa) in the 2 populations. Whereas, among patients with SP, SSA tended to be more frequent in IBD patients (10/21, 47.6% vs 16/42, 38%, NS) and presented more often dysplasia than in non-IBD patients (6/21, 28.6% vs 8/42, 19%, $p<0.05$). Their macroscopic aspect was different with IIb of Paris classification in IBD patients. In IBD patients, SSA tended to be larger (10.3 +/- 12.7 vs 4.7 +/- 2.1 mm, $p<0.01$). In IBD group, SSA were localized all along the colon, whereas in non-IBD the SSA were preferentially localized in the right colon.

Nb of pts with SP	Non-IBD (42/75, 56%)	IBD (21/154, 13.6%)	p
Total nb of SP lesions	195	154	-
Nb of pts with HP	26 (26/42, 62%)	11 (11/21, 52.4%)	NS
Nb of pts with SSA	16 (16/42, 38%)	10 (10/21, 47.6%)	NS
Nb pts with SSA with dysplasia	8 (8/42, 19%)	6 (6/21, 28.6%)	<0.05
Total nb of SSA	37 (37/195, 19%)	37 (37/154, 24%)	NS
Total nb of SSA with dysplasia	13 (13/37, 35%)	14 (14/37, 37.8%)	NS
Mean size of SSA	4.7 +/- 2.1	10.3 +/- 12.7	<0.01
Paris classification of SSA	25 IIa, 12 Is	23 IIa, 10 IIb, 4 Is	-
Localization of SSA	24 RC, 13LC	20 RC, 17 LC	-

CONCLUSION: In IBD patients, the size, Paris classification and localization of serrated polyps differ from those of non-IBD patients. IBD patients presented more often SSA with dysplasia, suggesting that SSA could be involved in cancer pathway. This hypothesis has to be verified by following prospectively the cohort of IBD patients.
Disclosure of Interest: None declared

OP212 INVESTIGATION OF DIFFERENTIALLY EXPRESSED MICRORNAS IN COLITIS ASSOCIATED DYSPLASIA AND ADENOCARCINOMA

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INTRODUCTION: A number of recent studies have identified microRNA (miRNA) expression profiles associated with Ulcerative Colitis (UC). Our study aimed to discover miRNAs related to disease progression in order to identify dysplasia and colitis associated cancer (CAC) in patients with UC.
AIMS & METHODS: Total RNA was extracted from archived paraffin embedded tissue and allocated to 4 'discovery' groups: UC (n=4), CAC (n=4), low grade dysplasia (n=4) and high grade dysplasia (n=4). MiRNA expression profiling was performed using Applied TaqMan® human miRNA array cards v2.0. Quantitative RT-PCR using individual miRNA assays was subsequently used to validate the results in a further independent cohort: normal (n=21), UC (n= 22), Dysplasia (n=7) and CAC (n=12).
RESULTS: Intergroup comparison of the initial array data identified a progressive increase in the differential expression levels of miR-10b, 18a, and 32 from dysplasia to CAC.
The validation cohort showed a significant differential expression of miR-18a, 21 and 135b (table 1.0).

Table to abstract OP212

Combined Tissue Groups	MiR-18a P Value	MiR-18a Fold Change	MiR-21 P Value	MiR-21 Fold Change	MiR-135b P Value	MiR-135b Fold Change
Normal vs. UC	0.092	2.8	0.0358*	1.4	< 0.0001*	6.6
Normal vs. CAC and Dysplasia	< 0.0001*	6.4	< 0.0001*	3.9	< 0.0001*	11.4
UC vs. CAC and Dysplasia	0.022*	3.6	0.0002*	2.4	0.0008*	4.8

Table 1.0: MiR expression in different tissue groups.
Furthermore mir-31 appeared to be increased in the acute phase of UC and combining selected miRNA profiles (mir18a and 21) showed significant variance ($p<0.05$).
CONCLUSION: Several miRNAs were increased in dysplastic and CAC tissues and may contribute to pathological processes, such as dysregulation of apoptosis and impairment of epithelial barrier dysfunction. Further investigation of these miRNAs may enable clinicians to monitor disease progression in patients with UC and distinguish those at increased risk of developing CAC.
Disclosure of Interest: None declared

OP213 RISK OF DYSPLASIA AND CANCER COMPLICATING COLONIC STRICTURES IN INFLAMMATORY BOWEL DISEASE: A GETAID STUDY

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INTRODUCTION: Management of colonic strictures complicating inflammatory bowel disease (IBD) is a challenge in clinical practice and leads frequently to surgical resection because of the fear of associated dysplasia/cancer. The risk of intestinal dysplasia or cancer complicating colonic strictures in both ulcerative colitis (UC) and Crohn's disease (CD) is unknown.
AIMS & METHODS: We aimed to determine the frequency of dysplasia and cancer among adult patients with IBD undergoing intestinal resection for a colorectal stricture without dysplasia or cancer known at the time of surgery. The GETAID conducted a nationwide retrospective study. Only centers having a database of all consecutive IBD patients who underwent intestinal resection for IBD during a given period could participate in this study. All patients with preoperative evidence of dysplasia/cancer were excluded. Demographical, clinical, endoscopic, surgical, and histopathological data and outcomes were collected.
RESULTS: Among 12 013 IBD patients operated for IBD in 16 GETAID centers between August 1992 and January 2014, we identified 293 patients operated for a colonic stricture, including 248 CD, 39 UC and 6 IBD unclassified. 51% were males and the median age at stricture diagnosis was 38 years (Q1=25-Q3=51). All patients underwent preoperative colonoscopy. The stricture was not passable in 66% of cases. The median disease duration at stricture diagnosis was 8 (3-14) years. Strictures presented a median length of 6 cm (4-10), and were symptomatic in 73% of patients. They were located in the right colon, transverse, or left or rectal in respectively 16%, 14%, 64% and 6% of CD patients, and respectively 6%, 13%, 62% and 19% in UC. The median stricture duration before surgery was 6.3 (1.6-20) months in CD and 3 (0.6-9.6) months in UC. Surgical procedure was segmental, subtotal colectomy and coloprotectomy in respectively 79%, 19% and 10% of CD patients and in respectively 18%, 28% and 54% in UC. In CD, low-grade dysplasia was observed in 3 patients (1%), high-grade dysplasia in one patient (0.4%) and cancer in 2 patients (0.8%). In UC, cancer was observed in 2 (5%) patients, high-grade dysplasia in 1 (2%) and low-grade dysplasia in 1 patient (2%). The median follow-up after strictures resection was 4.3 years (1.4-8.1). All patients with dysplasia or cancer received a curative surgery, but one patient died of colorectal cancer.
CONCLUSION: In this cohort of 293 IBD patients undergoing intestinal resection for colonic stricture, dysplasia or cancer were observed in 3% of cases. These findings should be taken into account to guide decision in IBD patients with colonic strictures in clinical practice.
Disclosure of Interest: None declared

OP214 FORTY-YEARS OF ULCERATIVE COLITIS SURVEILLANCE FOR COLORECTAL CANCER: PREVALENCE OF MULTIFOCAL NEOPLASIA AND INTERVAL CANCER, TIME TREND IN CANCER RISK, AND THE NATURAL HISTORY OF PROGRESSION OF EACH GRADE OF DYSPLASIA

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INTRODUCTION: The prevalence of multifocal neoplasia and interval cancer in patients with ulcerative colitis (UC) is unclear. Furthermore, there is a continuing debate on the change in colorectal cancer (CRC) incidence over time and the risk of progression from each grade of dysplasia to CRC. This study reports on data collected from patients with extensive UC between 1971 and 2012 at a large tertiary center in the UK, with an aim to answer these important questions.
AIMS & METHODS: A retrospective analysis of UC patients enrolled in long-term surveillance was performed. Data were obtained from medical records, surgical, endoscopy and histology reports. The primary end point was defined as death, colectomy, withdrawal from surveillance, or the census date (January 1, 2013). Raised dysplastic lesions arising within a diseased segment were classified as sporadic adenoma or UC-associated dysplasia according to the clinical consensus made at the time of diagnosis. Cox proportional hazards models and Kaplan-Meier curves were generated to assess the risk of cancer progression.
RESULTS: A total of 1,375 patients underwent 8,650 colonoscopies (median, 5 per patient; interquartile range (IQR), 3 – 8 per patient) during 16,037 patient-years of follow-up (median, 11 years; IQR, 7 – 17 years). Colorectal cancer was detected in 72 patients (5% of study population). The rate of interval cancer was 23.8%. Out of 64 CRCs where a surgical specimen was available, 24 (37.5%) had synchronous cancers or a spatially distinct focus of dysplasia. The cumulative incidence of CRC by disease duration was 0.07% at 10 years, 2.9% at 20 years, 6.7% at 30 years and 10% at 40 years. Linear regression revealed no significant change in the overall incidence of CRC during the four decades of the surveillance program ($R = -0.13$; $p=0.42$). However, there was a significant reduction in incidence of colectomy performed for dysplasia or CRC over time ($R = -0.43$; $p=0.007$). The risk of developing CRC for each type of neoplasia compared with patients with no neoplasia was: sporadic adenoma (hazard ratio (HR), 0.50; 95% confidence interval (CI), 0.15 – 1.64; $p=0.25$), indefinite for dysplasia (HR, 6.1; 95% CI, 1.7–21.5; $p=0.005$), low-grade dysplasia (HR, 7.8; 95% CI 2.4–25.7; $p<0.001$), and high-grade dysplasia (HR, 33.1; 95% CI, 9.7–112.9; $p<0.001$). There was no significant difference in the risk of CRC between indefinite for dysplasia and low-grade dysplasia group (log-rank; $p=0.786$).
CONCLUSION: The overall risk of CRC was considerably lower than previously reported. However, there was no significant change in CRC incidence over time. Multifocal neoplasia and interval cancer was common, highlighting the importance of careful inspection with advanced imaging technologies to ensure lesions are not missed. High-grade dysplasia is a strong indication for colectomy. Indefinite for dysplasia may have a similar risk of CRC compared with low-grade dysplasia and the differential patient management decisions should not be made solely on the histological finding.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 14:00–15:30

NORMAL AND ABNORMAL CROSS-TALK AT THE MUCOSAL BORDER: RELEVANCE FOR GI FUNCTION AND DYSFUNCTION – HALL L/M

OP215 ANTIBIOTIC INDUCED DYSBIOSIS AND CORRECTIVE IMPACT OF SACCHAROMYCES BOULARDII IN HEALTHY VOLUNTEERS

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INTRODUCTION: Interactions between the microbial flora of the intestine and the human host play a critical role in maintaining intestinal health and in the pathophysiology of a wide variety of disorders including antibiotic associated diarrhea, *Clostridium difficile* infection and inflammatory bowel disease. Antibiotics disrupt the normal intestinal microflora whereas probiotics, such as *Saccharomyces boulardii*, have the potential to reduce these harmful effects and to restore a more healthy and balanced intestinal microbiota.
AIMS & METHODS: The aim of this study was to evaluate the effects of an antibiotic (Amoxicillin/Clavulanate), a probiotic (*Saccharomyces boulardii*), Florastor®) and the combination on the microbiota of healthy adult volunteers. Healthy subjects were randomized to one of four study groups (n=12 for each): 1) *S. boulardii (SB)*, 500 mg twice daily for 14 days, 2) Amoxicillin/Clavulanate (AC), 875/125 mg twice daily for 7 days, 3) Amoxicillin/Clavulanate plus *S. boulardii* (each dosed as above), 4) Control (no treatment).
Seven stool samples were collected from subjects in the active groups (groups 1, 2 & 3) and 3 stool samples from controls. Gastrointestinal symptom questionnaires were also completed by the participants. 16S rRNA gene pyrosequencing was used to identify the predominant bacterial genera in stool samples and to monitor changes in the microbiota in each study group.
RESULTS: Subjects showed a complex microbiome at study entry that appeared to segregate into groupings or "enterotypes" as previously described. Antibiotic treatment (AC group) was associated with marked microbiome changes and these persisted for some time after treatment ended. Antibiotic treatment led to a markedly reduced prevalence of the genus Ralstonia and parallel increases in Parabacteroides and Escherichia / Shigella. *S. boulardii* treatment alone did not substantially modify the microbiome. However, when *S. boulardii* was administered in combination with Amoxicillin/Clavulanate the antibiotic-induced changes in the genera Ralstonia, Parabacteroides and Escherichia / Shigella were significantly attenuated ($P<0.05$ for each). Diarrhea scores (measured using the Gastrointestinal Symptom Response Score (GSRS)) increased during antibiotic treatment in parallel with increases in the prevalence of Escherichia / Shigella in the stool ($R^2 = 0.9993$ by Linear regression, $P<0.001$). *S. boulardii* treatment in combination with the antibiotic prevented the increase in Escherichia/shigella prevalence and also prevented antibiotic associated diarrhea ($P<0.05$ for each).
CONCLUSION: The microbiomes of healthy individuals show substantial diversity but remain stable over time. Antibiotic treatment is associated with marked microbiome changes with both reductions (Ralstonia) and increases (Parabacteroides, Escherichia / Shigella) in different genera. *S. boulardii* treatment can prevent some antibiotic-induced microbiome changes and, in parallel, can reduce antibiotic associated diarrhea. Future studies are warranted to explore whether the strong correlation between an increased prevalence of Escherichia / Shigella and increased symptom scores for antibiotic associated diarrhea represent a cause and effect association that is positively influenced by *S. boulardii*.
Disclosure of Interest: C. Kelly Financial support for research from: Biocodex Inc, Other: Travel support, T. Kabbani Other: Travel support, K. Pallav: None declared, J. Villafuerte-Gálvez: None declared, R. Vanga: None declared, N. Castillo: None declared

OP216 GUT PERMEABILITY IN IBS IS SITE SPECIFIC, SUBTYPE DEPENDENT AND AFFECTED BY CONFOUNDING FACTORS

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INTRODUCTION: Altered intestinal barrier function is one of the assumed pathophysiological mechanisms of irritable bowel syndrome (IBS). Intestinal permeability has previously been studied in small IBS populations, but findings were contrasting and difficult to compare due to differences in methodology.
AIMS & METHODS: Objectives of the present study were 1) to assess intestinal permeability at different sites of the GI tract, in a large group well characterised IBS patients and healthy controls (HC) and investigate differences between subtypes, and 2) to assess potential confounding effects of multiple patient-related factors.
IBS patients (all according to ROME III criteria) and HC of a large IBS cohort underwent a validated multi-sugar test to assess intestinal permeability on four sites of the GI tract. Sucrose excretion and the lactulose/rhamnose (L/R) ratio in 0-5 h urine indicated gastroduodenal and small intestinal permeability, respectively. Sucralose/erythritol (S/E) ratio in 0-24 and 5-24 h urine was used as indicators of whole gut and colonic permeability, respectively. Linear regression analysis was used to assess the association between IBS and IBS subtypes and intestinal permeability and to adjust for possible confounding factors, *i.e.* demographics (age, sex, BMI), psychological symptoms (anxiety or depression), lifestyle factors (smoking history, (defined as current or previous smoker) and alcohol intake of >15 units/week), and use of medication in the 2 weeks prior to inclusion (NSAID, PPI, SSRI and medication that affects motility).
RESULTS: 91 IBS patients, *i.e.* 37% diarrhoea predominant (IBS-D), 23% constipation predominant (IBS-C), 33% with mixed (IBS-M) and 7% with unspecified stool pattern (IBS-U), and 94 HC were enrolled. Sucrose excretion was significantly increased in the total IBS group versus HC (median [Q1; Q3] in µmol: 5.26 [1.82; 11.03] vs. 2.44 [0.91; 5.85], $p<0.05$), as well as in IBS-C (7.40 [2.37; 18.29], $p<0.01$) and IBS-D (4.22 [2.12; 8.03], $p<0.05$) versus HC. However, the differences attenuated when adjusting for confounders. Factors with significant confounding effects were higher BMI, smoking history and use of drugs that positively affect motility.
Furthermore, the L/R ratio was increased in IBS-D patients compared to HC (0.023 [0.013; 0.038] vs. 0.014 [0.008; 0.025], $p<0.05$), which remained significant after adjustment for confounders.
There was no significant difference between groups in 0-24 and 5-24 hour S/E ratio.
CONCLUSION: Small intestinal, but not gastroduodenal, colonic and whole gut permeability is increased in patients with IBS-D when compared to HC, irrespective of possible confounding factors. Adjustment for possible confounders is necessary when studying intestinal permeability, especially in a heterogeneous disorder as IBS.
Disclosure of Interest: Z. Mujagic: None declared, S. Ludidi: None declared, D. Keszthelyi: None declared, M. Hesselink: None declared, J. Kruimel: None declared, K. Lenaerts: None declared, N. Hanssen: None declared, J. Conchillo: None declared, D. Jonkers: None declared, A. Masclee Consultancy for: Pentax medical, Grünenthal GmbH, Ferring

TUESDAY, OCTOBER 21, 2014 14:00-15:30
UPDATE ON CAPSULE ENDOSCOPY - HALL N

OP217 THE USE OF SMALL BOWEL CAPSULE ENDOSCOPY IN THE INVESTIGATION OF IRON DEFICIENCY ANAEMIA. ADHERENCE TO BSG GUIDELINES AND IMPACT ON DIAGNOSTIC YIELD

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INTRODUCTION: Iron deficiency anaemia (IDA) occurs in 2-5% of adult men (M) and postmenopausal women (F) in the developed world[1] and is a common reason for referral to Gastroenterology[2]. Small bowel (SB) capsule endoscopy (CE) has revolutionised investigation of SB disorders. British Society of Gastroenterology (BSG) guidelines suggest considering CE if the Haemoglobin (Hb) cannot be restored or maintained with iron therapy[3]. The few studies examining diagnostic yield (DY) of CE in IDA alone have demonstrated a wide variability in positive findings (30%[5]-71%[6]).
AIMS & METHODS: To determine if use of CE in IDA adhered to BSG guidelines, and the effect of adherence to guidelines on DY. A retrospective audit of CEs performed in our institution over 5 years from 2009-2013 was performed. All patients with the indication of IDA were identified and their CE reports examined. Data were collected on blood indices from the laboratory system. IDA was defined, according to local laboratory indices, as: Hb in M of $<$140g/l (if $<$70yrs) or $<$116g/l (if $\geq$70yrs) and in F of $<$120g/l ($<$70yrs) or $<$108g/l ($\geq$70yrs), along with a serum ferritin in M of $<$20µg/l and in F of $<$7µg/l ($<$50yrs) or $<$10µg/l ($\geq$50yrs).
RESULTS: From 2009-2013, 391 CEs were performed. 131 (33.5%) had IDA as the recorded indication. Following review, 22 were excluded (5 as indication was overt bleeding, 7 no CE report, 10 no blood results available). 10 were incomplete (poor bowel prep): 6 were not repeated and therefore excluded, 4 were repeated and the incomplete study excluded. Therefore a total of 99 patients were included in the study. The capsule was retained at a stricture in 4 patients- these patients were included. Retention was confirmed with abdominal x-ray at 2 weeks in 2 patients (2%). Combined with the incomplete studies, this gives a completion rate of 87.2%.
The number of CE performed per year for IDA increased over the study period. The mean age was 60 (17-90) of which 46.5% (n=46) were M and 53.5% (n=53) were F.
In 71.7% (n=71) CE was performed according to BSG guidelines: 38.4% (n=38) Hb not restored with iron therapy and 33.3% (n=33) Hb restored but not maintained. In the remaining 28.3% (n=28) CE was performed out with BSG guidelines: 14.1% (n=14) Hb restored and maintained, 7.1% (n=7) Hb checked once and was restored but not checked again to determine if maintained and in 8.1% (n=8) no bloods were checked after initial blood tests before CE.
46 studies had positive SB findings giving a DY of 46.5%. Findings were angiodysplasia 23.2% (n=23), inflammation/ulceration/stricture 15.2% (n=15), angiodysplasia and inflammation 3% (n=3), active bleeding 2% (n=2), polyp/mass 2% (n=2) and blunted villi 1% (n=1). In addition to this, 12 studies had significant findings outside the SB giving a DY of 12.1% and an overall DY of 58.6%.
Overall DY was higher when CE was performed in accordance with BSG guidelines [64.8% (46/71) versus 42.9% (12/28) (p=0.07)].
CONCLUSION: Adherence to BSG guidelines for use of CE in IDA was 71.7%. Overall DY was high at 58.6% but improved to 64.8% when guidelines were adhered to.
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Disclosure of Interest: None declared

OP218 SMALL BOWEL CAPSULE ENDOSCOPY IN CLINICAL PRACTICE: PROSPECTIVE DATA FROM A REGIONAL REGISTRY 2011-2013 (REGISTRO LOMBARDO DELLE COMPLICANZE)

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INTRODUCTION: Data on small bowel capsule endoscopy (SBCE) mostly come from retrospective studies
AIMS & METHODS: The primary outcome was to prospectively describe the extent of use, indications, results, complications, and practical issues of SBCE in clinical practice. The secondary outcome was to compare the distribution of the VCE in the different districts of the region.All the 32 centers performing capsule endoscopy in Lombardia region were invited and agreed to participate in the data collection. In January 2011 a dedicated registry has been set up to collect data on diagnostic yield, practical issues and complications for each performed procedure. Each center was asked to update the registry every three months.
RESULTS: Between January 2011 and December 2013, 93.7% (30/32) centers accessed the registry, recording 3191 procedures. The main indications for SBCE were: obscure gastrointestinal bleeding (OGIB) / unexplained anemia 76.1%, suspected Crohn's disease 4.5%, known Crohn's disease 1.0%, chronic diarrhea 3,0%, suspected small bowel tumor 1.5%, others 13.9%. Overall, SBCE was positive in 48.2 % of patients, negative in 41.8% and undefined in 10.0%. In 37.0% of the cases SBCE was performed as an inpatient procedure, 61.9% as an outpatient procedure and in 1.1% in a "day hospital" setting. Patients who performed the VCE as outpatients were younger: mean 60.2±17.2 vs. 65.9±17.3 yrs respectively ($p<0.001$), whereas there was no difference for gender, indications, results and prescriber. 86.7% of patients were evaluated directly by the physician at his own medical center before performing the VCE, 10 .7% came from other hospitals and only 2.6% directly from the general practitioner. Of 3191 patients, 27 (0.84%) experienced capsule complications; 18 (0.56%) of them required endoscopic or surgical retrieval. Acute obstruction occurred in 5 (0.15%) patients. The distribution of the centers and activity of VCE is however not homogeneous in 11 district of Lombardia.
CONCLUSION: Our prospective data confirm that OGIB is still the leading indication for SBCE. VCE is a safe outpatient procedure, usually performed by local district hospitals. Its distribution among the regional district is however not homogeneous.
Disclosure of Interest: None declared

OP219 IRON DEFICIENCY ANEMIA DESPITE EFFECTIVE GLUTEN-FREE DIET IN CELIAC DISEASE: DIAGNOSTIC ROLE OF VIDEO-CAPSULE ENDOSCOPY

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INTRODUCTION: Iron deficiency anemia (IDA) is frequently associated with celiac disease (CD). Although gluten free diet (GFD) and adequate oral or parenteral iron supplementation is an efficient treatment for IDA, iron deficiency remains a relatively frequent finding during follow-up and it is usually correlated to both clinical and serological lack of response to GFD. Little is known on patients with persistent IDA despite effective GFD treatment, a finding observed in approximately 8% of patients[1].
AIMS & METHODS: To evaluate the role of video-capsule endoscopy (VCE) in CD patients with IDA non-responsive to adequate GFD.
We evaluated consecutive patients affected by CD undergoing GFD for at least 24 months with persistent concomitant IDA. All patients were assessed for IgG and IgA transglutaminase (t-TG) and endomysium (EMA) antibodies and, if negative, underwent complete endoscopic evaluation.
RESULTS: We evaluated 32 consecutive female patients (mean age 43.1±8.9 years) on GFD for a mean of 6.2±4.9 years and concomitant IDA with negative antibody work-up. Six were excluded for gynecological disorders or major recent surgery. None of the patients presented signs of overt gastrointestinal bleeding. Twenty six patients were eventually included in the study and underwent gastroscopy, colonoscopy and VCE. Altogether, eleven patients resulted positive at endoscopy. Gastroscopy showed mucosal lesions potentially causing anemia in seven (27%): erosive duodenitis (n=1), active CD (n=3), erosive gastritis (n=2), esophagitis (n=1). Colonoscopy showed only 2 potentially associated finding (hemorrhoids). At VCE we documented small bowel involvement in 6 cases (23%): 3 erosive jejunitis (1 eventually diagnosed as refractory CD, 2 Crohn's disease), 2 jejunal teleangectasias, 1 diffuse jejunal lymphangectasia. Some overlap was observed between endoscopic procedures since in four subjects EGDS and VCE produced significant findings. However, in three cases VCE was successful in unraveling a more severe/extensive disease that could not have been picked up or correctly assessed by gastroscopy. Low albumin levels were significantly associated with a positive outcome at VCE in celiac disease ($p<0.009$). No correlation was found for vitamin B12, vitamin D, folate, or transferrin serum levels.
CONCLUSION: VCE allows the identification of significant clinical findings in approximately 23% of CD patients with IDA despite adequate GFD. These are associated to hypoalbuminemia, indicating their occurrence at more severe stages of the disease.
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Disclosure of Interest: None declared

OP220 BULGES ON SMALL BOWEL CAPSULE ENDOSCOPY: INNOCENT LESIONS WE SHOULD TAKE WITH A PINCH OF SPICE

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INTRODUCTION: A drawback of Small Bowel Capsule Endoscopy (SBCE) is represented by the difficulty to distinguish submucosal masses from innocent bulges, in particular when alarm signs are lacking (e.g. bleeding, irregular surface, polyp-like appearance). A correct interpretation of the endoscopic images is necessary in order to avoid patients unnecessary investigations.
AIMS & METHODS: Aims of our study were 1. to evaluate prospectively the prevalence of bulges on SBCE and 2. to discriminate innocent bulges from submucosal tumours with a previous validate score (SPICE[a]) in a large cohort of

patients referred to a teaching hospital. Consecutive patients undergoing SBCE from January 2010 to December 2013 were considered eligible. All SBCE data were analysed by expert readers (> 200 SBCE analysed). Patients with a protruding lesion as the main finding of SBCE were included and the SPICE score applied. All these patients were either investigated by Computed Tomography Enterography or Magnetic Resonance Enterography and clinically followed-up in the long period.

RESULTS: 640 consecutive patients (male/female 330/310, median age 55) underwent SBCE between January 2010 and December 2013. Patients had a median follow-up period of 26 monthes (range 4-48). 30 patients (4.7%) showed at least one bulging area without alarm signs. Out of them three patients (10%) had a SPICE score > 2 and in 2 a neoplastic lesion was diagnosed (1 carcinoid and 1 ovarian cancer). Among the 27 patients with a SPICE score < 2, seven (26%) had peritoneal adhesions whereas in 20 (74%) all investigations showed normal findings.

CONCLUSION: Bulges represent a rare finding (4.7%) when SBCE is evaluated by experienced physicians. SPICE score can predict the presence of malignant lesion and identify low risk patients in whom further invasive investigations can be avoided. Indeed, in our large cohort 2/3 of suspected lesions were eventually diagnosed as innocent bulges.

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Disclosure of Interest: None declared

OP221 CORRELATION BETWEEN FAECAL CALPROTECTIN AND LEWIS SCORE IN SMALL-BOWEL CAPSULE ENDOSCOPY; A MULTICENTRE STUDY

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INTRODUCTION: Faecal calprotectin (FC) remains an invaluable, non-invasive biomarker of gut inflammation. Small-bowel capsule endoscopy (SBCE) is a prime imaging modality for the small-bowel. The Lewis score (LS) has been developed to standardize inflammation reporting of in SBCE. Previously, we showed that LS shows only moderate correlation with FC levels, although this seems to improve for FC levels $<100\mu g/g$.[1]

AIMS & METHODS: To check the validity of the above observation across other SBCE centres. Retrospective study; 6 centres (5 university hospitals and 1 district general hospital), offering SBCE, in Canada, Finland, Israel, Sweden, and UK; 2 SBCE systems (PillCam®SB; Given®Imaging Ltd, Israel and MiroCam®; IntroMedic Co, Seoul, Korea) and 2 types of FC assays (quantitative and semi-quantitative). An interval of >3 months between FC measurement and SBCE was considered exclusion criterion. Spearman's rank correlation coefficient (r_s) was employed as non-parametric measure of statistical dependence between two variables. A two-tailed *P* value of <0.05 was considered statistically significant.

RESULTS: In the aforementioned period, a total of 333 SBCE have been performed fulfilling the inclusion criteria. Of those, 283 were 'attached' to an ELISA quantitative estimation of FC and the remainder to semi-quantitative assays. In the former group, by convention, FC levels below the detection threshold (i.e. undetectable) were considered as 0. The mean FC, LS and the time interval between FC measurement and SBCE was 100.36 ±190.67 $\mu g/g$, 435.96 ±970, and 28.3 ±39.3 days, respectively. In this subgroup, the correlation between FC and LS was only moderate (r_s=0.385), as previously showed [1].

Although 2 different SBCE systems were used (PillCam®SB: 132 and MiroCam®: 151), there was no statistically significant difference between FC levels (100.37 ±191.24 $\mu g/g$ *vs* 90.71 ±166.1 $\mu g/g$; *P*=0.649), time interval between FC/LS (28.4 ±39.4 days *vs* 20.63 ±29.5 days; P=0.059), prokinetic (P=0.547) or bowel prep used (P=0.717). Eventually, no LS/FC correlation difference was recorded between the 2 SBCE systems, despite the fact that LS calculator is only available in the proprietary review software from Given®Imaging Ltd, (P=0.1188). In the group of semi-quantitative FC measurement (n=50), the interval between SBCE and FC was 40.1 ±58.4 days (i.e. not different to the quantitative FC group; P=0.07) and the r_s between LS and FC was 0.092, P=0.126.

When the 2 FC thresholds of 100 $\mu g/g$ and 250 $\mu g/g$ where used, irrespective of FC assay, no difference in the time interval between FC and LS was noted (P=0.945), while the r_s between FC and LS for the 2 threshold levels was 0.247 and 0.337, respectively (P=0.307).

CONCLUSION: This multicentre study confirms that LS low to moderate correlation with FC levels.

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OP222 ASSESSMENT OF THE PERFORMANCE OF THE COLONIC PILLCAM PCCE-2 IN PATIENTS WITH ACTIVE COLONIC CROHN'S DISEASE: A PILOT STUDY

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INTRODUCTION: Treatment goals in Crohn's disease (CD) have evolved in recent years from symptom control to mucosal healing, usually visualized by optical ileocolonoscopy. The Pillcam colon capsule endoscope (PCCE-2, Given Imaging, Israel), an ingestible capsule equipped with a video camera at both ends, was designed for visualization of the colon. This multicenter pilot exploratory study was designed to investigate and validate the value of the PCCE-2 in patients with active CD.

AIMS & METHODS: A cohort of 39 patients with active CD was prospectively studied with serial PCCE-2 and optical colonoscopy. The primary aim of the study was to compare the assessment of CD activity using the PCCE-2 with colonoscopy, which was used as the gold-standard technique.

Inclusion criteria: patients with a CDAI > 200, an elevated serum CRP (> 5 mg/L) and faecal calprotectin (FC > 200 µg/g) in whom a colonoscopy was clinically indicated and with prior documentation of involvement of at least 2 colonic segments by CD. Exclusion criteria: any contraindication for optical colonoscopy or colon capsule examination. Evaluation: CDEIS & SES-CD, serum CRP & FC levels, CDAI, PCCE-2 passage time and side effects. Independent investigators reviewed recordings of colonoscopy and PCCE-2 procedures. Statistics: Pearson's correlation coefficient was used to calculate correlations.

RESULTS: Thirty-nine patients were enrolled with ages ranging from 18 to 60 years. The mean baseline CDAI was 292 (+/- 94); serum CRP 51 (+/- 76) mg/L; FC 1201 (+/- 725) $\mu g/g$. The average capsule passage time through the entire gastrointestinal tract was 7:11 (+/- 5:52) hours. In 65% of the cases, the capsule was expelled from the rectum in less than 6 hours. No episodes of capsule retention were reported.

The mean CDEIS and SES-CD were 8.0 (+/- 5.6) and 10.9 (+/- 7.1) for PCCE-2, and 11.0 (+/- 7.0) and 15.9 (+/- 9.5) for colonoscopy, respectively. A strong correlation was found between the two techniques when assessing CDEIS (Pearson = 0.75, p = 0.01) and a moderate correlation was found for SES-CD (Pearson = 0.65, p = 0.01).

	PCCE-2: CDEIS	PCCE2: SES-CD	Colonoscopy: CDEIS	Colonoscopy: SES-CD
PCCE-2:CDEIS	1	.904**	.749**	.704**
PCCE-2:SES-CD		1	.653**	.648**
Colonoscopy:CDEIS			1	.929**
Colonoscopy:SES-CD				1

Table 1: Showing Pearson's correlation coefficients for the techniques used to assess CD activity.

When comparing the PCCE-2 scores with CDAI and CRP measurements, a poor correlation was seen. FC measurements showed slightly better correlation with PCCE-2 CDEIS but the correlation remained weak and did not reach statistical significance (Pearson 0.27, p = 0.11).

CONCLUSION: This pilot study comparing PCCE-2 to standard colonoscopy in patients with active colonic CD has shown a strong correlation for assessing CDEIS and moderate correlation for SES-CD. No capsule retention was observed. The present data should encourage further large trials to confirm the utility of PCCE-2 in assessing colonic CD activity.

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TUESDAY, OCTOBER 21, 2014 14:00–15:30

FROM RISK STRATIFICATION TO ABLATION IN BARRETT'S OESOPHAGUS – HALL 0

OP223 IMPACT OF SURVEILLANCE FOR BARRETT'S ESOPHAGUS ON SURVIVAL OF PATIENTS WITH NEOPLASTIC PROGRESSION: RESULTS OF A LARGE MULTICENTER PROSPECTIVE COHORT STUDY

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INTRODUCTION: Surveillance is recommended for Barrett's esophagus (BE) to detect esophageal adenocarcinoma (EAC) at an early stage. However, the value of BE surveillance is under discussion given the overall low incidence of neoplastic progression, large screening base, and lack of discriminative tests for risk stratification.
AIMS & METHODS: The aim of this study was to evaluate the impact of BE surveillance on the survival of patients with neoplastic progression. 783 patients with BE of at least two centimeter were included in a multicenter prospective cohort study and followed during surveillance according to the ACG guidelines. Incident cases of high-grade dysplasia (HGD) and EAC were identified during follow-up. Patients with neoplastic progression were treated with intensive surveillance or endoscopic treatment for HGD or early EAC, and esophagectomy for advanced EAC. Survival data were collected for all patients in the study, cross-checked using death and municipal registries and compared to survival data from patients with EAC in the general population based on data from the Dutch cancer registry. Information on cause of death was obtained from the general practitioner or gastroenterologist and was compared to cause of death in age and gender matched controls in the general population based on data from the Dutch central statistical office. Cox-regression models were used to calculate hazard ratio's (HR) and 95% confidence intervals (CI).
RESULTS: During follow-up 53 patients developed HGD or EAC with an incidence rate of 1.2 per 100 person-years. Thirty-five patients (66%) were classified as stage 0 disease, 14 (26%) as stage 1, and 4 (8%) as stage 2. EAC was diagnosed at a significantly earlier stage during BE surveillance than in the general population ($P<0.001$). The survival of BE patients with neoplastic progression during surveillance was worse than those of BE patients without neoplastic progression during surveillance (HR 2.98, 95% CI 1.62-5.50), better than those of patients with EAC in the general population (HR 0.16, 95% CI 0.09-0.29), and comparable to those of patients with stage 0 or stage 1 EAC in the general population. The overall 5-year survival was 74% in BE patients with neoplastic progression during surveillance, 94% in BE patients without neoplastic progression during surveillance and 17% in patients with EAC in the general population. The majority of BE patients died due to malignancies (36%) or cardiovascular diseases (29%). Four percent of BE patients died due to EAC. The cause of death for BE patients was comparable to those of age and gender matched controls in the general population.
CONCLUSION: BE surveillance enables the detection of EAC at an early and curable stage when endoscopic treatment is still feasible. The 5-year overall survival of patients with neoplastic progression during surveillance is 74% which corresponds to the survival of patients with stage 0 or stage 1 EAC in the general population.
Disclosure of Interest: None declared

OP224 SEX HORMONES AND BARRETT'S OESOPHAGUS - A FUTURE THERAPY OR JUST A HOT FLUSH?

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INTRODUCTION: The presence of Barrett's Oesophagus (BO) and subsequent development of Oesophageal Adenocarcinoma (OA) is up to four-times more common in male patients compared to females. The reasons behind this gender difference remain unclear, and whilst hormones have been an attractive area for investigation, the results have been quite variable, probably owing to the multifactorial mechanisms underlying carcinogenesis.
The pro-inflammatory transcription factor, NF-kB has been implicated in a number of infectious and malignant processes. Given that Barrett's Oesophagus arises in an inflammatory environment associated with the reflux of acid and bile, it has not been surprising to note increased NF-kB activity in these tissues during the progression of Barrett's metaplasia through the dysplastic sequence to OA. In-vitro studies have demonstrated activation of NF-kB p65 and nuclear localisation following exposure to bile and acid. In other cell lines, NF-kB has also been demonstrated to be under the influence of hormonal control, both directly as well as through the inhibition of alternate immunomodulatory pathways.
AIMS & METHODS: We aimed to investigate the effects on nuclear localisation of NF-kB p65 following hormone therapy in oesophageal cell lines to attempt to explain the observed gender differences in BO and OA.
We investigated the possible protective effects of 17B-Estradiol on OE33 cell lines through ELISA analysis of activated NF-kB p-65 levels. We subsequently interrogated members of the NF-kB pathway to better understand the mechanisms underlying observed effects using western blotting and RT-PCR of in-vitro treated cells, as well as immunohistochemical staining of endoscopically obtained oesophageal biopsies. Analysis of the effect of estradiol on immortalised normal squamous epithelium HET1A cell line through ELISA analysis as well as Western Blotting was also undertaken.
Finally, the effect of Estrogen blockade through Tamoxifen treatment on the effect on the NF-kB pathway was evaluated.
RESULTS: Pre-incubation with estradiol at physiological concentrations reduces baseline nuclear NF-kB p-65 levels ($p<0.05$). Furthermore, this treatment abrogated the NF-kB inducing effect of deoxycholic acid.
Immunohistochemical staining of endoscopically retrieved biopsies of Barrett's metaplasia, OA and squamous tissue adjacent to cancer revealed that female patients have higher levels of inactive cytoplasmic p-65 than men ($p=0.006$), as well as lower levels of activating pIKK than their male counterparts (non-significant).
Finally, the inhibitor of NF-kB, ikB was significantly increased in both OE33 and HET1A cell lines exposed to Estradiol ($p<0.01$).
CONCLUSION: Given that female patients have higher cytoplasmic p65 levels than males, it is possible that the mechanisms underlying this could be through reduced nuclear localisation following exposure to sex hormones. This is supported by the *in-vitro* demonstration that 17B-Estradiol reduces nuclear p65 levels.
It is plausible therefore that estrogen could have a role in reducing inflammation in the oesophageal mucosa following exposure to noxious chemicals present in refluxate, and this protective effect may be through its activity on the NF-kB pathway.
Disclosure of Interest: None declared

OP225 ACTIVATED METABOLIC PATHWAYS IN BARRETT'S OESOPHAGUS ACCORDING TO BODY COMPOSITION OR BMI AND PROGRESSION TO CANCER

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INTRODUCTION: Barrett's oesophagus (BE) remains the strongest risk factor for oesophageal adenocarcinoma (OAC). Several studies describe an association between BE and obesity through mechanical and metabolic consequences. Visceral fat is a recognised endocrine organ. Adipokines and insulin resistance have an impact on obesity related diseases and cancer pathways.
AIMS & METHODS: In sequential patients (pts), undergoing upper gastrointestinal endoscopy, we assessed BMI, waist-hip ratio (WHR) and presence of metabolic syndrome, to evaluate the correlation between BMI and body composition with metabolic indexes and adipokines in BE compared to controls. A blood sample was obtained to test fasting insulin, glucose, lipids, HbA1c and serum adiponectin and leptin. All pts were classified to overweight, obese and abdominally obese (by WHR). Biopsies were obtained from BE and histological progression to cancer was correlated with metabolic indexes. Chi square, Fisher, t-Student test and logistic analysis were used for comparison.
RESULTS: 480 patients (250 cases; F/M: 193/287; mean age: 58.08±15.51) were enrolled. Insulin levels (10.2 *vs* 7.2μIU/ml; $p=0.001$), Hba1c (5.8 *vs* 5.1%; $p<0.01$), metabolic syndrome (33.2 *vs* 20%; OR 1.95; $p= 0.0017$), insulin resistance (47 *vs* 27%; OR 1.54; $p<0.01$), dyslipidaemia (72.8 *vs* 53.9; OR 2.3; $p<0.0001$) and hypertension (37.4 *vs* 21.3%; OR 2.4; $p<0.001$), were higher in BE compared to controls.
MS was present in 39.7 *vs* 34.2% (OR 3.05; $p<0.001$), 43.7 *vs* 21.9% (OR 5.2; $p<0.001$), 92.1 *vs* 54.9% (OR 8.08; $p<0.0001$), in overweight, obese, abdominal obese pts with BE and controls, respectively.
Insulin resistance was present in 39.2 *vs* 33.8% (OR 1.3; $p<0.05$), 38 *vs* 22.3% (OR 1.7; $p<0.01$) and in 82.5 *vs* 54.5% (OR 1.5; $p<0.001$) in overweight, obese and abdominal obese pts, respectively.
A trend was observed for decreased adiponectin levels in BE *vs* controls while leptin showed no correlation.
In BE pts, the presence of dysplasia was associated with MS (42 *vs* 25%; $p=0.005$) and and insulin resistance (51.4 *vs* 34.0%; $p=0.005$).
CONCLUSION: BE association with dyslipidaemia, insulin resistance, MS and hypertension suggests activation of specific metabolic pathways in pts with altered body composition or BMI. The strongest risk factor is abdominal obesity. Progression to cancer appears modulated by metabolic dysfunction in MS and a carcinogenic insulin pathway.
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Disclosure of Interest: None declared

OP226 OUTCOMES OF ENDOSCOPIC SURVEILLANCE IN BARRETT'S OESOPHAGUS: A POPULATION BASED COHORT STUDY IN THE UK

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INTRODUCTION: The impact of endoscopic surveillance in patients having Barrett's oesophagus (BO) is not clear. We compared oesophageal cancer incidence and mortality in a cohort of patients with BO undergoing surveillance and another of those not being surveyed.
AIMS & METHODS: We used linked UK Clinical Practice Research Datalink, Hospital Episode Statistics, Office of National Statistics Death records, and Cancer Registry Data. We identified cases with Barrett's oesophagus and categorized them as surveyed or not surveyed based on subsequent endoscopic examination(s) starting at least 1 year after Barrett's diagnosis. We estimated oesophageal cancer incidence and mortality as well as all cause mortality after excluding the first year of follow-up and compared them in the two groups. Cox proportional hazard regression models were used to estimate hazard ratios and their 95% confidence intervals.
RESULTS: In total 15704 subjects with Barrett's oesophagus were identified of which 3499 were surveyed. Mean ages were 61 and 65 in those surveyed and not surveyed respectively. While risk of occurrence of oesophageal cancer (HR=3.89 95%CI 1.91-7.92) and oesophageal adenocarcinoma (HR=4.04 95%CI 1.88-8.70) in those undergoing surveillance was four times higher compared with those not being surveyed after adjusting for age, sex, smoking, alcohol and BMI, their risk of death due to oesophageal cancer showed only a 26% non-significant excess (HR=1.26 95%CI 0.68-2.36) and their risk of death due to all causes was significantly lower (HR=0.81 95%CI 0.68-0.98).
CONCLUSION: At present less than a quarter of those with BO in the UK are surveyed. Those who are surveyed have a lower risk of death overall, suggesting a rational targeting of surveillance resources. If the increased incidence of carcinoma in the surveyed is real (rather than just representing earlier diagnosis due to surveillance) then the far lower excess of death than occurrence might suggest surveillance is of benefit.
Disclosure of Interest: None declared

OP227 SOX2 AS A NOVEL MARKER TO PREDICT NEOPLASTIC PROGRESSION IN BARRETT'S OESOPHAGUS

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INTRODUCTION: The value of surveillance for patients with Barrett's oesophagus (BO) based on histological diagnosis of low-grade dysplasia (LGD) remains debated given the lack of discriminative power to stratify BO patients at high risk for neoplastic progression of those at low risk. The use of biomarkers in addition to histological assessment improves risk stratification and has the potential to improve cost-effectiveness of BO surveillance. SOX2 plays a pivotal role in the development of oesophageal and gastric epithelium and is down regulated in intestinal metaplasia and gastric cancer.
AIMS & METHODS: The aim of this study was to investigate the value of SOX2 in BO patients to predict neoplastic progression and to combine the results with our previously reported p53 immunohistochemical data within the same. We conducted a case-control study within a large prospective cohort of 720 BO patients, with a total follow-up time of more than 5600 years. In total 44 BO patients with neoplastic progression defined as development of high-grade dysplasia (HGD) or oesophageal adenocarcinoma (OAC)(cases) and 44 BO patients without neoplastic progression (controls) were selected and matched for age and gender. SOX2 protein was detected by immunohistochemistry in more than 3000 biopsies and was scored independently by two investigators blinded for long-term outcome. The results were combined with p53 immunohistochemical data. Hazard ratios (HRs) were calculated by Cox-regression models adjusted for age, gender, BE length and esophagitis.
RESULTS: Normal BO epithelium showed homogeneous strong nuclear expression of SOX2, while expression of SOX2 was progressively lost in dysplastic epithelial cells. Loss of SOX2 expression was seen in 9% of biopsy series without dysplasia, in contrast to 37% of biopsy series with LGD and 70% of biopsy series with HGD or OAC. Multivariate analysis showed that loss of SOX2 expression (HR 2.3; 95% CI:1.1-4.6) and aberrant p53 expression (HR 3.7; 95% CI:1.8-7.8) were independent predictors for neoplastic progression (multiplied HR of 8.5), whereas presence of LGD was no longer predictive. The positive predictive value for neoplastic progression increased from 47% with histological diagnosis of LGD, to 83% with LGD and concurrent aberrant SOX2 expression, to 87% with LGD and concurrent aberrant p53 expression and to 91% with aberrant SOX2 and p53 expression.
CONCLUSION: SOX2 is lost during transition from non-dysplastic BO to HGD/OAC. Loss of SOX2 and aberrant p53 expression are independent predictors for neoplastic progression in patients with BO and more powerful than the histological diagnosis of LGD. SOX2 and p53 immunohistochemistry may be useful as a discriminative test to improve risk stratification of Barrett surveillance.
Disclosure of Interest: None declared

OP228 THE SURF TRIAL PRE-ASSESSMENT COHORT: SPATIAL EXTENT OF LOW-GRADE DYSPLASIA AND EXTENT OF AGREEMENT BETWEEN EXPERT PATHOLOGISTS ARE ASSOCIATED WITH RISK OF MALIGNANT PROGRESSION

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INTRODUCTION: Low-grade dysplasia (LGD) in Barrett's oesophagus (BO) is an accepted risk factor for progression to high-grade dysplasia (HGD) or oesophageal adenocarcinoma (OAC). However, the diagnosis of LGD is subjective and it is unclear which additional factors can help identify LGD patients at increased risk of progression. For the purpose of this study, all patients screened for the SURF trial were separately reviewed by 3 expert pathologists. The SURF trial is a randomized study showing that prophylactic ablation of BO with confirmed LGD reduces progression to HGD/OAC.[1]
AIMS & METHODS: We aim to investigate predictors of malignant progression in BO patients diagnosed with LGD. 234 LGD patients (78% male; mean 63 years ±10.7) underwent histology review by 3 expert pathologists, who separately evaluated each available level of biopsies from the BO segment. Confirmed LGD was defined as a majority diagnosis from the expert pathologists. Primary outcome was neoplastic progression (HGD/OAC) during endoscopic follow-up (FU). Median duration of FU was 41 months (IQR 22-61). Cox regression analysis was performed on the risk of malignant progression.
RESULTS: 36/61 patients (59%) with confirmed LGD at baseline developed HGD/OAC. 10/173 patients (6%) who were downstaged at baseline to non-dysplastic BO (NDBO) demonstrated malignant progression. The hazard ratio (HR) for baseline confirmed LGD was 15.1 (95% CI 7.4-30.5). The number of expert pathologists confirming the presence of LGD and the number of levels within the BO segment with confirmed LGD predicted progression, as shown in the table below.

		No of events	Hazard ratio (95% CI)
Pathologists confirming LGD:	None	4.1% (5/122)	-
	1/3	9.8% (5/51)	2.6 (0.77-9.14)
	2/3	51.5% (17/33)	17.4 (6.39-47.24)
	3/3	67.9% (19/28)	28.6 (10.60-77.29)
Extent of LGD*:	No LGD	5.8% (10/173)	-
	1 level LGD	58.3% (21/36)	13.8 (6.49-29.39)
	2 levels LGD	50% (5/10)	14.6 (4.90-43.52)
	3 levels LGD	83.3% (5/6)	26.4 (8.84-78.98)

15/173 patients who were downstaged to NDBO at baseline developed confirmed LGD at a subsequent FU endoscopy, of whom 5 patients had malignant progression. Time-dependent Cox regression yielded a HR of 20.8 (95% CI 8.80-49.07) for occurrence of confirmed LGD at any time during follow-up.
CONCLUSION: A consensus LGD diagnosis is the most important predictor of malignant progression. Multilevel LGD and extent of agreement between expert pathologists were strongly associated with risk of HGD/OAC. These characteristics might help select BO patients with LGD for prophylactic ablation therapy.
REFERENCES
1. Phoa et al. *JAMA* 2014; 311: 1209-1217.
Disclosure of Interest: L. Duits: None declared, K. Phoa: None declared, T. Pham: None declared, F. Ten Kate: None declared, C. Seldenrijk: None declared, G. Offerhaus: None declared, M. Visser: None declared, S. Meijer: None declared, K. Krishnadath: None declared, R. Mallant-Hent: None declared, J. Tijssen: None declared, J. Bergman Financial support for research from: Covedien GI Solutions

TUESDAY, OCTOBER 21, 2014 14:00-15:30
CHALLENGES IN THE TREATMENT OF PANCREATIC AND BILIARY TRACT CANCER – LOUNGE 5

OP229 CLINICOPATHOLOGICAL CHARACTERISTICS OF PANCREATIC RESECTION SPECIMENS OF INHERITED/ FAMILIAL VERSUS SPORADIC PANCREATIC DUCTAL ADENOCARCINOMA

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INTRODUCTION: There is a growing interest towards pancreatic cancer screening in individuals with an increased inherited or familial risk for this disease. When designing screening programs aiming to identify high-risk lesions for early resection, knowledge of the pathology of the disease is essential. In this current study we focus on the clinicopathological characteristics of pancreatic resection specimens of patients with inherited or familial pancreatic cancer in comparison to sporadic cases.
AIMS & METHODS: Pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) were quantified in surgical

resection specimens of patients with inherited/familial pancreatic cancer and patients with sporadic pancreatic cancer. Inherited/familial pancreatic cancer was defined as patients with at least one first degree relative with pancreatic cancer and/or carriers of a pancreatic cancer prone gene mutation.
RESULTS: Pancreatectomy specimens were evaluated from 16 patients with inherited/familial PDAC (mean age 63, SD 8.9) and 19 patients with sporadic PDAC (mean age 69, SD 8.9). PanIN lesions were the most common precursor lesions for both groups, IPMNs were seldom detected. A significant difference was observed in the mean number of precursor lesions (9.3 vs. 2.7, p=0.04). The number of patients in whom at least two high-grade precursors were detected was significantly higher in the inherited/familial group. More patients within the inherited/familial group had PanIN-3 lesions and the number of PanIN-3 lesions found in these patients was significantly higher compared to the sporadic group. Furthermore, in significantly more patients within this group multiple PanIN lesions were detected.
CONCLUSION: This study shows that the number of high-grade PanIN-lesions in patients with inherited or familial PC are higher than in patients with sporadic PC. These high-grade precursor lesions are an important target for screening and surveillance of high-risk individuals for which the most suitable test has yet to be identified.
Disclosure of Interest: None declared

OP230 EXPLORING THE EFFECTS OF FACTORS ASSOCIATED WITH THE OUTCOME OF PANCREATIC CANCER SCREENING IN HIGH-RISK INDIVIDUALS

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INTRODUCTION: There are several disease-related aspects of pancreatic cancer (PC) that indicate that screening for this cancer type among high-risk individuals (HRI) could be worthwhile. However, we currently lack scientific evidence to recommend screening for PC in HRI outside research protocols. By using an established simulation model, we aimed to analyse which parameters have the highest impact when estimating the effects of a pancreatic cancer screening program.
AIMS & METHODS: The Microsimulation Screening Analysis (MISCAN) model (Habbema JD, 1985) was used. The majority of the model assumptions were based on the recommendations as stated in the consensus paper of the international Cancer of the Pancreas Screening (CAPS)-consortium (Canto MI, 2013). By performing sensitivity analyses we explored which parameters had the highest impact on the effects of screening.
RESULTS: The mortality reduction (MR) was 35% and 58% (436 and 722 cases per 10,000 persons) for 5 yearly and annual screening, respectively. In the base case situation for 5 yearly screening, the number needed to screen (NNS) was 117.1 and number needed to treat (NNT) was 2.5 to prevent one cancer death. The NNT was lowest in case all screen positives with preinvasive stage 3 or cancer are treated (2.4, MR 32%). If only persons are treated who are already in an (early) invasive stage of disease, the NNT was 5.3 (MR 10%). Results were sensitive for PDAC risk (risk doubled: NNS 64.3, NNT 2.7, MR 38%) and duration of the preclinical stage of the disease (increased to 30 years: NNS 92.6, NNT 3.2, MR 46%). Results were less sensitive for test characteristics.
CONCLUSION: By building a comprehensive microsimulation model, we identified which parameters potentially have the highest impact on the outcome of a PC screening program. FU strategy of screen positives and duration of the preclinical stage are important as is inclusion of patient populations that are exposed to a certain risk to develop PC. To identify these risk groups and to assess their risk level, more epidemiological research needs to be done. The true effect of the PC surveillance including the impact of various FU strategies can only be derived from clinical trials with long term follow up. The present study provides some guidance as to which choices could be made.
Disclosure of Interest: None declared

OP231 REPEATED PANCREATIC SURVEILLANCE IN HIGH RISK INDIVIDUALS FOR PANCREATIC CANCER: THE PSYCHOLOGICAL BURDEN

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INTRODUCTION: Pancreatic cancer (PC) is one of the most fatal human malignancies with a median survival of <6 months. There is great interest in PC surveillance for high risk individuals to detect PC or precursor lesions in an earlier, potentially curable stage. Studies assessing the feasibility of such PC surveillance programs have, however, not addressed the psychological burden for participants. The aim of this ongoing, prospective study is therefore to evaluate the psychological burden of repeated pancreatic surveillance of individuals at genetically high risk to develop PC.
AIMS & METHODS: Individuals with a lifetime risk of developing PC>10%, who are offered yearly pancreatic surveillance with MRI and endoscopic ultrasound (EUS) in a Dutch ongoing prospective multicenter cohort study (FPC-study), were invited to complete a questionnaire each year to assess their experience with MRI and EUS, and their psychological distress (assessed with the Cancer Worry Scale (CWS) and the Hospital Anxiety and Depression Scale (HADS)). The questionnaires were sent after intake for participation but before the first MRI and EUS (T1), after the first MRI and EUS (T2), and after the MRI and EUS one (T3), two (T4) and three years (T5) after initial intake.
RESULTS: A total of 477 out of 512 questionnaires were returned (93%) by 141 participants: 36, 69, 128, 108, 85 and 51 T0, T1, T2, T3, T4 and T5 questionnaires respectively. The mean age of participants was 52 years. An average of 90% experienced the MRI as 'not' or 'a little' burdensome (86%, 92%, 90% and 94% at T2, T3, T4 and T5 respectively) versus an average of 89% in case of an EUS (91%, 94%, 95% and 94% at T2, T3, T4 and T5 respectively). Prior to the first MRI and EUS (T1), 34% of individuals dreaded the EUS while only 3% of individuals dreaded the MRI. However, after their first MRI and EUS, the percentage of individuals dreading their next EUS decreased significantly to 5-9% (T2-T5); the percentage of individuals dreading a next MRI remained stable (0-8%, T2-T5). The mean CWS-score (13) remained stable and low as surveillance progressed. An average of 7% showed clinical relevant anxiety levels (HADS-A-score ≥11) and an average of 5% clinical relevant depression levels (HADS-D-score ≥11).
CONCLUSION: The psychological burden of repeated pancreatic surveillance seems tolerable with an average of 90% of high risk individuals experiencing no or little burden of the yearly MRI and EUS. Participants also have few worries about cancer and the percentage of individuals with clinical relevant levels of anxiety and depression is comparable to that of the general population. Therefore, from a psychological point of view, yearly pancreatic surveillance of high risk individuals seems feasible.
Disclosure of Interest: None declared

OP232 EFFICACY OF NEOADJUVANT THERAPY IN BORDERLINE RESECTABLE PANCREATIC CANCER WITH ABUTMENT OF THE SUPERIOR MESENTERIC ARTERY

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INTRODUCTION: Neoadjuvant therapy may be beneficial for patients with borderline resectable pancreatic cancer (BRPC) due to selection of the patients likely to experience the most favorable surgical outcome. Such selection excludes patients who develop distant metastasis during treatment, precludes delayed postoperative adjuvant therapy that results from surgical complication or delayed recovery, and reduces the risk of margin-positive resection. Until now, few reports have demonstrated that the outcome of patients with BRPC treated with neoadjuvant therapy was directly comparable to that of patients with BRPC who initially underwent resection without neoadjuvant therapy. In actuality, patients with severe superior mesenteric-portal vein (SMPV) impingement or occlusion of the short segment, defined as one of the criteria of BRPC, initially have undergone resection with considerable frequency. The aim of this study was to compare the outcome of patients with BRPC treated with and without neoadjuvant therapy.
AIMS & METHODS: We retrospectively reviewed 27 patients with BRPC, according to the National Comprehensive Cancer Network (NCCN) classification system, who underwent resection with or without neoadjuvant therapy, and 53 patients with locally advanced but resectable pancreatic cancer (LAPC) who initially underwent resection between 2001 and 2012. We divided the patients with BRPC into three groups: 1) the patients with severe SMPV impingement or occlusion of the short segment, pathologically confirmed as invasion, treated without neoadjuvant therapy (BRPC-P(-); n=10); 2) the patients with superior mesenteric artery (SMA) abutment <180 degrees, treated without neoadjuvant therapy (BRPC-S(-); n=9); and 3) the patients with SMA abutment <180 degrees, treated with neoadjuvant therapy (BRPC-S(+); n=8). We evaluated the outcome of these three groups, and that of the LAPC patients.
RESULTS: The R0 resection rates were 50% in the BRPC-P(-) group, 56% in the BRPC-S(-) group, and 88% in the BRPC-S(+) group. Although the R0 resection rate of the BRPC-S(+) group was higher than that of the other two groups, the difference was not statistically significant. The median overall survival in the BRPC-S(+) group was 52 months, which was significantly better than that of the BRPC-S(-) (27 months, P=0.0345) and BRPC-P(-) (8 months, P=0.0192) groups.
The LAPC group had a significantly more favorable median overall survival compared with the BRPC-P(-) group (29 months and 8 months, respectively, P=0.0345).
CONCLUSION: BRPC patients with SMA abutment should be treated with neoadjuvant chemotherapy. When SMPV invasion is very suspicious, such as radiological findings of SMPV deformity or occlusion, initial resection may be avoided.
Disclosure of Interest: None declared

OP233 SECOND-LINE CHEMOTHERAPY FOR ADVANCED BILIARY TRACT CANCER AFTER FAILURE OF GEMCITABINE PLUS PLATINUM: RESULTS OF AN AGEO MULTICENTER RETROSPECTIVE STUDY

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INTRODUCTION: First-line chemotherapy (CT1) with the combination of gemcitabine + platinum has become a new standard in advanced biliary tract cancer (ABTC) but data on second-line CT (CT2) are lacking. The aim of this study was to evaluate the efficacy and tolerability of CT2 in patients with ABTC who received gemcitabine-platinum in CT1.
AIMS & METHODS: We retrospectively reviewed data of consecutive patients who received CT2 for ABTC after failure to gemcitabine-platinum in 17 French institutions from November 2002 to December 2013. Progression-free survival (PFS) and overall survival (OS) were estimated from the start of L2 CT using Kaplan Meier method. Cox models were applied for multivariate analyses.
RESULTS: Among 603 patients who were treated by gemcitabine-platinum in CT1, 196 patients (median age, 63 years, range: 28-82; male, 51.5 %) received a CT2. CT1 included gemcitabine + cisplatin (7%) or oxaliplatin (93%), with a median PFS of 9.7 months and an ORR of 31%. Characteristics at the beginning of CT2 were: metastatic disease, 94%; 1-2 metastatic sites, 68%; ECOG PS 0-1, 68%. CT2 CT was 5FU-irinotecan (n=62), 5FU-oxaliplatin (n=17), 5FU-cisplatin (n=37), 5FU/capecitabine (CAP) (n=39) or other various regimens (n=41). Among the 186 evaluable patients, there were 22 partial response (12%) and 70 stable disease (38%). After a median follow-up of 26.4 months, median PFS and OS were 3.2 and 6.7 months respectively. There was no significant difference between CT regimens in terms of PFS (5FU-irinotecan, 2.6 months; 5FU-oxaliplatin/5FU-cisplatine, 4.0 months; 5FU/CAP, 3.2 months and others, 3.7 months; p=0,27) and OS (6.0 months, 6.3 months, 5.6 months and 9.7 months respectively; p=0.27). There was no significant difference between 5FU/CAP monotherapy and 5FU-based doublet chemotherapy (5FU-irinotecan, 5FU-cisplatin and 5FU-oxaliplatin), in terms of PFS (3,0 months and 3,3 months; p=0,91) and OS (5,6 months and 6,3 months; p=0,93). In multivariate analysis, PS 2-3, bilirubine > 17 µmol/L and CA19.9 > 400 UI/mL were significantly associated with a shorter PFS while PS 2-3, CA19.9 > 400 UI/mL and non-response to CT1 with a shorter OS. A grade 3-4 toxicity was observed in 32% of patients (neutropenia, 33%; diarrhea, 17%) and a toxic death occurred in 1.4% of patients.
CONCLUSION: CT2 is associated with a disease control in a half of patients with ABTC who received gem-platinum in CT1. Nevertheless, the short median PFS observed in this study should encourage the evaluation of new treatments in patients with good clinical conditions and an adequate biliary drainage.
Disclosure of Interest: None declared

OP234 TEMOPORFIN PHOTODYNAMIC THERAPY IN LOCALLY ADVANCED BILIARY TRACT CARCINOMA: A MULTICENTER PROSPECTIVE PHASE II STUDY

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INTRODUCTION: Photodynamic therapy using porfimer (P-PDT) is established local tumor ablative therapy in non-resectable hilar bile duct cancer (hBDC) improving palliation and survival time. In a pilot trial, temoporfin PDT (T-PDT) showed improved tumoricidal penetration depth, if compared with P-PDT.
AIMS & METHODS: We investigated clinical effectiveness and safety of T-PDT in a single-arm phase II study (NCT01016002; from 2005 to 2011). In respect of previous publications on P-PDT, results were compared concerning OS, local tumor control (TTP), and adverse events (ADE). Twenty-nine patients with unresectable hBDC received median 1.0 (range 1-4) T-PDT plus stenting and were followed up at three-month intervals.
RESULTS: OS after treatment was median 17.3 (12.6 – 22.0, 95% CI) months for 19 patients of category M0, and 15.4 months for all patients (M0 + M1, 11.7-19.1, 95% CI). Median time to local tumor progression was 6.5 months (3.6-9.4, 95% CI). Cholestasis improved significantly in patients with initially elevated bilirubin levels and 74% of patients with occluded segments at baseline showed local response with reopening of median 3.0 segments. A significant improvement of palliation could be achieved (Karnofsky performance status, median +10%, range -20% - +40%). PDT was technically successful in all cases and was generally well tolerated; there was no grade 4 toxicity and no treatment-associated mortality. Adverse events were phototoxic skin reactions (n=9), three late phototoxic skin reactions (at T-injected vein), cholangitis (n=4), and liver abscess (n=1).
CONCLUSION: T-PDT can be delivered safely to patients with biliary tract cancer and shows improved time to treatment patency and prolonged survival compared to P-PDT. It is statistically not inferior to P-PDT concerning improvement of cholestasis and palliation. It is highly tumoricidal and associated with similar rates of infectious complications, but with an elevated rate of skin phototoxicity, which could have been possibly avoided, taking specific precautions.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 14:00–15:30
COLORECTAL CANCER: NOVEL MECHANISMS, NOVEL TARGETS – LOUNGE 6

OP235 ZINC FINGER PROTEIN 545 IS A NOVEL TUMOR SUPPRESSOR THROUGH INHIBITING RIBOSOMAL RNA TRANSCRIPTION IN COLON CANCER

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INTRODUCTION: *Zinc finger protein 545* (*ZNF545*) is a member of Krüppel-associated box containing Zinc-finger proteins.
AIMS & METHODS: We aim to clarify its biological function as a tumor suppressor in colon cancer. ZNF545 methylation was evaluated by bisulfite genomic sequencing. The biological function of ZNF545 was determined by apoptosis and autophagy assays. ZNF545 target pathway was identified by promoter luciferase assay, immunofluorescence, electrophoretic mobility shift assay (EMSA) and co-immunoprecipitation assays.
RESULTS: ZNF545 was silenced or downregulated in all 8 colon cancer cell lines by promoter hypermethylation. Partial and dense promoter methylation of ZNF545 was detected in 41.7% (25/60) of cancer tissues. Restoring ZNF545 expression in colon cancer cell lines induced apoptosis as well as autophagy. These effects were attributed to inhibition of ribosomal RNA (rRNA) transcription. To elucidate the binding sites of ZNF545 on rDNA promoter, two deletion mutants in rDNA promoter were constructed based on pHrD-IRES-Luc construct containing the human rDNA promoter (from -410 to +81). pHrD-IRES-Luc-deletion-1 is from -268 to +81 containing far upstream control element (UCE), UCE and rDNA core promoter element and pHrD-IRES-Luc-deletion-2 is from -172 to +81 containing UCE and rDNA core promoter element. We found that ZNF545 significantly suppressed the promoter transcriptional activity on both rDNA promoter reporter deletion constructs, indicating that the binding site(s) of ZNF545 should be at least present within the minimal rDNA promoter region. To further refine the binding site(s) of ZNF545, EMSA was performed using six overlapping biotinylated DNA probes spanning minimal rDNA promoter region (~60bp). Our results showed that two regions in rDNA promoter exhibited strong binding to Flag-tagged ZNF545 proteins derived from nuclear extracts. One was within the linking region between UCE and core promoter element (from -97 to -62), and the other was located downstream of the transcription start site (from +41 to +78). Bioinformatic analysis demonstrated that ZNF545 protein contains twelve C2H2 zinc fingers arranged in two distinct clusters which are separated by a degenerate zinc finger motif (*Z5*). The first cluster, referred to as Hand1, contains zinc fingers 1 to 4, and the second cluster, in the carboxyl terminus, referred to as Hand2, contains zinc fingers 6 to 13. To explore which part of the multiple adjacent zinc fingers participate in promoter DNA interaction, ZNF545 Hand1 and Hand2 were individually cloned and fused at the N-terminal end to GFP protein or its KRAB domain. Fluorescence microscopy imaging and EMSA assay indicated that both Hand1 and Hand2 were capable of binding to rDNA promoter independently. Luciferase reporter assay demonstrated that transcriptional repression KRAB domain coupled Hand1 and Hand2 still exhibited significant negative influence on rDNA promoter activity, albeit to a lesser extent compared with the full-length ZNF545, suggesting that ZNF545 needed both Hand1 and Hand2 for firmly binding to rDNA promoter for rRNA transcription inhibition. Moreover, KRAB domain of ZNF545 was responsible for recruiting KAP1, a scaffold corepressor for recruiting other co-repressors as evidenced by co-immunoprecipitation.
CONCLUSION: ZNF545 acts as a functional tumor suppressor in colon cancer through inhibiting rRNA transcription.
Disclosure of Interest: None declared

OP236 SEPT9 AND SFRP1 DNA HYPERMETHYLATION IN COLORECTAL CANCER: RESTRICTION TO A SINGLE CPG ISLAND AND EXPANSION TO THE GATEKEEPER MYOFIBROBLASTS

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INTRODUCTION: Several genes are regulated by DNA methylation and the aberrant alteration of this mechanism can lead to cancer formation. Septin 9 (SEPT9) and secreted frizzled-related protein 1 (SFRP1) are known to play role in colorectal cancer, however, the DNA methylation pattern of these genes in the epithelial and stromal cells in colorectal cancer remains unknown.
AIMS & METHODS: Our aim was to analyse DNA methylation patterns in DNA methylation-regulated genes in healthy and diseased colonic epithelial and stromal cells. Colonic epithelial and stromal cells were collected separately using laser capture microdissection (LCM). Microdissected samples were subjected to bisulfite treatment and direct bisulfite sequencing was used to analyze the methylation status of ten regions within SEPT9, SFRP1 genes in tissue samples obtained from normal (n=3), adenomatous (n=3) and colorectal cancer (n=3) samples. In addition SEPT9 and SFRP1 protein expression was assessed using immunohistochemistry on independent healthy (n=10), adenomatous (n=14) and CRC (n=13) samples. Stromal myofibroblast cells were detected by alpha-SMA immunohistochemistry, the immunopositive cells were LCM separated and SFRP1 DNA methylation was assessed by high resolution melting analysis (HRM).
RESULTS: The regions analysed in SEPT9 were unmethylated in normal tissues except for a methylation boundary detected downstream of the largest CpG island within SEPT9. In adenoma and tumor samples, the epithelial cells displayed markedly increased methylation levels ($>80\%$, $p<10^{-4}$), but only within one of the CpG islands investigated. In stromal cells increased methylation (up to 50%, $p<10^{-4}$) was only seen in tumor patients and in histologically normal tissue close to the tumor, but not in adenoma. The analyzed region of SFRP1 also showed remarkable increase in the adenoma and tumor epithelial cells. Protein level of SEPT9 and SFRP1 showed significant ($p<0.05$) decreasement in adenoma and tumor tissue samples compared to the healthy controls. Alpha-SMA immunopositive myofibroblast cells were identified as the main source of stromal SFRP1 protein, that was found to be downregulated by DNA hypermethylation only in carcinoma, but not in adenoma.
CONCLUSION: Hypermethylation of SEPT9 and SFRP1 could be detected in the analysed adenoma and cancer samples compared to the healthy control samples. According to the results of the laser microdissected samples, the DNA methylation alterations originated in epithelial cells, while stromal cells appear to acquire hypermethylation only subsequently via field effects. The DNA hypermethylation of the analyzed genes result in decreased protein level, that can contribute to colorectal cancer formation and invasion.
Disclosure of Interest: A. Kalmar: None declared, R. Wasserkort Shareholder of: Epigenomics AG, Other: former employee of Epigenomics AG, S. Spisak: None declared, G. Valcz: None declared, B. Wichmann: None declared, K. Toth: None declared, K. Leiszter: None declared, B. Bartak: None declared, T. deVos Other: employee of Epigenomics Inc., B. Molnar: None declared, Z. Tulassay: None declared

OP238 IS MEASURING THE DEPTH OF SUBMUCOSAL INVASION A MEANINGFUL APPROACH IN MANAGEMENT OF T1 COLORECTAL CARCINOMAS AFTER ENDOSCOPIC TREATMENT?

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INTRODUCTION: According to the current Japanese guideline, additional surgical colectomy with lymph node (LN) dissection should be considered after endoscopic treatment even for cases where the depth of SM invasion is 1000μm or more. However, many patients who underwent additional colectomy did not have LN metastasis. This over-surgery problem has become a major issue.
AIMS & METHODS: The aim is to investigate the necessity of measuring the depth of submucosal invasion in T1 colorectal carcinomas after endoscopic treatment.
A total of 21060 colorectal neoplasms excluding advanced cancers have been resected endoscopically or surgically at our unit from April 2001 to September 2013. Of these, 902 SM-invasive cancers were included. Initial or additional surgical colectomy with LN dissection was performed in 568 cases, and of which LN metastasis was found in 54 cases (9.5%). There are two ways to measure the depth of SM invasion. One is to directly measure the vertical distance from the line of muscularis mucosae. The other is, when the line of muscularis mucosae is not easily identified due to cancer invasion, the surface layer of the lesion is used as a baseline. According to this rule, a pathologist in our unit categorized 816 lesions and measured each depth of SM invasion. Then, we analyzed the correlations between the depth of SM invasion and the other pathological factors including LN metastasis.
RESULTS: Of these 568 lesions, the muscularis mucosa could be identified in 180 lesions (31.7%), and 60 lesions were invaded SM 1000μm, 120 lesions showed SM $\geqq$1000μm. For the other 388 lesions (68.3%), the muscularis mucosa was recognized broken or disappeared and the depth of SM invasion was measured from the surface layer. All the results turned out to be $\geqq$1000μm. Once the muscularis mucosae was judged to be unclear and the surface layer was applied as the baseline, all the cases would be considered $\geqq$1000μm. It indicates that there is no need to measure the invasion depth in this case. In some lesions, it is hard to decide the baseline. Because the muscularis mucosae sometimes split up and both of them or their surface can be considered as the baseline. The depth of SM invasion is associated with the morphology of the lesion to some extent. Many of depressed-type lesions invade downward, but protruded types often grow upward. Sometimes the depth of SM invasion becomes shorter after being more massively invaded. Some lesions collapse in tumor development. LN metastasis was found in 4 (6.7%) out of 60 lesions with SM $<$1000μm and in 50 cases (9.8%) out of 508 lesions with SM $\geqq$1000μm (p=0.49). The depth of SM invasion was not a statistically significant risk factor for LN metastasis.
CONCLUSION: There are several problems in measuring the depth of SM invasion. The reconsideration should be needed concerning the depth of SM invasion.
Disclosure of Interest: None declared

OP239 ECTOPIC COLORECTAL FAT ACCUMULATION ASSOCIATES WITH ABDOMINAL OBESITY AND INSULIN RESISTANCE IN JAPANESE COLORECTAL POLYP PATIENTS

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INTRODUCTION: Several lines of epidemiological evidence have suggested that obesity and insulin resistance are independent risk factors for the development of colorectal adenoma and cancer (Ref. 1, 2). Obesity is known to be associated with ectopic fat accumulation in the liver and skeletal muscle. However, obesity-related accumulation of fat in the colorectal tissue has not been reported.
AIMS & METHODS: We conducted the present study to seek evidence of obesity- or insulin resistance-related colorectal accumulation of fat in patients with colorectal polyps. For the 27 patients (15 males and 12 females) with colorectal polyps enrolled in this study, we measured the triglyceride, total cholesterol, and phospholipid contents of non-tumorous tissues surrounding the polyps which were resected by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). Non-tumorous colorectal tissues of 32 patients (13 males and 19 females) with colorectal cancer, obtained from surgical resection, were used for immunohistochemistry examination using anti-perilipin (PLIN1) antibody to examine the location of lipid droplets. The contents of lipid droplets were divided into three grades (0 to + 2), and then the grades of the lipid contents were compared with visceral fat areas assessed by CT scan.
RESULTS: The tissue triglyceride/phospholipid value was significantly correlated with serum triglyceride, fasting plasma insulin (FPI), and HOMA-IR ($P < 0.01$, $P < 0.01$, and $P < 0.01$, respectively; Spearman rank test). Tertile analysis of the triglyceride/phospholipid value to assess factors associated with higher triglyceride/phospholipid values showed that serum triglyceride ($P = 0.025$), FPI ($P = 0.041$), and HOMA-IR ($P = 0.013$) were significantly higher in the highest tertile than in the lowest tertile. Serum adiponectin level ($P = 0.046$) was also significantly lower in the highest tertile. Lipid droplets were observed in the submucosal region of non-tumorous colorectal tissue in 27 of 32patients (grade +1 in 13 and grade +2 in 5), and the grades of fat droplet correlated with BMI, abdominal circumstance and visceral fat area ($P = 0.04$, $P < 0.01$, and $P < 0.01$, respectively; Kruskal-Wallis test).
CONCLUSION: Triglyceride content of colorectal tissue was increased in colorectal polyp patients with insulin resistance. Ectopic colorectal fat accumulation was observed in the submucosal region, correlating with BMI, abdominal circumstance and visceral fat accumulation. Thus, the results in the present study suggest an association of the ectopic fat accumulation with abdominal obesity and insulin resistance.
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Disclosure of Interest: None declared

OP240 RISK OF METACHRONOUS ADVANCED COLORECTAL NEOPLASIA AFTER POLYPECTOMY OF SMALL AND DIMINUTIVE ADENOMAS

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INTRODUCTION: As screening colonoscopy is increasing for colorectal cancer prevention, colorectal polyps $<$10 mm in diameter are encountered more frequently. Generally, surveillance colonoscopy is recommended considering the index colonoscopy findings. However, it is not well established what factors are related with developing advanced neoplasia after polypectomy of small and diminutive polyps.
AIMS & METHODS: The study was conducted to reveal the risk of advanced colorectal neoplasia after polypectomy in patients with small and diminutive adenomas. We enrolled 3,526 patients (mean age 53.9 year, 2,164 male), who underwent surveillance colonoscopy after index colonoscopy from January 2002 to June 2012 in Korea University Hospital. We reviewed the medical records and pathology reports to evaluate the risk for the development of advanced colorectal neoplasm in surveillance colonoscopy. According to the largest size and number

of adenoma in index colonoscopy, the patients were divided into the subgroups and analyzed.
RESULTS: Among a total 3,526 patients, 1,949 (55.3%) had colorectal adenoma and 528 (15.0%) of them had advanced adenoma in index colonoscopy. During a median follow-up period of 46.5 months, colorectal adenoma was diagnosed in 1,401 (39.7%), 115 (3.3%) of whom had advanced neoplasm. In the patients with polypectomy in index colonoscopy, metachronous advanced neoplasia were higher among patients with 4 or more baseline adenomas, those with an adenoma 6 mm in diameter or greater. In subgroup analysis, the risk of metachronous advanced adenoma was increased with the adenoma number and size. However, the risk in the group with multiple (≥3) diminutive adenomas was not higher than the group with 1 or 2 small adenomas. In multivariate analysis, age (OR 1.06, 95%CI 1.03-1.08) was significantly associated with an increasing metachronous advanced neoplasm, as were the number and size of baseline adenomas ($p < 0.01$ and $p < 0.01$, respectively).
CONCLUSION: As risk of metachronous advanced neoplasia is associated with the number and size of prior adenomas, it will be needed to modify the surveillance interval considering the size and number of previous adenomas.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45-17:15
VIDEO CASE SESSION - HALL A

OP241 ENDOSCOPIC RESECTION OF A GIANT ESOPHAGEAL SUBMUCOSAL LIPOMA

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INTRODUCTION: Lipomas are extremely rare in the esophagus, constituting less than 0.5% of esophageal neoplasias. If large enough, esophageal lipomas can cause symptoms such as dysphagia, bleeding and airway obstruction. If symptoms are cumbersome a resection is indicated. The resection of big esophageal lipomas is usually performed through surgery. To our knowledge there is no previous description of endoscopic resection of a giant esophageal lipoma.
AIMS & METHODS: A 68-years-old male patient was referred to our clinic from abroad, due to the presence of a big esophageal submucosal lesion with endoscopic, radiologic and ultrasonic characteristics of lipoma. The lesion caused progressive dysphagia and the patient refused surgery. Physical examination on admission was normal. Upper endoscopy revealed the presence of a 14cm long esophageal subepitelial, yellow and hard lesion, occupying more than ½ of luminal circumference and causing severe luminal narrowing. The surrounding mucosa was normal. Endoscopic ultrasound shown the presence of an avascular, hyperecogenic, regular and homogeneous lesion in the submucosal layer, with 32x42mm of transverse diameters.
RESULTS: After multidisciplinary discussion, discussion with the referring doctor and informed consent, an endoscopic resection was performed at our endoscopy unit under general anesthesia. First, a submucosal tunnel was created and the tumor was completely enucleated in one piece using endoscopic submucosal dissection (ESD). Although the use of different techniques and instruments, it was not possible neither to retrieve the lesion en bloc, nor to fragment it using a snare, due to its hardness and size. The lipoma needed to be fragmented inside the luminal esophagus using a combination of ESD knife and a conventional snare, being completely removed. There were no major complications such as bleeding or perforation during or after the procedure. The patient started oral diet the day after the procedure and was discharged at day 6. The pathological analysis confirmed the presence of a well differentiated lipoma with negativity for MDM2 immunohistochemistry. On the follow-up there were no signs of stricture, remaining the patient asymptomatic 4 months after the procedure.
CONCLUSION: Esophageal lipomas are rare. Endoscopic resection can be a safe, feasible, and effective alternative to surgery even in cases of giant esophageal lipomas.
Disclosure of Interest: None declared

OP242 PURELY ENDOSCOPIC REMOVAL OF A GIANT, DOUBLE-HEADED ESOPHAGEAL FIBROVASCULAR POLYP

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INTRODUCTION: The surgical approach is generally recommended for the excision of giant esophageal fibrovascular polyps to ensure adequate hemostasis and clear resection of the base. Only single cases of merely endoscopic removal of this rare benign tumor have been described in the literature.
AIMS & METHODS: To demonstrate possibilities of successful resection of a giant fibrovascular polyp of the esophagus via an endoscope. A 50-year-old man was admitted to our hospital with a 6-month history of globus sensation, mild intermittent dysphagia during swallowing, occasional heartburn and epigastric pain. In a barium swallow and repeated EGDs a giant double-headed polyp with smooth overlying mucosa, arising from the upper esophagus just near the level of the cricopharyngeus at the pharyngo-esophageal junction and extending from 17 to 34 cm from the incisors settling in the distal esophagus was revealed. It had a broad 18mm basis, distal head 32 mm at its maximum diameter with 2 ulcerations on the apex, proximal head 25 mm in diameter and length, with the ramification at the distance of 45 mm from the stalk's base. EUS detected the lesion originated from the submucosal layer with inhomogeneous echo-texture with both hyper- and hypoechoic features with a number of vascular structures within the stalk.
RESULTS: Removal of the polyp was performed under general anesthesia with elective intubation, started with GIF-H180 following by GIF-2T160, using the Maxim-402 electrosurgical unit and CO2 insufflation. The equipment for intervention included 4 endo-loops, grasping forceps and large electrosurgical snare. At first, we applied two loops at the level of ramification, resected the first 75 mm fragment above the loop and removed it. Then, we placed 2 another loops at the very base of the pedicle and removed the second fragment, thus performed total polypectomy, leaving the ligated 10 mm long stalk stump in place. Neither bleeding nor other complications occurred. The total length of the resected esophageal lesion measured 135 mm. Histology showed the mixture of fibrous and adipose tissue accompanied by an abundant network of large vessels, covered by a normal squamous epithelium. The patient was discharged from the hospital on the 4th day. A month later control EGD was performed, it revealed just tiny scar at the level of the upper esophageal sphincter and no other changes of the esophageal wall.
CONCLUSION: The removal of the giant esophageal polyp using modern endoscopic equipment can be safely performed without open surgery.
Disclosure of Interest: None declared

OP243 MUCOSAL INJURIES DURING PERORAL ENDOSCOPIC MYOTOMY: ARE SEVERE COMPLICATIONS JUST AROUND THE CORNER?

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INTRODUCTION: After Peroral Endoscopy Myotomy (POEM) the integrity of esophageal mucosa is crucial for the safety of the procedure. Nevertheless a variety of mucosal injuries may occur during POEM
AIMS & METHODS: Between 2011 and April 2014, 156 patients underwent POEM in a single center. Before oral feeding patients underwent EGD to rule out for mucosal injuries. Four different types of mucosal injuries occurred: intraoperative mucosal perforations, large mucosal tearing, postoperative ulcers and extended mucosal flap necrosis.
RESULTS: Mucosal perforations occurred in 7 patients (4.5%): in 5 cases, during the submucosal dissection, the knife inadvertently perforated the mucosa at the esophagogastric junction (EGJ). In one case the tip of the endoscope perforated the mucosal flap. In the last case, during the myotomy, the operator did not recognize the cleavage between the mucosa and the muscular layer and cut the mucosa by mistake. In all these cases, the perforation was immediately repaired with clips and the postoperative course was uneventful.
In one patient (0.6%), despite submucosal dissection seeming to proceed regularly, when the endoscope was almost at the EGJ, a 12 cm long tearing of the mucosa, likely caused by the shaft of the endoscope, was recognized. The procedure aborted, and the mucosal tearing was clipped. No complications occurred, the patient was fed after 24 hours.
In 49 patients (31.4%) an ulceration, more likely related to thermal injury during dissection, was observed at the EGJ. In 14 cases (16%) ulcers were larger than 1cm. Despite the potential risk of mediastinal infection, none of the patients experienced fever, pain or symptoms, and they were fed after a median of 2.5 days.
In one patient, a complete necrosis of the mucosal flap, extended from the mucosal incision to the EGJ was diagnosed. A suspected full thickness perforation was identified at the EGJ. CT scan was negative for mediastinal and abdominal collections. A conservative treatment, including fasting and antibiotics was instituted. The patient was fed with a soft diet after a negative EGD and esophageal X-ray, 7 days later. The mucosal necrosis eventually resulted in a esophageal stricture, that is still being dilated using bougies
CONCLUSION: Mucosal injuries are relatively frequent after POEM. Nevertheless, mucosal injuries are asymptomatic in the vast majority of cases, and do not usually alter substantially the post-operative course. However, endoscopists should take particular care of the mucosal flap during submucosal dissection, because severe complications may be just around the corner.
Disclosure of Interest: None declared

OP244 FEASIBILITY OF USING THE MASTER TO PERFORM FLEXIBLE ENDOSCOPIC SUTURING AND KNOT-TYING

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INTRODUCTION: We employed Master and Slave Transluminal Endoscopic Robot (MASTER) to performed gastric ESD in 5 patients & endoscopic full thickness resection in animal model [1,2]. Endoscopic closure of a gastrointestinal defect remained the most challenging task. This is related to complexity of suturing and lack of instrumental dexterity. The latter could be mitigated with a flexible 2-arm robotic assisted system. We aimed to investigate the feasibility

of performing flexible endoscopic suturing and knot-tying using a revised version of MASTER.
AIMS & METHODS: The MASTER was equipped with a pair of graspers and needle holder. We used grasper to hold up the tissue and the other to drive the needle through. The motions for suturing were controlled with external consoles. Feasibility studies on endoscopic robotic suturing were conducted in a phantom and a live pig. In phantom experiment, we examine continuous suturing & knot typing using MASTER with 4-O V-Loc™ (Covidien Co Ltd). In live pig, suturing was performed with 4-O suture (Ethicon Co Ltd) in a rectal incision. The needle was grasped by the MASTER needle holder introduced through a 6.5 mm instrument channel. The MASTER endoscope was then inserted into the rectum without overtube. The timings to complete various stages of suturing in different environments were recorded.
RESULTS: In phantom experiment, a total of 8 minutes 30 seconds was taken to complete suturing with 2 knots. The operator took 1 minute 25 seconds to orient the needle for suturing. Another 1 minute 17 seconds was spent to drive the needle through the two edges. The needle was then cut, followed by the first hitch in 1 minute 28 seconds and first knot tightened in 28 seconds. In the live animal, the operator took 24 seconds to transfer the needle from the grasper to needle holder with proper orientation. The needle was driven through tissue in 1 minute and 11 seconds. The MASTER's needle driver was able to hold the needle steadily without rotation during the entire process.
CONCLUSION: We have shown that flexible robotic-assisted endoscopic system can perform endoluminal suturing and knot-tying using commercially available sutures and needles.
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Disclosure of Interest: P. Chiu Consultancy for: Scientific Advisory Board member of Endomaster, S. J. Phee Directorship(s) for: Co-founder of Endomaster, Other: Developer of MASTER robot, S. Chung: None declared, K. Y. Ho Directorship(s) for: Co-founder of Endomaster, Other: Developer of MASTER robot

OP245 CLINICAL CASES OF NON-EXPOSED ENDOSCOPIC WALL-INVERSION SURGERY WITH SENTINEL NODE BASIN DISSECTION AS A NEW CONCEPT OF MINIMALLY INVASIVE SURGERY FOR EARLY GASTRIC CANCER

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INTRODUCTION: Non-exposed endoscopic wall-inversion surgery (NEWS) was invented as a novel method of full-thickness resection without intentional perforation and therefore without the risk of tumor seeding. Especially, NEWS combined with sentinel node navigation surgery (SNNS) has been expected as a minimally-invasive, function-preserving surgery for possibly node-positive early gastric cancer (EGC)[1)].
AIMS & METHODS: We aimed to verify the feasibility of NEWS with sentinel node basin dissection (SNBD). After obtaining an approval from the institutional review board of the hospital, NEWS with SNBD was performed in 2 cases. One was 2 cm, diffuse-type mucosal cancer with ulceration, and the other was a post-endoscopic submucosal dissection (ESD) case (25 mm, slightly invasive submucosal cancer with lymphatic invasion). Under general anesthesia, mucosal markings were placed and 0.5 ml of indocyanine green (ICG) solution (5 mg/ml) was injected into the submucosa at 4 quadrants around the lesion. After 10 min of injection, stained lymph nodes were identified as sentinel node (SN)s and a SN basin including the SNs was dissected. After confirming no metastasis in the SNs by intraopearative pathological diagnosis, NEWS was performed. After placing serosal markings laparoscopically and circumferential submucosal injection endoscopically, circumferential sero-muscular incision was made, followed by sero-muscular suturing as the lesion and a surgical sponge inverted toward the lumen. Subsequently, circumferential mucosal incision was made as the sponge was picked out. The lesion was retrieved perorally and endoclips were placed on the anastomosis. The completeness of the procedure and complications were assessed.
RESULTS: NEWS with SNBD was successfully finished in the both cases. The operation time and intraoperative blood loss were 270 min and 260 min, and less than 10 ml and 40 ml, respectively. They were discharged without complications on the postoperative day 13 and 10, respectively. The primary lesion was completely resected and final pathological diagnosis was identical with preoperative one in the former case. No cancer was detected in the resected gastric wall in the latter case. No cancer cell was identified in the dissected SN basins in the both cases.
CONCLUSION: We demonstrated that NEWS with SNBD was feasible for EGC cases. This method might become a new standard of minimally invasive gastrectomy to cure EGC which is out of indication of ESD and also is a candidate of SNNS.
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Disclosure of Interest: None declared

OP246 FIRST GASTRODUODENAL ANASTOMOSIS WITH PURE NOTES APPROACH IN HUMAN BEING

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INTRODUCTION: Pures NOTES gastrointestinal anastomosis with tissue apposition stent might offer a safe, reliable and efficient procedure. After conducting an experimental study in live pigs with 100 % success (1) following a two years period research (2), we decided performing this procedure in human being.
AIMS & METHODS: The patient was a 30 years-old man with complete duodenal stenosis due to chronic pancreatitis and complicated with severe portal hypertension related to portal vein thrombosis. Access to the peritoneal cavity was done under EUS guidance, with 19G FNA needle and guidewire, in front of the duodeno-jejunal angle (Video1). Then a 20 mm balloon dilatation over the guide wire was performed to allow the passage of double working chanel gastroscope. After passing in the peritoneal cavity, the bowel loop was selected, held with a twin grasper and the Hot Axios (X Lumena, California, USA) was introduced in the duodenal lumen. The distal flange was deployed and the scope was pulled back in the gastric cavity, bringing back the duodenal loop to the gastric serosa. The proximal flange of the stent was released in the gastric lumen, making a tight anastomosis
RESULTS: The procedure was uneventful. The patient was refed at day 2 with soft diet and with normal diet ay day 4 without any problem. Ct scan and endoscopic control were performed at day 5 (Video2) and the patient was discharged from the hospital at day 6. At one month the stent was retrieved without any difficulty showing an efficient anastomosis.
CONCLUSION: After a long and challenging period in experimental studies, we believe that NOTES gastrointestinal anastomosis is feasible and safe in human beings. We planned to start a pilot prospective study.
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Disclosure of Interest: None declared

OP247 SINGLE-SESSION ERCP AFTER ROUX-EN-Y GASTRECTOMY USING A MODIFIED PERCUTANEOUS-ASSISTED TRANSPROSTHETIC ENDOSCOPIC THERAPY (PATENT) APPROACH

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INTRODUCTION: ERCP remains challenging following Roux-en-Y. Transenteric ERCP via PEG or percutaneous jejunostomy tracks is an option in selected cases. PATENT is a novel technique for percutaneous ERCP that avoids the need for PEG tract maturation (Law R et al, Endoscopy2013;45:671-5). The PEG tract is protected by a self-expandable metal stent (SEMS) placed transmurally to allow immediate, safe percutaneous scope passage into the GI tract. PATENT has so far being used only through the stomach.
AIMS & METHODS: We report ERCP in a Roux-en-Y gastrectomy patient by means of a modified PATENT through the jejunum. A biflanged saddle-shaped lumen-apposing metal stent (LAMS) was used for track protection and Ovesco clips were used for jejunal closure.
RESULTS: A 76-year-old man with symptomatic common bile duct stones had failed ERCP because of prior Roux-en-Y total gastrectomy. He had several other comorbidities, prior abdominal surgeries and relapsing episodes of adhesion-related bowel obstruction. At the time of failed ERCP, abdominal transillumination was achieved next to the afferent jejunal limb anastomosis. Two T-tags were used to hold the small bowel in place prior to insertion of a Russell introducer into the jejunum. After track dilation, a 15mm diameter LAMS (X-Lumena, Mountain View, Ca) was placed percutaneously, with the distal flange deployed in the jejunum under endoscopic monitoring, and the proximal flange deployed at the skin access site. After forced balloon expansion, a standard gastroscope was passed through the LAMS into the jejunum up to the papilla. Cannulation, sphincterotomy and stone removal were performed. Single-scope cholangioscopy was instrumental to clear cystic duct stones.
After ERCP and cholangioscopy, the gastroscope was withdrawn towards the jejunostomy, then redirected retrogradelly towards the esophagus through the efferent jejunal limb. Another gastroscope with the Ovesco clip in place was passed per-orally. Dual scope rendezvous facilitated identification and Clip-closure of the jejunostomy. Methylene-blue was used to check for leakage. A balloon PEG-tube was left for temporary drainage. No procedural complications ensued.
CONCLUSION: PATENT is also feasible through the jejunum. LAMS instead of SEMS and Ovesco-clip closure are technical choices worth considering to enhance overall PATENT safety. PATENT widens the options for endoscopic biliary therapy in cases where enteroscopy-based ERCP is not feasible.
Disclosure of Interest: None declared

OP248 EUS-GUIDED HEPATIC INTRA-ARTERIAL CHEMOEMBOLIZATION

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INTRODUCTION: Intra-arterial chemotherapy is an effective modality to treat unresectable hepatic metastasis from colorectal primaries if systemic chemotherapy has failed. This technique has some advantages over systemic chemotherapy, such as: very high concentrations of agents in a pre-determined region (FUDR provides 15-fold increase); anoxic damage that increases vascular permeability and provides better chemotherapy infiltration; cytotoxic effect that leads to vasculitis by occlusion/ischemia; and free-radical injury due to toxicity to the tumor during reperfusion.
AIMS & METHODS: In this presentation, we will demonstrate an EUS guided fine-needle intra-arterial injection of chemotherapy.
This technique was performed in a 53-year-old woman with an advanced sigmoid colon cancer who presented with abdominal pain six months after sigmoidectomy. CT revealed multiple nodules in segments III, VI, VII and VIII of the liver. The patient underwent trans-arterial chemoembolization (TACE), with 70% regression of all nodules, except for one measuring 4cm on segment III.
By a single-step procedure, the EUS linear equipment was positioned at the proximal gastric wall and the hepatic nodule was identified. With the use of Doppler imaging, we localized the arterial vessel that supplies the nodule. After that, it was performed EUS-guided hepatic intra-arterial puncture, with a 22-gauge needle, confirmed by contrast media injection. With this confirmation, the intra-arterial injection was performed with chemotherapies substances and lipiodol.
RESULTS: In this patient, the CT showed regression on the tumor size of 20%, 40% and 60% after 7 days, 1 and 3 months.
Our group has demonstrated in a previous study of EUS-guided or Interventional radiology to hepatic intraarterial chemotherapy: a prospective trial, that response rate, median survival, and median complication free survival were similar in both of the treatment modalities, but the median duration of hospitalization was smaller in the EUS-guided approach patients.
CONCLUSION: EUS-guided intra-arterial chemotherapy appears to be safe and feasible in a subset of patients with metastatic liver disease. Further studies are necessary before a formal recommendation is made.
Disclosure of Interest: None declared

OP249 EUS-GUIDED ANASTOMOSES AS CONDUIT FOR ENDOTHERAPY OF COMPLICATED HEPATOLITHIASIS

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INTRODUCTION: EUS-guided anastomoses using covered Self-Expandable Metal Stents (SEMS) are used for pseudocyst drainage and necrosectomy. This concept could be applied to stone clearance of hepatolithiasis, shifting from percutaneous to endoscopic intervention, with potentially improved patient quality of life.
AIMS & METHODS: We performed EUS-guided hepatico-gastrostomy (HGS) with a covered SEMS followed by removal of left-sided hepatolithiasis through the HGS. A right liver lobe abscess was also drained transduodenally under EUS, and retained stones removed.
RESULTS: A 48 y.o. cholecystectomized female had relapsing biliary colic and cholangitis. ERCP showed stones filling the left ductal system above a stricture at the confluence. ERCP-based lithotripsy was not deemed feasible, and plastic biliary stents were placed. Left hepatectomy was considered and dismissed in favour of a radical attempt at endoscopic removal. EUS-guided HGS was performed with a covered biliary SEMS. Two-weeks later, a nasobiliary drain was placed via ERCP into the left hepatic duct, and transgastric cholangioscopy performed through the HGS for lithotripsy and retrograde stone clearance into the stomach. Mild postprocedure cholangitis subsided. Retained stone fragments were cleared at second look cholangioscopy. The HGS SEMS was removed. She remained well for 8 months but then had severe sepsis caused by liver abscess on segments VI-VII. After failed abscess resolution and persistent sepsis following percutaneous drainage, EUS-guided transduodenal abscess drainage was performed. Procedural steps for HGS were replicated: 1) EUS identification and 19G needle puncture of target; 2) 0.035" guidewire passage into the abscess through needle; 3) Serial over-the-wire puncture tract dilation with a 6.5F cystotome and 4mm balloon; 4) 4cm covered SEMS placement across puncture tract under combined fluoroscopy and endoscopy. The distal stent end was clipped to the duodenal mucosa to minimize migration risk. Balloon cholangiography through the SEMS showed communication with a dilated intrahepatic duct and retained stones. A7F plastic stent was placed through the SEMS into the bile-duct. Abundant pus drained from the abscess into the duodenum. Sepsis improved within hours. Stones were cleared electively through the SEMS 2-weeks later, once a mature track had developed. The patient recovered uneventfully.
CONCLUSION: EUS-guided anastomoses using covered biliary Self-Expandable Metal Stents (SEMS) allowed interval biliary drainage and delayed treatment of left-sided hepatolithiasis and right-sided liver abscess.
Disclosure of Interest: None declared

OP250 A VERY STRANGE POLYP OF THE SIGMA IN COLO-RECTAL SCREENING COLONOSCOPY

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INTRODUCTION: Productive colo-rectal lesions observed during a screening colonoscopy performed in a faecal-occult-blood-test (FOBT)-positive female patient are sometimes a challenge both for endoscopists and pathologists.
AIMS & METHODS: We describe the case of a 52-year-old asymptomatic woman who underwent a screening colonoscopy after having being found positive at FOBT, as well as diagnostic difficulties thereof, subsequent follow-up and final diagnosis.
RESULTS: During a screening colonoscopy after FOBT, on 16th December 2009, an unusual huge sessile polyp of the sigmoid region was observed. Biopsies showed a nonspecific chronic inflammation and the pathologist reported the presence of iron pigment deposits. Follow-up colonoscopy three months later confirmed the lesion, with macrobiopsies suggestive of deep cystic colitis. On 19th of April 2011 a CT scan was reported as unremarkable. The patient remained asymptomatic and we performed a control colonoscopy on 11th October 2011, which showed an important regression of the lesion. Histological examination in two of six biopsies showed an incipient tubular adenoma with mild dysplasia and in the other four biopsies acute and chronic inflammation. At this point the lesion was considered an adenomatous polyp and the patient was referred to surgery, due to the judgment of endoscopic unresectability. The patient refused surgery and we performed a new colonoscopy on the 9th of March 2012, when we noted a further regression of the lesion.
At a deeper enquiry in her medical history she reported very painful menses associated with temporary constipation. For this reason she had performed several pelvic ultrasounds as well as gynaecological examinations, all reported normal. Moreover, she reported the occurrence of her last menstrual cycle at the time of the first colonoscopy. On this basis, new biopsies were sent to the pathologist with the clinical suspect of endometriosis. The reassessment of the CT scan showed a thickening of the sigmoid wall. An endoscopic ultrasound showed a hypoechoic thickening of the sigmoid with impairment of the normal wall stratification. The ultimate histopathological report confirmed the diagnosis of endometriosis.
CONCLUSION: 1) endometriosis can present as an unusual sessile polyp mimicking colonic carcinoma (1).
2) the presence of iron pigments in the first histological report could suggest the diagnosis.
3) the regression of the lesion due to menopause facilitated in this case the diagnosis, which saved an unnecessary surgical resection.
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Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45–17:15
HOW TO MANAGE IBD IN 2014 – HALL D

OP251 LONG-TERM OUTCOMES OF TOP-DOWN VERSUS STEP-UP TREATMENT IN NEWLY DIAGNOSED CROHN'S DISEASE

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INTRODUCTION: Early combined immunosuppression ('top-down' (TD)) is more effective than conventional management ('step-up' (SU)) for induction of remission and reduction of corticosteroid use in patients with recently diagnosed with Crohn's disease (CD). However, it remains unknown whether short-term benefits are sustained long-term and if the natural history of CD can be altered. Therefore, we aimed to investigate the long-term effects of TD (induction IFX and maintenance azathioprine (AZA)) vs. conventional SU treatment in CD.
AIMS & METHODS: Long-term follow-up data was retrospectively collected from patients who participated in a randomized controlled trial evaluating TD vs. SU in patients with newly diagnosed Crohn's disease (1). Data collection was performed in 15 of the 18 participating centers. For 16 semesters following the original 2-year trial, the following data was abstracted from patients' medical records: clinical disease activity by global assessment, significant flares of CD, medication use, hospitalization, surgery and the occurrence of new fistulas. Comparisons were done by intention-to-treat analysis. Time to event data was evaluated using the Kaplan-Meier and log-rank test. Proportions were compared using Fisher's exact test. Colonoscopy reports were scored as one of the following: Normal (0), aphthous ulcers (1), small ulcers (2) or large/deep ulcers (3).
RESULTS: 124 patients (SU n=63) were included in the analysis. At the start of follow-up, 81.8% (60.0% AZA, 21.8% methotrexate (MTX)) vs. 66.0% (50.9% AZA, 11.3% MTX) of patients used an immunomodulator, and 20.0% vs. 15.1% received IFX in TD and SU, respectively. The number of semesters in full clinical remission did not differ between between TD and SU (68.0% vs. 68.0%; p=1.0). However, patients in the TD group had fewer semesters with a flare (13.2% vs. 20%; $p<0.01$), and longer flare-free survival (median 9 vs. 5 semesters; p=0.03). Mean time to first hospitalization was 13.8 vs. 13.2 semesters (p=0.47), mean time to first new fistula was 15.2 vs. 14.1 semesters (p=0.21) and

mean time to Crohn-related surgery was 15.1 vs. 14.1; p=0.19) for TD and SU, respectively. 157 endoscopy reports of 75 patients were scored. 19.4% of TD and 38.5% of SU patients had at least one endoscopy with large ulcers (p=0.08). 66.7% of TD and 56.4% of SU patients had at least one endoscopy with no ulceration (p=0.48).
CONCLUSION: Top-down treatment resulted in a reduction of flares and a longer flare-free survival compared to step-up treatment. These results suggest that TD algorithms might be beneficial in newly diagnosed CD. However, TD treatment did not result in differences in remission rates, surgery, or other outcomes, although a trend was observed for the presence of large ulcers during endoscopy.
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Disclosure of Interest: D. Hoekman: None declared, J. Stibbe: None declared, F. Baert Financial support for research from: Abbott, Lecture fee(s) from: Merck, Abbott, Consultancy for: Merck, Abbott, Falk, P. Caenepeel: None declared, P. Vergauwe: None declared, M. de Vos: None declared, A. van Bodegraven Lecture fee(s) from: Abbott, Ferring, Consultancy for: Abbott, MSD, S. Vermeire Financial support for research from: UCB Pharma, MSD, Abbvie, Lecture fee(s) from: Abbvie, Merck, Ferring, UCB Pharma, Centocor, Consultancy for: UCB Pharma, AstraZeneca, Ferring, Abbvie, Merck, Ferring, Shire, Pfizer, G. D'Haens Financial support for research from: Abbott, Jansen Biologics, Given Imaging, MSD, DrFalk Pharma, Photopill, Lecture fee(s) from: Abbott, Tillotts, Tramedico, Ferring, MSD, UCB Farma, Norgine, Shire, Consultancy for: Abbott, Actogenix, Centocor, Cosmo, Engene, Ferring, GlaxoSmithKline, Jansen Biologics, Millenium Pharmaceuticals, MSD, Novonordisk, PDL Biopharma, Pfizer, SetPoint, Shire, Takeda, Teva, UCB Farma

OP252 MANAGING PEDIATRIC ACUTE SEVERE ULCERATIVE COLITIS ACCORDING TO THE 2011 ECCO-ESPGHAN GUIDELINES: EFFICACY OF INFLIXIMAB AS A RESCUE THERAPY

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INTRODUCTION: Acute severe ulcerative colitis (ASC) is a potentially life-threatening event. Scarce pediatric data are available about success rates of Infliximab (IFX) as a second line therapy.
AIMS & METHODS: This study was performed in consecutively observed pediatric patients with ASC and aimed at assessing the long-term efficacy of IFX and clinical predictors of poor outcome. Patients had been recruited, after reporting of the 2011 ECCO-ESPGHAN guidelines on pediatric ASC[1]. Children who experienced an episode of ASC, defined as a PUCAI of at least 65 points, were evaluated. Clinical assessment through PUCAI and laboratory data (ESR, CRP, hemoglobin, albumin, hematocrit, ferritin) were recorded at admission and at day 3 and 5. All patients were treated according to the above mentioned guidelines for ASC and received intravenous (iv) corticosteroids (CS). IFX was administered as second-line therapy in CS-refractory patients. In a 2-year follow up we assessed the overall colectomy rate and efficacy of IFX.
RESULTS: Thirty-one patients (age: 10.6±4.88, 52% female) met the criteria for ASC: 21 (68%) responded to iv CS, while 10 (32%) received IFX for CS-refractoriness. Among the latter, 2 (20%) underwent urgent colectomy; however, at a 2-year follow up, 5 (50%) needed elective colectomy, while only 3 of the CS-responders required surgery (14%). Compared to CS-responsive patients, those CS-refractory showed a significantly shorter interval from the diagnosis of ulcerative colitis to the episode of ASC (p= 0.04) and a higher rate of colectomy at maximum follow-up (p=0.007). Patients needing colectomy differentiated from those responding to medical therapy for more frequent courses of CS prior to ASC (p=0.02), but not for laboratory values, sex, disease location, disease extension, therapy, mean PUCAI, serological markers and family history.
CONCLUSION: Although it has short-term effectiveness as a rescue therapy to avoid urgent colectomy in CS-refractory children, IFX does not modify the long term colectomy rate in ASC. Frequent courses of CS are predictive of a poor long-term outcome.
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Disclosure of Interest: None declared

OP253 IMPACT OF DISEASE DURATION ON CLINICAL OUTCOMES WITH ADALIMUMAB TREATMENT IN PATIENTS FROM IMAGINE 1

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INTRODUCTION: Adalimumab (ADA) was shown to be an effective treatment in inducing and maintaining remission in children with moderately to severely active Crohn's disease (CD) in the IMAgINE 1 trial[1]. The impact of baseline disease duration on the safety and efficacy of ADA is evaluated in patients (pts) from IMAgINE 1.
AIMS & METHODS: In IMAGINE 1, pts aged 6-17 years (yrs) with baseline PCDAI >30 received open-label (OL) induction of ADA at weeks 0/2 according to body weight (≥40kg, 160/80mg; <40kg, 80/40mg). At week 4, pts were randomized according to body weight to double-blind higher-dose (HD) ADA (≥40kg, 40mg every other week [EOW]; <40kg, 20mg EOW) or lower-dose (LD) ADA (≥40kg, 20mg EOW; <40kg, 10mg EOW) to week 52. Pts experiencing disease flare or non-response could move to blinded weekly dosing after week 12, then to OL weekly HD ADA for continued flare/non-response. Pts with loss of response or intolerance to infliximab (IFX) could enroll in IMAgINE 1. Remission (PCDAI≤10) and response (PCDAI decrease ≥ 15 points from baseline) were assessed in pts, regardless of dose, at weeks 26 and 52 according to disease duration at IMAgINE 1 baseline: ≤1, >1-≤2, >2-≤3, >3 yrs. The impact of prior IFX use and disease duration on remission rates was also assessed in the disease duration subgroups. Data were analyzed using non-responder imputation (NRI), whereby pts with missing data or that obtained after moving to weekly dosing were considered not to have efficacy, and a modified NRI (mNRI) whereby only pts with missing data were considered as non-responders.
RESULTS: Greater rates of remission and response were observed across the three disease duration subgroups ≤ 3 yrs at both weeks 26 and 52 relative to those with disease duration > 3 yrs (Table). IFX naive pts had numerically higher rates of remission relative to IFX exposed pts regardless of disease duration subgroup. Rates of serious adverse events (AEs) and AEs leading to discontinuation were lower in pts with shorter duration of CD (≤ 3 yrs).
Table. Week 26 and 52 remission and response rates in ADA-treated patients by baseline disease duration subgroup

	≤1.0 yr N=43		>1.0-≤2.0 yrs N=30		>2.0-≤3.0 yrs N=43		>3.0 yrs N=72	
	NRI	mNRI	NRI	mNRI	NRI	mNRI	NRI	mNRI
Remission, n (%)								
Week 26	13 (30.2)	16 (37.2)	15 (50.0)*	15(50.0)*	17 (39.5)	17 (39.5)	18 (25.0)	21 (29.2)
Week 52	7 (16.3)	13 (30.2)	14 (46.7)†	15 (50.0)	12 (27.9)	15 (34.9)	20 (27.8)	23 (31.9)
Response, n (%)								
Week 26	20 (46.5)	28 (65.1)	21 (70.0)*	23(76.7)*	26 (60.5)	28 (65.1)	34 (47.2)	40(55.6)
Week 52	9 (20.9)	21 (48.8)	17(56.7)*†	20(66.7)*	17 (39.5)	24 (55.8)	23 (31.9)	30(41.7)

CONCLUSION: Higher efficacy rates and lower incidence of serious adverse events in pts with a shorter duration of CD suggests early treatment with ADA may be beneficial for pts.
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Disclosure of Interest: M. Dubinsky Financial support for research from: Janssen, Consultancy for: AbbVie, Janssen, Takeda, Pfizer, Prometheus labs, Santarus, UCD, J. Hyams Lecture fee(s) from: Janssen Orthobiotech, Consultancy for: Janssen Orthobiotech, AbbVie, TNI Biotech, EnteraHealth, Pfizer, Soligenix, Takeda, Other: Expert testimony and payment for development of educational presentations: Janssen Orthobiotech, J. Rosh Financial support for research from: AstraZeneca, AbbVie, Janssen, UCB, Lecture fee(s) from: Abbott Nutrition, Prometheus, Consultancy for: AbbVie, Janssen, Soligenex, Other: Board membership: GI Health Foundation, J. Markowitz Consultancy for: AbbVie, Janssen OrthoBiotech, UCB, Soligenix, F. Ruemmele Lecture fee(s) from: Shering-Plough, Nestlé, MeadJohnson, Ferring, MSD, Johnson & Johnson, Centocor, Other: Board membership: SAC:DEVELOP (Johnson & Johnson), invited to MSD France, Nestlé Nutrition Institute, invited to Nestlé Health Science, invited to Danone, invited to MeadJohnson, Biocodex, S. Eichner Shareholder of: AbbVie, Other: Employee: AbbVie, A. Lazar Shareholder of: AbbVie, Other: Employee: AbbVie, Y. Li Shareholder of: AbbVie, Other: Employee: AbbVie, B. Pappalardo Shareholder of: AbbVie, Other: Employee: AbbVie, R. Thakkar Shareholder of: AbbVie, Other: Employee: AbbVie

OP254 PARADOXICAL PSORIASIS IN A LARGE COHORT OF IBD PATIENTS TREATED WITH ANTI-TNF ALPHA: 5 YEARS-FOLLOW-UP STUDY

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INTRODUCTION: New onset of psoriasiform skin lesions is an emerging paradoxical side effect in a subgroup of patients with inflammatory bowel disease (IBD), treated with anti-TNF alpha. For most of them with severe lesions unresponsive to topical therapy, it is necessary to withdraw from treatment, with relevant impact on the management of disease. To date the pathogenesis is not fully understood, but smoking seems to be a risk factor for developing these lesions. Aim of this study was to estimate the incidence of psoriasiform skin lesions in a large cohort of IBD patients treated with anti-TNF alpha and to analyze its clinical correlates.
AIMS & METHODS: A retrospective cohort study on all IBD patients who started anti-TNF alpha at our IBD Center from January 2008 to December 2013 was performed. We recorded clinical characteristics at baseline: sex, type and duration of disease, extra-intestinal manifestations, smoking habit, type of anti-TNF alpha and concomitant immunosuppressive therapy. Information on time-dependent variables was updated at each clinical visit. Baseline characteristics of patients who did and did not develop psoriasis were compared with t-test, Mann-Whitney and Fisher exact test as appropriate. Proportional hazards regression models were used to estimate the association between each predictor

and time to development of psoriasis. Time-dependent predictors were updated at each available time point.
RESULTS: A total of 401 patients started anti-TNF alpha (both infliximab and adalimumab) between January 2008 and December 2013. There was preponderance of Crohn's disease (60%) and infliximab treated patients (60%), with a mean age at diagnosis of 40 ± 14 years. The median duration of disease was 6 years (range 0-29 years). Thirty-one percent of patients had also concomitant extra-intestinal manifestations and 21% were started on concomitant immunosuppressive therapy. Participants contributed a total of 738 person-years of follow-up, during which 42 incident cases of psoriasis were recorded, all of them confirmed by punch biopsies, with an incidence rate of 5.7 per 100 person-years. Comparing IBD patients with and without skin lesions, we found higher rate of smokers in the subgroup of patients who developed psoriasis (18% vs 36%, p = 0.01). Cox-regression survival analysis confirmed smoking as independent predictor of psoriasis (HR 2.52, 95%CI 1.33, 4.76, p = 0.01). Conversely, concomitant immunosuppressive therapy was inversely related to psoriasis (HR 0.34, 95% CI 0.12, 0.95, p = 0.04). The association with other predictors was not statistically significant.
CONCLUSION: New onset of psoriasis is a relevant side effect of anti-TNF alpha therapy, with an incidence rate of 5.7 per 100 person-years. Smoking is confirmed as the main risk factor for developing lesions. The combination therapy with anti-TNF alpha plus immunosuppressants was associated with a reduced risk for psoriasis.
Disclosure of Interest: D. Pugliese: None declared, P. Ferraro: None declared, M. Marzo: None declared, C. Felice: None declared, L. Celleno: None declared, O. Nardone: None declared, G. Andrisani: None declared, F. Pizzolante: None declared, A. Papa: None declared, I. De Vitis: None declared, G. Rapaccini: None declared, L. Guidi Financial support for research from: AbbVie, MSD, A. Armuzzi Lecture fee(s) from: AbbVie, MSD, Chiesi, Ferring, Nycomed, Takeda and Otsuka, Consultancy for: AbbVie, Lilly, MSD and Takeda

OP256 SAFETY OF VEDOLIZUMAB ALONE OR WITH CONCOMITANT CORTICOSTEROIDS AND/OR IMMUNOSUPPRESSANTS IN PATIENTS WITH ULCERATIVE COLITIS OR CROHN'S DISEASE

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INTRODUCTION: Safety and efficacy of vedolizumab (VDZ) in treating ulcerative colitis (UC) and Crohn's disease (CD) were established in the GEMINI 1[1] and 2[2] trials, respectively, wherein rates of some infections (eg, nasopharyngitis) were higher with VDZ therapy than with placebo (PBO). This analysis evaluates infection rates in patients treated with VDZ alone or with concomitant corticosteroids (CSs) and/or immunosuppressants (IMs) in GEMINI 1 and 2.
AIMS & METHODS: The randomized PBO-controlled GEMINI 1 and 2 studies each consisted of a 6-wk induction phase (VDZ 300 mg or PBO at wks 0 and 2) followed by a 46-wk maintenance phase (VDZ 300 mg or PBO every 4 or 8 wks). Data from both phases of both studies were pooled, and percentages of patients with adverse events (AEs) and serious adverse events (SAEs) in the *Infections and Infestations* System Organ Class (MedDRA® version 15) were determined for those who received VDZ or PBO during *both* induction and maintenance. Data were analyzed by baseline concomitant CS and IM use.
RESULTS: In GEMINI 1 and 2, 1434 patients received VDZ and 297 received PBO during *both* the induction and maintenance phases. Percentages of patients with infection AEs and infection SAEs were similar among subgroups, regardless of whether VDZ was used as monotherapy or with a CS and/or IM (Table).
Table to abstract OP256

	No. (%) of Patients			
Event Preferred Term	VDZ Only (n=445)	VDZ + CS Only (n=506)	VDZ + IM Only (n=247)	VDZ + CS + IM (n=236)
Infection AEs[a]				
Any infection AE	196 (44)	214 (42)	112 (45)	100 (42)
Nasopharyngitis	67 (15)	52 (10)	27 (11)	34 (14)
Upper respiratory tract infection	34 (8)	33 (7)	21 (9)	18 (8)
Bronchitis	20 (4)	20 (4)	9 (4)	8 (3)
Influenza	18 (4)	18 (4)	5 (2)	10 (4)
Sinusitis	13 (3)	18 (4)	3 (1)	10 (4)
Urinary tract infection	14 (3)	17 (3)	7 (3)	11 (5)
Infection SAEs[b]				
Any infection SAE	19 (4)	17 (3)	12 (5)	9 (4)
Anal abscess	6 (1)	3 (<1)	5 (2)	4 (2)
Abdominal abscess	2 (<1)	2 (<1)	0	1 (<1)
Appendicitis	2 (<1)	0	0	0
Sepsis	0	0	0	2 (<1)
Wound infection	0	2 (<1)	0	0

In general, the percentages of patients with individual infection AEs were similar between the PBO and VDZ subgroups, except for nasopharyngitis, which was less common with PBO (range across all PBO subgroups, 4% > 12%). Also, percentages of patients with individual infection SAEs across all PBO subgroups were similar to or nominally lower than those across all VDZ subgroups.
CONCLUSION: These data suggest that the infection AE and SAE profiles in patients with UC or CD are similar whether VDZ is used as monotherapy or with concomitant IM and/or CS therapy. Infection rates were generally similar among the VDZ and PBO groups, although length of exposure tended to be longer for VDZ than for PBO. The rarity of individual infection SAEs limits the interpretation of these data.
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Disclosure of Interest: J.-F. Colombel Consultancy for: Abbott, Amgen, Biogen, M. Boehringer-Ingelheim, BMS, Cellerix SL, Chemocentryx, Centocor, Cosmo Tech Ltd, Elan, Genentech, Giuliani SPA, Given Imaging, GSK, Immune Pharmaceuticals, Merck & Co, Millennium Pharmaceuticals, Neovacs SA, Ocera Therapeutics, Pfizer, Prometheus, Sanofi, Schering, Shire, Synta, Takeda, Teva, Tikvah Therapeutics, Inc., Therakos, TxCell, UCB Pharma, Wyeth, C. Siegel: None declared, B. Abhyankar Other: Employee of Takeda Global Research & Development Centre Ltd., E. Loftus, Jr. Financial support for research from: AbbVie, UCB Pharma, Janssen, Takeda, Amgen, Pfizer, Genentech, Santarus, Shire, Bristol-Myers Squibb, GlaxoSmithKline, Robarts Clinical Trials, Consultancy for: AbbVie, UCB Pharma, Janssen, Takeda, Immune Pharmaceuticals, J. Lewis Financial support for research from: Bayer, Shire, Centocor, Nestle, Takeda, Consultancy for: Takeda, Rebiotix, Amgen, Millennium Pharmaceuticals, Prometheus, Lilly, Shire, AstraZeneca, Janssen Pharmaceuticals, Merck, AbbVie, Other: Served on a Data and Safety Monitoring Board for clinical trials sponsored by Pfizer, S. Sankoh Other: Employee of Takeda Pharmaceuticals International Co., M. Smyth Other: Employee of Takeda Global Research & Development Centre Ltd., C. Milch Other: Employee of Takeda Pharmaceuticals International Co.

TUESDAY, OCTOBER 21, 2014 15:45-17:15

NOVEL APPROACHES FOR THE TREATMENT OF LIVER METASTASES - HALL B

OP257 INCREASED COLORECTAL CANCER RISK IN FIRST-DEGREE RELATIVES OF PATIENTS WITH SERRATED POLYPS WHO DO NOT FULFIL WHO CRITERIA FOR SERRATED POLYPOSIS SYNDROME

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INTRODUCTION: Diagnosis of serrated polyposis syndrome (SPS) is made by the fulfillment of any of the WHO criteria. These criteria have been considered to be very stringent. Patients with multiple serrated polyps can also show high risk of colorectal cancer (CRC) without fulfilling these criteria.
AIMS & METHODS: 1) To determine if patients with multiple serrated polyps non-fulfilling WHO criteria show a similar clinical and molecular profile to SPS cases. 2) To determine the risk of cancer in patients with multiple serrated polyps and their relatives.
Patients from the EPIPOLIP study, a multicenter nationwide project that aimed to investigate causes of multiple colonic polyps, were included. A total of 54 patients fulfilling WHO criteria for SPS were included. As well, 64 patients with more than 10 polyps throughout the colon, more than 50% of them serrated, without fulfilling WHO criteria for SPS (SPS-like group) were also included for comparison. Clinical and pathological characteristics of patients with SPS and SPS-like were compared. Moreover, mutation analysis of KRAS and BRAF was performed in a total of 1504 polyps of all the patients from both groups and also from a third group of 73 patients with sporadic serrated polyps. Age- and sex-adjusted standardized incidence ratios (SIRs) of CRC in first-degree relatives were calculated in SPS and SPS-like pedigrees. SIR from a random sample of 115 families with sporadic CRC was used for comparisons.
RESULTS: Patients with SPS-like show a lower number of polyps (mean 46 *vs* 26; p < 0.001), higher number of adenomas (median 1 vs 3; p=0.002) and an older age at diagnosis (49 vs 53years; p=0.03). There were no differences in family history of CRC or polyps (48% vs 46%) either personal history of CRC (20% vs 17%). KRAS or BRAF somatic mutations have been shown in at least 25% of the polyps in all the SPS cases and in 96% of SPS-like patients. In both groups, somatic mutations of BRAF and KRAS share a very close profile in sessile serrated adenomas (SSA) and hiperplastic polyps (HP) (BRAF: SSA SPS 89%; SSA SPS-like 78%; HP SPS 69%; HP SPS-like 64%; KRAS: SSA SPS 2.8%; SSA SPS-like 8.2%; HP SPS 15.1%; HP SPS-like 9.9%). However, the molecular profile in sporadic serrated polyps is very different, with lower frequency of BRAF mutation and higher of KRAS (BRAF: SSA sporadic 50%; HP sporadic 30%, p < 0.001; KRAS: SSA sporadic 50%; HP sporadic 28.5%, p < 0.001). The incidence of CRC was similar in first-degree relatives (FDR) of patients from both groups, and significantly higher than in relatives of cases with sporadic CRC (SPS: 3.12; SPS-like 3.20; sporadic CRC, 0.45; p < 0.001).
CONCLUSION: Patients with multiple serrated polyps non-fulfilling WHO criteria show a clinical and molecular profile very similar to patients with SPS. Moreover, FDR from these patients show a CRC risk also similar to SPS patients. These patients and their relatives should be considered as high risk population.
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Disclosure of Interest: None declared

OP258 ANALYSIS OF DNA METHYLATION IN BOWEL LAVAGE FLUID FOR DETECTION OF COLORECTAL CANCER

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INTRODUCTION: Aberrant DNA methylation could potentially serve as a biomarker for colorectal neoplasms. In an earlier study, we demonstrated that DNA methylation is detectable in the mucosal wash fluid from colorectal tumors, which can be collected during colonoscopy [1]. Importantly, wash fluid from invasive cancers exhibited significantly higher levels of methylation of tumor-related genes than noninvasive tumors. This prompted us to postulate that wash fluid from invasive tumors contained greater numbers of exfoliated tumor cells, and that the methylation was a potential biomarker predictive of tumor invasiveness.
AIMS & METHODS: In the present study, we assessed the feasibility of using DNA methylation detected in bowel lavage fluid (BLF) for colorectal cancer (CRC) screening. A total of 508 BLF specimens were collected from patients with CRC (n = 56), advanced adenoma (n = 53) or minor polyp (n = 209) and healthy individuals (n = 190) undergoing colonoscopy. Methylation of 15 genes (*miR-1-1*, *miR-9-1*, *miR-9-3*, *miR-34b/c*, *miR-124-1*, *miR-124-2*, *miR-124-3*, *miR-137*, *SFRP1*, *SFRP2*, *APC*, *DKK2*, *WIF1*, *LOC386758* and *ZNF582*) was then analyzed in MethyLight assays, after which receiver operating characteristic (ROC) curves were analyzed to assess the diagnostic performance of BLF methylation.
RESULTS: After analyzing BLF specimens in a training set (n = 345), we selected the three genes showing the greatest sensitivity for CRC detection (*miR-124-3*, 71.8%; *LOC386758*, 79.5%; *SFRP1*, 74.4%). A scoring system based on methylation of those three genes (M-score) achieved 82% sensitivity and 79% specificity, and the area under the ROC curve (AUC) was 0.834. The strong performance of this system was then validated in an independent test set (n = 153, AUC = 0.808). No significant correlation was found between M-score and the clinicopathological features of the CRCs.
CONCLUSION: Our results demonstrate that DNA methylation in BLF specimens may be a useful biomarker for detection of CRC. BLF methylation tests could potentially improve the diagnostic performance of other screening methods, including the fecal occult blood test and computed tomographic colonoscopy.
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Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45–17:15
EVIDENCE-BASED TREATMENT OF ACHALASIA – HALL C

OP259 IS GASTROESOPHAGEAL REFLUX DISEASE A MAJOR DRAWBACK OF PERORAL ENDOSCOPIC MYOTOMY? ANALYSIS OF CLINICAL, PROCEDURAL AND FUNCTIONAL FACTORS, ASSOCIATED WITH GERD AND ESOPHAGITIS

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INTRODUCTION: Per-Oral Endoscopic Myotomy (POEM) combines the long term efficacy of an esophagogastric myotomy with the benefits of an endoscopic, minimally invasive, procedure for the treatment of achalasia. An anti-reflux wrap is usually associated to surgical myotomy. No antireflux procedures are performed after POEM. Previous studies demonstrated that POEM is a safe and effective procedure at mid-term follow-up. However, incidence of GERD after POEM has been not satisfactorily analyzed.
AIMS & METHODS: Aim of this study is to evaluate the incidence of GERD after POEM in a large consecutive series of patients, and to identify the clinical factors associated with the disease.
A total of 156 patients underwent POEM in a single endoscopy center between 2011 and April 2014. After POEM patients underwent a regular follow-up. Postoperative GERD was systematically investigated with an esophageal manometry, EGD, and pH-monitoring (usually between the 6-month and 12-month follow-up). During a mean follow-up of 11 months, 81 patients had a complete GERD evaluation and were included in the study. Demographics (sex and age), data on the clinical history (BMI, medications, alcohol and tobacco consumption), the esophageal manometry (postoperative basal LES pressureand 4sIRP) and the procedure (length of myotomy) were prospectively collected and analyzed. GERD was defined by an altered esophageal acid exposure at pH-monitoring (total reflux time > 5%). Esophagitis was classified according to the Los Angeles classification. Fisher's Exact test and ANOVA test were used to identify factors associated with GERD incidence and esophagitis.
RESULTS: An altered esophageal acid exposure was demonstrated in 44 patients (54%; mean total reflux time 23% [range 6.6% – 69.8%]; mean DeMeester score 82.9, [22.7-224.1]). Twenty patients (24.7%) had reflux esophagitis (10 grade A, 4 grade B, 4 grade C, 2 grade D). Only 38,6% of patients with GERD had heartburn, including 45% of patients with esophagitis. All the symptomatic patients, and those with esophagitis received pantoprazole 40mg /day, with a complete symptoms relief. No medications were prescribed in case of normal findings at EGD and/or no symptoms
At univariate analysis, altered esophageal acid exposure was correlated only with the age of patients (50.477 year (GERD) vs 41.86 years (no GERD), p=0.029) and IRP (8.897 (GERD) vs 12.033 (no GERD), p=0.012). Reflux esophagitis was correlated with 4sIRP (6.821 mmHg (esophagitis) vs 11.524 mmHg (no esophagitis), p=0.001). BMI was substantially higher in patients with esophagitis (27.1 Kg/m2 vs 24.7 Kg/m2, p=0.06). GERD or esophagitis were not associated with sex, length of myotomy, postoperative basal LES pressure, alcohol consumption or tabagism.
CONCLUSION: GERD is a frequent adverse event after POEM, and may represent a significant drawback of the procedure. Nevertheless, the majority of patients with have no symptoms. Heartburn and esophagitis can be easily managed with standard medications. GERD is significantly correlated with patient's age and a low post-operative 4sIRP. The clinical impact of POEM-related GERD should be evaluated by larger studies with long term follow-up, and comparative trials vs. Heller-Dor and vs. pneumodilation.
Disclosure of Interest: None declared

OP260 PERORAL ENDOSCOPIC MYOTOMY (POEM) IS A SAFE AND EFFECTIVE RESCUE THERAPY AFTER A FAILED HELLER MYOTOMY: RESULTS OF A CONSECUTIVE SERIES OF PATIENTS

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INTRODUCTION: Symptoms recurrence occurs in approximately 10% of patients with achalasia after Heller myotomy. Pneumatic balloon dilation is the first line treatment in case of recurrence, with only partial benefits at long term. Peroral Endoscopic Myotomy combines the long term benefits of a surgical myotomy with the advantages of a less invasive intervention. Differently from surgery, POEM can be easily performed everywhere in the esophagus, also including the posterior esophageal wall. POEM can be thus considered as viable treatment after a failed surgical myotomy.
AIMS & METHODS: We report on a consecutive series of patients who underwent POEM after a failed Heller. Perioperative data were compared with those of a standard POEM population.From 2011 to April 2014, 156 patients with achalasia underwent POEM in a single tertiary referral center. Five (3.2%) patients (3 female, mean age 63.6 years [range 53–72]) were treated for symptoms recurrence after surgery. Previous operations included: 1 open Heller/Lortat-Jacob procedure; 2 thoracotomic Heller myotomy without antireflux wrap; 1 laparoscopic Heller-Dor procedure; 1 laparoscopic Heller-Thal procedure. POEM was performed a mean of 20 years (2-48 years before) after surgery. Data on the clinical history and the procedure were prospectively collected. Esophageal manometry, and EGD were performed before POEM and during the follow-up. Esophageal pH-monitoring was performed 3 months after POEM. The procedural data of the 5 patients treated after a failed Heller myotomy (FH-group) were compared with those of the other patients treated with POEM (n=151) in our department (POEM-group).
RESULTS: POEM was successfully completed in all the patients of the FH-group. POEM aborted in 7 of the 151 patients (4.5%) of the POEM-group.In the FH-group, mean preoperative basal LES pressure and 4sIRP were 31.3 mmHg (9-50 mmHg) and 23 mmHg (10-45 mmHg), respectively. Mean preoperative Eckard score (ECK) was 7(5-9).Operating time was similar in the FH-group and POEM group (67 minutes [57-161] and 78 minutes [38-161], respectively). Mean length of the submucosal tunnel was 15 cm in the FH-group and 14 in the POEM-group. Mean length of myotomy was 10.8 cm (range 8–13 cm) in the FH-group and 12 cm (7-17) in the POEM-group. Mean post-operative hospital stay was similar in the FH-groups and POEM-group, 3.5 days and 3 days respectively. No perioperative complications occurred in the FH-group. One patient in the POEM-group (0.6%) experienced a large mucosal-flap ulcer that resulted in an esophageal stricture. At 3-month follow-up, a significant drop of the ECK (from 7 to 0.2) was documented in all the cases. Average weight gain after the procedure was 4.5 kg. Postoperative basal LES pressure and 4sIRP was 20.14 mmHg and 7.5 mmHg respectively. Gastroesophageal reflux was documented in 3 of the 5 patients (60%). Two patients suffered from esophagitis but only one patient referred daily heartburn.
CONCLUSION: Our results confirm the feasibility, safety and efficacy of POEM in patients with symptoms recurrence after Heller myotomy. Additional studies with a long term follow-up, and comparative trials vs. pneumodilation are necessary to confirm the role of POEM in the treatment of patients after the failure of a surgical myotomy.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45–17:15
ENDOSCOPIC MANAGEMENT OF EARLY COLORECTAL NEOPLASIA – HALL G/H

OP261 COMPLICATIONS AFTER ENDOSCOPIC MUCOSAL RESECTION OF LARGE COLORECTAL LESIONS. A MULTICENTER SPANISH EMR GROUP STUDY

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INTRODUCTION: The main complications of endoscopic mucosal resection (EMR) of large colonic lesions are delayed bleeding (DB) (2-22%) and perforation (0.6-1.4%). There are no standardized preventive procedures for these complications.
AIMS & METHODS: The aim was to describe the complications rate after EMR of large colorectal lesions and to identify potential risk factors involved. We analysed data from 881 EMRs of colorectal lesions ≥20 mm. 660 EMRs were prospectively registered from February 2013 to March 2014 at 17 hospitals as part of a Spanish multicenter study. Data were registered on features of patients and lesions, procedural characteristics and outcomes. DB was defined as a clinical evident bleeding, a decrease of hemoglobin in more than 2 g/dL or of blood pressure in more than 20 mmHg or an increase of the beat rate in more than 20% evidenced 24 h or later after EMR.
RESULTS:

	DB (n=36)	p (Vs no DB)	All patients (N=881)
Size(mm ≥30/≥40	**77.8/47.2**	<0.01/0.01	55.9/28.4
Location Proximal transverse/proximal splenic flexure	**63.9/72.2**	<0.01	39.2/49.9
Age(years) ≤60/61-74 / ≥75	17.1/25.7/**57.1**	0.02	21.3/43.1/35.6
ASA I/II/III/IV	8.3/36.1/**52.8**/2.8	0.03	15/51.3/30.6/3.1
Aspirin No/ Yes (ceased)/ 7emsp;Yes (during EMR)	**66.7**/22.3/11.1	0.03	83.2/13.2/3.7
Clips Mucosal defect complete closure	**5.6**	0.06	17.3

A total of 881 EMR were performed. There were 36 (4.0%) cases of DB and 11 (1.2%) perforations. Factors associated with DB were increasing lesion size, proximal location, patients older than 75 years, higher ASA classification and aspirin treatment. Only 2 of the EMR which had their mucosal defect fully clipped underwent DB (1.3%(2/151) Vs 4.7% not closed, p=0.06). Lesions that had been treated with APC for coagulation did not suffer DB (p=NS). All DB were successfully managed endoscopically with the exception of one patient who required a vascular interventional radiology treatment. Two patients required surgery due to perforation (0.2%). No risk factors has been associated to perforation.
CONCLUSION: DB rate after EMR of large colorectal lesions in our study was 4.0 %. DB occurred most frequently in lesions ≥30-40 mm located in the proximal colon, in older patients with comorbidities (ASA III–IV) and in those taking aspirin (p<0.05). Perforation rate in this study was 1.2%. No risk factors has been associated to this complication.
Disclosure of Interest: None declared

OP262 EFFICACY AND SAFETY OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR EARLY STAGE COLORECTAL NEOPLASIA; RESULTS FROM A NATIONWIDE REGISTRY THROUGHOUT JAPAN

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INTRODUCTION: In the West, when endoscopic polypectomy or mucosal resection is not possible for early stage colorectal neoplasms, surgery is the standard of care. Endoscopic submucosal dissection (ESD) can potentially fill this gap between polypectomy and surgery, giving another endoscopic treatment option that preserves the native anatomy. However, while high en bloc resection rates for colorectal ESD have been reported, these earlier reports were limited to specialized institutions.
AIMS & METHODS: This study is, therefore, aimed to elucidate the efficacy and safety of ESD for early stage colorectal neoplasms from a nationwide registry throughout Japan not only in referral centers.
The Japan Gastroenterological Endoscopy Society (JGES) conducted a nationwide registry for colorectal ESD. Rates of en bloc resection, en bloc plus R0 (tumor-free margins) resection and ESD related complications were collected prospectively.
Registry inclusion criteria were 1) Early colorectal cancer >2 cm not amenable to EMR; 2) Adenoma with non-lifting sign preventing safe EMR; 3) Residual or recurrent adenoma after EMR, >1 cm, not amendable to EMR. The registry protocol was approved by the ethics committee of each participating hospital and the JGES. The trial was registered with UMIN-Clinical Trials Registry, number UMIN-CTR 000004040.
RESULTS: From August 2010 to January 2012, 1564 consecutive patients from 69 institutions (561 adenomas, 747 mucosal cancers, 235 submucosal invasive cancers, 2 cancers with unknown depth, 12 other lesions, 7 lesions with unknown histology) were entered into this registry. ESD was completed in 1544 (98.7%) patients. En bloc resection and en bloc plus R0 resection rates were 1484 (94.9%) and 1278 (81.7%) respectively. Additional surgery was necessary in 133 (8.5%) patients. Postoperative bleeding, intraoperative perforation, postoperative perforation, penetration and peritonitis occurred in 43 (2.8%), 47 (3.0%), 6 (0.4%), 19 (1.2%) and 8 (0.5%) patients, respectively. Emergency surgery was necessary in 8 (0.5%) patients (4 for intraoperative perforation and the other 4 for postoperative perforation). Blood transfusion was required in one patient (0.06%) due to postoperative bleeding. Follow up in one year revealed a 0.90%(11/1217) rate of local recurrence.
CONCLUSION: This nationwide registry throughout Japan reveals that colorectal ESD has matured to a standard treatment for early stage colorectal neoplasia based on efficacy, safety and short-term outcome.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45-17:15
SAFETY IN ENDOSCOPY - HALL I/K

OP263 HOW SAFE AND EFFECTIVE IS ORAL REHYDRATION THERAPY IN CORRECTING THE METABOLIC DISTURBANCES POST-COLECTOMY IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS?

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INTRODUCTION: There is evidence that colon is an active metabolic organ, the removal of which leads to chronic activation of the renin-angiotensin-aldosterone system (RAAS) which in turn results in sodium depletion, hyperaldosteronism and abnormal glucose tolerance. Previous work has studied patients who have undergone colectomy for inflammatory bowel disease (IBD)[1,2]. Patients with Familial adenomatous polyposis (FAP) undergo prophylactic colectomy with ileorectal anastomosis (IRA) or restorative proctocolectomy (RPC) or colectomy with end-ileostomy in their late teens. We have established (60 FAP participants) that colectomy results in RAAS activation, abnormal glucose tolerance and poor quality of life.
AIMS & METHODS: To evaluate if oral rehydration therapy (ORT) is safe and effective in restoring water and electrolyte balance post-colectomy.
Blinded placebo-controlled randomised cross-over trial. 30 patients with demonstrated hyperaldosteronism from the on-going observational study were recruited. Patients were randomised to receive either placebo or ORT first in a cross-over trial for 4 weeks with an intervening washout period of 4 weeks. Patients attended clinical investigation day (CID) once at the end of each 4 weeks. **CID**: After fasting, urine and blood samples were collected to measure sodium loss, hydration status and RAAS activation. Oral glucose tolerance test was performed. Health related quality of life (HRQoL) was assessed using SF-36 and FACIT-F questionnaires.
RESULTS: **Cross-over RCT**: **Biochemistry results:** Data acquired so far in 16 patients (n=48 patient CIDs) have demonstrated fasting plasma aldosterone concentration post-ORT to be significantly lower compared to baseline [189.25 (7.24) *vs* 536.25 (12.56) pmol/L; *p*=0.05]. ***HRQoL results***: **SF 36** –Post-ORT, patients reported improvement in six of the eight dimensions of health as compared to baseline. **FACIT-F** – Post-ORT, patients reported higher scores on four of the five scales with higher total scores when compared to baseline.
CONCLUSION: ORT forms a safe and effective intervention to correct the metabolic disturbances post-colectomy resulting in restoration of metabolic homeostasis and a positive impact on quality of life.
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Disclosure of Interest: None declared

OP264 INCIDENCE AND RISK FACTORS FOR SEDATION-ASSOCIATED COMPLICATIONS IN GI-ENDOSCOPY — RESULTS OF OVER 250,000 ENDOSCOPIES: THE PROSPECTIVE, MULTICENTER REGISTRY OF THE GERMAN WORKING GROUP OF LEADING HOSPITAL GASTROENTEROLOGISTS (ALGK): PROSED 2 - STUDY

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INTRODUCTION: Administering sedation is an established standard practice in gastrointestinal endoscopy. Sedation is unquestionably associated with a certain

risk of complications. The data so far published on sedation-associated complications are limited, in the majority of cases derived from studies including only small numbers of patients and with clear methodological weaknesses.
AIMS & METHODS: The aim of the present study was to record the incidence and type of sedation-associated complications. Risk factors were also to be identified. Sedation-associated complications were recorded and documented with computer support, using the input template of an endoscopy documentation system (E&L Ltd., Erlangen, Germany) that only allows an examination to be entered as complete if the sedation form has been filled out — ensuring 100% data recording.
RESULTS: Data from 34 participating study centers were evaluated. The study period was from December 2009 to February 2014 (median inclusion period 2 years). A total of 276,764 endoscopies were documented. Of these, 31,267 were carried out without sedation. Propofol-based sedation was administered in 85% of the cases; 16,513 endoscopies (6%) were carried out on an emergency basis. A total of 25 major complications occurred (0.01%; definition: meeting at least one of the following criteria: admission to intensive care; intubation; resuscitation; death). Six patients (0.002%) died. Five of these six patients were in American Society of Anesthesiologists (ASA) class 3 or higher and/or were undergoing emergency endoscopy (two of six, 33%). Endoscopic retrograde cholangiopancreatography (ERCP) was carried out in four of the six patients. The proportion of ERCP examinations in all endoscopies conducted was 6.6%.
CONCLUSION: The present study is the largest prospective multicenter study to have been carried out worldwide to document complications of sedation. The data show that severe sedation-associated complications are rare in gastrointestinal endoscopy. Risk factors include ASA class 3 status or higher, emergency endoscopy, and/or ERCP procedures.
Disclosure of Interest: A. Behrens Financial support for research from: E&L medical systems GmbH, C. Ell: None declared

OP265 GASTROENTEROLOGIST-ADMINISTERED BALANCED PROPOFOL SEDATION IS SAFE, EFFECTIVE AND FEASIBLE TO USE FOR OUTPATIENT COLONOSCOPY EXAMINATIONS

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INTRODUCTION: Given its rapid onset and short duration of action, Propofol is an effective and appealing drug for conscious sedation in endoscopy. Current product labeling dictates its administration only in the presence of personnel trained in administering general anesthesia. Unfortunately, this significantly raises the costs of endoscopy by requiring anesthesiology services. Only limited data have demonstrated that Propofol can be safely and effectively administered by a Propofol-trained endoscopy team.
AIMS & METHODS: We aimed to evaluate, during outpatient colonoscopy procedures, the safety of gastroenterologist-administered balanced propofol sedation (BPS) consisting of fentanyl, midazolam and propofol without an anesthesiologist or nurse anesthetist present. We performed a retrospective observational study using prospectively collected endoscopy data from a tertiary care university hospital endoscopy unit where gastroenterologist-administered BPS is routine practice. All gastroenterologists undergo standardized conscious sedation training and testing every two years and are required to have up to date advanced cardiac life-saving certification. We evaluated patient-level demographic variables including: age, gender, ASA score, indication for colonoscopy. We also evaluated clinical and patient outcome variables including: BPS drug dosages, pre- and post-colonoscopy oxygen saturation levels, pulse, systolic/diastolic blood pressure, need for mask bag ventilation or endotracheal intubation, aborted colonoscopy procedure due to sedation, hospital admission post colonoscopy, and mortality. This study was Helsinki committee approved.
RESULTS: From April 1 to November 30, 2013, n=1036 patients (mean age 56.4 years, 570 (55%) males) underwent ambulatory colonoscopy and received gastroenterologist-administered BPS from any one of 12 gastroenterologists who perform endoscopy in the endoscopy unit. Reason for colonoscopy included: CRC screening / surveillance n=352 (34.0%), evaluation of lower GI symptoms n=404 (39.0%), positive FOBT n=156 (15.1%), and IBD follow up n=124 (11.9%). ASA scores were: ASA I n=332 (32.1%), ASA II n=611 (59.0%), ASA III n=93 (8.9%). BPS dosages (mean±SD) per patient were as follows: Fentanyl 0.05mg (fixed dose), Midazolam 1.6mg ± 0.5mg, and Propofol 104mg ± 62mg. Post-colonoscopy (mean±SD) O_2 saturation levels were 98% ± 4%. Pre and post colonoscopy blood pressures were 133/77 mmHg vs. 118/67 mmHg (p-value <0.001) and pulse 75/min vs.66/min (p-value<0.001). No patient required bag mask ventilation, endotracheal intubation, or hospital admission. There were no aborted colonoscopies secondary to sedation and no mortality. All patients were discharged from the endoscopy unit recovery area directly to home.
CONCLUSION: Gastroenterologist-administered BPS appears safe, effective and feasible to use, including in ASA II and III level patients, undergoing outpatient colonoscopy. Although pre-post colonoscopy blood pressures and pulse rates were found to be statistically significantly different, this difference does not appear to be clinically meaningful (15 point SBP and 10 point DBP reduction, 9 beats/min pulse reduction). There were no observed adverse events or mortality associated with gastroenterologist-administered BPS in this study population.
Disclosure of Interest: None declared

OP266 SAFETY OF PROPOFOL ADMINISTERED BY GASTROENTEROLOGISTS AND TRAINED NURSES IN AN ENDOSCOPY UNIT. A LARGE PROPECTIVE STUDY

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INTRODUCTION: Sedation in gastrointestinal endoscopy performed by a specially trained nurse, guided by endoscopist, is increasingly common in European countries. Numerous published studies support the efficacy and safety of this technique, in which propofol is administered during endoscopic procedures, based on weight, age, and clinical status of the patient. However, there are controversies on the use of propofol by non-anesthesiologists in gastrointestinal endoscopy despite the evidence on its safety.
AIMS & METHODS: The aim of our study was to describe our experience on the safety and effectiveness of propofol administered by medical and nursing staff of an endoscopy unit. We prospectively recorded all esophagogastroduodenoscopies (EGDs) and colonoscopies performed in our unit between June 2012 and March 2014. Sex, age, weight, anesthetic risk, propofol dose, type of examination, complications, and patient and physician satisfaction data were prospectively collected. We excluded procedures not sedated by endoscopist, and patients with two endoscopic procedures performed on the same day. Statistical analysis was performed with the SPSS v20.0 program.
RESULTS: We performed 7,707 procedures, 4148 (53.8%) were colonoscopies and 3559 (46.2%) EGDs. Propofol was used in all patients at an initial dose of 0.5-1 mg/kg. Colonoscopies also received a fixed dose of 50 mcg of fentanyl. 54.6% of patients had an anesthetic risk ASA I; 41.4%, ASA II; and 4%, ASA III. The mean age was 54 ± 16.8 (30.4% were ≥65years). There were 20.7% therapeutic procedures.
The mean dose of propofol was 129.8 ± 58.06mg. In patients ≥65years it was 99.2 ± 50.8mg (P= 0.001). The mean dose of propofol in EGDs was 124.3 ± 52.6mg and 134.4 ± 61.9mg in colonoscopies (P= 0.0001).
We recorded 125 (2.6%) adverse events, all minor (85 desaturation, 31 bradycardia, 5 hypotension and other 4). Most were recovered with chin lift maneuver (only 3 needed bag-valve-mask ventilation), atropine and volume expansion. 71 adverse events (48 desaturation, 17 bradycardia, 3 hypotension and other 3) occurred in ≥65 years (P = 0.03), being ASA II in 69.1% (P = 0.001). 97.7% of the procedures were complete, and only 4 (0.1%) were discontinued due to complications with sedation. Overall satisfaction recorded by the endoscopist was excellent-good in 99.6% and moderate in 0.3%, being the patient tolerance excellent in 99.8%.
CONCLUSION: The use of propofol administered by the endoscopist assisted by nurse is an effective and safe method of sedation, allowing a more comfortable exploration for both the physician and patient.
Disclosure of Interest: None declared

OP267 SERIOUS ADVERSE EVENTS OF NONANESTHESIOLOGIST-ADMINISTERED PROPOFOL IN RELATION WITH GASTROINTESTINAL ENDOSCOPIC PROCEDURE

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INTRODUCTION: The serious adverse events (SAE) of nonanesthesiologist-administered propofol (NAAP) would depend on the gastrointestinal endoscopic procedure.
AIMS & METHODS: To determine the SAE of NAAP rate regarding the gastrointestinal endoscopic procedure. Through a prospective database were registered all consecutives patients that underwent to endoscopic procedure with NAAP sedation, during the last 5 years. We recorded the SAE: bradycardia <40 bpm, tachycardia >150bpm, severe systolic hypotension (<70mmHg), severe systolic hypertension (>250mmHg), severe lower oxygen saturation (SpO2 <70%), laryngospasm, aspiration, seizures, cardiac arrest and death. We had also included the following entries: balloon ventilation requirement, tracheal intubation, defibrillation and the patients who needed additional support from anaesthesiologist or critical care specialist.
RESULTS: Between 27971 endoscopic procedures we observed 251 SAE of NAAP (0.9%). Age: 59.4±16.4 y; women: 40.6%. Severe bradycardia and tachycardia were more frequent in ERCP: 8(0.4%); p=0.000 and 4(0.2%); p=0.017, respectively; as well as hypertension: 4(0.2%); p=0.001 and SpO2 <70%: 38(1.8%); p=0.000. Laryngospasm was most frequent in EUS 2(0.4%); p=0.002. Aspiration was registered only in gastroscopy 4(0.0%) and ERCP 2(0.1%); p=0.042. We observed seizures in gastroscopy 3(0.0%), although without statistic significance p=0.430. We required balloon ventilation in gastroscopy, colonoscopy and ERCP: 23(0.2%), 4(0.0%) y 4(0.2%); p=0.017, respectively. We did tracheal intubation and it was necessary additional support from anaesthesiologist or critical care specialist mainly in gastroscopy: 4(0.0%); p=0.277 and 8(0.1%); p=0.061. In colonoscopy, the complication rate was the lowest: 63(0.6%); p=0.000. We had not needed defibrillation and there were no deaths.

	Gastroscopy n=14567	Colonoscopy n=10787	EUS n=559	ERCP n=2058	TOTAL n=27971	p
Total Complications	124 (0,9%)	63 (0,6%)	8 (1,4%)	56 (2,7%)	251 (0,9%)	0,000
Bradycardia < 40 bpm	16 (0,1%)	31 (0,3%)	1 (0,2%)	8 (0,4%)	57 (0,2%)	0,000
Tachycardia >150 bpm	10 (0,1%)	2 (0%)	0	4 (0,2%)	16 (0,1%)	0,017
Hypertension >250mmHg	7 (0%)	0	0	4 (0,2%)	11 (0%)	0.001
Sp02 <70%	66 (0,5%)	14 (0,1%)	5 (0,9%)	38 (1,8%)	123 (0,4%)	0,000
Laryngospasm	9 (0,1%)	2 (0%)	2 (0,4%)	0 (0%)	13 (0%)	0,002
Aspiration	4 (0%)	0	0	2 (0,1%)	6 (0%)	0,042
Balloon ventilation	23 (0,2%)	4 (0%)	0	4 (0,2%)	31 (0,1)	0,017
Anesthesio.-CCS support	8 (0,1%)	0	0	0	8 (0%)	0,061

CONCLUSION: In nonanesthesiologist-administered propofol the serious adverse events rate is very low (0.9%). The ERCP recorded the highest rate: more tachycardia, hypertension, severe lower oxygen saturation and aspiration while the colonoscopy was the lowest.
Disclosure of Interest: None declared

OP268 MULTICENTER RANDOMIZED CONTROLLED STUDY TO ASSESS THE PREVENTIVE EFFECT OF PROPHYLACTIC CLIPPING FOR POST-POLYPECTOMY BLEEDING

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INTRODUCTION: Prophylactic clipping has been widely used to prevent post-polypectomy bleeding. However, its efficiency has not been confirmed and so far there is no consensus on the usefulness of prophylactic clipping.
AIMS & METHODS: To evaluate the preventive effect of prophylactic clipping for post-polypectomy bleeding.
A multicenter randomized controlled study was conducted from April 2004 to July 2013 in Japan. Inclusion criteria were patients who were >20 years old and had polyps <2cm. Patients were divided into the clipping group or the non-clipping group by cluster randomization. After endoscopic polypectomy, patients allocated to the clipping group underwent prophylactic clipping, whereas in those allocated to the non-clipping group, the procedure was finished without clipping. When spurting bleed occurred shortly after polypectomy, hemostatic treatment had done and its polyp was excluded from this study. When oozing bleed or visible vessels were found, coagulation were added by the tip of a snare, the procedure was continued according to the method in each group.
The occurrence of post-polypectomy bleeding was compared between the two groups.
RESULTS: Seven hospitals participated in this study. 3365 polyps in 1499 patients were evaluated. The clipping group consisted of 1636 polyps in 752 patients, and the non-clipping group of 1729 polyps in 747 patients. Post-polypectomy bleeding occurred in 1.10 % (18/1636) of the cases in the clipping group, and in 0.88% (15/1729) of those in the non-clipping group. The difference was -0.22% (95%CI:-0.96, 0.53). The upper limit of 95%CI was lower than the non-inferiority margin (1.5%), so we could prove the non inferiority of non-clipping against clipping. The main risk factor of post-polypectomy bleeding was polyp size in both groups. Furthermore, additional coagulation was also a risk factor in the non-clipping group.
CONCLUSION: Prophylactic clipping is not necessary to prevent post-polypectomy bleeding. Because additional coagulation was one of the risk factors of post-polypectomy bleeding, we consider cold polypectomy without high frequency coagulation as an effective alternate procedure.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45–17:15
NOVEL INSIGHTS INTO THE IMMUNOPATHOGENESIS OF COLITIS – HALL R

OP269 HUMAN MONONUCLEAR PHAGOCYTES REGULATE THE BALANCE BETWEEN INTESTINAL GROUP1 AND GROUP 3 INNATE LYMPHOID CELLS

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INTRODUCTION: Recently we identified a human CD127$^+$ innate lymphoid cell (ILC) subset, which produces high amounts of IFNγ following activation, and expresses the transcription factor T-bet. This ILC subset was termed ILC1. It is likely that these cells are important for the innate immune response against pathogenic bacteria, as similar ILC1 identified in mice mediate immunity against *Salmonella Enterica*. ILC1 may also be pathogenic by itself, as they accumulate in inflamed intestinal tissues of Crohn's patients, whereas the frequency of IL-22 producing ILC3 is diminished.
ILC3 are the predominant ILC subset in the small bowel and maintain the integrity of the intestinal mucosa. Obviously the balance between the protective ILC3 and the inflammatory ILC1 should be tightly regulated to reduce the risk for chronic inflammatory responses leading to disease. However it is yet unclear how this is achieved.
AIMS & METHODS: In this study we set out experiments to determine the physiological triggers that drives ILC1 and ILC3 differentiation. Furthermore, we aimed to identify the cellular source of the regulators of the ILC1/ILC3 balance.
RESULTS: Here we demonstrate that CD127$^+$ ILC1 - but not CD103$^+$ intraepithelial NK or conventional NK cells – differentiate towards ILC3 in response to IL-23 and IL-1β, a process, which is synergistically enhanced by retinoic acid. Furthermore, we found that ILC3 differentiate towards IFNγ-producing CD127$^+$ ILC1 under influence of the pro-inflammatory cytokine IL-12.
In experiments aimed to identify the cellular source of the regulators of the ILC1/ILC3 balance, we found that tissue-infiltrating monocytes produce IL-12 and drive ILC1 differentiation, whereas tissue-resident CD103$^+$ dendritic cells can convert ILC1 towards ILC3.
CONCLUSION: These findings reveal that the balance between pro-inflammatory ILC1 and protective ILC3 is regulated by environmental cues. An efficient mechanism presents itself by which ILC can quickly adapt to changes inflicted by pathogens without the need of recruiting new cells from circulation.
Disclosure of Interest: None declared

OP270 INNATE LYMPHOID CELLS TYPE 1 AND TYPE 3 ARE A SOURCE OF INFLAMMATORY CYTOKINES IN CELIAC DISEASE

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INTRODUCTION: Innate lymphoid cells (ILCs) are an emerging family of hematopoietic cells involved in host defence, immune homeostasis and tissue repair. Various subsets of ILCs producing specific repertoires of cytokines have been identified and implicated in the pathogenesis of immune-mediated diseases.
AIMS & METHODS: In this study, we have phenotypically characterized ILCs in celiac disease (CD), a gluten-driven enteropathy, and determined whether these cells are a source of cytokines in this disease. ILC subpopulations were analyzed in lamina propria mononuclear cells (LPMCs), isolated from duodenal biopsies of patients with active CD, patients with inactive CD on a gluten-free diet and normal controls and jejunal specimens of patients undergoing gastrointestinal bypass by flow cytometry. Cytokines, transcription factors and receptors for interleukin (IL)-15, interferon (IFN)-alpha and Toll-like receptors (TLR) were assessed in ILCs either freshly isolated or following incubation of control LPMC with IL-15, IFN-alpha and poly I:C, a TLR agonist, by flow cytometry.
RESULTS: The frequency of ILCs in the intestinal lamina propria of patients with active CD did not differ from that in normal controls and inactive CD patients on a gluten-free diet. However, the fractions of T-bet-expressing ILCs type 1 and ROR-gammat-expressing ILCs type 3 were increased in active CD as compared to controls, and these ILC subsets produced IFN-gamma and IL-17A, respectively. ILCs expressed IL-15 receptor a and toll-like receptors 2, 3 and 9. Treatment of normal intestinal lamina propria mononuclear cells with IL-15 and Poly:IC, a TLR3 ligand, increased production of IFN-gamma, but not IL-17A, by ILCs.
CONCLUSION: These data indicate that CD mucosa is infiltrated with ILCs type 1 and ILCs type 3 that produce inflammatory cytokines and suggest that ILCs could make a contribution to the CD-related inflammatory response.
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Disclosure of Interest: None declared

OP271 THE TLR-9 AGONIST DIMS0150 DIRECTLY UPREGULATES INTERLEUKIN-10 POSITIVE CELLS IN THE COLONIC MUCOSA OF ULCERATIVE COLITIS PATIENTS

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INTRODUCTION: The oligonucleotide DIMS0150 is a Toll like receptor 9 (TLR9) agonist and has been shown to be therapeutically efficacious in the treatment of refractory ulcerative colitis. In cultured PBMCs, DIMS0150 induced a variety of anti-inflammatory cytokines, including Interleukin (IL)-10. In order to gain a deeper understanding of the mechanism of action of DIMS0150, we analyzed its effect in cultured LPMCs *in vitro* and on histological sections from colon biopsies taken at different time points before and after local application of DIMS0150 in ulcerative colitis patients during a clinical trial.
AIMS & METHODS: A randomized, double-blinded, multicenter phase II trial was performed with DIMS0150 in steroid refractory patients with ulcerative colitis of moderate degree (EudraCT number: 2006-001846-15). Patients were randomized to a single rectal administration of either 30 mg of DIMS0150 or placebo. Clinical response at week 1 and 4 was 41.2% and 52.9% in the DIMS0150 treated group and 9.1% and 36.4% in the placebo treated group.

Colon biopsies of ulcerative colitis patients were taken before, 7 and 28 days after DIMS0150 or placebo treatment and its cross sections were stained for cell apoptosis (TUNEL) and IL-10, respectively. Immunofluorescence microscopy subsequently allowed quantification of positive intestinal immune cells. LPMCs were isolated from colonic biopsies or surgical specimen and cultivated overnight with and without 100 μM DIMS0150. IL-10 expression was determined with ELISA and flow cytometry.
RESULTS: Analysis of cross-sections from colon biopsies of ulcerative colitis patients treated with DIMS0150 revealed no induction of apoptosis in LPMCs. This result was further confirmed by cultured LPMCs, where DIMS0150 treatment similarly did not lead to apoptosis induction. Quantitative analysis of sections from colon biopsies of ulcerative colitis patients taken before and after application of DIMS0150 treatment (n=11-16) clearly indicated a significant induction of IL-10 positive mucosal immune cells after DIMS0150 treatment which was not observed in the placebo group (n=5-7). Double staining revealed that the main IL-10 producers were mucosal CD4+ T-cells and CD11b positive monocytes and macrophages. Correspondingly, it could be shown that DIMS0150 directly induced IL-10 production *in vitro* in lamina propria CD4+ and CD14+ cells.
CONCLUSION: In clinical trials, topical administration of DIMS0150 has shown promising effects in the treatment of therapy refractory ulcerative colitis patients. Our data reveal that application of DIMS0150 significantly induced IL-10 production by T-cells, monocytes and macrophages in the colonic mucosa. Thus, induction of the anti-inflammatory cytokine IL-10 could be the central therapeutic mechanism of action of the late stage clinical candidate DIMS0150 in ulcerative colitis patients.
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OP272 FLAVONOID CONFERS COMMUNICABLE PROTECTION AGAINST COLITIS THROUGH THE NLRP6 INFLAMMASOME

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INTRODUCTION: NLRP6-inflammasome dictates host-microbiota interactions that are protecting against intestinal inflammation through mechanisms which remain largely undefined.
AIMS & METHODS: To further understand the signaling pathways downstream of NLRP6, we performed a two-hybrid screening with the Pyrin domain of mouse NLRP6 as bait. Dextran sodium sulfate-induced colitis was used as an experimental model of inflammatory bowel disease in both single-housed and co-housed mice. Cell growth was daily measured over a 7 day-period by Countess® device and trypan blue exclusion according to manufacturer instructions. U0126 was used as a MAPK/ERK kinases (MEK) 1/2 inhibitor.
RESULTS: Herein, we show that flavonoid maintain gut microbial ecology by regulating NLRP6-mediated regulation of cell proliferation. Our two-hybrid screening revealed that NLRP6 interacted with casein kinase 2 (CSNK2) that is a serine/threonine-selective protein kinase involved in maintenance of cell growth. Consistently, pharmacological inhibition of CSNK2 by apigenin conferred protection against intestinal inflammation. Co-housing experiments revealed that the protective activity of the microbiota of apigenin-treated mice is transmissible to adult wild-type mice, but not to NLRP6- and caspase1/caspase11-deficient mice. Mechanistically, NLRP6 deficiency was found to enhance cell growth and survival through activation of extracellular signal-regulated kinases 1 and 2.
CONCLUSION: Collectively, our results demonstrate a key role of flavonoid-microbiota interactions on the NLRP6-mediated control of the renewal of the intestinal barrier.
Disclosure of Interest: None declared

OP273 CENTRAL MUSCARINIC CHOLINERGIC ACTIVATION ALTERS INTERACTION BETWEEN SPLENIC CENDRITIC CELL AND CD4+CD25- T CELLS IN EXPERIMENTAL COLITIS

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INTRODUCTION: Inflammatory bowel disease (IBD) patients present dysautonomia with decreased vagus nerve activity, dendritic cell and T cell over-activation. In experimental colitis, the cholinergic anti-inflammatory pathway (CAP) is based on VN activity that regulates macrophage and dendritic cell responses in the spleen through alpha-7 nicotinic acetylcholine receptor (α7nAChR) signaling. However, some controversy exists related to the type of inflammatory model used. Recently, we have shown that central stimulation of the VN decreases experimental colitis and is associated with a down regulation of MHC II and IL-12p40 release by splenic dendritic cell (DC).
AIMS & METHODS: The aim of this study was to investigate whether central activation of the CAP alters the function of DC and sequential T cell activation in the context of a T-cell mediated experimental colitis. Groups of C57Bl/6 mice were subjected to sub-diaphragmatic bilateral vagotomy (VXP), neurectomy (NRX) or splenectomy (SPX) and i.c.v. cannulation. I.c.v. infusion of the M1mAChR agonist McN-A-343 (5mg/kg/day) or vehicle were initiated 8 days later and one day before induction of colitis with 2,4 dinitrobenzen sulfonic acid (DNBS; 4mg diluted in Ethanol 30%). After 3 days, mice were euthanized and inflammation was evaluated clinically (macroscopic score, colon length) and by colonic tissue IFN-γ, IL-17 and serum amyloid protein (SAP) levels. IL-12p70 and IL-23 levels in isolated splenic DCs were determined and IFN-γ, IL-17 levels in DC/$CD4^+CD25^-$ T cell co-culture were studied in the presence or absence of anti p19-mAb, p35-mAb or IL-12p70 or IL-23 recombinant proteins.
RESULTS: Clinical score, colonic IFN-γ, IL-17 and SAP levels were significantly decreased in McN-A-343-colitic groups. Splenic level of acetylcholine was increased in McN-A-343 groups. Attenuation of inflammatory markers by McN-A-343 treatment was not observed in SPX mice. Splenic DC isolated from McN-A-343-colitic groups showed a significant decrease of IL-12p70 and IL-23 release and a reduced T cell priming capacity reflected by a decrease of IFN-γ and IL-17 release from $CD4^+CD25^-$T cells. VXP or NRX exacerbated serum, colonic and *in vitro* markers and abolished the beneficial effect of the McN-A-343 treatment. Addition of anti p19-mAb in the medium abolished the deleterious effect on IL-17 in $CD4^+CD25^-$T cells conditioned with splenic $CD11c^+$DCs isolated from VXP and NRX colitic mice, whereas, in the presence of anti p35-mAb only IFN-γ level was affected. Conversely, addition of IL-12p70 or IL-23 recombinant proteins restore IFN-γ and IL-17 levels in $CD4^+CD25^-$T cells conditioned with splenic $CD11c^+$DCs isolated from colitic mice treated with McN-A-343.
CONCLUSION: Suppression of splenic immune cell activation and altered interaction between DCs and T cells are important aspects of the beneficial effect of brain activation of the CAP in experimental colitis. These findings may lead to improved therapeutic strategies in the treatment of IBD.
Disclosure of Interest: None declared

OP274 PRIMARY INTESTINAL MYOFIBROBLASTS EXPRESS THE TNF-LIKE CYTOKINE TL1A/TNFSF15 FOLLOWING STIMULATION WITH PRO-INFLAMMATORY MEDIATORS

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INTRODUCTION: TL1A belongs to the TNF superfamily of cytokines (TNFSF15). It provides co-stimulatory signals for activated lymphocytes that express the functional receptor DR3. TL1A and DR3 are highly upregulated in intestinal areas with active IBD-related inflammation. Recently it was reported that transgenic mice with lymphoid- or myeloid-specific overexpression of TL1A develop colonic fibrosis.
AIMS & METHODS: Our aim was to determine whether primary human intestinal myofibroblasts (IM) express TL1A under stimulation with IBD-associated pro-inflammatory cytokines. IM were isolated from endoscopically-obtained colonic biopsies from healthy controls (HC) and patients with Crohns' disease (CD). IM were cultured unstimulated or stimulated under various conditions: a. with rhTNF-a and/or rhIL-1a; b. with supernatants from colonic tissues obtained from HC and CD patients; and, c. with supernatants from epithelial HT-29-cell cultures which were unstimulated or stimulated with rhTNF-a and/or rhIL-1a and/or rhIFN-g). Total RNA was extracted from the cultured IM and the mRNA expression of TL1A and the receptor DR3 was measured by real-time RT-PCR.
RESULTS: Stimulation of IM with either TNF-α or IL-1α resulted in significant upregulation of the relative expression for TL1A mRNA at 6h (unstimulated, 2.89±5.20 average±sdev; IL-1α, 93.58±17.44; TNF-α, 66.59±15.53; IL-1α+TNF-α, 127.04±19.40, $P<0.00001$ for any condition vs. control). The average increase in TL1A expression was 32.8-fold for IL-1α, 23-fold for TNF-α, and 43.9-fold for their combination. No difference was seen at 1h whereas at 24h only stimulation with TNF-α was significantly higher than the control condition. We did not detect DR3 mRNA in IM under any of the above conditions. We also found that supernatants from cultured HT-29 epithelial cells were able to induce the expression of TL1A in IM when TNF-α was used for stimulation of the epithelial cells either alone or in combination with IL-1a and/or IFN-g ($P<0.05$ for any combination vs. unstimulated HT-29 cell supernatant). Finally, supernatants from CD-derived colonic tissue cultures induced a significantly higher upregulation of TL1A mRNA expression in cultured IM (>5-fold increase over tissue cultures form healthy controls, $P<0.01$). The soluble TL1A protein content was also higher in IM cultures stimulated with supernatants from CD-derived colonic tissue cultures.
CONCLUSION: Pro-inflammatory cytokines that are abundantly expressed in intestinal areas with active CD (TNF-a, IL-1a, IFN-g) induce the expression of the co-stimulatory cytokine TL1A in IM either directly or through the induction of epithelial-derived mediators. Our results raise the possibility that interactions between IM-derived TL1A and its receptor, DR3 on epithelial cells or lymphocytes may participate in the pathogenesis of chronic intestinal inflammation.
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Disclosure of Interest: None declared

OP275 CULTURED BLOOD T CELLS AS A PROGNOSTIC BIOMARKER FOR ANTI-TNF THERAPY RESPONSE IN PATIENTS WITH ULCERATIVE COLITIS

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INTRODUCTION: Anti-TNF therapy is used for treatment of ulcerative colitis (UC). However, only 60-70% of UC patients are responders and so far it has not been possible to predict therapy response. Therefore, it is of clinical interest to identify biomarkers of therapy response before therapy initiation.
AIMS & METHODS: To identify prognostic biomarkers of infliximab therapy response in anti-TNF naïve UC patients before therapy start.
Mucosal biopsies and blood cells were obtained from UC patients before therapy start. Biopsies were cultured for 24h with or without 1μg/ml infliximab and used for quantitative proteomic analysis using mass spectrometry. Blood cells were stimulated *in vitro* with influenza vaccine with and without 10μg/ml anti-TNF for 7 days. Receptor expression and cytokine release were determined by flow cytometry and the Meso Scale Discovery® platform. Linear Discriminant Analysis (LDA) was used for generation of the prediction model. To assess the accuracy of the LDA rule, Leave-one-out cross-validation (LOOCV) was used. Therapy response was assessed by the validated Mayo score 12-14 weeks after treatment initiation. Response was defined as a decrease in Mayo score of $\geq$3.
RESULTS: We have included 34 UC patients into the study. Sixteen patients responded to anti-TNF therapy, whereas eighteen patients did not respond. Therapy responders and non-responders showed no significant differences in gender distribution, age, smoking habits, disease duration, Mayo score, CRP, fecal calprotectin, TNF levels in serum or use of immunomodulatory therapy before start. Proteomic analysis of cultured biopsies showed that infliximab affected protein expression differently in therapy responders and non-responders. In particular, reduced activity of NF-κB and pro-inflammatory cytokine pathways were recorded in therapy responders. This was verified in cultured blood cells where infliximab induced stronger suppression of CD25 (p=0.0004), TNF receptor 2 (p=0.02) and β7 (p=0.05) expression on T cells, as well as reduced secretion of interleukin (IL)-4 (p=0.002) and IL-1β (p=0.02), in therapy responders as compared to non-responders (Table 1). By the use of LDA, CD25 and IL-4 were used to create a rule for classification of therapy response. When performing LOOCV, correct classification of future therapy response was achieved in 85% of the cases.
Table 1. Surface epitope expression on T cells and cytokine secretion in blood cells cultured *in vitro* with and without 10μg/ml anti-TNF.Data shown as median (25-75 percentiles).

	Responders(%)	Non-responders(%)	p-value
$CD25^+CD4^+$Tcells	60.6(48.0-65.7)	74.2(67.1-85.3)	0.0004
$TNFR2^+CD3^+$Tcells	55.3(47.2-70.4)	70.6(57.3-82.0)	0.02
$\beta7^+CD4^+$Tcells	81.0(69.7-82.7)	93.5(82.4-104.3)	0.05
IL-4	20.2(1.6-60.2)	73.1(41.4-161.1)	0.002
IL-1β	33.2(14.9-52.6)	101.8(59.4-185.5)	0.02

CONCLUSION: The effect of infliximab on cultured blood T cells, obtained before therapy start, differs between therapy responders and non-responders. The discrepancy in cellular response between responders and non-responders can be used for prognostic evaluation of infliximab therapy response in order to tailor treatment.
Disclosure of Interest: None declared

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IBD: EPIDEMIOLOGY AND DISEASE OUTCOMES - HALL N

OP276 COMPARISON OF FETAL RISKS IN PREGNANCY BEFORE AND AFTER DIAGNOSIS OF INFLAMMATORY BOWEL DISEASE: A PROSPECTIVE STUDY

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INTRODUCTION: Inflammatory bowel disease (IBD) commonly affect young women during the reproductive years. The fetal prognosis of pregnancy occurring in IBD is generally considered as good.
AIMS & METHODS: To evaluate the impact of IBD on pregnancy (P), we studied the fetal outcome in 112 patients suffering from ulcerative colitis (UC) and 112 with Crohn's disease (CD), who have been pregnant before and / or after onset of disease.
In this prospective study we have compared during a 5 year period (1/1/2005 to 31/12/2009) outcome of the pregnancy which occurred before or after onset of disease.
Statistic study used Student Fisher's t test and Mann Whitney's U test.
RESULTS: - We recorded 303 pregnancies including 95 before diagnosis of UC and 208 after the disease, and 294 pregnancies including 88 before diagnosis of CD and 206 after the disease.
- Mean number of pregnancy was 0.84 and 1.85 in UC and 0.76 and et 1.84 in CD before and after the disease respectively.
- There was no statistical significant difference (SSD) as regards to fetal risk in UC considered before and after pregnancy.
- In CD, the rate of caesarean (10.7% Vs 4.5%), spontaneous abortion (6.8% Vs 2.5%), Stillborn (1.9% Vs 0%) were significantly higher after the diagnosis of the disease, than before.
- Comparing UC to CD, we found no statistical significant difference (SSD) as regards to fetal risk in UC and CD before the disease; however, the rate of caesarean (10.7% Vs 4.9%) was higher in patients with CD after diagnosis.
- After diagnosis, the rate of caesarean (UC: 19.2% Vs 2.7%; $p<0.001$; CD: 35.7% Vs 6.7%; $p<0.001$), stillborn (UC: 3.8% Vs 1%; $p<0.8034$; CD: 3.6% Vs 1.6%; $p<0.9426$) and congenital abnormalities (UC: 3.8% Vs 0%; $p<0.2664$; CD: 3.6% Vs 0.5%; $p<0.6505$) were higher in primiparous than in multiparous patients.
CONCLUSION: Our data suggest that conception should not be discouraged in patients with IBD. However, CD in the post diagnosis phase and a primiparous statute have some negative influence on outcome of pregnancy; thus pregnancy in those IBD patients should be closely monitored.
Disclosure of Interest: None declared

OP277 INCIDENCE RATE OF MICROSCOPIC COLITIS IN THE NETHERLANDS

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INTRODUCTION: Chronic diarrhea is a common problem and affects the quality of life of patients. Microscopic colitis (MC) is increasingly recognized as important cause of chronic diarrhea in the elderly. The incidence rate (IR) of MC, including two entities: lymphocytic (LC) and collagenous colitis (CC), increased in recent years. This may be due to detection bias because more diagnostic colonoscopies are being performed. Up to date incidence studies accounting for this are lacking.
AIMS & METHODS: We aimed to estimate the IR of MC in the general population in the Netherlands and in relation to the number of colonoscopies.
We conducted a cohort study using data from a primary care database containing electronic medical records of 1.6 million subjects in the Netherlands. Study period was from January 1st 2003 to May 31st 2013. Microscopic colitis (CC, LC and unspecified) cases were identified by free text search and manual validation. Only diagnostic index colonoscopies were counted and validated against the national number of colonoscopies per capita in the Netherlands. Standardized software provided age- and sex-specific IR for LC and CC separately.
RESULTS: The study population of 1,458,410 subjects contributed to 4,158,573 person-years (PYS). We identified 210 incident MC cases (LC: 122; CC: 88; unspecified: 54), yielding an overall IR of 5.1/100,000 PYS; 2.1/100,000 PYS for CC; 1.6/100,000 PYS for LC and 1.3/100,000 PYs for unspecified MC. IR of MC overall, CC and LC separately remained stable from 2003 (IR MC overall: 3.5/100,000 PYS) until 2013 (IR MC overall: 2.5/100,000 PYS). IR of LC increased after the age of 50-54 years (3.0/100,000 PYS) until 75-79 years (7.2/100,000 PYS), whereas for CC the IR increased already from the age of 45-49 years (1.2/100,000 PYS) until 80-84 years of age (7.9/100,000 PYS). However, across age groups IRs of CC, and LC were comparable. Across all ages and calendar years, IR was 2-4 times higher for females than males. Accounting for possible detection bias: IR of MC decreased from 5.6/1,000 colonoscopies in 2003 to 2.4 in 2012.
CONCLUSION: Incidence rates of microscopic colitis remained fairly stable during a 10-year period from 2003-2013 in the Netherlands, taking into account the increase in the total number of colonoscopies over this period. IR of MC increased with advanced age, starting at 50 years for collagenous colitis and at 60 years for lymphocytic colitis. IR was 2-4 times higher for females than males across all ages.
Disclosure of Interest: None declared

OP278 DEVELOPMENT OF A PREDICTION MODEL TO ASSESS THE RISK OF CHRONIC GASTROINTESTINAL ISCHEMIA IN REFERRED PATIENTS

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INTRODUCTION: Chronic gastrointestinal ischemia (CGI) is a challenging disease entity. Clinical symptoms may differ amongst patients.
AIMS & METHODS: We analyzed data of a prospective cohort study. Between 2006 and 2013 self-reported symptoms were collected by a structured questionnaire of 431 consecutive patients referred to an academic hospital for evaluation of possible CGI. All patients received the standard work-up of CGI, consisting of radiological imaging of the gastrointestinal arteries, and functional testing for detection of mucosal ischemia by means of visible light spectroscopy (VLS) or tonometry. The results were discussed in a multidisciplinary expert panel leading to a consensus diagnosis, which was monitored during follow-up. Predictors for

the diagnosis of CGI were obtained by comparing the self-reported symptoms in the questionnaire to the diagnosis of CGI. Multivariable logistic regression analysis was used to combine the strongest predictors in a prediction model. We aimed to establish predictors for CGI based on self-reported variables and to combine these in a prediction model in order to distinguish low, intermediate and high risk patients for CGI.

RESULTS: Postprandial pain, exercise-induced pain or weight loss was present in more than 90% of patients. The diagnosis of CGI was established in 192 (45%) patients. Clinical variables showing strong association with CGI were age ≥60 years (OR1.4, 95%CI 0.99-1.9), female gender (OR2.5, 95%CI 1.6-3.8), concomitant cardiovascular disease (OR1.4, 95%CI 0.9-2.2), smoking (OR1.4, 95%CI 0.95-2.0), severe postprandial pain (OR1.3, 95%CI 0.9-2.0), weight loss (OR1.2, 95%CI 0.99-1.5) and no use of analgetics (OR1.7, 95%CI 1.1-2.5). Ongoing symptoms of >6 months (OR0.9, 95%CI 0.8-1.0) did not favor CGI. A c-statistic for the prediction model was obtained of 0.64. Based on the scoring system patients were categorized as low (30%), intermediate (47%) or at higher risk (64%) for CGI.

Predictors	Score
Age, years <60 ≥60	0 1
Gender Male Female	0 3
Cardiovascular comorbidity No Yes	0 1
Severe postprandial pain No Yes	0 1
Weight loss, kg/month <3 ≥3	0 1
Smoking, packyears <25 ≥25	0 1
Use of analgetics No Yes	2 0
Duration of symptoms, months ≤6 >6	1 0
Scorepoints 0-4 5-8 9+	**Risk of CGI 30% 47% 64%**

CONCLUSION: We present a scoring system for the presence of CGI on clinical features and risk profiles alone for patients suspected of CGI. This tool may be useful for clinicians to assess the risk of CGI and to decide whether further diagnostic work-up by means of radiological imaging of the gastrointestinal arteries and functional testing is indicated and worthwhile.

Disclosure of Interest: None declared

OP279 CLINICAL AND RADIOLOGICAL OUTCOMES PRE AND POST THE ANTI-TNF ERA FOR PERIANAL CROHN'S FISTULAS

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INTRODUCTION: Anti-tumor necrosis factor (TNF) therapies are used to treat fistulising perianal Crohn's disease (CD). We evaluated the clinical and radiological outcomes of patients with perianal Crohn's fistulas in the pre anti-TNF and in the post –anti-TNF era.

AIMS & METHODS: A local database of 263 consecutive patients with Crohn's disease treated at our institution between 2000 and 2014 was established. Data on patient demographics and relevant outcomes were collated from medical, electronic and radiological reports. Chi Squared analysis was carried out to determine differences between the anti-TNF and non-anti-TNF groups. Cox regression analysis was undertaken to compare difference in time to clinical and radiological response between the two patient groups. Binary logistic regression was carried out to determine independent predictors of clinical remission and response. At the univariate level, variables that reached a p value of <0.10 were included into a multivariate regressional model. At multivariate analysis, a p value of <0.05 was considered to be significant.

RESULTS: Ninety patients were in the non-anti-TNF group and 173 were treated with anti-TNF therapy (Infliximab or Adalimumab). Clinical response rates were significantly higher in the anti-TNF group compared with the non-anti_TNF group (74% vs 62%, p=0.04). Similarly, radiological response rates were higher in the anti-TNF group (56% vs 28%, p<0.01).

Cox Regression analysis demonstrated fistula duration (p=0.01) and biologic therapy (p=<0.01) to be significant at the univariate level. Factors such as sex, age, smoking status, diabetes status, Montreal classification, the presence of proctitis and the use of other immunosuppressive agents were not significant. At the multivariate level, patients on anti-TNF therapy had a faster radiological response over a 6 year follow up period as compared with the non-anti-TNF group (OR=2.25, CI= 1.14-4.46, p=0.02). A short duration of Crohn's disease (less than 5 years) contributes to a faster time to clinical response (OR=1.77, CI=1.03-3.05, p=0.04) compared with patients who were diagnosed with the disease for longer.

Multivariate binary logistic regression revealed treatment with anti-TNF therapy to be an independent predictor of radiological response (OR 3.55, CI 1.59-7.91, p<0.01). Patients with L1 luminal disease are 3 times more likely not to go into clinical remission on both univaraite and multivariate analyses (OR=3.08, CI=1.47-6.46, p=0.01). The duration of Crohn's diagnosis is also a poor predictor of clinical response to therapy (p<0.01).

CONCLUSION: Patients on anti-TNF therapy have improved clinical and radiological response rates compared with patients without anti-TNF treatment. Anti-TNF therapy is a positive predictor of radiological response to therapy. Montreal classification of L1 ileal disease is a poor predictor of clinical healing of perianal fistulas in both groups of patients.

Disclosure of Interest: None declared

OP280 FAMILIAL RISK OF INFLAMMATORY BOWEL DISEASE: A POPULATION-BASED COHORT STUDY 1977-2011

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INTRODUCTION: The inflammatory bowel diseases (IBD) – ulcerative colitis (UC) and Crohn's disease (CD) - are caused by complex gene-environment interactions. This study provides updated familial aggregation patterns in a large population-based Danish IBD cohort.

AIMS & METHODS: Our cohort study was based on the entire Danish population during 1977-2011 (n=8,295,773). Through a unique personal identification number assigned to each Danish citizen, sex, date and location of birth, identity of parents, and information on vital status and emigration were available. This information was used to establish kinship in the entire population. Individuals receiving at least 2 diagnoses of IBD during the time period (n=45,780) were identified using the Danish National Registry of Patients. Risk of IBD in family members to individuals with IBD was assessed by Poisson regression analysis.

RESULTS: The overall proportion of familial CD cases was 12.2% of all CD cases, whereas familial UC accounted for 8.8% of all UC cases from 2007-2011. The ratio of CD was 9.36(6.75-12.99) increased in 1st degree relatives to at least two individuals with IBD, 7.78(7.07-8.57) fold increased in 1st degree relatives to one family member with CD, and 2.82(2.51-3.16) increased if the 1st degree relative had UC. The same pattern was observed for the ratio of UC with a risk ratio of 6.92(5.28-9.06) in 1st degree relatives to at least two individuals with IBD, 2.57(2.28-2.90) in 1st degree relatives to one family member with CD, and 4.09(3.81-4.38) if the 1st degree relative had UC. Furthermore, the risk was influenced by an interaction with age resulting in rate ratios above 20 among infants and young adults belonging to families with more than one IBD affected member. Second-degree relatives to patients with CD or UC were also at significantly increased risk not only of the same but also the other subtype of IBD, whereas the risk of IBD was less pronounced in third degree relatives to individuals with IBD. The overall pattern described above was stable across several sensitivity analyses.

CONCLUSION: This large-scale population-based study provides updated numbers of familial aggregation of IBD. Familial exposure to CD not only increases the risk of CD but also of UC markedly and vice versa, and the ratio rises with closer familial ties and in families with multiple affected members. Also we found that individuals belonging to IBD affected families had particularly high risk of IBD in early life.

Disclosure of Interest: None declared

OP281 A PROSPECTIVE OBSERVATIONAL COHORT STUDY TO EVALUATE MUCOSAL HEALING IN ULCERATIVE COLITIS: HAVE MAYO 1 AND MAYO 0 SCORES REALLY THE SAME PROGNOSTIC VALUE?

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INTRODUCTION: Mucosal healing has become a common endpoint in most therapeutic trials and an important objective to be reached in patients with ulcerative colitis (UC). Despite important differences between endoscopic Mayo sub-scores 0 and 1, most important trials consider both as mucosal healing. We hypothesized that only an endoscopic Mayo score of 0 should be defined as mucosal healing.

AIMS & METHODS: The aim of this study was to evaluate the differences between endoscopic Mayo-0 and Mayo-1 scores in the clinical course of UC patients.

A prospective observational cohort study was designed. All UC patients who presented mucosal healing in a colonoscopy were consecutively included and classified according to the Montreal Classification. Mucosal healing was defined as an endoscopic Mayo sub-score of 0 or 1. In order to minimize potential interpretation bias, all colonoscopies were performed and scored by the same endoscopist. Mayo-0 was defined as normal or inactive disease and Mayo-1 as the presence of erythema, decreased vascular pattern or mild friability. Clinical relapse was defined as the need for remission induction treatment, any treatment escalation, hospitalization or colectomy. In order to assess the clinical course of UC, all clinical relapses were evaluated at months 6 and 12 after inclusion colonoscopy. The influence of demographic variables in the clinical course was also evaluated. Results are shown as odds ratio (OR) and 95%CI and analyzed by the chi-squared test and multiple regression whenever appropriate.

RESULTS: 187 UC patients with mucosal healing [127 (67.9%) Mayo-0 and 60 (32.1%) Mayo-1] were included. 94 were male (50.3%), mean age 52 years, range 22 to 85 years. UC was classified as E1 in 31.3% of patients, E2 in 42.2% and E3 in 26.5% according to the Montreal Classification. 9.4% of patients with Mayo-0 score and 36.6% with Mayo-1 score presented with a relapse during the first 6 months of follow up (p<0.001). Patients with Mayo 1 score suffered more frequently from a relapse than those with Mayo 0 score in all three Montreal groups (E1, E2 and E3). The disease relapsed in patients with Mayo 0 and 1 scores at a similar rate during the following 6 months (14.6%vs 16.6%, respectively, p=0.868). The only factor significantly and independently associated with UC relapse during follow-up in the multivariate analysis was a Mayo-1 endoscopic sub-score (OR= 6.27 CI 95% 2.75-14.30, p<0.001).

CONCLUSION: UC patients with Mayo sub-score 1 have a higher risk of relapse than those with Mayo sub-score 0, regardless of the extension of the

disease. This study demonstrates that mucosal healing should be only defined as an endoscopic Mayo score of 0.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45-17:15
CYSTIC PANCREATIC LESIONS: A CLINICAL DILEMMA - HALL O

OP282 NEEDLE-BASED CONFOCAL LASER ENDOMICROSCOPY (NCLE) FOR THE DIAGNOSIS OF PANCREATIC CYSTS: VALIDATION OF THE DESCRIBED CRITERIA

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INTRODUCTION: Needle-based Confocal Laser Endomicroscopy (nCLE) is an imaging technique, which enables microscopic observation of the inner wall of pancreatic cysts, *in vivo* and in real-time, during an EUS-FNA procedure. A prospective multicentric French study (CONTACT) aims at evaluating the accuracy of nCLE for the diagnosis of lonely pancreatic cysts. Two criteria have been previously evaluated (INSPECT, CONTACT 1): papillae for IPMN, superficial vascular network for serous cystadenoma (SCA). Two new criteria have been highlighted during CONTACT 1 study: a field of bright and black particles for pseudocyst (PC) and an epithelial border for mucinous cystadenoma (MCN). The aim of this study is to evaluate retrospectively the yield of nCLE for the diagnosis of pancreatic cysts based on all these criteria.
AIMS & METHODS: Over 10 months (June 2012 to April 2013), 43 patients with a lonely pancreatic cyst, > 2 cm large, without communication with the pancreatic duct at EUS and MRI were prospectively enrolled. Patients with calcified chronic pancreatitis were excluded. Following EUS examination, the AQ-Flex miniprobe was introduced in a 19G needle and real-time video of the cyst wall was recorded. Fluid obtained by FNA was analyzed. Twelve patients were excluded of the analysis due to protocol failure or absence of diagnosis consensus. Final diagnosis of the 31 remaining patients (13 SCA, 7 PCs, 5 IPMN, and 6 MCNs) was based on histological analysis of the surgical specimen (n=6), on undoubtedly positive FNA sample using cell blocs (n=16), or on consensus between the 5 investigators (n=9). As a first step, the investigators (5 experts), individually and blindly, reviewed the nCLE records of the 31 cases and were asked to give a diagnosis (SCA, PC, IPMN, MCN). When no criteria was evidenced, the diagnosis was indeterminate. Secondly, the investigators reviewed together the cases with discrepancies, to assess, if possible, a consensus diagnosis.
RESULTS: The intial agreement between observers was complete in 35 % of cases. For the 65% other cases, a consensus was obtained. Finally a diagnosis was concluded in 54 % of cases. Inter-observer agreements (IOA) were good (table 1).Finally the specificity of the nCLE criteria was 100 % for the diagnosis of SCA, PC and mucinous cyst.

		Non mucinous Cyst		Mucinous Cyst			
		SCA (n=13)	PC (n=7)	Mucinous lesion *(n=11)*	*IPMN (n=5)*	*MCN (n=6)*	**Total**
NCLE diagnosis	true	9	2	6	*2*	*2*	17
	wrong	0	0	0	*(1)*	*(1)*	(2)
Indeterminate nCLE diagnosis		4	5	5	*2*	*3*	14
Diagnostic performances per criteria (%)	Sensitivity	69	29	55	40	33	
	Specificity	100	100	100	67	67	
IOA per criteria		0,77	0,89	0,68	0,77	0,37	0,70

CONCLUSION: Based on these four described criteria 46 % of cases remained indeterminate. When a diagnosis was proposed the specificity of nCLE was excellent for the diagnosis of SCA and mucinous cysts, with a sensitivity > 50%. This should have a strong clinical impact. An external validation and a prospective evaluation of the yield of nCLE are both ongoing to confirm these good results.
Disclosure of Interest: None declared

OP283 PROTEOMIC STUDIES ON ASPIRATES FROM CYSTIC NEOPLASMS OF THE PANCREAS PROVIDE NEW CLUES TO THEIR MOLECULAR BACKGROUND AND REVEAL NOVEL BIOMARKER CANDIDATES

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INTRODUCTION: IPMN and MCN have recently been identified as macroscopic precursors of pancreatic cancer. However, our understanding of the molecular backgrounds of these tumors is still incomplete, and their diagnosis remains challenging. We performed a systematic proteomic analysis of cyst fluid from different pancreatic cystic neoplasms to further elucidate their pathogenesis and identify new biomarkers.
AIMS & METHODS: Aspirates from 24 patients with pancreatic cystic lesions (15 females, median age 63), obtained through EUS-FNA were utilized for the analyses. Samples were selected to represent triplicates of the most common cystic tumors: serous cystic tumors, MCN, cystic ductal adenocarcinomas, and IPMN of the gastric, intestinal and pancreatobiliary type. For comparison, six pseudocysts were included. 9 samples were characterized as intrinsically benign, 5 as premalignant and 10 as malignant (minimum high-grade dysplasia). Histology was procurable in 20/24 cases (83%), including 17/18 (94%) cystic tumors. Pseudocysts were, in the absence of histology, identified by their spontaneous regress/resolution. Samples were prepared by the filter aided sample preparation (FASP) method (modified), and digested by trypsin, before analysis by nano-LC MS/MS on a Q-Exactive instrument. Data were searched against the UniProt/Swissprot database, using the Andromeda search engine integrated in MaxQuant. Pathway analyses were performed by Ingenuity Pathway Analysis (IPA).
RESULTS: A total of 1385 proteins were identified. After filtering out single occurrences, 541 proteins were found to be unique to lesions with malignant potential, and 273 to malignant tumors. Pathway analysis revealed the transcription factors XBP1 (ER stress response) and NFE2L2 (defense against oxidative stress) as prominent upstream regulators for proteins that were differentially expressed in lesions with malignant potential (MCN, IPMN and ductal adenocarcinoma). PI3K/AKT and ERK5 were central components of the molecular networks generated for these tumors. Activation of c-MYC and KRAS were identified as major events in malignant transformation. Notable predicted upstream regulators by tumor type were: TGFβ for serous cystic tumors, c-MYC for MCN, IL22 for IPMN, and EGFR for cystic ductal adenocarcinomas. Butyrate (which may be produced by bacteria) and XBP1 were identified as regulators for intestinal IPMN; KRAS and Catenin beta-1 (Wnt signalling pathway) for pancreatobiliary IPMN. Furthermore, the study identified several novel biomarker candidates (Table 1).

Biomarker	Identifies	*P*-value (Fisher-Exact Test, 2-tailed)
TFF2	Malignant potential	0.002
AGR2	Malignant potential	0.007
PSCA	Malignancy	0.02
DDAH1	Malignancy	0.03
TXNDC5	IPMN	0.003
TFF3	Intestinal-type IPMN	0.0005

CONCLUSION: This proteomic study has tentatively identified molecular pathways/events that have not previously been described in the context of MCN and IPMN. Moreover, several new biomarker candidates have been selected for further study. Targeted quantitative proteomic studies to define cut-offs and validate these markers are underway.
Disclosure of Interest: None declared

OP284 THE SAFETY OF FOLLOW-UP FOR IPMN OF THE PANCREAS: A SINGLE INSTITUTION EXPERIENCE

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INTRODUCTION: IPMN of the pancreas is highly prevalent in the general population. The strategy of following up the majority of these patients is currently considered best clinical practice, even though consensus regarding an appropriate follow-up interval is lacking.
AIMS & METHODS: This study analyzes the results of a follow-up program for patients with IPMN.
From January 2008 to December 2013, 503 patients diagnosed with IPMN were observed at the Pancreas Unit of Karolinska Institute. 452 patients (89.8%) were followed-up, while 51 (10.2%) underwent surgery. The patients under follow-up represented the study series population.
RESULTS: Overall, 258 (57%) females and 194 males (43%) were analyzed. The mean patient age was 67.3 yrs, the mean follow-up 932 days. 395 of the patients (87.4%) were under surveillance according to the prevailing guidelines (group 1), whereas 57 (12.6%) patients (group 2) were followed-up because of contraindications for surgery (poor general condition, locally advanced or metastatic IPMN cancer, synchronous other extrapancreatic cancer. In group 1, 55 patients (13.9%) required surgery for progression of their IPMN after a median follow-up of 560 days. In 2 patients (0.5%), a synchronous pancreatic cancer developed during follow-up. The 1, 3 and 5 years survival rate for the patient series was 96.5%, 92.4% and 87.1%, respectively. In group 1, 33 patients (8.3%) died under follow-up: 4 (1%) due to IPMN progression, 5 (1.3%) because of extrapancreatic

cancer and 24 (6%) for other causes. The 1, 3 and 5 years survival rate in group 2 were 74.8%, 48.7% and 40.5%, respectively. In this group 22 patients (38.6%) died due to IPMN progression (10, 17.5%), extrapancreatic cancer (5, 8.8%), or for other reasons (7, 12.3%).
CONCLUSION: This study confirms the safety of a surveillance program for patients with non-surgical IPMN. Incidence of pancreatic cancer and IPMN-related mortality were low during follow-up. Even if patients with an indication for surgical treatment were for excluded from surgery for various reasons, survival was acceptable, particularly when compared with pancreatic cancer patients.
Disclosure of Interest: None declared

OP285 ARE IPMN OF THE PANCREAS ASSOCIATED TO AN INCREASED PREVALENCE OR INCIDENCE OF EXTRA-PANCREATIC NEOPLASMS? A MULTICENTRE EUROPEAN OBSERVATIONAL STUDY

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INTRODUCTION: Although different studies showed an association between pancreatic IPMN and extrapancreatic neoplasms (EPN), the available data remain inconclusive.
AIMS & METHODS: This multicentre observational study assessed the prevalence and the incidence of EPN in patients with IPMN. Patients diagnosed with IPMN from 2000 to 2013 were assessed for EPN prevalence. For the incidence analysis, patients with an EPN previous or synchronous to the IPMN, and patients with a follow-up <12 months were excluded. Tumor prevalence and the incidence of EPN that developed during follow-up were compared with European cancer data. The standardized prevalence and incidence ratios (SPR, SIR), and the 5- and 10-year incidence rates were calculated.
RESULTS: The study population included 1340 patients. At the time of IPMN diagnosis, 289 patients developed at least one previous or synchronous EPN (prevalence of 21.6%). The EPN prevalence was greater than the general population (SPR=4.04, 95%CI 3.61-5.51). 816 patients were included in the incidence analysis. At a median follow-up of 44 months, 50 patients developed an EPN (cumulative incidence of 6.1%). The incidence of EPN was not greater than expected (SIR=1.16, 95% CI 0.85-1.54), with a 5- and 10-year incidence rate of 5.9% and 20.1%.
CONCLUSION: The prevalence of EPN at the time of IPMN diagnosis is greater than expected by 4-fold, likely because cancer patients are at increased medical screening and are diagnosed with IPMN more frequently. This concept is substantiated by the fact that the incidence of new EPN during the follow-up period was not greater in comparison with the general population.
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Disclosure of Interest: None declared

OP286 PANCREATIC SEROUS CYSTADENOMA RELATED MORTALITY IS ALMOST NIL. RESULTS OF A MULTINATIONAL STUDY UNDER THE AUSPICES OF THE INTERNATIONAL ASSOCIATION OF PANCREATOLOGY AND THE EUROPEAN PANCREATIC CLUB

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INTRODUCTION: Serous cystadenoma (SCA) is a pancreatic cystic neoplasm which is frequently resected. The purpose of the study was to compare their related mortality to the perioperative mortality and to examine their natural history.
AIMS & METHODS: A retrospective multinational study was conducted to analyze epidemiological and natural history of SCA diagnosed between 1990 and 2014. A questionnaire about clinical and radiological characteristics of SCA at diagnosis and at the last visit or time of surgery was sent to the participating centers.
RESULTS: 1786 are presented here. 1357 patients were females (76%, $p < 0.05$). The median age at diagnosis was 57 years [16-91]. Patients were asymptomatic (62%), had non specific abdominal pain (28%), bilio-pancreatic symptoms (9%) or diabetes mellitus (4%). SCA was microcystic (45%), macrocystic (31%), mixed (20%) or solid (4%). There was no predominant location inside the pancreas. 48% of patients were operated on during the first year after diagnosis (median size: 4 cm [0.2-20]), 10% had resection beyond one year of follow-up (3,1 years [1-20], size: 2,5 cm [0.4-14]), 42% had no surgery (3.6 yr [1-23], size: 2,5 cm [0.5-20]). Surgical indications were: uncertain diagnosis with malignant tumor (55%), symptoms (29%), increase in size (14%) or adjacent organ compression (7%). In patients followed beyond one year (n=935) size increased in 39% of cases (growth rate: 4,2 mm / year), were stable in 55%, decreased in 6%. There were 4 serous cystadenocarcinomas. Post operative mortality was 0.7% (n=7), SCA's related mortality was 0,1% (n=1) (NS).
CONCLUSION: SCA related mortality is almost nil, whereas operative mortality is not. SCA is a benign tumor, exceptionally symptomatic with slow growth. Uncertainty diagnosis is a too frequent surgical indication even though reliable diagnostic criteria have been established. SCA without complication should be followed and not operated.
Disclosure of Interest: None declared

OP287 EVALUATION OF PATIENTS UNDERGOING PANCREATIC RESECTION: HIGH INCIDENCE OF PANCREATIC CANCER IN PATIENTS WITH AUTOIMMUNE PANCREATITIS

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INTRODUCTION: Autoimmune pancreatitis (AIP) is a rare, benign, fibroinflammatory disease that may present with signs and symptoms mimicking pancreatic cancer (PC). AIP is characterized by a dramatic response to corticosteroid therapy. Thus, patients diagnosed with AIP can avoid surgery and undergo immunosuppressive treatment. Despite the availability of well-defined AIP criteria, still a large portion of AIP patients undergoes unnecessary surgery. Only a few cases of PC in AIP patients have so far been reported worldwide.
AIMS & METHODS: The objective of our study was to assess the proportion of AIP in all pancreatic resections performed in our center for focal pancreatic enlargement and to determine clinical characteristics of this subgroup.
We performed a retrospective analysis of data of all patients who underwent pancreatic resection in our center for suspected cancer/focal pancreatic enlargement between January 2000 and July 2013.
RESULTS: Two hundred and ninety-five pancreatic resections were performed in 201 males and 94 females (mean age 60 years, range 36-78 years). Indication for surgery was tumor suspicion based on clinical symptoms, imaging methods and laboratory findings. In 19 patients (6.4%, 13 males, 6 females), autoimmune pancreatitis was diagnosed based on histology of the resected specimen. 10 patients were diagnosed as AIP type 1 (9 males, 1 female), 9 patients had distinct histopathological features of AIP type 2 (4 males, 5 females). In 6 AIP patients (31.6%, all males, 3 AIP type 1), pancreatic adenocarcinoma was also present in the resected tissue. No differences were observed in the preoperative characteristics of patients with and without cancer (CT, EUS, ERCP, bile duct involvement, laboratory findings including Ca 19-9). In none of the patients the diagnosis of AIP was made prior to surgery; however the diagnostic algorithm was not fully completed.
CONCLUSION: A considerable number of resected patients with AIP had synchronous PC in our study. The preoperative diagnosis of AIP in patients with focal pancreatic enlargement may not always rule out the simultaneous presence of cancer.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45–17:15
VISCERAL SENSITIVITY: CLINICAL AND TRANSLATIONAL SCIENCE ASPECTS – LOUNGE 5

OP288 CORTICOTROPHIN-RELEASING HORMONE INCREASES OESOPHAGEAL SENSITIVITY TO MECHANICAL DISTENTION IN HEALTH

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INTRODUCTION: Oesophageal hypersensitivity has been proposed as an important pathophysiological factor in patients with gastro-oesophageal reflux disease (GORD) refractory to acid suppressive therapy. Stress is well-known to affect visceral sensitivity in humans. It has been shown that a real-life stressor is able to exacerbate heartburn in GORD patients. A recent study from our group showed that, in humans, an acute psychological stressor increases duodenal permeability in a mast cell dependent way and that this effect on barrier function is mimicked by IV administration of exogenous corticotrophin-releasing hormone (CRH).
AIMS & METHODS: The aim was to investigate the effect of CRH-administration on oesophageal sensitivity in health.This cross-over, randomized, single-blind study was performed in 10 HV (4m/6f, mean age 31.6±11.5y) with no prior history of digestive disease. Oesophageal multimodal sensitivity was quantified after administration of CRH (100μg IV) and placebo (0.9% NaCl IV), with 1 week interval. After an overnight fast, a multimodal oesophageal stimulation probe was positioned in the distal oesophagus. Thermal (recirculating a heated solution), mechanical (increasing balloon volume), electrical (2 stimulation electrodes) and chemical sensitivity (modified Bernstein) were tested. Perception scores were assessed using Visual Analogue Scale (VAS) and stimulus intensities corresponding to pain perception threshold (VAS 5) and pain toleration threshold (VAS 7) were assessed. Anxiety and angor were assessed by the State-Trait Anxiety Inventory (STAI-state) and Profile of Mood Schedule (POMS) questionnaire before and after the stimulations. Thresholds were compared between CRH and placebo, and differences in questionnaire data before and after stimulations (Δ) were analysed using paired t-tests. A p-value <0.05 was considered significant.
RESULTS: After CRH administration, VAS 5 levels during mechanical stimulation were significantly lower compared to placebo administration, with a large size effect (Cohen's d=1.2; Table 1)). Five HV (50%) did not reach VAS 7 in the placebo condition at inflation to the maximal volume of the balloon (50ml), whereas this was only the case in 1 HV (10%) in the CRH condition. CRH had no significant influence on oesophageal sensitivity to both thermal and electrical stimulations compared to placebo condition (Table 1). Since both VAS 5 and VAS 7 were not reached in the majority of the HV at the endpoint of the chemical stimulation, we were unable to analyse these data. The ΔPOMS-anxious was slightly higher (p=0.06) in the CRH condition compared to placebo. No significant effects on STAI-scores were observed. After CRH administration 5/10 HV had mild transient facial flushing.
Table 1 Results of oesophageal stimulation test (mean ± SD).

	CRH	Placebo	p uncorrected	Cohen's d+
Temperature (°C)				
VAS 5	43.95±3.15	45.42±4.43	0.15	0.4
VAS 7	46.68±2.61	47.92±3.95	0.17	0.4
Mechanical (ml)				
VAS 5	23.21±4.39	33.83±11.29	**0.0057***	1.2
Electrical (mA)				
VAS 5	14.57±9.16	15.37±7.27	0.43	0.1

CONCLUSION: CRH administration increased oesophageal sensitivity to mechanical distention in HV and was also associated with a slightly higher anxiety level. The exact mechanisms of this CRH-induced visceral hypersensitivity need to be further explored.
Disclosure of Interest: None declared

OP289 MECHANISMS OF THE ADENOSINE A2A RECEPTOR-INDUCED MECHANICAL SENSITIZATION OF VAGAL C-FIBERS INNERVATING THE ESOPHAGUS

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INTRODUCTION: Studies in patients with noncardiac chest pain indicate that adenosine acting on esophageal nociceptive pathways contributes to the pathogenesis of pain originating from the esophagus. Our group has previously reported that a specific type of esophageal nociceptors, the vagal nodose C-fibers, express the adenosine A2A receptors that can induce mechanical sensitization (Am J Physiol Gastrointest Liver Physiol. 300:G485-93).
AIMS & METHODS: The mechanisms underlying the mechanical sensitization induced by the adenosine A2A receptor are unknown. Here we investigated the mechanisms of adenosine A2A receptor-induced mechanical sensitization of nodose C-fibers. Extracellular single unit recordings were made from the vagal nodose nociceptive afferent nerve fibers with the mechanosensitive terminals in the esophagus in the isolated vagally-innervated guinea pig esophagus preparation.
RESULTS: The selective adenosine A2A receptor agonist CGS21680 sensitized mechanical response of nodose C-fibers to distention (10-60mmHg) of the esophagus with EC50 of 1-3nM. CGS21680 (3nM) induced (2.4±0.3)-fold increase in mechanical response (measured by esophageal distention with 30mmHg, n=10, $p<0.01$). The protein kinase A (PKA) activator forskolin mimicked the sensitizing effect of CGS21680 by causing a (1.9±0.3)-fold (n=8) and (2.2±0.2)-fold (n=7) increase in mechanical response at concentrations 1μM and 10μM, respectively ($p<0.05$). The protein-kinase A (PKA) inhibitor H-89 partially inhibited the CGS21680-induced increase in excitability. In the presence of H-89 (30μM), CGS21680 (3nM) caused only insignificant (1.5±0.3)-fold increase in mechanical response (n=9). The TRPA1 receptor selective antagonist AP18 inhibited the CGS21680 (3nM)-induced increase in mechanical response. In the presence of AP18 (30μM), CGS21680 (3nM) only caused insignificant (1.3±0.3)-fold increase in mechanical response (n=8).
CONCLUSION: Our data show that the activation of adenosine A_{2A} receptor in the vagal nodose C-fibers induces increase in mechanical excitability that is mimicked by the activation of PKA activator forskolin. Our data indicate that that the adenosine A_{2A} receptor sensitizes vagal nodose C-fibers via protein kinase A and TRPA1. The activity of sensitized vagal C-fibers may modulate perceptions in patients with noncardiac chest pain. Supported by BioMed Martin (ITMS: 26220220187)
Disclosure of Interest: None declared

OP290 UP-REGULATIONS OF GASTRIC TRPV RECEPTORS AND DECREASED SERUM CONCENTRATION OF BDNF IN PATIENTS WITH FUNCTIONAL DYSPEPSIA (FD)

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INTRODUCTION: Immune activation has been implicated in the mechanism of post-infectious functional dyspepsia. However, the role of immune activation in FD patients without infection remains unclear.
AIMS & METHODS: To compare the gastric mucosal and serum expression of brain-derived neurotropic factor (BDNF), transforming growth factor beta (TGFB) families and transient receptor potential vanilloid type (TRPV) families between FD patients and healthy controls.
Consecutive adult FD patients (Rome III) with no recent history of gastroenteritis and age-and-sex matched asymptomatic healthy controls were recruited for upper endoscopy. Subjects with GERD and IBS as predominant symptoms, diabetes mellitus, current or previous *H. pylori* infection, psychiatric illness and recent use of NSAID or PPI were excluded. Serum and mucosal biopsies from the gastric corpus were obtained for quantitative assay of mRNA TRPV1, TRPV2, TGFB1 by RT-PCR. Serum concentrations of TGFB families and BDNF were analyzed using immunoassay. The gastric mucosal inflammation was evaluated using Sydney classification. The associations between these assays and dyspeptic symptoms were evaluated.
RESULTS: 45 [M:F=8:37, mean age: 35.9(9.1)] FD patients were matched with 23 healthy controls [M:F= 8:15, mean age: 36.6(10.2)] respectively. FD patients had PDS as predominant sub-type (PDS: 43, EPS:2). There was no significant difference in the median inflammation score between FD patients and controls (FD: 0 (0-1) Vs Control: 0 (0-1), p=0.54). However, FD patients had significantly higher mRNA expression of gastricTRPV1 (FD: 0.008±0.002, Control: 0.003 ± 0.001, p=0.03), TRPV2(FD:0.006±0.001, Control: 0.002±0.001, p=0.01)and a trend of increased gastric TGFB1 (FD: 0.013±0.003, Control:0.005±0.002, p=0.07) compared to controls.
The serum concentration of BDNF(FD: 240.7±11.0, Control: 389.6±22.7, $p<0.001$) were significantly lower in FD patients. Serum TGFB1 and TGFB2 concentrations were significantly correlated with symptoms of belching(R=0.441, p=0.01) and vomiting (R=0.378, R=0.04) in FD patients.
CONCLUSION: Despite the absence of gastric mucosal inflammation, up-regulations of gastric mucosal TRPV1, TRPV2, TGFB1 and down-regulation of serum BDNF were observed in FD patients. The immune activation is associated with symptoms of belching and vomiting. These findings suggest that mucosal immune activation also contributes to the development of FD in those without history of infection.
Disclosure of Interest: None declared

OP291 MODULATION OF GASTRIC VAGAL AFFERENT SATIETY SIGNALS BY THE MOUSE OESTERUS CYCLE AND 17B-OESTRADIOL

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INTRODUCTION: During oestrus in rodents there is a decrease in meal size and an overall reduction in food intake[1]. This occurs immediately after a peak in plasma oestradiol (E2) levels. Exogenous E2 reduces meal size and overall food intake in ovariectomized rats[2]. Whilst E2 can act on the arcuate nucleus to reduce food intake the E2 receptors, ERα, ERβ and GPR30 are also expressed in vagal afferent cell bodies located in the nodose ganglia[3]. Furthermore, E2 has been shown to increase the excitability of cultured vagal neurons[4]. Together this suggests there may also be a peripheral E2 site of action on food intake via mechanosensitive gastric vagal afferents, the activation of which induces satiety.

AIMS & METHODS: We aimed to determine whether E2 can act on gastric vagal afferents to modulate satiety signals and whether the reduction in food intake during oestrus may have a vagal component. To investigate this the oestrous cycle stage of 8 week old female C57BL/6 mice was determined by vaginal cell cytometry[5] (N=3/cycle stage). Single fibre recordings of gastric vagal afferent mechanoreceptors were made[6] in the absence and presence of E2 (10-1000pM). Recordings were also taken after pre-incubation with the ERα selective antagonist, fulvestrant. Nodose ganglia were collected, RNA was extracted and ERα, ERβ and GPR30 mRNA levels were quantified by QRT-PCR.
RESULTS: Tension receptor response to stretch (3g) was increased by 107% in mice during oestrus ($p<0.05$ vs. diestrus, one-way ANOVA). There was no difference in the response of mucosal receptors to mucosal stroking with a von Frey hair (50mg) at any stage of the oestrous cycle ($p>0.05$, one-way ANOVA). Exogenous E2 dose-dependently potentiated mucosal and tension receptor responses to mucosal stroking (10-1000mg, $p<0.001$, two-way ANOVA) and stretch respectively (1–5g, $p<0.05$, two-way ANOVA). There was no difference in the level of potentiation induced by application of exogenous E2 between oestrous cycle stages ($p>0.05$, two-way ANOVA). The potentiation caused by E2 on both tension and mucosal receptors was blocked by pre-incubation with fulvestrant. All three E2 receptors were present within the nodose ganglia, but there was 60 and 25 times more ERα mRNA present than ERβ or GPR30 respectively ($p<0.001$, one-way ANOVA).
CONCLUSION: Taken together these data suggest that E2 potentiates gastric vagal afferent activity via an ERα pathway, thereby increasing gastric tension receptor mechanosensitivity which may, at least in part, mediate the reduction in food intake observed during oestrus.

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Disclosure of Interest: None declared

OP292 PHENOTYPES OF THE TRPV1-POSITIVE AND TRPV1-NEGATIVE VAGAL AFFERENT NEURONS INNERVATING THE RAT STOMACH

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INTRODUCTION: Gastric afferent nerves regulate the function and mediate perceptions from the stomach. Although these nerves were extensively studied, the dependence of their phenotypes on embryonic origin has not been established. Primary afferent neurons innervating visceral tissues originate from two embryonic sources: neural crest (spinal dorsal root ganglia and vagal jugular neurons) and placodes (vagal nodose neurons). We addressed the hypothesis that the vagal afferent neurons innervating the stomach express markers consistent with the origin from embryonic placodes.
AIMS & METHODS: Detailed microdissection was performed to identify components of the vagal afferent ganglion complex. Vagal primary afferent neurons innervating the stomach were retrogradely traced by using DiI injection into the stomach wall (n=19). In some studies DiI was selectively injected into the gastric corpus or fundus (forestomach). Single cell RT-PCR detection of phenotypical markers and selected receptors was performed in individual labeled neurons.
RESULTS: The nodose and jugular portions of the rat vagal jugular-petrosal-nodose ganglion complex can be grossly identified by their caudal and rostral locations, respectively, and their positions relative to branches of cranial nerves. The vagal afferent neurons labeled from the stomach were localised exclusively in the nodose portion of the vagal afferent ganglion complex. This location indicates the placodal origin. In single cell RT-PCR analysis we first focused on neurons positive for the capsaicin receptor TRPV1 because the embryonic markers have been previously established in the TRPV1-positive population. We found that the vagal aferent neurons retrogradely labeled from both gastric fundus and the corpus expressed TRPV1, but the population of neurons innervating the fundus was enriched in TRPV1-positive neurons (≈80%, 16/20) compared with corpus (≈40%, 11/27) ($p<0.01$). TRPV1-positive neurons expressed placodal markers including the ATP receptor $P2X_2$ (26/27) and neurotrophic receptor for BDNF - TrkB (23/27), but they rarely expressed neurocrestal markers, the artemin receptor $GFRalpha_3$ (2/27), preprotachykinin-A PPT-A (2/27). Gastric TRPV1-positive neurons occasionally expressed the NGF receptor - TrkA (8/27) that is often found in both placodes- and neural crest-derived neurons. TRPV1-positive neurons also expressed the serotonine $5\text{-}HT_{3A}$ receptor (11/27) and adenosine A_1 receptor (13/27) indicative of a chemosensitive function. Some TRPV1-negative neurons expressed markers found in the placodes-derived neurons - $P2X_2$ (10/20) and TrkB (5/20), but these neurons did not express markers found in the neural crest-derived neurons - $GFRalpha_3$ (0/20) and PPT-A (1/20). Consistent with their putative mechanosensory function TRPV1-negative neurons did not express $5\text{-}HT_{3A}$ receptor (2/20) and adenosine A_1 receptor (1/20).
CONCLUSION: Our data support the conclusion that the vagal afferent neurons innervating the stomach in the rat originate exclusively from embryonic placodes. The putive chemosensitive (TRPV1-positive) innervation predominates in gastric fundus while the corpus is innervated similarly by putative chemosensors and mechanosensors (TRPV1-negative neurons).
Disclosure of Interest: None declared

OP293 PRELIMINARY RESULTS FROM THE "GLUTOX" TRIAL: A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED CROSSOVER STUDY ON "NON CELIAC GLUTEN SENSITIVITY"

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INTRODUCTION: Non Celiac Gluten Sensitivity (NCGS) is a recently described syndrome characterized by gastrointestinal symptoms arising after gluten ingestion. [1] Although NCGS is thought to be present in a large part of patients affected by gastrointestinal "functional" diseases, the lack of diagnostic criteria represents a relevant problem.
AIMS & METHODS: Aim of our study was to evaluate the presence of NCGS in patients reporting different gastrointestinal symptoms. The present study is a prospective multicenter trial characterized by a double blind gluten challenge, placebo-controlled with crossover. Patients reporting aspecific gastrointestinal symptoms or affected by functional disorders (Roma III criteria) have been invited to follow a 21 day-long gluten free diet (GFD) under nutritional control. In all the enrolled patients the presence of celiac disease or wheat allergy have been excluded before starting GFD. Severity of symptoms before and after GFD was evaluated by means of 10 cm Visual Analogical Scales (VAS). Patients reporting a significant clinical, VAS-proved improvement after GFD underwent 7 day-long gluten challenge (or placebo with crossover). Gluten was administered in capsules, 5.6 g per day. Symptoms were always evaluated by VAS also during challenge. Patients reporting a relevant symptomatic relapse during gluten ingestion but not placebo were considered NCGS.
RESULTS: Sixty one patients (6 males, mean age 38.4 ± 11, BMI 21.7 ± 3.9) were enrolled. After the 21 day-long GFD, 46 subjects (3 males, mean age 37.9±11.4, BMI 21.7±4.2) reported a symptomatic improvement after GFD (Mean VAS score 7.5±2.5 *vs* 3.3±2.2 before and after GFD respectively, p=0.001). These underwent the double blind, placebo-controlled, gluten challenge and 16 (1 male, mean age 38.5±12, BMI 21.9±2.8) reported a severe symptomatic relapse after blind gluten ingestion and thus they were classified as NCGS. No demographic parameters resulted statistically significant between the investigated groups.
CONCLUSION: Our study identified a 26% of patients as truly NCGS among "functional" patients. If these data will be confirmed the proposed algorithm could be inserted in the diagnostic flowchart of functional diseases.

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Disclosure of Interest: None declared

TUESDAY, OCTOBER 21, 2014 15:45–17:15

LIVER STEATOSIS: THE ROAD FROM INFLAMMATION TO FIBROSIS – LOUNGE 6

OP294 INHIBITION OF KRUPPEL-LIKE FACTOR-4(KLF4) BY MIR-143/145 PROMOTES ACTIVATION OF HEPATIC STELLATE CELLS

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INTRODUCTION: Activation of hepatic stellate cells plays a key role in liver fibrosis/cirrhosis. MicroRNAs (miRNAs) have emerged as pivotal regulator in HSCs activation. Krüppel-like Factor-4 (KLF4) is a negative regulator of lung fibrosis, and a target of miR-143 in vascular smooth muscle cells. However, the potential role of KLF4 and miR-143 in HSCs activation or even liver fibrosis keeps unclear.
AIMS & METHODS: To characterize miR-143 and KLF4 in activated HSCs and liver cirrhotic patients, and declare a novel molecular basis by which miR-143 modulates HSCs.
Rat primary HSCs were culture activated or stimulated with TGF-β. miRNAs expression profile on quiescent and activated HSCs were detected by microarray analysis. miR-143 mimics or inhibitor were transfected to rat primary HSCs for 48 hours. Activated rat primary HSCs or human HSCs line-LX2 were transfected for 48 hours with KLF4 shRNA or KLF4 overexpression plasmid to loss or gain function of KLF4. Gene expressions of α-SMA, collagen-I, KLF4, miR-143/145 were detected by quantitative RT-PCR (Q-PCR). The protein expressions ofα-SMA, collagen-I, KLF4 were evaluated by western blot.
RESULTS: KLF4 were dramatically down-regulated during the process of cultured HSCs activation, while miR-143 and -145 were significantly up-regulated. Additionally, liver KLF4 level in cirrhotic patients were significantly down-regulated. α-SMA and collagen type I were increased after inhibition of KLF4 by specific shRNA in both rat primary HSCs and LX-2 cell line. Forced KLF4 led a reduction of α-SMA and collagen type I expression on HSCs. TGF-β rapidly inhibited KLF4 through induction of miR-143 which negatively regulated KLF4

expression. Inhibition of miR-143 prevented the activation of HSCs induced by TGF-β by targeting KLF4.
CONCLUSION: KLF4 down-regulated by miR-143 is crucial to HSCs activation and liver fibrosis partially through TGF-β signaling pathway.
Disclosure of Interest: None declared

OP295 3-MERCAPTOPYRUVATE SULFURTRANSFERASE DOWNREGULATION AMELIORATES HEPATIC STEATOSIS AND OXIDATIVE STRESS INVOLVED IN NONALCOHOLIC FATTY LIVER DISEASE

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INTRODUCTION: The mitochondrial enzyme 3-mercaptopyruvate sulfurtransferase (MPST) is a source of endogenous hydrogen sulfide (H_2S), a gaseous signaling molecule implicated in a wide range of physiological processes. Nonalcoholic fatty liver disease (NAFLD) is currently considered to be the most common liver disorder in western countries, and is rapidly becoming a serious threat to public health. The mechanisms of pathogenesis underlying NAFLD remain unclear at present. The possible role of MPST in the development of NAFLD has never been investigated.
AIMS & METHODS: A variety of cellular and molecular approaches were used to study the effects of MPST on hepatic steatosis and oxidative stress involved in NAFLD. The NAFLD cell model was established by treating L02 cells with free fatty acid (FFA) overload. Small interfering RNA (siRNA) was used to knock down MPST level. The expression of MPST and key enzymes associated with lipid accumulation and oxidative stress in L02 cells were determined by western blotting. ATP, hydroperoxide (H_2O_2), H_2S levels, mitochondrial membrane potential (MMP) and interleukin 6 (IL-6) were measured for potential mechanism exploration.
RESULTS: After culturing L02 cells by FFA for 24h, we detect the increased protein level of MPST. MPST knockdown in L02 cells resulted in a marked decrease of lipid accumulation and downregulation of SREBP-1 pathway showing reduced levels of p-SREBP-1 and its downstream proteins including FAS and ACC. Additionally, administering MPST siRNA exhibited a melioration of oxdiative stress, embodied in decreased level of H2O2, MDA and IL-6, meanwhile, increased levels of ATP and MMP. Unexpectedly, we observed a significantly increased level of H2S after the siRNA-mediated knockdown of MPST. The expression of another H2S-synthesizing enzyme namely cystathionine γ lyase (CSE) is enhanced when the MPST is decreased. Further, MPST knockdown in L02 cells demonstrated weakened of reactive oxygen species (ROS)-related signaling pathway that are JNK-1/c-jun signaling as well as IKKβ/NF-B pathway.
CONCLUSION: Our results show that MPST downregulation ameliorates hepatic steatosis via the decreased activation of SREBP-1 pathway. And MPST knockdown could stimulate the compensatory process of CSE, thus causing the increasing of H_2S which is recently considered as a novel antioxidant gas. Furthermore, the suppression of ROS-related JNK-1/c-jun signaling and IKKβ/NF-B pathway synergistically contributes to the improvement of oxdiative stress. These findings suggest that MPST is implicated in NAFLD and provide new insight into the pathogenic mechanisms of NAFLD, pointing to potential target for therapeutic strategy.
Disclosure of Interest: None declared

OP296 DEFICIENT AUTOPHAGOSOMAL-LYSOSOMAL FUNCTION INDUCED P53 AND HEPATIC APOPTOSIS IN EXPERIMENTAL NUTRITIONAL STEATOHEPATITIS

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INTRODUCTION: Macroautophagy is an essential cellular pathway mediating the lysosomal degradation of long-lived proteins and damged organelles. During the development of nonalcoholic steatohepatitis (NASH), excessive cellular lipid accumulation impairs autophagic function. Yet the cellular process of autophagic dysfunction is not well understood.
AIMS & METHODS: In this study, we aimed at discovering the underlying mechnism of impaired autophagy and investigating whether pharmacological modulation of autopahgy could have beneficial effect on NASH. C57BL/6 mice or db/db (C57BL/KsJ-db-/db-) mice were given control or methionine and choline-deficient (MCD) diet to induce NASH. Liver tissues were analyzed to determine hepatic triglycerides, lipoperoxide and serum alanine aminotransferase levels. Markers of autophagy (e.g. LC3 and p62/SQSTM1) and apoptosis (e.g. p53 and caspases-3/7) were evaluated by Western blots and immunohistochemistry. TUNEL assay was performed to in situ staining of apoptotic cells. Endoplasmic reticulum (ER) stress/unfolded protein response (UPR) markers were determined by real-time PCR and Western blots. Autophagy was blocked in murine hepatocyte cell line (AML12) or C57BL/6 mice using pharmacological inhibitors bafilomycin A1 and chloroquine (CQ) respectively. Acridine orange staining was performed to determine the acidic vesicular organelles *in vitro*. Autophagy enhancers, namely rapamycin (R) and carbamazepine (CBZ), were given in control and MCD mice for 21 days.
RESULTS: In both C57BL/6 mice and db/db mice, the development of NASH by MCD diet impaired the autophagic flux as shown by accumulation of LC3-I/II and p62. Accumulation of autophagosomes was also present in AML12 cells cultured with MCD medium. Lysosomal function was impaired in NASH as indicated by reduced cathepsin D cleavage and diminished lysosomal acidification. Of interest, we observed that the deficiency in autophagic degradaton triggers ER stress/UPR in mice with NASH, as evident by the elevated of mRNA levels of activating transporter factor (ATF6), asparagine synthetase, C/EBP homologous protein (CHOP) and caspase 12 and increased protein expression of glucose-regulated protein 78 (GRP78). NASH induction also caused increased p53 expression and apoptosis of hepatocytes. Immunoreactivity of p53 was colocalized with diffused cytoplasmic staining of LC3-I/II. Impairment of lysosomal function by CQ in mice recapitulated NASH-associated molecular dysfunctions, including impaired autophagic flux, induction of ER stress/UPR, increased p53 levels, and activation of caspases. However, induction of autophagosome formation by R or CBZ showed no alleviation of NASH development.
CONCLUSION: This study demonstrates that autophagic function was impaired at late stage through inhibition of lysosomal acidificiation, thus concomitantly inducing ER stress/UPR and p53 followed by hepatic apoptosis in the pathogenesis of NASH. These findings imply that restoring lysosomal function in the liver instead of stimulating autophagosome formation is crucial to mitigate the pathology associated with NASH.
Disclosure of Interest: None declared

OP297 LIPOTOXICITY IN LIVER INDUCED BY PALMITATE IN VIVO

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INTRODUCTION: Obesity has reached epidemic proportions around the world due to a modern lifestyle characterized by increased consumption of foods rich in energy and saturated fatty acids (FAs), combined with reduced physical activity. Free fatty acid (FFA) levels are elevated in obese subjects and elevated levels of circulating FFAs are known to be associated nonalcoholic fatty liver disease (NAFLD). The deleterious effects of FFAs, such as arteriosclerosis[1)] and exacerbation of diabetes[2)], are termed 'lipotoxicity'. Based mainly on in vitro studies, it was proposed that palmitate, which is the most abundant saturated FFA in blood, induces hepatocyte lipoapoptosis[3)4)]. However, the molecular mechanisms by which FFAs induce liver injury in vivo remain poorly understood. We established a method to selectively increase the circulating free palmitate level in mice and analyzed its effects in liver.
AIMS & METHODS: Ethyl palmitate (EP) was dissolved with lecithin and glycerol in water to produce the mixture of 600 mM EP. This mixture was then emulsified using a sonicator. The lecithin-glycerol-water solution was used as the vehicle. The right jugular veins of three-month-old C57BL/6 mice (average body weight: 26 g) were catheterized. Following a 5μl/g bolus injection of either emulsified EP solution or vehicle, the mice were continuously infused with the solutions at 0.01 μl/g/min.
RESULTS: Serum ALT levels were significantly increased in mice infused ith EP, whereas no elevation of serum ALT levels was observed in mice infused for 3 and 12hr with vehicle (control group). Hepatic TNF-α, ccl2 (one of monocyte chemoattractant proteins) and cxcl2 (one of neutrophil chemotactic factors) mRNA expression levels were significantly higher in mice infused for 3 hr with EP than control group. The number of neutrophil elastase, F4/80, alpha smooth muscle actin (alpha-SMA) positive cells in the liver was higher in mice infused EP than control group. Immunoblot analysis showed that increased phosphorylation of c-Jun were observed in the liver of mice infused EP than control group. Primary hepatocyte of wild-type responded to palmitate by expressing ccl2 and cxcl2. By contrast, cells from Tlr4-/- did not respond to palmitate, indicating that hepatocyte sense palmitate via TLR4.
CONCLUSION: The effects of palmitate in liver have never been directly tested in vivo by selectively increasing circulating palmitate levels. In this study, we show that the saturated FA palmitate induces expressing chemokines and recruiting macrophages and neutrophils to the liver, in addition, alpha SMA positive cells indicate palmitate activate hepatic stellate cell. The molecular interactions in this study could provide novel therapeutic targets for the treatment of NAFLD.
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Disclosure of Interest: None declared

OP298 CELL-SELECTIVE DELIVERY OF INTERFERON GAMMA PEPTIDOMIMETIC INHIBITS CHRONIC HEPATIC FIBROSIS AND TUMOR ANGIOGENESIS IN VIVO

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INTRODUCTION: Fibroblasts and myofibroblasts-like cells play a key role in the pathogenesis of hepatic fibrosis. Thus, pharmacological inhibition of these cells might lead to an effective therapeutic therapy for liver fibrosis. Among the potent anti-fibrotics, Interferon gamma (IFNγ) is highly efficacious but it failed in clinical trials due to reduced efficacy and increased adverse effects. Here, we employed an IFNg peptidomimetic (mimIFNg) that lacks the extracellular receptor recognition sequence but retains the agonistic activities of IFNg. Since platelet-derived growth factor receptor beta (PDGFbR) expression is highly over-expressed on key pathogenic cells, we conjugated mimIFNg to a bicyclic PDGFbR-binding peptide (BiPPB) for selective delivery.
AIMS & METHODS: The synthesized targeted IFNg peptidomimetic (mimg-BiPPB) was extensively investigated for anti-fibrotic and adverse effects in acute or chronic CCl_4-induced liver fibrosis mouse models. Furthermore, the construct was investigated for anti-angiogenic and anti-tumor effects in C26-colon carcinoma mouse model.
RESULTS: The targeted mimg-BiPPB construct markedly inhibited early and established hepatic fibrosis in mice. Native IFNg induced only moderate reduction in fibrosis, while untargeted mimIFNg and BiPPB had no effect. In addition, untargeted IFNg significantly induced systemic inflammation and MHC-II expression in brain while mimg-BiPPB did not induce any off-target effects. Furthermore, in C26-colon carcinoma tumor-bearing mice, mimg-BiPPB exhibited significant reduction in tumor angiogenesis and size via inhibitory effects on stromal cells, whereas other treatments showed no effect.
CONCLUSION: The present study demonstrates the beneficial effects of cell-specific targeting of IFNg peptidomimetic to the disease-inducing cells and therefore represents a highly potential therapeutic approach to treat chronic diseases.
Disclosure of Interest: R. Bansal: None declared, J. Prakash: None declared, K. Poelstra Shareholder of: in BiOrion Technologies

OP299 MICROPARTICLES RELEASED BY FAT-LADEN CELLS ACTIVATE IN A PARACRINE WAY NLRP3 INFLAMMASOME IN BOTH HEPG2 CELLS AND MACROPHAGES

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INTRODUCTION: Hepatocytes or HepG2 cells overloaded with saturated lipotoxic free fatty acids, a condition that mimics lipid accumulation occurring in the liver in some forms of steato-hepatitis, have been recently reported to release pro-angiogenic micro-particles (MPs) in a caspase 3-dependent manner, an event which occurs also in vivo and may have a role in the pathogenesis of NAFLD/NASH (1).
AIMS & METHODS: In this study we investigated whether MPs released from fat-laden cells may affect in a paracrine way NLRP3 inflammasome, which is known to be progressively activated in vivo in NAFLD/NASH conditions.
MPs were collected and purified as released by fat-laden HepG2 (i.e., HepG2 exposed for 24 hr to 0.25 mM palmitic acid or PA), as recently described (1). HepG2 resting cells were then incubated (15 min-24hrs) with MPs, LPS (100 ng/mL-1 μg/mL) or PA (150 – 500 μM), the latter known to induce NLRP3 inflammasome in hepatocytes. In other experiments activated human THP1 macrophages (48 hrs activation by PMA 25 nM plus 24 hrs in fresh medium) were exposed up to 24 hrs to MPs released by fat-laden HepG2 cells. Expression of NLRP-3, pro-caspase and cleaved caspase 1, pro-IL-1 and cleaved IL-1β was evaluated by Western blot analysis in cell lysates, whereas ELISA assays were used to measure IL-1β and IL-18 levels released by resting HepG2.
RESULTS: MPs were very early (i.e., 1-6 hrs) efficiently internalized by both HepG2 cells and THP1 macrophages, as revealed by means of confocal microscopy. MPs induced a time-dependent increase in the expression of NLRP3 inflammasome components in resting HepG2 cells starting from 6hr and then reaching a plateau at 16-24 hrs, with a kinetics that overlapped the one exerted by PA and was delayed as compared to LPS (1-3 hrs). Interestingly, both MPs and PA, but not LPS, significantly induced caspase-1 activation and consequent release in particular of IL-1β in a time-dependent manner. Moreover, MPs also up-regulated NLRP3 inflammasome expression in THP1 human macrophages within 3-6 hrs, resulting in a significantly increased release of IL-1β.
CONCLUSION: Fat-laden cells, by releasing MPs in a paracrine way, can efficiently trigger inflammasome activation in surrounding hepatic cells as well as macrophages, thus identifying an additional new molecular mechanism of inflammation in NASH pathogenesis.
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Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
BEST USE OF IMMUNOSUPPRESSANTS IN IBD – HALL E

OP300 LONG-TERM NATURAL HISTORY OF POSTOPERATIVE RECURRENCE IN PATIENTS ON PREVENTIVE TREATMENT WITH AZATHIOPRINE

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INTRODUCTION: The postoperative recurrence (POR) in Crohn's disease (CD) occurs in >75% within the first year after intestinal resection if no preventive treatment is started. Nowadays, azathioprine (AZA) is the most prescribed drug to prevent POR, but its long-term efficacy is unknown and no recommendations about POR monitoiring beyond the first year after surgery are available.
AIMS & METHODS: To evaluate the long-term clinical and endoscopic outcomes of CD after intestinal resection and early preventive therapy with AZA. From an specific database in which all patients with CD who underwent resection with anastomosis at our institution since 1998 were prospectively included and followed, we identified those who initiated AZA (associated or not with metronidazole or 5-ASA) within the first month after surgery and with at least a follow-up of 3 years. *Endoscopic recurrence* (ER) was defined as a Rutgeerts score >1 and *clinical recurrence* (CR) as the development of symptoms that required changes in the treatment for CD. *Surgical recurrence* (SR) was considered as the need for surgery. We defined a *Combined Outcome* as any combination of the following events: rescue with biological agents, CR or SR.
RESULTS: 189 patients were included of whom 57% male, 64% active smokers at the time of surgery, 54% penetrating behaviour. 58% of patients had ER after a median of 22 months (IQR 11.5-44.5). The cumulative probability of ER was 35%, 48% and 59%, the probability of CR was 18%, 27 and 34 % and for SR was 3% 10% and 16%, at 3, 5 and 10 years, respectively. Only active smoking after surgery was associated with POR. The risk for the combined outcome was 21%, 23% and 46% at 3, 5 and 10 years. In patients without ER at the first endoscopic control, the probability at 3, 5 and 10 years of CR was 14%, 22% and 27%; for SR 6%, 9% and 9%; and for the combined outcome of 13%, 26% and 38%, respectively. In the log-rank analysis, the cumulative probability of CR or SR was significantly higher among those patients with early ER (at the first control after surgery -p=0.044 and p=0.05-).
CONCLUSION: The use of AZA after surgical resection in Crohn's disease is associated with a low rate of CR and SR, probably because of early introduction of rescue therapy with biological in those patients with advanced endoscopic lesions. Patients without early ER, although at lower risk have a slow but steady increase in the development of ER and CR upon time, suggesting that periodical assessment of POR should be kept indefinitely.
Disclosure of Interest: None declared

OP301 ORAL VERSUS SUBCUTANEOUS METHOTREXATE IN PEDIATRIC CROHN'S DISEASE: A MULTICENTER PROPENSITY SCORE STUDY

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INTRODUCTION: The question whether methotrexate (MTX) can be effectively administered orally has never been addressed systematically in Crohn's disease (CD), although avoiding weekly injections can improve quality of life, especially in children, and reduce costs. In this largest cohort of children receiving MTX to date, we aimed to use a robust statistical method, propensity score (PS), to compare effectiveness and adverse events of orally versus subcutaneously administered MTX in pediatric CD.
AIMS & METHODS: 226 children with established CD treated with oral or SC MTX, without prior biologics, entered a multicenter, international retrospective cohort study with follow-up of at least 1-year (62% males, mean age 13.8±2.8 years, 88% previously treated with thiopurines, median disease duration 1.9 (IQR 0.9-4) months, 48% with mild and 45% with moderate-severe disease activity at MTX initiation). 38 (17%) were commenced MTX orally from the outset (ie PO group), 98 (43%) started SC and switched to PO during the first year (i.e. SC/PO group), and 90 (40%) were treated with SC only. Matching and "doubly robust" regression weighting were based on the PS method, a powerful tool to control for confounding-by-indication bias in retrospective cohorts. 11/23 pre-treatment basic variables were initially different between the three treatment groups, but none remained significant after adjustment with the PS weighting, indicating that PS modeling balanced the treatment groups appropriately.
RESULTS: 76 children (34%) had sustained steroid-free remission (SSFR), 92 (41%) had catch-up growth, 91(40%) required treatment escalation, 40 (18%) had significant elevated liver enzymes, and 49 (22%) had severe nausea. No significant differences were found in SSFR between the PO and the SC groups (OR=1.72 (95%CI 0.5-5.9); P=0.52) by PS weighted model, but the SC/PO group was superior to both (P=0.0004 and P=0.004), likely representing differences in local practice (most children from this group were from one site). There

were no differences in the need for treatment escalation (P=0.24, P=0.58 and P=0.13). Height velocity was lower in the PO group vs. the SC group (P=0.006) and the SC/PO group (P=0.0004), but in an individual matching of highly homogenous 23 pairs, the PO group was not inferior to the SC in this and the other outcomes. There were no differences between the PO and the SC group in the rate of elevated liver enzymes (P=0.59) and severe nausea (P=0.85). According to Fleming test giving higher weight to long survivors, the time to remission was delayed in the PO vs the SC group (P=0.036), but according to the log-rank test P=0.23.
CONCLUSION: In the largest cohort to date, no significant differences were found between PO and SC administered MTX in children with CD, suggesting that it may be reasonable to switch children treated with SC MTX in complete remission to the oral route while monitoring closely disease activity.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
CHALLENGES IN GORD – HALL B

OP302 MODEL OF TWO IMPORTANT STEPS IN THE PATHOGENESIS OF GASTROESOPHAGEAL REFLUX DISEASE: IMPACT OF ACIDIC PH AND PROTEASE-ACTIVATED RECEPTOR-2 (PAR2) ON MUCOSAL IL-8 SECRETION

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INTRODUCTION: Activation of protease-activated-receptor-2 (PAR2) is considered to be a relevant factor for the proposed immuno-pathogenesis of gastroesophageal reflux disease (GERD). In esophageal mucosa of patients with gastroesophageal reflux disease, interleukin-8 (IL-8) and PAR2 were found upregulated when compared to patients without GERD. In vitro studies have shown increased levels of IL-8-secretion after specifically activating of PAR2.
AIMS & METHODS: To investigate the effects of PAR2-activation upon pH stimulation in a human esophageal epithelial cell line model.
Normal human esophageal epithelial cells (HEEpiC) have been maintained for 5 days in sixwell plates creating an epithelial monolayer. In a first sequence, cells were incubated at different pH (7.4; 6.0 or 5.0) sequentially every 7 hours followed by 17 hours in basal medium (pH 7.4) for a total of 48 hours. In a second sequence of 48 hours this monolayer was stimulated with the specific PAR2 agonist SLIGKV-NH_2 for 7 hours of at pH 7.4.
RESULTS: After stimulation with different pH, gene expression levels of PAR2 and IL-8 were 4-fold upregulated with decreasing pH (p: 0.015-0.06). However, there was no upregulation for IL-8 protein in the cell pellets or in the supernatant. The additional PAR2 activation after sequential pH stimulation led to IL-8 secretion into the supernatant with increased concentrations after stimulation with lower pH (27.3 +/- 2.2 vs. 36.12 +/- 4.6 vs. 62.07 +/- 6.7 pg/ml, p=0.003), while IL-8 levels in the pellets did not differ.
CONCLUSION: A 2-step-mechanism seems to be involved in the mucosal immuno-pathogenesis of GERD. Acidic stimulation causes upregulation of mucosal PAR2 and IL-8. A following activation of the upregulated PAR2 induces the release of IL-8 with a proinflammatory cytokine response of the esophageal mucosa.
Disclosure of Interest: None declared

OP303 PRESENCE OF BASAL CELL HYPERPLASIA AND DILATION OF INTERCELLULAR SPACES AND THEIR ASSOCIATION WITH BASELINE IMPEDANCE VALUES IN PATIENTS WITH POSITIVE SYMPTOM ASSOCIATION DESPITE NORMAL ACID EXPOSURE SUPPORTS THEIR ROLE IN SYMPTOMS GENERATION IN NERD

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INTRODUCTION: Recently, Microscopic Esophagitis (ME) was positively related with severity of GERD and negatively with esophageal Baseline Impedance (BI). Thus, both ME and BI may be helpful to distinguish patients with GERD from those without. However, several histological features characterize the diagnosis of ME [basal cell hyperplasia (BCH), papillary enlongation (PE), dilated intercellular spaces (DIS) and epithelial neutrofilic/eosinophilic infiltration (Neu/Eos)] and few data are available about the role they may play individually in the pathogenesis of GERD, in particular in well-defined subgroup of reflux patients.
AIMS & METHODS: To determine frequency and role of histologic features of ME in different GERD subpopulations and to explore their association with mucosal integrity as expressed by BI values. Twenty healthy volunteers (HVs; 11F/9M; mean age 44) and 104 consecutive patients with typical reflux symptoms underwent upper endoscopy. Biopsies were taken at Z-line and 2cm above it to assess the presence and severity of BCH, PE, DIS and Neu/Eos [0 (absent), 1 (mild), 2 (marked)]. Within 3 days from endoscopy patients underwent impedance-pH testing off-therapy. We evaluated BI values at 3 and 5cm above the LES, during the overnight rest, for at least 30 minutes excluding swallows and reflux induced changes.
RESULTS: We included 20 patients with erosive esophagitis (EE; endoscopy +; 11F/9M; mean age 46yy), 31 with non-erosive reflux disease (NERD; endoscopy - and abnormal esophageal acid exposure (AET); 10F/21M; 47yy), 34 with hypersensitive esophagus (HE; endoscopy - and normal AET but positive reflux-symptom association; 24F/10M; 45yy) and 19 with functional heartburn (FH; endoscopy -, normal esophageal AET, negative reflux-symptom association and negative response to acid suppressors; 11F/8M; 43yy). There were no differences in terms of frequency of BCH, PE, DIS and Neu/Eos between HVs and FH (p=ns). BCH and DIS were more frequent in HE than FH ($p<0.05$), but not PE and Neu/Eos (p=ns). NERD had more severe PE and DIS alteration than HE ($p<0.05$), but not BCH and Eos (p=ns). Frequency and severity of all lesions were higher in EE than the other groups ($p<0.05$). Moreover, for each histologic feature, BI levels at 3 and 5 cm were lower in patients with severe lesions (score 2) compared to those with mild or no lesions (0-1) ($p<0.01$)[Table].
CONCLUSION: Frequency and severity of BCH and DIS are greater in patients with positive reflux-symptom association than in HVs and FH, regardless of AET, whereas PE seems requiring the concomitant presence of abnormal acid exposure. Thus, the increased frequency of the former lesions and the positive association between their severity and lower BI values further supports their role in symptoms generation at least in NERD patients.
Disclosure of Interest: None declared

OP303

	BCH		PE		DIS		Neu/Eos	
	BI at 3 cm	BI at 5 cm	BI at 3 cm	BI at 5 cm	BI at 3 cm	BI at 5 cm	BI at 3 cm	BI at 5 cm
Grade 0 -1	2300 (840-4225)	2100 (560-3300)	2415 (560-4225)	2282 (640-3300)	2930 (880-4225)	2850 (560-3540)	2200 (560-4225)	2080 (580-4060)
Grade 2	980 (770-4060)	890 (580-2980)	1050 (590-4060)	995 (580-2980)	1045 (830-4060)	1000 (580-3610)	980 (590-2640)	910 (600-2490)

OP304 IN-VIVO EVALUATION OF MICRO ALTERATIONS IN PATIENTS WITH EROSIVE ESOPHAGITIS AND NON-EROSIVE REFLUX DISEASE (NERD) USING PROBE BASED CONFOCAL ENDOMICROSCOPY (PCLE)

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INTRODUCTION: In the US, up to 60 % of patients suffer with GERD. Unfortunately, the "gold standard" for the diagnosis of gastroesophageal reflux disease is still lacking, and the sensitivity of 24-hour pH monitoring for diagnosing NERD is unsatisfactory. Recent technological advances make the evaluation of the integrity of esophageal mucosa possible. Previous studies using confocal endoscope have demonstrated esophageal mucosal breaks and intrapapillary loops (IPCLs) in patients with gastroesophageal reflux disease.
Confocal laser endomicroscopy is a newly developed endoscopic technique that allows the observation of living cells, tissue as well as vascular networks of the mucosal layer in the gastrointestinal tract during ongoing endoscopy. The highly magnified images of the gastrointestinal tract mucosa can permit real-time histological analysis of the site during endoscopy. Therefore, pCLE can provide precise assessment of the esophageal squamous epithelial cells and IPCLs without the need of biopsy. We investigated the use of pCLE for *in-vivo* evaluation of the micro alterations of the esophagus not observed by standard endoscopy in patients with NERD.
AIMS & METHODS: A total of 19 patients with long standing reflux undergoing standard high definition upper endoscopy to evaluate for esophagitis. Eleven patients were diagnosed with NERD by the absence of endoscopic mucosal injury/breaks. At the time of endoscopy 2.5cc of 10% fluorescein was injected. The confocal probe was placed and optical biopsies obtained within 2 cms above the gastroesophageal junction (GEJ). Histologic specimens were also obtained randomly within 2 cm of GEJ. Transmission Electron Microscopy was performed in 7 patients. The endomicroscopy images were interpreted by 2 experienced endoscopists.
CONCLUSION: This is the first pilot study examining the utility of probe based confocal endomicroscopy in the setting of NERD. The intercellular spaces and IPCL size were found to be largest in esophagitis group. They are also larger in NERD patients in comparison to the normal patients. pCLE could potentially provide a in-vivo diagnosis via "optical biopsy". It may be useful for evaluating microalterations of the esophagus in real time and assist the diagnosis of NERD. It could also be used as a marker to demonstrate therapeutic response for tissue healing in NERD patient and define define the abnormalities at the microscopic level during endoscopy in pH negative and proton pump inhibitor unresponsive patients. Further prospective study with a larger cohort is warranted.
Disclosure of Interest: None declared

OP304

	Number	PPI	Hiatal Hernia (n)	Microscopic esophagitis (n)	Sex M/F (n)	IPCL size (Mean /range m)	Fluorescein leak	Size of intercellular channels / DIS (mean /range, μm)	Reflux disease questionnaire (score)
Normal	3	2	0	0	1/2	15.1 (14.5-17)	0	2.5 (1.4-3.5)	0
NERD	11	4	0	4	5/6	24.7(12.5-54)	0	4.8 (1.2-7.9)	>10
Endoscopic esophagitis	5	3	1	5	4/1	31.2 (25-44)	3	6.53 (5.1-9)	>10

OP305 TASTE MISPERCEPTION AND SENSITIVITY IN SUBSETS OF GERD PATIENTS

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INTRODUCTION: Patients with gastroesophageal reflux disease (GERD) may experience an altered taste perception. However, no studies have explored the ability of GERD patients to discriminate primary taste. We aimed to investigate the individual ability to recognize primary tastes in GERD patients.
AIMS & METHODS: Sixty-four clinically diagnosed GERD patients without known nasal and oral pathologies (27 males, age range 25–69 years) and fifty healthy subjects (HS) (21 males, age range 23-68 years) were studied. Among GERD patients 26 were ON therapy and 38 OFF therapy (with or without proton pump inhibitors therapy, respectively). All subjects underwent a standardized taste-testing to evaluate the ability to identify sweet (acesulfame K), bitter (quinine), salty (NaCl), umami (monopotassium glutamate + inosine monophosphate) and sour taste (citric acid), scoring the intensity of taste perception by using a 100 mm line visual analogue scale (VAS). In addition, GERD patients underwent pH-impedance 24h monitoring, in order to measure the pH and the extent of the refluxes.
RESULTS: The percentage of overall taste misperception was significantly higher in OFF and ON therapy GERD patients than in HS (22.4±15% and 20.4±18% vs 13.6±15%, respectively; p=0.028). OFF and ON therapy GERD patients more frequently failed to correctly identify sweet tastant compared to HS (10.5±20.7% and 9.6±24.5% vs 100±0%, respectively; p=0.007), whereas a significant lower perception of salty taste was observed for GERD patients, both OFF and ON therapy, compared to HS (OFF: 48±19.2 and 53±25 vs 66.1±17.2 mm, respectively; $p < 0.001$). A negative association was found between both acid and non-acid reflux extent and umami perception (r=-0.45, p=0.002; r=-0.43, p=0.043), whereas a positive association was found between non-acid reflux extent and sour perception (r=0.32, p=0.032).
CONCLUSION: GERD patients, independently of current proton pump inhibitors therapy, showed a lower ability to discriminate and perceive primary tastes. In particular, GERD patients showed a poor ability to recognize sweet taste and to perceive salty taste. Interestingly, we found that refluxes extent is associated to taste impairment with a hypo- and hypersensitivity for humami and sour tastants, respectively. Given the absence of macroscopic ORL lesions in our population, the impairment of gustatory function in GERD patients might be due to refluxes-induced neuro-mediated or microscopic mucosal changes, that may affect molecular transduction pathways of gustatory signals.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
ADVANCES IN DIAGNOSIS AND MANAGEMENT OF LIVER NODULES – HALL C

OP306 CANCER STEM-LIKE SPHERE CELLS INDUCED FROM DE-DIFFERENTIATED HEPATOCELLULAR CARCINOMA-DERIVED CELL LINES EXERTS LIVER METASTATIC POTENTIAL AND CHEMORESISTANCE

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INTRODUCTION: Cancer stem cells (CSCs) are thought to play important roles in carcinogenesis, recurrence, metastasis, and therapy-resistance. Recently, it was suggested that the possible existence of plasticity between CSCs and their more differentiated derivative cancer cells. We hypothesized that poorly-differentiated hepatocellular carcinoma (HCC) has potential that convert to CSC, which would responsible for metastasis and recurrence.
AIMS & METHODS: To identify molecular tartgets for HCC treatment, we induced cancer stem-like cells from HCC cell lines using a unique medium, and examined their potentials. The human HCC cell lines SK-HEP-1, HLE, Hep 3B, and HuH-7 were used to induce cancer stem-like cells with our sphere induction medium supplemented with neural survival factor-1. Liver metastatic potential was examined by injection of the cells to immune-deficient mice spleen. Cell viability was measured by MTS assay. 9 anti-cancer agents (5-Fluorouracil, Cisplatin, Carboplatin, Docetaxel, Doxorubicin, SAHA, Irinotecan, Sorafenib, Sunitinib) were used. The mRNA and protein levels were examined by real-time PCR and flow cytometry analyses. Reactive oxygen species (ROS) activity was measured with the cell-permeable fluorogenic probe. Comprehensive analyses were performed by DNA chip for mRNA and microRNA expressions and by iTRAQ-labeled 2D-LC-MS/MS analysis for protein expressions. Integrated analysis of those comprehensive analyses was performed using the Ingenuity Pathway Analysis software.
RESULTS: Poorly differentiated HCC derived SK-HEP-1 and undifferentiated HCC derived HLE cell lines efficiently formed spheres of cells (SK-sphere and HLE-sphere), but well-differentiated HCC-derived HuH-7 and Hep 3B cells did not. SK-spheres showed increased NANOG, LIN28A, and ALDH1A1 mRNA levels compared to parental cells. SK-sphere cells showed increased liver metastatic potential compared to parental cells. As regards epithelial-mesenchymal transition (EMT), increased expression of Vimentine and Snail were observed in SK-sphere cells compared to parental cells. The cell viability of SK-spheres was significantly higher than that of SK-HEP-1 cells in the presence of several anti-cancer drugs except sorafenib (1.7- to 7.3-fold, each $P < 0.05$). Similarly, HLE-sphere showed increased chemoresistace. Regarding drug efflux, ABCG2 expression was higher in SK-sphere than in SK-HEP-1 cells. The cell cycle of SK-sphere was arrested at the G0/G1 phase compared to SK-HEP-1. In addition, SK-sphere showed induced P21 mRNA. Furthermore, SK-sphere showed higher HIF1A mRNA expression, more CD44 variant-positive cells, and lower ROS production compared to parental cells. Integrated analysis with 373 molecules showed that HIF1A and its downstream genes were up-regulated in SK-sphere ($P < 0.001$). SK-sphere cells was correlated with mitochondrial dysfunction ($P < 0.001$) and was activated in invasion of cells ($P < 0.001$).
CONCLUSION: Our novel method successfully induced cancer stem-like cells, which showed increased metastatic potential and chemoresistace. Moreover, it was suggested that EMT, cell cycle dormancy, drug efflux, and decreased production of ROS were responsible for those SK-sphere characteristics.
Disclosure of Interest: None declared

OP307 SOMATIC LOSS OF ALLELES FROM HEPATIC CYST EPITHELIUM ALLOW IDENTIFICATION OF CANDIDATE GENES IN POLYCYSTIC LIVER DISEASE

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INTRODUCTION: Autosomal dominant polycystic liver disease (PCLD) is characterized by presence of multiple fluid-filled hepatic cysts. Germline mutations in *PRKCSH* or *SEC63* underlie 20% of PCLD cases, but despite widespread presence of the encoded protein(s), the phenotype is restricted to the liver. We hypothesized that the second allele of these genes is somatically deleted in cyst epithelium, and that this may also occur for other, as yet unknown PCLD genes. Loss of somatic allele copies in cystic fluids, which can be detected by genome-wide SNP microarrays, may therefore directly point to the location of the germline mutation (the first hit).
AIMS & METHODS: We collected 50 cyst fluid samples from patients with isolated hepatic cysts. Cyst fluid samples were obtained by aspiration sclerotherapy and subjected to centrifugation, cytokeratin-19 staining and fluorescent-activated cell sorting of cholangiocytes. Flow-sorted cells were lysed and DNA was amplified using whole-genome-amplification (WGA, Repli-G single cell kit, Qiagen). Genome-wide SNP analysis on a CytoScanHD array (Affymetrix) followed to identify regions with loss of heterozygosity (LOH).
RESULTS: Hundreds to thousands of cytokeratin-19-positive cholangiocytes were sorted. We isolated and amplified DNA from these cells in 8 PCLD patients. Cyst fluid with a clear content was eligible to process for further analysis. Genome-wide SNP analysis identified multiple somatic deletions from 0.5 to 12.5Mb. Therefore, genome-wide SNP microarrays of genomic DNA were simultaneously conducted.
Our experiment was confirmed in a PCLD patient with heterozygous germline mutation *PRKCSH c.292+1G>C* which is present in a homozygous state in hepatic cyst epithelium. In addition, a PCLD patient without a known *PRKCSH* or *SEC63* germline mutation harbored the largest (12.5Mb) homozygous region on chromosome 3 in hepatic cyst epithelium. Subsequently, whole-exome sequencing of genomic DNA identified candidate genes for PCLD.
CONCLUSION: Cyst epithelium in PCLD is characterized by multiple somatic loss of genomic regions. These regions may contain genes that contribute to the phenotype.
Disclosure of Interest: None declared

OP308 PRP19 FACILITATES TWIST1-INDUCED EPITHELIAL-MESENCHYMAL TRANSITION AND PROMOTES INVASION OF HEPATOCELLULAR CARCINOMA

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INTRODUCTION: A large body of evidence demonstrates abnormality of ubiquitination contributes to the development of various cancer including hepatocellular carcinoma (HCC). In our previous work, deubiquitinating enzyme

UCH37 promoted invasion and postoperative recurrence of HCC, and decreased ubiquitin/proteasome-dependent degradation of pre-mRNA processing factor 19 (Prp19), making Prp19 a potential downstream effector to mediate invasion of HCC. As one member of protein-ubiquitin ligase, Prp19 participates in activation of mRNA splicesome, DNA damage response, and ubiquitin/proteasome dependent degradation of proteins.Although dysfunction of aforementioned activities is closely correlated with oncogenesis, the role of Prp19 in the development of HCC is less understood.

AIMS & METHODS: We investigated the expression of Prp19 and underlying mechanisms linked to its pro-invasive role in HCC. rp19 expression in tumor and paratumor tissues from 169 HCC patients was detected by immunochemistry staining and western blot, and its correlation with clinical features was analyzed. Biological behaviors of HCC cell lines with ectopic Prp19 expression were then assessed *ex vivo* and *in vivo*.

RESULTS: Prp19 expression was up-regulated in most HCC tissues and cell lines, which was positively correlated with vascular invasion, absent tumor capsule and poor prognosis. Prp19 knockdown significantly attenuated migratory and invasive capacity of HCC cells both *ex vivo* and *in vivo*, whereas Prp19 overexpression had the opposite effects. Moreover Prp19 promoted epithelial-mesenchymal transition (EMT) of HCC cells via sustaining Twist1stability, which was dependent on p38 mitogen-activated protein kinase (p38 MAPK) mediated Ser68 phosphorylation within Twist1. Prp19 interacted with transforming growing factor-β activated kinase 1 (TAK1) and facilitated k63-linked polyubiquitination of TAK1 in HCC cells, leading to strengthened activation of p38 mitogen-activated protein kinase (p38 MAPK). Prp19/p38 MAPK/Twist1 regulatory axis was further attested in orthotopic xenografts models of HCC in nude mice and human HCC specimens.

CONCLUSION: Increased Prp19 expression promotes HCC invasion by facilitating EMT via p38 MAPK/Twist1 pathway. These studies imply that gain of Prp19 is a pivotal oncogenetic event during HCC progression, rendering it a promising therapeutic target for advanced HCC.

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Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30

NEW FRONTIERS IN BARRETT'S OESOPHAGUS – HALL F2

OP309 PROSPECTIVE, MULTI-CENTRE, CASE-CONTROL STUDY TO EVALUATE A NOVEL CYTOSPONGE™–TFF3 TEST FOR DIAGNOSING BARRETT'S OESOPHAGUS

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INTRODUCTION: Barrett's oesophagus (BE) is a common condition which is often undiagnosed and predisposes to oesophageal adenocarcinoma. A minimally-invasive cell sampling device, the Cytosponge™, coupled with an immunohistochemical marker, trefoil factor 3 (TFF3), has shown promise as a diagnostic tool.

AIMS & METHODS: A multicentre, prospective study was performed to evaluate the safety, acceptability and accuracy of the Cytosponge™-TFF3 test in patients with reflux and dyspepsia symptoms without BE (controls) and cases with BE (≥ 1cm circumferential BE or ≥3 cm tongues). The data were compared with endoscopy.

RESULTS: 1,110 individuals took part comprising 463 controls (median age 56 years (interquartile range (IQR) 44-66), Male:Female ratio 1.0:1.3) and 647 cases (median age 66 years (IQR 58-73), Male:Female ratio 4.0:1.0). 1,042 (93.9%) patients successfully swallowed the Cytosponge™ and no serious adverse events were attributed to the device. Using a visual analogue scale, the Cytosponge™ was rated favourably compared with endoscopy (p=0.0003) and patients who were not sedated for endoscopy were more likely to rate the Cytosponge™ higher than endoscopy (Mann-Whitney test, $p < 0.001$). The overall sensitivity of the test was 79.9% (95% confidence interval (CI) 76.4-83.0%) increasing to 87.2% (95%CI 83.0-90.6%) for BE segments with ≥3 cm of circumferential BE. There was no loss of sensitivity in patients with dysplasia. The specificity for diagnosing BE was 92.4% (95%CI 89.5-94.7%).

CONCLUSION: The Cytosponge™-TFF3 test is safe, acceptable and has very good accuracy for diagnosing BE. This test warrants consideration as an alternative to endoscopy for diagnosing BE with potential applicability to screening in primary care.

Disclosure of Interest: C. Ross-Innes: None declared, I. Debiram: None declared, M. O'Donovan: None declared, E. Walker: None declared, S. Varghese: None declared, P. Lao-Sirieix Other: Pierre Lao-Sirieix is now employed partly by Covidien GI Solutions, L. Lovat: None declared, M. Griffin: None declared, K. Ragunath: None declared, R. Haidry: None declared, S. Sami: None declared, P. Kaye: None declared, M. Novelli: None declared, B. Disep: None declared, R. Ostler: None declared, B. Aigret: None declared, B. North: None declared, P. Bhandari: None declared, A. Haycock: None declared, D. Morris: None declared, S. Attwood: None declared, A. Dhar: None declared, C. Rees: None declared, M. Rutter: None declared, P. Sasieni: None declared, R. Fitzgerald Other: Since this study was conducted the Cytosponge™-TFF3 technology has been licensed to Covidien GI solutions by the Medical Research Council.

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30

NOVEL APPROACHES TO RECTAL CANCER – HALL G/H

OP310 INCIDENCE OF RECTAL ADENOCARCINOMA AND IMPACT OF NEOADJUVANT TREATMENTS ON PATIENTS SURVIVAL BETWEEN 1990 AND 2009 IN THE DISTRICT OF FINISTERE (FRANCE)

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INTRODUCTION: During the past decades, total mesorectal excision techniques and neoadjuvant treatments have been applied in order to improve the prognosis of rectal cancer.

AIMS & METHODS: The aim of this study performed in the district of Finistere (France) between 1990 and 2009, was to analyze the variations in incidence of rectal adenocarcinoma, as well as access to neoadjuvant treatments and their impact on patients survival.

All cases of rectal adenocarcinoma diagnosed between January 1, 1990 and December 31, 2009, recorded in the datbase of the digestive cancer registry of Finistere, were included in the study. Four 5-years periods were compared. The studied variables were gender, age, cancer stage at diagnosis (UICC) and first type of treatment applied. Qualitative variables were compared using the Chi 2 test; survival curves were established using the Kaplan-Meier method and compared with the log-rank test.

RESULTS: 2838 patients were included in the study. The incidence of rectal cancer did not change significantly during the study period (1990-1994: 7.51 ± 0.33; 2005-2009: 7.97 ± 0.32 per 100 000 inhabitants). A significant change in the distribution of cancer stages was noted over time ($p = 0.04$): the proportion of stage 4 cancers increased from 16.4% to 21.6% between the first and last period. The proportion of patients who received a neoadjuvant treatment with radiation therapy or chemoradiotherapy, increased over time for stage 2 and stage 3 cancers (23% between 1990 and 1994, 55% between 2005 and 2009.) The proportion of patients with a stage 4 cancer and treated by chemotherapy increased from 17 to 65%. Overall 5 years survival rates are presented in the table. The variation of survival was statistically significant ($p = 10^{-5}$). The highest variation in 5-year survival was noted for patients with stage 3 cancer (29.3% to 65.4%).

	Survival					
Period	1 year	2 years	3 years	4 years	5 years	Total
1990-1994	75%	59,9%	49,3%	41,3%	**37,3%**	**630**
1995-1999	76,3%	64,2%	54,9%	48,2%	**43,8%**	**716**
2000-2004	77,9%	64,7%	55,7%	51,3%	**45,8%**	**706**
2005-2009	81,9%	70,5%	61,5%	54,3%	**49,8%**	**780**

Table: survival (in %) at 1, 2, 3, 4 and 5 years, for each period

CONCLUSION: The incidence of rectal adenocarcinoma has not changed in the Finistere district between 1990 and 2009. Despite a significant increase in the proportion of advanced stages, there was a significant increase in survival rates with time, to be compared with the increase in the proportion of patients who received neoadjuvant treatment or exclusive medical treatment with chemotherapy.

Disclosure of Interest: None declared

OP311 ADDITIONAL SURGICAL RESECTION AFTER ENDOSCOPIC REMOVAL OF T1 COLORECTAL CARCINOMA IS ASSOCIATED WITH IMPROVED OVERALL SURVIVAL

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INTRODUCTION: Controversy exists on the adequate management of patients with pathologically confirmed T1 colorectal carcinoma (pT1 CRC) after initial endoscopic removal. It is currently not well known whether additional surgery following endoscopic resection of a pT1 CRC indeed improves the prognosis of patients. Moreover, it is unknown in which subgroups of patients additional surgery is actually performed in clinical practice.

AIMS & METHODS: We collected data on current treatment strategies in a cohort of patients with pT1 CRC to compare the overall survival between patients undergoing additional surgery versus endoscopic resection only and to identify factors associated with the decision to perform additional surgical resection after endoscopic resection. All patients diagnosed with pT1 CRC between 1995 and 2011 in the area of the Eindhoven Cancer Registry (southern part of the Netherlands) were included. The Cochrane-Armitage Trend test was used to evaluate trends over time in endoscopic resection of pT1 CRC. Multivariable

logistic regression was used to assess patient and tumour characteristics associated with additional surgical resection. Crude 5-year overall survival was based on Kaplan-Meier curves and Cox regression analysis was used to discriminate the independent effect of additional surgical resection on the risk of death after adjusting for relevant patient and tumour characteristics.
RESULTS: A total number of 1965 patients with pT1 CRC were identified, of whom 827 (42%) were treated with endoscopic resection (with (n=567, 69%) or without (n=260, 31%) additional surgery) and 1138 with primary surgical resection. The rate of endoscopic resection in pT1 CRC patients remained stable over time (41% in 1995 and 43% in 2011, p=0.45). Patients in whom additional surgical resection was performed were younger (mean age 65 vs. 69 years, $p<0.01$), more often had no comorbidities (34% vs. 25%, $p<0.01$) and more often had a colon than a rectum tumour (71% vs. 63%, p=0.017), compared to patients undergoing endoscopic resection only. In multivariable analysis, younger patients (OR for patients <50 years versus ≥ 70 years 1.95, 95%CI 1.05-3.59) and patients with a tumour in the colon (OR for colon versus rectum tumours 1.54, 95%CI 1.11-2.15) were more likely to undergo additional surgery. Crude 5-year overall survival was higher in patients with additional surgical resection after endoscopic resection compared to patients with endoscopic resection only (82% versus 75%, $p<0.01$). The association remained significant after adjusting for patient and tumour characteristics (adjusted HR 0.68: 95% CI 0.50-0.93). Female gender, younger age, higher socioeconomic status and absence of comorbidity were all independently associated with lower mortality.
CONCLUSION: In a large cohort of pT1 CRCs, one third of patients, particularly younger patients with a colon tumour, undergoing endoscopic resection, underwent additional surgical resection, which was independently associated with an improved overall survival rate.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
COLORECTAL CANCER SCREENING: STRATEGIES AND OUTCOMES – HALL I/K

OP312 GETTING OLD WITH LYNCH SYNDROME IN NORTHEASTERN ITALY

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INTRODUCTION: Lynch Syndrome (LS) is an inherited cancer predisposition bringing about 2-3% of all new cases of ColoRectal Cancer (CRC), caused by mutation in mismatch repair (MMR) genes. LS patients have a lifetime risk to develop a CRC up to 75% in men and 52% in women and an Endometrial Carcinoma (EC) up to 71%. The cancer spectrum involves other organs (ovary, stomach, urinary tract and small bowel), but with a lower risk.
AIMS & METHODS: We report our experience of a hospital LS registry collecting cases mainly from Northeastern Italy focusing on the clinical history of patients through aging. Families included in the study were registered in the ''Registro Tumori Ereditari del colon-retto'', settled since 1992 at our Institution. Pathogenic mutations in MSH2, MLH1 and MSH6 were identified in 37 unrelated families. We tested 251 members of the families including the probands: 113 (45%) were gene carries (44M and 69F) and 138 were wild-type. 25 families displayed mutation in MSH2, 11 families in MLH1 and one in MSH6. Surveillance program included colonoscopy from age 22 with an interval of 1-2 years, abdominal ultrasound, urine cytology every two years and upper GI endoscopy every 4 years from age 35. For women, the gynecological work out included transvaginal ultrasonography and endometrial biopsy every two years from 30-35 years.
RESULTS: The first cancer diagnosed was CRC in almost all males. EC and CRC were equally diagnosed in women. The number of CRC increased abruptly until age 40 and decreased slowly with aging. Extra-colonic cancers (EXC), instead, increased from age 50. 78 (69%) patients developed at least one cancer: 57 (50.4%) CRC and 32 female patients (46.4%) EC. However, cancer of any type occurred in all patients over age 60. 66 (56.4%) had multiple primary cancers related to aging. A progressive increase of CRC and EXC was seen and patients with six EXC had a mean age of 74 years. The deaths registered were 11 (9.7%): 2 (1.7%) for pancreatic cancer and 9 (7.9%) for other diseases between 69 and 83 of age. Colonic surveillance lasted for an average period of 10.5 years (2-22 years). 5 patients (4.4%) out of 113 had CRC at stage T1 (2 pts), T2 (2 pts) and T2N1 (1 pt) and 38 (33.6%) patients had 121 advanced adenomas.
CONCLUSION: Getting old, all LS patients displayed at least one cancer and more than 50% had multiple primary cancers. Colectomy with ileo-rectum anastomosis is the therapy of choice at first CRC diagnosed to avoid any further surgical procedures for that disease. Surveillance of organ targets (pancreas, small bowel, duodenum, urinary tract and stomach) should be included in long survivors from CRC.
Disclosure of Interest: None declared

OP313 SCREENING FOR COLORECTAL CANCER: A RANDOMIZED TRIAL COMPARING PATIENT RESPONSE OF SIGMOIDOSCOPY VS. CT COLONOGRAPHY

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INTRODUCTION: CT colonograpphy has been proposed as non invasive, potentially acceptable, primary screening test for colorectal cancer (CRC). Only one randomised trial (1) has been conducted in a population base program, comparing CT colonography and colonoscopy.
AIMS & METHODS: The aim of the study is to compare the participation rate of people invited to perform a Flexible Sigmoidoscopy (FS) to the response rate to the invitation to performa a CT Colonography (CTC), in the context of a population-based screening program.
A sample of 58 years olds in the general population living in Turin, Italy were randomly allocated (1:1) to be invited by mail for primary screening with FS or CTC. Those with a history of CRC, adenomas, inflammatory bowel disease, recent colonoscopy, or two first-degree relatives with CRC were ineligible. Non-responders to invitation for FS screening were re-invited to attend for screening with CTC or immunological Fecal Occult Blood Test (FOBT). The primary outcome was screening participation rate, defined as numbers of invitees undergoing to the screening relative to the total number of invitees. Participation rates were also compared in a multivariate model to assess the effect of covariates (gender and screening arm). We conducted also a survey of a sample of participants and of refusers to compare screenee experience with the two tests and to study reasons for non-participation.
RESULTS: Of the 1984 eligible subjects included in the study, 995 and 989 were randomly assigned to CTC and FS arm, respectively. After excluding 27 people who could not be traced (1.4% across intervention groups), the participation rate following the first invitation and mail remainder was 27.1% (265/977) for FS and 30.5% (299/980) for CTC (P=0.09).
Participation in screening with CTC was significantly better than with FS (34%, 95% CI: 30-39% vs. 26%, 95% CI: 22-31; OR, 1.6; 95% CI: 1.1-2.3; P=0.01) among men, while no difference between CTC and FS screening was observed among women (OR, 0.91; 95% CI: 0.7-1.2; P=0.53). Invitation for FS non-responders to undergo screening with CTC or FOBT increased participation (80-100 days after invitation) by 5% (18 of 330 invitees) and 4.8% (16 of 330 invitees), respectively.
CONCLUSION: A trend toward increased participation in CTC vs. FS screening was seen. Moreover, men were significantly more likely to adhere to screening with CTC than with FS. Additional effort may be needed to improve participation of women in CRC screening.
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Disclosure of Interest: C. Senore: None declared, N. Segnan: None declared, L. Correale Other: Dr. Correale is employed bu I-m3d spa. The company developed the CAD system used for the study and it contributed to the funding of the study together with the Piedmont Region Health Authrority, G. Iussich: None declared, C. Hassan: None declared, D. Regge: None declared

OP314 OUTCOMES OF THE FRENCH COLORECTAL CANCER POPULATION-BASED SCREENING PROGRAMME USING GUAIAC FAECAL OCCULT BLOOD TEST

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INTRODUCTION: With more than 42 000 new cases and more than 17 000 deaths each year, colorectal cancer is the third most common cancer and the second most common cause of cancer-related death in France. Due to its large and growing burden, an organized biennial population-based on a guaiac Fecal Occult Blood Test (g-FOBT) screening programme has been launched, and generalized since 2008 in 46 French districts, and progressively spread throughout the country and now covers all (99) French districts.
AIMS & METHODS: Biennially, all average-risk men and women aged 50 to 74 years are invited to perform a g-FOBT. Individuals with positive g-FOBT were referred to a gastroenterologist to undergo a total colonoscopy. Early performance indicators for the third round (January 1, 2012 to December 31, 2013) were evaluated according to European guidelines, and then compared with those of the second round (2010-2011), when available. The TNM classification of malignant tumours, (7th edition 2009) has been used.
RESULTS: More than 18 million people were invited for this third-round and 5.1 million people performed a g-FOBT. Participation rate was 31% (- 3.4% since the previous-round). It increased with age and was higher in women than in men (33% vs 29%). Positive rate was consistent with the expected (2.2%, men 2.5% vs women 1.9%), and varied widely with age and across the districts. Compared to the previous-round, the positive rate decreased from 2.6% to 2.2%, a decrease of 15.4%. During the period 2010-2011, follow-up colonoscopy compliance rate was 87%, and varied across the districts from 17% to 98%. Advanced adenoma detection rate was 4‰ (men: 5.9‰ vs women 2.5‰), that of colorectal cancer was 1.5‰ (men: 2.1‰ vs women 1.0‰). A total of 3949 colorectal adenocarcinomas were detected (in situ: 27% vs invasive: 73%). Stage I was 39.5% (resp., 38.1%), stage II 26.2% (resp., 26.3%), stage III 22.1% (resp., 25.6%) and stage IV 12.2% (resp., 10%) for men (resp., women). As expected,

cancers detected at subsequent screening are more often diagnosed at earlier stages (stage I and II) then those diagnosed during a first screening (68% vs 63%).
CONCLUSION: Five years after the generalization of the French population-based screening programme throughout the country, participation rate fail to achieve the European minimum recommended goal (45%). More efforts should be done to identify the profile of non-adherent to the programme for developing most effective communication strategies for these targeted people. One can hope that the next implementation of fecal immunochemical tests to replace g-FOBT tests might contribute to enhanced the adherence to screening.
Disclosure of Interest: None declared

OP315 COLORECTAL CANCER SCREENING PILOT IN NORWAY - COMPARATIVE EFFECTIVENESS RESEARCH OF FLEXIBLE SIGMOIDOSCOPY (FS) AND FECAL IMMUNOCHEMICAL TEST (FIT)

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INTRODUCTION: Although several modalities are being used in colorectal cancer (CRC) screening, only fecal occult blood testing (FOBT) and FS have been subjected to randomized trials and long-term follow-up. Both have been found to reduce CRC mortality compared to no screening (18% and 28%, respectively), but a direct comparison between the two has never been done with end-point CRC incidence and mortality. It is also not clear which modality is the most cost-effective in any given population. In Norway, a country with high colorectal cancer incidence and little prior CRC screening, the government decided to start a comparative effectiveness research pilot in 2012.
AIMS & METHODS: The pilot aims to randomize 1x1 the entire population aged 50–74 in a defined geographical area in South-East Norway (approximately 140 000 individuals) to one of two screening modalities, FIT (OC-Sensor Diana, Eiken Ltd) or once only FS. The enrollment will take six years and the pilot includes a number of sub-studies to determine how the screening is perceived in the target population. We report the results from the enrollment in the main trial after the first 24 months.
RESULTS: A total of 51500 women and men have been invited so far, 33.373 to FIT and 18.127 to FS. Participation rates have been 49% in the FS arm, and 57% in the FIT arm, with slightly higher rates among women than men. Positive FS was defined as advanced neoplasia or three or more adenomas. A total of 10.3% of the FS patients have been referred to colonoscopy. The cut-off value for positive FIT was set to 75 ug/L, and 1287 patients (6.9%) have so far tested positive and referred to colonoscopy.
Forty-three cases of CRC have been detected in the FS group so far, at a rate of 5/1000 examined, somewhat higher in men (5.7/1000) than in women (4.3/1000). Forty-nine cancers have been found in the FIT group after first screening round (2.6/1000 examined), with 3.7/1000 in men and 1.7/1000 in women. Overall the adenoma detection rate at sigmoidoscopy is 14.4 %. A total of 853 high-risk adenomas (adenomas >10 mm, or with high-grade dysplasia or villous features) have been detected. Adenoma detection rate in the population referred for colonoscopy is 59%. One perforation has occurred due to the enema installation prior to sigmoidoscopy. At colonoscopy the rate of serious adverse events needing hospitalization is currently 8/1000, the main ones being reported are burned serosa and bleeding, while no perforation has occurred.
CONCLUSION: Participation rates in both arms are slightly below the expected 50% for FS and 60% for FOBT. Cancer rates among those screened are higher in the once-only FS than after first round of biennial FIT screening, but rates are within the expected range.
Disclosure of Interest: None declared

OP316 IMMUNOCHEMICAL FECAL OCCULT BLOOD TESTING TO SCREEN FOR COLORECTAL CANCER: CAN THE SCREENING INTERVAL BE EXTENDED?

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INTRODUCTION: Colorectal cancer (CRC) screening programs based on fecal immunochemical testing for hemoglobin (FIT) typically use a screening interval of 2 years. Studies have shown that the diagnostic yield of the first re-screening round (reSR) is significantly lower as compared to the initial screening round (inSR), which raises the question whether the first reSR could be skipped. This would lead to a longer screening interval that could be advantageous regarding adherence and organizational effort. Given the quantitative nature of FIT, the skipped round could be compensated for by lowering the cutoff level (CL) of FIT at the initial round (i.e., increasing sensitivity at the cost of decreasing specificity). We aimed to explore how such alternative FIT strategies compare to conventional ones in terms of CRC detection and positivity rate.
AIMS & METHODS: We analyzed longitudinal data of 4523 Dutch individuals (50–74 years) participating in the inSR of a 1-sample FIT screening program, of which 3427 individuals also participated in the first reSR after 1-3 years. FIT50 was used in both rounds (i.e., a CL of ≥50 ng haemoglobin (Hb)/ml, corresponding to 10 μg Hb/g faeces). The cohort was followed up until 2 years after the first reSR. We determined the cumulative number of (screen-detected) CRCs for the 2 FIT50 rounds and compared it to the number of CRCs that would have been detected at a hypothetical, single inSR with a lower CL. For the latter, we considered persons who were diagnosed with CRC (screen-detected or interval CRC) until the end of the follow-up period and examined whether their FIT level at the inSR was beyond a certain value. We first looked at FIT11 (i.e., a CL of ≥11 ng Hb/ml, corresponding to 2 μg Hb/g faeces). This CL is - according to published literature on diagnostic performance - expected to yield a similar number of advanced adenomas as detected in the 2 FIT50 rounds combined. We also compared positivity rates for the different scenarios.
RESULTS: In the 2 FIT50 rounds, 28 CRCs were detected, of which 22 (79%) were at an early stage (UICC stages I-II). The cumulative positivity rate was 14%. In a hypothetical inSR with FIT11, 27 CRCs would have been detected. Of these, 19 (70%) would definitely have been detected at an early stage. Two of the 27 CRCs were detected at UICC stage III 9 months and 2 years after the inSR, respectively, and thus might have been at an early stage if detected at the inSR. The positivity rate of a hypothetical inSR with FIT11 would have been 18%. All CRCs detected with FIT11 would also have tested positive with CLs up to 24ng/ml. The positivity rate of a hypothetical inSR with FIT24 would have been 12%.
CONCLUSION: We provide first empirical evidence regarding alternative FIT strategies using extended screening intervals in combination with a lower than usual positivity threshold. The findings remove concerns that such strategies would go along with a significant increase in the rate of interval cancers or in the overall positivity rate. Although the approach taken here to lower the positivity threshold (i.e., CLs below 50 ng/ml) would require careful consideration regarding test-retest reliability, the findings suggest that, in principle, such alternative FIT strategies could be interesting options and provide the basis for planning next research steps in this direction.
Disclosure of Interest: None declared

OP317 THE 10 YEARS EVALUATION OF THE CZECH COLORECTAL CANCER SCREENING PROGRAM EFFICACY BASED ON THE LONG-TERM IMPACT INDICATORS

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INTRODUCTION: In the Czech Republic, there is 3.75 million inhabitants aged over 50. The Czech Colorectal Cancer (CRC) Screening Program was introduced in 2000 based on guiac fecal occult blood testing (gFOBT). In the last decade, the program has continuously evolved. Currently the annual immunochemical FOBT (FIT) is offered at the age 50 – 54, followed by FOBT+ colonoscopy, if positive. In age of 55, there is a choice of either FIT biannually or screening colonoscopy in 10 years interval.
AIMS & METHODS: Three main quality control long-term impact indicators recommended by the European Guidelines (published in 2010) have been compared in 10 years interval (decrease of CRC incidence and mortality and the increase of the proportion of early stage cancers) to assess the CRC screening program efficacy. The data from the Czech National Cancer Registry have been used.
RESULTS: The CRC incidence in years 2000 and 2010 reached the level of 42.23 and 39.19 (the world standard, ASR-W) and 7,553 and 8,265 (absolute numbers, +712, 9.4%). The CRC mortality recorded in the same years was 23.79 and 17.20 (ASR-W) and 4,508 and 3,991 (absolute numbers, -517, -11.5%). The comparison of CRC stages in years 2000 and 2010 is shown in the table.

Stage	2000	2010	Change
Stage I	16 %	23 %	+7%
Stage II	27 %	24 %	-3%
Stage III	17 %	24 %	+7%
Stage IV	23 %	23 %	0%
Stage unknown	18 %	6 %	-12%

CONCLUSION: The ten years results show that the Czech CRC screening program is effective. All three main long-term impact indicators are fulfilled, the incidence and mortality are decreasing and the ratio of stage I cancers diagnosed is rising.
This project has been supported by the Czech Ministry of Health grant No. NT 13673
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Disclosure of Interest: None declared

OP318 LONG-TERM IMPACT OF THE DUTCH COLORECTAL CANCER SCREENING PROGRAMME ON CANCER INCIDENCE - EXPLORATION OF THE SERRATED PATHWAY

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INTRODUCTION: The Netherlands has recently started with the stepwise implementation of a colorectal cancer (CRC) screening programme consisting of biennial faecal immunochemical test (FIT) screening in individuals aged 55 to 75 years.
AIMS & METHODS: 1) To evaluate the impact of the Dutch screening programme on the long-term CRC incidence and colonoscopy demand. 2) To explore the impact of assumptions concerning the serrated pathway on these long-term predictions.
The Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model was set up to simulate the Dutch CRC screening programme between 2014 and 2044. Based on pilot studies, we assumed a participation rate of 62% for FIT testing. We adopted an open-model approach by simulating multiple birth cohorts and combining the results while accounting for the ageing of the population. Besides a no screening scenario, we evaluated three screening scenarios differing in the contribution of the serrated pathway to the CRC incidence (0%, 15% and 30%). Model-predicted outcomes were CRC incidence and the colonoscopy demand per year from 2014 until 2044. In addition to the contribution of the serrated pathway to the CRC incidence, we assessed the impact of other natural history assumptions regarding the serrated pathway.
RESULTS: Due to ageing, the model-predicted CRC incidence in the no screening scenario increased from 77/100,000 in 2014 to 109/100,000 in 2044. In the screening scenarios, the predicted CRC incidence first increased compared to no screening due to the detection of asymptomatic, prevalent tumours. In 2014, the CRC incidence was predicted to peak between 105/100,000 (under the assumption that all CRCs arise from adenomas) and 109/100,000 (under the assumption that 30% of CRCs arises from serrated lesions). After this peak, the predicted incidence under screening gradually decreased. In 2044, the estimated CRC incidence under screening reached a new equilibrium between 65/100,000 and 71/100,000 under the assumption that 100% versus 70% of CRCs originate via the adenoma-carcinoma pathway, respectively. Due to the stepwise implementation, the predicted number of colonoscopies required for the screening programme increased gradually over time. In 2014, the expected number of colonoscopies under screening was estimated to be around 38,000 (752,199 invitees) whereas in 2044, the predicted colonoscopy demand was estimated to be around 117,000 (2,154,875 invitees). Except for the contribution of the serrated pathway to the CRC incidence, model predictions were robust for other assumptions regarding the natural history of the serrated pathway.
CONCLUSION: The Dutch screening programme will markedly decrease the CRC incidence. With the results of this study, decision-makers on health care planning can anticipate the expected change in CRC-related health care use and colonoscopy demand. Although the natural history of the serrated pathway has not yet been fully clarified, different assumptions for these unknown parameters have limited impact on model predictions. However, the estimate of the proportion of CRCs arising through the serrated pathway does influence the predicted effectiveness of screening.
Disclosure of Interest: None declared

OP319 REPEATED FIT SCREENING: THE INFLUENCE OF SUBJECT'S CHARACTERISTICS AND SCREENING HISTORY ON THE POSITIVE PREDICTIVE VALUE AND NEOPLASIA YIELD

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INTRODUCTION: There is limited experience of colorectal cancer (CRC) screening with fecal immunochemical tests (FIT) over several screening rounds.
AIMS & METHODS: To assess FIT screening performance among people performing consecutive tests in 3 population based programs in Italy and to explore the impact of modulating positivity cuf-off to account for screenee's characteristics and screening history. The participating programs target people aged 50 to 74 (Aosta), 59 to 69 (Turin) and 50 to 69 (Reggio Emilia), offering single sample biennial FIT, with 100 ng haemoglobin (Hb)/ml buffer (20 μg/mg faeces) positivity cut-off. We measured the positive predictive value (PPV), the number needed to scope (NNScope) and the detection rate (DR) for advanced adenoma (AAd) and CRC, and the interval CRC (IC) rate (ICs x 10,000 subjects with negative FIT), among people aged 50 to 69. We simulated the impact of modulated positivity thresholds, accounting for age, gender and Hb level at previous tests, among people undergoing their third screening.
RESULTS: The PPV, the NNScope and the DR for AAd and CRC, stratified by subject's age at screening, are presented in table 1. The PPV for advanced neoplasia (AAd + CRC) is higher among older people at the initial (p=0.047), but not at subsequent screening (p=0.076). The DR is higher among men than among women both at the initial and at subsequent tests. Setting the positivity cut-off at 200 ng/ml for women with 0-49 ng Hb/ml at the 2 previous FITs, and for men with no Hb at the initial FIT and 0-49 ng Hb/ml at the second FIT, would result in a 26% reduction in the colonoscopy (TC) workload and in a 17% AAd and 6% CRC miss rate. The IC rate over the 2-year period after the initial negative FIT was 2.5 (N=10) and 7.2 (N=25) x 10,000 women aged 50-59 and 60-69 respectively; the corresponding figures for men were 3.6 (N=12) and 8.3 (N=24) x10,000; the Hb level at the preceding FIT was 0 in 39.4% of the cases. Among people with 2 negative FITs the IC rate was 3.9 (N=19) and 3.9 (n=16) x 10,000 women and men respectively; no Hb was detected in the previous 2 FITs in 34.3% of these cases.

Age 50-59	N examined	FIT+	TC	PPV AAd	PPV CRC	DR AAd	DR CRC	NNScope
1 FIT	88935	4,3%	91,5%	35,3%	4,2%	1,40%	0,17%	2,5
2 FIT	46692	3,3%	93,0%	25,0%	2,5%	0,77%	0,08%	3,6
3 FIT	24009	3,0%	93,3%	22,7%	2,8%	0,64%	0,08%	3,9
4 FIT	3569	2,9%	94,3%	33,3%	1,0%	0,92%	0,03%	2,9
Age 60-69	**N examined**	**FIT+**	**TC**	**PPV AAd**	**PPV CRC**	**DR AAd**	**DR CRC**	**NNScope**
1 FIT	76934	6,6%	88,7%	34,6%	7,1%	2,01%	0,41%	2,4
2 FIT	61922	4,6%	91,3%	26,7%	3,5%	1,13%	0,15%	3,3
3 FIT	41882	4,2%	91,6%	24,0%	3,2%	0,93%	0,12%	3,7
4 FIT	19166	4,0%	90,2%	23,3%	3,0%	0,84%	0,11%	3,8

CONCLUSION: The high DR of AAd over several screening rounds is suggestive for a larger impact of FIT screening on CRC incidence, as compared to guaiac-FOBT. Gender, age and stool Hb at previous tests could be used to modulate the cut-off at subsequent tests, to reduce TC workload. Apparently a substantial proportion of ICs may not bleed.
Disclosure of Interest: None declared

OP320 COLONPREDICT STUDY: DEVELOPMENT AND VALIDATION OF A PREDICTIVE MODEL FOR COLORECTAL CANCER DETECTION IN SYMPTOMATIC PATIENTS

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INTRODUCTION: Predictive models for colorectal cancer (CRC) detection in symptomatic patients are based on subjective clinical criteria and have low diagnostic accuracy.
AIMS & METHODS: We designed a prospective blind diagnostic tests study aimed to develop and validate a CRC predictive model in symptomatic patients based on clinical and laboratory variables. We compared its diagnostic accuracy with the National Institute for Health and Care Excellence (NICE) referral criteria for the detection of colorectal cancer in symptomatic patients. We included consecutive patients with gastrointestinal symptoms referred for colonoscopy. In each patient, the symptoms were collected in a structured protocol; fecal calprotectin (Bühl Quantum Blue ®) and hemoglobin (OC-Sensor ®) concentrations, serum carcinoembryonic antigen (CEA) and hemoglobin were determined and the findings in anorectal examination were described. A predictive model was developed based on a binary logistic regression and was internally validated using the split-sample technique. To compare COLONPREDICT model with NICE criteria, we used ROC curves and AUC to detect differences in overall diagnostic accuracy and McNemar test to determine differences in sensitivity and specificity for CRC detection.
RESULTS: Between March 2012 and September 2013, 1572 patients were included and were valid for analysis. We detected 215 (13.7 %) CRC. The variables included in the predictive model were age (years) (OR 1.04, 95% CI 1.02-1.06), sex (male) (OR 2.27, 95% CI 1.5-3.44), fecal hemoglobin$\geq$ 100ng/ml (OR 17.2, 95% CI 10.18-29.03), hemoglobin ($<$ 10g/dL) (OR 4.76, 95% CI 2.19-10.37) (10-12g/dL) (OR 1.8, 95% CI 1.09-2.96), CEA ($\geq$ 3ng/mL) (OR 4.52, 95% CI 3-6.9), treatment with acetylsalicylic acid $>$ 1 year (yes) (OR 0.42, 95% CI 0.24-0.74), colonoscopy in the last 10 years (yes) (OR 0.12, 95% CI 0.06-0.25), mass on digital rectal examination (yes) (OR 17.19, 95% CI 10.18-29.03), benign anorectal disease (yes) (OR 0.27, 95% CI 0.17 to 0.44), rectal bleeding (yes) (OR 2.27 95% CI 1.5-3.44) and change in bowel habits (yes) (OR 1.7, 95% CI 1.14-2.51). The AUC of COLONPREDICT model was 0.92 (95% CI 0.91 to 0.94), significantly higher than the AUC of NICE criteria (AUC 0.59, 95% CI 0.55-0.63; $p < 0.001$). At a COLONPREDICT model cut-off with a 90% sensitivity for CRC detection, the predictive model is statistically more sensitive (89.3 %, 67.9 %; $p < 0.001$) and specific (79.3 %, 50.3 %; $p < 0.001$) than the NICE criteria.
CONCLUSION: COLONPREDICT is a predictive model with high diagnostic accuracy for the detection of CRC in symptomatic patients. External validation is required for widespread use in the indication and priorization of colonoscopy.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
GENETIC INFORMATION IN UPPER GI CANCER: ALREADY CLINICALLY RELEVANT? – HALL L/M

OP321 A NOVEL TUMOR SUPPRESSOR MDGA2 ACTIVATES ANTI-TUMOR DMAP1/ATM/P53 PATHWAY AND IS AN INDEPENDENT PROGNOSTIC FACTOR IN GASTRIC CANCER

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INTRODUCTION: By using genome-wide promoter methylation screening assay, we identified that MDGA2 (MAM domain containing glycosylphosphatidylinositol anchor 2) was preferentially methylated in gastric cancer (GC). However, the role of MDGA2 in tumorigenesis remains unexplored.
AIMS & METHODS: This study aimed to elucidate the epigenetic regulation, clinical significance, biological function and molecular mechanism of MDGA2 in GC. Promoter methylation was evaluated by bisulfite genomic sequencing and combined bisulfite restriction analysis. Gene expression was examined by RT-PCR, western blot and immunohistochemistry. The biological functions of *MDGA2* were examined by MTS assay, colony formation, flowcytometry, Ki-67 and Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) stainings in vitro and *in vivo* tumorigenicity analysis. The molecular mechanism of MDGA2 was explored by promoter-luciferase activity assay, cDNA array, etc.
RESULTS: MDGA2 was silenced in 90.9% (10/11) GC cell lines, which was closely related to promoter methylation. After treatment with demethylation agent, expression of MDGA2 was restored in silenced GC cells. MDGA2 expression was also significantly lower in gastric tumors as compared to their adjacent normal tissues (P=0.001). Importantly, MDGA2 methylation was detected in 62.4% (136/218) of primary gastric tumors. Multivariate analysis revealed that MDGA2 methylation is an independent factor for poor survival in GC patients [P=0.005, RR=1.85 (1.21-2.84)]. Kaplan-Meier survival curves showed that MDGA2 methylation was significantly associated with shorter survival of GC patients (1.59y *vs*. 4.87y, median; P=0.001).
We further tested the biological function of MDGA2. Re-expression of MDGA2 in GC cell lines (AGS and BGC823) significantly suppressed cell viability, reduced cell proliferation, inhibited clonogenicity, caused cell cycle arrest at G1 phase and induced cell apoptosis. On the other hand, knockdown of MDGA2 promoted cell growth by accelerating cell cycle progress and reducing apoptosis in MKN1 GC cells. *In vivo* growth of BGC823 GC cells was markedly inhibited by MDGA2 transfection in both subcutaneous ($P<0.001$) and orthotopic ($P<0.001$) xenograft models in nude mice.
The molecular mechanisms of the tumor suppressive effect of MDGA2 were further characterized. We demonstrated that MDGA2 activated p53 pathway by p53-luciferase reporter assay. In keeping with this, downstream mediators of p53 signaling were also upregulated by MDGA2, including p63, p73, caspase 9, p21 and ATM. Moreover, MDGA2 directly upregulated and binded to DMAP1 (an essential regulator of ATM activity) as evidenced by mass spectrometry analysis of immunoprecipitation products and pull-down assays using MDGA2 and DMAP1 recombinant proteins. MDGA2-DMAP1 subsequently activated ATM and p53, followed by upregulation/activation of p53 signaling mediators. Activating of DMAP1/ATM/p53 signaling pathway contributes to the suppression of tumor growth in gastric cancer.
CONCLUSION: MDGA2 is a novel tumor suppressor inactivated by promoter methylation in gastric cancer. MDGA2 methylation is significantly associated with shorter survival of GC patients. MDGA2 exhibits tumor suppressive effect by directly upregulating DMAP1 to stimulate ATM/p53 signaling pathway.
Disclosure of Interest: None declared

OP322 BIOMARKER ASSESSMENT FROM EUS GUIDED BIOPSY PREDICTS OUTCOMES AND TREATMENT IN PANCREATIC CANCER

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INTRODUCTION: Current methods of pre-operative predicting outcome of pancreatic cancer and related pancreatectomy are limited. Although several prognostic biomarkers, including S100A2 and S100A4, are associated with poor outcome, currently these can only be assessed in operatively resected specimens. The amount of tissue from EUS guided fine needle aspiration is often insufficient for biomarker assessment. Procore needles aim to acquire larger volumes of tissue that may be suitable for pre-operative biomarker assessment.
AIMS & METHODS: (i) To evaluated the feasibility of S100A2 and S100A4 assessment in EUS guided biopsy specimens using the Procore needle, and (ii) to evaluate the relationship of these biomarkers with outcomes. **METHODS**: Clinico-pathological, treatment and survival data from 138 patients (70±2yrs; 70M:68F) with pancreatic ductal adenocarcinoma (PDAC) were prospectively acquired. All subjects had EUS guided biopsy with a 22G Procore needle and cell-block preparation was performed. Sections of cell-block material were assessed for S100A2 and S100A4 protein expression using immunohistochemistry (IHC).
RESULTS: Pre-operative biomarker assessment from EUS acquired specimens was possible in 92% (127/138) of patients. IHC stain for the biomarkers was positive in 59 (46%) patients and co-expressed 31 (56%) patients. Pancreatectomy was performed in 28 (22%) patients. Overall median survival was 11 (5-16) months with patients who had (i) S100A2/A4 -ve PDAC on EUS (8 vs. 20 months, $P<0.0001$) and (ii) pancreatic resection (18 vs. 12 months, P=0.002) had a significantly better median survival. Of patients who had pancreatectomy, patients with S100A2/A4 expressing PDAC had shorter survival (12.0 vs. 22.0 months; P=0.02). In the non-surgical treated patients, the presence of S100A2/A4 was also associated with poorer survival (7 vs. 19.9 months; $P<0001$). Amongst patients with S100A2/A4 expressing PDAC, pancreatectomy, however, led to a small survival benefit compared with those with non-surgical treatment (12 vs. 7 months, P=0.03). Chemotherapy was given to 86 (68%) patients (3 neo-adjuvant, 17 adjuvant and 66 palliative). Amongst patients who received palliative chemotherapy, patients who had S100A2/A4 expressing PDAC had significantly poorer survival (7 vs. 22 months, $P<0.0001$), and were similar to those who had no treatment (vs. 7months, P=0.47).
CONCLUSION: Biomarker assessment from EUS guided biopsy specimens is feasible and successful in over 90% of cases. In patients with PDAC, the presence of S100A2 and S100A4 expression predicts both survival, and influences the responses to both pancreatectomy and palliative chemotherapy. These findings support the potentially important role of pre-operative EUS guided biopsy for biomarker determination and guide clinical decision-making, particularly with regard to selection for operative resection of PDAC.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
DIAGNOSIS AND TREATMENT OF CONSTIPATION AND FAECAL INCONTINENCE – HALL R

OP323 THE BALLOON EXPULSION TEST: REPRODUCIBILITY AND AGREEMENT WITH RECTAL MANOMETRY AND PELVIC FLOOR EMG

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INTRODUCTION: The balloon evacuation test (BET) measures the time required to evacuate a 50 ml water-filled balloon. We aimed to assess reproducibility of the BET, determine the upper limit of normal, and assess concordance with anorectal manometry (ARM) and pelvic floor surface electromyography (EMG).
AIMS & METHODS: BET was tested in 286 chronically constipated patients before and after 30-days of conservative treatment at a tertiary gastroenterology clinic in Italy. BET was performed with a 16 FR Foley catheter filled with 50 ml of tepid water. Up to five minutes were allowed to evacuate the balloon while sitting on a conventional toilet in a private bathroom. BET was tested twice, 7-days apart, in 40 healthy controls recruited among hospital personnel and Med students. The 238 constipated patients who did not respond to conservative therapy (increased fluids and fiber, laxatives no more than twice a week) received an ARM, EMG, and digital rectal examination (DRE). Forty-seven patients with conflicting ARM and BET results received defecography.
RESULTS: Patients averaged 44 years and 91% were females; controls averaged 38 years and 92% were females. Balloon evacuation was achieved within 1 min by 37/40 healthy controls, but 3 (8%) required 1-2 minutes. In constipated patients, 148/286 passed the balloon within 5 minutes including 110 in 1 minute, 35 in 1-2 minutes, and 3 in 2-5 minutes. BET showed perfect reproducibility in 280/286 (98%) constipated patients when a BET interval over two minutes is defined as abnormal. Agreement between BET and ARM for dyssynergia was 78% and agreement between BET and EMG was 83%. In 32 patients, BET was abnormal but ARM was normal, and 31 of these cases showed inadequate straining (n=11) or anatomical defects which might explain failed BET (n=20).
CONCLUSION: The optimal upper limit of normal for the BET is two minutes. Test re-test reproducibility is excellent (98%). The BET shows good agreement with ARM and EMG. A normal BET almost rule out a disordered defecation syndrome.
Disclosure of Interest: None declared

OP324 ENDOFLIP: A NEW DIAGNOSTIC MODALITY FOR MEASURING ANAL CANAL FUNCTION

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INTRODUCTION: Anorectal manometry is the most well established and commonly used technique for investigating anorectal function but despite its widespread use, it has well established limitations. Functional Lumen Imaging Probe (FLIP) is a novel technique for measuring anorectal function. Its repeatability and validity of in anorectal studies has already been established. This study looked at its utility in establishing dynamic properties of anal canal with and without rectal distension, in particular to demonstrate the sampling reflex, the poorly understood physiological mechanism of which remains uncertain.
AIMS & METHODS: To establish dynamic and non-homogenous properties of the anal canal in healthy volunteers using EndoFLIP. Demonstrate the segmental differences in anal canal. Methods: 19 healthy volunteers were recruited (9 females), mean age 34 (20-75). Purpose built catheters incorporating rectal and

anal canal balloon were used. Appropriate sized catheter anal canal balloon (2, 3 and 4cm long) corresponding to the length of subject's anal canal (based on manometry) was used. 3 cross sectional area (CSA) readings were obtained with 2cm balloon, 5 with 3cm and 10 with 4cm balloon. In order to obtain meaningful results, the anal canal balloon was required to be touching the lumen wall and this was achieved by using different inflation volumes, according to the balloon size, determined by analysing the pre-study test results. Rectoanal inhibition reflex (RAIR) was recorded by inflating the rectal balloon while recording the anal canal CSAs with the anal canal balloon. Participants underwent standard water-perfused anal manometry followed by FLIP on the same day. The anal canal was divided into distal, mid and proximal parts based on anatomy and preliminary data analysis. Paired t-test was done comparing CSA in the following segments (across all the balloon volumes), distal with mid anal canal, mid with proximal anal canal and distal with upper anal canal. The parameters looked at included CSA at rest, squeeze and during RAIR.

RESULTS: Statistically significant difference was noted in between CSAs of the three segments both at rest and squeeze (Table 1). In all the three phases of rest, squeeze and RAIR, distal segment had the lowest mean CSA followed by mid and proximal segment respectively (Table 1). Analysis of RAIR revealed a significant difference in CSAs between proximal and distal segments (p = <.0001) but not between mid and the proximal segments (p = .351).

Segmental cross sectional areas

Anal Canal Segment	Rest Mean CSA (in mm)(SD)	Squeeze Mean CSA (in mm)(SD)	RAIR Mean CSA (in mm)(SD)
Distal	13.27 (3.19)	12.04 (2.55)	12.37 (3.38)
Mid	15.25 (3.37)	14.40 (3.14)	13.85 (3.88)
Proximal	15.44 (3.97)	15.18 (3.96)	14.03 (4.14)
p values for intra-segmental comparison of CSA			
Measured phase	**Distal - M id**	**M id - Proximal**	**Distal - Proximal**
Resting	.000	.013	.000
Squeeze	.023	.000	.000

CONCLUSION: EndoFLIP allows detailed segmental description of the anal canal. CSA differences in three segments of anal canal clearly reveal its dynamic nature. The distal-most part of anal canal has the lowest distension followed by mid and proximal part, both at rest and squeeze. This segmental difference in the anal profile demonstrates the anatomical and physiological basis of the sampling reflex.

Disclosure of Interest: None declared

OP325 EXPLORING THE POTENTIAL OF GENE THERAPY FOR HIRSCHSPRUNG DISEASE: STUDIES IN THE MIRET51 MOUSE MODEL

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INTRODUCTION: Hirschsprung disease (HSCR) affects 1:4500 births and is characterized by aganglionosis of the distal bowel, caused by a failure of development of the enteric nervous system (ENS) from neural crest cells (NCC). The RET receptor tyrosine kinase is part of a key signalling pathway for ENS development and is implicated in the majority of HSCR cases. In mice and humans, RET is expressed as two main isoforms, Ret^{51} and Ret^{9}. Mice expressing only the Ret^{51} isoform (monoisoformic-$miRet^{51}$) have distal colon aganglionosis and are an established model of human HSCR.

AIMS & METHODS: (i) Characterise ENS development in $miRet^{51}$ mice in terms of NCC migration, proliferation and neuronal differentiation by lineage tracing with YFP. (ii) Label and isolate ENS progenitor cells (EPCs) from $miRet^{51}$ and wild type animals using a GFP retroviral vector. (iii) Perform genetic rescue of $miRet^{51}$ EPCs by infecting with a retrovirus carrying a Ret^{9}-GFP cassette.

To label all NCC with YFP, $miRet^{51}$ mice were crossed with $Rosa^{26}YFP^{stop}Wnt1^{cre}$ mice. Immunolabelling of whole guts and sections of embryos from $miRet^{51}$ and control littermates was performed using GFP (to identify YFP cells) plus antibodies to investigate migration, proliferation (BrdU) and neuronal differentiation (HuC/D). To generate EPCs, cells were infected with a GFP retroviral vector and positive cells were isolated via fluorescent activated cell sorting (FACS). To rescue the $miRet^{51}$ defect, cells from $miRet^{51}$ gut were infected with a Ret^{9}-GFP retrovirus and neuronal differentiation studied.

RESULTS: Migration of NCC in $miRet^{51}$ guts was impaired compared to controls at all stages in development as determined by immunolabelling of whole gut and embryo sections. Proliferation was reduced in $miRet^{51}$ cells compared to control littermates both *in vitro* and *in vivo*. At E10.5, 6.8±0.9% $miRet^{51}$ cells divided versus 19.05±0.9% in controls; $p<0.05$. At E14.5, proliferation was 13.95±3.51% in $miRet^{51}$ cells versus 25.5±3.78% in controls; n=6, $p<0.05$. Neuronal differentiation and axonal outgrowth, *in vivo*, was reduced throughout development. At E18.5, 17.9±4% of YFP+ cells were positive for HuC/D in $miRet^{51}$ versus 36.1±10% in control embryos; n=4, $p<0.05$. EPCs isolated from $miRet^{51}$ guts also displayed reduced neuronal differentiation *in vitro* compared to controls (5.45±1.4% in $miRet^{51}$ and 16.9±4.7% in controls; $p<0.05$). This deficit was rescued when $miRet^{51}$ EPCs were infected with a retrovirus expressing Ret^{9}-GFP. Here, the percentage of neurons changed from 5.45±1.4% in $miRet^{51}$ to 17.3±4.4% in $miRet^{51}$;Ret^{9} EPCs versus 21.6±3.5% in control EPCs; p=0.06.

CONCLUSION: Our results indicate that expression of both RET isoforms, which underpins normal RET activity, is required for the migration, proliferation and differentiation of NCC ultimately leading to the formation of a functional ENS. EPCs from $miRet^{51}$ animals can be isolated and most importantly, the neuronal differentiation deficit in these cells restored by introducing the Ret^{9} isoform into $miRet^{51}$ cells. The isolation of EPCs and the ability to manipulate and rescue key HSCR genes such as RET paves the way for generating novel therapies for gut motility disorders.

Disclosure of Interest: None declared

OP326 LIBERTAS: A MULTICENTRE, PHASE II, DOUBLE BLIND, RANDOMISED, PLACEBO CONTROLLED INVESTIGATION TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF LOCALLY APPLIED NRL001 IN PATIENTS WITH FAECAL INCONTINENCE

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INTRODUCTION: Faecal incontinence (FI) affects up to 8% of the general population, rising to c.50% among nursing home residents. FI is under-reported and can have devastating effects on quality of life (QoL). Although non placebo-controlled studies have shown a reduction in Wexner score, FI episodes and the FIQOL, little is available to inform appropriate management strategies as few well-designed, placebo-controlled clinical trials of FI treatment have been conducted.

AIMS & METHODS: The aim of Libertas, a robustly-designed, multicentre, Phase II, double-blind, randomised, placebo-controlled, parallel-group study was to investigate the efficacy and safety of α1-adrenoceptor agonist NRL001 (1R,2S-methoxamine hydrochloride) in the treatment of non-retentive FI (ClinicalTrials.gov: NCT01656720). Patient recruitment was across 55 European study centres. Patients with FI were randomised into four groups (approximately n=110 each) to receive once-daily self-administered doses of NRL001 (5mg, 7.5mg, 10mg or placebo suppositories) for 8 weeks. Libertas' primary objective was to assess the impact of NRL001 versus placebo on severity and frequency of FI episodes (Wexner scores) at 4 weeks. Key secondary outcomes for NRL001 versus placebo include: efficacy at 8 weeks (Wexner score and FI episodes); safety and tolerability; quality of life (FIQoL) following 4 and 8 weeks therapy; and overall patient satisfaction with the treatment.

RESULTS: Patients (n=466) were randomised evenly into each of the 4 arms. Patient demographics were broadly similar in each group: 84% female, mean age 62 (range 19-91) years, mean study entry score ranged from 12.9 to 13.3 points on the Wexner score. There was a 2.4-3.0 point reduction from baseline in Wexner score at Week 4 in all four arms with a non-significant treatment effect (p=0.6867). There was a 3.1-3.6 point reduction from baseline in Wexner score at Week 8 in all four arms with a non-significant treatment effect (p=0.5005). There was a reduction in FI episodes of between 4.8-7.3 episodes per week at Week 8 with a non-significant treatment effect (p=0.5278). NRL001 tolerability profile in each of the active treatment arms was comparable to placebo. A similar increase in FIQOL was seen at week 8 in each arm. Patient satisfaction was high in all arms; 74.7-85.6% of patients would choose to take a suppository of either NRL001 or placebo again.

CONCLUSION: Although NRL001 was safe and effective with improvements in both clinical outcome scores and QoL at the end of 8 weeks treatment compared with baseline, this improvement was also observed in the placebo arm. This outcome is of interest to the scientific community in that it demonstrates for the first time in a robust study design that there is a significant placebo response in this patient population that should be considered in all future study designs investigating FI.

Disclosure of Interest: D. Walker Other: Employee of Norgine, D. Jones Other: Employee of Norgine, J. Pilot Other: Employee of Norgine, R. Ng Kwet Shing Other: Employee of Norgine

OP327 PRELIMINARY SIGNIFICANT FINDINGS FROM A RANDOMISED CONTROL TRIAL OF POSTERIOR TIBIAL NERVE STIMULATION IN SYSTEMIC SCLEROSIS ASSOCIATED FAECAL INCONTINENCE

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INTRODUCTION: The gastrointestinal tract is affected in up to 90% of Systemic Sclerosis (SSc) patients with faecal incontinence (FI) being reported in up to 38%. Passive faecal incontinence secondary to internal anal sphincter atrophy is the characteristic finding. We have shown that neuropathic changes are implicated in SSc patients with FI and sacral nerve stimulation has emerged as a potentially beneficial therapy in SSc. However this is expensive, invasive, not widely available and we have shown that medium term efficacy is poor. Posterior tibial nerve stimulation (PTNS) is a potential alternative to modulate the sacral plexus indirectly, with none of these disadvantages. This is the preliminary data on a randomized placebo controlled trial of PTNS versus sham PTNS to determine if nerve modulation is an effective treatment in SSc associated FI.

AIMS & METHODS: We commenced a prospective randomised single-blind study of SSc patients with FI in February 2013 from a specialist Scleroderma unit. Baseline symptom scoring (bowel diary, Wexner), manometry and endoanal

ultrasound were completed prior to randomization to PTNS or sham. PTNS was administered conventionally, by insertion of an acupuncture needle according to anatomical landmarks, connected to an electrical stimulator. Sham PTNS was administered in identical fashion but the PTNS surface electrode was not connected and instead separate TENS surface electrodes were connected to a TENS unit. Each patient underwent blinded intervention for 30 minute periods, once a week for 12 weeks. The primary endpoints were the percentage reduction in faecal incontinence episodes and change in Wexner incontinence scores.
RESULTS: A total of 13 SSc patients (11 f), mean age 61 (36-72) completed the trial by October 2013. Of these 6 (5 f) underwent PTNS and 7 (6 f) patients underwent sham stimulation. All PTNS patients showed a reduction (5-100%) in the number of FI episodes in comparison to 0 sham patients at 12 weeks ($p<0.01$ (CI -81.49-14.34)). This matched an improvement in mean Wexner scores from baseline to treatment end (14.8 to 10.8 vs 13.4 to 13.6, true vs sham respectively, p=0.03.
CONCLUSION: This pilot data is demonstrating significant effects of PTNS in Scleroderma-associated FI. We present this significant initial data but anticipate having at least 25 completed patients by October 2014.
Disclosure of Interest: None declared

OP328 TREATMENT OF SLOW-TRANSIT CONSTIPATION (STC) IN CHILDREN WITH HOME-BASED TRANSCUTANEOUS ELECTRICAL STIMULATION (TES)

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INTRODUCTION: Slow-transit constipation (STC) is generally resistant to medical treatments. We have shown that transcutaneous electrical stimulation (TES) using interferential current given by physiotherapists, sped up colonic transit [1], reduced soiling [2] and increased defecation [3]. Battery-operated machines allow stimulation at home [3].
AIMS & METHODS: To determine if TES administered at home can improve STC in children. We tested 2 types of treatment. Group 1) if TES added onto existing treatment and administered daily at home can improve defecation, soiling, abdominal pain and laxative use in STC children. Group 2) if TES combined with selected laxatives and bowel education was more effective than TES alone. Children with treatment–resistant constipation with no palpable faecaloma who presented to a surgical unit at a tertiary children's hospital were sent for radionuclear colonic transit study [4]. Children with slow motility in the proximal colon were diagnosed with STC. Parents were trained to give TES. Four sticky electrodes (4cm x 4cm) were placed, 2 on the belly and 2 on the back at the umbilical level and connected so currents crossed right front to left back and left front to right back. A beating interferential current (4kHz carrier frequency, 80-160Hz beat frequency, 30mAmps[3]) was given 1 hr/day. Daily continence diaries and laxative use were recorded for 1 mth before and during TES. Defecation, soiling and laxative use were compared before (pre) and after 2-6 mth stimulation (post). In Group 1, 62 children (23 male; 2-16yrs) had TES added onto existing laxatives. In Group 2, 33 children (17 males, 4-16yrs) were educated on diet and water intake, best time for toileting and correct toilet posture, transferred to low doses of polyethylene glycol (PEG) and sodium picosulphate laxatives, then had TES for 2-3mths.
RESULTS: Gr 1: At the start, 56/62 had < 3 bowel actions (BA)/wk. 6/62 children (10%) had no improvement. Defecation frequency increased in 54/56 from 1.6±1.6 to 3.5±1.9 BA/wk, mean±SD, $p<0.05$) with 32/54 (59%) patients increased ≥3 BA/wk). Soiling reduced in 56/57 (4.6±2.4 to 0.7±1.1 days soiling/wk, $p<0.001$). Urge to defecate started as nil or weak and developed to moderate/strong in half. Laxative use reduced (15/60 (25%) stopped & 30/60 (50%) reduced). **Gr 2:** All started with <3 BA/week. 32/33 (97%) increased to >3 BA/wk with 29/33 (88%) to 7 BA/wk. Stool output improved from 1 (0-2) cups/wk to 7 (2-10) cups/wk ($p<0.001$). Mean number of soiling episodes decreased from 5 to 0 episodes/wk ($p<0.001$).
CONCLUSION: TES is a painless non invasive treatment and can be administered at home. In treatment-resistant patients presenting to a surgeon, home-based TES added onto existing treatment increased defecation into the normal range in half. With the addition of selected oral laxatives and education on diet and toileting prior to TES improvement occurred in more patients, was bigger improvement and was more rapid than with TES alone.
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Disclosure of Interest: B. Southwell Consultancy for: GI Therapies, Other: Product supplied with no restrictionsby Norgine, Inventor of new TES device to treat constipation in development by GI Therapies, Y.-I. Yik: none, J. Jordan-Ely: none, K. Dobson: none, J. Hutson Other: Inventor of new TES device to treat constipation in development by GI Therapies

OP329 COMPARISON OF THE EFFECT OF POLYETHYLENE GLYCOL 3350, PRUCALOPRIDE, BISACODYL AND PLACEBO ON COLONIC MOTILITY ASSESSED WITH INTRALUMINAL COLONIC HIGH-RESOLUTION MANOMETRY IN HEALTHY SUBJECTS: THE QUANTITATIVE ANALYSIS

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INTRODUCTION: PEG, bisacodyl and prucalopride were demonstrated to be superior to placebo for treatment of chronic constipation (Ford AC 2011). Impaired colonic propulsive motility is considered a major pathophysiological mechanism underlying constipation. The effect of these treatments on colonic motility has never been directly compared.
AIMS & METHODS: To compare the effect of PEG, prucalopride, bisacodyl and placebo on colonic motility and on number of high amplitude contractions (HAPCs) assessed with high resolution manometry (HRM).
In 10 volunteers (29±3 ys) four colonic HRM studies were performed, at least 10 days apart, after an overnight fast and tap water enema preparation. During colonoscopy under conscious sedation the HRM catheter (40 solid state sensors, 2.5 cm spaced) was advanced as far as possible and clipped to the mucosa. After 90 min of basal recording, PEG 13.8 mg, prucalopride 2 mg, bisacodyl 10 mg or placebo were administered orally in a single-blind, randomized, cross-over fashion, and the recording continued for 180 min before and after a standardized meal. During the meal, in case of PEG, a second dose (13.8 mg) was administered. Colonic motility index (MI; averaged every 15 min in the right and left colon and in the rectum, and expressed as ratio of the baseline value) of four periods (180 minutes before meal, first, second and third hour after the meal) was compared between treatments by means of a mixed models analysis with post-hoc t-tests and Bonferroni correction. The characteristics of HAPCs were compared by means of Student's t test. Data are mean±SEM.
RESULTS: The catheter was clipped to the right colon mucosa in 23/40 studies, and at least to the splenic flexure in the remaining cases, with no difference according to treatment arm. Baseline MI did not differ between treatments in the right (2.6±0.36 for PEG, 3.6±0.72 for prucalopride, 3.6±0.87 for bisacodyl, 3.9±0.26 for placebo, NS), left colon (2.7±0.49, 3.6±0.49, 3.2±0.74, 3.6±0.41, NS) and rectum (2.7±0.53, 4.1±0.79, 3.2±0.81, 3.8±0.50, NS). At mixed models analysis, a significant treatment effect was found in each region of the colon (all $P\leq0.001$). In the right colon, the ratio of the baseline value was significantly higher after PEG (P=0.01) and borderline significant after prucalopride (P=0.05) as compared to placebo for all the time points after the meal. In the left colon, the ratio was significantly higher after PEG than placebo for all the time points after meal (P=0.01). In the rectum, the ratio was significantly higher after PEG than placebo during the first hour after meal (P=0.01). Bisacodyl induced HAPCs in a significantly higher number of subjects as compared to prucalopride (9 vs. 3, Fisher's exact test P= 0.01), PEG (9 vs. 1, P=0.001) and placebo (9 vs 1, P= 0.001). The amplitude of HAPCs was significantly higher after prucalopride than bisacodyl (292±14 vs 200±12 mm Hg, P= 0.01) while duration, length and velocity did not differ between treatments.
CONCLUSION: In man, PEG, prucalopride and bisacodyl have distinct effects on colonic phasic activity. While PEG mainly increases phasic activity, bisacodyl mainly induces HAPCs. Prucalopride has no major effect on colonic phasic activity but increases HAPCs amplitude.
Disclosure of Interest: None declared

OP330 ENTERIC NEUROPROTECTION IN HUMAN NEURONS: EFFECTS MEDIATED BY PRUCALOPRIDE, A SEROTONINERGIC FULL 5-HT4 SELECTIVE AGONIST

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INTRODUCTION: Serotonin (5-hydroxytryptamine, 5-HT) and related transporters and receptors are involved in a wide array of digestive functions and disorders. Specifically, 5-HT_4 receptors play a major role in intestinal peristalsis and among agonists, prucalopride (a full 5-HT_4 agonist) is an effective enterokinetic agent in the treatment of chronic constipation. In addition, 5-HT_4 receptor agonists may evoke enteric neuroprotection. We tested whether prucalopride exerts protective effects on enteric neuron cell cultures exposed to damaging factors, i.e. oxidative agents e.g. H_2O_2. Specifically, we aimed to: *i*) evaluate the expression and selective identification of 5-HT_4 receptors in human enteric neurons; and *ii*) define the 5-HT_4 receptor-mediated neuroprotection in human cell cultures by assessing the anti-apoptotic effect exerted by different doses of prucalopride.
AIMS & METHODS: Human enteric neurospheres were generated from human gut tissue*; cells from neurospheres were seeded onto 35-mm Petri dishes coated with fibronectin (2 μg/cm2) and maintained in Dulbecco's modified Eagle medium (DMEM)/F-12 medium. Western blotting (WB) analysis were performed using the following primary antibodies: anti-5-HT_4 receptor (Abcam, 1:200), anti-HuC/D (Invitrogen, 1:200; a paneuronal marker), anti p75_NTR (Thermoscientific, 1:200) and anti-vinculin (Sigma-Aldrich, 1:50.000). In addition to neurosphere-derived cells, the expression of the $5HT_4$ receptor was also evaluated in the following cell lines: human embryonic kidney (HEK293); mouse neural crest-derived N2A; and human neuroblastoma cell line (SH-SY5Y). SulfoRhodamine B (SRB) assay was used to determine the neuronal survival of SH-SY5Y cells following H_2O_2 (200 μM for 30 min) exposure and the neuroprotective effect exerted by prucalopride on these cells. GR 113808 (10 nM for 30

min) was applied to SH-SY5Y cells to reverse the protective effect of prucalopride.
RESULTS: WB analysis demonstrated that all cell lines as well as cells from human neurospheres expressed the $5HT_4$ receptor. SRB assay showed that SH-SY5Y cells previously exposed to prucalopride at different concentrations (10, 100 pM; 1, 10 and 100 nM; 100 μM; 1 and 20 mM) were protected by the noxious effect induced by H_2O_2. Specifically, prucalopride at 10 pM to 1 nM concentrations exhibited the best neuroprotective effect compared to neurons exposed to H_2O_2 only ($>76.5\pm0.1\%$ of neuronal survival vs. $33.3\pm0.1\%$, respectively) ($P<0.05$). Prucalopride concentrations applied alone to SH-SY5Y neurons did not show any toxicity and resulted in $91\pm0.1\%$ of neuronal survival. In contrast, the neuroprotective effect of prucalopride was reversed by the $5\text{-}HT_4$ antagonists GR 113808 (10nM for 30 min).
CONCLUSION: Prucalopride, a $5\text{-}HT_4$ receptor full agonist, mediated significant neuroprotection against oxidative-mediated proapoptotic effects. These results may pave the way to novel application of $5\text{-}HT_4$ agonists as neuroprotective agents in enteric neuropathies.
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Disclosure of Interest: None declared

OP331 INTEREST IN A MORPHOLOGICAL EVALUATION OF INTERSTITIAL CELLS OF CAJAL (ICC) IN PATIENTS WITH SEVERE COLONIC INERTIA (SCI) REQUIRING SUBTOTAL COLECTOMY. A CASE-CONTROL STUDY

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INTRODUCTION: Subtotal colectomy is the last resort treatment in patients with SCI refractory to a well-conducted and optimized treatment. In this condition, some studies reported an ICC hypoplasia by using a semi-quantitative analysis. The aims of this case-control study were (1) to determine the best technique to quantify colonic ICC, (2) to search a relationship between the number of ICC and the severity of constipation and (3) to evaluate functional results 1-year after colectomy
AIMS & METHODS: Clinical and pathological data from patients with SCI having colectomy with ileo-rectal anastomosis in 3 academic hospitals have been collected. Quantification of ICC immunostained with CD117 was performed in 3 colonic segments in patients and in sex and age matched controls by 2 independent observers using a semi-quantitative technique (muscularis propria on ten high power field (HPF)) according to Wang et al, followed by a morphometric quantitative technique (% of ICC/10 HPF). ICC hypoplasia was defined as <7 ICC/HPF using Wang et al method or as a mean percentage of ICC < 1 % using morphometry. Functional results were evaluated 1-year after colectomy.
RESULTS: Over a 10-year period, 20 patients (female: 85 %; mean age: 46.2 ± 11.6 years) had a colectomy for SCI. Constipation had been present since childhood or adolescence in 76.4 % of patients. Mean number of stool was 0.9 ± 0.4/week with optimized treatment and 45 % of patients have been hospitalized at least once for colonic occlusion related to fecaloma. All patients were in optimized treatment failure. Mean colonic transit time (CTT) was 128.2 ± 11.6 h, ano-rectal manometry did not show megarectum and small bowel manometry was normal in all patients. According to Wang et al method, 30 % of patients (n = 6) display ICC hypoplasia and all controls had normal ICC. Using morphometry, the percentage of colonic ICC was significantly decreased in patients vs. controls (1.04 ± 0.16 % vs. 1.97% ± 0.21 %; P = 0.005) with no differences between the 3 colonic segments (P = 0.25) and 60 % of patients (n=12) had ICC hypoplasia $<$ 1% vs. 20 % (n = 4) of controls (P = 0.009). ICC hypoplasia was not significantly associated with CTT or occlusion related to fecaloma. After a one-year follow-up, 17 patients (85 %) were satisfied with at least 1 stool/d, and 3 still had constipation.
CONCLUSION: In patients with severe colonic inertia requiring surgery, morphometric analysis is more sensitive than semi-quantitative analysis to detect a defect in ICC In our study, the severity of constipation seems unrelated to the importance of this defect and ICC evaluation has little clinical interests. Clearly, patients with SCI are satisfied after colectomy.
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Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
UPDATE ON ENDOSCOPIC RESECTION OF EARLY COLORECTAL NEOPLASIA – HALL N

OP332 ENDOSCOPIC SUBMUCOSAL DISSECTION VERSUS ENDOSCOPIC MUCOSAL RESECTION FOR LARGE COLORECTAL TUMORS: A META-ANALYSIS

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INTRODUCTION: Colorectal lateral spreading tumors (LST) ≥20 mm are best treated by Endoscopic submucosal dissection (ESD) or Endoscopic mucosal resection (EMR). EMR is a safe and effective treatment for most colorectal granular-LST (G-LST) lower than 40 mm. ESD should be preferred for both greater G-LST and non-granular type LST (NG-LST), especially the pseudo-depressed type, which has a higher potential for invasion and requires a precise histological evaluation (GIE 2007;66:966). ESD is technically more demanding and has a relatively high complication rate; EMR is limited by its inability to achieve en-bloc resection. Hybrid resection techniques (ESD with snaring, EMR after circumferential pre-cutting or small incision) have been introduced to make ESD and EMR easier, safer and quicker (DDS 2013;58:1727).
AIMS & METHODS: To perform the first meta-analysis on colorectal ESD-EMR to assess their impact on their safety and effectiveness in removing colorectal LST ≥20 mm. Medline, PubMed, and Google searches (June 2009-October 2013) were considered to identify appropriate RCTs that compared ESD with EMR for colorectal LST ≥20 mm. Keywords were: ESD, EMR, colorectal tumors, LST. Reviews, case reports and abstracts were excluded. The existence of noninvasive pattern, determined by magnification chromoendoscopy, was the minimum requirement for all lesions candidates for ESD and EMR. Primary end-points were en bloc resection rate, curative resection rate and local recurrence. Secondary end-points: rate of bleeding and perforation. Fixed or random-effect models were used as appropriate based on homogeneity or heterogeneity of data according to I2 statistic.
RESULTS: 8 studies (7 retrospective and 1 prospective) were identified. Data are expressed as odds ratio (OR) and 95% confidence interval (CI) [95% CI]. A total of 4023 lesions were found: 2104 were treated by ESD, 1919 by EMR, respectively. The tumor size was significantly larger in the ESD group (30.6±5mm vs 24±3.1 mm, $p<0.05$). The ESD group had a significantly higher proportion of NG-LST (38.0% vs 27.3%, $p<0.001$). Adenocarcinomas-sm1 were more frequent in the ESD group than in the EMR group (18.3% vs 9.2%, $p<0.001$). ESD was associated with a longer procedure time (89±33 min vs 22±7 min, $p<0.001$). Meta-analysis confirmed that, compared to EMR, ESD achieved higher en bloc resection OR 9.77 [7.9-12.0], curative resection OR 2.04 [1.6-2.57], and lower local recurrence irrespective of lesion size OR 0.08 [0.04-0.18]. ESD had higher number of perforations OR 3.6 [2.19-5.93]. Bleeding was similar between the two groups: OR 1.15 [0.73-1.81].
CONCLUSION: The current meta-analysis shows that ESD has considerable advantages regarding en bloc resection rate, curative resection rate and absence of local recurrence, at the expense of a higher perforation rate and longer procedure time. ESD appeared to be an effective and safe procedure, at least in expert hands, for lesions otherwise difficult to be radically treated with snare-based endoscopic resection techniques. Better ESD standardization and a more widespread and systematic implementation in Western countries are required.
Disclosure of Interest: None declared

OP333 WHICH IS THE STRONGEST PREDICTOR TO MOVE FROM ESD TO PIECEMEAL EMR (PEMR) WHEN EN BLOC RESECTION CANNOT BE COMPLETED?

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INTRODUCTION: Endoscopic submucosal dissection (ESD) allows en bloc resection of gastrointestinal tumors regardless of their size. However, a high level of expertise is needed in the early learning curve to perform en bloc resection by ESD and piecemeal endoscopic mucosal resection (pEMR) is frequently needed to complete the resection.
AIMS & METHODS: To analyse the factors associated with changing the initially planned ESD to pEMR in a clinical practice setting where $<$ 100 procedures have been performed. We included prospectively the first 85 ESDs performed in our hospital, from September 2008 to April 2014. All ESD procedures were performed by two teams with 2 endoscopists in each one (A-team: J.C.M.G. & J.D.T.; and B-team: S.R.M. & A.P.G.) in equal numbers. We recorded characteristics of the lesions and the procedure to predict the need for pEMR to complete the resection.
RESULTS: Main characteristics of the patients and lesions are shown in table 1. ESD had to be changed to pEMR in 37 patients (43.5%) to complete the resection of the lesion. In the univariate analysis, the factors that showed a statistically significant association with moving to pEMR were: location of the lesion other than in the stomach (54.7% vs. 25%; $p=0.007$), procedure duration longer than 180 min (57.9% vs 31.9%; $p=0.016$) and a maximum diameter more than 30 mm (63.6% vs. 28%; $p=0.001$). None of the following factors showed statistically significant association with moving the therapeutic approach to pEMR: depressed morphology (28.6% vs. 48.4%; $p=0.11$), lesions treated after the first 50 ESDs were performed (48% vs. 37.1%; $p=0.32$), previous electrosurgery of the lesion (62.5 vs. 41.6%; $p=0.29$), team who performed the ESD (41.2% vs. 47.1%; $p=0.59$) or the presence of deep submucosal invasion in the histological specimen (66.7% vs. 41.8%; $p=0.39$). In the logistic regression model, the size of the lesion with a maximum diameter $>$ 30 mm, was the only factor independently correlated with moving to pEMR (OR: 3.2; CI 95%: 1.1 – 8.3).

Table 1. Characteristics of the lesions, procedure and patients.
Table to abstract OP333

n	85
Age (mean ± SD)	**68** ± 12
Male / Female n;%	**48/37** (56.5 / 43.5)
Mean tumor size, mm (mean ± SD)	**30.4** ± 14.9
En bloc resections (n; %)	**48** (56.5)
Snare use (Hybrid ESD)	**12** (14.1)
Piecemeal resections (n; %)	**37** (43.5)
R0 (n; %)	**33** (38.8)
Procedure time (mean ± SD)	**183** ± 87

CONCLUSION: When the experience with ESD is low, with < 100 procedures performed, the size of the lesion, with a maximum diameter > 30 mm, is the strongest predictor for the need to complete the resection with pEMR.
Disclosure of Interest: None declared

OP334 RETROSPECTIVE COHORT STUDY TO ELUCIDATE LONG-TERM CLINICAL OUTCOMES OF COLORECTAL ENDOSCOPIC SUBMUCOSAL DISSECTION

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INTRODUCTION: Endoscopic submucosal dissection (ESD) is performed as a curative treatment for colorectal neoplasms.[1-5] Long-term clinical outcomes, however, are necessary to clarify whether colorectal ESD truly has a favorable effectiveness beyond lower recurrence rates.
AIMS & METHODS: The aim of this retrospective cohort study is to elucidate long-term clinical outcomes for colorectal ESD. To allow five-year follow-up data, out of 418 consecutive patients who were treated by ESD at National Cancer Center Hospital, Tokyo, Japan, between February 1998 and December 2008, we conducted a survey on patients followed-up longer than three years. After exclusion criteria of squamous cell carcinoma, carcinoid tumor, coexistence of advanced cancer, familial adenomatous polyposis and ulcerative colitis, 408 patients were enrolled. Long-term outcome data were collected between March and September 2013. Incomplete and missing data were retrieved from the referral hospital by asking their chief physician by letter; including last examination data, date of recurrence, treatment history of any recurrence and the date of death. Finally, we had complete data of the outcome of 286 patients (70%) and the survival analyses were conducted. The primary endpoint was 5-year overall survival rate (OS) and the secondary endpoints were recurrence free survival rate (RFS) and cause specific survival rate (CSS). R0 resection was defined as cancer-free resection margins. Curative resection was defined when the pathological findings revealed R0, irrespective of piecemeal or en-bloc resection, with non of the following features: deep submucosal invasion (≧1,000 μm, T1b), lymphovascular invasion, or poorly differentiated adenocarcinoma component. An adenoma with an unknown lateral margin also classified curative resection.
RESULTS: The 5-year OS, RFS and CSS were 95%, 91% and 100%, respectively, after the 5.4-year (0.3-11.1) median follow-up period. In 220 curative patients, the 5-year OS, RFS and CSS were 95% 95% and 100%, while the CSS was low in 66 non-curative patients as 95%, 80% and 100%, respectively. In the curative patients, three local recurrences including one intramural recurrence were detected in two patients with multiple piecemeal resections and one with R0 resection for recurrence lesion. Two of these patients were successfully treated by additional ESD and no recurrence was detected in more than 5 years after the second ESD, respectively, and the other patient underwent salvage surgery. In the non-curative patients, 38 patients were followed without additional surgery and 10 recurrences (26%) including 4 distant metastases were detected. In contrast, only one distant metastasis (3%) was detected in 28 patients who underwent additional surgery. These patients with recurrence received salvage surgery and/or chemotherapy.
CONCLUSION: The present study has shown favorable long-term clinical outcomes of colorectal ESD for patients with intramucosal and submucosal superficial invasive cancer. Therefore, colorectal intramucosal and superficial submucosal cancer can be well managed by endoscopic resection when it achieves curative resection.
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Disclosure of Interest: None declared

OP335 KNIFE ASSISTED RESECTION (KAR) OF LARGE AND REFRACTORY COLONIC POLYPS AT A WESTERN CENTRE: FEASIBILITY, SAFETY AND EFFICACY STUDY TO GUIDE FUTURE PRACTICE

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INTRODUCTION: ESD enables large lesions to be resected en bloc. This reduces recurrence rates, but ESD is technically challenging with high complication rates and hence not widely practiced in the west.
We have used a novel Knife Assisted Resection (KAR) technique.
AIMS & METHODS: We aim to evaluate the outcome of KAR in the treatment of large and refractory colonic polyps and identify polyp features that can predict complications and recurrence after KAR.
Cohort study of patients referred to our centre for resection of refractory polyps. All patients who had knife assisted resection of colonic polyps over 20mm in size from 2006 to Feb 2013 were included. All procedures were performed by a single experienced endoscopist.
The technique starts with submucosal (SM) injection followed by mucosal incision using a dual knife (Olympus KD-650L). This is followed by variable degrees of SM dissection and completion of circumferential mucosal incision. Finally a snare assisted resection is performed in an en bloc or piecemeal fashion, depending on the polyp size and extent of SM dissection.
RESULTS: 127 polyps in 127 patients of mean age 71 years. Mean polyp size 46mm (20-170mm). 27% were >50mm. 27% were scarred from previous attempted resection. 26% were in the right colon.
En bloc resection: 58/127(46%). Size of polyp <50mm was a significant **(p=0.001)** predictor of en bloc resection (88% vs. 12%).
The complication rate was 11/127(8.6%) with 5(3.9%) bleeds, 4(3.1%) diathermy damage to muscle fibres and 1(0.78%) perforation. Complications were not linked to polyp size, scarring or resection site. A single patient with perforation required surgery. All other complications were managed endoscopically.
The recurrence rate was 14/106(13%). This was significantly higher for polyps >50mm **(p= 0.009)** and in scarred polyps **(p= 0.024)**.
On sub-analysis of the unscarred polyps, polyps ≤50mm with no scarring had a very low recurrence rate of 3.2% as compared to 25% in polyps >50mm **(p= 0.005)**.
Table: Factors associated with recurrence
CONCLUSION: This is the largest reported western series demonstrating the feasibility, safety and efficacy of KAR for large and refractory polyps, with or without scarring, at all colonic sites. Our data demonstrates that complications of KAR are not related to size but the recurrence rate is. Size >50mm and scarring seem to be predictors of recurrence.
We propose flat polyps 20 – 50mm in size as the ideal indication for KAR in the western setting.
Disclosure of Interest: None declared

OP336 EFFECTIVENESS AND SAFETY OF ENDOSCOPIC SUBMUCOSAL DISSECTION USING THE BALL-TIP BIPOLARCURRENT NEEDLE KNIFE WITH WATER-JET FUNCTION (JET B-KNIFE) FOR THE TREATMENT OFCOLORECTAL TUMORS

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INTRODUCTION: ESD is a technically difficult and time-consuming procedure for the treatment of large colorectal tumors. In Japan, Ball-Tip Bipolar Current Needle Knife (BB-knife) has been used as a device for safe treatment in ESD by minimizing the damage in deeper tissues of colorectal neoplasms. In May 2012, a BB-knife combined with Water-Jet function (Jet B-knife) was newly developed.
AIMS & METHODS: The aim of this study was to examine the effectiveness and safety of Jet B-knife, which is the Bipolar Current Needle Knife with a ball tip and 1.5 mm in length. The endoscope we used was Olympus H260AZI or PCF260AI. Electorosurgical unit was VIO300D(ERBE) with dry cut mode (effect 3,60W) or spray coagulation mode (effect 2 60W). Translucent hood had been always attached to the point of the endoscope. We treated 276 lesions by ESD using BB-knife between March 2007 and April 2012(group A) and 101 lesions using Jet B-knife between May 2012 and March 2014 (group B). We retrospectively evaluated including the diameter of resected tumor, the time required for resection, the rate of en-block complete resection, the rate of perforation, and compare these data between two groups.
RESULTS: The median time required for the resection was 103 min. in group A and 61 min. in group B. The difference was statistically significant ($p < 0.01$). And the median diameter of tumor in group A was 23.1mm and that in group B was

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	SIZE		RESECTION TYPE		SITE		SCARRED	
	≤50mm	>50mm	En bloc	P meal	LC	RC	yes	no
ALL POLYP RECURRENCE 14/106 (13%)	6/78 (7.6%)	8/28 (28.5%)	1/42 (2.3%)	7/44 (15.9%)	13/83 (15.6%)	1/23 (4.3%)	6/20 (30%)	8/86 (9.3%)
	P= 0.009		**P= 0.001**		P= 0.15		**P= 0.024**	
UNSCARRED POLYP RECURRENCE 8/86 (9.3%)	2/62 (3.2%)	6/24 (25%)	1/42 (2.3%)	7/44 (15.9%)	8/68 (11.7%)	0/18 (0%)		
	P=0.005		P=0.058		P=0.195			

26.6mm. The difference was statistically significant ($p < 0.01$). On the other hand, the en-block complete resection rate was 94% in group A and97% in group B. The rate of perforation was 1.8% in group A and 2.0% in group B. These differences were not statistically significant.
CONCLUSION: The resection time was significantly shortened using Jet B-knife, although the mean size of lesions was significantly larger than the other. This may be not only due to the improvement of cutting skill but also due to the efficient water jet function during the procedure of hemostasis and the enhanced lifting effects of lesions by launching it at the submucosal layer. In conclusion, the use of Jet B-knife may contribute to time-saving and safe procedure in ESD for the colorectal tumors.
Disclosure of Interest: None declared

OP337 STRATEGY TO OVERCOME A DIFFICULTY OF THE ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) FOR COLORECTAL TUMORS ACCOMPANIED BY FIBROSIS IN SUBMUCOSAL LAYER

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INTRODUCTION: The safety and curability of one-piece resection of colorectal tumor using ESD technique sometime depends on the degree of fibrosis in the submucosal (SM) layer. ESD for the tumors accompanied by hard and tight fibrosis are thought to be most difficult to complete. The aim of this study is to establish the strategy to overcome a difficulty of the ESD for colorectal tumors accompanied by fibrosis in SM.
AIMS & METHODS: ESD was performed for 766 cases of colorectal neoplasm in 760 patients (male: female = 449:311; mean age, 65.7 years). Among these cases, 190 cases were accompanied by SM fibrosis. These cases were divided into three groups, absent with fibrosis (type A), fibrosis due to benign causes (type B), and fibrosis due to submucosal cancer invasion (type C). And these were classified into mild (grade 1), moderate (grade 2), and severe (grade 3) degree. In this study, we compared the one-piece resection rate between these three groups according to the degree of SM fibrosis.
RESULTS: We completed ESD procedure on 758 of 766 colorectal tumors, and 8 cases were abandoned due to severe degree fibrosis relating deep SM cancer invasion and screen-like fibrosis. Among the 190 cases with SM fibrosis, 59 cases were considered related to cancer invasion (type C), and 131 cases were related to benign cause (type B). The fibrosis of non-cancerous origin was caused by prior inadequate endoscopic treatment, biopsy, and others. We classified the endoscopic findings as mild degree (B-1), moderate degree (B-2), and 'screen-like' as severe degree (B-3). Otherwise, a white or brown hump and rich abnormal vessels were identified in the cases with SM cancer invasion (C-1 to 3). We performed one-piece resection for 723 (94.4%) cases of 766 ESD cases. One-piece resection rate of type A as 97.6% (562/576) and type B+C was 84.7% (161/190). And the one-piece resection rate according to the degree of fibrosis as follows, type B-1; 68/71(95.8%), B-2:27/30(90.0%), B-3:18/30 (60.0%), type C-1;31/31(100%, average SM depth:822.6μm), C-2:7/8(87.5%, average SM depth:2,067.1μm), C-3:10/20(50%, average SM depth:3,078.9μm). These dates of B-3, and C-3 were showing unwilling results. We experienced only one case (0.13%) of perforation in type B. Therefore, in cases accompanied by severe degree fibrosis, one–piece resection becomes more difficult due to the risk of perforation. We designed safe technique by using endo-clips to prevent perforation before dissection in 3 type B-3 cases, and successfully completed ESD procedure. And in other type B-3 cses, we have searched a dissection line just above muscle layer carefully. Because of these results, type B-1, type B-2, type C-1, and type C-2 become standard indication of ESD, type B-3 becomes relative indication of ESD, and type C-3 was thought to be an indication of laparoscopic surgery. Recently, we established the laparoscopy endoscopy cooperative surgery (LECS) procedure applied with ESD technique to complete an one-piece resection for the tumors accompanied by wide and hard fibrosis(type B-3), and we performed one-piece resection for 4 cases successfully.
CONCLUSION: Endoscopic intra-operative evaluation of the cause and degree of SM fibrosis is very important to complete safe and curative ESD procedure for early colorectal cancers.
Disclosure of Interest: None declared

OP338 POLYPECTOMY PRACTICES IN THE ENGLISH BOWEL CANCER SCREENING PROGRAMME

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INTRODUCTION: Most polyps are <10 mm in size and a range of polypectomy techniques are available with wide variations in practice. We aimed to examine the techniques employed for removal of <10mm polyps in relation to polyp characteristics, completeness of excision, safety and changes over time.
AIMS & METHODS: Data relating to removal of polyps <10mm between Jan 2010 and Dec 2012 were retrieved from the national Bowel Cancer Screening Programme (BCSP) database. Categorical data was compared using *x2*.
RESULTS: 147174 polyps <10mm were removed during 62679 colonoscopies. A range of techniques was used (cold biopsy forceps (CBF) 19.7%, cold snare (CS) 22.1%, hot biopsy forceps (HBF) 12.2%, hot snare (HS) 35.1%, EMR 10.9%). EMR was used more frequently in the right colon compared to the left (14.3% vs. 8.3%, OR 1.84, 95% CI 1.78-1.90, P <0.01).
Most pedunculated polyps were removed using HS; this proportion was lower in the right vs. left colon (69.6% vs. 88.3%, OR 0.30, CI 0.28-0.33, $p < 0.01$).
CS was most common for non-pedunculated polyps in the right colon (29.8% vs. 19.0% in left, OR 1.81 CI 1.76-1.85, P <0.01); whereas most common in the left colon was HS (34.8 vs. 22.5% in right, OR 1.84 CI 1.79-1.88, P <0.01).
Surgeons were more likely than physicians to use diathermy irrespective of site or morphology (65.6% vs. 56.5%, OR 1.46 CI 1.43-1.51, P < 0.01).
In 60% of polyps removed completeness of excision was not histologically assessable. 21.2% were completely excised, 5.8% incomplete and 13% not stated. For non-pedunculated polyps, histologically-confirmed complete excision was more common after EMR (23.4% vs. 6.2%, OR 1.16, CI 1.08-1.25, p <0.01) compared to other techniques (CBF 17.7%, CS 15.1%, HBF 19.1%, HS 21.5%); for pedunculated polyps it was more common after EMR (42.3%) and HS (42.0%)].
Sub-analysis of colonoscopies where only polyps <10mm were removed (45227), complications were rare. 12 (0.03%) bleeding episodes required transfusion; the rates for single and multiple polypectomy cases were 0.01% and 0.04% respectively (OR 5.01, CI 1.10-22.8, P = 0.02). The HS technique was most commonly used. There were 16 (0.04%) perforations; 0.02% for single vs. 0.05% for multiple polypectomies (OR 2.20, CI 0.77-6.34, P = 0.13). No technique dominated for single compared with HS for multiple polypectomies.
Between 2010 and 2012, use of CBF, CS and EMR increased, whereas HBF and HS decreased (p < 0.01). **Table 1**
Table 1 Change in trends according to technique

	2010(%)	2012(%)	OR, 95% CI
CBF	15.2	23.0	OR 1.67, CI 1.61-1.72
CS	21.3	23.3	OR 1.12, CI 1.09-1.16
HBF	14.1	10.1	OR 0.68, CI 0.66-0.71
HS	41.0	31.1	OR 0.65, CI 0.63-0.67
EMR	8.5	12.5	OR 1.55, CI 1.48-1.62

CONCLUSION: The removal of polyps <10mm within the BCSP is safe, but histological evidence of complete excision is poor with all techniques. Wide variations in practice reflect the lack of evidence guiding these decisions, although use of cold resection techniques has increased over time.
Disclosure of Interest: None declared

OP339 ENDOSCOPIC FULL THICKNESS RESECTION IN THE LOWER GASTROINTESTINAL TRACT USING A NOVEL OVER-THE-SCOPE DEVICE

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INTRODUCTION: Diagnostic or therapeutic endoscopic full thickness resection in the colon may be indicated for non-lifting adenomas and other indications. However, to date there is a lack effective and safe endoscopic methods and devices. The FTRD (Full Thickness Resection Device", Ovesco, Tübingen, Germany) is a novel over-the-scope device developped for endoscopic full thickness resection.
AIMS & METHODS: Between 07/2012 until 03/2014, 21 patients underwent endoscopic full thickness resection at two tertiary referral centers. All resections were conducted with the FTRD mounted on a standard colonoscope. Resection technique: The lesion to resect was pulled into a long transparent cap, a 14 mm Over-The-Scope Clip (OTSC) was deployed and the pseudopolyp above the clip was resected with a preloaded snare.
In this study we report our first clinical experience with this novel full thickness resection technique.
RESULTS: Indications for endoscopic full thickness resection were: recurrent or incompletely resected adenoma with negative lifting sign (9); untretated adenoma with high-grade dysplasia and negative lifting sign (1), adenoma involving the appendix (3), flat adenoma in a patient with coagulopathy (1), diagnostic re-resection after incomplete resection of a T1-carcinoma (3), adenoma involving a diverticulum (1), submucosal colonic tumor (2), diagnostic resection in a patient with suspected Hirschsprungs disease. The lesions were located as followed: coecum (3), ascending colon (4), transverse colon (2), descending colon (4), sigmoid (2), recosigmoid transition (3) and rectum (3). Reaching the target lesion with the endoscope and the mounted FTRD was possible in 20/21 patients (95.2%). Having reached the target lesion, macroscopically complete resection was achieved in 19/20 patients. Full thickness resection was confirmed histologically in 17/20 cases (85%). Histologically complete resection was achieved in 17/20 cases (85%). No perforations or relevant bleeding was observed during or after resection. Two patients developed a post-polypectomy syndrome which was managed with antibiotic therapy.
CONCLUSION: Full thickness resection in the lower GI tract with the novel FTRD is feasible and effective. Prospective studies are needed to further evaluate the technique and device.
Disclosure of Interest: A. Schmidt Lecture fee(s) from: Ovesco Endoscopy, M. Damm: None declared, C. Gubler: None declared, K. Caca: None declared, P. Bauerfeind: None declared

OP340 ELRR OR TATMR BY TEM FOR TREATMENT OF LOW RECTAL CANCER

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INTRODUCTION: From the beginning of the 90's, the authors have introduced an original technique of loco-regional resection by Transanal Endocopic Microsurgery (TEM) named "Endoluminal Loco-Regional Resection" (ELRR). In selected patients, this technique is a valid alternative to traditional surgery for early (Tis-T1) and for T2N0 rectal cancer after neoadjuvant radio-chemotherapy (n-RCT). Sphincter-saving procedures in patients with low rectal cancer are largely successful, but there is no universally adopted standardized technique. From 2008, the authors have developed a new combined technique: Transabdominal Transanal Total Mesorectal Resection (TATMR) by TEM in patients not eligible for ELRR (T2-T3N0/N+). Transanal TME is achieved with a modified original TEM rectoscope. The abdominal part is performed laparoscopically, followed by colo-anal anastomosis and ileostomy.
AIMS & METHODS: From 2001 to 2014, 135 patients (82 males, 53 females, median age 65 years) with rectal cancer were selected. All patients were studied preoperatively with tumor markers' assay (CEA, Ca19.9, Ca125), digital rectal examination, colonoscopy with macrobiopsies, vital staining, peri-tumoral tattooing on histologically normal mucosa, total body CT scan, pelvic MRI and endorectal ultrasound. One hundred and nineteen patients with T1-T2N0 rectal cancer underwent ELRR by TEM and sixteen patients with T2-T3N0/N+ underwent TATMR. All T2-T3 patients underwent n-RCT.
RESULTS: Mean operative time for ELRR and TATMR was 138 min (range 40-300) and 450 (range 360-600), respectively. No intraoperative complication was observed. Final staging was pT0N0 (5), pTis (51), pT1 (46), pT2 (24), pT3N0 (5), pT3N1 (4). Mean hospital stay was 4 days for ELRR and 16 days for TATMR. No late complications were observed in ELRR group. In the TATMR group, anastomotic leakage occurred in 6 cases. Mortality was observed in two patients for unrelated causes.
CONCLUSION: In patients with low rectal cancer, quality of life should be a primary objective, without compromising the oncological results. TME is the gold standard, but postoperative functional sequelae are often observed. Several surgical alternative procedures are described, but none has been universally adopted. In selected T1 or T2 (after n-RCT) patients, ELRR by TEM is a valid alternative to traditional surgery. The authors described a new technique named TATMR to treat patients with T2-T3 rectal cancer. The main advantages are the preliminary identification of the distal margin of the tumor and dissection of the intact distal mesorectal fascia, in order to detect peri-rectal tumor invasion and to verify the possibility to perform a sphincter-saving procedure. Adequate experience in TEM is a pre-requisite.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
PATHOPHYSIOLOGY AND MANAGEMENT OF PAIN AND FIBROSIS IN CHRONIC PANCREATITIS – HALL O

OP341 RISK OF RECURRENT PANCREATITIS AND PROGRESSION TO CHRONIC PANCREATITIS AFTER A FIRST EPISODE OF ACUTE PANCREATITIS

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INTRODUCTION: Recurrent pancreatitis (RP) and chronic pancreatitis (CP) may occur after a first episode of acute pancreatitis. Data on incidence and risk factors for these events are scarce.
AIMS & METHODS: A cross-sectional survey and retrospective review of a prospectively collected cohort of patients with a first episode of acute pancreatitis was performed. Primary endpoints were RP and CP. CP was defined in two way: 1. based on clinical diagnosis by treating physician, and 2. based on the M-ANNHEIM diagnostic criteria. Both definitions were analysed seperately. Risk factors were evaluated using regression analysis. The cumulative risk was assessed using Kaplan-Meijer analysis.
RESULTS: 669 patients were included, with a median follow-up of 57 months. RP and CP were observed in 117 (17%) and 42 (6%) patients, respectively. Rates of RP were 12%, 24% and 25% in patients with biliary, alcoholic and idiopathic/other etiology, respectively. CP developed in 2%, 15% and 7% for these etiologies, respectively. Etiology, smoking and necrotizing pancreatitis were independent risk factors for both RP and CP (Table 1). APACHE-II score on admission was independently associated with RP only. Cumulative risk for RP over 5 years was highest among smokers (40%). Patients with alcoholic etiology and current smokers had a comparable cumulative risk for CP of about 15%. With both factors present the risk doubled to 30%.
Table 1. Multivariable analysis of risk factors for progression to chronic pancreatitis

	CP diagnosed clinically		CP as defined by the M-ANNHEIM criteria	
	odds ratio (95% confidence-interval)	P-value	odds ratio (95% confidence-interval)	P-value
Etiology	1	<0.001	1	0.001
- Biliary	6.48 (2.53 – 16.58)	-	4.22 (1.83 – 9.73)	-
- Alcohol	4.66 (1.71 – 12.74)	<0.001	3.98 (1.64 – 9.65)	0.001
- Idiopathic/other		0.003		0.002
Current smoking	2.52 (1.19 – 5.31)	0.02	2.90 (1.42 – 5.93)	0.004
Pancreatic necrosis	3.45 (1.68 - 7.09)	0.001	6.65 (3.40 – 13.01)	<0.001

CONCLUSION: Five years after a first AP episode, about 1 out of 6 patients develop RP and 1 out of 15 patients develop CP. Smoking was the predominant risk factor for RP, while the combination of alcohol and smoking resulted in the highest cumulative risk for CP. Based on these results, pancreatic specialist should not only advise patients to discontinue alcohol use after a first pancreatitis episode, but should emphasize the importance of smoking cessation as well.
Disclosure of Interest: None declared

OP342 DISRUPTION OF FRACTALKINE/CX3CR1 SIGNALLING ATTENUATES PANCREATIC PAIN IN EXPERIMENTAL CHRONIC PANCREATITIS

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INTRODUCTION: Chronic pancreatitis (CP) is a chronic inflammatory condition of the pancreas leading to severe pain and fibrosis. Fractalkine is a chemokine that chemoattracts inflammatory cells through its highly selective receptor CX3CR1 and has been suggested to aggravate pancreatic inflammation. Fractalkine is moreover known to be expressed on spinal neurons and sensory afferents where it has shown major pain-modulatory effects in different experimental pain states.
AIMS & METHODS: We aimed to investigate the course of experimental chronic pancreatitis in CX3CR1-/- deficient mice and the potential therapeutic implications of a CX3CR1 inhibitor. CP was induced in CX3CR1-knockout and wild-type mice by repetitive intraperitoneal cerulein injections. Treatment groups received an orally available small molecule CX3CR1 inhibitor. Hyperalgesia was assessed by systematic behavioural observation, locomotion analysis, and measurement of abdominal mechanical sensitivity. Pancreatic tissue was harvested after sacrifice for further analyses.
RESULTS: Both CX3CR1-knockout and CX3CR1-blocking treated mice showed significantly less pain related behaviour ($p < 0.0001$) and significantly less weight loss ($p < 0.01$) when compared to their wild-type controls, with a clear dose-response correlation in the treated mice. This reduction in pain related behaviour was confirmed in IHC and WB analysis of pain markers. Unexpectedly, there was no difference in inflammatory cell infiltrations, fibrosis, Amylase/Lipase levels, and Trypsin/MPO activity.
CONCLUSION: Fractalkine/CX3CR1 signalling seems to be crucial in initiating chronic pancreatic hyperalgesia. It does however not seem to have a direct effect on inflammatory cell infiltration and fibrosis. Nevertheless, these novel findings reveal CX3CR1 as a promising new target for the treatment of chronic pancreatic pain.
Disclosure of Interest: None declared

OP343 PATHOPHYSIOLOGIC EVENTS IN PANCREATIC ACINAR CELLS ASSOCIATED WITH PANCREATITIS IN RESPONSE TO TOBACCO COMPARED TO ALCOHOL

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INTRODUCTION: Pancreatitis is characterized by the development of inflammatory process secondary to intracellular premature activation of digestive enzymes, alteration of intracellular calcium levels and enzyme secretion, reactive oxygen species (ROS) production and death of pancreatic acinar cell. Tobacco is generally recognized as a relevant risk factor for pancreatitis, but its effect on acinar cells is unknown
AIMS & METHODS: To evaluate the role of tobacco compared with alcohol in the pathophysiologic events associated with pancreatitis in pancreatic acinar cells.
Acinar cells isolated from Swiss mice pancreas by enzymatic and mechanic degradation were stimulated with different concentrations of alcohol (10-100mM) or tobacco (0.001-0.4mg/ml) and with CCK (positive control). Intracellular enzyme activity, ROS production, necrosis and intracellular calcium were evaluated by

fluorescence with rodhamine, DCFDA, propidium iodide and fluo-4 substrates, respectively. Amylase secretion was evaluated with p-nitrophenyl-maltohexaoside as substrate. NFκB activation was measured by Western blot. Interleukin-1β and TNFα secretion was analyzed by ELISA in the supernatant. Apoptosis was evaluated by caspase 3 activity (western blot). LDH was quantified as a marker of cytotoxicity. Statistic analysis was performed by ANOVA.
RESULTS: Neither alcohol nor tobacco induced a significant activation of intracellular enzyme. Tobacco significantly increased intracellular calcium levels [11.38±4.89% (0.1mg/ml) - 56.26±13.14% (0.5mg/ml)] similarly to alcohol [14.40±2.06% (10mM) - 59.8±2.57% (75mM)]. This was associated to an increase in amylase secretion only after tobacco (21%, 0.4mg/ml). Tobacco, but not alcohol, induced activation of NFκB (2.69+1.05 fold increase of p65 translocation at 0.1 mg/ml over negative control). Neither tobacco nor alcohol induces interleukin-1β and TNFα release. Moreover, tobacco, but not alcohol, produced a significant citotoxicity ($p<0.05$) and induced acinar cell necrosis at 0.3 y 0.4 mg/ml (14.3% and 19.4%, respectively). This was associated with ROS production in a dosis-dependent manner ($p<0.05$). In addition, tobacco stimulated the activation of caspase 3 at 0.01 and 0.1 mg/ml (2.53±0.38 and 1.77±0.12 vs negative control).
CONCLUSION: High concentrations of tobacco induce a significant increase of intracellular calcium levels, amylase secretion, ROS production and necrosis in pancreatic acinar cells. At lower concentrations, tobacco initiates the inflammatory process through the activation of NFκB and induces apoptosis in pancreatic acinar cells. Alcohol does only induce an increase of intracellular calcium levels in the same experimental model. These results support the relevant role of tobacco as an etiological factor of pancreatitis.
Disclosure of Interest: None declared

OP344 IS TOBACCO A TRIGGER FACTOR OF PANCREATIC FIBROGENESIS? EVIDENCE FROM THE INTERACTION BETWEEN ALCOHOL AND TOBACCO IN PANCREATIC STELLATE CELLS

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INTRODUCTION: Alcohol has been associated with the activation of pancreatic stellate cells (PSC) and survival of activated PSC. The effect of ethanol is partly mediated by the generation of oxidative stress within the cells but other factors are required for pancreatic fibrogenesis to develop. Tobacco is recognized as an etiological factor of chronic pancreatitis (CP). Tobacco has been shown to activate fibrogenesis in tissues such as heart, liver and kidney, but its effect on the pancreas is unknown. We hypothesized that tobacco alone or in combination with alcohol stimulates pancreatic fibrogenesis by PSC activation through the generation of oxidative stress within the cells.
AIMS & METHODS: Our aim was to evaluate the effect of tobacco alone and in combination with alcohol on the activation of PSC and production of extracellular matrix (ECM) proteins, secretion of proinflammatory molecules and the generation of oxidative stress within the cells.
PSC were isolated from rat pancreas Sprague-Dawley and exposed to tobacco (cigarette smoke condensate) alone (0.01mg/ml) or in combination of increasing concentrations of ethanol (5 to 50mM). PSC activation (α-SMA expression) was measured in both early and primary cell culture by Western blot. Fibronectin-1 (FNT-1) was evaluated by western blot and immunochemistry. Collagen-I was measured by western blot and Masson trichrome. As proinflammatory molecules, fractalkine secretion was analyzed by Enzyme-linked immunosorbent assay. Oxidative stress was examined using 2'-7'-dichlorofluorescin diacetate (DCF-DA) and was detected by flow cytometry. Results are expressed as mean±SEM. Statistical analysis was carried out one-way ANOVA followed by Fisher's LSD *post hoc* test.
RESULTS: Tobacco alone (α-SMA 1.83±0.3; p=0.003 *versus* negative control) or in combination with 50 mM ethanol (α-SMA 1.53±0.2; p=0.04 *versus* negative control) induced PSC activation in early culture. Tobacco in combination with 50 mM ethanol increased the expression of collagen-I (3.9±1.2, $p<0.001$ *versus* negative control) and FNT-1 (3.6±0.3, $p<0.001$ *versus* negative control and ethanol alone). Tobacco also increased the expression of FNT-1 in combination of 10mM alcohol (2.23±0.1, p=0.007 *versus* negative control). Tobacco in combination with 50 mM ethanol induced fractalkine secretion at 48 hours (11.5±3.3 pg/mL *vs* 5±1.25 pg/mL negative control; p=0.017). Ethanol (50mM) alone (3.06±0.77, p=0.008 *versus* negative control) or in combination with tobacco (0.01mg/mL) (2.68±0.49 E50, p=0.027 *versus* negative control) increased the reactive oxygen species fluorescence emission.
CONCLUSION: Tobacco alone or in combination with alcohol induces the activation of PSC. Tobacco associated with alcohol increases the expression of extracellular matrix proteins, fractalkine secretion and it is a potential inducer of oxidative stress. These results support for the first time the synergistic effect of alcohol and tobacco in the pathogenesis of chronic pancreatitis.
Disclosure of Interest: None declared

OP345 SMOKING CESSATION BUT NOT ALCOHOL ABSTINENCE REDUCES THE MORPHOLOGICAL PROGRESSION OF TOXIC CHRONIC PANCREATITIS: A PROSPECTIVE, LONGITUDINAL COHORT STUDY

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INTRODUCTION: Smoking and alcohol are recognized risk factors for chronic pancreatitis (CP). Smoking enhances ethanol-induced pancreatic injury and accelerates the development and progression of CP. However, the effect of stopping the consumption of tobacco and alcohol on the progression of CP has not been well defined.
AIMS & METHODS: We aimed at investigating the effect of cessation the consumption of tobacco and alcohol on the morphological progression of CP as evaluated by endoscopic ultrasound (EUS).
A prospective, longitudinal cohort study was designed. Inclusion criteria were patients diagnosed of toxic non-calcific CP by EUS. All patients should be active smokers at inclusion. Minimum follow-up was 2 years. EUS was performed under conscious sedation by the lineal Pentax echoendoscope and HITACHI ultrasound at inclusion and at 2-year intervals during follow up. Standard EUS criteria for the diagnosis of CP were evaluated (5 parenchymal criteria and 5 ductal criteria). Progression was considered when the total number of EUS criteria of CP increased during follow-up. Data regarding smoking and alcohol consumption were recorded at baseline and during follow-up. Data are shown as mean and 95%CI, and compared by the t-student test. A multivariable logistic regression analysis was performed to determine the effect of maintained alcohol and tobacco consumption on the progression of CP.
RESULTS: 68 patients (61 male, 7 female, mean age 48.9 years, range 23-74 years) were finally included. 44 of them (64.7%) were drinkers. Median follow-up time was 56 months (range 24-123 months). Regarding toxic habits, 24 (35.3%) patients stopped smoking, and 26 (59.1%) stopped alcohol consumption. Morphological progression of the disease was observed in 34 patients (50%) during follow-up. Eight (8.8%) patients developed calcifications. A morphological progression of the disease was observed in 28 out of the 44 patients who continued to smoke (66.6%) and in 6 out of the 24 patients who stopped smoking (25%) (p=0.005). Morphological progression of CP was observed in 61.5% of patients who stopped alcohol intake and in 50% of those who continued drinking (n.s.). The only factor significantly and independently associated with the morphological progression of the disease during follow-up was maintained tobacco consumption (OR=5.25, 95%CI 1.73-15.92). Maintained alcohol consumption was not associated with the progression of CP (OR=1.0, 95CI% 0.34-2.93).
CONCLUSION: Smoking is a major factor in the morphological progression of toxic CP. Smoking cessation should be strongly encouraged in these patients. Maintained alcohol intake was not associated with the progression of the disease in this study.
Disclosure of Interest: None declared

OP346 POTENTIAL MECHANISMS OF THERAPEUTIC CANNABIS USE IN CHRONIC PANCREATITIS

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INTRODUCTION: Cannabis has been a traditional medicine used for centuries to treat a broad range of disorders from asthma to multiple sclerosis. Several studies using cannabinoid receptor agonists show possible anti-inflammatory and anti-carcinogenic effects *in vitro* and *in vivo*. However, the molecular pathways underlying these effects remain unclear. Chronic pancreatitis is characterized by an ongoing inflammation leading to irreversible changes, and is associated with increased risk of developing pancreatic cancer.
AIMS & METHODS: We hope to reveal the signalling pathways that are activated after ingestion of medicinal cannabis in patients suffering from chronic pancreatitis.
Cannabis-naïve volunteers drank a medicinal cannabis preparation (Bedrobinol®). Peripheral blood was obtained before and 1 hour after ingestion. Comprehensive descriptions of signal transduction were obtained in these samples employing kinome profiling on peptide chips exhibiting 960 different kinase substrates. We calculated mean phosphorylation levels for all 960 substrates before and after the treatment with medicinal cannabis. Additionally, we analyzed peripheral blood from 3 patients enrolled in a phase 2 clinical trial comparing purified Δ9-Tetrahydrocannabinol (Namisol®) against placebo in chronic pancreatitis patients (clinicalTrials.gov ID: NCT01551511) to confirm our findings in abovementioned kinome array.
RESULTS: As expected there is a great deal of similarity between the two phosphoproteomes ($r^2=0.87$). Phosphorylation of 106 substrates on the 960 array differs significantly between the two data sets. Of particular interest was the strong down regulation of cell cycle kinases: Cdk2, Cdk5, and Cdk7. The inhibition of the G1 to S phase kinase, Cdk2, is apparently mediated via a ATM/ATR-p53-p21-dependent pathway. Furthermore, we observed a down regulation of p38 MAP kinase, suggesting a specific anti-inflammatory effect. Finally, there was also increased activity of the PI3K-Akt-mTOR signaling pathway, which was confirmed in flow cytometry. Activation of the mTOR pathway is shown to inhibit autophagy, possibly leading to enhanced cell death in tumors.

CONCLUSION: The observation that medicinal cannabis impairs activation of specific components of the inflammatory cellular signal transduction provides a mechanistic rationale for the use of medicinal cannabis in chronic pancreatitis patients and selected autoimmune diseases. Furthermore, the inhibition of cell cycle proteins leading to cell cycle arrest and upregulation of mTOR signaling may contribute to anti-cancer properties of medicinal cannabis, justifying its use in terminal cancer patients.
Disclosure of Interest: None declared

OP347 DECREASED CFTR ACTIVITY AFTER ETHANOL CONSUMPTION AND IN ALCOHOLIC PANCREATITIS

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INTRODUCTION: Excessive ethanol consumption is one of the most common causes of acute and chronic pancreatitis. It is also documented that genetic defects of CFTR can lead to pancreatitis, however the effects of alcohol consumption on CFTR function in the pancreas is not known.
AIMS & METHODS: Our aim was to investigate the role of CFTR in the pathogenesis of alcohol-induced pancreatitis. The effects of ethanol and ethanol metabolites (fatty acids and fatty acid ethyl esters) on CFTR function and expression were examined in human (volunteers, patients and cell lines) and in animal models (guinea pigs and CFTR-/- mice).
RESULTS: Sweat chloride concentration was increased in alcohol intoxicated patients but not in healthy volunteers, indicating impaired CFTR function. Moreover, decreased CFTR expression was found in pancreas specimens from patients with acute or chronic alcohol-induced pancreatitis. In functional studies, we detected strong inhibitory effects of alcohol and fatty acids on CFTR activity and $HCO3^-$ secretion in pancreatic ductal epithelial cells. The inhibition was mediated by intracellular calcium overload, decreased cellular cAMP levels and ATP depletion. In addition, we reproduced the alcohol-induced decrease in CFTR expression in cultured pancreatic epithelial cells and in vivo in guinea pigs, which was caused by a combination of reduced CFTR mRNA levels, decreased cell surface stability and folding defect of CFTR. Finally, we showed that genetic deletion of CFTR lead to more severe pancreatitis in CFTR knock-out mice induced by ethanol and fatty acids.
CONCLUSION: The findings indicate that alcohol-induced loss of CFTR function is critical in the development of alcoholic pancreatitis; therefore, correcting CFTR function should offer therapeutic benefit.
Our research was supported by the Hungarian National Development Agency grants (TÁMOP-4.2.2.A-11/1/KONV-2012-0035, TÁMOP-4.2.2-A-11/1/KONV-2012-0052; TÁMOP-4.2.2.A11/1/KONV-2012 - 0073; TÁMOP-4.2.4.A2-11-1-2012-0001, TÁMOP- 4.2.4.A2-SZJÖ-TOK-13-0017), the Hungarian ScientificResearch Fund (OTKA NF100677).
Disclosure of Interest: None declared

OP348 EXPRESSION PATTERN OF IL1R1 AND IL13RA2 IN PATIENTS WITH CHRONIC PANCREATITIS AND CLINICOPATHOLOGICAL CORRELATIONS

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INTRODUCTION: Chronic pancreatitis (CP) is a major inflammatory disease of the pancreas, characterized by vast inflammatory cell infiltration, pancreatic fibrosis and severe abdominal pain. IL1 has been shown to have an important role in the pathogenesis of pancreatitis, where IL1b overexpression in the murine pancreas was associated with CP. IL13 is a major profibrogenic cytokine that has recently been shown to promote pancreatic stellate cell proliferation suggesting its role in pancreatic fibrogenesis. While evidence in animal models is constantly growing, little is known on the expression status of these cytokines and their receptors in the chronically inflamed human pancreas. In order to evaluate their therapeutic potential, we therefore aimed to investigate the expression of the IL1 receptor IL1R1 and the IL13 receptor IL13Ra2 for the first time in human tissue samples and correlate these with clinicopathological parameters.
AIMS & METHODS: The expression and localization of IL1R1 and IL13Ra2 was investigated in CP (n=69), and normal pancreas (NP; n=32) by QRT-PCR and immunohistochemistry analyses. Results were correlated with clinicopathological parameters including the severity of fibrosis, pain, neuritis, and neural hypertrophy.
RESULTS: There was no difference in the mean relative expression of the receptor IL1R1 in NP vs. CP. In 16/32 patients with NP, a slight IL1R1 immunoreactivity was exclusively evident in acinar cells. In CP, a slight immunoreactivity in acinar cells was present in 18 out of 60 tested patient samples. IL1R1 mRNA expression showed a moderate but significant correlation with neural hypertrophy.
The mean relative expression of IL13Ra2 did not differ between NP and CP. In 17/32 patients with NP, a slight to moderate IL13Ra2 immunoreactivity was evident in acinar cells, islets, and especially in intrapancreatic ganglia, whereas intrapancreatic nerves as such did not show any IL13Ra2 immunoreactivity. In CP, a slight IL13Ra2 immunoreactivity was observed in acinar cells, tubular complexes and islets and moderate immunoreactivity in intrapancreatic ganglia in 33 out of 60 tested patient samples. IL13Ra2 mRNA expression correlated significantly with the presence of pain and showed a significant negative correlation with the severity of fibrosis.
CONCLUSION: Although IL1 and IL13 have been suggested to play major roles in the pathogenesis of CP in mice models, their receptors IL1R1 and IL13Ra2 are not overexpressed in human CP. Furthermore, IL13Ra2 expression was even negatively correlated with the severity of fibrosis. These targets may therefore not be as promising as therapeutic targets in CP as initially hypothesized.
Disclosure of Interest: None declared

OP349 SERUM IGG4 IN ACUTE, CHRONIC AND AUTOIMMUNE PANCREATITIS

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INTRODUCTION: Type 1 autoimmune pancreatitis (AIP) is the pancreatic manifestation of a systemic IgG4-related fibroinflammatory disorder (IgG4-RD). It may be challenging to distinguish AIP from acute and chronic pancreatitis, as they share clinical and radiological features.
AIMS & METHODS: The aim of our study was to evaluate the diagnostic value of IgG, IgG-subclasses, and IgE, in distinguishing type 1 AIP from other forms of pancreatitis. Between March 2007 and May 2011, sera were obtained from consecutive patients presenting with AIP and chronic pancreatitis (CP) in a Dutch tertiary referral center. Sera from patients with acute pancreatitis (AP) were selected, stratified for gender and cause of pancreatitis, from a database of 732 patients, who participated in a Dutch multicentre trial between March 2004 and March 2007. Causes of acute pancreatitis were alcoholic, biliary and idiopathic. Serum levels of IgG, IgG1-IgG4, and IgE were determined.
RESULTS: A total of 174 patients were included; 32 with AIP, 90 with acute pancreatitis, and 52 with chronic pancreatitis. Elevated IgG4 levels ($\geq$ 1.4 g/L) were found in 27 AIP patients (84%), but also in 7 AP (8%) and 9 CP patients (17%; $p<0.001$). IgG4 levels >2x the upper limit of normal (ULN) were found in 66% of AIP patients, compared to none of the AP and 3 CP patients (6%; $p<0.001$). Median serum IgG4 was higher in AIP than in AP and CP (Table 1). Total IgG, IgG1, IgG3, and IgE levels were also increased in AIP patients, compared to the other types of pancreatitis. There was no difference in serum IgG2 levels between the three groups.
In AP and CP patients with elevated IgG4, none of the other subclasses was useful in distinguishing them from AIP patients. However, median total IgG and IgE levels were lower in these patients, as compared to AIP patients ($p=0.02$ and <0.001, respectively). In IgG4-negative AIP patients, serum IgE was higher than in AP and CP patients ($p=0.013$). Total IgG and the other IgG subclasses were comparable in IgG4-negative AIP and the other types of pancreatitis.
Table 1 Serum IgG, IgG subclasses and IgE in patients with AIP, AP and CP.
Table to abstract OP349

Variable	AIP (n=32)	AP (n=90)	CP (n=52)	p-value[1]
Total IgG[¶]	12.7 (10.5-21.7)	9.5 (7.7-11.1)	10.5 (8.9-12.6)	< 0.001*
IgG1[¶]	7.7 (5.9-11.9)	5.4 (4.3-6.9)	6.2 (5.3-7.9)	< 0.001*
IgG3[¶]	0.6 (0.4-1.0)	0.4 (0.3-0.7)	0.4 (0.3-0.6)	0.003*
IgG4[¶]	4.5 (1.7-7.7)	0.4 (0.2-0.9)	0.6 (0.3-1.1)	< 0.001*
IgE[¶]	302 (50-978)	38 (16-104)	47 (19-102)	< 0.001*

CONCLUSION: IgG4 levels are higher in AIP, but can be elevated in AP and CP patients as well. Therefore, elevated serum IgG4 does not exclude a diagnosis of AP and CP, and must be interpreted with caution in patients clinically suspected for AP or CP. Combined IgG4 testing with IgG or IgE, may contribute to the differentiation between AIP and other types of pancreatitis.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 8:30–10:30
HOT TOPICS IN SMALL INTESTINAL DISEASES – LOUNGE 5

OP350 SAFETY AND EFFICACY OF LONG-TERM TEDUGLUTIDE TREATMENT FOR PATIENTS WITH SHORT BOWEL SYNDROME AND INTESTINAL FAILURE: FINAL RESULTS OF THE STEPS-3 STUDY

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INTRODUCTION: Patients with intestinal failure associated with short bowel syndrome (SBS–IF) require parenteral support (PS) because of malabsorption caused by intestinal resection or dysfunction. Chronic PS is associated with serious complications and reduced life quality. Teduglutide (TED), a recombinant analogue of human glucagon-like peptide 2, improves absorption by increasing small bowel mucosal surface area.[1] In a 24-week, placebo-controlled, phase III study (STEPS) and its 2-year, open-label extension (STEPS-2), TED significantly reduced PS volume requirements and number of infusion days in patients with SBS–IF.[2,3] STEPS-3 was undertaken to further evaluate long-term efficacy and safety of TED in patients with SBS–IF and provide prior clinical trial patients with TED access while awaiting marketing authorisation.
AIMS & METHODS: STEPS-3 was a 1-year, open-label, multicentre study of subcutaneous TED (0.05 mg/kg/day) conducted in patients who enrolled in STEPS and completed STEPS-2. Patients randomised to TED in STEPS (TED/TED group) were exposed to TED for ≤42 months. Patients randomised to placebo in STEPS (PBO/TED) and patients who qualified for STEPS but were not treated because of full enrolment (NT/TED) were exposed to TED for ≤36 months. Baseline was considered the start of TED treatment in STEPS (TED/TED group) or STEPS-2 (PBO+NT/TED group).
RESULTS: 14 patients enrolled (mean age, 56 years [range, 40–80 years]; 12/14 [86%] white; 10/14 [71%] women; 8/14 [57%] with colon-in-continuity; mean±SD prescribed PS volume at baseline, 12.9±8.1 L/week); 13 completed the study. At the last dosing visit, PS was reduced from baseline by 9.8 L/week (50%), 3.3 L/week (35%), and 5.2 L/week (73%) in the TED/TED (n=5), PBO/TED (n=6), and NT/TED (n=3) groups, respectively. Compared with baseline, mean weekly PS infusions were reduced by 3.0 days/week in the TED/TED group, 1.7 days/week in the PBO/TED group, and 2.8 days/week in the NT/TED group. 2 patients achieved independence from PS after 126 and 130 weeks of TED treatment (as of 1st visit off PS); 2 additional patients who were weaned off PS in STEPS-2 maintained enteral autonomy throughout STEPS-3. Treatment-emergent adverse events (AEs) occurred in all patients; the most common were asthenic conditions and diarrhoea (both n=3). No malignancies; gallbladder-, biliary-, or pancreatic-related events; episodes of gastrointestinal obstruction; or deaths were reported. Furthermore, no patient discontinued the study because of an AE.
CONCLUSION: Long-term TED treatment for up to 42 months is associated with sustained efficacy in patients with SBS–IF, as shown by continued reductions in PS requirements and achievement of PS independence in some patients. The safety profile was consistent with prior studies; no unexpected safety signals were detected.
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OP351 SAFETY AND EFFICACY OF LONG-TERM TEDUGLUTIDE TREATMENT: FINDINGS FROM A 2-YEAR, OPEN-LABEL EXTENSION TRIAL, STEPS-2

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INTRODUCTION: Teduglutide (TED), a glucagon-like peptide-2 analogue, enhances intestinal absorptive capacity and enables reduction of parenteral support (PS) requirements in patients with intestinal failure associated with short bowel syndrome (SBS–IF). In the pivotal, phase III, placebo-controlled STEPS study, 63% of patients treated with TED had a 20%–100% reduction in PS from baseline at Weeks 20 and 24 vs 30% of patients receiving placebo (P=0.002).[1] STEPS-2 was a 2-year, open-label, multicentre, multinational extension study of STEPS designed to assess the long-term safety and efficacy of TED.
AIMS & METHODS: Enrolled patients included those participating in STEPS who completed 24 weeks of TED (TED/TED) or placebo (PBO/TED) treatment or those who qualified but were untreated (NT/TED) owing to full study enrollment. Patients received subcutaneous TED 0.05 mg/kg/day for ≤24 months (NT + PBO/TED) or ≤30 months (TED/TED). Clinically meaningful response was defined as 20%–100% reduction from baseline in weekly PS volume; baseline was determined at enrollment in STEPS (TED/TED) or STEPS-2 (NT + PBO/TED).
RESULTS: Of the 88 patients enrolled (TED/TED, n=37; NT + PBO/TED, n=51) in STEPS-2, 65 (74%) completed the study. Among patients who completed the study, clinically meaningful response was achieved in 93% of TED/TED, 55% of PBO/TED, and 67% of NT/TED patients. PS requirement was reduced by 7.6, 3.1, and 4.0 L/week in TED/TED, PBO/TED, and NT/TED groups, respectively. 18 patients in TED/TED, 5 in PBO/TED, and 2 in NT/TED were able to achieve ≥3 days/week off PS. Responses to TED were observed regardless of age, remnant anatomy, underlying disease aetiology, or baseline PS requirements (subgroup analysis). Patients <45 years of age had a 61% reduction, those between 45–64 years had 65% reduction, and those ≥65 years of age had 76% reduction in PS from baseline. Patients with colon-in-continuity had a 70% reduction and those without colon-in-continuity had a 57% reduction of PS from baseline. 21/22 patients who were responders with TED in STEPS and completed STEPS-2 sustained their response after 2 years of TED treatment. 13/88 patients with varying baseline characteristics were able to achieve independence from PS with TED treatment. TED was generally well tolerated. The most common gastrointestinal (GI) adverse events (AEs) were abdominal pain (34%), nausea (19%), and abdominal distension (16%). The most common non-GI AEs were catheter sepsis (28%), episodes of weight decrease (25%), and asthenic conditions (23%). Although 64% of patients reported serious AEs, only 10% were considered treatment related. The serious AEs included 3 cases of cancer (2 resulting in death and 1 considered treatment related) and 1 additional death (not considered treatment related).
CONCLUSION: In patients with SBS–IF, long-term treatment with TED was generally well tolerated and resulted in durable and sustained response as demonstrated by continued reductions in PS, and, in some patients, independence from PS. This effect was observed across a range of varying baseline characteristics.
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OP352 INDEPENDENCE FROM PARENTERAL SUPPORT DURING TREATMENT WITH TEDUGLUTIDE AMONG PATIENTS WITH INTESTINAL FAILURE ASSOCIATED WITH SHORT BOWEL SYNDROME (SBS–IF)

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INTRODUCTION: The intestinotrophic agent teduglutide (TED) was associated with clinically significant reductions in parenteral support (PS) in clinical trials in patients with SBS–IF.[1-4]
AIMS & METHODS: We report the clinical characteristics of patients who achieved complete independence from PS while receiving TED 0.05 mg/kg/day in either of 2 phase III randomised controlled trials (RCTs)[1,2] or their extensions.[3,4] PS was reduced (at 4-week intervals in RCTs and 4- to 12-week intervals in extension studies) if clinical status was stable and 48-hour urine output was increased by ≥10% over baseline (target urine output: 1–2 L/day).
RESULTS: A total of 134 patients were treated with TED 0.05 mg/kg/day. Of these, 16 patients achieved independence from PS after 12–130 weeks of TED treatment (as of first visit off PS). The duration of PS dependency at baseline (start of treatment with TED) ranged from 1–16 years in these patients. Baseline demographics and disease characteristics varied widely (**Table 1**). However, more patients who achieved PS independence had colon-in-continuity (n=12/16) and/or lower baseline PS requirements (<7 L/week, n=11/16). Adverse reaction profile of all treated patients was consistent with underlying cause of SBS, concomitant medication use, pharmacologic effect of TED within the gastrointestinal (GI) tract, and PS requirements. The most commonly reported serious adverse event (AE) in all treated patients was catheter sepsis; GI AEs were common and were the main reason for discontinuation.

Table 1. Baseline Characteristics of Patients Who Achieved Independence From PS With TED (0.05 mg/kg/day)

Table to abstract OP335

	SIZE		RESECTION TYPE		SITE		SCARRED	
	≤50mm	>50mm	En bloc	P meal	LC	RC	yes	no
ALL POLYP RECURRENCE 14/106 (13%)	6/78 (7.6%)	8/28 (28.5%)	1/42 (2.3%)	7/44 (15.9%)	13/83 (15.6%)	1/23 (4.3%)	6/20 (30%)	8/86 (9.3%)
	P= 0.009		**P= 0.001**		P= 0.15		**P= 0.024**	
UNSCARRED POLYP RECURRENCE 8/86 (9.3%)	2/62 (3.2%)	6/24 (25%)	1/42 (2.3%)	7/44 (15.9%)	8/68 (11.7%)	0/18 (0%)		
	P=0.005		P=0.058		P=0.195			

CONCLUSION: A number of patients with widely varied baseline characteristics were able to achieve enteral autonomy and independence from PS with TED treatment.

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OP353 RISK OF HYPOGLYCEMIA WAS LOWER WITH ADMINISTRATION OF PROTOCOLIZED INSULIN INSIDE PARENTERAL NUTRITION (PN) BAG COMPARED TO CONVENTIONAL INSULIN ADMINISTERED SEPARATELY DURING TOTAL PARENTERAL NUTRITION (TPN)

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INTRODUCTION: Insulin dose adjustment for diabetic patients with inpatient parenteral nutrition (PN) is required to achieve glycemic control. Route of administration with concomitant protocolized insulin inside the PN bag is perceived to have a higher risk of hypoglycaemia compared to conventional ad-hoc insulin administered separately.

AIMS & METHODS: We aim to compare the rate of hypolycemia between those who received protocolized intra-PN bag insulin and ex-PN bag ad-hoc (sliding scale) insulin (administered separately) among diabetic patients who received inpatient TPN.

Retrospective analysis was conducted for all inpatient diabetic patients who received TPN between April 2008 to August 2012 in National University Hospital Singapore. Demographic data such as age, gender, and body mass index (BMI) as well as glycemic reading was recorded. Hypoglycemia was defined as blood glucose level of <4.0 mmol/L based on ASPEN guidelines. Besides the conventional model of using the total number of glucose readings from all patients between the 2 groups (by 'population'), we also analysed other 'glucometrics' using other analytic models 'by patient-day' and 'by (individual) patient' as previously proposed (Goldberg PA et al. 2006) in order to have a more comprehensive result. 'By patient-day' model was done by grouping the glucose readings into per single day readings per patient as denominator. 'By patient' model was done by grouping glucose readings of the entire stay using each individual patient as denominator.

RESULTS: Total of 97 patients were analysed (56 ex-PN insulin; 41 intra-PN insulin) with total 3664 glucose readings. Results were summarised in Table. Demographic characteristics (age, gender, and BMI) were similar between the 2 groups. The hypoglycaemic rate for Intra-PN insulin group was not higher than Ex-PN insulin group. The rate of hypoglycaemia was not significantly different between Ex-PN insulin and Intra-PN insulin group using analysis model 'by patient' (10/56[17.9%] vs. 9/41[22%], respectively; p=0.462) and 'by patient-day' (21/438 [4.8%] vs. 12/422 [2.8%], respectively; p=0.182). In fact, the number of glucose reading with hypoglycaemia was significantly higher in Ex-PN insulin group using analysis model 'by population' (31/1876 [1.7%] vs. 16/1788 [0.9%]; p=0.042).

TABLE. Analysis Results

Variables	Ex-PN Insulin (n=56)	Intra-PN Insulin (n=41)	p-value
Mean Age	65.910±13.369	65.76±10.178	0.949
Male (%)	44.6%	43.9%	0.942
Mean BMI	23.918±4.556	22.552±4.894	0.166
% hypoglycemia (<4.0) by Population	31/1876 (1.7%)	16/1788 (0.9%)	**0.042**
% hypoglycemia (<4.0) by Patient-Day	21/438 (4.8%)	12/422 (2.8%)	0.182
% hypoglycemia (<4.0) by Patient	10/56 (17.9%)	9/41 (22%)	0.462

CONCLUSION: Protocolized administration of insulin inside PN bag has lower risk of hypoglycaemia compared to Ex-PN insulin and can be safely administered.

Disclosure of Interest: None declared

OP354 LARGE DELETION IN THE EPCAM GENE RESPONSIBLE FOR THE MILDER PHENOTYPE OF CONGENITAL TUFTING ENTEROPATHY

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INTRODUCTION: A number of point mutations within the *EPCAM* gene have been found to be responsible for congenital tufting enteropathy (CTE). We previously described a milder phenotype of CTE in a cohort of Maltese patients[1]. EpCAM staining was negative in the whole cohort[1], suggesting a defective *EPCAM* gene in the milder phenotype.

AIMS & METHODS: To identify the underlying genetic abnormality within the *EPCAM* gene responsible for the milder CTE. In the period 1985 – 2012, eight Maltese patients with CTE from six unrelated families were retrospectively identified. Genomic DNA was extracted from peripheral blood. Primers for all nine exons within the *EPCAM* gene were designed and optimized. PCR products were amplified and sequenced. To sequence exon 4 – exon 6 region, the PCR product was purified from the gel and ligated in a TA Vector. The ligated products were transformed into DH5α bacteria and cultured on ampicillin-containing agar plates. The cultured DNA was extracted and sequenced. All DNA sequences were compared with controls. Unaffected family members (parents) and healthy controls were screened for the deletion.

RESULTS: Genetic analysis of the *EPCAM* gene in Maltese CTE patients revealed a novel homozygous 1773bp deletion in seven patients, starting from 1170bp downstream of exon 4, up to 721bp upstream of exon 6, resulting in complete deletion of exon 5. The remaining patient was a heterozygote for the deletion. The mutant homozygous variant resulted in a frameshift, introducing 23 novel amino acids, formation of a premature stop codon, p.Ala164Metfs*24. loss of the transmembrane domain and complete lack of EpCAM protein within the intestinal epithelium. Three sets of parents of 3 affected patients were all heterozygous for this deletion. 98 out of 100 healthy controls tested were homozygous wild type and two (2%) were heterozygous for the deletion.

CONCLUSION: This novel large deletion within the *EPCAM* gene was found to be responsible for the milder phenotype of Maltese CTE patients. The heterozygous mutation of the patients' parents confirms the autosomal recessive pattern of inheritance of CTE. This genetic deletion present in all patients implies a founder effect and we propose this as the first genotype-phenotype correlation in isolated intestinal TE patients.

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Disclosure of Interest: None declared

OP355 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS INJURE THE SMALL INTESTINE THROUGH NLRP3 INFLAMMASOME ACTIVATION

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INTRODUCTION: Non-steroidal anti-inflammatory drugs (NSAIDs) induce intestinal overexpression of tumor necrosis factor (TNF)-α in a Toll-like receptor 4 (TLR4)-dependent manner, causing small intestinal damage (Watanabe et al, Gut, 2008). Although like TNF-α, interleukin (IL)-1β is a potent proinflammatory cytokine, its role in this damage remains unknown. The inflammasome consists of one of several NOD-like receptors (NLRs) including NLRP3, NLRP6, and NLRC4, the adaptor protein apoptosis-associated speck-like protein containing CARD (ASC), and pro-caspase-1. The inflammasome is a large multiprotein complex whose assembly leads to pro-caspase-1 processing into cleaved caspase-1, which promotes the processing of pro-IL-1β into its mature active form.
AIMS & METHODS: The aim of this study was to investigate the role of inflammasomes and IL-1β. Indomethacin (10 mg/kg) was administered orally to wild-type, NLRP3 knockout (KO), caspase-1 KO, or TLR4 KO mice. The small intestines were removed 3, 6, 12, and 24 h after administration. Intestinal damage was assessed by measuring the ulcerated area in the intestinal mucosa; mRNA expression of inflammatory mediators was assessed using RT-PCR. Protein levels of pro-IL-1β and IL-1β in the small intestine were measured using a specific ELISA. NLRP3, cleaved caspase-1, and IL-1β localization was determined by immunohistochemistry. Further, to clarify the role of IL-1β in the damage, wild-type mice were intraperitoneally administered mouse recombinant IL-1β (rIL-1β), anti-IL-1β-neutralizing antibodies, or vehicles after indomethacin administration.
RESULTS: Small intestinal damage developed 3 h after indomethacin administration and was accompanied by increases in IL-1B mRNA expression and proIL-1β and IL-1β protein levels in the small intestine. IL-1β immunoneutralization attenuated small intestinal damage by 53%, while rIL-1β aggravated the damage. NLRP3 mRNA expression increased after indomethacin administration, whereas that of other NLRs such as NLRP6 and NLRC4 did not. Compared to the wild-type mice, the NLRP3 KO and caspase-1 KO mice showed intestinal damage inhibition by 58% and 87%, respectively, with IL-1β protein level reduction, although pro-IL-1β levels were similar between the wild-type and two types of KO mice. Genetic depletion of TLR4 prevented indomethacin-induced overexpression of NLRP3 mRNA and IL-1β protein in the small intestine and inhibited intestinal damage by 78%. Immunoreactivity for cleaved caspase-1 and IL-1β was mainly observed in inflammatory cells such as macrophage, while NLRP3 was diffusely expressed on many types of cells including inflammatory and epithelial cells.
CONCLUSION: Our results suggest that the NLRP3 inflammasome plays a crucial role in NSAID-induced small intestinal damage, and the TLR4 signaling pathway may trigger NLRP3 inflammasome activation.
Disclosure of Interest: None declared

OP356 REGENERATING ISLET-DERIVED 3-ALPHA IS A BIOMARKER OF ORGANIC ENTEROPATHIES

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INTRODUCTION: The clinical presentation of organic and functional intestinal disorders can overlap and clinicians rely often on invasive and time-consuming procedures to make a final diagnosis. Regenerating islet-derived 3-α (Reg3α), a Paneth cell-derived antimicrobial protein, is detectable in the circulation of patients with intestinal graft-versus host disease (GVHD) and patients with inflammatory bowel disease.
AIMS & METHODS: The aim of our study was to determine whether serum Reg3α testing is useful for discriminating patients with structural enteropathies from those with functional intestinal disorders. We prospectively included 39 patients with active celiac disease (ACD), 11 patients with refractory celiac disease (RCD), 40 patients with active Crohn's disease, 6 patients with common variable immunodeficiency (CVID), and 14 patients with irritable bowel syndrome (IBS)-related diarrhea. Serum samples were also taken from 10 CD patients before and after 6-12 months of a gluten-free diet (GFD). Sera of 22 healthy volunteers were used to determine the cut-off value. Reg3α levels were measured by a commercial ELISA kit.
RESULTS: Levels of Reg3a exceeded the cut-off value of the assay in 35/39 (89.7%) ACD patients, 11/11 (100%) RCD patients, 6/6 (100%) CVID patients, and 34/40 (86.7%) Crohn's disease patients. None of the IBS patients had increased levels of Reg3a. Reg3a levels distinguished organic enteropathies from IBS with a sensitivity of 89% and a specificity of 100%. Reg3a levels significantly decreased following a GFD.
CONCLUSION: Reg3α is a serum biomarker of intestinal damage that can be combined with clinical data to identify patients who should undergo invasive tests for diagnosing organic enteropathies.
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Disclosure of Interest: None declared

OP357 THE DIAGNOSTIC YIELD OF THE 75SEHCAT TEST IN PATIENTS WITH CHRONIC DIARRHOEA

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INTRODUCTION: The ^{75}SeHCAT test mirrors the turnover rate of bile acids and is used to diagnose bile acid diarrhoea (BAD). Retention $<10\%$ on day 7 is considered abnormal. Where this is not due to ileal disease (type 1), or associated with other pathologies (type 3) it is termed idiopathic bile acid diarrhoea (type 2).
AIMS & METHODS: We aimed to study the distribution of the ^{75}SeHCAT test values in different conditions with chronic diarrhoea, and to determine if there are diagnostic groups where the test is unnecessary. The prevalence of idiopathic BAD was also evaluated. 2112 consecutive ^{75}SeHCAT tests performed at our university hospital were reviewed. Medical records from the referring clinic were also investigated. Patients were included if referred for the investigation of diarrhoea and excluded if there was insufficient data to establish a cause of referral. Results in each diagnostic group were then compared to 29 previously published healthy controls using non-parametric tests. Patients were considered to have BAD if ^{75}SeHCAT on day 7 (S7) was less than 10%.
RESULTS: Median S7 was significantly lower compared to controls in all diagnoses except coeliac disease. The relative risk (RR) for a positive ^{75}SeHCAT test in these patients was 7.2 compared to healthy controls. In those with ileocaecal Crohn's disease and ileocaecal resection in particular RR was 13.5/12.0. Female gender was more prevalent in all groups referred for testing, except patients with UC. Though there were more female patients in those witout a predisposing condition, there was a higher proportion of males testing positive for BAD in this group of patients (54% vs. 42%, $p<0.005$).

Clinical feature (n)	SeHCAT retention <10	Median S7 (perc. 10, 90)	%female	Relative risk (95% CI)
All patients (n=1602)	49.7% (n=796)	10.7* (1.00, 36.0)	66.3	7.2 (1.9-27.3)
No predisposing condition (n=700)	46.4% (n=325)	12.0* (1.86, 34.0)	61.4	6.8 (1.8-25.9)
Cholecystectomy (n=231)	67.5% (n=156)	6.50* (1.00, 24.0)	85.3	9.8 (2.6-37.3)
Collagenous colitis (n=171)	35.1% (n=60)	16.0* (3.03, 36.0)	79.5	5.0 (1.3-19.5)
Crohn's disease (n=58)	93.1% (n=54)	1.40* (0.01, 9.12)	56.9	13.5 (3.5-51.5)
Ileocecal resection (n=58)	82.8% (n=48)	2.40* (0.01, 13.2)	63.8	12.0 (3.1-45.9)
Lymphocytic colitis (n=53)	34.0% (n=18)	15.0* (1.2, 39.8)	66.0	4.9 (1.2-19.7)
Coeliac disease (n=53)	20.8% (n=11)	27.0 (3.86, 64.2)	77.4	3.0 (0.71-12.7)
Ulcerative colitis (n=38)	28.9% (n=11)	20.0* (4.80, 49.7)	28.9	4.2 (1.01-17.5)

CONCLUSION: The ^{75}SeHCAT test is a valuable tool in the diagnostic work-up of chronic diarrhoea. However, in patients with ileal Crohn's disease, or post ileocaecal resection, it may be unnecessary as the test can be presumed to be positive. Patients who are referred for the test are predominantly female, however, the likelihood of finding a positive test appears, if anything, to be greater in males.
Disclosure of Interest: None declared

OP358 SM22 AS POTENTIAL BIOMARKER FOR THE DETECTION OF TRANSMURAL ISCHEMIC INJURY OF THE INTESTINES

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INTRODUCTION: Acute mesenteric ischemia is an abdominal emergency requiring rapid diagnosis and treatment since the duration of ischemia is the most important determinant of outcome. Current biomarkers only detect ischemic mucosal injury, whereas differentiation between mucosal and transmural ischemic intestinal damage is imperative because only the latter mandates emergency surgery. Our previous study showed that SM22 (22-kDa protein exclusively expressed in visceral smooth muscle tissue) is a potential plasma biomarker for intestinal transmural injury. The aim of this study was (1) to investigate whether SM22 could be detected in plasma and urine after intestinal ischemia in rats, (2) to obtain insight into the organ-specific release and clearance of SM22, and (3) to provide first data on the diagnostic potential of SM22 plasma levels to detect transmural ischemia in man.
AIMS & METHODS: SM22 release was investigated in 42 rats subjected to mesenteric ischemia for up to 24 hours (h) by jejunal blood supply ligation. Blood, urine and tissue was sampled at baseline and after 2, 4, 6, 8, 12 and 24h of ischemia. Six rats were sham-operated. SM22 concentrations were measured using a newly built ELISA. Organ-specific SM22 release and clearance was studied in blood drawn from portal, hepatic, renal veins and an artery in rats and in 10 patients undergoing major upper abdominal surgery. Next, SM22 and Intestinal Fatty Acid Binding Protein (I-FABP) (a sensitive marker to study enterocyte damage) were quantified in plasma of 12 patients with proven

intestinal ischemia and 50 healthy volunteers. Tissue sections were stained with haematoxylin/eosin (HE) and anti-SM22. Data are presented as mean±SEM and analyzed using Kruskal Wallis tests. A P-value <0.05 is considered statistically significant.
RESULTS: In rats, histological assessment revealed degeneration of the mucosa and necrosis of the muscular layers of the intestinal wall in jejunum from 6h ischemia onwards as compared to control or sham. Staining for SM22 revealed a decrease in staining intensity or even a total absence of SM22 protein in the muscular layers after 8h ischemia. Baseline plasma SM22 levels were ≤0.1 ng/ml in all animals. After 4h ischemia, SM22 plasma concentrations were significantly increased compared to baseline (7.30±1.97 ng/ml vs 0.45±0.09 ng/ml, $P<0.05$), and remained elevated until 24h. Urinary SM22 concentrations were significantly higher in rats with intestinal ischemia compared to sham (0.14±0.08 ng/ml vs 3.05±0.67 ng/ml, $P<0.05$). Transorgan measurements showed that SM22 was specifically released from the intestines and removed from circulation by the kidneys, resulting in a plasma half-life of about 16 minutes in rats and 22 minutes in man. SM22 levels were significantly higher in patients with histopathological proven transmural infarction(n=6) compared to patients with only ischemic mucosal injury (n=6) and healthy controls (5.9 ng/ml vs 0.6 ng/ml and 0.4 ng/ml ($P<0.001$), respectively).
CONCLUSION: SM22 is released into the circulation after severe intestinal ischemic injury and is a potentially useful marker of transmural injury during intestinal ischemia.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 11:00–12:30
ADVANCED COLONOSCOPIC IMAGING – HALL C

OP359 SIMPLE NEW DIAGNOSTIC FEATURES OF SESSILE SERRATED ADENOMA/POLYPS ON MAGNIFYING NARROW BAND IMAGING: A PROSPECTIVE STUDY OF DIAGNOSTIC ACCURACY

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INTRODUCTION: The narrow band imaging classification system (NICE classification) classifies colorectal polyps very accurately, including differentiating adenomatous from hyperplastic polyps (HPs). However, it is often difficult to discriminate sessile serrated adenoma/polyps (SSA/Ps) from HPs.
AIMS & METHODS: The aim of this study was to establish and evaluate new simple diagnostic features for SSA/Ps using magnifying narrow band imaging (M-NBI).
We performed a prospective, single-arm observational study of diagnostic accuracy in two stages, as follows: phase 1 (seeking stage), development of simple diagnostic features for SSA/P and definition of diagnostic criteria based on retrospective assessments of M-NBI; and phase 2 (validation stage), prospective validation and evaluation of the simple new diagnostic criteria. (Trial registration number: UMIN-CTR 000009808)
RESULTS: In the seeking stage, we identified brownish, oval, expanded crypt openings and thick branched vessels on the surfaces of SSA/Ps. We named these "expanded crypt openings" (ECOs) and "dilated and branched vessels" (DBVs), respectively. In the validation stage, we enrolled 796 polyps in 261 patients. We classified 126 polyps as NICE Type 1; all these lesions were endoscopically removed and assessed histopathologically. The sensitivity, specificity, and accuracy of ECOs for SSA/Ps were 82.4%, 84.3%, and 81.1%, respectively; whereas the sensitivity, specificity, and accuracy of DBVs were 59.2%, 45.1%, and 68.9%, respectively. M-NBI provided a sensitivity of 98% and specificity of 59.5% for discrimination of SSA/Ps from other lesions classified as NICE Type 1.
CONCLUSION: Identification of ECOs, supplemented with DBVs, has high sensitivity for the diagnosis of SSA/P. These findings may facilitate the use of endoscopic optical diagnosis in clinical practice.
Disclosure of Interest: None declared

OP360 CLINICOPATHOLOGICAL FEATURE AND RISK FACTOR OF INTERVAL CANCER

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INTRODUCTION: Colorectal cancers diagnosed with a few years after index colonoscopy can arise from missed lesions or development of a new tumor and recently such cancers are reported as "interval cancer".
AIMS & METHODS: We analyzed 59125 cases out of 43210 patients who underwent colonoscopy. Patients were defined as having an interval cancer (IC) if they detected colorectal submucosal invasive or deeper invasive cancer within 36 months from index colonoscopy. Another cancer was defined as a non-interval cancer (NIC). We investigated the clinical difference between IC and NIC. And investigated to clarify clinicopathological features and risk factors of IC.
RESULTS: We identified 35 cases of IC and 1030 cases of NIC. IC/NIC were male; 82.9%/65.3% (p=0.03), diameter (T1stage); 15.9mm/21.1mm (p=0.002), diameter (T2stage); 30.6mm/51.0mm (p=0.002), respectively. Average interval from index colonoscopy of IC was 18.1month. At the index colonoscopy, patients which co-exist three or more lesions were 57.1%/36.7% in IC/NIC (p=0.012), and who has over 10mm concomitant lesion were 45.7%/19.0% in IC/NIC (p=0.001) respectively.
Regarding the location of tumor, right colon/left colon was 51.4%/48.6% in IC group and 32.8%/67.2% in NIC group (p=0.02).
By analysis of covariance, cumulative incidence of IC were always higher in right colon during the whole examination period (p=0.001).
Percentage of patient whose insertion time over 10min was 60.0%/39.8% in IC/without IC (p=0.001).
CONCLUSION: Characteristics of clinicopathological features of IC were small size, located mostly in the right colon. Regarding the predictive factors of IC at the index colonoscopy, three or more tumor co-existence, co-existing of tumor over 10mm, and over 10min insertion time could be predictive factors.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 11:00–12:30
ENDOSCOPY MEETS PATHOLOGY: EARLY NEOPLASIA IN THE UPPER GI TRACT – HALL I/K

OP361 INFLUENCE OF REVIEWERS' CLINICAL BACKGROUNDS OVER INTERPRETATION OF CONFOCAL LASER ENDOMICROSCOPY FOR SUPERFICIAL GASTRIC LESIONS. AN INTERNATIONAL MULTI-CENTRIC STUDY

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INTRODUCTION: Confocal laser endomicroscopy (CLE) is a novel endoscopic technology which provides real-time histological tissue analysis during standard endoscopic observation. In current endoscopic management strategy for gastric cancer, substantial discrepancy exists between East and West countries due to diversity in clnical backgrounds such as prevalence of gastric neoplasias. We surmised that accuracy of CLE interpretation could vary depending on reviewers' clinical backgrounds.
AIMS & METHODS: Aims of this study were to elucidate the influence of reviewers' clinical backgrounds over the CLE deferential diagnosis for superficial gastric lesions (neoplastic or non-neoplastic) in collaboration with German and Japanese institutions. Thirty WLE and 30 fluorescein assisted probe based CLE movie clips (30sec) of 18 neoplastic and 12 non-neoplastic lesions were reviewed by 39 reviewers. The reviewers had web-based self-training prior to the video review. The WLE and CLE review was done back to back for each lesion and initiated by the WLE interpretation. Each clip was then classified as either neoplastic or non-neoplastic. The results of the video reviews were compared with the final histological diagnosis of the studied sites. The outcomes were analyzed by reviewers' country, specialty, expertise and experience of pathological training, GI endoscopy and CLE independently.
RESULTS: The table below demonstrated the accuracy of the differential diagnosis. The accuracy of CLE was generally higher than the accuracy of WLE regardless of reviewers' clinical background. Outcomes of GI experts and Japanese were better than outcomes of pathologists and Germans respectively (GI/Pathologist: p=0.038 for WLE, p=0.002 for CLE, German/Japanese p=.001 for WLE, p<0.001 for CLE). There was no significant correlation between the accuracies, and the experience of CLE and pathological training (Expert with experience of over 1000 GI endoscopy cases with/without pathological training: p=0.93 for WLE, p=0.067 for CLE).

Clinical background of reviewers	WLE	95%CI	WLE+CLE	95%CI	p-value
Overall (n=39)	65.64	62.84-68.36	73.93	71.3-76.42	0.0002
with CLE experience (n=7)	64.29	57.4-70.76	75.71	69.34-81.35	0.0195
without CLE experience (n=32)	65.94	62.84-68.93	73.54	70.63-76.31	0.0028
GI physians and surgeons (GI) (n=33)	66.87	63.84-69.80	75.66	72.86-78.30	<0.01
Pathologists (n=6)	51.32	51.32-66.15	64.44	56.9-71.42	0.63
German (n=7)	55.71	48.72-62.55	64.9	57.40-70.76	NS
Japanese (n=32)	67.81	64.75-70.76	73.21	73.21-78.71	<0.01
Expert w pathological training (n=14)	67.38	62.66-71.84	73.33	68.83-77.50	p=0.002
Expert w/o pathological training (n=17)	67.64	63.39-71.69	77.25	73.37-80.82	p=0.002

CONCLUSION: The results of this study demonstrated that reviewers' clinical backgrounds influenced CLE diagnosis for superficial gastric lesions and the disease-specific expertise of standard endoscopic observation might benefit the CLE diagnosis accuracy. The interpretation of unstable en face fluorescein assisted CLE image might be more similar to real-time endoscopic diagnosis than histological analysis of sliced fixed tissues.
Disclosure of Interest: None declared

OP362 QUANTITATIVE ANALYSIS OF VOLUMETRIC LASER ENDOMICROSCOPY IMAGES WITH HISTOLOGICAL CORRELATION OF EX-VIVO ENDOSCOPIC RESECTION SPECIMENS OF BARRETT'S OESOPHAGUS WITH AND WITHOUT EARLY NEOPLASIA

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INTRODUCTION: Early neoplastic lesions in Barrett's oesophagus (BO) are difficult to detect with white-light endoscopy. Volumetric laser endomicroscopy (VLE) is a new optical coherence tomography (OCT)-based imaging technique that provides large circumferential sub-surface maps of the superficial oesophageal wall layers at a resolution of low-power microscopy. VLE data can be quantified by measuring the attenuation coefficient (μ_{OCT}), the decay of detected backscattered light versus depth. μ_{OCT} has the potential of providing quantitative optical diagnosis of interrogated mucosa because it relates to the organization of tissue.
AIMS & METHODS: To investigate the feasibility of μ_{OCT} for identification of early neoplasia in BO.
Endoscopic resection (ER) specimens from BO patients with and without neoplasia were scanned ex-vivo with VLE. Histopathology slides from the specimens were correlated one-to-one with VLE scans based on in-vivo and ex-vivo placed electrocoagulation markers. Quantification of VLE signal attenuation (μ_{OCT}) was performed on areas of interest (AoIs) from VLE scans that were matched with histology in order to differentiate non-dysplastic (NDBO) and dysplastic BO mucosa.
RESULTS: In this pilot study, 14 endoscopic resection (ER) specimens yielded 14 histology-VLE matches with 25 AoIs consisting of 21 NDBO and 4 dysplastic BO AoIs (LGD n=1, HGD n=3). Median μ_{OCT} values (mm^{-1}) of the different mucosa types were compared: NDBO 0.41 (IQR 0.17-1.82) and dysplastic BO 3.31 (IQR 1.43-5.49). A statistically significant difference was observed between these groups ($p = 0.04$).
CONCLUSION: Quantitative VLE by means of μ_{OCT} may potentially differentiate between NDBO and dysplastic BO. Further research in larger sample size is needed to validate μ_{OCT} for the distinction between dysplastic and non-dysplastic BO.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 11:00-12:30
THERAPEUTIC DRUG MONITORING IN IBD - HALL R

OP363 TIME SINCE LAST DRUG EXPOSURE IN PREGNANCY DETERMINES ADALIMUMAB AND INFLIXIMAB LEVELS IN NEONATES (ERA STUDY)

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INTRODUCTION: Recent studies suggest no adverse pregnancy outcomes in babies exposed to anti TNF antibodies (ATA). However, the long term implications are unknown. This study aimed to examine drug levels of ATA in cord blood of newborns exposed to ATA in pregnancy, and to correlate these with maternal levels, the duration of therapy during pregnancy, and time to clearance of ATA in infants.
AIMS & METHODS: Women with IBD exposed to infliximab (IFX) or adalimumab (ADA) during pregnancy were included from 2012-present at 14 hospitals in Denmark, Australia and New Zealand. ATA levels were measured using an ELISA in cord and maternal blood at delivery (Matriks Biotek). If positive at birth, the infants were tested every third month until ATA were undetectable. Demographics, disease phenotype, disease activity in pregnancy, duration of ATA use in pregnancy, medication and pregnancy outcomes were prospectively collected by questionnaire and from the treating doctor.
RESULTS: 53 mother-baby pairs have been tested (27 IFX and 26 ADA). An inverse correlation between duration since last exposure and cord ATA levels at birth was found (IFX: $r = -0.58$, $p = 0.002$; ADA: $r = -0.42$, $p = 0.047$). This was also the case for maternal levels at birth (IFX: $r = -0.59$, $p = 0.002$; ADA: $r = -0.52$, $p = 0.01$). There was a strong correlation between cord blood and maternal levels at delivery (IFX: Pearson's $r = 0.80$, $p < 0.0001$; ADA: $r = 0.80$, $p < 0.0001$). Drug was ceased prior to gestational week (GW) 30 in 15 (28%) women. In them, mean serum concentrations were 0.81 µg/ml (IFX) and 0.08 µg/ml (ADA), and the cord blood level at delivery was < 3 µg/ml in 11/15 (73%). So far 30 babies have completed testing for detectable ATA levels, and testing is ongoing in the remaining 23 babies. Complete clearance of ATA was seen in 7, 5, 12 and 6 babies at birth, by 3, 6 and 9 months, respectively. To date there has been one detectable ATA level at 9 months. Three women (5.7%) gave birth preterm (GW 33-35). No congenital malformations were detected and all babies are developing normally.
CONCLUSION: Maternal and neonatal ATA levels were inversely correlated with the duration since last exposure. Cord blood ATA levels were strongly correlated with maternal level at delivery. Maternal cessation of ATA prior to week 30 successfully reduced fetal exposure to drug in the vast majority of cases. Follow up will determine whether high neonatal levels have any negative consequences.
Disclosure of Interest: M. Julsgaard: None declared, L. Christensen Lecture fee(s) from: Ferring, MSD, AbbVie, Other: Member of the advisory board for MSD A/S, P. Gibson Financial support for research from: Janssen, AbbVie, Ferring, Lecture fee(s) from: Janssen, AbbVie, Abbott, Fresenius Kabi, Astrazeneca, Consultancy for: AbbVie, Janssen, Ferring, Takeda, Nestle, Danone, J. Fallingborg Financial support for research from: Centocor, Abbvie, MSD, UCB, Other: Advisory board member for Abbvie and MSD, R. Gearry Financial support for research from: AbbVie, Ferring, Lecture fee(s) from: AbbVie, Janssen, MSD, Consultancy for: AbbVie, Janssen, MSD, A. Walsh Consultancy for: Janssen, AbbVie, J. Kjeldsen: None declared, W. Connell Lecture fee(s) from: Janssen, Abbvie, M. Sparrow Financial support for research from: Ferring, Lecture fee(s) from: Janssen, Abbvie, Ferring, Other: Advisory Board: Janssen, G. Radford-Smith: None declared, J. Andrews Financial support for research from: Janssen, AbbVie, Abbott, MSD, Ferring, Orphan, Fresenius Kabi, Shire, Astrazeneca, Nycomed, Lecture fee(s) from: Janssen, AbbVie, Abbott, MSD, Ferring, Orphan, Fresenius Kabi, Shire, Astrazeneca, Nycomed, S. Connor Financial support for research from: Abbvie, Ferring, Orphan/Aspen, Shire, Lecture fee(s) from: Abbvie, Janssen, Shire, Ferring, Consultancy for: Abbvie, Janssen, Vifor, I. Lawrence: None declared, S. Wildt: None declared, G. Moore: None declared, L. Svenningsen: None declared, O. Rosella: None declared, A. Grosen: None declared, S. Bell: None declared

OP364 CROSS-IMMUNOGENICITY: ANTIBODIES TO INFLIXIMAB IN REMICADE-TREATED IBD PATIENTS SIMILARLY RECOGNIZE THE BIO-SIMILAR REMSIMA

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INTRODUCTION: Remsima, an infliximab bio-similar, recently received European approval for use in IBD. However, the cross-immunogenicity of Remsima with the originator drug Remicade in IBD patients is unknown.
AIMS & METHODS: Sera of Remicade-treated IBD patients with measurable antibodies to Remicade were tested by anti-lambda ELISA for their cross-reactivity to two batches of Remsima. Sera negative for anti-Remicade antibodies were tested in parallel as controls. Anti-Remicade antibodies were tested for their functional inhibition of TNFalpha-binding by either Remsima or Remicade using a competition assay. Cross-reactivity of anti-adalimumab antibodies with Remicade and Remsima was also investigated.
RESULTS: In total, 124 sera were tested. All 68 positive anti-Remicade IBD sera were cross-reactive with Remsima. In negative controls (16 healthy individuals, 40 IBD patients), there was a slightly higher background signal in the ELISA assay for Remsima compared to Remicade, but all 56 control sera which were anti-Remicade negative also tested negative for anti-Remsima antibodies. Moreover, the measured titers of anti-drug antibodies were very similar when reacted against Remicade or Remsima (rho values between 0.92 to 0.99, $p < 0.001$ for all experiments, Spearman correlation test). Anti-Remicade antibodies of IBD patients (n=10) exerted a similar functional inhibition on Remsima and Remicade TNFalpha-binding capacity (P=NS for all points on the inhibition curves). Antibodies to adalimumab in adalimumab-treated IBD patients (n=7) did not cross-react with neither Remicade nor Remsima.
CONCLUSION: Antibodies-to-Remicade in Remicade-treated IBD patients recognize Remsima to a similar extent, suggesting shared immuno-dominant epitopes on these two infliximab agents. In contrast, there is no cross-reactivity of anti-adalimumab antibodies to Remsima or Remicade.
Disclosure of Interest: S. Ben-Horin Financial support for research from: CELLTRION, Consultancy for: Abbott, Janssen, Takeda & Schering-Plough, M. Yavzori: None declared, E. Fudim: None declared, O. Picard: None declared, B. Ungar: None declared, S. Lee Other: CELLTRION employee, S. Kim Other: CELLTRION employee, Y. Chowers Consultancy for: Abbott, Janssen, Takeda & Schering-Plough

OP365 EARLY APPEARANCE OF ANTIBODIES TO INFLIXIMAB PREDICTS LACK OF RESPONSE TO INFLIXIMAB INDUCTION TREATMENT IN PATIENTS WITH MODERATE-SEVERE ULCERATIVE COLITIS

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INTRODUCTION: Antibodies to infliximab (ATI) and low serum concentrations of infliximab (IFX) have been suggested as a cause of lack of response to this treatment in Ulcerative Colitis (UC). However, the measurement of antibodies with conventional assays is limited in the presence of circulating drug. Therefore early development of ATI during IFX induction therapy and its relation to IFX concentrations and response have not been studied to date.

AIMS & METHODS: We aimed to determine serum concentrations of IFX and ATI during induction therapy in patients with moderate-to-severe UC (endoscopic Mayo 2/3) in a multicenter prospective study. Serum samples were collected at 10 serial time points during the first 6 weeks of therapy. IFX serum concentrations and ATI were measured with a homogeneous mobility shift assay (Prometheus Laboratories, San Diego, CA). Endoscopic response was defined as improvement by at least 1 Mayo point at week 6-8.
RESULTS: Twenty patients were included, all but one receiving IFX according to standard induction regime (5mg/kg at week 0,2,6). 8/19 patients were endoscopic non-responders. ATI were detected in 7/20 patients, as early as on day 18 from baseline (4 days after second infusion). In ATI positive patients week 6 median IFX trough level was 0 (0-11) ug/ml compared to 12 (8-15) ug/ml in ATI negative patients ($P<0.01$). During the induction phase 6/8 endoscopic non-responders tested ATI positive compared to 1/11 endoscopic responders ($P<0.01$, OR:30, 95%CI:2.2-406.2). 3/12 patients that used concomitant immunomodulatory treatment developed ATI versus 4/8 without co-immunomodulatory treatment (ns).
CONCLUSION: Early development of anti-IFX antibodies impairs IFX drug concentrations and predicts non-response in patients with Ulcerative Colitis.
Disclosure of Interest: J. Brandse Lecture fee(s) from: MSD, Abbvie and Takeda, G. van den Brink: None declared, J. Jansen: None declared, M. Löwenberg: None declared, C. Ponsioen: None declared, G. D'Haens Financial support for research from: Abbott Inc, Jansen Biologics, Given Imaging, MSD, DrFalk Pharma, Photopill, Lecture fee(s) from: Abbott Inc, Tillotts, Tramedico, Ferring, MSD, UCB, Norgine, Shire, Consultancy for: Abbott Laboratories, Actogenix, Centocor, Cosmo, Engene, Ferring Pharmaceuticals, GlaxoSmithKline, Jansen Biologics, Millenium Pharmaceuticals, MSD, Novonordisk, PDL Biopharma, Pfizer, SetPoint, Shire, Takeda, Teva, UCB

OP366 PERSISTENCE OF ANTIBODIES TO INFLIXIMAB FOR MORE THAN TWO MONTHS STRONGLY PREDICTS LOSS OF RESPONSE TO INFLIXIMAB IN INFLAMMATORY BOWEL DISEASES

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INTRODUCTION: Antibodies to infliximab (ATI) are frequent and may be associated with worse outcomes in Inflammatory Bowel Disease (IBD). The value of ATI (ATI threshold value, duration and kinetics) in predicting loss of response (LOR) is unknown.
AIMS & METHODS: We have studied, from a prospective cohort, all consecutive IBD patients treated with infliximab (IFX) who had at least 2 blood samples for ATI measurement. Non primary responders to IFX were excluded. Loss of clinical response was defined by an increase in clinical symptoms requiring a therapeutic change (IFX dose intensification, initiation of another IBD-related medication, or surgery).
RESULTS: 93 patients (mean age 30 years, sex ratio 1.2, 59 Crohn's disease, mean duration of follow up 17.2 months) were included in the study representing 481 blood samples. 32 patients (34.4%) lost clinical response during follow-up: 34 patients (38%) had normal C-reactive protein (CRP), 27 patients (30%) had positive ATI levels (14/27 only once and 13/27 more than 50% of their samples). A significant correlation was found between positive ATI level and LOR ($p = 0.011$) and between positive CRP level and LOR ($p = 0.0003$). At time of first sample, an ATI threshold > 20 ng/mL predicted LOR with 94% specificity and 22% sensitivity (likelihood ratio 3.39, AUROC 0.59). Presence of positive ATI in more than 50% of one patient's samples was associated with more than 50% of LOR to IFX during follow up, and with systematic clinical relapse in case of permanent ATI ($p = 0.0044$). The rate of LOR increased in parallel with the number of consecutive samples positive for ATI (66.7% of LOR when at least 2 positive samples), whereas transient ATI were not associated with LOR ($p = 0.01$). Concomitant thiopurines, duration and dose of IFX were not associated with LOR neither with detectable ATI (permanent or transient) ($p = NS$). Independent predictive factors of LOR were ATI > 20 ng/mL ($p = 0.0071$) and CRP > 5 mg/L ($p = 0.0046$). Their association was a better predictor of treatment relapse than each one separately: relative risk of maintaining clinical remission was 0.21 [CI 95%, 0.08-0.55] for CRP > 5 g/L in association with ATI > 20 ng/mL, 0.64 [CI 95%, 0.46-0.9] for ATI > 20 ng/mL alone, and 0.65 [CI 95%, 0.43-0.9] for CRP > 5mg/mL alone. There was a significant inverse correlation between IFX and ATI levels; the highest association was found between IFX trough levels at time 0 and ATI levels at time +1 (e.g. next infusion), indicating that IFX trough level decreases before ATI induction.
CONCLUSION: ATI kinetics has a strong value to predict LOR to IFX therapy. The presence of more than 50% of samples positive for ATI (> 20 ng/mL) for a given patient is associated with more than 50% of LOR. Permanent ATI levels are always associated with treatment relapse. Only one sample positive for ATI does not predict LOR. Two consecutive samples positive for ATI are associated with 66.7% of LOR whereas transient ATI were not associated with LOR. ATI and CRP levels are predictors of LOR. Preventing ATI formation is crucial to reduce LOR to IFX in clinical practice.
Disclosure of Interest: None declared

OP367 IMPACT OF POSTINDUCTION INFLIXIMAB TROUGH LEVEL AND DISEASE ACTIVITY ON PRIMARY RESPONSE IN CROHN'S DISEASE

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INTRODUCTION: Primary non-response to infliximab (IFX) induction therapy occurs in 10-20% of cases in clinical series. Few data have been reported on the clinical impact of low serum IFX trough levels after the induction treatment and their relation with clinical response, disease activity or the development of immunogenicity.
AIMS & METHODS: There are two primary aims of this study: 1. To assess the clinical relevance of a low serum IFX level during induction therapy. 2. To identify possible risk factors associated with reduced serum levels of IFX.
We included 36 Crohn's disease patients with moderate to severe disease under infliximab induction treatment. Patients were treated with IFX 5mg/kg at 0, 2 and 6 weeks as induction dose, followed by 5mg/kg every 8w.
Blood samples were drawn at standardized time points before and after induction therapy (at 0, 6, 14 and 30w) just before IFX treatment. Serum IFX trough levels and anti-Infliximab antibodies (ATI) were measured using an enzyme-linked immunosorbent assay (ELISA). Disease activity was assessed at the same time points by means of the Harvey-Bradshaw Index (HBI; remission < 3, mild-moderate disease 4-14, and severe disease > 15) and CRP/calprotectin levels.
RESULTS: After IFX induction therapy, the median serum IFX trough level was significantly higher in patients in clinical remission (IFX: 7.62ug/ml) than in patients with active disease (IFX 0.032 ug/ml $P<0.01$).
Receiver operating characteristic curve analysis indicated a cut-off value of 3ug/ml at week 6. The positive predictive value of high postinduction IFX trough level (IFX > 3 ug/ml at 6w) for prediciting good response and sustained remission after IFX induction was $> 90\%$.
ATI levels were detected in 26% of IFX treated patients and were significantly related to low trough levels and infusional IFX reactions. Low postinduction IFX trough levels were related to primary failure in 80% of patients. The cumulative number of patients with low IFX trough levels were significantly higher in patients with severe disease activity and ATI detection
CONCLUSION: 1. Low post-induction IFX trough levesl are associated with primary failure.
2. Optimal predictors of postinduction clinical remission to IFX were week 6 trough level > 3ug/ml and a low disease activity before treatment.
Disclosure of Interest: None declared

OP368 DEVELOPMENT OF AN ALGORITHM INCORPORATING PHARMACOKINETICS OF ADALIMUMAB IN INFLAMMATORY BOWEL DISEASES

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INTRODUCTION: Several decision algorithms based on the measurement of infliximab (IFX) trough levels and antibodies to infliximab (ATI) have been proposed (1). Whether such algorithms can be extrapolated to the pharmacokinetics of adalimumab (ADA) has yet to be determined.
AIMS & METHODS: A prospective study included all consecutive patients with IBD having a disease flare while being on ADA 40 mg every two weeks monotherapy were included. All patients were primary responders to ADA and anti-TNF naive. ADA trough levels and antibodies to adalimumab (AAA) were measured in blindly to clinical data (Elisa LISA-Tracker, Theradiag). All patients were optimized with ADA 40 mg weekly. Four months later, in the absence of clinical remission (CDAI < 150 for Crohn's disease (CD), and Mayo score < 2 for ulcerative colitis (UC)), patients were treated with IFX therapy. Patients were y divided into three groups based on ADA trough levels based on previous studies:
Group A: ADA > 4.9 μg/mL
Group B: ADA < 4.9 μg/mL and undetectable levels of AAA (< 10 ng/mL)
Group C: ADA < 4.9 μg/mL and AAA > 10 μg/mL
RESULTS: 82 patients were included (55% CD, mean age = 43 years, disease duration = 7.4 years, duration of ADA therapy= 17 months). After optimization of ADA treatment, 29.2% of patients achieved clinical remission in the group A (N = 41), 67% in the group B (N = 24), and 12% in the group C (N = 17) ($p < 0.01$ between groups A/B and B/C). CRP level at the time of relapsee, disease duration, duration of ADA therapy and type of IBD were not predictive of clinical remission after optimization by univariate analysis. The response to ADA optimization was significantly more durable in the group B (15 months) than in groups A and C (respectively 4 and 5 months). Fifty seven patients who failed following ADA optimization (69%) were treated with IFX and 31.6% of them achieved clinical remission. Clinical remission rates following IFX initiation were 12 %, 25% and 80% in groups A, B and C ($p < 0.01$ between groups C/A and C/B), respectively. Duration of response to IFX was significantly higher in the group C than in groups A and B (14 *vs.* 3 and 5 months, respectively, $p < 0.01$).
CONCLUSION: The presence of low ADA trough levels in serum without AAA is strongly predictive of a favorable clinical response after ADA optimization

(67%). Conversely low ADA levels with detectable AAA are associated with failure of ADA optimization and a switch to IFX should be considered. ADA trough levels > 4.9 μg/mL are associated with clinical response to two anti- TNF (optimisation and switch) in only 10% of cases and must provide an other treatment than anti-TNF (class change).
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 11:00–12:30
IMPROVING SAFETY OF ERCP – HALL N

OP369 NOVEL ERCP PHANTOM WITH X-RAY SIMULATION – OPTIMIZED AND SAFE TRAINING WITHOUT RADIATION EXPOSURE

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INTRODUCTION: ERCP is a challenging endoscopic procedure which requires profound knowledge of anatomy and pathology as well as optimal diagnostic and therapeutic experience in handling of the equipment as well as a good manual dexterity.
In the meantime simulator training becomes more and more relevant for learning how to perform ERCP since MRCP has replaced diagnostic ERCP procedures. But until now all training concepts neglect the important role of X-ray in different aspects (diagnostic yield, adjustment of the equipment and especially exposure to radiation). Measurements, calculations and literature REFERENCES show high X-ray exposure already in clinical routine – in training situations X-ray doses far exceed all legal levels. This is – especially for female trainees and tutors – intolerable and inacceptable.
To summarize, a good training setting should include an anatomically correct phantom and a possibility for optimal hands-on training as well as training of X-ray adjustment and learning without X-ray exposure.
AIMS & METHODS: Our established hands-on ERCP phantom ("Tübingen Biliphant") has been additionally supplemented with a virtual reality module to eliminate the need of real X-ray exposure. This VR module consists of an X-ray simulation system which generates the radiologic image virtually, based on a complex sensor system inside the phantom. The reality-like virtual radiologic image is depicted simulanteously with the endoscopic pictures on an external "X-ray monitor". With this system the movements of guidewires and instruments can be recorded by incorporated sensors, processed as a X-ray image and visualised realistically and synchronously with the hands-on manoeuvres. The adjustment of the X-ray system with all its features, e.g. widefield, zoom, pulsed mode, scatters etc. is controlled on a virtually generated panel displayed on a touch screen; the virtual X-ray picture changes according to the adjustments.
RESULTS: The Tuebingen training phantom "Biliphant" meets the high requirements for a realistic hands-on training of ERCP and in combination with the virtual reality module for X-ray simulation opens the possibility for an unlimited training time and repetition rate for all interventional procedures without any X-ray exposure.
This is an important factor especially for female trainees. This universal ERCP training system with its reality-like X-ray modules overcomes the disadvantages of traditional ERCP training phantoms. For the first time both – endoscopy and radiology – can be trained in a reality-like clinical setting but without X-ray exposure. Due to the modular construction of the model individual training situations can be simulated and each training step in the full range of all diagnostic and therapeutical interventions can safely be repeated as often as desired.
CONCLUSION: In conclusion, the virtual X-ray simulation system allows hands-on ERCP training without X-ray exposure for a safe training session in a realistic hospital-like setting.
Disclosure of Interest: None declared

OP370 COMPLICATIONS OF PROPHYLACTIC PANCREATIC STENTING USED FOR THE PREVENTION OF POST-ERCP PANCREATITIS WITH REGARDS TO STENT TYPES: RESULTS OF A PROSPECTIVE, CONTROLLED STUDY

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INTRODUCTION: Post-ERCP pancreatitis (PEP) is the most common complication of ERCP, which can be severe and life threatening especially in high risk patients. Prophylactic pancreatic stent (PPS) insertion is suggested to prevent PEP. Although it is a safe procedure a few complications have been described. The aim of the study was to analyze these in terms of stent types in our prospectively collected database.
AIMS & METHODS: 317 patients with high risk of PEP were considered for PPS placement over the past 5 years. PEP was categorized as mild, moderate and severe according to the Cotton consensus criteria. Three different types of 5 Fr, 3-5 cm long PPSs were used (straight with or without internal flap, and Freeman type stent (FTS) with internal flap and outer pigtail end). Complications such as unsuccessful PPS insertion, early stent dislodgement and proximal migration were identified.
RESULTS: PPS insertion was unsuccessful in 29 patients (9.15%). PEP developed in 41.38% of these patients (n=12; 7 mild, 4 moderate, 1 severe) compared to 10.07% of the 288 successfully stented patients (n=29; 24 mild, 4 moderate, 1 severe). The complications rate was 2.78% (n=8) in the successfully stented group. We found early stent dislodgement in 5 patients (2 stents without internal flaps, 3 FTSs), who all developed mild PEP. Of the 3 patients who received FTS 1 had severe postpapillotomy bleeding one day after the ERCP, while the other 2 had papillary balloon dilation which might have contributed to early stent dislodgement. Proximal stent migration into the pancreatic duct occurred in 3 patients, all inserted stents were straight with internal flaps. Stent extraction was possible in 2 patients, while it was unsuccessful twice in 1 patient, who finally underwent distal pancreatectomy. We did not observe this complication since the introduction of FTSs into our practice. Although it has been described earlier we have not observed pancreatitis due to stent removal.
CONCLUSION: PPS insertion is a safe method however complications may occur. The most severe is proximal stent migration, which may lead to surgery in minority of cases when endoscopic removal remains unsuccessful. The use of FTS might prevent this complication. Other complications are mild and can be managed conservatively.
Disclosure of Interest: None declared

OP371 PROPHYLACTIC PANCREATIC STENT PLACEMENT AFTER DUODENAL ENDOSCOPIC SNARE PAPILLECTOMY; PROSPECTIVE, RANDOMIZED STUDY

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INTRODUCTION: Endoscopic snare papillectomy (ESP) is an efficient treatment for benign tumors of the duodenal major papilla. However, acute pancreatitis is the most common and serious complication following an ESP.
AIMS & METHODS: The aim of this study was to compare the rate of post-ESP pancreatitis in patients who did or did not receive prophylactic pancreatic stent placement.
From March 2010 to March 2014, consecutive patients who were to undergo ESP were randomized to pancreatic stent placement group (stent group) after ESP or to no pancreatic stent placement group (no stent group). The overall outcomes after ESP including complications were compared between two groups.
RESULTS: The 37 patients who received ESP for the treatment of major duodenal papillary tumors were enrolled. 19 patients were assigned to the stent group and 18 patients to the no stent group. Post-ESP pancreatitis developed in 8 patients (21.6 %, 8/37), 5 cases occurred in the stent group and 3 cases occurred in the no stent group. One case in the stent group was considered moderate grade pancreatitis and the others were considered mild grade pancreatitis. The overall incidence of post-ESP pancreatitis were 26.3% (5/19) in the stent group and 16.7% (3/18) in the no stent group (p=0.693). Although there was no statistic significance, post-ESP pancreatitis was higher in the stent group.
CONCLUSION: The development of post-ESP pancreatitis were not significantly different in patients with prophylactic pancreatic stent placement compared to those without it. Our data suggest that the effectiveness of prophylactic pancreatic stent placement after ESP may be doubtful. Therefore, more large scaled prospective, randomized controlled studies regarding the effectiveness of pancreatic duct stent placement to reduce incidence of post-ESP pancreatitis are needed.
Disclosure of Interest: None declared

OP372 PANCREATIC STENTS WITH A DIAMETER EXCEEDING FIVE FRENCH SEEM TO HAVE A PROTECTIVE EFFECT ON POST ERCP PANCREATITIS - A NATIONWIDE, REGISTER-BASED STUDY

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INTRODUCTION: The role of pancreatic stenting as a prophylactic measure to reduce post ERCP pancreatitis (PEP) has yet to be determined. In the literature there are conflicting views as of the beneficial effects of pancreatic stenting where some studies advocate that temporary small-caliber pancreatic stenting reduce the risk of PEP(1) whereas other studies indicate the opposite(2). However, most studies are either single institution studies(1) or small in numbers(2).
AIMS & METHODS: The present report aims to address the use of pancreatic stenting in a wider clinical perspective as well as analyzing its effect on the risk of developing PEP.
We performed a nationwide study of ERCP procedures, with or without pancreatic stenting, registered in the Swedish Registry for Gallstone Surgery and ERCP (GallRiks), between 2005 and 2013. Data were collected from the web-based registry where ERCP procedures are registered prospectively. The primary outcomes were pancreatitis and postoperative adverse events.
RESULTS: Data from 47,486 ERCP procedures were analyzed (1163 with pancreatic stenting). In this unselected study population pancreatitis (OR 3.03; 95% CI 2.48-3.67) and postoperative adverse events (OR 1.45; 95% CI 1.25-1.69) were significantly increased in the group that received pancreatic stents. However, the main indications for the group that received pancreatic stents significantly differed from those without pancreatic stenting. One single factor of importance for the risk of adverse events in ERCP is cannulation of the pancreatic duct. The risks of pancreatitis (OR 3.37; 95% CI 3.06-3.70) and postoperative adverse events (OR 1.36; 95% CI 1.28-1.44) were significantly increased when the pancreatic duct was cannulated. In order to get a better estimation of the protective effect of pancreatic stenting we did a subgroup analysis of the ERCP procedures mainly directed towards cannulating the bile duct and where the pancreatic duct was accidentally cannulated. In this group the risk of pancreatitis (OR 1.17; 95%

CI 0.73-1.81) and postoperative adverse events (OR 0.98; 95% CI 0.79-1.35) was not affected by pancreatic stent placement. However, we noted a significantly increased risk for pancreatitis if the diameter of the pancreatic stent was ≤5 Fr as compared to if the diameter was >5Fr (OR 4.08; 95% CI 1.31-18.02).
CONCLUSION: Pancreatic stents with a diameter exceeding 5Fr seems to have a protective effect on the risk of pancreatitis.
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Disclosure of Interest: None declared

OP373 THE ROUTINE USE OF RECTAL NSAIDS FOR PREVENTION OF POST-ERCP PANCREATITIS: A META-ANALYSIS

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INTRODUCTION: Acute pancreatitis is a common complication of endoscopic retrograde cholangiopancreatography (ERCP). Rectal nonsteroidal anti-inflammatory drugs (NSAIDs) prevent post-ERCP pancreatitis (PEP); however, it is not clear whether rectal NSAIDs should be used to prevent PEP prior to routine ERCP.
AIMS & METHODS: PubMed and Embase were searched to identify randomized controlled trials (RCT), published in English, that assessed the effectiveness of rectal NSAIDs to prevent PEP. These RCTs were included in a meta-analysis to evaluate the efficacy of routine rectal NSAIDs for the prevention of PEP.
RESULTS: Our search identified 6 RCTs (Murray et al., 2003; Sotoudehmanesh et al., 2007; Montaño Loza et al., 2007; Khoshbaten et al., 2008; Otsuka et al., 2012; Elmunzer et al., 2012), enrolling 1,666 patients, that assessed rectal NSAIDs in the prevention of PEP. Three trials (Murray et al., Khoshbaten et al., and Elmunzer et al.) enrolled "high-risk" patients; the other three examined all patients undergoing ERCP. A fixed-effects meta-analysis of the six RCTs showed a pooled odds ratio [OR] for PEP of 0.380 (95% confidence interval [CI] 0.268 to 0.539; $P < 0.001$) without heterogeneity ($P = 0.450$; $I^2 = 0$). The pooled number needed to treat (NNT) with rectal NSAIDs to prevent one episode of PEP is 7. A fixed-effects meta-analysis of the three RCTs that enrolled all patients (Sotoudehmanesh et al., Montaño Loza et al., and Otsuka et al.), totaling 744 patients, found that the routine use of rectal NSAIDs was associated with a significant risk reduction, with a pooled OR for PEP of 0.328 (95% CI 0.171 to 0.628; $P < 0.001$) without heterogeneity ($P = 0.578$; $I^2 = 0$). The NNT with the routine use of rectal NSAIDs to prevent one episode of PEP is 16. There were no adverse events related to the routine use of rectal NSAIDs.
CONCLUSION: Routine use of rectal NSAIDs prevents PEP.
Disclosure of Interest: None declared

OP374 ENDOSCOPIC FIBRIN GLUE INJECTION AS A RESCUE THERAPY FOR REFRACTORY POST-SPHINCTEROTOMY AND POST-PAPILLECTOMY BLEEDING

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INTRODUCTION: Bleeding is the second most common complication after therapeutic ERCP. Endoscopic hemostasis can be achieved by epinephrine, hemoclip, thermal coagulation or combining these options[1,2]. In case of failure, the last options were radiological or surgical treatment[1]. Fibrin glue injection has been proposed for endoscopic hemostasis in this subgroup of patients[3]. Results of endoscopic injection of fibrin glue, for refractory post-sphincterotomy and post-papillectomy bleeding, were analyzed in a large series.
AIMS & METHODS: Between October 2007 and April 2014, all patients with intraoperative or delayed bleeding following endoscopic sphincterotomy or papillectomy were collected from a prospective database. Bleeding was initially treated by diluted ephinephrine injection, hemoclips or thermal coagulation; when these methods failed, fibrin glue (Tissucol, Baxter, frozen storage; Beriplast P, CSL Behring, refrigerator storage) was injected using 2 separate 23G needles to avoid lumen clogging. After fibrin glue injection the bile duct was always drained with a stent or a naso-biliary drain (NBD) to avoid cholangitis due to possible biliary obstruction from clot or glue migration[3].
RESULTS: Over a 6 year period, 3224 sphincterotomies (2928 biliary, 154 pancreatic major papilla, 50 minor papilla, 12 both major and minor pancreatic papilla, 80 both biliary and pancreatic) and 80 papillectomies were performed at our Unit. Bleeding occurred in 256 (7.9%) cases, 208 intraoperative (6.4%) and 48 delayed (1.5%). Hemostasis was successful in 221 (86.3%) cases by diluted ephinephrine injection, hemoclips or thermal coagulation. In 35 (13.7%) cases (mean age 59.4 range 19-96) with refractory bleeding, 22 post-sphincterotomy and 13 post-papillectomy, fibrin glue injection was used as rescue therapy. Stable hemostasis was reached in 33 (94.3%) patients after one session. A mean of 3.8 ml of fibrin glue was injected. One patient had re-bleeding after 48 hours and was successfully retreated by fibrin glue injection. In one case hemostasis failed after fibrin glue injection and also after fully covered metal stent insertion; emergency arteriography diagnosed and successfully treated a gastroduodenal artery pseudoaneurism. After fibrin glue injection 16 patients received a biliary stent, 16 a NBD, 3 patients both. Cholangiography through the NBD showed an intraductal fibrin clot in 2 cases (5.7%) easily removed with a Dormia basket. No cases of pancreatitis were reported after fibrin glue injection.
CONCLUSION: Endoscopic fibrin glue injection for refractory post-sphincterotomy and post-papillectomy bleeding could represent a safe and effective treatment. Main limitation of this series is the lack of a control group.
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Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 11:00–12:30
SHEDDING NEW LIGHT ON MICROBIOTA IN IBD – HALL O

OP375 ACTIVATION OF THE GCN2/EIF2ALPHA/ATF4 PATHWAY TRIGGERS AUTOPHAGY RESPONSE TO INFECTION WITH CROHN'S DISEASE-ASSOCIATED ADHERENT-INVASIVE ESCHERICHIA COLI

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INTRODUCTION: A high prevalence of the adherent-invasive E. coli (AIEC) in the intestinal mucosa of Crohn's disease patients has been shown. We previously showed that upon AIEC infection, autophagy is induced in host cells to restrain AIEC intracellular replication. The underlying mechanism, however, remains largely unknown.
AIMS & METHODS: Here, we investigated the role of the GCN2/eIF2α/ATF4 pathway in autophagy response to AIEC infection. Autophagic activity was assessed by Western blot and immunofluorescent labelling of LC3. Intracellular bacterial number was determined by bacterial invasion assay and confocal microscopy. Binding of ATF4 to autophagy gene promoters was assessed by Chromatin immunoprecipitation (ChIP) assay. Wild type (WT) and GCN2 knockout (KO) mice were infected with an AIEC reference strain LF82 by gavage.
RESULTS: Infection of human intestinal epithelial T84 cells with AIEC LF82 strain activated the GCN2/eIF2α/ATF4 pathway as shown by increased phospho-GCN2 and phospho-eIF2α levels, enhanced ATF4 protein expression, and upregulated mRNA expression levels of ATF4 target genes. To explore the role of this pathway in host responses to AIEC infection, we used GCN2-deficient mouse embryonic fibroblasts (GCN2-/- MEF). GCN2 depletion suppressed eIF2α activation and inhibited the increase in ATF4 protein level induced by LF82 infection. mRNA expression levels of the autophagy genes p62, MAP1lc3, Beclin1, atg3 and atg7 were significantly increased in WT MEF upon LF82 infection, and this was blocked in GCN2-/- MEF. ChIP assay showed that GCN2 depletion inhibited the LF82-induced binding of ATF4 to the promoters of these autophagy genes. Consequently, autophagy induction upon LF82 infection was suppressed in GCN2-/- MEF, leading to increased LF82 intracellular replication and elevated pro-inflammatory cytokine production, compared to WT MEF. In vivo study consistently showed that LF82 infection activated the GCN2/eIF2α/ATF4 pathway in enterocytes from WT mice, but not GCN2 KO mice. In response to AIEC infection, autophagy was induced in WT mouse-derived enterocytes, and this was not observed in KO mice. LF82 persistence in the gut was increased in KO mice, leading to aggravated intestinal inflammation, compared to that in WT mice.
CONCLUSION: The GCN2/eIF2α/ATF4 pathway is activated in host cells upon AIEC infection, which is served as a defense mechanism to induce a functional autophagy to control the intracellular replication of AIEC.
Disclosure of Interest: None declared

OP376 CHANGE OF INTESTINAL FUNGAL COMMUNITY COMPOSITION IN THE CHEMICALLY INDUCED INFLAMED GUT AND THEIR PROTECTIVE ROLE IN THE COLON

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INTRODUCTION: Increasing studies have reported the important relationships between gut microbes and the intestinal diseases. However, previous studies paid much attention on the intestinal bacteria, while neglected the role of many other microbes (such as fungi, virus and parasites, etc).
AIMS & METHODS: The aim of our study was to investigate the eukaryotic fungal community distribution in the normal and chemical induced-inflamed gut as well as the relationship between fungi and colitis. C57B/L6 mice were given drinking water containing 2.5% (w/v) Dextran sulphate sodium (DSS) ad libitum for 7 days and water for two additional days, then the mucosa and feces in different part of the gut (ileum, cecum and colon) were collected when the mice were sacrificed on the day 9 to isolate the total DNA. The ITS1-2 domain of fungal DNA were amplified and detected by Illumina HiSeq 2000 platform. Bioinformatic analysis was performed with the Quantitative Insight

Into Microbial Ecology (QIIME) software and a previously described fungal ITS reference database was used to classify the fungi. Shannon-Weiner biodiversity index was calculated to represent the diversity of fungi. Quantitation of 18S rDNA in the mucosa and stool samples were used to represent the amount of fungi. To compare the role of bacteria and fungi in the intestinal inflammation, we depleted the intestinal bacteria or fungi by giving mice an antibiotic cocktail (AB) containing four different antibiotics or fluconazole in drinking water respectively for 23 days. Sixty mice were randomly divided into six groups: Normal diet group, DSS group, AB group, fluconazole group, AB+DSS group and fluconazole+DSS group. The AB and fluconazole were provided to the mice from day 1 to day 23 if these anti-microbial drugs were used. In the DSS, AB+DSS and fluconazole+DSS group, DSS was added into the drinking water only from the day 15 to day 21 at a concentration of 2.5% (w/v). The body weight change, colon length and colonic inflammation scoring of the colonic haematoxylin / eosin-staining paraffin sections were calculated.

RESULTS: Fungi distribution varied and increased from ileum to colon, the diversity and richness of fungi both decreased in the gut of DSS-treated mice compared with the Normal control. In the colon of DSS-treated group, Ascomycota was increased while Basidiomycota was decreased at the phylum level and the Asperigillus, penicillium and Candida were augmented while the Cladosporium and Cryptococcus were reduced at the genus level. Although depleting the intestinal bacteria cannot prevent the happening of colitis, it can dampen the colitis by a reduced weight loss, colon shortening and colonic inflammation scoring in comparison with the DSS group. On the contrary, depleting the intestinal fungi caused aggravated intestinal colitis by an increased weight loss, colon shortening and colonic inflammation scoring.

CONCLUSION: Intestinal fungi are part of the normal enteric microbiota, which could play a protective role in alleviating the intestinal inflammation. The fungal community changed in different locations and conditions of the gut, whereas it remains to be answered which fungi participate in protecting the gut and whether the fungal community interplay with the bacterial flora in the intestinal canal or not.

Disclosure of Interest: None declared

OP377 CAUSATIVE ROLE OF THE INTESTINAL MICROBIOTA IN CROHN'S DISEASE-LIKE ILEITIS USING GERM-FREE AND ANTIBIOTIC-TREATED TNFΔARE MICE

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INTRODUCTION: Dysbiosis of the human gut microbiota is associated with ileal Crohn's disease (CD). Functional evidence for the causative role of commensal gut bacteria in the development of chronic inflammation in the small intestine is lacking. We used the genetically-driven $TNF^{\Delta ARE}$ mouse model of CD-like ileitis in different housing conditions (including germ-free) and in combination with antibiotic treatments or caecal microbiota transplants (CMT) to test the disease-conditioning role of intestinal bacteria.

AIMS & METHODS: To compare intestinal disease development, $TNF^{\Delta ARE}$ and $TNF^{+/+}$ wildtype mice were housed in germfree (GF), specific pathogen free (SPF) or conventional (CONV) conditions until the age of 18 weeks. To change the intestinal microbial composition, CONV mice were treated between 8 and 12 weeks of age with vancomycin and metronidazole (V/M), V/M and norfloxacin and neomycin (Mix) or ampicillin (Amp). Recurrence of inflammation after ending V/M therapy was assessed for 6 weeks. To test transferability of protective effects, in CMT experiments, the cecal microbiota of V/M-treated or untreated mice was gavaged (three times in week 12) to untreated and V/M-treated $TNF^{\Delta ARE}$ mice and inflammation was analyzed 6 weeks after CMT. Intestinal pathology was assessed by microscopic observation of distal ileal & proximal colonic tissue sections. Gut luminal and mucosa-associated bacteria were analyzed by 16S rRNA gene sequencing. For qPCR analysis, RNA was isolated from total ileal tissue. Plasma cytokine levels were analyzed by ELISA.

RESULTS: While GF $TNF^{\Delta ARE}$ mice had no signs of intestinal inflammation, SPF and CONV mice developed CD-like ileitis. Inflammation of the proximal colon was observed only in CONV housing. In SPF housed $TNF^{\Delta ARE}$ mice 16S rRNA gene sequencing showed separation of caecal microbial composition according to genotype or ileitis severity.

Antibiotic treatments significantly reduced ileitis in $TNF^{\Delta ARE}$ mice. Relapse was observed 6 weeks after V/M treatment. Ileal TNF and IL-17 transcript levels were reduced under conditions of disease protection, suggesting the absence of pro-inflammatory triggers during antibiotic treatment. Improvement of inflammation following antibiotic treatment was accompanied by a significant drop in bacterial diversity, but total bacterial load was not affected. Comparative taxonomic analysis identified decrease of *Bacteriodales* associated with disease protection in all antibiotic treatments. Interestingly, recurrence of inflammation after antibiotic treatment was clearly associated with preceding regain of a disease-conditioning microbiota. Transfer of caecal microbiota from V/M-treated ileitis-free $TNF^{\Delta ARE}$ or untreated WT mice to antibiotic-treated recipient $TNF^{\Delta ARE}$ was not sufficient to postpone recurrence of inflammation.

CONCLUSION: A causal role of commensal microorganisms in $TNF^{\Delta ARE}$ mice is strongly supported by the fact that GF and antibiotic-treated mice were free of ileitis. Relapse was associated with the resilience of the disease-conditioning microbiota. The potential of single bacteria or bacterial consortia to modulate immune responses and induce inflammation after colonization of GF $TNF^{\Delta ARE}$ mice is currently under investigation.

Disclosure of Interest: None declared

OP378 FAECAL MICROBIOTA IN INFLAMMATORY BOWEL DISEASE PATIENTS WITH AND WITHOUT ARTHROPATHY

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INTRODUCTION: Inflammatory bowel disease (IBD) is considered to result from an abnormal innate immune response elicited by components of the gut microbiota in genetically predisposed individuals. The gut microbiota shows alterations (dysbiosis) in IBD. Joint disease or arthropathy occurs in IBD. We hypothesized that the gut microbial alterations in IBD patients would be different in those with arthropathy compared to those without arthropathy.

AIMS & METHODS: To compare gut microbial phylotypes in IBD patients with and without arthropathy.

IBD patients were recruited from outpatient departments of Christian Medical College from January 2007 to March 2009. Clinical details, laboratory results, and severity of joint involvement (by Steinbrocker's criteria) (RC & DD) were entered into structured forms. Patients who had received antibiotics in the 60 days prior to study were excluded. This study was approved by Institutional research board. Fresh samples were stored, DNA extracted and DNA libraries prepared using primers targeting hypervariable regions (HVR) 3 and 4 of the 16S rRNA gene using multiplex identifier sequence tags. The DNA libraries were sequenced in a 454 sequencing platform. The metagenomic diversity and phylogenetic analysis was assessed using the MG-RAST pipeline. Taxonomic comparison of bacteria between the groups was performed using Kruskal-Wallis test and pairwise Wilcoxon test in linear discriminate analysis effect size (LEfSe) program.

RESULTS: Twenty four IBD patients (12 with and 12 without arthropathy) were recruited for study. Arthropathy patients included five each with isolated axial and peripheral and 2 with mixed type of joint involvement. A total of 800,968 reads were generated for the current study. The median read count of the samples was 24,884 (range 17,774-48,477). Alpha (Shannon) diversity index was significantly different between the groups (21.7 ± 4.4 Vs 38.41 ± 4.1; $p<0.05$) with significantly higher diversity in IBD with arthropathy. The taxonomic comparison between the groups revealed that statistically significant differences in the microbial phylotypes were noted from Class to Strain levels. The important observation noted in the study that *Enterococcaceae, Enterococcus* and *Enterococcus faecium* were increased in IBD with arthropathy compared to IBD without arthropathy.

CONCLUSION: An increase in the abundance of *Enterococcus* and its species in the faeces differentiated IBD patients with arthropathy from those without arthropathy. Enterococcus may be relevant to the pathogenesis of arthropathy in IBD.

Disclosure of Interest: None declared

OP379 CARD9 DEFICIENCY LEADS TO A PROINFLAMMATORY GUT MICROBIOTA

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INTRODUCTION: The exact pathogenesis of inflammatory bowel diseases (IBD) is still unknown but a deviation of the gut microbiota composition called dysbiosis has been reported and several susceptibility loci in genes involved in the interaction with microorganisms have been identified. Among these genes, Card9 (Caspase Recruitment Domain 9) is an adapter protein for innate immunity toward a wide range of microorganisms including many intestinal commensals and pathogens. Moreover, we showed that Card9-null mice are more susceptible to dextran sulfate sodium (DSS)-induced colitis than wild-type mice as a result of delayed recovery characterized by impaired expression of IL-6, IL-17, IFN-g and IL-22 in colon[1]. Moreover, the gut microbiota composition is abnormal in Card9-null mice. Our aim was to explore the role of the gut microbiota in the susceptibility of Card9-null mice to DSS colitis.

AIMS & METHODS: Forty germ-free (GF) C57BL/6 wild-type mice were randomly assigned in two groups and inoculated by oral gavage with fresh stools from conventional wild-type C57BL/6 (GF FWT) or Card9-null C57BL/6 (GF FKO) mice and maintained in separated isolators. Three weeks after inoculation, water containing 2% DSS was administered for 7 days (acute injury), followed by 5 days of water (recovery). Animals were monitored daily for scoring using the disease activity index (DAI) and for weight loss. Colon tissue was fixed in 4% paraformaldehyde and embedded in paraffin. Sections (5µm) were stained with H&E. Tissues were scored blindly using a scoring system as described previously[1]. Transcripts of 179 inflammation-associated genes were quantified in colon using Nanostring® technology (Mouse inflammation CodeSet). Statistical analysis was performed using non parametric tests. Differences with *P* value less than 0.05 were considered significant.

RESULTS: Colitis severity was higher in GF FKO mice compared to GF FWT with greater body weight loss and DAI score during recovery period ($p<0.05$ from day 8 to day 12). Histological score was also significantly higher in GF FKO mice. Colon transcriptomics analysis showed a different pattern between the 2 groups. GF FKO mice had a higher expression of Th1 and Th17 cytokines (IFN-g, IL-22, IL-6, IL-1b, IL-23a, IL-12a) but lower expression of Th2 cytokines (IL-4, IL-5, IL-13). Moreover many chemokines (such as CCL2, CCL3, CXCL1, CXCL2) were overexpressed in GF FKO mice.

CONCLUSION: GF wild type mice colonized with the microbiota of Card9-null mice are more susceptible to DSS colitis than GF wild type mice colonized with

the microbiota of wild type mice. Immune response in GF FKO mice is skewed toward Th1/Th17. This study shows that the gut microbiota plays a role in the susceptibility of Card9-null mice to DSS-induced colitis. On top of its direct implication in immune response, Card9 could play a role in IBD pathogenesis by modulating the gut microbiota.

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Disclosure of Interest: None declared

OP380 RISK OF INVASIVE PNEUMOCOCCAL INFECTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A NATIONWIDE DANISH COHORT STUDY

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INTRODUCTION: Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are a result of an inappropriate immune response. Therefore, the main purpose of the medical treatment is to moderate the immune response thus reducing disease activity, leading to a theoretically increased risk of invasive pneumococcal infection (IPI).
The objective of this study was to examine the impact of IBD on the risk of IPI.
AIMS & METHODS: Patients diagnosed with IBD from 1977 to 2013 were identified from the Danish National Patient Register. For each IBD patient, 20 individuals matched according to sex, age, and municipalities were selected from the Danish Civil Registration System. The IBD and control group data were linked with IPI data from the national laboratory surveillance.
Using Cox regression with time since onset of IBD/date of matching as underlying time axis we calculated hazard rate ratios (HRRs) for IPI after IBD.
RESULTS: Among 83,358 IBD cases we found 316 IPI cases giving an incidence of 38 per 10,000, whereas the controls had an incidence of 26 per 10,000. The HRRs for CD and UC within the first 6 months after IBD diagnosis were high (>3) and then decreased to a constant level which for CD was significantly higher (approximately twofold) than for the controls and for UC non-significantly just above 1.
CONCLUSION: We found an increased risk of IPI infections among patients with IBD, which was most pronounced in the first years after diagnosis but remained increased over time, especially in CD.

Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 11:00–12:30

CLINICAL PERSPECTIVES ON GASTRIC MALIGNANT TUMOURS – LOUNGE 5

OP381 THE INCIDENCE AND SEVERITY OF GASTRIC PRENEOPLASTIC LESIONS ASSOCIATED WITH GASTRIC CANCER

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INTRODUCTION: Gastric cancers are the result of a cascade of histological changes or precancerous lesions, such as atrophic gastritis, intestinal metaplasia and dysplasia.
AIMS & METHODS: Our batch consisted of 61 consecutive patients diagnosed with gastric cancer that underwent surgery. As witness group we used antral biopsies taken from 96 patients admitted with dyspeptic syndrome. We followed the incidence and severity of precancerous lesions and infection with *H. pylori* in both the gastric cancer group and the witness group.
RESULTS: There were 43 males and 18 females included (average age = 59.34 years). According to the Lauren classification, gastric carcinomas studied were divided in three categories: intestinal type (62.3%), diffuse type (27.9%) and mixed carcinomas (9.8%). Intestinal type gastric carcinomas develop most frequently on the background of chronic atrophic gastritis (65.8%), with moderate (28.9%) or severe (23.7%) atrophy of gastric mucosa, accompanied by intestinal metaplasia. Chronic atrophic gastritis is observed significantly more often in intestinal type carcinomas, compared with the diffuse ones (p=0.012). Diffuse type carcinoma is associated significantly more often with chronic superficial gastritis (41.2%) compared with intestinal type carcinoma (p=0.009) and with the witness group (p=0.003). Intestinal metaplasia was observed significantly more often in intestinal type (68.4%), with moderate and severe extension and in mixed type (66.7%) compared with diffuse type carcinomas (23.5%) ($p<0.001$). Type III intestinal metaplasia is much more frequent in carcinomas in comparison with benign lesions studied (p=0.00006). Dysplastic lesions are noted significantly more often in gastric carcinomas of mixed type (66.7%) and intestinal type (60.5%) in comparison with the diffuse type (23.5%) (p=0.001). High-grade dysplasia is much more frequent in mixed type (50%) and intestinal type carcinomas (23.7%) in comparison with the witness group (2.1%). The incidence of bacterial colonization is significantly greater in patients with intestinal type (73.7%) and diffuse type carcinomas (64.7%) in comparison with the witness group (p=0.007).
CONCLUSION: Our observations sustain the different histogenesis of cancers divided after Lauren classification, the incidence of chronic atrophic gastritis and intestinal metaplasia being significantly higher in the intestinal vs. diffuse type. Histochemical assessment of type III intestinal metaplasia is very useful in early diagnosis of gastric cancer, having significance for prognosis and surveillance. The frequent association of *H. pylori* with gastric carcinomas is equally expressed for the intestinal type, as well as for the diffuse type carcinomas, confirming the etiopathogenic role of the bacterium in developing both histological types of gastric cancer.

Disclosure of Interest: None declared

OP382 THE IMPLICATION OF ULCER IN EARLY GASTRIC CANCER: CAN WE PREDICT THE CLINICAL BEHAVIOR OF EARLY GASTRIC CANCER?

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INTRODUCTION: Although the presence of ulcer in early gastric cancer (EGC) is important for the feasibility of endoscopic resection, only a few studies have examined the implication of ulcer on clinicopathologic factors in EGC.
AIMS & METHODS: This study aimed to determine the role of ulcer as a predictor of clinical behavior in EGC. Medical records of patients with EGC who underwent surgery between January 2005 and December 2012 were reviewed retrospectively. The clinicopathologic characteristics were analyzed according to the presence and stage of ulcer in EGC. The stage of gastric ulcer was categorized into active (A1, A2), healing (H1, H2) and scar (S1, S2) based on the endoscopic findings.
RESULTS: Of the 3249 patients who included in this study, the presence of ulcer was observed in 2317 (71.3%) patients. The proportions of ulcer according to the stage were 6.9% (A1), 21.4% (A2), 28.9% (H1), 30.0% (H2), 9.8% (S1) and 3.0% (S2). Submucosal invasion, lymphovascular invasion (LVI), perineural invasion, and undifferentiated-type histology such as poorly differentiated adenocarcinoma or signet ring cell carcinoma were significantly higher in ulcerative EGC than non-ulcerative EGC. When compared according to the stages of ulcer, submucosal invasion, LVI, and undifferentiated-type histology were significantly associated with active ulcer stages (A1 and A2). These features were significantly common in order from active, healing and scar stage in EGC. However, lymph node metastasis was not significantly different according to the presence of ulcer and ulcer stages.
CONCLUSION: Ulcerative EGC showed more aggressive behavior than non-ulcerative EGC. In addition, the stage of ulcer may predict the clinicopathologic behavior of EGC. Therefore, endoscopic appearance of ulcer should be carefully examined for an adequate management strategy in EGC.

Disclosure of Interest: None declared

OP383 CLINICAL OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR SUBMUCOSAL SUPERFICIAL EARLY GASTRIC CANCER

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INTRODUCTION: Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) is now widely accepted in Japan based on the absolute and expanded histopathological criteria for curative endoscopic resection (Table) [1]. Although EGC with submucosal superficial invasion ($<500\mu$m; SM1) is included the curative resection criteria, it is very difficult to diagnose the depth of invasion of SM1 before ESD and almost SM1 EGCs are evaluated histopathologically in the resected specimen. There are a few reports of recurrence of such cases [2-3], so our aim is to investigate clinical outcomes for ESD of differentiated type SM1 EGC.
AIMS & METHODS: Patient/lesion characteristics and short-/long-term outcomes evaluated for 160 patients/163 EGCs diagnosed histopathologically as curative resection of SM1 in the resected specimens among 2,429 patients/2,767 lesions treated by ESD with curative intent from 1999 to 2008. Excluded cases involved EGCs in remnant stomach/gastric tube; residual/recurrent lesions; patients with follow-up periods <1 year.
RESULTS: Male/female, 139/21; mean age ± SD, 67.1±8.4; location: U/M/L, 53/60/50; macroscopic type: 0-IIa/IIc/IIa+IIc/others, 36/105/17/5; median tumor size, 15mm (range, 4-30); positive ulcer finding, 37 (22.7%); median procedure time, 60 minutes (10-300); and perforation/delayed bleeding rates, 0% (0)/1.3% (2). Curative patients included 1 with local recurrence/regional lymph-node metastasis (LNM)/distant metastasis detected after ESD at 86 months and died at 108 months; 1 with regional LNM detected after ESD at 50 months who underwent surgery and is alive without further recurrence. Metachronous gastric cancer (MGC) was detected in 11 patients including 7 underwent curative ESDs for 10 MGCs and 4 received surgeries with 2 resulting non-curative ESDs, and 2 surgical patients died from MGC. The median interval between ESD for SM1 EGC and treatments for first MGC was 74 months (12-142). As a result, there were 20 deaths including 1 from SM1 EGC, 2 from MGC and 17 from other causes. Five- and ten-year overall/disease-specific survival rates for curative patients were 91.1%/99.3% and 77.5%/94.0% (median follow-up period, 74.1 months [13-160]), respectively.

Table: The absolute and expanded histopathological criteria for curative endoscopic resection
Table to abstract OP383

En-bloc resection
Negative horizontal and vertical margin
No lymphovascular infiltration
Absolute indication
- Differentiated type intramucosal cancer ≤20mm in size without ulceration
Expanded indications
- Differentiated type intramucosal cancer >20mm in size without ulceration
- Differentiated type intramucosal cancer ≤30mm in size with ulceration
- Differentiated type submucosal superficial cancer (SM1) ≤30mm in size
- Undifferentiated type intramucosal cancer ≤20mm in size without ulceration

CONCLUSION: Clinical outcomes of ESD for differentiated type SM1 EGC ≤30mm were favourable, but one patient resulting curative ESD died from SM1 EGC. The careful attention must be taken for possible metachronous GC and regional LNM even if more than 5 years passes from ESD for SM1 EGC.
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Disclosure of Interest: None declared

OP384 CHARACTERISTICS OF SYNCHRONOUS AND METACHRONOUS GASTRIC NEOPLASMS AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION

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INTRODUCTION: Endoscopic submucosal dissection (ESD) has become accepted as a minimally invasive treatment for gastric neoplasms such as early gastric cancers (EGC) and gastric adenomas. However, gastric neoplasms found after initial ESD have become a major problem.
AIMS & METHODS: The aim of this study was to evaluate the clinicopathological features of synchronous and metachronous gastric neoplasms after ESD. We studied 345 consecutive EGCs or gastric adenomas from 265 patients who had undergone ESD between June 2007 and December 2012. They were periodically followed up with endoscopic examination after 1 year or more. Patients with remnant stomach or additional surgery were excluded from this study. We defined a second neoplasm found within 1 year after ESD as "synchronous" and a second neoplasm found after more than 1 year as "metachronous." In this study, we investigated the incidence, clinical features and endoscopic findings associated with synchronous or metachronous gastric neoplasms. In cases with metachronous lesions, data for the initial lesion were analyzed. In cases with synchronous lesions, data for the initial or largest lesion were analyzed.
RESULTS: The median period of endoscopic follow up was 34 months (range 12 to 77 months). In total, 199 patients (75.1%) had solitary lesions and 66 patients (24.9%) had multiple lesions. In patients with multiple lesions, 49 patients had synchronous multiple lesions, 25 patients had metachronous multiple lesions, and 8 patients had both. No difference existed between age or gender among patients with solitary, synchronous, and metachronous lesions. Additionally, no significant differences existed between the three groups in terms of lesion location, macroscopic type, or tumor size. However, marked atrophy (grading O2-3 according to Kimura and Takemoto's criteria) was significantly more frequent in patients with solitary lesions than in patients with synchronous or metachronous lesions. Concerning metachronous lesions, all 28 lesions (25 second and 3 third lesions) in the 25 patients were underwent re-ESD. Of 28 lesions, 7 adenomas, and 20 mucosal carcinoma were treated curatively with re-ESD; only one lesion underwent additional surgery because it invaded the submucosa to a depath into 500μm less with ulceration.
CONCLUSION: To detect metachronous gastric neoplasms at a stage early enough for a curative re-ESD, an annual endoscopic examination is effective surveillance after initial ESD, especially for patients with marked atrophy of gastric mucosa.
Disclosure of Interest: None declared

OP385 CLINICOPATHOLOGICAL RISK FACTORS FOR LYMPH NODE METASTASIS IN EARLY GASTRIC CARCINOMA DIAGNOSED WITH THE WHO CRITERIA IN 380 CHINESE PATIENTS

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INTRODUCTION: Endoscopic resection is the preferred strategy for patients with early gastric carcinoma (EGC) because of a minimal risk for lymph node metastasis (LNM), based on the clinical research results primarily from Japan. However, it remains unclear as to LNM risk factors in Chinese patients with EGC diagnosed with the updated WHO criteria.
AIMS & METHODS: We followed the 2010 WHO criteria to diagnose EGC in resection specimens with nodal dissection and investigated clinicopathologic risk factors for LNM with the Cox logistic regression analysis.
RESULTS: Over an 8-year period from January 2005 to December 2012, we identified 380 EGC gastrectomies with lymph node dissection performed at the Nanjing Drum Tower Hospital in China. The average number of lymph node retrieved and reviewed was 17 (± 10) per case. LNM was detected in 49 (12.9%) cases. The patient mean age in the LNM group was significantly younger (54.2 ± 12.8 years) than that in the non-LNM group (60.7 ± 11.4, $p<0.05$). The M/F ratio was also significantly higher in the former (1.33) than in the latter (2.28, $p<0.05$). Univariate analysis of clinicopathologic risk factors showed a significantly positive correlation with LNM for the followings: distal gastric cancer (DGC), tumor size larger than 3.1 cm, ulcerated pattern, invasion into submucosa (SM1, SM2), undifferentiated cancer, poorly cohesive carcinoma, micropapillary carcinoma, poor differentiation, and lymphovascular invasion. Multivariate analysis revealed that lymphovascular invasion (OR = 25.891, CI = 9.077 – 73.849, $P<0.001$) and DGC (OR = 6.735, CI = 1.438 – 31.532, $P<0.05$) were significant independent risk factors for LNM.
CONCLUSION: DGC and lymphovascular invasion are the independent risk factors for LNM include. Therefore, EGC in the proximal stomach appears to be more suitable than DGC for endoscopic resection.
Disclosure of Interest: None declared

OP386 GASTRIC MALT LYMPHOMA: ANALYSIS OF A SERIES OF CONSECUTIVE PATIENTS OVER 20 YEARS

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INTRODUCTION: Gastric extranodal marginal zone lymphoma of mucosal associated lymphoid tissue, gastric MALT lymphoma (GML), is associated with *Helicobacter pylori* (HP) infection and characterized by an indolent course.
AIMS & METHODS: To evaluate demographic, clinical and endoscopic characteristics, status HP, stage, response to therapeutic and long-term prognosis of patients followed in our institution. Data of consecutive patients with GML (1993-2013) staged by Ann Arbor classification / Musshoff were analyzed. Statistics: chi2, Kaplan-Meier (SPSS 20).
RESULTS: 144 patients (76 men; 68 women), mean age: 56 years (13-83), 67% presented with dyspepsia. Most frequent endoscopic appearance and location were erosions / ulcers (46%) in antrum or antrum-body transitional zone (57%), respectively. HP infection was detected in 71.5%. 127 patients (88%) were diagnosed at stage IE/IIE (103/24). Stage IE: 94/103 patients (92%) received HP eradication regimens, 78 (83%) achieved remission after a mean period of 7 months (1-63) and 67 (86%) were in remission after a mean follow-up time of 105 months. Diffuse and antrum plus body lymphomas were significantly ($p=0.007$) associated with lower remission rate. Relapse occurred in 11/78 (14%) patients after a mean period of 21 months. Patients that needed ≥2 eradication regimens had higher recurrence rate ($p=0.008$). Stage IIE: eradication was performed in 17/24 patients but only 5 experienced remission (30%). There were no patients diagnosed at stage III and among 16 patients diagnosed at stage IV, 9 achieved remission after chemotherapy ± surgery and 3/7 without remission died due to disease progression. After a mean follow-up time of 109 months (4-246), 112 patients are still alive (99 without disease) and 32 died (5 due to disease). 5, 10 and 15-year overall survival rates were 91.8%, 82.8%, 66.9%, respectively.
CONCLUSION: Most patients were diagnosed at stage IE and among them HP eradication was an effective strategy. The diagnosis at an early stage avoided the need for aggressive therapies. The overall prognosis is favorable with high long-term survival rates.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 14:00-15:30
TARGETING NEW PATHWAYS IN IBD - HALL L/M

OP387 DOWN REGULATION OF THE MICRORNA 200 FAMILY IN STRICTURED INTESTINAL RESECTION SPECIMENS FROM CROHN'S DISEASE PATIENTS INDICATES A ROLE FOR EPITHELIAL TO MESENCHYMAL TRANSITION

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INTRODUCTION: The development of intestinal fibrosis in patients with Crohn's disease (CD) results in complications which represent a major clinical challenge for professionals, a significant cause of morbidity for patients and a considerable cost to healthcare services. Understanding the processes that initiate and regulate intestinal fibrosis will facilitate the development of effective preventative and therapeutic strategies. Specific microRNAs (miRNAs) have been shown to have defined roles in fibrogenesis in several organ models. The miR-200 family has been implicated in the development of murine intestinal fibrosis, possibly via a process termed epithelial to mesenchymal transition, although human studies are lacking.
AIMS & METHODS: Our aim was to analyse the expression profiles of miRNAs in surgical resection specimens from patients with CD between areas of stricture and non-stricture. From each patient, mucosal and submucosal samples were harvested from within a stricture as well as the normal surgical resection margins in order for every patient to serve as their own internal control. Formal histology reports were checked to ensure that fibrosis was present in the strictured areas used. Matched paired samples were selected (n=4) and sent for microarray analysis using the miRCURY LNA™ microRNA Array platform (7th Gen, Exiqon, Denmark). The expression of differentially expressed miRNAs was subsequently validated on eight new paired resection samples (stricture and

non-stricture). Total RNA including miRNA was extracted from the mucosa and submucosa of resection specimens and validation performed by qRT-PCR.
RESULTS: The microarray data revealed 32 distinct miRNAs significantly differentially expressed (p value <0.05) between the strictured and non-strictured samples. These included members of the miR-200 family, all of which were down regulated in strictured specimens: miR-141 (p=0.013), miR-200b-3p (p=0.045) and miR-200c-3p (p=0.009). The remaining members were also downregulated, but not significantly so: miR-200a (p=0.135) and miR-429 (p=0.053).
QRT-PCR validation confirmed these findings. MiR-200 family members were downregulated in the strictured samples compared to the non-strictured samples: miR-141 (fold change 0.361, p=0.002), miR-200a (fold change 0.432, p=0.001), miR-200b-3p (fold change 0.721, p=0.117) and miR-200c-3p (fold change 0.401, p=0.002).
CONCLUSION: These findings demonstrate for the first time that members of the miR-200 family are significantly downregulated in strictured fibrotic regions of intestine compared to non-strictured regions in patients with fibrostenosing CD. This mirrors findings in other organ systems, where the miR-200 family has been implicated in the development of fibrosis via epithelial to mesenchymal transition. Further well-phenotyped human studies are warranted.
Disclosure of Interest: None declared

OP388 CIRCULATING MICROVESICLES IN CROHN'S DISEASE: NOVEL MEDIATORS OF ANGIOGENESIS

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INTRODUCTION: Circulating microvesicles (cMVs) are small membrane bound fragments released by a number of cell types, including endothelial cells (ECs), platelets, leukocytes, macrophages, and smooth muscle cells. Though initially dismissed as cellular debris, cMVs are instead important mediators of cell signaling and molecular communication between cells. Indeed, cMVs are enriched with nucleic acids and proteins, shuttle specific mRNAs and miRNAs, and transfer biological information between cells. MVs form through exocytosis from multivesicular bodies, which leads to the formation of exosomes, or budding of MVs directly from a cytoplasmatic membrane, which results in the formation of so-called microparticles (MPs). In recent years, there has been increasing appreciation of the role played by cMVs in the regulation of angiogenesis. For instance, platelet-derived MPs (PMPs) induce angiogenesis both in vitro and in vivo and injection of MVs into the ischemic myocardium improves revascularization after chronic ischemia. The aim of our study was to assess number, immunophenotype, and angiogenic content and activity of cMVs in subjects with active Crohn's disease (CD).
AIMS & METHODS: We studied 10 subjects with active CD and 10 healthy controls (HC). Clinical disease activity was determined by the CD Activity Index (CDAI). Disease was considered active for CDAI index >220. Platelet-free plasma was used for fluorescence activated cell sorting (FACS) studies, to determine the cellular origin of circulating MPs, in particular whether they were derived from ECs (EMPs), platelets (PMPs), monocytes (MMPs), or apoptotic cells (AMPs). Next, we analyzed the angiogenic content of cMVs, in terms of both mRNAs and proteins, using specific profiler PCR arrays for angiogenic pathways and specific angiogenic antibody arrays. Finally, we determined the functional activity of the angiogenic message carried by cMVs, by stimulating human umbilical ECs (HUVECs) with proteins extracted from cMVs isolated from the peripheral blood of either subjects with active CD or control individuals.
RESULTS: Activated PMPs, AMPs and MMPs were significantly higher in CD when compared to HC. The presence of 84 angiogenesis-related mRNAs was investigated in CD and HC. Data analysis of PCR arrays showed 16 significantly modulated genes, in particular 14 up-regulated and 2 down-regulated. To determine whether, in CD subjects, cMVs have the ability to induce neovessel generation in vitro, we used a tube formation matrigel assay. We found that the number of branching points was significantly greater when HUVECs were incubated with proteins derived from cMVs of CD patients, compared with HC.
CONCLUSION: In CD, angiogenesis is a hallmark of active disease. Our findings demonstrate that, in active CD, cMVs carry a potent and functionally active angiogenic message. This novel finding increases our understanding of the mechanisms that underlie development and progression of the disease, with potentially important biological, clinical, and therapeutic implications.
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Disclosure of Interest: None declared

OP389 THE EFFECT OF VEDOLIZUMAB THERAPY ON COLONIC MUCOSAL GENE EXPRESSION IN PATIENTS WITH ULCERATIVE COLITIS

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INTRODUCTION: Inflammatory bowel disease (IBD) is characterized by continuous recruitment of leukocytes towards the inflamed gut. This migration is mainly regulated by adhesion molecules which are interesting targets for IBD therapy. Vedolizumab (VDZ) is an antibody to the adhesion molecule $\alpha4\beta7$-integrin which is uniquely expressed on gut-homing lymphocytes, and thereby selectively blocks the lymphocyte trafficking to the gut.
AIMS & METHODS: This study investigated the effect of VDZ therapy on colonic mucosal gene expression in ulcerative colitis (UC). In total 120 endoscopically-derived colonic biopsies from 44 UC patients were collected at protocol-specified time points [week (W) 0, W6, W12 and W52] during 2 randomized-controlled studies of VDZ[1] (Millenium C13006 and C13008). Biopsies were compared with 12 normal colonic non-IBD biopsies and colonic biopsies before and 4-6 weeks after first infliximab therapy from 23 UC patients. Mucosal healing (=Mayo endoscopic subscore 0 or 1) was assessed at W6, W12 and W52. Total RNA from biopsies was used to analyze whole genome gene expression via Affymetrix GeneChip® Human Gene 1.0 ST arrays. Data were analyzed using Bioconductor and Ingenuity Pathway Analysis software.
RESULTS: In VDZ responders showing mucosal healing, no gene expression differences at W6 and only 5 significant (false discovery rate $<5\%$ and >2-fold) gene probe sets (down: *IDO1*, *REG3A*, *KLK6*, *SAA2* and up: *PCK1*) at W12 were found when compared to W0, while many differences in gene expression were found at W52. A total of 593 (462 down and 131 up) gene probe sets were significant in VDZ responders with mucosal healing at W52 vs. W0, and 375 (63%) of these probe sets overlapped with the significant probe sets identified in infliximab responders at W4-6 vs. W0. The common probe sets encoded genes mainly involved in immune cell trafficking, cellular movement and inflammatory response. Interestingly, even in VDZ responders showing mucosal healing at W6, W12 and W52, many gene probe sets remained significantly dysregulated (266, 566 and 99 probe sets respectively for W6, W12 and W52) when compared with controls, and a great overlap of these significant genes was observed with the ones identified in infliximab responders vs. controls. Further, we found only few genes with significantly increased expression (*IGJ*, *IGK*, *IGKC*, *TNFRSF17*) in VDZ responders with mucosal healing vs. infliximab responders.
In contrast with the predictive mucosal gene signature identified for response to infliximab[2], we could not identify genes predictive of response to VDZ by comparing the pre-VDZ treatment gene expression array profiles of responders showing mucosal healing with non-responders.
CONCLUSION: VDZ influenced colonic mucosal expression of many genes involved in immune-related functions at W52, but not yet at W6 or W12. The observed changes were similar with those seen at W4-6 after first infliximab therapy, suggesting similar mechanisms of action for both therapies. As also observed in infliximab responders, the expression of many genes remained abnormal in VDZ responders with mucosal healing, indicating that maintenance therapy is necessary to control the intestinal inflammation.
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OP390 AMELIORATION OF ACTIVE ULCERATIVE COLITIS USING AN ORALLY AVAILABLE TOLL-LIKE RECEPTOR-9 MODULATOR (BL-7040): A PROSPECTIVE OPEN-LABEL, MULTI-CENTER PHASE II TRIAL

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INTRODUCTION: Current treatment of active ulcerative colitis (UC) may be associated with significant adverse events and loss of response. Toll-like receptor (TLR)-9 mediates innate and adaptive immune response towards intestinal microorganisms. BL-7040 is a novel orally available synthetic oligonucleotide, which directly modulates TLR-9. BL-7040 has an anti-inflammatory effect in murine models of colitis as well as in patients with auto immune diseases such as myasthenia gravis, with a good safety profile.
AIMS & METHODS: We performed a prospective multi-center, open-label phase IIa, proof-of-concept trial to evaluate the efficacy, safety and tolerability of BL-7040 in patients with moderately active UC, defined by a Mayo score of ≥ 5 and ≤ 9, and having an endoscopic sub-score ≥ 2 and rectal bleeding sub-score

≥ 1. Concomitant mesalamine and steroids (≤ 10 mg prednisone/day) were allowed. Patients received BL-7040 12mg/day for 3 weeks, followed by BL-7040 40 mg/day for 2 weeks. Effect was evaluated using the Mayo score, histology, and mucosal cytokines levels. Side effects were registered.
RESULTS: Sixteen of the 22 enrolled patients completed a full five-week treatment course and two-week follow-up. The primary endpoint, i.e. a ≥ 3 point decrease and 30% reduction from baseline in the Mayo score, and a ≥ 1 point reduction in rectal bleeding sub-score, or absolute ≤ 1 rectal bleeding sub-score, was met in 8 (50%) patients. The other 8 patients remained stable. Furthermore, mucosal healing evaluated by endoscopy sub-score improved. Neutrophil levels and mucosal interleukin-6 (IL-6) levels were significantly reduced in responders, and correlated with clinical improvement (p=0.002 and p=0.046 compared to non-responders, respectively). BL-7040 was well tolerated with one serious adverse event (hemoglobin decrease to 5.7gr%) considered unrelated to study drug, and 29 mild-to-moderate adverse events, mainly UC exacerbation (n=4, 18.2%), influenza-like symptoms (n=3, 13.6%), and dry mouth, fatigue, and headache (for each n=2, 9.1%).
CONCLUSION: In this prospective, open label phase IIa trial, oral administration of the TLR-9 agonist BL-7040 was associated with clinical response and mucosal healing in 50% of UC patients with moderately active disease. The decrease in mucosal inflammation was reflected by significantly lower neutrophil counts and decreased IL-6 levels. BL-7040 was safe and well tolerated. The efficacy and safety of BL-7040 for the treatment of active UC should be further evaluated.
Disclosure of Interest: I. Dotan Lecture fee(s) from: BioLineRx, Ferring, Falk Pharma, Janssen, Abbvie, Consultancy for: BioLineRx, Genentech, Pfizer, Janssen, Abbvie, E. Levy-Nissenbaum: None declared, Y. Chowers Lecture fee(s) from: Abbvie, Janssen, Consultancy for: Abbvie, Janssen, Takeda, Pharmacosmos, Vecta, A. Fich: None declared, E. Israeli: None declared, T. Adar: None declared, S. Shteingart: None declared, H. Soreq: None declared, E. Goldin Consultancy for: BioLineRx, Immune Pharmaceutical

OP391 RANDOMISED, DOUBLE-BLIND, SINGLE-DOSE, PHASE 2 TRIAL ASSESSING EFFICACY AND SAFETY OF THE NOVEL ANTI-NKG2D MONOCLONAL ANTIBODY NNC0142-0002 IN CROHN'S DISEASE: INSIGHTS FROM AN EXPOSURE-RESPONSE ANALYSIS

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INTRODUCTION: NNC0142-0002 (anti-NKG2D mAb) is an antagonising human IgG4 monoclonal antibody that binds to NKG2D receptors. These receptors are located on T- and natural killer cells, which exhibit inflammatory and cytotoxic properties, and may be linked to mucosal damage.
AIMS & METHODS: A total of 78 patients (aged ≥18 and ≤75 years) with Crohn's disease for ≥3 months, a Crohn's disease activity index [CDAI] ≥220 and ≤450, and either C-reactive protein ≥10 mg/L or endoscopic evidence of inflammation, were randomised 1:1 to a single subcutaneous (s.c.) dose of 2 mg/kg NNC0142-0002 or placebo. Primary outcome was change in CDAI (ΔCDAI) from baseline to Week 4. Secondary outcomes included ΔCDAI through Week 12, NKG2D receptor occupancy, pharmacokinetics and safety. Exposure-response analysis of ΔCDAI from baseline to Week 4, based on mean NNC0142-0002 concentrations over Weeks 1, 2 and 4 was performed. Four-level stratification based on two binary factors was implemented: failure to biologic therapy (yes/no) and baseline CDAI (<330 or ≥330). Pre-specified significance level was 10% (p≤0.10; two-sided test). Primary efficacy outcome was analysed via a mixed-effect model, whereas the exposure-response analysis was based on observed means. Due to slow recruitment a futility analysis was instituted, resulting in discontinuation of recruitment.
RESULTS: Mean ΔCDAI from baseline to Week 4 (primary outcome) was not significantly different between NNC0142-0002 and placebo (ΔCDAI = –16); however, there was a significant difference by Week 12 (ΔCDAI = –55; p≤0.10). Significant improvements were noted in the non-failure to biologics group (treated with NNC0142-0002 [n=28]) from Week 1 onwards. NNC0142-0002 resulted in a median NKG2D occupancy of >80% for 8 weeks. When patients with high baseline CDAI (≥330) were partitioned into placebo or tertiles based on exposure, larger magnitude CDAI changes were observed with higher concentrations (see table). No signs of exposure-response at Week 4 were observed for patients with baseline CDAI <330.

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Exposure (n)	Median concentration (μg/ml) Weeks 0–4	Mean (SE) ΔCDAI Week 4
Placebo (14)	0	–96 (21)
Low (6)	5.9	–96 (38)
Medium (5)	7.8	–129 (26)
High (6)	10.5	–174 (37)

Adverse event frequencies were comparable between NNC0142-0002 and placebo. Most events were mild (49%) or moderate (43%) and were primarily gastrointestinal disorders, pyrexia, anemia, arthralgia and nasopharyngitis.
CONCLUSION: A single s.c. dose of 2 mg/kg NNC0142-0002 (anti-NKG2D mAb) did not reduce disease activity at Week 4 (primary outcome) compared with placebo, but significantly reduced disease activity at Week 12, and was well tolerated. Exposure-response analysis in patients with baseline CDAI ≥330 provides supportive evidence for a treatment effect of NNC0142-0002 and suggests that higher doses and repeated dosing may further optimise the effect of NNC0142-0002 in Crohn's disease.
Disclosure of Interest: M. Allez Financial support for research from: Novo Nordisk, Consultancy for: Novo Nordisk, R. Petryka: None declared, B. Skolnick Other: Full-time employee of Novo Nordisk at the time of data analysis, M. Wisniewska-Jarosinska: None declared, R. Overgaard Other: Employee and stock holder of Novo Nordisk A/S

OP392 EFFICACY AND SAFETY OF TRICHURIS SUIS OVA FOR TREATMENT OF MILDLY-TO-MODERATELY ACTIVE CROHN'S DISEASE: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE II STUDY

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INTRODUCTION: Until now only open-label data have been available showing that a dosing of 2.500 embryonated viable eggs of *Trichuris suis* (TSO) every 3 weeks for 12 weeks led to clinical remission (CDAI<150) in 19 of 29 patients (65.5%) with active Crohn's disease (CD) refractory to standard CD-therapy before enrolment (Summers et al., Gut. 2005;54(1):87-90).
AIMS & METHODS: This is the first double-blind, randomised, multicentre POC study to evaluate the efficacy and safety of different TSO dosages vs placebo for the treatment of mildly-to-moderately active, ileo-/colonic, uncomplicated CD. Patients being neither steroid-dependent/-refractory nor on immunosuppressants with a CDAI of 220-350 and biochemical signs of inflammation were eligible for this study. Patients received either 250, 2.500, or 7.500 TSO, or placebo at fortnightly intervals for 10 weeks. Primary endpoint was the rate of clinical remission (CDAI<150) at week 12 (last observation carried forward [LOCF]).
RESULTS: 252 patients (154 females; mean age: 37 yrs; mean CDAI: 269) were randomised. Efficacy is presented below. Administration of TSO did not result in any serious adverse drug reaction (ADR). Review of non-serious suspect ADRs following intake of TSO did not reveal a safety concern.
CONCLUSION: Administration of 250 – 7.500 TSO fortnightly over 12 weeks was safe and showed a dose-dependent immunological response, but none of the TSO dosages could show a clinically relevant effect over placebo for the induction of clinical remission or response in mildly-to-moderately active, ileo-/colonic CD.
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		TSO250 (N=39)	TSO2.500 (N=71)	TSO7.500 (N=72)	Placebo (N=70)
CDAI<150 at wk12 LOCF	**N(%)**	15(38.5%)	25(35.2%)	34(47.2%)	30(42.9%)
	Δ[95%CI]	-4.4%[-23.6;14.8]	-7.5%[-23.7;8.4]	4.4%[-12.0;20.7]	
	p-value	0.6725	0.8240	0.3006	
ΔCDAI at wk12 LOCF	**Mean (SD)**	-67 (100.6)	-83 (111.6)	-102 (111.4)	-83 (127.0)
% change eos (BL-wk8)	**Mean (SD)**	148 (191)	167 (373)	241 (363)	25 (111)

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WEDNESDAY, OCTOBER 22, 2014 14:00–15:30

SYMPTOMS IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL DISORDERS – HALL R

OP393 WHICH MEASURE OF FECAL INCONTINENCE SEVERITY IS THE BEST PREDICTOR OF FECAL INCONTINENCE QUALITY OF LIFE (FIQL)?

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INTRODUCTION: Published measures of fecal incontinence (FI) severity all assess the frequency of FI, but they differ with respect to whether they discriminate between types of stool loss, volume of stool loss, urgency preceding FI episodes, and pad use.
AIMS & METHODS: Our aim was to compare two frequently used FI severity instruments, the Fecal Incontinence Severity Index (FISI) and the Fecal Incontinence and Constipation Assessment (FICA) scale, with respect to which instrument and which items within instruments are best able to predict variations in FIQL. A nationally representative gender, age and ethnicity stratified sample of U.S. adults with FI (FIPs) were recruited by market research company Cint USA, Inc. to complete an internet survey including the FISI, FICA, and FIQL questionnaires. The study was described as a health survey to minimize selection bias. Stepwise linear regression was used to identify variables that are independently predictive of FIQL. Demographic variables were entered as a block in Step 1, the FISI was entered in Step 2, the FICA in Step 3, and the Somatization scale of the Brief Symptom Inventory was entered in Step 4. The Somatization scale was included to confirm that estimates of the effects of FI severity on FIQL were not confounded by a general tendency to endorse more symptoms. The regression analysis was repeated with individual items from each severity scale to identify which questions explain the separate contribution of each scale.
RESULTS: Out of 234 survey completers, 48 (20.5%) were excluded from analysis because they gave inconsistent responses to two questions repeated for quality control, leaving 186 for analysis: 52% were women, mean age was 48.9 years (range 20-91), and race/ethnicity was 9% Hispanic and 8% African American. Post-bacalaurate education was over-represented (39.2%). The 4 subscales of the FIQL were averaged together because they are highly correlated with each other (r= 0.72 – 0.88) and it is desirable to have a single dependent measure for regression analysis. Average scores were: FIQL, 2.57 (95% CI 2.44, 2.69) on a 1-5 scale; FISI, 29.9 (95% CI 27.4, 32.4) on a 0-61 scale; FICA, 8.4 (95% CI 8.0, 8.9) on a 1-13 scale; Somatization T-score 65.6 (95% CI 63.7, 67.5). In the initial regression analysis, the adjusted R^2 for demographic variables alone was .269. Adding FISI increased the R^2 to .608, and adding the FICA increased the R^2 to .666. Adding somatization to the model increased R^2 to .690. In the final model, FICA and FISI both made significant contributions ($p \leq .001$) to FIQL even after adjusting for Somatization. A follow-up regression analysis was performed to identify individual items in each scale that predict FIQL (all items from both severity scales plus Somatization: adjusted R^2 =.711). The significant independent predictors were FISI frequency of liquid FI and gas leakage in the past month, and FICA frequency of stool leakage and having to rush to the toilet in the past year.
CONCLUSION: Four FICA and FISI variables make independent contributions to FI impact on quality of life: FISI frequency of liquid and gas leakage and FICA frequency of any FI and of having to rush to the toilet. [Supported by a grant from Salix Pharmaceuticals]
Disclosure of Interest: W. Whitehead Financial support for research from: Salix Pharmaceuticals, Consultancy for: Takeda Pharmaceuticals, Ironwood Pharmaceuticals, Entera Health, O. Palsson: None declared, S. Heymen: None declared

OP394 IBS AND OVER-REPORTING OF ABDOMINAL PAIN IN RETROSPECTIVE QUESTIONNAIRES: ADVANTAGES OF EXPERIENCE SAMPLING METHOD AS NEW DIGITAL TOOL IN SYMPTOM MEASUREMENT

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INTRODUCTION: Irritable Bowel Syndrome (IBS) is a prevalent gastro-intestinal (GI) disorder with chronic and fluctuating symptoms, of which abdominal pain is the most prominent. Standardized and well validated methods to assess abdominal pain are lacking and the available methods, *i.e.* retrospective questionnaires, display limitations, such as recall bias and failure to detect triggers and recognize cognitive and emotional aspects. A possible solution is the Experience Sampling Method (ESM); a digital tool, developed to measure 'real time' symptoms at multiple time points per day.
AIMS & METHODS: 1) To evaluate ESM as an assessment tool for GI symptoms and psychological complaints, with a focus on abdominal pain, in IBS patients with and without comorbid panic disorder and 2) to compare the ESM to retrospective paper questionnaires.
27. IBS patients (Rome III) were recruited. A subgroup of 17 patients was diagnosed with comorbid panic disorder (DSM-IV-TR). For 7 days patients carried a digital device (ESM), which randomly sent off beep signals 10 times/day and patients filled in symptom scores on the device following every beep. Additionally participants fulfilled a paper end-of-day GI symptom diary during 14 days and the Gastrointestinal Symptom Rating Scale, Hospital Anxiety and Depression Scale and the Rand-36-item Health Survey at the end of the test period. Somers'd test (for ordinal data) was used to assess correlations between ESM and paper questionnaire data. Mean and maximum ESM scores per day and mean end-of-day diary scores were calculated and analyzed using two-way ANOVA for repeated measurements.
RESULTS: For the total group of 27 IBS patients correlations between corresponding items on ESM and end-of-day diary, *i.e.* abdominal pain, nausea, belching, bloating and flatulence, were all highly significant (Somer's d (t) = 6.43 – 40.05, $p<0.001$), and interestingly the weakest correlation was found for abdominal pain (t = 6.43). When comparing mean and maximum pain scores of ESM data with the pain scores of end-of-day diary, scores filled in at the end of the day were higher than the mean ESM scores, with a mean difference of 0.4 point (significant on 6 of 7 days, $p<0.05$) on a 5 point Likert scale. The pain scores of the end-of-day diary correlate best with the maximum pain scores on ESM. Furthermore, ESM items were significantly associated with 31 corresponding items on the different GI and psychological symptom questionnaires (t = 4.63 – 26.06, $p<0.001$). Overall, the results for the group with and without panic disorder were comparable.
CONCLUSION: IBS symptoms assessed 'real time' by ESM significantly correlate to GI and comorbid psychological symptoms assessed by paper retrospective questionnaires, in IBS patients with and without comorbid panic disorder. However the weakest correlation was found for abdominal pain and our data show that patients report the most intense pain of the day in an end-of-day diary, rather than average pain over the day. This indicates over-reporting of pain by IBS patients in retrospective questionnaires, and demonstrates an advantage of ESM as a new digital symptom assessment tool.
Disclosure of Interest: Z. Mujagic: None declared, C. Leue: None declared, L. Vork: None declared, R. Lousberg: None declared, M. Hesselink: None declared, J. van Os: None declared, A. Masclee Consultancy for: Pentax medical, Grünenthal GmbH, Ferring, J. Kruimel: None declared

OP395 SYMPTOM-BASED CRITERIA FOR THE DIAGNOSIS OF IRRITABLE BOWEL SYNDROME PERFORM POORLY: A META-ANALYSIS

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INTRODUCTION: Irritable bowel syndrome (IBS) remains difficult to diagnose. Symptom-based criteria, the latest adaptation of these being the Rome III criteria, are the current gold standard for diagnosing IBS. However, these have not been well-validated, and recently attention has turned to novel approaches to the diagnosis of IBS, including biomarkers and markers of psychological affect. We performed a systematic review and meta-analysis to assess the performance of various methods for diagnosing IBS.
AIMS & METHODS: A literature search was conducted using MEDLINE (through to January 2014). Eligible studies had to assess the accuracy of accepted symptom-based diagnostic criteria, biomarkers, psychological markers, or combinations thereof, in diagnosing IBS against an accepted reference standard. For each study identified, we extracted the raw data from the paper, in order to calculate the positive and negative likelihood ratios (LRs) of each of the diagnostic tests. Where a diagnostic method was reported by >1 study we pooled the LRs from each study using meta-analytic techniques.
RESULTS: LRs with confidence intervals (CIs), of each of the diagnostic methods, are shown in table 1. Five studies validated the Manning criteria, two studies the Rome I criteria, and one study the Rome II and Rome III criteria. Two studies validated the same 10-biomarker algorithm in diagnosing IBS. One of these studies also added 24 biomarkers to the original 10-biomarker panel, and also combined this new 34-biomarker panel with measures of psychological affect. This same study also used psychological markers alone. One study used faecal volatile organic metabolites (VOMs), chemicals that are released in faeces. Finally, four studies validated the Kruis statistical model.

Table 1- Positive and Negative LRs of Diagnostic Methods for IBS
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Diagnostic Method	Number of studies	Number of participants	Positive LRs (95% CI)	Negative LRs (95% CI)
Manning	5	2428	3.04 (1.88, 4.90)	0.33 (0.18, 0.60)
Rome I	2	2468	3.86 (3.00, 3.53)	0.14 (0.01, 1.52)
Rome II	1	1848	3.19 (2.92, 3.48)	0.14 (0.10, 0.19)
Rome III	1	1848	3.35 (2.97, 3.79)	0.39 (0.34, 0.46)
10-biomarker panel	2	760	3.03 (1.48, 6.23)	0.52 (0.43, 0.64)
34-biomarker panel	1	244	2.28 (1.67, 3.11)	0.30 (0.21, 0.42)
Faecal VOMs	1	140	22.00 (8.27, 58.50)	0.21 (0.10, 0.42)
Psychological markers	1	760	2.95 (1.98, 4.40)	0.35 (0.26, 0.46)
Biomarkers and psychological markers	1	760	8.63 (2.89, 25.80)	0.18 (0.12, 0.25)
Kruis statistical model	4	1171	7.14 (3.85, 13.23)	0.26 (0.17, 0.41)

CONCLUSION: Available symptom-based diagnostic criteria for IBS perform modestly, and with striking similarity. Serum biomarkers are disappointing, given their potentially expensive nature. Faecal VOMs appear promising but warrant replication in other studies. The superior performance of a combination of biomarkers and psychological markers, and the Kruis statistical model, over symptom-based diagnostic criteria perhaps suggests the future of IBS diagnostics lies in combining demographic data, gender, symptoms, biomarkers, and psychological markers. However, this may come at the price of increasing complexity.
Disclosure of Interest: None declared

OP396 PHENOTYPING PATIENTS WITH IRRITABLE BOWEL SYNDROME WITH DIARRHOEA (IBS-D): MECHANISTIC STUDY LOOKING AT STOOL CALPROTECTIN AND GENE EXPRESSION IN COLON BIOPSIES

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INTRODUCTION: Irritable bowel syndrome is a heterogeneous condition with multiple factors leading to the symptoms of IBS such as stress, infection and diet. Recent demonstration of 'immune activation' in the gut has prompted trials of 5-aminosalicylates; however identifying the phenotype of who will respond remains elusive.
AIMS & METHODS: Our previous multicentre study[1] showed Mesalazine (M) was not effective in unselected IBS-D patients. Here we report the value of a number of biomarkers collected in this same trial in an attempt to identify ''responders''. Stool samples and sigmoid biopsies were collected at baseline and 12 weeks later at the end of study from IBS-D patients and were randomised into either M or placebo(P) to be taken for 12 weeks in Nottingham. Group 1:53 pairs of stool samples were obtained. Stool calprotectin (SCal) was analysed by using a commercial Elisa kit. High level of SCal level is defined as ≥100 ug/ml. Group 2:43 pairs of sigmoid biopsies obtained. These samples were compared with biopsies obtained from 21 healthy volunteers(HV). Gene expressions were analysed by mRNA quantification via 2 step reverse transcription quantitative polymerase chain reaction technique. Relative expression levels for each mRNA were calculated using mean Ct values of 4 mRNA endogenous genes.
RESULTS: [Mean (SD)] Group 1: SCal levels did not improve with M[mean difference(md)=-12.16 (82.69);p=0.43] when compared to P[md=0.10 (87.05); p=0.73]. Baseline SCal negatively correlated with anxiety score (Spearman r=-0.28;p=0.04). There was no correlation between baseline SCal with clinical symptoms such as abdominal pain severity, urgency, bloating, stool frequency or stool consistency. When Scal were divided into 2 subgroups of high and low levels, the total hospital and anxiety (HAD) scores in the high SCal group [5.7(3.5)] were significantly lower than the low SCal group [8.6 (4.4)];p=0.03 however there were no significant differences in abdominal pain severity, average stool frequency or stool consistency. Group 2: Toll-like receptor 4(TLR-4) and myeloid differentiation primary response 88(MYD88) mRNA were both elevated compared to HV. Quantity mRNA (mRNAq) for TLR-4 in HV vs IBS-D were 0.75(0.42) and 1.96(0.86);p=<0.01. When treated with M, TLR-4 levels showed significant reduction [md=-0.29(0.68) compared to P group [md=0.22(0.78)];p=0.03. There was no correlation between TLR-4 and SCal (Spearman r=0.17; p=0.26). mRNAq for MYD88 was significantly higher in IBS-D vs HV being 1.12(0.42) vs 0.63(0.25); p<0.01. Treatment with M did not alter MYD88 levels [md=0.03(0.37)] compared to placebo [md=0.12(0.39)]; p=0.43.
CONCLUSION: A small cohort of IBS-D patients demonstrated patients with low SCal are more anxious and depressed that those with high SCal suggesting their symptoms may be centrally rather than driven by changes in the gastrointestinal tract. Elevated gene expression in TLR-4 and MYD88 could be a feature in a small subgroup of IBS-D patients where symptoms are driven peripherally by mucosal/microbiome interactions. Further larger studies are needed to confirm this.
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Disclosure of Interest: C. Lam: None declared, M. Lingaya: None declared, Y. Falcone: None declared, A. Bennett: None declared, R. Spiller Financial support for research from: Grants from Lesaffre and Ironwoom, Consultancy for: Almirall, Astellas, Danone, Sanofi, Other: Free drug from Norgine

OP397 THE ODDS OF GASTROESOPHAGEAL REFLUX SYMPTOMS INCREASE BY 35% PER DECADE IN A 23 YEAR PROSPECTIVE, LONGITUDINAL STUDY

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INTRODUCTION: The assumption that the prevalence of gastroesophageal reflux symptoms (GERS) increase with time needs to be confirmed in prospective studies of the general population.
AIMS & METHODS: By means of a validated questionnaire on gastrointestinal symptom (the Abdominal Symptom Questionnaire, ASQ) an adult population was surveyed 4 times over 23 years: 1988 (n=1156, 21-79 years of age (yoa) response rate of original number approached (rr) 90%), 1989 (n=1097, 22-80 yoa, rr 87%), 1995 (n=1139, 20-87 yoa, rr 82%) and 2011 (n=1175, 20 yoa and above, rr 64%). Altogether 490 persons participated in all four surveys.
The effect of time on GERS prevalence was calculated using random effects logistic regression models using GERS as the dependent variable and gender, age and time as independent variables. All participants in all surveys are included in the analyses (1847 participants, 4466 observations).
RESULTS: GERS increased significantly with time, the odds of reporting reflux increasing by 35% per decade (OR:1.34; 95%CI: 1.18-1.53, p<.001) independent of gender and age. This increase was driven by an increase in heartburn (OR:1.53; 95%CI: 1.35-1.73, p<.001) and in acid regurgitation (OR:1.30, 95%CI: 1.14-1.47, p<.001).
In this 23 year prospective longitudinal study on an adult population, the odds of GERS has increased by 35% per decade. On an individual basis, there is a large symptom turnover both within a year and over longer periods, reflecting the natural history of GERS.
Table. Prevalence and turnover of GERS in participants completing all surveys (N=490)

	Prevalence GERS			Loss from GERS to non-GERS		Gain from non-GERS to GERS	
Year	N	%	Year	N/N GERS	%	N/N non-GERS	%
1988	86	17.7 (14.5-21.4)	1988-1989	31/86	36.1	36/404	8.9
1989	91	18.6 (15.2-22.3)	1989-1995	29/91	31.9	36/399	9.0
1995	98	20.0 (16.5-23.8)	1995-2011	53/98	54.1	59/392	15.1
2011	104	21.2 (17.7-25.1)					

CONCLUSION: In this 23 year prospective longitudinal study on an adult population, the odds of GERS has increased by 35% per decade. On an individual basis, there is a large symptom turnover both within a year and over longer periods, reflecting the natural history of GERS.
Disclosure of Interest: None declared

OP398 DISCREPANCIES BETWEEN UPPER GI SYMPTOMS DESCRIBED BY THOSE WHO HAVE THEM AND THEIR IDENTIFICATION BY CONVENTIONAL MEDICAL TERMINOLOGY: A SURVEY IN FOUR COUNTRIES

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INTRODUCTION: Modern self-administered questionnaires assessing upper GI symptoms are usually designed by reconciling the descriptive vocabulary used by symptomatic individuals with conventional medical terminology for symptoms (e.g. heartburn, regurgitation, epigastric discomfort etc.). It is often assumed that the conventional medical vocabulary is able to identify the symptoms adequately.
AIMS & METHODS: We aimed to develop a self-administered questionnaire for upper GI symptoms based on lay vocabulary without imposition of medical concepts or terminology for use in a large survey of symptom occurrence among sufferers in 4 countries.
The questionnaire was designed by integrating symptom descriptions used by 38 symptomatic adults in Brazil, Russia, UK and USA. The resulting questionnaire, in the appropriate language, was distributed on-line daily for 6 weeks to individuals experiencing upper GI symptoms in the 4 countries. Detailed information was sought on up to 7 symptom episodes occurring on different days, identifying the nature, severity, timing and duration of the predominant symptom on each occasion together with other symptoms experienced concurrently. They were also asked what term they would use to describe their symptoms to a friend or a doctor.
RESULTS: The questionnaire development identified and described 9 symptoms using non-medical vocabulary. They occurred with a frequency of 24 – 61 % in 2665 survey respondents who reported on 10,659 symptom episodes. One of the symptoms appeared to correspond with regurgitation while two distinct symptoms (experienced by 28% and 34% of subjects) possibly corresponded with heartburn. However, 58% of individuals who reported these two concurrently on some occasions reported one being present without the other on other

occasions. Five 'stomach' or abdominal symptoms were recognised and distinguished and there was one chest symptom, reported by about 30% of subjects in all 4 countries, for which a corresponding medical term was uncertain. Statistically significant differences in occurrence and severity of some symptoms were evident between countries, between genders and between age groups. Both the predominant symptom and the pattern of concurrent symptoms often varied from one symptom episode to another. Respondents' use of the terms heartburn, reflux, regurgitation, 'burning stomach' and indigestion to describe their symptoms to a friend or doctor varied considerably between countries.
CONCLUSION: Discrepancies between the symptoms described by those who suffer them and the way in which they can be described by conventional medical terminology were evident in all four countries. These discrepancies deserve more attention with a view to identifying the limitations of current upper GI symptom enquiry and developing validated questionnaires, possibly derived solely from the vocabulary of individuals suffering the symptoms, which will improve symptom identification and assessment.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 14:00–15:30
INNOVATIONS IN BILIARY STENTING – HALL N

OP399 METALLIC VS. PLASTIC STENT IN THE PREOPERATIVE TREATMENT FOR BILIARY OBSTRUCTION OF RESECTABLE PERIAMPULLARY TUMOURS: A RANDOMIZED CONTROLLED TRIAL

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INTRODUCTION: The fully covered self-expanding metal stents (SEMSc) could be a cost-safe alternative instead of plastic stents (PS) for preoperative endoscopic drainage of resectable periampullary tumours.
AIMS & METHODS: To compare the safety and costs of SEMSc vs. PS in the preoperative endoscopic drainage for biliary obstruction due to periampullary tumours potentially resectable with curative intent.
Method: Open label randomized controlled trial. **Participants:** Patients with malignant biliary obstruction caused by resectable periampullary tumours. Inclusion criteria: total bilirubin >15 mg/dl, unable to operate in <10 days, to pass guidewire through biliary obstruction in ERCP. **Intervention:** We randomly assigned patients to receive either a SEMSc (Wallflex®) or a PS (Flexima®). **Main outcome measures**: Complications related to stent type during the stent-surgery interval. **Secondary outcomes measures**: Number of admissions and hospitalization days in preoperative period, re-intervention requirement (additional ERCP and others), direct costs, surgical difficulties attributable to stent, surgical and postsurgical complications.
RESULTS: We included 63 patients. Age: 68.03±8.5 y; 42 men. There were 35 pancreatic tumours, 11 cholangiocarcinomas and 17 ampullary carcinomas. Were placed 35 SEMSc and 28 PS. 13 patients were finally ruled out to surgery. Regarding intention-to-tread there were 3/35 (8.6%) preoperative complications in SEMSc group and 10/28 (35.7%) in PS group (p=0.012), while per protocol there were 1/26 (3.8%) in SEMSc group and 9/24 (37.5%) in PS group (p=0.004). Stent-surgery interval (days): SEMSc group = 37.5; PS group = 37; p=0.9. Hospitalization days during the stent-surgery interval: SEMSc group: 0.2±1.0; PS group: 2.7±4.7; p=0.011. In SEMSc group were necessary additional interventions in 8.6% of patients and in PS group in 25%; p=0.077. The average direct costs were lesser in SEMSc group than PS group 1486±129 vs. 2117±643€; p=0.34. It was done a resected surgery in 38 patients while in 12, only a bypass procedure without differences between both groups. In SEMSc group there were anatomical disorders in the hepatic hilum attributable to stent in 42.3 % of patients and in 25% in PS group, although these disorders did not difficult the surgery. There were not differences, neither in surgical and postsurgical complications (follow-up by 1 month post discharge) nor in hospitalization days at ICU or in the number of deaths.
CONCLUSION: The SEMSc showed lower complication rate, lesser hospitalization days and re-interventions during preoperative period without increase of costs. We consider that SEMSc should be the first option for preoperative endoscopic drainage of resectable periampullary tumours.
Disclosure of Interest: None declared

OP400 THE COSTS OF PLASTIC STENT FAILURE IN MALIGNANT JAUNDICE

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INTRODUCTION: Metal biliary stents have better patency rates than plastic stents, but cost substantially more. A current European guideline recommends that plastic stents are used where expected survival from malignant disease with biliary obstruction is less than 4 months[1]. This is a subjective judgement that is difficult to apply in clinical practice. We retrospectively reviewed the performance of biliary stents placed at endoscopic retrograde cholangiopancreatography (ERCP) to determine the full healthcare costs of stent failure. We then performed a cost comparison of the two stent types in patient subgroups.
AIMS & METHODS: We reviewed all ERCPs performed at Colchester General Hospital from January 2008 to December 2010 and identified cases where a patient received a stent for malignant biliary obstruction for the first time. We then collected data on (i) tumour size and presence of metastases on computed tomography (CT) at diagnosis, (ii) subsequent ERCPs, (iii) subsequent hospital admissions for biliary problems and (iv) survival. Using costings provided by the hospital finance department, we assessed the total cost of failure of plastic stents. Using costings provided by our supplier of metal stents we then performed a comparison of the cost implications of metal and plastic stents for different patient groups. This analysis was based on the prediction derived from meta-analysis that the metal stent failure rate is 52% of the plastic stent failure rate[2].
RESULTS: 111 patients received a 1st plastic stent, of which 11 later had surgery, leaving 100 cases where plastic stents were used for palliation alone. All these patients have now died. 82 had successful relief of jaundice but the success rate for Klatskin tumours was only 5/11. In 77 cases no further biliary intervention was required. The remaining 23 patients had 38 subsequent biliary problems, requiring 27 admissions (totalling 403 days) and 33 further ERCPs. In the table actual costs after plastic stenting per patient are compared with predicted costs had a metal stent been used instead.

PATIENT SUBGROUP	n	Median survival (days)	Total costs with plastic stent	Total costs with metal stent
KLATSKIN	11	21	£1717.45	*Not applicable*
METASTATIC	37	62	£689.16	*£857.92*
TUMOUR > 2CM	26	62	£281.12	*£645.74*
TUMOUR < 2CM	8	238.5	£1126.50	*£1085.34*
TUMOUR NOT SEEN	15	258	£2160.27	*£1622.90*
OTHER	3	No CT performed		
TOTAL	100	74.5	£934.07	*£985.28*

CONCLUSION: Metal stents should be used for patients with small tumours (less than or equal to 2cm) with no metastases. Plastic stents remain the lower cost option for larger tumours and metastatic disease.
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Disclosure of Interest: None declared

OP401 MULTIPLE PLASTIC STENTS OR FULLY COVERED SELF-EXPANDABLE METAL STENTS FOR ENDOSCOPIC MANAGEMENT OF REFRACTORY BILIARY LEAKS?

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INTRODUCTION: Endoscopic management of postcholecystectomy biliary leaks is widely accepted as the treatment of choice. However refractory biliary leaks after combination of biliary sphincterotomy and placement of a large-bore (10-French) plastic stent can occur and the optimal rescue endotherapy for this situation is unclear.
AIMS & METHODS: We compared the clinical effectiveness of 2 types of endotherapy: use of a Fully covered self-expandable metal stent (FCSEMS) or placement of multiple plastic stents (MPS) for the treatment of postcholecystectomy refractory biliary leaks. This study prospectively evaluated 2 groups of 40 consecutive patients with refractory biliary leaks who underwent temporary placement of either multiple plastic stents (n=20) or FCSEMSs (n=20). Data were collected to analyze the clinical outcome of endotherapy as well as technical success, adverse events, need for reinterventions and prognostic factor for clinical success.
RESULTS: Endotherapy was possible in all patients. At the end of endotherapy closure of the leak was obtained in 13 patients (65%) submitted to placement of MPS and in 20 patients (100%) submitted to the use of FCSEMS respectively (P=0.004). The Kaplan-Meier (log-rank) leak-free survival analyze showed a statistically significant difference between the two patient populations ($\chi 2(1)=8.30$; $P<0.01$) in favor of the FCSEMS group. A number of plastic stents less than 3 (P=0.015), a plastic stent diameter below 20 French (P=0.006) and a high-grade biliary leak (P=0.004) proved to be significant predictors of treatment failure with MPS. The 7 patients in whom placement of MPS failed were retreated with a FCSEMS with closure of the leak in all cases.
CONCLUSION: Temporary placement of a FCSEMS in postcholecystectomy refractory biliary leaks is the treatment of choice and has a high success rate.
Disclosure of Interest: None declared

OP402 MULTICENTRE COMPARATIVE EVALUATION OF ENDOSCOPIC PLACEMENT OF EXPANDABLE METAL STENTS FOR MALIGNANT DISTAL CBD OBSTRUCTION BY ERCP OR EUS-GUIDED APPROACH IN PATIENTS WITH OR WITHOUT DUODENAL STENOSIS

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INTRODUCTION: ERCP is the procedure of choice for relief of jaundice due to distal malignant biliary obstruction. However ERCP may fail in up to 10% patients. A single session EUS-guided biliary drainage (EUS-BD) can be performed in patients with or without duodenal stensosis (DS). There is no study comparing results of EUS-BD and ERCP for relief of distal malignant biliary obstruction.
AIMS & METHODS: To compare the outcome of self-expandable metallic stent (SEMS) placement for malignant distal biliary obstruction by ERCP or EUS-BD. Patients with malignant distal CBD obstruction, who failed a previous ERCP, formed the EUS-BD group (choledocho-duodenostomy (CDS) and antegrade (AG) procedures). Data for ERCP group was collected from consecutive patients at one center (Mumbai).
RESULTS: There were 117 patients in the ERCP group and 98 patients in EUS-BD (67 CDS, 31 AG). SEMS placement was successful in 113 patients in ERCP and 93 patients in EUS-BD group (96.6% vs.94.8%, p=0.734). The complication rates in the ERCP and EUS-BD group were 5.1%, and 9.1% respectively (p=0.285). The ERCP group had 5 pancreatitis, compared to none in the EUS-BD group (p=0.065). The mean procedure time in ERCP and EUS-BD group was not significantly different (30.10 and 35.95 minutes, p=0.052). There was no significant difference in the success rate, complications, and mean procedure time between CDS and AG procedures. The success rate of EUS-BD was significantly higher (p=0.0001) in patients with type II DS.
CONCLUSION: In patients with malignant distal bile duct obstruction requiring SEMS placement, the short-term outcome of EUS-BD is comparable to ERCP in patients with normal duodenum, and those with type I DS. EUS-BD has significantly superior success rate than ERCP in patients with type II DS.
Disclosure of Interest: None declared

OP403 QUALITY OF LIFE AFTER STENT PLACEMENT FOR PALLIATION OF COMMON BILE DUCT OBSTRUCTION: A RANDOMIZED CONTROLLED TRIAL COMPARING PLASTIC AND METAL STENTS

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INTRODUCTION: Endoscopic stent placement is the procedure of choice for palliation of common bile duct (CBD) obstruction. It is known that self-expandable metals stents (SEMS) are superior to plastic stents in terms of stent patency and occurrence of stent dysfunction. However, it is unknown whether this also translates in improved quality of life (QoL) in patients with SEMS.
AIMS & METHODS: Our aim was to compare QoL between patients treated with a plastic stent or SEMS for the palliation of CBD obstruction. We performed a randomized multicentre trial in 18 hospitals with 219 patients randomized to plastic stent (n=73) or SEMS (n=146) placement. QoL was assessed with two general questionnaires (EQ-5D-5L with visual analogue scale (VAS) and QLQ-C30) and one disease specific questionnaire (PAN-26). Questionnaires were filled out before treatment, 14 days and 1-6 months after treatment. We compared QoL scores using linear mixed model analyses and included all patients with baseline and at least one follow-up measurement. Quality-adjusted life months (QALMs) were calculated using EQ-5D utilities.
RESULTS: Baseline questionnaires and at least one follow-up measurement were available in 140/219 patients (64%), 71 patients (32%) declined participation and in 8 patients (4%) only baseline questionnaires were available. In patients with QoL data, significantly more patients had a SEMS (42% vs. 29%, p=0.05), a second stent placement (26% vs. 14%, p=0.04) and metastatic disease (59% vs. 39%, p=0.005). Baseline characteristics from the patients that QoL data were the same for patients with a plastic stent or SEMS. The mean functional stent time was significantly longer in the SEMS group (289 days, 95% CI 258-320) compared to the plastic stent group (148 days, 95% CI 101-196, p<0.005). Survival was not different between the two stent groups with an overall mean survival of 158 days (95% CI 136-178). On the QLQ-C30, the interaction between follow-up time and type of stent was significantly different on two of five functional scales (physical functioning (p=0.004) and emotional functioning (p=0.01)) in favor of patients with a SEMS. Strong trends in favor of SEMS were seen in global health (p=0.09), EQ-VAS (p=0.08), role functioning (p=0.096) and cognitive functioning scales (p=0.07). EQ-VAS scores significantly decreased in time in both treatment groups. On all other scales scores of the SEMS group remained stable and decreased in the plastic stent group. On the PAN-26 a reduction of hepatic symptoms was seen in both groups during the first month after stent placement with no significant difference between the groups (p=0.13). After 1 month, the score for hepatic symptoms remained stable in the SEMS group, while in the plastic stent group there was a trend towards an increase of symptoms (p=0.09). Digestive symptoms significantly increased in both groups, with a significant stronger increase in the plastic stent group (p=0.003). Mean QALMs were 2.13 in patients with a plastic stent and 2.47 in patients with SEMS (p=0.52).
CONCLUSION: In patients with malignant extrahepatic bile duct obstruction SEMS placement results in better scores on both general- and disease specific HRQoL scales over time compared to plastic stent placement. In addition, the number of QALMs was higher in the SEMS group, although this difference was not statistically significant.
Disclosure of Interest: D. Walter: None declared, P. Siersema Financial support for research from: Boston Scientific, USA, Consultancy for: Boston Scientific, USA, F. Vleggaar: None declared

OP404 IN VIVO ENDOSCOPIC BILIARY IN-STENT PHOTODYNAMIC THERAPY USING POLYMERIC PHOTOSENSITIZER-EMBEDDED MEMBRANE-COVERED METAL STENT IN A SWINE MODEL

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INTRODUCTION: The photodynamic therapy (PDT) which has been used for palliative treatment of cholangiocarcinoma, has some limitations and drawbacks in clinical application.
We developed a polymeric photosensitizer-embedded membrane-covered metal stent (PDT-stent), and performed *in vitro* release test and *in vivo* animal experiment of photodynamic activities against xenografted tumor.
AIMS & METHODS: The aim of this study is to estimate the safety, efficacy and photosensitizer stability of the switch on and off and repeated endobiliary in-stent PDT using PDT-stent in swine model. Single session of endoscopic biliary in-stent PDT was performed with various energy amount of laser (670 nm; 40, 70, 100, and 150 J/cm^2) after the insertion of PDT-stent in the common bile duct (CBD) of twelve mini pigs to determine proper energy level of laser for PDT. Two days later, all the animals were euthanized and bile ducts were extracted for the pathologic examination. And 3 or 5 sessions of endoscopic biliary in-stent PDT with 70 J/cm^2 of light energy, and cholangiogram were repeated at 2-week intervals over a period of 4 weeks or 8 weeks after PDT-stent insertion in 6 swine to assess the safety and photosensitizer stability of repeated PDT. Then the bile ducts and the inserted stent of all the animals were obtained after two days for pathologic analysis and quantification of fluorescence intensity (FI) for Pheoporbide A (Pheo-A) remained from PDT-stent.
RESULTS: There was no evidence of bile duct perforation in all animals on follow up cholangiograms after single or repeated biliary PDT. Repeated PDT with fixed energy level, 70 J, caused only surface mucosal necrosis in all animals and the degree of inflammation was constant irrespective of number of PDT session. The FI of Pheo-A from PDT-stent was reduced to 50 and 60% of baseline FI for 100 and 150 J/cm^2 group, respectively after single session of PDT. After 3 or 5 sessions of PDT at 2-week intervals over a period of 4 weeks or 8 weeks with 70 J/cm^2, the FI of PDT-stents observed to be similar to that of the PDT-stent before laser irradiation.
CONCLUSION: Endoscopic biliary PDT using the PDT-stent was safe, effective, and repeatable over a period of 8 weeks for the treatment of cholangiocarcinoma.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 14:00–15:30
EOSINOPHILIC OESOPHAGITIS AND OTHER IMMUNE MEDIATED UPPER GI DISEASES – HALL O

OP405 DEVELOPMENT OF A SYMPTOM-BASED ACTIVITY INDEX FOR EOSINOPHILIC ESOPHAGITIS

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INTRODUCTION: Instruments assessing disease activity in adult patients with eosinophilic esophagitis (EoE) are urgently needed to provide endpoints for clinical trials and for disease monitoring in observational studies. The international Eosinophilic Esophagitis Activity Index (EEsAI) study group developed 3 instruments to assess clinical, endoscopic, and histologic activity of EoE. The clinical activity was assessed by the means of patient-reported outcomes (PRO) instrument.
AIMS & METHODS: We aimed to develop a PRO instrument and score based on the items that best explain the variability in patient global assessment of EoE severity (PatGA) (on a Likert scale from 0 to 10). To assess whether endoscopic and histologic findings help to explain the variability in PatGA. The EEsAI PRO instrument assesses, among others, dysphagia characteristics, including dysphagia due to foods with 8 distinct consistencies, the time needed to eat a meal, and behavioral adaptations to dysphagia, such as food modification and avoidance.

Patient input for item generation was gained using a mixed methods approach, involving psychologist-guided focus group interviews, individual patient cognitive interviews, and patient questionnaires using open-ended questions. Physician input by Delphi rounds was used to develop the hypothetical framework. Patients were asked to recall symptoms and behavioral adaptations over the previous 24 hour-, 7 day-, and 30 day-periods. Linear regression and analysis of variance (ANOVA) was used to evaluate the extent to which variations in patient-reported disease characteristics explain the variability in PatGA. ANOVA was used to examine the extent to which variations in endoscopic, histologic and laboratory parameters help to explain the variability in PatGA over and above PRO items.
RESULTS: The PRO instrument was evaluated in 153 adult EoE patients (72.5 % males, median age 38 years) recruited in Switzerland and in the United States. A recall period of 7 days was best suited to measure EoE severity. The following 7 PRO items explained 67 % of the total variability in PatGA: frequency of dysphagia, duration of dysphagia, swallowing-associated pain, the visual dysphagia questionnaire (VDQ©, 1 item), food avoidance, modification and slow eating. The VDQ© assesses dysphagia in the context of consuming foods of 8 different consistencies. The EEsAI PRO score ranges from 0 to 100. Addition of endoscopic and histologic features into the model explained only an additional 4 % of the PatGA.
CONCLUSION: Seven PRO items can be used to assess clinical EoE symptom severity over a 7-day recall period. Endoscopic and histologic features contributed negligibly over and above PRO items. The validity of the current PRO score is currently being tested in a second independent patient group.
Disclosure of Interest: None declared

OP406 A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED, EUROPEAN MULTICENTRE TRIAL OF TWO NEW BUDESONIDE FORMULATIONS FOR TREATMENT OF ACTIVE EOSINOPHILIC ESOPHAGITIS

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INTRODUCTION: Swallowed topical corticosteroids have been shown effective in the treatment of Eosinophilic Esophagitis (EoE), but so far no approved therapy with an esophageal-adjusted formulation including an optimal dosing is available.
AIMS & METHODS: To evaluate the efficacy and safety of two different budesonide formulations (effervescent tablet [BET] and viscous suspension [BVS]) and two different doses for short-term treatment of EoE.
Adults with active EoE (n=76) randomly received 14-days treatment with either BET 2x1mg/d (BET1, n=19) or BET 2x2mg/d (BET2, n=19), or BVS 2x2mg/d (BVS, n=19) or placebo (n=19) in a double-blind, double-dummy fashion, with a 2-week follow-up. Primary endpoint was histological remission (mean of <16 eos/mm^2 hpf). Secondary endpoints included endoscopy score, dysphagia score, and preference of drug formulation.
RESULTS: Histological remission occurred in 100%, 93.8%, and 93.3% of budesonide (BET1, BET2, BVS, respectively) and in 0% of placebo recipients ($p<0.0001$). The improvement in total endoscopic intensity score was significantly higher in the 3 budesonide groups compared with placebo. Dysphagia improved in all groups at the end of treatment. The improvement persisted during the 2-weeks follow-up only in those treated with BET1 and BET2, with BET1 showing a significant difference to placebo ($p=0.0196$). There was suspected local fungal infection in 3 patients in each of the three budesonide groups. However, in a *post-hoc* histopathology analysis hyphae were only found in 2 patients in each of the budesonide groups. Neither serious adverse events nor clinically relevant changes in plasma cortisol were observed. 80% of patients preferred the effervescent tablet.
CONCLUSION: Budesonide administered as effervescent tablet or as viscous suspension was highly effective and safe for short-term treatment of EoE. The 1mg BID dose was equally effective as the 2mg BID dose. The majority of patients preferred the effervescent tablet formulation.
The first two authors contributed equally to the first authorship
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OP407 EFFECTS OF DIETARY TREATMENT OVER THE MAST CELL POPULATIONS AND GENE EXPRESSION IN ESOPHAGEAL MUCOSA OF ADULTS WITH EOSINOPHILIC ESOPHAGITIS

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INTRODUCTION: Mast cells (MC) are increased in the inflammatory infiltration which characterizes eosinophilic esophagitis (EoE). However, MC nature and changes after dietary treatment have been not assessed.
AIMS & METHODS: To characterize MC population in the esophageal mucosa of adult EoE patients by analysing MC-related gene expression and immunohistochemistry, define its chemotactic factors, and evaluate changes induced after dietary treatment. Esophageal mucosal samples from 10 consecutive adult EoE patients obtained before and after 6 weeks of treatment with an empiric six-food elimination diet (SFED) and from 10 control subjects were analyzed. qPCR and immunohistochemistry were used to analyze the expression levels of MC-related proteases (CPA3, CMA & TPSB2) and to define MC-types densities. Changes in gene expression of chemoattractants for eosinophils (eotaxins) and MC (SCF & TGF-β) and their receptors (CCR3 & c-KIT) were assessed.
RESULTS: The mean density of esophageal MC was significantly increased in EoE regarding to controls, and decreased after diet (from 18.6 to 1.44 cells/hpf; $p<0.001$). The 90% of MC observed in the inflammatory infiltrate in EoE patients were MC_{TC} subtype, and only 10% was MC_T subtype. Atopic background of patients did not associate with differences in MC counts or gene expression levels. Genes of most chemotactic factors for MC and its receptors were upregulated in EoE patients compared to controls (Table), and significantly downregulated after a SFED; however, TGF-β and c-KIT remained unchanged after diet. Statistically significant relationships (Spearman Rho) between gene expression levels and epithelial MC counts were documented in EoE samples. Peak MC significantly correlated with pick eosinophil count in baseline EoE samples (rho=0.808) and with symptoms score (rho=0.782). **Table**: Genes analized, fold changes in active EoE and p values compared to controls.

CCL11	8.5	0.008	SCF	5.6	0.003
CCL24	12.2	0.001	TGF-β	-	0.740
CCL26	51.1	0.002	c-KIT	3.7	0.002
CCR3	3.7	0.039	CPA3	3.2	0.011
CMA	3.2	0.049	TPSB2	1.7	0.025

CONCLUSION: MC_{TC} subtype was the predominant in the inflammatory infiltrate of EoE patients. MC densities correlated with eosinophil counts and symptoms. Dietary treatment significantly reduced gene expression of MC-related proteases and chemotactic factors.
Disclosure of Interest: None declared

OP408 EMPIRIC FOUR-FOOD ELIMINATION DIET FOLLOWED BY RESCUE SIX-FOOD ELIMINATION DIET FOR ADULT EOSINOPHILIC ESOPHAGITIS: A PROSPECTIVE MULTICENTER STUDY

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INTRODUCTION: Eosinophilic oesophagitis (EoE) is an esophageal disorder predominantly triggered by food antigens. A six-food elimination diet (SFED) achieves remission in over 70% of adult EoE patients. After individual food reintroduction, just one or two food triggers for EoE can be identified in 65%$>$85% of patients, so some dietary restrictions and endoscopies after food challenge may be unnecessary.
AIMS & METHODS: We aimed to evaluate the efficacy of a four-food elimination diet (FFED) (dairy products, wheat, egg and legumes) for adult EoE patients. Prospective multicenter study. All patients were re-evaluated after 6 weeks on a FFED. Response to FFED was defined by clinical and histological (<15 eos/HPF) remission. Responders underwent reintroduction of each individual food over 6 weeks followed by endoscopy and esophageal biopsies. Nonresponders were offered a rescue SFED.
RESULTS: 52 adult patients were included, of whom 12 patients (23%) had previous failure to topical steroid therapy. 28/52 patients (54%) achieved clinicopathological remission on FFED and 6/19 (31%) nonresponders to FFED were successfully rescued with SFED. 22/28 responders to FFED (78%) finished the individual food reintroduction challenge. Milk was identified as an EoE trigger in 11 patients (50%), egg in 8 (36%), wheat in 7 (31%) and legumes in 4 (18%). All patients had just 1 or 2 food triggers, being milk the only causative food in 27% of patients.
CONCLUSION: A FFED achieved clinico-pathologic remission in 54% of adult EoE patients. SFED was effective in almost a third of FFED nonresponders, coming to a combined efficacy of both strategies of 72%.
Disclosure of Interest: None declared

OP409 TRANSGLUTAMINASE EXPRESSION AND COELIAC AUTOANTIBODY BINDING TO THE PANCREAS IN DIABETES MELLITUS

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INTRODUCTION: Coeliac disease and type-1 diabetes (T1DM) are often co-existing and share common genetic background. However, it is still a question whether coeliac disease can directly induce damage of the pancreas leading to beta cell loss and endocrine insufficiency. The aim of this study was to investigate if pancreas tissue is an autoantigenic target for coeliac anti-transglutaminase (TG2) antibodies *in vivo*.
AIMS & METHODS: Frozen pancreas and full thickness duodenum tissue specimens from cadaveric organ donors with T1DM (n=22), diabetes antibody positive subjects (n=11) and non-diabetic controls (n=21) were kindly provided by the Network of Pancreatic Organ Donors with Diabetes (nPOD). None of these subjects had a coeliac disease diagnosis during lifetime. The tissues were investigated for transglutaminase and glucagon expression, *in vivo*- bound celiac disease-related IgA antibodies, CD3 and gamma-delta T cell counts by immunohistochemistry in a blinded fashion without knowledge of the clinical details.
RESULTS: Pancreas specimens expressed abundantly TG2 around the islets and acinar structures corresponding to the reticulin network of the pancreas. Furthermore, TG2 was also present in vessel walls of islet capillaries. IgA class coeliac autoantibodies bound to TG2 were detected on the surface of TG2 in 5 of the diabetic pancreas specimens and in the corresponding duodenum samples within the mucosa and in the gut wall muscular layer endomysium. The presence of villous atrophy consistent with untreated coeliac disease was confirmed from H&E sections from the same subjects in 4 of these cases, all adults (one specimen being inadequately orientated). All control pancreas samples were negative for IgA deposition. One non-diabetic donor had slight endomysial positivity in the gut without villous antrophy and had no IgA in the pancreas.
CONCLUSION: Pancreas tissues express the transglutaminase 2 autoantigen important for coeliac disease pathology. Celiac antibodies bound to the pancreas may initiate inflammation and tissue damage leading to diabetes. A fraction of T1DM cases may be preventable by screening and treatment for coeliac disease at an early age.
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Acknowledgments: Network of Pancreatic Organ Donors with Diabetes, Juvenile Diabetes Research Foundation, TÁMOP 4.2.2.A-11/1/KONV-2012-0023, OTKA K101788.
Disclosure of Interest: None declared

OP410 TREATMENT WITH SOMATOSTATIN ANALOGUES OF RECURRENT TYPE I GASTRIC CARCINOID IN PATIENTS WITH AUTOIMMUNE CHRONIC ATROPHIC GASTRITIS

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INTRODUCTION: The treatment of type 1 gastric carcinoids (GC1) is still debated, in view of their usual benign behaviour.
AIMS & METHODS: To evaluate the outcome of patients with recurrent GC1 treated with somatostatin analogues (SSA).
From January 2000 to September 2013, among 111 patients with chronic autoimmune atrophic gastritis, 23 patients were diagnosed with GC1. After they had the GC endoscopically removed, they underwent regular clinical and endoscopic follow-up. Plasma chromogranin A (CgA) and gastrin levels were measured in all patients. Patients showing recurrent GC1 were treated with SSA until gastrin fell below 400 pg/mL and there was no endoscopic and histological evidence of GC1 anymore.
RESULTS: 12 patients (52%) showed GC1 recurrence and were treated with SSA for a median time of 13 months. At baseline, median gastrin and CgA levels were 719 pg/mL and 33 U/L, respectively and they decreased to 389 pg/mL (p=0.001) and 14 U/L (p=0.005), respectively, after a six-month period of treatment. In all but one patient, GC1 disappeared after a median treatment of 12 months. In one case it was necessary to extend the therapy for 32 months to get the carcinoid disappearance. After SSA discontinuation, 4 patients (36%) showed GC1 recurrence after a median of 19.5 months and they were successfully retreated with a schedule of 12 months on treatment alternated to 6 months off treatment.
CONCLUSION: This cohort study confirms that GC1 tend to recur. SSA, administered in cycles of 12 months, represent an effective treatment.
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Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 22, 2014 14:00–15:30
VIRAL HEPATITIS, CYTOKINES AND LIVER REGENERATION – LOUNGE 5

OP411 HBX DIRECTLY MEDIATES DEREGULATION OF SEVERAL LNCRNAS IDENTIFIED BY CHIP-SEQ EXPERIMENT

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INTRODUCTION: HBx regulatory protein is required for HBV cccDNA transcription/viral replication and contributes to HBV oncogenicity. HBx affects the epigenetic control of HBV viral chromatin, by preventing HDACs recruitment onto the cccDNA, as well as of cellular chromatin, by favouring the recruitment of acetyl-transferase on activated target genes and of DNMT3a on repressed genes. (Guerrieri et al. 2013). LncRNAs are broadly defined as endogenous cellular RNAs molecules longer than 200 nt capable to regulate gene expression at various levels, including chromatin modification, transcription and post-transcriptional processing. DLEU2 encodes a putative lncRNA, with one exon directly overlapping the first exon of the TRIM13 gene in the opposite orientation (Skoblov et al. 2006). Upregulation of specific DLEU2 splicing variants correlates with HCC (Garding et al. 2013). TRIM13 induces autophagy and increase ectopic levels of p53 (Tomar D et al, .2012).
AIMS & METHODS: Aim of this study was to indentify HBx role in the lncRNA regulation.
High-throughput sequencing of anti-HBx ChIP-enriched DNA fragments (ChIPSeq) was performed in HepG2 cells. Chromatin immunoprecipitated from mock, wt and HBx-mt monomeric linear full length HBV DNA cells was analysed by TaqMan real-time PCR using lncRNA specific primers. HBx target lncRNAs levels were assessed both by PCR and real-time RT-PCR.
RESULTS: ChIPSeq analysis of HBx chromatin recruitment revealed a specific binding to a large number of new and known target sequences. In particular HBx binds to 39 long non coding RNAs. Focusing on DLEU2 lncRNA, we demonstrated that HBx is able to deregulate its expression and the neighboring genes. We show that HBx can bind DLEU2 promoter and modifies its epigenetic status. Therefore, HBx occupancy results in a different DLEU2 splicing profile leading to down-regulation of hsa-mir-15 and hsa-mir-16, as previously published, but also to up-regulation of the antisense autophagic gene TRIM13. Selective degradation of DLEU2 RNA resulted in a reduced H4 acetylation on TRIM13 promoter and a ~50% reduction of TRIM13 expression in HBV replicating HepG2 cells. These results directly link DLEU2 RNA species with TRIM13 transcriptional regulation in the presence of HBx. In silico analysis indicates that DLEU2 RNA potentially binds HBx and using a RIP (RNA Immune Precipitation) approach we confirmed HBx-DLEU2 interaction. Finally we found that DLEU2 inactivation has a profound impact on pgRNA transcription, thus suggesting a functional relevance of the DLEU2-HBx interaction of HBV replication.
CONCLUSION: HBx is recruited to 39 lncRNA promoters. HBx binds to the DLEU2 promoter region and affects its epigenetic status and expression by inducing a different DLEU2 splicing profile. HBx also directly binds DLEU2 and affects HBV replication.
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Disclosure of Interest: None declared

OP412 MAPPING OF ACCURATE LOCATION FOR COMBINATION OF HEPATITIS B VIRUS X PROTEIN AND CYTOCHROME C OXIDASE III

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INTRODUCTION: Human hepatitis B virus (HBV) infection has been strongly associated with development of hepatocellular carcinoma(HCC). The mechanisms whereby HBV causes malignant transformation remain uncertain. Much of the evidence available supports a pathogenetic role for the product of the HBV x gene, the HBx. However, the molecular mechanisms underlying effects of HBx protein on transcription, cellular proliferation and transformation are only partially defined. As HBx has no ability to bind dsDNA, protein–protein interaction seems to be crucial for HBx function. Identification of cellular HBx -interactive proteins would provide insight into the mechanism of HBV cellular effects.
AIMS & METHODS: In previous study, we have screened a new HBx-interacting protein, cytochrome C oxidase subunit III(COXIII). The aim of this study is to map an accurate binding site in HBx protein with COXIII. Two fragments of

HBx mutants (X1 aa1-72; X2 aa1-117) were amplified by polymerase chain reaction (PCR) and inserted into pAS2-1 to reconstruct the mutant plasmids. PCR and gene sequencing were used to confirm the mutants fragments expressed in the plasmids. PCR showed the mutants fragments expressed in yeast cells and western blot testified the fusion proteins were translated correctly in yeast cells. Hybrid in solid medium and β–gal activity detection mapped the key domain for combination of HBx and COXIII. Coimmunoprecipitation was performed to confirmed specific interaction between HBx mutant proteins with COXIII.
RESULTS: Two mutant plasmids which contain HBx aa1-72 and aa1-117 were successfully constructed respectively. PCR and gene sequencing confirmed the two mutant fragments were inserted in the plasmids. PCR and Western blot proved the mutant genes expressed the mutant proteins correctly in yeast cells. Hybrid in solid medium and β–gal activity detection indicated the binding site of HBx with COXIII is located between aa72 to aa117. The specific interaction between HBxX2 protein and COXIII was verified by coimmunoprecipitation.
CONCLUSION: For the first time, it is reported aa72-117 of HBx are key binding peptides for combination of HBx with COXIII.
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Disclosure of Interest: None declared

OP413 HEPATITIS C NONSTRUCTURAL PROTEIN 3/4A DAMPENS INFLAMMATION AND CONTRIBUTES TO SLOW FIBROSIS PROGRESSION DURING CHRONIC LIVER INJURY IN MICE

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INTRODUCTION: Hepatitis C virus (HCV) primarily infects hepatocytes and the infected hepatocytes with ongoing inflammation appear to promote fibrogenesis. To date, the underlying mechanism of HCV-induced fibrogenesis remains unclear. The aim is therefore to understand the role of HCV non-structural protein (NS3/4A) in the disease progression.
AIMS & METHODS: We used HCV non-structural NS3/4A expressing transgenic mice (NS3/4A-Tg) to accomplish the aims of the study. Hepatic fibrosis was induced in wild-type and NS3/4A-Tg mice either by single injection of carbon tetrachloride (acute) or multiple injections for 4 or 8 weeks. Fibrotic parameters (collagen and HSC markers), inflammatory response (macrophages) and hepatocyte turnover (proliferation and apoptosis) were examined.
RESULTS: Hepatic expression of NS3/4A did not induce spontaneous liver damage. During acute liver injury and intermediate fibrosis (4 weeks), NS3/4A-Tg mice exhibited enhanced liver fibrogenesis. Surprisingly, reduced fibrosis was observed in NS3/4A-Tg during chronic liver fibrosis (8 weeks). No difference in inflammation and hepatocyte turnover was observed in 4 weeks fibrosis model, while decreased inflammation was observed in NS3/4A-Tg during chronic liver fibrosis. Interestingly, increase in M2 macrophages and increased hepatocyte proliferation (and decreased apoptosis) was found in NS3/4A transgenics during chronic liver fibrosis.
CONCLUSION: During early fibrogenesis, HCV induces liver damage. While during chronic liver fibrosis, HCV (or HCV NS3/4A) dampens inflammation and induces hepatocyte proliferation thereby contributing to slow fibrosis progression to promote its survival or persistence.
Disclosure of Interest: None declared

OP414 THE SYNTHETIC FXR AGONIST PX20606 ATTENUATES BACTERIAL TRANSLOCATION, INTESTINAL INFLAMMATION, AND REDUCES SPLANCHNIC BLOOD FLOW IN PORTAL HYPERTENSIVE MICE

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INTRODUCTION: The farnesoid X receptor (FXR) is expressed in liver and gut, and affects bile acid and lipid homeostasis. In addtion, FXR agonists have been shown to be antifibrotic and enteroprotective.
AIMS & METHODS: The aim of our study was to assess the effects of the non-steroidal FXR agonist PX20606 (PX) on hemodynamics, intestinal barrier and bacterial translocation in a portal hypertensive mouse model. Male C56/Bl6 mice underwent partial portal vein ligation (PPVL) or sham-operation (SO) and were treated with FXR agonist PX20606 (PX,10mg/kg/day, gavage) or vehicle (VEH=DMSO). Hemodynamic measurements were performed after 7 days of treatment including mean arterial pressure (MAP), heart rate (HR), portal pressure (PP) and superior mesenteric artery blood flow (SMABF). Genes involved in inflammatory response, antibacterial response, and innate immunity were assessed by RT-PCR RNA-array from ileum. Bacterial translocation was assessed by mesenteric lymph node culture and LBP-ELISA.
RESULTS: In the PPVL group, both portal hypertension (PP: 10.5±3.2 vs. 8.8±2.4mmHg, p=0.059) and splanchnic blood flow (SMABF: 0.177±0.031 vs. 0.110±0.003 mL/min/g; p=0.024) were reduced by PX treatment. HR and MAP were not affected by PX treatment in SO or PPVL animals. Positive lymph node cultures were observed in 60% of PPVL-VEH mice but reduced to 30% in PPVL-PX mice. LBP serum levels were non-significantly decreased in PPVL-PX vs. PPVL-VEH mice (20.3±6.9 vs. 27.3±12.1mg/mL; p=0.067). PPVL upregulated proinflammatory gene expression, while PX treatment suppressed selective pro-inflammatory genes (TLR2, TNF, IL-1, IL-6). However, genes involved in antibacterial defense (iNOS) were not suppressed upon FXR activation.
CONCLUSION: The FXR ligand PX20606 reduced splanchnic blood flow and portal pressure in PPVL mice. A reduction of bacterial translocation and a modified intestinal expression of proinflammatory and immunoregulatory mediators indicate beneficial non-hepatic/non-hemodynamic mechanisms of FXR agonism in portal hypertension.
Disclosure of Interest: None declared

OP415 LYMPHOCYTE SUBSETS AND CYTOKINES IN ASCITIC FLUID OF DECOMPENSATED CIRRHOTIC PATIENTS WITH AND WITHOUT SPONTANEOUS ASCITES INFECTION

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INTRODUCTION: Spontaneous bacterial peritonitis (SBP) is a frequently encountered and important complication of decompensated liver cirrhosis. The immune system plays an important role in the development or eradication of this infection. A number of compositional and functional alterations in immune system cells have been demonstrated in cirrhotic patients; however, there is a lack of knowledge about this issue in ascitic infections.
AIMS & METHODS: The aim of the present study was to evaluate lymphocyte subsets and levels of some ascitic and lymphocytic intracytoplasmic cytokines in decompensated cirrhotic patients with or without spontaneous bacterial peritonitis. This case-control study included 50 decompensated cirrhotic patients. Patients with ascitic polymorphonuclear leukocyte count ≥250/mm3 and/or positive ascitic bacterial cultures were classified as the 'patients group' (n=25, mean±SD of age was 57.84 ± 6.66 years). Patients with ascitic polymorphonuclear leukocyte count <250/mm3 and/or negative ascitic bacterial cultures were classified as the 'controls group' (n=25, mean±SD of age was 60.36 ± 6.51years). Comparison was made between the patients and controls groups for the following parameters: ascites leukocyte counts and differentiations; ascitic fluid protein; albumin levels and serum-ascites albumin gradients; flow cytometric detection of ascitic lymphocyte subsets (CD3, CD4, CD8, CD4/CD8 ratio, CD19, CD45) and ascitic cytokine TNF-alpha.
RESULTS: Ascitic total protein and albumin levels were significantly decreased in patients group. The CD4, CD19, CD45 and CD4/CD8 ratio were significantly decreased in the patients group. Furthermore, ascites CD3, CD8 and TNF-α levels were significantly elevated in this group. The incidence of renal impairment, gastrointestinal bleeding and hepatic encephalopathy was higher in patients group and there was a significant correlation between TNF-alpha and renal impairment in this group.
CONCLUSION: These results suggest that a cytotoxic, especially Th1, immune response predominates in ascites infections. It also demonstrates that TNF-α might be involved in the pathogenesis of ascites infections.
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OP416 LGR5+ LIVER ORGANOIDS AS A MODEL TO STUDY POLYCYSTIC LIVER DISEASE

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INTRODUCTION: Liver stem cells are capable of expanding into LGR5+ organoids constituted of cholangiocytes. Important features of polycystic liver

disease (PLD) are increased cholangiocyte proliferation and fluid secretion, which can be suppressed by somatostatin analogues such as lanreotide. PLD is caused by mutations in genes such as *PRKCSH, SEC63, LRP5* and *PKD2*. There is no human *in vitro* model available that truly recapitulates polycystic liver disease. We hypothesize that PLD cholangiocytes can form LGR5+ liver organoids with aforementioned features of cyst development.

AIMS & METHODS: We aim: 1.) To isolate cholangiocytes from human cyst biliary epithelium and cyst fluid and expand these into LGR5+ liver organoids. 2.) To characterize stem cell, cholangiocyte and PLD-associated gene expression and polarization of liver organoids. 3.) To determine the effect of lanreotide on liver organoids.

Cholangiocytes from patient cyst biliary epithelium and cyst fluid were isolated and placed under conditions suitable for expansion of adult liver stem cells. Following organoid development, *LGR5, SOX9, KRT7, KRT19, PRKCSH, SEC63, LRP5* and *PKD2* expression were determined by quantitative real-time polymerase chain reaction. Confocal microscopy staining for β-catenin was performed to determine organoid polarization. In three independent experiments, control (0.1 M acetic acid) or lanreotide (10^{-7}M in 0.1M acetic acid) was added twice a day, at 12-hour intervals for seven days. Organoid development was followed by light microscopy and circumferential areas were quantified by Image J software (NIH). Data were expressed by percentage change in circumferential area (mean $\pm$ SEM) on day 7 in comparison to day 1. Statistical analysis was performed by Student's t-test.

RESULTS: We successfully isolated cholangiocytes from cyst biliary epithelium and cyst fluid that were expanded as liver organoids. Organoids form cysts with monolayered walls, which display predominant basolateral membranous β-catenin staining. In addition, they express *LGR5, SOX9, KRT7* and *KRT19,* as well as PLD-associated genes *PRKCSH, SEC63, LRP5* and *PKD2*. Lanreotide significantly decreases expansion of liver organoids in comparison to control (197% $\pm$ 46% versus 547% $\pm$ 28%; p: 0.038).

CONCLUSION: LGR5+ liver organoids are an appropriate *in vitro* model to study PLD. Organoids respond to lanreotide by decreased expansion. Our model has potential to be used for large scale drug screening.

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