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MONDAY, OCTOBER 17, 2016 08:00–10:00

OPENING SESSION: PART 1 – ROOM A

OP001 LAPAROSCOPIC ILEOCECAL RESECTION VERSUS INFLIXIMAB TREATMENT OF TERMINAL ILEITIS IN CROHN'S DISEASE: THE LIR!C TRIAL

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Introduction: The optimal therapeutic approach to ileocecal Crohn's disease (CD) remains unclear.
Aims & Methods: The objective of this study was to compare infliximab with laparoscopic ileocecal resection in patients with thiopurine or steroid refractory recurrent CD of the terminal ileum, with respect to quality of life (QoL) and costs. A multicentre randomised controlled, open-label trial was performed in 33 centres in the Netherlands and the UK. Adult patients with CD of the terminal ileum who failed > 3 months of thiopurine treatment or steroids without signs of a critical stricture were randomised to infliximab or laparoscopic ileocecal resection. Patients with a prior ileocecal resection, a diseased length > 40 cm, abdominal abscesses or fluid collections or an American Society of Anaesthesiologists (ASA) score of III or IV were excluded. The primary endpoint was QoL measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) at one year follow-up. Furthermore, the mean direct costs per individual patient were prospectively documented and analysed according to intention-to-treat until one year after start of treatment. Dutch Trial Registry NTR1150.
Results: Between May 2008 and October 2015, 143 patients were randomised (32.9% male) with a median age of 27.0 years (interquartile range (IQR) 22.0–40.0). Eventually, 65 patients started with infliximab treatment and 70 patients were operated. On April 28th 2016, 96.5% of the patients have completed follow-up. At baseline, the mean difference (MD) in IBDQ score was 4.9 points in favour of the resection group. After correction for the baseline difference, the MD at one year follow-up was 5.8 points in favour of resection (95% confidence interval (CI) −4.7 to 16.3, p = 0.28). The mean direct total costs per patient at one year were €14,589 in the infliximab group and €10,318 in the resection group (MD 04,270, 95% CI 01,325 – 07,126, p = 0.005). Infliximab was stopped in 21 patients (30.0%) due to intolerance or insufficient response, 13 of whom underwent an ileocecal resection after a median time of 27.0 weeks (IQR 11.0–33.5) after start of infliximab treatment. CD related serious adverse events in terms of Clavien Dindo IIIb complications occurred in three patients (4.1%) in the laparoscopic ileocecal resection group and in one patient allocated to infliximab eventually going for surgery. Three patients (4.1%) in the resection group were started on infliximab within one year. Readmissions (for flares or additional surgery or dilatation) during follow-up were comparable (21.4% of patients in the infliximab versus 17.8% in the resection group).
Conclusion: QoL at one year was not significantly different between the laparoscopic ileocecal resection and infliximab group. Given the lower bound of the 95% CI, laparoscopic ileocecal resection can be considered a non-inferior alternative for infliximab treatment at significantly lower cost.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP002 CELL AUTONOMOUS AND NON-CELL AUTONOMOUS RESCUE OF NNOS DEFICIENT MOUSE COLON FOLLOWING IN VIVO ENTERIC NERVOUS SYSTEM STEM CELL TRANSPLANTATION

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Introduction: Enteric neural stem cells (ENSC) have been identified as a possible treatment for enteric neuropathies following successful colonization of recipient gut after transplantation. However, the ability of ENSC to rescue pathophysiological conditions remains unclear. Loss of neuronal subtypes, including neuronal nitric oxide synthase (nNOS), has been implicated in many enteric neuropathies. $nNOS^{-/-}$ mice display slow colonic transit providing a model to test ENSC rescue in a pathological setting.
Aims & Methods: Our aim was to assess the functional integration of transplanted ENSC within recipient $nNOS^{-/-}$ colon. Initially, donor ENSC were obtained from Wnt1-cre;YFP transgenic mice allowing specific fluorescent labeling, FACS selection and fate mapping of cells. YFP+ ENSC were transplanted to $nNOS^{-/-}$distal colon at post natal day (P)14. Subsequently, integration and functionality were assessed using immunolabelling and organ bath physiology after 4 weeks.
Results: After 1 month, YFP+/nNOS+ neurons were identified and transcriptional analysis showed specific expression of nNOS in recipient $nNOS^{-/-}$ colon. In NANC (non-adrenergic non-cholinergic) conditions, organ bath physiology revealed significant increases in electrical field stimulation (EFS)-induced relaxation (Area under curve;AUC) in transplanted $nNOS^{-/-}$ (-1.13 ± 0.16 g.s, n = 5) compared with non-transplanted $nNOS^{-/-}$ ($-0.31 \pm 0.0.08$ g.s, n = 5; P = 0.0016). In transplanted colonic segments, addition of the nitric oxide synthase blocker L-NAME resulted in significant reductions in the observed EFS-induced relaxation (-0.74 ± 0.17 g.s vs -0.12 ± 0.16 g.s, n = 4; P = 0.0389) demonstrating restoration of nitrergic responses after transplantation. Interestingly, significant increases in basal contractile amplitude were also observed in transplanted $nNOS^{-/-}$ colonic segments (0.30 ± 0.06 g, n = 5) compared with both C57BL/6J (0.10 ± 0.01 g, n = 5; P = 0.0093) and non-transplanted $nNOS^{-/-}$ mice (0.05 ± 0.008 g, n = 5; P = 0.0025). These high-amplitude contractions were unaffected by application of tetrodotoxin, suggesting that transplantation of ENSC can also lead to changes in underlying myogenic motility patterns. To assess the mechanisms involved in these non-cell autonomous phenomena we sought to investigate potential changes in gut morphology. No significant change was observed in the diameter of the distal colon between transplanted $nNOS^{-/-}$ mice (1.04 ± 0.13 mm; n = 3) compared to either non-transplanted $nNOS^{-/-}$ (1.12 ± 0.68 mm; n = 3; P = 0.609) or sham-operated $nNOS^{-/-}$ (1.05 ± 0.02 mm; n = 3; P = 0.947). In addition, no change in muscle thickness was observed between transplanted $nNOS^{-/-}$ mice (55.33 ± 8.67 µm; n = 3) compared to either non-transplanted $nNOS^{-/-}$ (54.0 ± 8.0 µm; n = 3; P = 0.915) or sham-operated $nNOS^{-/-}$ (54.33 ± 2.96 µm; n = 3; P = 0.918). Ongoing work is targeting other potential processes such as modification of cell types involved in neuromuscular signaling, including interstitial cells of Cajal within the transplanted microenvironment.
Conclusion: Here we demonstrate, for the first time, that transplanted ENSC integrate and effect restoration of function, at the organ level, in a pathological GI disease model potentially via both ENSC-specific and non ENSC-specific processes.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 10:30–12:00
OPENING SESSION: PART 2 – ROOM A

OP003 MULTIVARIATE MODELLING OF GUT MICROBIAL PROFILES PREDICTS RESPONSIVENESS TO A DIET LOW IN FODMAPS

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Introduction: Dietary interventions may be recommended to IBS patients yet effects on gut microbiota and factors predicting response are largely unknown.
Aims & Methods: We aimed to determine how two different diets affect gut microbiota and if bacterial profiles and modelling thereof can be used to predict patient intervention response in a secondary analysis of a previously published intervention study (Böhn et.al 2015). After a 10 day screening period 61 IBS patients with at least moderately severe IBS symptoms according to IBS Symptom Severity Score (IBS-SSS) followed either a traditional IBS (n = 30) or low-FODMAP (n = 31) diet for 4 weeks. Faecal samples were collected and IBS-SSS were completed before and after the intervention. Food intake was recorded in 4-days food diaries before (baseline) and during the interventions. Responders were defined as having a reduction of IBS-SSS ≥50 after the intervention. Faecal bacterial composition was evaluated by GA-map™ Dysbiosis Test which measures probe signal intensity (PSI) of 54 DNA probes targeting ≥300 bacteria on different taxonomic levels. Bacterial profiles created for each patient were evaluated by multivariate discrimination analysis and graded from 1–5, relative to a healthy reference group. A dysbiosis index (DI) ≤2 signify normal microbiota composition and ≥3 signify altered microbiota composition (dysbiosis). For all models, both strong and moderate outliers were sequentially excluded.
Results: At baseline, 45 patients (25 randomized to traditional diet and 20 to low-FODMAP) had a DI ≥3, i.e. dysbiosis; of these, 10 patients following the traditional IBS diet and 3 following the low-FODMAP diet experienced an improvement in DI, while 6 following the traditional diet and 11 on the low-FODMAP diet had worsening of their dysbiosis; the rest experienced no change. In the low-FODMAP group, but not traditional diet group, non-responders (n = 19) had more severe dysbioisis than responders (n = 12) ((3 (3–4) DI; 2 (2–3) DI; p = 0.007) at baseline. Although patients on a traditional diet consumed significantly less protein, fat and alcohol, they experienced no change in overall bacterial composition after the intervention. Patients on a low-FODMAP diet ate significantly less carbohydrates, fibre, monosaccharides, fructose and total FODMAPS, and had significant reduction in potentially beneficial Bifidobacterium after the intervention (33 (25.4–122.4) PSI) compared to before (152 (45.7–70) PSI, p = 0.0005) which was even more prominent in non-responders. An OPLS-DA model of before the low-FODMAP intervention demonstrated satisfactory modelling and predictive abilities (R2Ycum 0.652, Q2 cum 0.541), showing that bacterial profiles differed between responders and non-responders. An OPLS-DA model of the traditional diet group was inadequate, showing good model fit but poor predictability (R2Ycum 0.742, Q2 cum 0.004), demonstrating that bacterial profiles did not differ between responders and non-responders.
Conclusion: Faecal bacterial profiles predict patient responsiveness to a low-FODMAP dietary intervention. Thus, before considering dietary interventions, bacterial profiles could be determined in order to identify patients whom are likely to respond favourably.
Disclosure of Interest: L. Öhman: Unrestricted research grants from AstraZeneca; Consultant/ Advisory Board member for Genetic Analysis; Speaker for Genetic Analysis, Takeda and Abbot.
All other authors have declared no conflicts of interest.

OP004 ENDOSCOPIC OR SURGICAL STEP-UP APPROACH FOR NECROTIZING PANCREATITIS, A MULTI-CENTER RANDOMIZED CONTROLLED TRIAL

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Introduction: Infected necrotizing pancreatitis is a potentially lethal disease that almost always requires an invasive intervention. In recent years, the surgical step-up approach has become standard of care replacing primary open necrosectomy. A promising minimally invasive alternative is the endoscopic step-up approach. We conducted a multicenter randomized trial (TENSION trial) comparing a endoscopic and surgical step-up approach in patients with infected necrotizing pancreatitis.
Aims & Methods: Patients with infected necrotizing pancreatitis were randomly assigned to the endoscopic or surgical step-up approach. The endoscopic step-up approach consisted of endoscopic transluminal drainage followed, if necessary, by endoscopic necrosectomy. The surgical step-up approach consisted of percutaneous catheter drainage followed, if necessary, by video-assisted retroperitoneal debridement (VARD). The primary endpoint was a composite of major complications (i.e. new onset organ failure, bleeding, perforation of a visceral organ, enterocutaneous fistula and incisional hernia) or death during 6 months of follow-up. Secondary endpoints included, among other, pancreatic fistula, length of hospital stay and costs.
Results: A total of 98 patients were enrolled in 19 Dutch hospitals. The primary endpoint occurred in 10 of 51 patients (20%) in the endoscopic group and in 13 of 49 patients (28%) in the surgical group (risk ratio 0.75; 95% CI 0.37 to 1.52, P = 0.35). There were no significant differences in the individual components of the primary endpoint (e.g. death 18% versus 13%; P = 0.50). In the endoscopic group, 21 patients (41%) as compared with 23 patients (49%) in de surgical group did not need necrosectomy after drainage as first step of treatment (risk ratio 0.84; 95% CI 0.54 to 1.31, P = 0.43). There was a lower incidence of pancreatic fistula (5% versus 32%; P = 0.001) and length of hospital stay was shorter (median 36 days versus 69 days; P = 0.03) in the endoscopic group. Furthermore, the difference in total mean costs was 013655 (19%, BCa 95% CI -10836–35782) in favour of the endoscopic group.
Conclusion: The TENSION trial did not show superiority of the endoscopic step-up approach, as compared with a surgical step-up approach, in reducing major complications or death in patients with infected necrotizing pancreatitis. However, the rate of pancreatic fistula, length of hospital stay and costs were significantly reduced in the endoscopic group.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 10:30–12:00
ESTABLISHED AND NEW DRUGS IN IBD – ROOM B

OP005 EFFICACY AND SAFETY OF DOSE ADJUSTMENT AND DELAYED RESPONSE TO USTEKINUMAB IN MODERATE–SEVERE CROHN'S DISEASE PATIENTS: RESULTS FROM THE IM-UNITI MAINTENANCE STUDY

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Introduction: Ustekinumab (UST) has been shown to induce and maintain clinical response and remission in moderate to severe Crohn's disease (CD) in 2 induction (UNITI-1 and 2) and 1 maintenance (IM-UNITI) randomized, placebo controlled Phase 3 trials. We evaluated the efficacy of UST in 2 additional groups in IM-UNITI: patients who underwent dose adjustment following loss of response (LOR) and patients who did not have a clinical response to IV UST during induction and had an additional subcutaneous (SC) dose.
Aims & Methods: Patients achieving clinical response after single dose IV induction were randomized to SC placebo (PBO), UST 90 mg every 12 weeks (q12w) or every 8 weeks (q8w). Patients who met LOR criteria, defined as a CDAI score of ≥ 220 and a ≥ 100 point increase from the maintenance baseline CDAI score, between weeks 8 and 32 of the maintenance trial could undergo a single dose adjustment as follows: PBO→q8w, q12w→q8w, and q8w→q8w (no dose adjustment) and were assessed for clinical response (≥ 100 point decrease in CDAI) and clinical remission (CDAI < 150) 16 weeks later. Separately, UST patients not in clinical response 8 weeks after the IV induction dose were given SC UST 90 mg and if in clinical response 8 weeks later were continued on q8w dosing.
Results: 51 (39%), 29 (23%), and 28 (22%) patients in the PBO, q12w and q8w groups, respectively, underwent dose adjustment after meeting LOR criteria. Among these patients, clinical remission and clinical response were observed in 39% and 71% of patients adjusting PBO→q8w (a situation similar to a drug holiday), 41% and 55% in the q12w→q8w group, and 32% and 46% in the q8w→q8w group when assessed 16 weeks later (Table 1). Median change in CDAI after adjustment was −121, −141 and −78.5 in the PBO→q8w, q12w→q8w and q8w→q8w groups, respectively. Of 467 patients not in response to UST following IV induction in UNITI1&2, 50.5% and 28.9% were in clinical response and remission 8 weeks after one additional UST dose (90 mg SC). Among the 251 of these patients continuing dosing at week 8 of maintenance, 68.1% were in response and 50.2% were in remission at Week 44. No increases or changes in patterns of adverse events were seen among patients who dose adjusted.
Conclusion: In patients who met LOR criteria, dose adjustment from UST 90 mg q12w to 90 mg q8w provided some additional clinical benefit compared to patients who remained on UST 90 mg q8w. Additionally, patients who were initial induction non-responders can benefit from continued treatment with at least 1 SC UST dose 8 weeks after IV induction.

Table 1: Proportion of subjects achieving clinical response and remission 16 weeks after dose adjustment

	Clinical Response	Clinical Remission
PBO→UST q8w	71%	39%
UST q12w→UST q8w	55%	41%
UST q8w → UST q8w	46%	32%

Disclosure of Interest: B.E. Sands: Investigator for Janssen Research & Development, LLC
C. Gasink: Employee of Janssen Research & Development, LLC
D. Jacobstein: Employee of Janssen Research & Development, LLC
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OP006 VEDOLIZUMAB EXPOSURE CORRELATES WITH CLINICAL, BIOLOGICAL AND ENDOSCOPIC OUTCOME IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Introduction: Vedolizumab (VDZ) specifically targets the $\alpha_4\beta_7$ integrin on gut-homing lymphocytes and has been approved for the treatment of patients with moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). We studied the relation between serum VDZ trough concentrations (TC) and clinical, biological and endoscopic outcomes in real-life practice.
Aims & Methods: The first 75 patients (49 CD, 26 UC) who initiated VDZ therapy (300 mg IV administered) in our tertiary referral center were sampled at trough during induction (w2 and w6) and early maintenance (w10, w14 and w22) treatment. Clinical response (clinical symptoms and physician global assessment) was correlated to VDZ TC. All patients with UC received sigmoidoscopy at baseline and w10 and mucosal healing was defined as a Mayo endoscopic subscore of 0 or 1. Biological response (CRP decrease ≥50% from baseline) and remission (CRP≤5 mg/L) were assessed at w6 and w22 in patients with CD. An ELISA for measuring serum VDZ TC was developed in house. TC are shown as median [IQR].
Results: A substantial interindividual variability in VDZ TC was observed at w2 (27.8 μg/mL [21.5–35.9]), w6 (25.5 μg/mL [16.4–36.3]), w10 (23.6 μg/mL [12.0–37.7]) and w22 (11.3 μg/mL [4.4–17.5]). VDZ TC at w14 are about twice as high in patients receiving an additional infusion at w10 (23.7 μg/mL [17.1–36.6], n = 42) compared to patients who did not receive a w10 infusion (13.1 μg/mL [6.6–19.3], n = 28) ($p < .0001$). Biological response and remission were achieved in 52% (14/27) and 30% (8/27) of patients with CD. Significantly higher VDZ TC were observed at w6 in case of biological response (23.8 μg/mL [16.1–33.8]), compared to non-response (11.8 μg/mL [7.2–18.2]) (p = .004) and when biological remission was achieved (25.4 μg/mL [23.7–35.5]), compared to when no remission was achieved (13.0 μg/mL [9.8–19.8]) (p = .0004). At w22, 59% (16/27) of patients with CD were in biological remission. Patients who were in biological remission at w22 had significantly higher VDZ TC throughout w2 to w22, compared to patients who were not in biological remission at w22 (table 1).

Table 1: Vedolizumab trough concentrations, in μg/mL, median [IQR] (n), during induction (w2 and w6) and early maintenance (w10, w14 and w22) treatment correlate with biological remission (CRP ≤5 mg/L) at w22 in patients with CD.

	Biological remission at w22	No biological remission at w22
w2*	31.8 [23.9–38.9] (23)	23.6 [18.4–31.9] (17)
w6**	33.5 [22.1–38.5] (23)	16.6 [9.0–31.4] (17)
w10***	37.9 [24.4–45.1] (15)	12.8 [7.5–19.3] (10)
w14**	25.8 [16.1–39.4] (22)	14.0 [9.7–18.6] (17)
w22***	16.1 [9.5–25.2] (23)	6.3 [2.8–11.2] (17)

*p < .05; ** p < .01; *** p < .001 Endoscopic healing was achieved in 65% (13/20) of patients with UC. Patients with endoscopic healing had significantly higher VDZ TC at w6 (30.5 μg/mL [18.6–38.0]), compared to patients who did not achieve endoscopic healing (16.6 μg/mL [11.0–29.3]) (p = .02). Clinical response was achieved in 69% (47/68) of the patients. Only in patients with UC, clinical response was associated with higher VDZ TC at w2 (27.8 μg/mL [22.3–37.1], n = 16) and w6 (32.0 μg/mL [17.8–37.7], n = 16) compared to absence of clinical response (21.6 μg/mL [16.0–25.2] and 16.6 μg/mL [11.0–20.6], resp., n = 7) (p = .03 and p = .02).

Conclusion: This is the first real-life experience with VDZ that shows substantial variability in exposure to VDZ between patients. A clear exposure-response correlation was observed as early as w2 and w6, with significant impact of higher VDZ TC on meaningful outcomes as biological response, remission and endoscopic healing. Our data support a potentially important role for early therapeutic drug monitoring also with VDZ.
Disclosure of Interest: A. Gils: Lecture fee(s): MSD, Janssen Biologicals, Abbvie, Pfizer, Takeda. Consultancy: UCB. Conflict with: license of infliximab, anti-infliximab and adalimumab ELISA from Institution to apDia and with lateral flow infliximab to R-Biopharm AG.
M. Ferrante: Financial support: research from Janssen Takeda, Lecture fees: Tillotts, Ferring, Boehringer-Ingelheim, Janssen, Chiesi, Falk, Zeria, Mitsubishi Tanabe, MSD, Takeda, and Abbie Consultancy: Abbvie, Ferring, MSD, Boehringer-Ingelheim and Janssen.
G. Van Assche: Gert Van Assche receives financial support for research from Abbvie and MSD, lecture fees from Janssen, Takeda, Ferring, MSD, and Abbvie and does consultancy for Abbvie, MSD, and Takeda.
S. Vermeire: Grant/research support Takeda, MSD, Abbvie Consultancy/speaker's fees from Abbvie, MSD, Takeda, Pfizer, Galapagos, Genentech/Roche, Mundipharma, Celgene, Hospira, Second Genome
All other authors have declared no conflicts of interest.

OP007 EARLY VEDOLIZUMAB DRUG LEVELS AND INDUCTION SUCCESS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Introduction: Vedolizumab is an anti-α4β7 monoclonal antibody effective in ulcerative colitis (UC) and Crohn's disease (CD). Data regarding pharmacokinetics/ pharmacodynamics of vedolizumab are still scarce.
Aims & Methods: Aim: To assess whether early vedolizumab trough levels (weeks 2, 6) correlate with response to vedolizumab induction therapy. Methods: A novel ELISA-based assay was developed for measuring vedolizumab levels, and employed in prospectively-followed IBD patients receiving vedolizumab induction therapy. Drug levels were assessed for association with clinical remission, defined by HBI < 5 and SCCAI < 3 for CD and UC, respectively. The primary outcome was the comparison of week 6 levels in patients with or without clinical remission at the same time-point. Association of week 2 and week 6 levels with week 14 clinical remission was also sought, as well as association of trough levels with inflammatory markers (Albumin and C-reactive protein, CRP).
Results: Seventy-two patients were included (47 CD, 25 UC), of whom 14 (30%) and 15 (32%) of CD patients and 6(25%) and 8 (32%) of UC patients reached clinical remission by weeks 6 and 14, respectively. The median level of vedolizumab at week 6 was not different between patients who achieved remission by week 6 and those who did not (37.3 vs. 29.4 μg/ml respectively, p = 0.85). Clinical remission rates at week 6 were also not associated with drug level quartiles at week 6. Similarly, neither week 2 or 6 levels were predictive of clinical remission at week 14 (35.4 vs. 44.8 μg/ml, p = 0.75, 33.9 vs. 25.5 μg/ml, p = 1, respectively). Vedolizumab levels were also not associated with steroid free remission (p = 0.1, p = 0.57) or with CRP normalization (p = 0.26, p = 0.73) at weeks 6 and 14, respectively. Among UC patients separately analyzed, week 2 levels were associated with clinical remission at week 14 (p = 0.04). However, statistical significance for this difference was not retained after Bonferroni correction for multiple testing. Finally, multivariable analysis for clinical remission at week 6 has been performed including baseline albumin level and patient weight. When adjusting for these co-variates, week 6 vedolizumab levels were not associated with clinical remission at week 6 (p = 0.56).
Conclusion: In this real-life cohort of consecutive IBD patients receiving vedolizumab, drug levels during induction were not associated with or predictive of clinical response to induction therapy and were not associated with CRP normalization or steroid-free clinical remission. Future studies are pertinent in order to elucidate the role of therapeutic drug monitoring of vedolizumab during induction and maintenance.
Disclosure of Interest: U. Kopylov: Dr. Kopylov recieved consultancy fees from Jannsen, research support from Jannsen and Takeda and lecture fees from Jannsen, Takeda, Abbvie and CTS.
Y. Chowers: Prof. Chowers recieved consulting and lecture fees as well as grant support from Takeda, Abbvie, Janssen, Pfizer, Ferring and Protalix.
R. Eliakim: Prof. Eliakim has received consulting and lecture fees from Takeda.
S. Ben-Horin: Prof. Ben-Horin has received consulting and/or advisory board fees from Janssen, Takeda, Celltrion, Abbvie, & Schering-Plough and research support from Celltrion and Abbvie
All other authors have declared no conflicts of interest.

OP008 PREDICTORS OF NON-RESPONSE OR LOSS OF RESPONSE TO TUMOUR NECROSIS FACTOR ANTAGONIST THERAPIES IN INFLAMMATORY BOWEL DISEASE

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Introduction: Tumour necrosis factor antagonists (anti-TNFs) are effective at inducing and maintenance disease remission in patients with moderate to severe ulcerative colitis (UC) or Crohn's disease (CD). However, considerable proportions of patients do not respond to therapy or lose response over time.

Aims & Methods: This study uses real-world data to identify predictors of non- or loss of response to anti-TNF therapy. The study recruited UC and CD patients from 6 countries [Canada, France, Germany, Italy, Spain, and the United Kingdom (UK)] aged ≥18 years who initiated anti-TNFs (infliximab/adalimumab) during June 2009 to June 2011 (CD) or June 2009 to June 2013 (UC). Data were collected on patient demographics, clinical characteristics and healthcare resource use. Patients were classified as having non- or loss of response if they: were hospitalized or required UC/CD surgery whilst on therapy, discontinued due to UC or CD flare, required dose-escalation or augmentation with steroids/immunosuppressants 4 months after therapy initiation, or disease severity became worse after therapy initiation. Multilevel multivariate logistic regression was used to identify predictors of non- or loss of response.

Results: The study included 1195 patients (45% UC, 55% CD; 9.6% Canada, 13% France, 22% Germany, 23% Italy, 19% Spain and 14% UK). Mean age: 40.3 (SD = 13.7); 51%: male. Most patients had a Charlson comorbidity index (CCI) score of 0–1 (83%), 16% were current smokers, mean BMI was 24.8 (SD = 7.18) and mean disease duration was 8 years (SD = 8.07). Most patients had a physician global assessment of moderate (45%) at study entry. Mean follow up was 3.4 years (UC) and 4.4 years (CD). Overall, 22% of patients had a primary non-response and 71% were classified as having non- or loss of response to anti-TNF therapy in the maintenance period (4 months after initiating anti-TNF) over a mean follow up period of 32 months (SD = 20.4). Significant predictors of non-/loss of response are shown in the Table 1.

Table 1: Predictors of non-response or loss of response among patients with ulcerative colitis and Crohn's disease

Baseline Variables	Odds Ratio (95% Confidence Interval)	P-value
Patients with Ulcerative Colitis		
Rectal Bleeding (Reference: None)	-	0.04
- Passing blood alone	0.24 (0.06–0.97)	
- Passing blood with stool ≥50% of time	0.35 (0.10–1.19)	
- Passing blood with stool <50% of time	0.17 (0.05–0.62)	
Endoscopic Findings (Reference: Inactive/Mild)	-	0.02
- Moderate	3.19 (1.14–8.97)	
- Severe	4.86 (1.61–14.7)	
Patients with Crohn's Disease		
Number of Liquid or Soft Stools per Day[1]	1.12 (1.00–1.24)	0.04
C-reactive Protein (CRP)[1,2]	1.02 (1.00–1.03)	0.03

Note: Only the significant predictors are included in the table above. Other non-significant variables included age, gender, body mass index, disease duration, Charlson comorbidity index score, and use of corticosteroids or immunomodulators. [1]Both were analyzed as continuous variables. [2]Highest CRP values during the baseline period were used.

Conclusion: In this cohort the majority of patients did not respond or lost response to anti-TNF therapy over time. Predictors for patients with UC included the absence of rectal bleeding and moderate/severe endoscopic scores, and for patients with CD included higher CRP and higher number of liquid or soft stools per day. These predictors should be considered when evaluating treatment options for patients.

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M. Munsaka: Employee of Takeda Development Center Americas Ltd, Deerfield, Illinois, USA.
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J.M. Khalid: Employee of Takeda Development Centre Europe Ltd, London, United Kingdom.

OP009 INFLAMMATORY BOWEL DISEASE COURSE AND THERAPEUTIC MANAGEMENT IN REAL LIFE PRACTICE IN THE CURRENT ERA OF ANTI-TNFS: ANALYSIS OF THE FRENCH ADMINISTRATIVE HEALTH DATABASES 2009–2014

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Introduction: Management of inflammatory bowel disease (IBD) has evolved in the last decade. Clinical trials have shown that the combination of anti-TNFs and thiopurines is more efficient than monotherapy with either of these. The impact of these results in real-life practice is unknown. Moreover, the frequency of treatment withdrawal has never been assessed in population-based cohort studies.

Aims & Methods: Our aim was to assess IBD course and therapeutic management including treatment withdrawal, surgery rates and hospital stays in the current era of anti-TNFs. Every patient affiliated to the French national health insurance with a diagnosis of IBD based on listed long-term diseases and/or hospital discharge diagnosis was included from 2009 to 2013, and followed up until 31 December 2014. Cumulative incidence rates were used to estimate the cumulative probabilities of medication use, surgery and hospitalization among prevalent and incident patients. Treatment sequences including treatment withdrawal after introduction of thiopurines, anti-TNFs and combotherapy were assessed for incident patients included between 2009 and 2012.

Results: 195,834 individuals were diagnosed with IBD (Crohn's disease (CD), 106 436 (31,353 incident patients); ulcerative colitis (UC), 89,398 (27,578 incident patients)). Among incident patients treated with thiopurines or anti-TNFs (17 566 CD and 8035 UC patients), the first treatment was thiopurines, anti-TNFs monotherapy, and combotherapy in 69.1%, 24.8% and 6.1% of CD patients and 78.2%, 17.7% and 4.1% of UC patients, respectively. Subsequently, 36.8% and 20% of CD patients were exposed to anti-TNFs monotherapy and combotherapy, respectively, 5 years after diagnosis. More than 25% of CD and UC incident patients included between 2009 and 2012 withdrew thiopurines or anti-TNFs, during more than three months after a first treatment course. Drug withdrawal was related to hospitalization or surgical procedures in less than 30% of these patients. Nearly 50% of CD patients and 40% of UC patients went back to their initial treatment after withdrawal. Around 5% of CD patients and 4% of UC patients stopped all IBD therapy during follow-up. Five years after diagnosis, the cumulative risks of first intestinal resection in CD, and colectomy in UC were 12.8% and 3.5%, respectively.

Conclusion: The step-up approach remains the dominant strategy in IBD, whereas exposure to anti-TNFs is high and surgery rates are low. Treatment withdrawal in IBD is more common than expected. This study emphasizes the growing need of studying de-escalation strategy in IBD.

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OP010 CHARACTERISTICS OF CHILDREN WITH CROHN'S DISEASE FAILING SUSTAINED REMISSION DESPITE ANTI-TNF EXPOSURE

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Introduction: The identification of chidren at risk for failure to reach sustained remission despite exposure to anti-TNF remains challenging in Crohn's disease (CD).

Aims & Methods: Data from BELCRO (Belgian observational prospective cohort of paediatric CD) were analysed after 5 yrs follow-up. Disease severity was scored at diagnosis and yearly thereafter as inactive, mild and moderate-to-severe on a 3-point scale based on PCDAI/PGA scores. Sustained remission was defined as inactive disease for $\geq$ 2 yrs follow-up. Univariate analyses were performed between anti-TNF exposed patients with or without sustained remission and correlations assessed between variables and the outcomes average disease severity and sustained remission.

Results: Of 66 anti-TNF exposed patients (median (IQR) age 13.1 (11.5–15.2) yrs, 50% male), 17% failed to reach sustained remission. Disease location was similar in both groups and mild disease at diagnosis (45% vs. 16%; p = .03) more frequent in the group failing sustained remission. There were no differences between age, gender, WBC or CRP at diagnosis and treatment between both groups. Percentages of infliximab and adalimumab use were similar in both groups, including drug switching and dose or interval adjustments. When stratified by follow-up clinic, infliximab in paediatric follow-up was less frequently associated with failure to reach sustained remission compared to sustained remission.

Univariate analyses of the type of follow-up clinic and anti-TNF treatment between patients with or without sustained remission (more than one anti-TNF possible).

Variable, number (%)	No sustained remission (n = 11)	Sustained remission (n = 55)	P value
Paediatric follow-up and infliximab	3 (27)	37 (67)	**.01**
Paediatric follow-up and adalimumab	1 (9)	8 (15)	.63
Adult clinic follow-up and infliximab	6 (55)	14 (25)	.05
Adult clinic follow-up and adalimumab	2 (18)	4 (7)	.25
Paediatric follow-up and adjustments	1 (9)	8 (15)	.63
Adult follow-up and adjustments	1 (9)	3 (11)	.65

Higher average disease severity (2.1 (2.0–2.3) vs. 1.6 (1.3–1.8); p < .001), adult clinic follow-up (73% vs. 27%; p < .01), surgery for CD (1 (0–3) vs. 0 (0–3); p < .01) and active disease after 5 yrs (91% vs. 24%; p < .05) were associated with failure to reach sustained remission. Both colonic disease and adult follow-up (AUC = .66; both p = .04) correlated with average disease severity (no correction for multiple testing). No other correlations were found.

Conclusion: Patient phenotype at diagnosis does not predict failure to reach sustained remission despite anti-TNF exposure. Mild disease may not trigger appropriate treatment and lead to active and complicated disease course. Sustained remission occurred most with infliximab in paediatric follow-up. Information on serum levels is lacking.

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MONDAY, OCTOBER 17, 2016 10:30–12:00

IS MASS ERADICATION OF H. PYLORI RATIONAL? – ROOM C

OP011 IS HELICOBACTER PYLORI ERADICATION ABLE TO IMPROVE THE SCORES OF ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA? – LONG-TERM FOLLOW-UP STUDY IN HIGH RISK POPULATION OF GASTRIC CANCER

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Introduction: *Helicobacter pylori* (*H. pylori*) is a risk factor of atrophic gastritis (AG) and intestinal metaplasia (IM) which can undergo to gastric cancer. However, the reversibility of AG and IM by *H. pylori* eradication is controversial, so far.

Aims & Methods: This study was performed to evaluate the reversibility of AG and IM by anti-*H. pylori* therapy in large number of patients for a long period in South Korea. A total of 810 patients with follow-up at least 1 year were enrolled from January, 2006 to September, 2014. On the basis of *H. pylori* infection status and eradication, the subjects were divided into three groups, as follows: Group A (n = 214) included those patients who were *H. pylori* negative. Group B (n = 580) had successful eradication result for *H. pylori*. Group C (n = 116) had not received eradication therapy or showed eradication failure. The histological features of the AG and IM in the antrum and body were measured, respectively, using Sydney system scores. All of three groups were followed at 1, 2, 4 and 5 or more years.

Results: In patients with successful eradication (Group B), grades of AG and IM in both antrum and body significantly decreased at 1, 2, 4 and 5 or more years (p < 0.001) (Table). In contrast, in the *H. pylori* negative group (Group A), no significant change was documented for grades of AG and IM in either antrum or body except for grades of IM in body at 2 years and AG in body at 4 years (Table). Similarly, in Group C, no significant change was documented for grades of AG and IM in either antrum or body except for scores of AG in body at 5 or more years (Table).

Table: Histological changes in atrophic gastritis and intestinal metaplasia at 1, 2, 4 and 5 or more years after eradication therapy.

	group	n	baseline	1 year	2 years	4 years	>5 years
AG in antrum	A	110	1.46 ± 0.66	1.35 ± 1.04	1.19 ± 1.06	1.03 ± 1.01	1.45 ± 0.89
AG in antrum	B	282	1.49 ± 0.62	**0.87 ± 0.86** [a]	**0.86 ± 0.90** [a]	**0.76 ± 0.88** [a]	**0.56 ± 0.89** [a]
AG in antrum	C	52	1.46 ± 0.70	1.24 ± 0.95	0.80 ± 1.10	1.17 ± 1.17	0.43 ± 0.79
AG in body	A	66	1.71 ± 0.72	1.38 ± 1.07	1.12 ± 1.12	**1.04 ± 0.91** [a]	1.82 ± 1.01
AG in body	B	195	1.62 ± 0.65	**0.77 ± 0.92** [a]	**0.78 ± 0.95** [a]	**0.75 ± 0.98** [a]	**0.25 ± 0.68** [a]
AG in body	C	34	1.85 ± 0.74	1.08 ± 1.14	1.50 ± 1.05	0.67 ± 1.03	**0.14 ± 0.38** [a]
IM in antrum	A	117	1.81 ± 0.68	1.61 ± 0.86	1.56 ± 0.87	1.63 ± 0.96	1.54 ± 0.89
IM in antrum	B	369	1.65 ± 0.66	**1.37 ± 0.83** [a]	**1.28 ± 0.94** [a]	**1.11 ± 0.92** [a]	**0.66 ± 0.88** [a]
IM in antrum	C	69	1.67 ± 0.66	1.68 ± 0.98	1.71 ± 0.85	1.06 ± 0.99	1.33 ± 1.00
IM in body	A	85	1.78 ± 0.70	1.52 ± 1.04	**1.25 ± 1.15** [a]	1.41 ± 1.06	1.54 ± 1.07
IM in body	B	247	1.64 ± 0.67	**1.24 ± 0.84** [a]	**1.00 ± 0.94** [a]	**0.92 ± 0.94** [a]	**0.73 ± 0.94** [a]
IM in body	C	48	1.71 ± 0.62	1.57 ± 0.95	1.20 ± 0.63	1.00 ± 1.00	1.00 ± 1.10

α: p < 0.001. Group A included those patients who were *H. pylori* negative. Group B had successful eradication result for *H. pylori*. Group C had not received eradication therapy or showed eradication failure. AG, atrophic gastritis; IM, intestinal metaplasia.

Conclusion: This study shows improvement of AG and IM in both antrum and body by *H. pylori* eradication, which could be underlying mechanism of the prevention of gastric cancer by *H. pylori* eradication.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP012 THE EFFECT OF CURRENT HELICOBACTER PYLORI INFECTION ON GASTRIC CANCER IN A LARGE POPULATION BASED STUDY

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Introduction: Although the association between risk of gastric cancer and *Helicobacter pylori* (*H. pylori*) in case-control study have evaluated, the effect of current *H. pylori* infection on the risk of gastric cancer has not been studied in a large general population.
Aims & Methods: Their first Health check-up persons, who underwent comprehensive screening including endoscopy and *H. pylori* test from 2003 to 2013, were enrolled. Current infection of *H. pylori* was defined as positive rapid urease test. Negative current infection was defined as negative rapid urease test and absence of previous *H. pylori* eradication. Adjusted regression analysis was performed and estimated odds ratio (OR) and 95% confidence interval (CI).
Results: Among 35519 persons with 19396 men, 113 gastric cancers and 158 gastric adenomas were detected. In adjusted analysis, age (OR 1.06, 95% CI 1.04–1.08), current infection of *H. pylori* (OR 2.39, 95% CI 1.53–3.74), first degree relatives with gastric cancer (OR 2.08, 95% CI 1.30–3.32), and high glucose (OR 1.66, 95% CI 1.04–2.65) increased the risk of gastric cancer, whereas high HDL ($\geq$60 mg/dL) reduced the risk of gastric cancer (OR 0.49, 95% CI 0.22–0.94). In sub-analysis by *H. pylori*, age was a common risk factor of gastric. First degree relatives (OR 3.23, 95% CI 1.39–7.50) increased gastric cancer risk in the absence of *H. pylori*, whereas high glucose (OR 1.98, 95% CI 1.16–3.39) increased gastric cancer risk in the presence of *H. pylori*.
Conclusion: Current infection of *H. pylori* increased the risk of gastric cancer about 2.4-fold in a large general population.
Disclosure of Interest: All authors have declared no conflicts of interest.

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AN UPDATE ON THE MANAGEMENT OF HEPATOCULLULAR CARCINOMA – ROOM G

OP013 APLN PROMOTES TUMORIGENICITY IN HEPATOCELLULAR CARCINOMA THROUGH ACTIVATING PI3K-AKT PATHWAY AND ITS EXPRESSION IS ASSOCIATED WITH POOR SURVIVAL IN PATIENTS

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Introduction: We have recently identified that Apelin (APLN) was highly expressed in 18 paired hepatocellular carcinoma (HCC) tumor tissues compared to adjacent normal liver specimen by transcriptome sequencing. APLN is an endogenous ligand for the G-protein-coupled APJ receptor. In this study, we aim to investigate its function, mechanism of action and clinical implication in HCC.
Aims & Methods: APLN expression was examined in paired human HCC tissues, HCC cell lines, and mouse models of liver cancer. Biological function of APLN was determined using cell viability, colony formation, cell cycle, apoptosis and murine xenograft assays. Downstream effectors and pathways were identified by promoter luciferase reporter assay and western blot. Clinical implication of APLN was assessed in two human HCC cohorts.
Results: Liver cancer was induced in genetically obese mice (db/db, deficient in leptin receptor) and wild-type mice with diethylnitrosamine. mRNA analysis of mice HCC tissues and adjacent non-HCC livers revealed that APLN was a top candidate gene consistently up-regulated in HCC tumor tissues compared to adjacent non-tumor tissues. APLN was also overexpressed in human HCC tissues as compared with adjacent normal tissues at mRNA level (28 pairs of non-alcoholic steatohepatitis (NASH) -HCC and 26 pairs of HBV-HCC patients) and protein level (9 pairs of NASH-HCC patients). APLN was ubiquitously expressed in eight HCC cell lines (7404, HepG2, Huh6, Huh7, PLC5, SKHEP1 and two NASH-HCC cell lines HKCI-2 and HKCI-10), whilst no or very low expression was observed in a normal liver cell line (MIHA) and human normal liver tissues. Ectopic expression of APLN (in Huh7, Miha, HKCI-2 and HKCI-10) was found to promote cell proliferation, accelerate G1/S phase progression by increasing cyclin D1 expression, and render cells more resistant to MG132 or staurosporine induced apoptosis. Silencing of APLN by shAPLN transfection (HepG2 and SK-Hep1) had the opposite effects in vitro and significantly inhibited xenograft tumor growth in vivo. Promoter luciferase reporter assays revealed that APLN promoted the PI3K/AKT pathway. Ectopic expression of APLN or exogenous addition of APLN peptide induced the phosphorylation of AKT and glycogen synthase kinase-3beta. Conversely, silencing of APLN or administration of ML221, an antagonist of APLN receptor, inactivated PI3K-AKT signaling. APLN expression was significantly higher in late stage HCC (II-IV) than early stage HCC (I) ($P < 0.05$ for our cohort, and $P < 0.01$ for TCGA cohort). Kaplan–Meier curves showed that higher APLN expression was significantly associated with shortened survival in patients with HCC ($N = 43$ for our cohort, and $N = 328$ for TCGA cohort; both $P < 0.05$).
Conclusion: APLN is commonly up-regulated in HCC. APLN plays an important ocogenic role in promoting liver tumor growth via activation of PI3K-AKT pathway. Higher expression of APLN is correlated with a more advanced clinical stage and worse prognosis in HCC patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP014 TUMORS SKEW THE CCR2-DEPENDENT ANTI-TUMOR IMMUNE RESPONSE INITIATED BY ONCOGENE-INDUCED SENESCENCE TOWARDS TUMOR GROWTH PROMOTION

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Introduction: Oncogene-induced senescence induces the immune-mediated clearance of these precancerous senescent hepatocytes, preventing malignant transformation and tumor initiation; a process termed 'senescence surveillance' (1). However, senescent hepatocytes can give rise to hepatocellular carcinomas (HCC), if the senescence program is abrogated and/or senescent cells are not cleared (1). We set out to identify the mechanism of recruitment of senescent cell-clearing macrophages. Furthermore, we studied the effect of senescence-associated immune responses on neighboring full-blown tumor cells in the liver.
Aims & Methods: To induce senescence in mouse livers, either oncogenic Nras (NrasG12V) or an effector loop mutant (NrasG12V/D38A), which is incapable of downstream signaling and senescence induction, were hydrodynamically delivered into C57BL/6, CCR2 KO and p19 KO mice. To achieve tumor development in senescent livers, luciferase-expressing hepatocellular carcinoma cells were intrasplenically injected into mice after hydrodynamic gene delivery. Tumor growth was assessed using weight and bioluminescence measurements as well as quantification of macroscopic tumors. Senescent livers with or without tumors were analyzed using flow cytometry and immunohistochemistry. Furthermore, peritumoral tissue of 226 HCC patients was hierarchical clustered based on the expression of 35 senescence-associated genes (2). Senescence-associated gene signature expression was then compared with chemokine expression and survival. In addition, human peritumoral tissue was analyzed by immunohistochemistry for the presence of senescence and myeloid cell markers.
Results: In tumor-free livers, senescent hepatocytes induced CCR2+ immature myeloid cell (iMC) accumulation, followed by iMC maturation into macrophages, which clear senescent hepatocytes. In CCR2 KO mice, iMC recruitment and macrophage accumulation was impaired, causing persistence of oncogenic Nras-expressing hepatocytes and ultimately HCC development. In contrast, however, tumor cells in senescent livers blocked the maturation of CCR2+ iMC into macrophages, which lead to an accumulation of iMC. These iMC inhibited NK cell cytotoxicity against tumor cells, as demonstrated by reduced NK cell degranulation in vivo. NK cell inhibition through senescence-recruited iMC lead to accelerated tumor growth. Accordingly, in CCR2 KO mice or C57BL/6 wild type mice depleted of iMC, senescence-induced tumor growth promotion was abrogated. Finally, gene expression and immunohistochemistry analyses in peritumoral tissue of patients with hepatocellular carcinoma confirmed the association of senescence-induced CCL2 expression, myeloid cell accumulation, NK cell inhibition and poor prognosis.
Conclusion: Senescence-induced CCL2-CCR2 signaling and the ensuing myeloid cell accumulation harbor context dependent functions in preventing HCC initiation, but also promoting progression of established HCC. These findings hold important translational significance for clinical practice: 1. CCR2 antagonists may fuel liver cancer growth in patients with chronic liver disease, in which senescent hepatocytes accumulate. 2. In patients with HCC, CCR2 antagonists may reduce senescence-augmented immunosuppression induced by liver tumors.
Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 10:30–12:00

IMPROVEMENTS OF ENDOSCOPIC RESECTION TECHNIQUES IN THE COLON – ROOM K

OP015 COLD FORCEPS AVULSION (CFA) WITH ADJUVANT SNARE TIP SOFT COAGULATION (STSC) IS AN EFFECTIVE AND SAFE STRATEGY FOR THE MANAGEMENT OF NON-LIFTING LARGE LATERALLY SPREADING COLORECTAL LESIONS (NL-LSLS)

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Introduction: Non-lifting (NL) large laterally spreading and colorectal lesions (NL-LSL) are challenging to resect endoscopically and often necessitate surgery. Previously attempted endoscopic resection, pre-resection biopsy and sub-lesion carbon particle suspension are common reasons for NL. Conventional endoscopic mucosal resection (EMR) techniques are often ineffective due to extensive submucosal fibrosis. Simple methods for safe and effective endoscopic management of NL-LSL have not been described.

Aims & Methods: The study aimed to evaluate the characteristics of NL-LSL and the safety and efficacy of endoscopic treatment by Cold Forceps Avulsion (CFA) followed by thermal ablation of the avulsion site by Snare Tip Soft Coagulation (STSC). Amongst a prospective observational study of patients referred for wide field EMR of LSL >20 mm, LSLs which could not be completely resected by snare due to NL were labelled NL-LSL. These were divided into previously attempted non-lifting LSLs (PANL-LSL) and naïve, non-lifting LSLs (NNL-LSL). [MB1] Such lesions had completion of resection using a standardized approach with CFA and STSC. The NL area was isolated by circumferential snare excision of all adjacent tissue including adenoma and/or normal mucosa to free the lateral margins. This then allowed effective CFA of NL adenoma. Systematic CFA was then performed to remove all visible NL adenoma. The exposed submucosa of the avulsion site and its margins were treated with controlled thermal ablation using STSC (ERBE effect 4, 80W). Scheduled surveillance colonoscopy was performed at 5 months (SC1) and 18 months (SC2) post the index procedure. The primary outcome was endoscopic and histological evidence of adenoma clearance. The secondary outcome was safety. Standard statistical analyses were performed to compare standard LSL with NL-LSL.

Results: From January 2012 to April 2016, 677 patients (mean age 69 years, 50.6% male) with 780 lesions (median size 35 mm (IQR 25–45 mm), 65.4% proximal colon) were referred for WF-EMR. 33 lesions were excluded due to suspicion for submucosal invasive cancer and the patients referred for surgery. EMR was performed on 83 NL-LSL and 664 standard LSL. 14 lesions were excluded at initial EMR as a two-stage procedure was required for their resection. Key comparisons between NL-LSL and standard LSL are presented in table 1. PANL-LSL (n = 33) were smaller and more likely to be non-granular (62.5 versus 33.9%, p = .003) than standard LSL. NNL (n = 50) were also more likely to be non-granular (46 versus 33.9%, p = .12) and were associated with previous biopsy (32 vs 13.8%, p = .001) and carbon particle suspension injection within 10 mm of the lesion (26 vs 3.8%, p < .001). Neither intra-procedural bleeding nor deep injury were more common in NL-LSL treated with CFA and STSC. The technique was technically successful in all cases. One perforation was recognised secondary to CFA in a previously attempted lesion and was successfully closed with endoscopic clips with no sequelae. Endoscopic recurrence at SC1 was not significantly different for PANL-LSL treated with CFA and STSC than LSLs treated with complete snare excision, whereas NNL-LSL recurred more frequently (16.0 vs 12.2%, p = .578 and 28.2 vs 12.2%, p = .005 respectively).

Conclusion: CFA and adjuvant STSC is a safe, effective and surgery-sparing therapy for the majority of NL-LSL. It is easy to use, inexpensive and does not require additional equipment. Early recurrence rates at SC1 are comparable between PANL-LSL and standard LSL. NNL-LSL recur more frequently. Non-granular LSLs were over-represented in both groups. They may be more susceptible to developing fibrosis after biopsy and therefore care should be taken to avoid significant tampering with these lesions prior to referral for definitive endoscopic treatment.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP016 SCISSORS TYPE KNIFE SIGNIFICANTLY IMPROVED SELF-COMPLETION RATE OF COLORECTAL ENDOSCOPIC SUBMUCOSAL DISSECTION PERFORMED BY SUPERVISED RESIDENTS: A PROSPECTIVE RANDOMIZED TRIAL

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Introduction: Colorectal endoscopic submucosal dissection (ESD) is currently not a common treatment for unskilled endoscopists because of technical difficulties. Recently, the scissors-type knife, SB knife Jr type (SB Jr), was launched to reduce the difficulty of colorectal ESD, although it can be a time-consuming procedure.

Aims & Methods: The aim of the present study was to evaluate the efficacy and safety of the combined SB Jr and Flushknife for colorectal ESD compared with using the Flushknife alone performed by supervised residents. This was a prospective randomized controlled trial in a cancer referral center. Eighty-five patients, with the same number of superficial colorectal neoplasms, were enrolled and randomly assigned to undergo ESD using the Flushknife alone (Flush group) or the SB Jr supported Flushknife (SB Jr group). The procedures were conducted by two residents. Primary endpoint was self-completion rate by the residents.

Abstract No: OP015

Table 1: lesions where cold forceps avulsion and snare tip soft coagulation (CFA and STSC) was used in the resection of PANL or NNL; p values represent comparison to LSL. Two stage procedures were excluded. SD – standard deviation, IQR – interquartile range, SC1 – surveillance colonoscopy 1, ICV – ileocaecal valve, PANL – previously attempted non lifting lesion, NNL – naïve non lifting lesion.

Patient	PANL n = 33	p	NNL n = 50	p	LSL n = 650
Age, mean (SD)	70.2 (8.6)	.121	73.0 (9.5)	**<.001**	66.9 (12.1)
Male, (%)	18 (54.5)	.598	29 (58.0)	.266	324 (49.8)
Lesion					
Median size (IQR)	25 (20–30)	**< .001**	37.5 (25–50)	.424	35 (25–45)
Morphology (%)					
Granular	8 (25.0)	**.003**	22 (44.0)	**.012**	323 (52.4)
Non granular	20 (62.5)		23 (46.0)		209 (33.9)
Unclassified	4 (12.5)		5 (10.0)		85 (13.8%)
Location (%)					
Rectum	11 (34.4)	.121	6 (13.0)	.091	121 (18.8)
Splenic to sigmoid	6 (18.8)		11 (23.9)		98 (15.2)
Transverse	5 (15.6)		14 (30.4)		132 (20.5)
Ascending and caecum (+ICV)	10 (31.3)		15 (32.6)		294 (45.6)
Submucosal fibrosis	33 (100)	**< .001**	50 (100)	**<.001**	179 (27.6)
Previous attempt at resection (%)	33 (100)	**< .001**	0 (0)	**< .030**	56 (8.7)
Previous biopsy (%)	na		16 (32.0)	**.001**	90 (13.8)
SPOT mark within 10 mm of lesion (%)	na		13 (26)	**< .001**	25 (3.8)
Histopathology (%)					
Conventional adenoma	25 (92.6)	.324	44 (90.0)	.147	482 (77.5)
Serrated adenoma	2 (7.4)		4 (10.0)		135 (21.7)
Cancer	0 (0)		0 (0)		4 (0.6)
Other	0 (0)		0 (0)		1 (0.2)
Procedure					
Duration, minutes, median (IQ range)	35 (18–45)	**.004**	25 (15–40)	**.003**	20 (10–30)
Intraprocedural bleeding requiring endoscopic control (%)	2 (7.7)	.078	11 (22.4)	.966	144 (22.2)
Deep injury (%)	6 (18.2)	.181	1 (2.0)	**.049**	66 (10.7)
Outcomes					
Endoscopic Recurrence at SC1 (%)	4 (16.0)	.578	11 (28.2)	**.005**	59 (12.2)

Results: Self-completion rate was 66.7% in the SB Jr group, which was significantly higher than that in the Flush group (39%, P = 0.01). Even after exclusion of four patients in the SB Jr group in whom ESD was completed using the Flushknife alone, the self-completion rate was significantly higher (62.8% vs. 39%; P = 0.03). The median procedure time among the self-completion cases did not differ significantly between the two groups (58.5 vs. 50.5 min; P = 0.14). No severe adverse events were observed in either group.
Conclusion: SB Jr supported Flushknife significantly improved residents' self-completion rate for colorectal ESD compared with the Flushknife alone, with no increase in procedure time or adverse events. (University hospital Medical Information Network Clinical Trials Registry number UMIN000009497).
Disclosure of Interest: All authors have declared no conflicts of interest.

OP017 FEASIBILITY, SAFETY AND EFFICACY OF KNIFE ASSISTED RESECTION (KAR) OF RECTAL POLYPS EXTENDING TO THE DENTATE LINE: HOW LOW CAN YOU GO?

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Introduction: Rectal polyps extending to the dentate line (RPDL) pose a technical challenge to endoscopic resection due to the narrow lumen, rich venous/haemorrhoidal plexus and proximity to the skin. Conventional snare EMR is challenging due to the restrcited space and lack of precision with the snare. This has led to the use of surgical techniques like TEMS and TAR for resection of RPDLs. **K**nife **A**ssisted snare **R**esection (KAR) allows for precise mucosal incision at the dentate line and the dissection of the polyp from the anorectal junction.
Aims & Methods: We aim to assess the feasibility, safety and efficacy of KAR for RPDLs. This is a prospective observational study of patients who underwent KAR with a mean follow-up of 32 months (range 1–83 months). All procedures were done on a day case basis and were carried out under sedation by two endoscopists using high-definition gastroscopes with a distal transparent cap. The polyp margin on the anal side was injected with lifting solution consisting of gelofusin, indigo carmine, 1% lignocaine and adrenaline. Haemostasis was maintained using a combination of the endoscopic knife and coag-grasper (Olympus Medical). A mucosal incision was extended around the margins of the polyp, followed by submucosal dissection to facilitate snare deployment to achieve complete polyp resection. Post-procedural antibiotics were not routinely given.
Results: A total of forty patients (20 female, median age 69 years) underwent KAR for RPDLs over the study period. The polyp characteristics and histology are described in Table 1. The curative resection after a single KAR was achieved in 33 (82.5%) patients. 7 of the 40 patients required further KARs, leading to a total curative resection rate to 97%. The risk factors for multiple resections are polyps measuring > 60 mm and encompassing > 50% of the circumference ($p < 0.01$). Overall, there was one complication where the patient had delayed bleeding which was managed conservatively. None of the patients experienced perforation, or post-procedural sepsis.

Table 1: Lesion characteristics and histology

Lesion size, median (range), mm	50 (12–150)
Morphology, n (%) LST – G, nodular mixed LST – G, homogenous LST – NG Is	29 (72.5) 2 (5) 2 (5) 7 (17.5)
Scarring, n (%)	13 (32.5)
Histology, n (%) Adenoma with LGD Adenoma with HGD Cancer Other – Condyloma acuminatum	30 (75) 6 (15) 3 (7.5) 1 (2.5)

Conclusion: This is the largest reported series of KAR for RPDLs. Our data demonstrates that for Western endoscopists, KAR is a very safe and effective technique in the treatment of RPDLs. As KAR is a viable alternative to full ESD, TEMS and TAR, it will play an increasingly significant role in the management of RPDLs.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP018 THERMAL ABLATION OF THE MARGIN OF THE POST ENDOSCOPIC MUCOSAL RESECTION (EMR) MUCOSAL DEFECT IS HIGHLY EFFECTIVE IN THE PREVENTION OF ADENOMA RECURRENCE FOLLOWING EMR. THE "SCAR" STUDY

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Introduction: Endoscopic mucosal resection (EMR) of large sessile and lateral spreading colonic lesions ≥20 mm (LSLs) is safe and effective. The main limitation is adenoma recurrence, which occurs in up to 20% at first surveillance colonoscopy (SC1), mandating a structured surveillance program. Surveillance procedures create compliance burdens, additional costs and potential patient morbidity. Endoscopically invisible micro-adenoma present at the margin of the resected LSL may account for adenoma recurrence. Adjuvant thermal ablation of the EMR defect margin may reduce adenoma recurrence rates.
Aims & Methods: A prospective multi-center randomized control study was performed (NCT01789749). The primary end-point was endoscopic and histological recurrence at SC1. Standard inject and resect EMR technique was used for all lesions. Exclusion criteria included previously attempted lesions, incomplete snare excision or involvement of the ileocaecal valve. After successful complete LSL excision by EMR and careful inspection of the defect to ensure no residual adenoma, mucosal defects were randomized 1:1 to either thermal ablation of the defect edges using snare tip soft coagulation (STSC) at 80w effect 4, or no additional treatment. SC1 was performed at 5–6 months, with standardized photo documentation and biopsies of the scar.
Results: Over 32 months to January 2015, 768 lesions ≥ 20 mm were referred for EMR at 4 centers (407 were enrolled, 48 were later excluded, 359 were randomized (null arm n = 178, active arm n = 181)). Patient, procedure and lesion characteristics were similar between the two groups. 267 (74.3%) patients have completed SC1. Endoscopic, and histologic recurrences at SC1 were significantly lower in the active arm (8/138 (5.8%) versus 26/129 (20.2%), $p < .001$, relative risk (RR) = 0.29 (95% CI 0.14–0.61) and 6/104 (5.8%) versus 20/97 (20.6%), p = 0.002, RR = 0.28 (95% CI 0.12–0.67) respectively) (Table 1). Endoscopic assessment of the post EMR scar had a sensitivity of 100%, a specificity of 98% and a negative predictive value of 100% for correctly identifying recurrence when compared to histology results. There was no difference in the rate of delayed bleeding between the active and null groups (8/124 (6.5%) versus 9/136 (6.6%), p = .957) and no difference in delayed perforation (0/124 (0%) vs 1/136 (0.7%), p = .341).

Table 1: Endoscopic and histological recurrence in patients randomised to null versus active arm of the SCAR study. Relative risk (RR); Confidence interval (CI)

	Null arm	Active arm	RR (95% CI)	P value
Endoscopic recurrence (95% CI)	26/129 20.2% (14.1–27.9%)	8/138 5.8% (2.9–11.0%)	0.29 (0.14–0.61)	< .001
Histological recurrence (95% CI)	20/97 20.6% (13.8–29.7%)	6/104 5.8 (2.7–12.0%)	0.28 (0.12–0.67)	0.002

Conclusion: Thermal ablation of the margin of the post EMR mucosal defect with STSC, results in significantly lower adenoma recurrence rates at first surveillance colonoscopy. Routine implementation of this simple and safe technique may enhance EMR efficacy and reduce surveillance requirements with fewer procedures and extended intervals.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP019 EVALUATION OF THE LONG-TERM OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION PERFORMED WITH A SCISSORS-TYPE KNIFE FOR EARLY COLORECTAL NEOPLASMS

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Introduction: Endoscopic submucosal dissection (ESD) is one of the most useful methods for treating early colorectal neoplasms, and an insulation-tipped knife, hook knife, or needle knife are conventionally used to perform ESD. However, because these devices are used without fixation of target tissue, there is the potential risk of complications due to an unexpected incision. To reduce the risk of complications associated with using a conventional knife to perform ESD, we used a scissors-type knife (stag beetle [SB] knife Jr, Akita Sumitomo Bakelite Co.) that maintains an adequate dissection layer and prevents an unexpected muscular layer injury. We previously reported that performing colorectal ESD with an SB knife Jr is an easy, safe, and technically efficient method. However, the long-term outcomes of this method are unknown.
Aims & Methods: We aimed to evaluate the feasibility and long-term outcomes of ESD performed with an SB knife Jr for treating early colorectal neoplasms. ESD was performed for 227 lesions in 211 patients (male:female ratio = 116:95; mean age = 69.1 years) between October 2010 and March 2016. We evaluated the patients' clinicopathological characteristics, en bloc resection rate, histological complete resection rate, R0 resection rate, tumor size, procedure time, complications, and long-term outcomes, including local recurrence, and the survival rate.
Results: The sites of the neoplasms were as follows: right colon, 94 lesions (41.4%); left colon, 58 (25.6%), and rectum, 75 (33.0%). Regarding the macroscopic type of lesions, there were 95 (41.9%) laterally spreading tumors (LSTs) of the granular type, 79 (34.8%) LSTs of the nongranular type, and 48 (21.1%) polypoid lesions. Histological examination findings showed that 102 lesions (44.9%) were intramucosal carcinomas, 22 (9.7%) were shallow submucosal invasive carcinomas (<1,000 μm), 25 (11.0%) were deep submucosal invasive carcinomas (>1,000 μm), and 78 (34.4%) were tubular adenomas. The mean size of the resected tumors was 32.0 ± 14.9 mm, and the median procedure time was 76.5 minutes (range, 10–420 minutes). The rates of en bloc resection, histological complete resection, and R0 resection were 98.2% (223/227 lesions), 93.8% (213/227), and 85.0% (193/227), respectively. All lesions were treated easily and safely without an unexpected incision, and no perforations occurred during the procedure. Delayed bleeding, delayed perforation, and rectal stricture occurred in 3.8% (6/227), 0.4% (1/227), and 0.4% (1/227) of the lesions, respectively, and all of these complications were cured conservatively. The median follow-up time was 558 days (range, 18–1,976 days). Local recurrence was observed in only 0.8% of the lesions (2/227). One patient (0.5%) died of colorectal cancer, and 5 patients (2.3%) died of other diseases. The 5-year overall survival rate and disease-specific survival rate were 94.8% and 98.7%, respectively.
Conclusion: ESD performed with an SB knife Jr is a technically efficient and safe method that is associated with favorable long-term outcomes in cases of early colorectal neoplasms.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP020 THE EFFICACY OF THE NOVEL TISSUE GRASPER-CLIPS TECHNIQUE FOR LARGE SIGMOID COLON PERFORATIONS IN EXPERIMENTAL SIMULATION MODEL

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Introduction: The incidence of iatrogenic colonic perforation has been gradually increasing. An effective method of treating iatrogenic perforations including visual recognition followed by immediate closure during colonoscopy reduces the incidence of sequelae and the morbidity and mortality. Perforations in the sigmoid colon are more frequent and more difficult to close due to the narrow lumen and considerable mobility.
Aims & Methods: This study was to evaluate the efficacy of combined use of endoclip and a novel tissue grasper closure technique using double channel endoscope for large colon perforation in sigmoid colon model. This study was designed as a prospective, randomized, experimental study using ex vivo porcine colorectal specimens. Thirty-five standardized and variable artificial perforations were closed in the hemoclip group (hemoclips) and twin-grasper group (hemoclips with a novel tissue grasper). We counted the number of hemoclips used per case to assess the cost and efficacy of the procedure.
Results: In the hemoclip group (n = 20), among the 1.5, 2.0, 2.5, and 3.0 cm defects, the mean number of clips (3.8 ± 0.8, 4.8 ± 0.8, 6.0 ± 1.6, and 8.4 ± 2.1, respectively, p = 0.001) and closure time (5.3 ± 1.8, 7.6 ± 0.5, 9.9 ± 3.3, and 13.9 ± 4.1 min, respectively, p = 0.001) differed significantly. In the twin-grasper group (n = 15), among the 2.0, 2.5, and 3.0 cm defects, the mean number of clips (4.0 ± 1.0, 5.0 ± 0.7, and 5.4 ± 1.1, respectively, p = 0.101) and closure time (7.7 ± 0.6, 8.3 ± 1.9, and 9.1 ± 2.7 min, respectively, p = 0.506) did not differ significantly. In 3 cm defects, the mean number of hemoclips used per case and total closure time were significantly lower in the twin-grasper group than the hemoclip group.

The results between hemoclip group and twin-grasper group

Groups	Number of endoclips	Procedure time(min)	Complete closure in water leak	Endoscopical fail
2.0 cm hemoclip	4.8 ± 0.8	7.6 ± 0.5	60%	0%
2.0 cm twin-grasper	4.0 ± 1.0	7.7 ± 0.6	80%	0%
p-value	0.207	0.776	0.545	
2.5 cm hemoclip	6.0 ± 1.6	9.9 ± 3.3	60%	0%
2.5 cm twin-grasper	5.0 ± 0.7	8.3 ± 1.9	60%	0%
p-value	0.233	0.384		
3.0 cm hemoclip	8.4 ± 2.1	13.9 ± 4.1	40%	20%
3.0 cm twin-grasper	5.4 ± 1.1	9.1 ± 2.7	60%	0%
p-value	0.022	0.06	0.58	

Conclusion: The twin grasper-clips technique seems to reduce the use of hemoclips and to result in more effective and rapid closure than does the conventional technique in large perforations of the sigmoid colon.
Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 10:30–12:00
HOT TOPICS FROM LATIN AMERICA – ROOM M

OP021 ENDOSCOPIC TREATMENT OF COMPLEX BILIARY STONES: SPYGLASS + ELECTROHYDRAULIC LITHOTRIPSY X BALLOON DILATION OF THE MAJOR PAPILLA - PRELIMINARY RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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Introduction: Endoscopic technique is the first choice for the treatment of bile duct stones, with success rates, ranging from 85% to 95%, and relatively low complication rate. However, some stones can become a great challenge for endoscopists. Complementary methods are available as mechanical lithotripsy and papillary balloon dilation after sphincterotomy. Single operator cholangioscopy combined with electrohydraulic lithotripsy (EHL) is emergent in this scenario.
Aims & Methods: We compare the success between two methods in the endoscopic removal of difficult bile duct stones: Spyglass associated with EHL X Balloon dilation of the major duodenal papilla. 100 patients were randomized into two groups. Group one was Spyglass + EHL and group 2 balloon dilation. From april of 2014 to present date (March 2016) we have enrolled 82 patients. Include criteria were: Over 18 years, difficult biliary stones, signed term of consent. All patients receive antibiotic prophylaxis with 400 mg of Ciprofloxacin IV. Failures in both groups were submitted to plastic stenting. To compare the methods we use the student t-test and Mann-Whitney Rank Sum test. Complications were analyzed by the Fisher test and Q squared.
Results: The average age was 55.1 +/− 16.9 years. Women corresponded to 76.54% of the patients. Success rate reached 77.77% in group 1 and 72.22% in group 2 (P = 0.568). Median procedure time was 71.08 minutes (17–150) in group 1 and 49.81 (17–180) in group 2 (P = 0.021). X-ray time was 10.89 minutes in group 1 and 10.16 in group 2 (P = 0.052). Median number of stones per patient was 2.31 (1–8) in group 1 and 2.22 (1–15) in group 2 (P = 0.605). Size of the stones in group 1 was 1.88 (1–3.5) and 2.09 (1–3.5) in group 2 (P = 0.015). Minor adverse event occurred in one patient of each group. There was one death not related to procedure (cardiologic cause).
Conclusion: To our knowledge this is the largest randomized controlled trial comparing this two techniques. We found so far an overall success rate of 77.77% in Spyglass + EHL procedure and 72.22% in balloon dilation group.

Abstract No: OP022

Characteristics of procedures, patients and outcome

PATIENT	AGE/ GENDER	CLINICAL PICTURE	NAIVE VS REFRACTORY	NUMBER OF PACKED RBC TRANSFUSED	NUMBER OF HYBRID APC TREATMENTS/ TIME	GAVE TYPE	COMPLICATIONS	PRE HYBRIDKNIFE HB (GR/DL)	POST HYDRIBKNIFE HB AT 1M (GR/DL)	POST HYBRYDKNIFE HB AT 6M (GR/DL)
1	58/F	Anemia	Naive	2	1	Watermelon	None	8	13.6	14.2
2	60/F	Melena	Refractory (4 APC)	10	1	Watermelon	Mild abdominal pain	3.5	6.6	13.3
3	61/F	Melena	Refractory (9 APC)	15	1	Punctate	None	6.1	9.2	12.9
4	79/F	Melena	Refractory (3 BL)	9	1	Watermelon	None	4.2	10.8	13.4
5	67/F	Anemia	Refractory (4 APC/4 BL)	12	2	Watermelon	None	6.3	8.4	13.1
6	55/F	Anemia	Naive	2	1	Punctate	None	7.2	10.1	14.5
7	67/F	Anemia	Naive	8	1	Watermelon	Mild abdominal pain	6.5	11.4	14.1
8	48/M	Melena	Naive	6	1	Watermelon	None	7.2	10.2	15.1
9	89/F	Melena	Refractory (5 APC)	14	1	Punctate	None	4.9	9.3	13
Total	Mean 64.7 ± 12.5 8F/ 1M	44.4% Anemia 55.6% Melena	44.4% Naive 55.6% Refractory	Median 9 (2–15)	88.8% 1 Treatment 21.2% 2 Treatments	66.6% Watermelon 33.4% Punctate	77.8% No complications 22.2% Mild abdominal pain	5.98 ± 1.49	9.95 ± 1.96	13.7 ± 0.76

It is important highlight that only one session of Spyglass + EHL was performed in each patient of our protocol. Better success rates can be achieved with two or more sessions and increase up to 90%. Cross-over of the failure cases in both groups is bringing us a very interesting result and suggests that in some cases the methods can be complementary. There was no statistical difference between the groups, although spyglass group had numerically a little higher success rate. The study provides us an evidence-based algorithm of difficult stones endoscopic treatments. In addition, we observed potential advantages when we associate the methods, providing one step more before declaring endoscopic failure in treating a difficult biliary stone.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP022 SAFETY AND EFFICACY OF HYBRID-APC IN GASTRIC ANTRAL VASCULAR ECTASIA (GAVE): A PILOT STUDY

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Introduction: Antral vascular ectasia (GAVE) is a capillary-like vascular malformation usually located in gastric antrum. Liver cirrhosis, autoimmune, cardiac and chronic renal disease are ussualy concomitant. Patients often require high number of RBC transfusions because of anemia or melena. Treatment includes argon plasma coagulation (APC), Band ligation (BL) and radiofrequency ablation (RFA). Patients usually respond to 3 to 5 APC, or 2 to 3 band ligation (BL) sessions, if not, refractory GAVE is considered and other treatments should be offered. RFA is effective but expensive and requires at least two sessions. Hybrid-APC is new technique that combines submucosal injection of saline solution to create a ''safety cushion'' with the use of APC, this could have the advantage of a deeper and safer treatment compared with other endoscopic modalities.

Aims & Methods: We aimed to evaluate the safety and efficacy of hybrid-APC in naïve or refractory GAVE patients. Methods: This is a prospective, longitudinal and comparative (before and after) pilot study that includes symptomatic patients with GAVE (endoscopic and histologic diagnosis). Naïve or refractory patients (defined as more than 5 previous APC or 3 BL without endoscopic, clinical and laboratorial response) between 18 and 90 years old were included. We excluded patients with GAVE without clinical manifestations or anemia of other GI source. After a creation of a ''saline cushion'' with the APC catheter in the GAVE zone, all received APC with forced coagulation at 80w effect 2 in a single session and then they were followed at 1,3 and 6 months. New session was applied if anemia and endoscopic picture of GAVE were documented. Characteristics of the patients were described and expressed in means and SD or median and IQR and percentages as appropriate. Comparisons between quantitative variables was done using paired T-test and considering $p < 0.05$ as statically significant.

Results. Between July 2015 and March 2016 9 patients were included, 8 women and 1 men. Mean age was 64.7 ± 12.5yo. 44.4% presented anemia and 55.6% melena. Median number of transfusions was 9 (2–15). 3 had liver cirrhosis, 2 chronic renal failure, 1 cardiac disease and 3 without any association. GAVE type was ''watermelon'' in 6 and ''punctate'' in 3. 44.4% were naïve and 55.6% refractories to previous treatment (3 in APC and 2 with BL). The median previous treatments in refractory patients were 4 (3–9). All patients reached normal Hb levels after 6months. The mean difference between prehybrid-APC (5.98 ± 1.49gr/dl) and 6m after hybrid-APC (13.7 ± 0.76gr/dl) was +7.74 gr/dl ($p < 0.000$/CI 95% 6.84–8.64) student T-test. 8 patients received 1 session and 1 required 2. No major complications were observed (Table 1).

Conclusion: Based on these preliminary results, Hybrid-APC is safe and effective for the treatment of GAVE (nave or refractory) with the advantage of needing only 1 or maximum 2 applications and with excellent results at medium term.

Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 10:30–12:00

PREVENTION OF GI CANCERS: NUTRITION AND CHEMOPREVENTION – ROOM 1.61/ 1.62

OP023 CD24 INDUCES THE ACTIVATION OF B-CATENIN IN INTESTINAL TUMORIGENESIS

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Introduction: CD24 is a GPI-linked protein that functions as an adhesion molecule and is overexpressed at an early stage of CRC.The Wnt/b-catenin signaling pathway plays an important role in CRC carcinogenesis process. We had shown that CD24 could affect the tumorigenesis process in Apc Min mice

Aims & Methods: Aim to study the cellular interactions between CD24 and β-catenin, and their effects on intestinal tumorigenesis Methods CD24-inducible 293T-Rex cells previously developed in our lab and SW480 CRC cells stably transfected with CD24were used to study this interaction in vitro. Apc Min and CD24 knockout (KO) mice, both on a C57BL/6J genetic background, were crossed to generate double KO transgenic mice. Genotypes were routinely verified by analysis ofDNA extracted from tail biopsies. Small and large bowel polyps were counted macroscopically following methylene blue staining and histology was verified microscopically. Colonic polyps were measured and counted

using mice colonoscopy. Histology confirmed by an experienced pathologist was used to study this interaction in vitro.
Results: In vitro Western blotting analyses showed that expression of CD24 in 293T-Rex cells induced the activation of β-catenin and co-immunoprecipitation studies of CD24 and β-catenin indicated that these two proteins might beinteracting, while down-regulation of CD24 in SW480 cells caused a decrease in the levels of active β-catenin and cytoplasmic/nuclear fractionation showed that more active β-catenin enters the nucleus in cells thatexpress CD24 (clone1) compared to control cells (clone 4). In addition, in both cell lines, TOP/FOPluciferase reporter assay showed a significant increase in Luciferase activity upon CD24 expression induction Depletion of CD24 alleles in Apc Min mice led to a significant reduction in the number of polyps in the intestine.C57BL6/J mice carrying the Apc Min mutation develop ∼24.3 ± 3.7 adenomas and several carcinomas in the smallintestine by the age of 16 weeks. The ApcMin/CD24 +/- mice developed 8 ± 1.4 polyps and ApcMin/CD24 -/- (doubleKO) mice developed ∼7 ± 1.7 polyps (p = 0.006). Colonoscopy showed a significant reduction in thenumber and size of polyps upon depletion of CD24 alleles. The ApcMin displayed severe splenomegaly (355 ± 68 mg)compared to (205 ± 51 mg) in ApcMin/CD24 +/- mice and (141 ± 49 mg) in double KO mice similar to WT mice (p = 0.006). Hb level was 3.8 ± 2.5 in the ApcMin significantly lower than in the double KO mice (8.2 ± 0.9) and the WT (p = 0.0009)
Conclusion: 1. CD24 plays a major role in intestinal tumorigenesis 2. Knocking down even one copy of CD24 almost completelyabolished formation in vivo, and prevent anemia and splenomegaly the whole mark of intestinal blood loss seeing inthe ApcMin 3. CD24 interacts with the Wnt pathway by activating β-catenin 4. Down regulation of CD24 maybe animportant aim in the therapy of CRC
Disclosure of Interest: N. Arber: Consultation Fee: Bio-View, Check-Cap, Bayer Stock Shareholder: Micromedic, Gi-VieW
All other authors have declared no conflicts of interest.

OP024 LOSS OF PTPN2 IN MACROPHAGES AGGRAVATES COLITIS BUT PROTECTS FROM COLORECTAL TUMOUR FORMATION

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Introduction: Variants in the gene locus encoding protein tyrosine phosphatase non-receptor type 2 (PTPN2) are associated with Crohn's disease (CD) and ulcerative colitis (UC). We have previously shown that loss of PTPN2 in T cells results in enhanced colitis and signs of autoimmunity. Inflammasomes form upon cytosolic presence of danger molecules and induce the cleavage of pro-IL-1β and pro-IL-18 into their active forms. Secretion of IL-1β is an important activator of innate and adaptive immune functions, while IL-18 is involved in epithelial cell protection.
Aims & Methods: In this study, we aimed to address whether loss of PTPN2 in macrophages affects inflammasome activation and whether this affects colitis severity and susceptibility for colorectal cancer. To specifically delete PTPN2 in macrophages, mice with a floxed PTPN2 gene were crossed with mice expressing Cre-recombinase under the Lysozyme promoter (PTPN2-LysMCre mice). Acute colitis was induced in 10–12 week old female mice by administration of 2% DSS for 7 days, chronic colitis by administration of four cycles of 1.5% DSS for 7 days, followed by 10 days normal drinking water each. For tumour induction, mice were injected with AOM at day 1 and day 10 of each DSS cycle during chronic colitis induction.
Results: PTPN2-deficient macrophages show enhanced levels of cleaved caspase-1 and IL-1β upon in vitro activation of the NOD-like receptor protein 3 (Nlrp3) and absent in melanoma 2 (AIM2) inflammasomes, finally resulting in enhanced secretion of active IL-1β and IL-18. This effect was mediated by increased phosphorylation of the inflammasome adaptor apoptosis associated speck-like protein containing a CARD (ASC), a mechanism recently shown to promote inflammasome activation. In vivo, PTPN2-LysMCre mice suffered from pronounced acute colitis, accompanied with enhanced secretion of mature IL-1β and IL-18, but concomitant decreased IL-10 production. On the other hand, no differences were observed in T cell subsets or other T helper cell associated cytokine expression/secretion. In chronic colitis, PTPN2-LysMCre mice again showed enhanced inflammasome activation in the intestine, and further developed metaplasia to squamous epithelium in the distal part of the colon epithelium, but there was no overt effect on colitis severity. Of interest, however, and in contrast to their WT littermates, PTPN2-LysMCre mice did not develop any tumours upon AOM-DSS treatment. Interestingly, when IL-1β was inhibited, acute colitis severity in PTPN2-LysMCre mice did not differ from that observed in WT animals. Further, inhibition of IL-1β restored susceptibility to AOM-DSS induced tumours in PTPN2-LysMCre mice.
Conclusion: PTPN2 is an important regulator of inflammasome activation, and loss of PTPN2 in macrophages enhances acute colitis. Further, during chronic intestinal inflammation, macrophage-specific loss of PTPN2 promotes metaplasia to squamous epithelium, but at the same time protects from tumour formation. This indicates an important, previously under-estimated macrophage-specific role for PTPN2 during intestinal inflammation and tumour induction.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 10:30–12:00
NEW PERSPECTIVES IN DIAGNOSTIC AND THERAPEUTIC EUS – ROOM N2

OP025 LOW PROCUREMENT YIELD AND DIAGNOSTIC ACCURACY OF EUS-GUIDED FINE NEEDLE BIOPSY OF TRANSDUODENAL LESIONS USING THE 19-GAUGE FLEXIBLE NEEDLE: A LARGE MULTICENTER PROSPECTIVE STUDY

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Introduction: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the procedure of choice to obtain samples for reaching the definitive diagnosis of lesions of the gastrointestinal (GI) tract and of adjacent organs (1). The procedure is safe and very accurate, especially when rapid on-site evaluation (ROSE) of the adequacy of the collected specimens is performed. However, in centers where ROSE is not available, it has been suggested that the performance of EUS-fine needle biopsy (EUS-FNB) can result in a greater chance to reach a diagnosis than a typical EUS-FNA sample. Based on a previous study (2), which reported a 19-gauge flexible needle to be able to sample transduodenal lesions and be diagnostic in all 32 included patients, an algorithm for EUS-tissue acquisition (EUS-TA) of solid lesions from the duodenum depending on the availability of ROSE has been proposed. Thus, in institutions with no availability of ROSE, for lesions accessed from the duodenum, which represent the most difficult sampling position because of the stiffness induced by the needle assembly on the echoendoscope shaft, the authors recommended the use of a 19-gauge needle made of nitinol with increased flexibility (3).
Aims & Methods: To test the validity of this recommendation we performed a prospective multicenter study aimed at evaluating the technical feasibility, procurement yield, and diagnostic accuracy of this newly developed 19-gauge nitinol flexible needle in patients with solid lesions or enlarged lymph nodes that could be punctured only from the duodenum. Consecutive patients with solid lesions who needed to undergo EUS sampling from the duodenum were prospectively enrolled in 6 tertiary care referral centers. Puncture of the lesion was performed with the 19-gauge flexible needle (Expect™ 19 Flex and Slimeline Expect™ 19 Flex) and at least 3 needle passes were performed in each case. The feasibility, procurement yield, and diagnostic accuracy were evaluated.
Results: 246 patients (144 males, mean age 65.1 ± 12.7 years) with solid lesions (203 cases, 82.5%) or enlarged lymph nodes (43 cases, 17.5%) were enrolled. The mean size of the target lesion was 32.6 ± 12.2 mm. The procedure was technically feasible in 228 (92.7%) patients, with an overall procurement yield of 76.8%. Two centers had suboptimal procurement yields of 66.7% and 64.2% (table). Major complications occurred in six patients (2.4%): two cases of bleeding, two of mild acute pancreatitis, one perforation that required surgery and one duodenal hematoma that resolved spontaneously. Considering malignant vs. non-malignant diseases, the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic accuracy were 70.7% (95% CI, 64.3–76.6), 100% (95% CI, 79.6–100), 35.3 (95% CI. 2.3–549.8), 0.3 (95% CI, 0.2–0.4), and 73.6% (95% CI, 67.6–79), respectively. On multivariate analysis, the only determinant of successful EUS-FNB was the center in which the procedure was performed.

Study Center	Technical success rates	Procurement yield
A	64/67 (95.5)	43/67 (64.2)
B	44/45 (97.8)	38/45 (84.4)
C	39/40 (97.5)	34/40 (85)
D	37/39 (94.9)	32/39 (82.1)
E	20/30 (66.7)	20/30 (66.7)
F	24/25 (96)	22/25 (88)

Conclusion: The findings of our study, with a procurement yield and diagnostic accuracy of only 76.8% and 73.6%, respectively, redefine the role of the 19-gauge flexible needle for transduodenal EUS-FNB. Thus, the correct diagnosis was missed in about 1 every 4 patients. Since the prevalence of malignant disease in our population was 86%, this finding cannot be considered negligible. The results of our study are of particular interest since we showed that the diagnostic performance of the 19-gauge flexible needle has a wide intercenter variability, not depending on the expertise of the endoscopist. In conclusion, our results suggest

Abstract No: OP026

Comparison of procedure outcomes according to needle size and use of suction

		22G No Suction (n = 88)	22G Suction (n = 88)	25G No Suction (n = 85)	25G Suction (n = 91)	p-value
ROSE-Diagnostic adequacy: n (%)		88 (100)	86 (97.7)	85 (100)	91 (100)	0.182
Total no. of passes for onsite diganostic adequacy	Mean (SD)	1.8 (1.9)	2.8 (2.7)	1.7 (1.5)	2.0 (2.2)	<0.001
	Median (IQR)	1 (1–2)	2 (1–3)	1 (1–1)	1 (1–2)	
Specimen bloodiness: n (%)	Mild	52 (59.1)	32 (36.4)	55 (64.7)	43 (47.3)	0.008
	Moderate	20 (22.7)	34 (38.6)	20 (23.5)	30 (33.0)	
	Severe	16 (18.2)	22 (25.0)	10 (11.8)	18 (19.8)	
ROSE-Diagnostic performance: % (95% CI)	Accuracy	98.9 (93.8–100)	93.2 (85.7–97.5)	97.6 (91.8–99.7)	97.8 (92.3–99.7)	0.230
	Sensitivity	100 (95.1–100)	92.6 (83.7–97.6)	97.1 (89.9–99.6)	98.8 (93.2–100)	-
	Specificity	93.3 (68.1–99.8)	95.0 (75.1–99.9)	100 (79.4–100)	90.9 (58.7–99.8)	-
	PPV	98.6 (92.7–100)	98.4 (91.6–100)	100 (94.6–100)	98.8 (93.2–100)	-
	NPV	100 (76.8–100)	79.2 (57.8–92.9)	88.9 (65.3–98.6)	90.9 (58.7–99.8)	-
Diagnostic cell block: n (%)	71 (80.7)	63 (71.6)	56 (65.9)	67 (73.6)	0.177	
EUS-FNA-Diagnostic performance: % (95% CI)	Accuracy	98.9 (93.8–100)	93.2 (85.7–97.5)	98.8 (93.6–100)	98.9 (94.0–100)	0.060
	Sensitivity	98.6 (92.6–100)	92.6 (83.7–97.6)	98.6 (92.2–100)	98.8 (93.2–100)	-
	Specificity	100 (78.2–100)	95.0 (75.1–99.9)	100 (79.4–100)	100 (71.5–100)	-
	PPV	100 (95.0–100)	98.4 (91.6–100)	100 (94.7–100)	100 (95.4–100)	-
	NPV	93.8 (69.8–99.8)	79.2 (57.8–92.9)	94.1 (71.3–99.9)	91.7 (61.5–99.8)	-
Technical failure: n (%)	0	5 (5.7)	1 (1.2)	7 (7.7)	0.011	
Adverse events: n (%)	4 (4.5)	3 (3.4)	7 (8.2)	10 (11.0)	0.179	

that the use of the 19-gauge flexible needle for transduodenal FNB cannot be widely suggested and its implementation should receive a local validation, with careful evaluation of both the local technical success rates and diagnostic yields.
Disclosure of Interest: L. Palazzo: Laurent Palazzo has received educational funds from Boston Scientific Corp.
A. Larghi: Alberto Larghi is a consultant for Boston Scientific Corp.
All other authors have declared no conflicts of interest.

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OP026 RANDOMIZED TRIAL COMPARING THE 22 AND 25 GAUGE NEEDLES USING THE SUCTION-IN AND NO-SUCTION (SINS) TECHNIQUES FOR EUS-GUIDED FNA OF PANCREATIC MASSES

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Introduction: Prior studies comparing the 22 and 25G needles and utility of suction for EUS-FNA of pancreatic masses were indefinite due to patient heterogeneity and small sample size. Also, the optimal tissue acquisition technique for onsite and offsite specimen assessment is unclear.
Aims & Methods: We aimed to compare the 22 and 25G needles and evaluate the role of suction in EUS-FNA of pancreatic masses. Methods: Consecutive patients with solid pancreatic masses were randomized to 1 of 4 cohorts: 22G needle with suction, 22G needle without suction, 25G needle with suction and 25G needle without suction. After two dedicated passes were performed for cell block (offsite) evaluation, an experienced pathologist rendered rapid onsite evaluation (ROSE) for specimen adequacy. Cross-over to alternate arms was permitted if ROSE was indeterminate at 8 passes. Diagnostic accuracy of ROSE was confirmed by final pathology interpreted by a second independent pathologist. Final diagnosis was established by surgical histology or patient follow-up at 12 months. Main outcome measures were to compare diagnostic adequacy and accuracy of ROSE, number of passes to establish onsite diagnostic adequacy, specimen bloodiness, diagnostic accuracy of cell block and operating characteristics between cohorts. To detect a 15% difference in diagnostic accuracy and cell block yield between the type of needles and use of suction at 80% power and type 1 error of 0.05, the total sample size was estimated at 352 patients.
Results: The median age of 352 patients was 69 years, 54.3% male, median size of mass was 3cm with vascular invasion in 55.4% and FNA passes were transduodenal in 68.5%. The final diagnosis was adenocarcinoma or other malignancy in 290 (82.4%) and benign or chronic pancreatitis in 62 (17.6%) patients. Interim analysis pending completion of 12-month follow-up is shown in the Table.
Conclusion: While there was no overall difference in operating characteristics between the 22 and 25G needles, the use of suction must be avoided in centers utilizing ROSE as it increases specimen bloodiness and number of passes needed to achieve diagnostic adequacy, particularly with 22G needles.
Disclosure of Interest: R. Hawes: Consultant for Boston Scientific Corporation and Olympus America Inc.
S. Varadarajulu: Consultant for Boston Scientific Corporation and Olympus America Inc.
All other authors have declared no conflicts of interest.

OP027 EUS-GUIDED BILIARY DRAINAGE VERSUS PERCUTANEOUS BILIARY DRAINAGE: RESULTS OF A MULTICENTER RANDOMIZED PHASE II STUDY

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Introduction: For 10 years, EUS-guided biliary drainage has been an option as EUS guided choledoco-duodenostomy or hepatico-gastrostomy. Two small randomized studies showed no difference between EUS guided BD vs Percutaneous drainage. The aim of this work was to evaluate in a multicenter randomized study the percutaneous biliary drainage (PBD) vs EUS-guided biliary drainage (EBD) in patients with an obstructive jaundice when ERCP failed or impossible due do duodenal involvement or previous Surgery as gastrectomy or Whipple resection.
Aims & Methods: Inclusion criteria were: benign or malignant obstructive jaundice with failure of ERCP. Exclusion criteria were: ascites, blood coagulation disorders, stenosis of the right bile duct. Randomization ratio was 1: 1, with a stratification by indication (benign vs malignant) and by centers (4 centers were included). The route of the biliary drainage was randomized as PTB (arm A) and EGD (arm B). But the choice of the EGD technique was free for the operator as (Anterograde transpapillary stenting, choledoco-duodenostomy, hepatico-gastrostomy). The main goal was to evaluate the specific morbidity and mortality during the 30 days following the biliary drainage in each arm. To prove a decrease of 50% of the morbidity rate in the EGD arm (A = 30%, B = 15%), 55 patients should be included in the EGD arm (B) as a Simon plan in 2 steps with an intermediate analysis to exclude severe adverse events in the EGD arm. Intermediate analysis was performed after inclusion of 47 patients and showed significantly higher morbidity rate in the PTB arm. Then, PTB arm was stopped and inclusions were made only in the EGD arm.
Results: Sixty-five patients from 4 centres were screened between 2011 to 2015. Eight patients were excluded (ascites, ERCP finally feasible). Fifty-six patients were randomized (Arm A = 21/ Arm B = 35). The 2 groups were similar except the sex ratio (Female: Arm A, n = 11; Arm B, n = 7; p = 0.012). The biliary stenosis was malignant in 52 cases (Arm A = 19; Arm B = 33). Biliary access was successful in 100% in the Arm A and in 94% in the Arm B. However, technical success was respectively 17/21 (85%) in the Arm A and 33/56 (94%) in the Arm B. No difference was showed regarding the decrease of the bilirubin level after the drainage in the two arms. Median hospitalization duration was shorter in the Arm B (6 days range 3–30 days) than the Arm A (12 days range 2–32 days). Ten patients died 30 days following the biliary drainage, 7 deaths were reliable to biliary drainage procedure (Arm A = 3, Arm B = 4) p = 1. Specific complication occurred in twelve patients (62%) in the Arm A vs 7 (31%) in the Arm B p = 0,0276: Bleeding (A = 5[24%], B = 3[9%]; ns), Cholangitis (A = 3 [14%], B = 1[3%]), Sepsis not related to cholangitis (A = 7 [35%], B = 5 [25%]), Peritonitis (A = 1[5%], B=1[3%], ns), external biliary fistula (A = 1[5%], B = 0[0%], ns).

Conclusion: This randomized prospective study showed similar high technical and clinical success rates in PTB and EUS-guided biliary approach. Specific complication rate was higher in the PTB arm than in the EUS-guided biliary drainage. EUS guided biliary drainage should be the first therapeutic approach after failure of ERCP, in selected patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP028 EUS-GUIDED GASTROENTEROSTOMY IS COMPARABLE TO ENTERAL STENTING IN TERMS OF TECHNICAL FEASIBILITY AND CLINICAL SUCCESS WITH LOWER RATES OF RE-INTERVENTION: AN INTERNATIONAL MULTICENTER COMPARATIVE STUDY

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Introduction: Endoscopic enteral stenting (ES) in malignant gastric outlet obstruction (GOO) is limited by high rates of stent obstruction. EUS-guided gastroenterostomy (EUS-GE) is a novel procedure that potentially offers sustained patency without tumor ingrowth/overgrowth.
Aims & Methods: The aim of this study is to compare EUS-GE with ES in terms of 1) need for re-intervention, 2) technical success (proper stent positioning as determined via endoscopy and fluoroscopy), 3) clinical success (ability to tolerate oral intake without vomiting), and 4) procedure-related adverse events (AEs). This is a multicenter retrospective study of all consecutive patients who underwent either EUS-GE at 4 centers between 2013 and 2015 or ES at one center between 2008 and 2010.
Results: A total of 82 patients (mean age 66-years ± 13.5 and 40.2% female) were identified: 30 in EUS-GE and 52 in ES. Technical and clinical success were not significantly different 86.7% EUS-GE vs. 94.2% ES ($p = 0.2$) and 83.3% EUS-GE vs. 69.2% ES ($p = 0.2$) respectively. Need for re-intervention, however, was significantly lower in EUS-GE 3.3% vs. 46.2% ES ($p < 0.001$). Post-procedure mean length of hospitalization was comparable at 11.3 days ± 6.6 for EUS-GE vs. 9.5 days ± 8.3 for ES ($p = 0.3$). Rates and severity of AEs (as per the ASGE lexicon) were also similar occurring in 16.7% EUS-GE vs. 11.5% ES ($p = 0.5$). On multivariable analysis, EUS-GE was independently associated with fewer needs for re-intervention (OR 0.03, $p = 0.002$).
Conclusion: EUS-GE may be ideal for malignant GOO with comparable effectiveness and safety to ES while being associated with fewer requirements for re-intervention.
Disclosure of Interest: M. Khashab: Consultant for Boston Scientific
All other authors have declared no conflicts of interest.

OP029 DEDICATED BI-FLANGED METAL STENT WITH ENDOSCOPIC "STEP-UP APPROACH" REDUCES THE NEED FOR DIRECT NECROSECTOMY IN WON - LARGE EXPERIENCE FROM A SINGLE TERTIARY CARE CENTRE

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Introduction: EUS-guided trans-mural drainage using plastic stents may be inadequate for pancreatic fluid collections (PFC) having solid debris, i.e. "Walled Off Necrosis (WON)". Recent publications have reported variable outcome using covered metal stents for PFC drainage, using either conventional or dedicated metal stents. There are few reports on dedicated metal stent for EUS guided drainage of only WON. Treatment strategy using a "step-up approach" by endoscopic methods has not been systematically addressed.
Aims & Methods: To evaluate the efficacy of a dedicated covered bi-flanged metal stent (BFMS) using a "step-up approach" in drainage of symptomatic WON. Consecutive patients with symptomatic WON undergoing EUS-guided drainage using BFMS were included from January 2013 to December 2015. Patients were reassessed at 48–72 hours for symptom improvement and reduction in size of collection. The endoscopic interventions were approached in a step-up manner to manage patients who did not have expected clinical improvement after index drainage of WON with BFMS. Declogging of blocked lumen of BFMS was the first step. Second step involved a naso-cystic catheter (NCT) placement through BFMS followed by intermittent irrigation with saline and hydrogen peroxide. Third step involved direct endoscopic necrosectomy (DEN), which was performed through BFMS in patients with persistent symptoms. Patients were reassessed between 4 to 8 weeks and BFMS were removed after documenting radiological resolution of collection. The main outcome measures studied were technical success, clinical success, adverse events and the need for various endoscopic reinterventions, using step-up approach.
Results: A total of 205 patients (mean age 34.8 ± 12.5 years, 181 males) underwent EUS-guided drainage with BFMS. Technical success was achieved in 203 patients (99%). Peri-procedure adverse events occured in 8 (3.9%) patients (bleeding in 6 and perforation in 2). WON resolved with BFMS in 158 (74.6%). Endoscopic re-intervention, required in 49 (23.9%) patients, for persistent or new onset symptoms, was approached in step-up manner. At first, declogging of BFMS alone succeeded in 10 out of 21. Second step of naso-cystic placement through BFMS followed by irrigation with saline and hydrogen peroxide improved 16 out of 39. At final step, DEN improved outcome in 19 out of 23. BFMS migrated in 5 (2.9%) patients (2 internal, 3 external). Four patients failed to achieve clinical success, requiring surgery ($n = 2$) or additional percutaneous drainage ($n = 2$). Overall, clinical success was achieved in 198 (96.5%) patients.
Conclusion: EUS-guided drainage with BFMS is safe and effective in WON. BFMS substantially reduces the requirement of DEN. Success rate incrementally improves with endoscopic step-up approach.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP030 CLINICAL OUTCOME AFTER BILIARY DRAINAGE FOR METASTATIC COLORECTAL CANCER: SURVIVAL ANALYSIS AND PRONOSTIC FACTORS

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Introduction: Biliary obstruction secondary to colorectal cancer liver metastases is associated with a poor prognosis without drainage especially when chemotherapy cannot be re started. However, little information is known about clinical benefits of such endoscopical and radiological interventions, as well as the impact of chemotherapy achievement. The aim of this study was to determine survival after biliary drainage and look for prognostic factors.
Aims & Methods: This retrospective study analyzed patients from two expert French centers between 2005 and 2014. Patients were included after first biliary endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) drainage for biliary obstruction secondary to liver metastases of colorectal cancer occurring during chemotherapy. Demographical, biochemical, and outcome data were registered. We used Kaplan-Meyer analysis to assess survival after first biliary stenting and cox models for univariate and multivariate analysis.
Results: The final analysis included 69 patients. Sixty patients underwent ERCP, 2 underwent PTC drainage, and 7 underwent both techniques. Overall median survival was 115 days (5–1876). In univariate analysis, a previous liver surgery, a technical and a functional success of drainage and restarted chemotherapy were significantly associated with an improved survival. Chemotherapy was restarted after a median of 27 days. When drainage was efficient survival improved from 33 days to 262 days ($p < 0.001$). In multivariate analysis, protective factors for survival included a previous hepatectomy (hazard ratio (HR) 0.41, 95% CI [0.22–0.75], $p = 0.004$), functional success drainage (HR 0.29, 95% CI [0.15–0.56], $p = 0.0002$). Predictive factors for death included increased lines of chemotherapy (HR 1.68, 95% CI [1.36–2.06], $p < 0.001$), and fever before drainage (HR 2.97, 95% CI [1.39–6.36], $p = 0.005$).
Conclusion: This the first study concerning benefits of biliary drainage during the course of chemotherapy of colorectal cancer with malignant biliary obstruction. A successful biliary drainage leads to improved survival and allows achievement of chemotherapy for 50% of patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 10:30–12:00
MECHANISMS OF PRIMARY SCLEROSING CHOLANGITIS – ROOM L7

OP031 BILE DUCT INFLAMMATION ASSESSED BY BILIARY CALPROTECTIN AND NEUTROPHILS CORRELATES WITH RISK OF BILIARY DYSPLASIA AND CHOLANGIOCARCINOMA

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of biliary epithelium leading to strictures intra- and extrahepatic bile ducts and finally to cholestasis and secondary biliary cirrhosis (1). The chronic inflammation is associated with increased proliferation of biliary epithelial cells and a markedly increased risk of biliary dysplasia and cholangiocarcinoma (2), SIR ranging from 55 to 973 (3–4). The lifetime risk of CCA is around 10% (5). CCA is the most common reason for death among PSC patients (6–7). CCA is thought to develop through metaplasia, low-grade dysplasia, and high-grade-dysplasia (8). Chronic inflammation has been regarded as risk factor for dysplasia and malignancy. Because CCA is generally a contraindication for liver transplantation (LT) and the prognosis of CCA is dismal, it would be feasible to screen the dysplastic changes of the biliary epithelium to treat patients with LT before development of advanced malignancy, detected based on imaging methods or symptoms.

Aims & Methods: We aimed to evaluate the grade of bile duct inflammation as a risk factor for dysplasia and cholangiocarcinoma in PSC patients. In total, 210 patients with confirmed PSC referred for ERC for disease surveillance were included (121 females, 179 males). After cannulation of the common bile duct bile sample was aspirated using balloon catheter and immersed immediately in liquid nitrogen (−196°C) and then stored in −20°C. Brush cytology (BC) was collected both from extra- and intrahepatic bile ducts for Papanicolau staining for grading dysplasia and inflammation. Neutrophilic inflammation in BC was evaluated semiquantitatively (0 = neutrophils/epithelial cells <0.05, 1 = neutrophils/epithelial cells 0.05–0.4, 2 = neutrophils/epithelial cells >0.4). Bile concentrations of calprotectin were analyzed using ELISA method. Liver function tests were taken at the time of ERC. ERC findings were scored according to modified Amsterdam score, [Helsinki score] (9).

Results: Bile duct inflammation assessed by biliary calprotectin correlated significantly with neurophils in BC, with S-CA19–9, S-ALP and S-AST levels and interestingly with S-IgG. Patients with dysplasia or CCA had markedly elevated B-calprotectin, as compared to those without dysplasia (34.7 vs 4.0 mg/l, respectively), see table. The risk of dysplasia was associated with advanced bile duct disease, (mERC score >8 vs <4, OR 15.2 [95% 1.8–127.9], $p=0.012$), increased bile duct inflammation based on BC-neutrophils (BC-Neurophil 1–2 vs 0, OR 8.2 [95%1.1–64.0], $p=0.044$), B-calprotectin higher than 45 mg/l (OR 3.3 [95%1.1–9.9], $p=0.0032$) and S-Ca19–9 >26 kU/l vs <26 kU/l (OR 7.4[95% 2.0–27.6], $P=0.003$).

Bile calprotectin in relation to variables of PSC activity

Variable	N	B-calpro, mg/l, median [25%–75%]	p-value
ERC-score≤4	94	0.4 [0.1–3.9]	<0.0001
ERC score>4	116	13.8 [1.6–96.3]	
Bil-Neutrophils			
- 0	74	0.2 [0–1.1]	<0.0001
- 1	100	5.3 [0.9–22.9]	
- 2	36	172.8 [59.1–286.8]	
Dysplasia			
- No	203	4.0 [0.2–41.0]	0.023
- Yes	14	34.7 [4.8–99.5]	
S-CA19–9 kU/l			
- <26 (UNL)	198	2.7 [0.2–28.5]	0.003
- ≥26 (UNL)	12	57.4 [19.4–179.3]	
S-ALP, U/l			
- ≤105 (UNL)	101	1.2 [0.2–9.6]	<0.0001
- >105 (UNL)	109	6.1 [0.5–81.9]	
S-AST, U/L			
- ≤40 (UNL)	141	1.4 [0.1–21.0]	<0.0001
- >40 (UNL)	69	8.3 [1.0–89.6]	
S-IgG, g/l			
- ≤15 (UNL)	177	2.8 [0.2–27.0]	0.008
- >15 (UNL)	33	19.5 [1.3–112.1]	

Conclusion: S-ALP, AST and IgG seem to be good surrogate markers for bile duct inflammation compared to biliary calprotectin levels. Risk of dysplasia is associated with bile duct inflammation assessed by brush cytology neutrophils, B-calprotectin and S-Ca19–9 levels >26 kU/l. These variables seem be useful for individual risk stratification for PSC patients for disease progression and dysplasia.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP032 TARGET-SPECIFIC ANTI-PANCREATIC ANTIBODIES ARE FREQUENT IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS AND ASSOCIATED WITH POOR DISEASE OUTCOME

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Introduction: Glycoprotein 2 [GP2] and CUB zona pellucida-like domain 1 [CUZD1] belong to protein families involved in gut innate immunity processes and have recently been identified as specific targets of anti-pancreatic autoantibodies [PAbs] in Crohn's disease [CD]. We aimed to determine the prevalence and prognostic potential of novel target-specific PAbs regarding long-term disease course in a cohort of a primary sclerosing cholangitis [PSC] patients.

Aims & Methods: Sera of 69 PSC patients (median age[range]: 32[5–79] years, concomitant IBD:67% and cirrhosis:20%) were tested by indirect immunofluorescence test [IIFT] system with GP2 and CUZD1 expressing transfected HEK 293 cells [anti-rPAg2 and rPAg1 IgA/IgG]. Classical serologic markers of IBD were also assessed (pANCA and aLFS IgA/IgG by IIFT, while ASCA IgG/IgA and anti-OMP Plus™ IgA by ELISA). A previously reported inflammatory bowel disease [IBD] patient cohort (CD:264 and UC:179) were the controls. Poor disease outcome was defined as orthotopic liver transplantation [OLTx] and/or liver-related death during the follow-up (median: 94 months].

Results: A total of 43.5% of PSC patients were positive for either of the two target-specific anti-PABs, with a significant difference compared to patients with CD [26.8%, $p<0.01$] or UC [7.6%, $p<0.001$]. Distribution of the two types of PAbs was equal and one-third of the positive cases showed double positivity. Anti-GP2 antibody positivity was exclusively IgA type, while anti-CUZD1 antibodies were of both IgA and IgG isotypes. No difference was found in the frequency of PAbs according to the baseline disease characteristics. Positivity for the IgA subtype of anti-GP2, but not for the classical serologic markers, predicted a faster progression of the disease. In Kaplan-Meier analysis, anti-GP2 IgA positivity was associated with shorter time to OLTx and/or liver-related death [pLogRank <0.01], and remained an independent predictor after adjusting for the presence of cirrhosis in Cox-regression analysis (HR: 4.31 [1.05–17.61]).

Conclusion: Our small-scale study has shown that occurrence of target-specific PAbs is common in PSC. Association of IgA type anti-GP2 antibody with faster disease progression serves as an additional hint towards the significance of gut-liver interaction in the disease course of PSC.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP033 GUT BARRIER FAILURE BIOMARKERS ARE ASSOCIATED WITH POOR DISEASE OUTCOME IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

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Introduction: Gut-liver interaction is a pathogenic feature of primary sclerosing cholangitis (PSC), however the effect of this cross-talk on the disease course has not been fully elucidated. A panel of serological markers that reflect either mechanical or immunological gut barrier dysfunction were assessed in a cohort of patients with PSC. Association of these markers with disease specific characteristics and the long-term disease course was evaluated.
Aims & Methods: Sera of 69 PSC patients (median age[range]:32[5–79] years, concomitant IBD: 67% and cirrhosis: 20%) were assayed for intestinal fatty acid-binding protein(I-FABP) and various immunoglobulin A (IgA) molecules (IgA1, IgA2 and secretory[s]IgA, anti-F-actin[AAA IgA] and anti-gliadin[AGA IgA/IgG]) by ELISA. Poor disease outcome was defined as orthotopic liver transplantation [OLTx] and/or liver-related death during the follow-up (median: 94 months]. 155 healthy subjects (HCONT) and 179 ulcerative colitis (UC) patients were the controls.
Results: In PSC, median I-FABP level was similar to that in HCONT (216 vs. 244 pg/mL) but higher than in UC (176 pg/mL, $p < 0.05$). sIgA level (95.7 μg/ml) was two- and three-fold higher compared to either the HCONT or the UC ($p < 0.001$, for both). 28.4%, 9% and 20.9% of PSC patients were positive for AAA IgA, AGA IgA and AGA IgG, respectively. Frequencies of AAA IgA ($p < 0.001$, for both) and AGA IgG ($p = 0.01$, for both) but not AGA IgA were significantly higher compared to HCONT and UC. Regarding disease-specific characteristics, sIgA level was significantly lower in PSC patients with concomitant IBD (80.7 vs. 160.4 μg/ml). In Kaplan-Meier analysis only target-specific IgAs and sIgA (>175 μg/ml) were associated with a shorter time to OLTx and/or liver-related death, whereas total IgA or IgA2/IgA1 ratio and I-FABP were not. All markers remained significant after adjusting for the presence of cirrhosis in Cox-regression analysis (HR[95%CI]: 3.67[1.05–12.82] for sIgA, 5.15[1.27–20.86] for AAA IgA and 5.07[1.25–20.54] for AGA IgA). Combining these markers further enhanced their predicative potential (HR[95%CI]: 11.30[2.84–44.93] for ≥2 marker positivity).
Conclusion: In our small-scale study, gut-related IgA type antibodies identified PSC patients with progressive disease, further highlighting the importance of the gut-liver interaction in PSC.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP034 COMPARISONS OF IMAGING AND BILIARY BIOPSY BETWEEN IGG4-RELATED SCLEROSING CHOLANGITIS AND EXTRAHEPATIC CHOLANGIOCARCINOMA

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Introduction: IgG4-related sclerosing cholangitis (IgG4-SC) often presents similar medical images to extrahepatic cholangiocarcinoma (ECC). However, the differentiation is crucial for further treatment.
Aims & Methods: To elucidate characteristics of medical images of IgG4-SC and ECC, we retrospectively analyzed images of multi-detector computed tomography (MDCT) and intraductal ultrasonography (IDUS). Biopsy-based diagnoses from stenotic bile ducts were also compared. From April 2005 to March 2013, 48 IgG4-SC patients and 50 ECC patients who underwent an initial ERCP at our institution were analyzed. Diagnosis of IgG4-SC was made based on the Japanese clinical diagnostic criteria (2012), and autoimmune pancreatitis (AIP) based on International Consensus Diagnostic Criteria (ICDC). The pathological criteria consist of four items: (1) marked lymphocytic and plasmacyte infiltration and fibrosis, (2) infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cell/HPF, (3) storiform fibrosis, and (4) obliterative phlebitis. In all cases of ECC, pathological evidence of carcinoma was obtained from biliary biopsy, cytology or surgical material. On MDCT, we defined the long thickened bile duct when the enhanced, biliary wall thickness was recognized at more than 10 mm upstream of the stenosis.
Results: Autoimmune pancreatitis (AIP) was accompanied in 88% (42/48) of IgG4-SC patients at the initial diagnosis. On MDCT imaging, the long thickened bile duct rate was higher in IgG4-SC cases than in ECC cases (76% of IgG4-SC and 32% of ECC, respectively). By IDUS, a continuous circular-symmetric wall thickness more than 10 mm upstream from stenosis was recognized in 84% of IgG4-SC cases and in 36% of ECC cases. In IgG4-SC cases, biliary biopsy revealed one or more positive pathological diagnostic items in only 13% of cases. In ECC cases, the sensitivity of biopsy was 92%, and brush cytology increased this by 6%. Among three out of six IgG4-SC patients without AIP, pancreatoduodenectomy was performed without careful examination. The remaining three underwent steroid trial after negative work up for malignancy.
Conclusion: A longitudinal biliary wall-thickness, upstream of the stenosis, was characteristic for imaging of IgG4-SC. Endobiliary forceps biopsy is effective for discriminating IgG4-SC from ECC.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP035 SELECTIVE TARGETING OF FXRA ISOFORMS BY NOVEL BILE ACID DERIVATIVES IS ASSOCIATED WITH INHIBITION OF LIPOTOXICITY IN LIVER CELLS

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Introduction: Farnesoid X receptor (FXR), a bile acid (BA)-activated nuclear receptor, plays a critical role in maintaining lipid, glucose and BA homeostasis. FXR expression is significantly decreased in livers of non-alcoholic fatty liver disease (NAFLD) patients and genetic ablation leads to hepatic steatosis and hyperlipidaemia. The FXR gene expresses four biologically active variants (FXRα1–4), which regulate hepatic and lipid metabolism in an isoform-dependent manner.
Aims & Methods: Our aim was to screen potential BA-derived FXR agonists for their ability to selectively activate different FXR isoforms and protect liver cells against free fatty acid (FFA)-induced steatosis and cytotoxicity. Nineteen novel BA derivatives, synthesized based on the cholic (CA), deoxycholic (DCA), chenodeoxycholic (CDCA) and ursodeoxycolic (UDCA) acid scaffolds were incubated in HepG2 cells transfected with a dual-luciferase reporter construct and overexpression vector plasmids for FXRα1–4 isoforms. Selected BA-derivatives were then co-incubated in HepG2 cells treated with 200 and 500 μM oleic and palmitic acid (2:1 ratio), for assessment of cellular cytotoxicity using the MTS, LDH and Toxilight™ assays, as well as intracellular lipid accumulation, by oil red O (ORO) staining. Additionally, mRNA levels of both direct and indirect key FXR-targets, namely SHP, SREBP1-c, PPAR-α, CYP7a1 and VLDLR, were assessed after incubation of primary mouse hepatocytes with the select BA-derivatives.
Results: As a result of the diverse structural modifications, BA derivatives showed differential activation of the FXRα1–4 isoforms, when compared to their precursor BAs. From the precursor BAs, only CDCA, a natural FXR ligand, significantly activated FXRα1 and α2 isoforms, with CA and UDCA displaying a modest activation of FXRα1 isoform only. Interestingly, 2 novel CA-, 1 DCA- and 4 UDCA-derivatives were stronger activators of both FXRα1 and α2, comparing with their corresponding precursors. Further, 3 novel CA-, 2 DCA-, 3 CDCA- and 4 UDCA-derivatives specifically and significantly activated FXRα3 and α4. Incubation of HepG2 cells with the FFAs mixture led to a ~5–25% reduction in cell viability and a ~10–35% increase in cell death, concomitantly with a dose-dependent accumulation of lipid droplets. Pre-incubation of cells with CA-derivatives preferentially activating FXRα2 over α1 isoform reverted most of the FFA-induced cell death and lipid accumulation. Of note, these derivatives were among the stronger inducers of SHP, VLDLR and PPAR-α mRNA expression in primary mouse hepatocytes.
Conclusion: Altogether, we describe a novel strategy to screen for selective agonists of FXRα1–4 isoforms and have identified new selective BA-derived FXRα1 through 4 agonists. In particular, derivatives with a higher FXRα2 over α1 binding ratios appear to be more effective in affording cytoprotection against lipotoxicity in liver cells. The differential functional effect of these new molecules will undoubtedly contribute for a better understanding of pharmacological targeting and therapeutic efficacy of FXR agonists in liver diseases such as NAFLD. (Supported by HMSP-ICT/0018/2011,SFRH/BD/110672/2015 and SFRH/BD/80975/2011 FCT, Portugal).
Disclosure of Interest: All authors have declared no conflicts of interest.

OP036 THE IMPACT OF PNPLA3 (RS738409 C>G P.I148M) ALLELE DOSE ON DISEASE COURSE IN PRIMARY SCLEROSING CHOLANGITIS (PSC)

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Introduction: PNPLA3 (patatin-like phospholipase domain containing 3) encodes carbohydrate-regulated lipogenic and/or lipolytic enzymes in liver. The mutation of isoleucine to methionine at position 148 (I148M) causes a loss of function effect leading to increased triglyceride synthesis and accumulation in liver (1). The PNPLA3 rs738409 C>G p.I148M has been associated with steatosis and fibrosis in various liver disease and increased risk for development of liver cirrhosis and hepatocellular cancer (2). The impact of PNPLA3 rs738409 [G] on liver damage has a strong environmental interaction and is usually associated concomitant liver insult. PSC is a chronic inflammatory disease of bile duct epithelium leading to strictures and may secondarily cause liver cirrhosis. PSC is also associated with inflammatory bowel disease and markedly increased risk of cholangiocarcinoma (3,4). PLPN3 variant has been associated with elevations of liver enzymes in IBD (5) and in increased risk of bile duct stenosis in male PSC patients (6). Survival free of liver transplantation is reduced in male PSC patients with development of dominant strictures in carriers of PNPLA3 I148M variant (5).

Aims & Methods: To evaluate the allele dose effect of PNPLA3 variant on the clinical manifestations, disease severity, progression and prognosis of PSC in a large patient population from single center.

Results: Of the 563 patients 334 (59.3%) had the wild type (CC), 197 (35%) were heterozygous (CG) and 32 (5.7%) were homozygous for the mutation (GG). A concomitant IBD was diagnosed in 80% of the males and 60% the females. Summary of the results are presented in the table.

PNPLA3 rs738409 in PSC

Variable, mean(SD)	CC, n = 334	CG, n = 197	GG, n = 32	p for linearity
Males, n (%)	195(58)	124(63)	17(53)	0.75
Age at diagnosis of PSC,y	38(14)	36(13)	35(13)	0.10
Weight, kg, males	82(14)	80(15)	81(14)	0.37
Weight, kg, females	69(7)	70(17)	71(13)	0.62
IBD, n (%)	263(71)	152(77)	21(65)	0.49
Age at dg of IBD	26(11)	26(11)	29(12)	0.74
ERC-score (0–16)	5.8(3.5)	5.4(3.3)	5.7(3.7)	0.88
Dominant strictures, n (%)	128(38)	61(31)	9(28)	0.061
Progression of ERC score/month*	0.014	0.002	0.004	0.44
Advanced fibrosis F3/4, (%)*	8.8	15.1	12.5	0.25
S-ALP, U/l <105	183(148)	194(170)	182(135)	0.60
S-GT, U/l, <60	191(249)	236(269)	189(154)	0.94
S-ALT, U/l, <50	74(125)	78(96)	61(50)	0.35
S-AST, U/l, <45	55(73)	54(63)	59(41)	0.68

*Adjusted for sex, age and IBD Cholangiocarcinoma was diagnosed in 12 (3.6%) patients with CC, in 6 (3.1%) of CG an in none of GG, (p for linearity=0.42; adjusted for sex, age and IBD). 49 patients underwent liver transplantation during 5 years mean follow up: 2.5% (95% CI: 1.2 to 5.1) in CC, 3.1% (95% CI: 1.3 to 7.3) in CG and 7.1% (95% CI: 1.8 to 24.4) in GG, (p for linearity = 0.12; adjusted for sex, age and IBD).

Conclusion: The PNPLA3 I148M variant did not have any significant impact on clinical manifestation, disease progression, development of dominant strictures, on risk of cholangiocarcinoma or liver transplantation in PSC.

Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 10:30–12:00
BASIC MECHANISMS OF INTESTINAL CARCINOGENESIS – ROOM L8

OP037 TRANSGENIC EXPRESSION OF HUMAN LYSOPHOSPHATIDIC ACID RECEPTOR (LPA2) IN MOUSE INTESTINAL EPITHELIAL CELLS INDUCES INTESTINAL DYSPLASIA

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Introduction: Colorectal cancer (CRC) develops through a series of genetic modifications that transform normal colonic epithelium to an adenoma and the adenocarcinoma. In addition to the genetic instability, the activation of growth factor pathways (eg. The activation of Cox-2, EGF, and VEGF) is common in the pathogenesis of CRC cells. Lysophosphatidic acid (LPA) acts on LPA2 receptor to mediate multiple pathological effects that are associated with tumorigenesis. LPA2 expression is increased in CRC patients and proportionally increases with the size of adenomas in rodent models. The absence of LPA2 attenuates tumor progression in rodent models of colorectal cancer, but whether overexpression of LPA2 alone can lead to malignant transformation in the intestinal tract has not been studied.

Aims & Methods: The aim of this study is to determine whether increased LPA2 expression in intestinal epithelial cells (IECs) alone is sufficient to induce spontaneous transformation in the intestinal tract. In this study, we expressed human LPA2 in IECs under control of the villin promoter. The transgene DNA was injected into the pronuclei of fertilized eggs of C57BL/6J mice. The transgenic mice were identified by PCR analysis of tail genomic DNA.

Results: Less than 4% of F1-generation mice had germline transmission of transgenic (TG) human LPA2 as such only 3 F1 mice out of 72 genotyped had TG expression. These TG mice appeared anemic with hematochezia and died shortly after birth. TG mice were smaller in size compared with the wild type mouse of the same age and sex. Morphological analysis showed that TG LPA2 colon had hyper-proliferation of IECs resulting in increased colonic crypt depth. Surprisingly, TG small intestine had villus blunting and decreased IEC proliferation and dysplasia. In both intestine and colon, TG immunohistochemical analysis revealed that expression of LPA2 compromised the terminal epithelial differentiation, consistent with epithelial dysplasia. Furthermore, we showed that epithelial dysplasia was observed in founder mouse intestine, correlating LPA2 overexpression with epithelial dysplasia.

Conclusion: We demonstrated that overexpression of LPA2 induces dysplasia in mouse intestine that alter IEC proliferation and differentiation. Our results reinforce the importance of the LPA-LPA2 axis in homeostatic regulation of IECs and its potential contribution to carcinogenesis in the intestinal tract.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP038 CELL-SPECIFIC ROLES OF CALCINEURIN IN INTESTINAL TUMOR DEVELOPMENT

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Introduction: Colorectal cancer (CRC) development is characterized by the sequential accumulation of somatic mutations, which promotes epithelial proliferation and subsequently tumor invasion. Calcineurin is a phosphatase, which contributes to innate and adaptive immunity through the activation of transcription factors of the family of nuclear factor of activated T cells (NFAT). Systemic inhibition of calcineurin as applied in human immunosuppression is associated with an increased incidence of CRC. However, calcineurin and NFAT are also expressed in CRC cell lines and rather promote than inhibit epithelial proliferation in vitro. These findings raise the question of whether calcineurin plays cell-specific roles in CRC and, in particular, whether intestinal epithelial calcineurin promotes tumor development in a cell-intrinsic manner.
Aims & Methods: To investigate the role of calcineurin and NFAT in intestinal tumor development, we generated mice with intestinal epithelial cell (IEC)-specific deletion of the regulatory B1 subunit of calcineurin and analyzed these mice in the $Apc^{fl/wt}$ and $Apc^{Min/+}$ models of genetically induced intestinal tumor development as well as in the AOM/DSS model of colitis-associated cancer. For mechanistic studies, organoid cultures, immortalized IECs and CRC cell lines as well as samples of more than 700 CRC patients were studied.
Results: We demonstrate that systemic inhibition of calcineurin with cyclosporine leads to increased intestinal tumor growth in $Apc^{Min/+}$ mice, which is consistent with an increased CRC incidence observed in patients receiving calcineurin inhibitors. In contrast, intestinal epithelial cell-specific deletion of calcineurin is associated with reduced intestinal tumor formation and growth in the $Apc^{fl/wt}$ and $Apc^{Min/+}$ model. Antibiotic treatment of mice as well as backcrossing to a Myd88-deficient background revealed that the activation of oncogenic epithelial calcineurin is dependent on the intestinal microbiota and results from tumor-associated alterations in microbial composition and stratification as well as from increased tumor-associated toll-like receptor expression. Tumor-promoting effects of epithelial calcineurin are elicited through NFAT-dependent transcriptional regulation of Lgr5-positive tumor stem cells as shown by chromatin immunoprecipitation (ChIP), gene expression analysis and functional studies together leading to control of tumor stem cell apoptosis and proliferation as shown by FACS and immunofluorescence staining. Moreover, somatic mutations identified in human CRC are associated with constitutive activation of calcineurin, while nuclear translocation of NFAT correlates with reduced survival in a large cohort of CRC patients.
Conclusion: These results support the concept of cell-specific roles of calcineurin in the regulation of colorectal carcinogenesis and reveal novel potential targets for the prevention and treatment of CRC.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP039 ALIX POSITIVE EXOSOMES IN COLORECTAL ADENOMA-CARCINOMA SEQUENCE

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Introduction: During colorectal carcinoma (CRC) formation exosomes play important roles as intercellular regulators in conveying complex signals between epithelial/carcinoma cells and their abnormal microenvironment.
Aims & Methods: Our aim was to characterize changes in exosome-based communication in the colorectal adenoma-carcinoma sequence by determining ALG 2-interacting protein X (ALIX) exosome marker production on mRNA and protein level. mRNA expression was analyzed using Affymetrix HGU133 Plus2.0 whole transcriptome data of healthy (n = 49), adenoma (n = 49) and CRC (n = 49) samples. Immunohistochemistry was performed on healthy (n = 27), adenoma (n = 42), CRC (n = 37) patients and stained for ALIX exosome, cytokeratin (CK) epithelial, podoplanin (PDPN) lymphatic vessel, Ki-67 proliferative and Musashi-1 (MSI1) stem cell markers. Slides were digitalized and analyzed with digital microscopy.
Results: We found significantly decreased ($p < 0.05$) ALIX mRNA expression both in adenoma and CRC samples compared to normal samples. Similarly, significantly reduced ($p < 0.05$) ALIX protein levels were detectable in adenoma and CRC samples compared to normal ones. The reduced protein expression was accompanied by gradual transition from diffuse cytoplasmic (in normal epithelium) expression to granular signals (in adenoma and CRC samples) with 0.6–2 μm diameter size range of multivesicular bodies. The granular ALIX expression was not limited to the proliferative and stem cells, but was also observed in budding CK+ and MSI1+ stromal cells, as well as in the lumen of PDPN+ lymphatic vessels in invasive CRCs.
Conclusion: The altered ALIX expression pattern in pre-neoplastic lesions suggests that abnormal exosome transport may play an important role in the adenoma to carcinoma transformation. Furthermore, the increased frequency of exosome marker expression in stromal and budding cancer cells, and also in the lumen of lymphatic vessels suggests that the exosome based information flow may be fundamental in the development of local and distant pre-metastatic microenvironments in CRC patients. This study was funded by the Research and Technology Innovation Fund, Hungary, KMR_12–1-2012–0216 and Hungarian Scientific Research Fund (OTKA-K111743 grant).
Disclosure of Interest: All authors have declared no conflicts of interest.

OP040 NHERF2 REGULATES COLON CANCER PROGRESS VIA STAT3

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Introduction: Scaffold proteins mediate protein-protein interaction to bring together key members of signaling pathways that drive cell division and growth. The Na+/H+ exchanger regulatory factor (NHERF) family of proteins is scaffolds that orchestrate interaction of receptors and cellular proteins. Among the NHERF proteins, NHERF1 and NHERF2 share most similarities with tandem PDZ domains and an ERM interacting motif in the carboxyl domain that enables anchoring to the actin cytoskeleton. One major function of NHERF1/2 is to recruit and spatially organize signaling proteins that either alters protein functions or downstream signaling pathways originating from receptor. NHERF1 is reported to be a tumor suppressor. However, the role of NHERF2 in cancer progress has not been reported.

Aims & Methods: We investigated the role of NHERF2 in colon tumor progression. We first determined NHERF2 expression in human colorectal cancer (CRC) using a tissue microarray. Next, the role of NHERF2 on colon cancer growth and invasion was assessed by a loss-of-function approach (shRNA) and a small peptide which blocked the PDZ domain of NHERF2 to bind using colon cancer cell lines (HCT116, SW480, and HT-29). We validated tumor growth change by xenograft model. Moreover, we used ApcMin/+ mouse model to investigate the tumorigenesis in intestine with NHERF2 homozygous deletion mice. To investigate the molecular mechanism of NHERF2 in tumor growth, we performed the transcriptom analysis.

Results: We found that NHERF2 expression is elevated in advanced-stage CRC. Knockdown of NHERF2 decreased cancer cell proliferation and invasion in vitro, and tumor growth in a mouse xenograft tumor model. Histologic analysis confirmed the reduction of cell proliferation by Ki67 immunostaining. In addition, deletion of NHERF2 in ApcMin/+ (ApcMin/+;Nherf2-/-) mice resulted in decreased tumor growth in ApcMin/+ mice and increased lifespan. Blocking NHERF2 interaction with a small peptide designed to bind the second PDZ domain of NHERF2 attenuated cancer cell proliferation. Although NHERF2 is known to facilitate the effects of lysophosphatidic acid receptor 2 (LPA2), transcriptome analysis of xenograft tumors revealed that NHERF2-dependent genes largely differ from LPA2-regulated genes. β-catenin and ERK1/2 activation was mitigated in ApcMin/+;Nherf2-/- adenomas. Moreover, Stat3 phosphorylation and CD24 expression levels were suppressed in ApcMin/+;Nherf2-/- adenomas. Consistently, NHERF2 knockdown attenuated Stat3 activation and CD24 expression in colon cancer cells. Interestingly, NHERF2-dependent increase in CD24 expression was blocked by inhibition of Stat3, suggesting that NHERF2 regulates Stat3 phosphorylation followed by the increase in CD24.

Conclusion: This study demonstrated NHERF2 stimulates colon cancer growth by intersecting at multiple signaling nodes. NHERF2 potentiates the oncogenic effects in part by regulation of Stat3 and CD24. This study provides NHERF2 as a new potential target for cancer treatment.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP041 THE EXTRACELLULAR MATRIX PROTEIN EMILIN2 AS A REGULATOR OF THE MYELOID RESPONSE IN A MODEL OF INFLAMMATION-INDUCED COLON CARCINOGENESIS

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Introduction: EMILIN2 is an extracellular matrix molecule belonging to the EMI Domain ENdowed (EDEN) protein family that exerts pleiotropic effects in the tumor microenvironment overall functioning as a tumor suppressive molecule (1–3). EMILIN2 affects tumor cell viability and proliferation by activating apoptosis and functioning as a negative regulator of the Wnt/β-catenin axis. Interestingly EMILIN2 expression is down-modulated by methylation in a number of tumors including breast and colorectal cancer (4). Our preliminary results highlight a possible new function for E2 in the control of CRC incidence. In particular these findings indicate that E2 seems to modulate the myeloid response and to profoundly affect the inflammatory microenvironment associated with CRC.

Aims & Methods: Given its involvement in the regulation of Wnt signaling, a crucial pathway in colon carcinogenesis, and its altered expression in colorectal cancer, we took advantage of the EMILIN2 null mouse model to assess its role in colorectal cancer (CRC) development, subjecting the mice to the inflammation-related AOM/DSS protocol. Colorectal tumors were induced subjecting the mice to a AOM/DSS treatment. Tumor development was assessed by colonoscopy. Histopathological and IHC analyses were performed on colon samples from treated mice. β-catenin activation was assessed by Western blot and qPCR. Multiplex serum cytokine analyses from the two mouse models were performed through Luminex Screening and peripheral blood cells were counted. The inflammatory infiltrate was analysed by flow cytometry.

Results: The EMILIN2 KO mice developed a significantly higher number of tumors compared to wt mice. Tumors from EMILIN2 KO mice were more undifferentiated and at an advanced stage compared to the tumors from control mice. Surprisingly, and contrary to our expectations, tumors from EMILIN2 KO mice did not display any changes in the activation of the Wnt/β-catenin pathway compared to the controls. Accordingly, the β-catenin target genes cyclin D1 and c-Myc were not altered in the tumors and in the normal mucosa of the two mouse models. Histopathological and IHC analysis indicated that the tumors from EMILIN2 KO mice where characterized by a higher number of macrophages and granulocytes than those from WT mice. Similar alterations in the KO model were found during the acute fase of inflammation: mice subjected to DSS treatment alone developed a more severe colitis than WT mice. Accordingly, the infiltration of myeloid cells within the intestinal mucosa was altered and the serum level of a number of cytokines, including IL-1b, INF-gamma, TNF-α and IL-10, was affected.

Conclusion: Our results let us suggest that EMILIN2 may affect colon carcinogesis impinging on the recruitment and/or the activation of myeloid cells. By altering the inflammatory microenvironment, EMILIN2 may significantly influence colon cancer development.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP042 THE ROLE OF MIRNA-145 IN COLON CANCER STEM CELL-LIKE CELLS

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Introduction: Cancer stem cells (CSCs) are thought to be responsible for tumour initiation, metastasis and relapse through their unlimited self-renewal and differentiation potential. miRNAs have recently emerged as promising candidates to target CSCs. miR-145 is a tumour suppressor miRNA, downregulated in colon cancer adenomas and carcinomas. It has been shown to be involved in tumour growth, metastasis and resistance to chemo/targeted agents, as well as in modulation of CSC-like properties in prostate cancer and lung adenocarcinoma. In this context, we hypothesise that miR-145 may play a role in the ability of colon CSCs (CCSCs) to self-renew and differentiate.
Aims & Methods: We aimed to evaluate the effect of miR-145 overexpression in maintaining CCSCs-like properties. We produced miR-145 overexpressing and empty vector control cells using HCT116, HT29, SW480 and SW620 colon cancer cell lines, and examined their ability to form colon spheres in ultralow-attachment plates and specific CCSC media. Colon spheres were dissociated to single cells and reseeded to yield the second and third generation of colon spheres. The number of spheres and cells per sphere were counted over 3 generations. mRNA expression levels of stemness markers were evaluated by SYBR Real-Time PCR. CD44 and CD133 expression levels and aldehyde dehydrogenase 1 (ALDH1) activity were evaluated by flow cytometry.
Results: Our results showed that forced miR-145 expression reduced colon sphere diameter and number of cells per sphere in HCT116, HT29, SW480 and SW620 cells. Moreover, miR-145 overexpression had an impact on HT29 and SW620 sphere formation, reducing the number of colon spheres. Similar results were observed with the second and third generation of cell line-derived colon spheres. mRNA expression levels of the stemness markers KLF4 and BMI1, were significantly reduced in colon spheres overexpressing miR-145 ($p < 0.01$). In addition, HT29 and SW480 cell line-derived colon spheres overexpressing miR-145 displayed reduced OCT4 mRNA levels. Furthermore, miR-145 overexpression significantly decreased the proportion of $CD44/CD133^+$ cells and ALDH1 activity ($p < 0.05$). The mature colonocyte marker, CK20, was increased in HCT116 spheres overexpressing miR-145 ($p < 0.01$).
Conclusion: miR-145 appears to be involved in colon sphere formation, self-renewal of colon spheres and differentiation ability of HCT116 colon spheres. miR-145 may contribute to the induction of CCSC differentiation to cells that are sensitive to chemotherapy and targeted agents.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 10:30–12:00
GASTRODUODENAL DAMAGE: H.PYLORI, ACID AND BILE – ROOM 1.86

OP043 PAN-EUROPEAN REGISTRY ON H. PYLORI MANAGEMENT (HP-EUREG): INTERIM ANALYSIS OF THE RESCUE TREATMENT WITH BISMUTH, LEVOFLOXACIN AND AMOXICILLIN

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Introduction: *H. pylori* rescue therapy is still a major concern for clinicians treating this infection. Although several rescue treatments have been proposed and tested, the selection of resilient strains or acquisition of resistance after failed eradication hinders the success rate of most proposed regimens. Traditionally rescue treatments in Europe have been divided in bismuth quadruple therapy or levofloxacin triple. Some authors have recently proposed a combination of both strategies by adding bismuth to the traditional levofloxacin triple therapy.
Aims & Methods: To evaluate the use and outcomes of a quadruple therapy containing a proton pump inhibitor, bismuth, levofloxacin and amoxicillin in the European Registry on *H. pylori* Management (Hp-EuReg). Methods: Systematic prospective registry of the clinical practice of European gastroenterologists regarding *H. pylori* infection and treatment (31 countries and 280 recruiting investigators). A local coordinator was selected from each country. Each coordinator selected a representative group of recruiting investigators from his/her country. An electronic clinical research file (e-CRF) was created on AEG-REDCap to systematically register all adult patients infected with *H. pylori*. Variables included: Patient's demographics, previous eradication attempts, prescribed eradication treatments, adverse events, and outcomes (cure rates, compliance, follow up, etc.). Patients with both eradication confirmatory test and with less than one year follow-up have been considered ongoing and were excluded from the analysis.
Results: Up to now, 16,025 patients have been included, and 12,921 have finished follow up (59% females, 87% Caucasian). Mean age was 55 years. The bismuth-levofloxacin quadruple treatment was prescribed to 327 patients (2% of all treatments registered): 7% in first-line, 76% in second, 12% in third, and 5% in following rescues. Overall efficacy was 84% (95%C.I. = 75–93%) by ITT and 92% (89–95%) by PP. First-line data is insufficient for analysis. Second-line efficacy was 85% (80–91%) by ITT and 92% (89–94%) by PP. Treatment was generally prescribed with esomeprazole (95%) and as a 14 day regimen (98%). Compliance with treatment was 95%. Adverse events were reported in 38% of cases and caused treatment discontinuation in 7 (2.1%) patients.
Conclusion: A 14-day regimen combining bismuth salts with levofloxacin triple therapy as second-line treatment for *H. pylori* eradication achieves near 90% eradication rates.
Disclosure of Interest: A.G. McNicholl: Speaker for allergan
M. Castro: Teaching activities for Allergan
J. Molina Infante: Scientific Advisory for Casen Recordati Teaching activities for Allergan and Zambon
J.P. Gisbert: Scientific advisory and teaching for Almirall, Allergan, AstraZeneca, Casen Recordati, Nycomed.
All other authors have declared no conflicts of interest.

OP044 ERADICATION RATES OF HELICOBACTER PYLORI USING A NEW GASTRIC ACID SUPPRESSANT, VONOPRAZAN, COMPARED WITH AN ESOMEPRAZOLE REGIMEN

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Introduction: A proton pump inhibitor (PPI)-based triple regimen containing two antibiotics (amoxicillin, APMC; and clarithromycin, CAM) was considered the gold standard for the eradication of *Helicobacter pylori* for more than a decade. However, low eradication rates have been reported worldwide because of increased prevalence of clarithromycin-resistant *H. pylori*. Insufficient acid inhibition during treatment also causes eradication failure. This is because the antimicrobial agents are unstable and degraded in the stomach.Esomeprazole (EPZ) is a relatively new PPI available in Japan since September 2011. EPZ has an improved pharmacokinetic profile as regards CYP2C19 genotype; therefore, it shows less individual variability. Vonoprazan (VPZ) is a potassium-competitive acid blocker (P-CAB). P-CABs are a new class of gastric acid suppressants available since February 2015 in Japan. VPZ has a potent and long-lasting anti-secretory effect on H+,K+-ATPase due to its high accumulation in, and slow clearance from gastric tissue. Therefore, VPZ is expected to have high eradication rates compared with conventional PPIs. The aim of this study was to compare *H. pylori* eradication rates with EPZ-based and VPZ-based triple therapies with CAM and AMPC.
Aims & Methods: A total of 807 patients who had undergone upper gastrointestinal endoscopy and diagnosis with *H. pylori* infection from November 2013 to March 2016 were enrolled. From December 2013 to September 2014, 431 patients were treated with EPZ-based triple therapy, while 376 patients were treated with VPZ-based triple therapy from April 2015 to March 2016. At baseline, demographical and clinical characteristics including gender, age, body mass index (BMI), smoking status, and consumption of alcohol were checked. The first-line eradication regimen was CAM 200 mg, AMPC 750 mg, and either EPZ 20 mg or VPZ 20 mg, each twice daily for 7 days. The second-line eradication regimen was metronidazole 250 mg, AMPC 750 mg, and either EPZ 20 mg or VPZ 20 mg, each twice daily for 7 days. The eradication of *H. pylori* infection was diagnosed using ^{13}C-urea breath tests at 4–8 weeks after each of therapy.
Results: The overall first-line eradication rate was 79.1% (341/431) for the EPZ regimen and 84.6% (318/376) for the VPZ regimen based on Intension to treat (ITT) analysis. The eradication rate by Par protocol (PP) analysis for the EPZ and VPZ regimens were 79.9% (341/427) and 85.3% (318/373) respectively. Significant differences were found both in ITT analysis ($p = 0.045$) and in PP analysis ($p = 0.046$). The overall second-line eradication rate was 72.6% (45/62) for the EPZ regimen and 85.3% (29/34) for the VPZ regimen based on ITT analysis. Using PP analysis, the eradication rate was 88.2% (45/51) for the EPZ regimen and 87.9% (29/33) for the VPZ regimen. There were no statistically significant differences found between the eradication rates in both groups, from both the ITT and PP analyses.
Conclusion: In conclusion, VPZ has a rapid, sustained, and possibly more potent acid-inhibitory effect than EPZ, irrespective of CYP2C19 genotype. The rate of *H. pylori* eradication obtained using the first-line VPZ regimen was significantly higher than that for the first-line EPZ regimen. However, for the second-line

treatment, there were no significant differences between the eradication rates from EPZ and VPZ regimens.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP045 STROMAL MYOFIBROBLASTS ORCHESTRATE GASTRIC EPITHELIAL WNT-SIGNALING AND STEM CELL KINETICS IN HEALTH AND DISAEASE

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Introduction: The gastric epithelium is characterized by constant, rapid self-renewal, which in the antrum is driven by long-lıved stem cells situated at the base of the glands. Infection with the gastric pathogen *Helicobacter pylori* is the main risk factor for gastric cancer and increases stem cell and the turnover kinetics of the glands. Wnt signaling is known to be crucial for stem cell homeostasis in several tissues and for long-term organoid culture of stomach epithelium, but it is not clear how Wnt signaling is spatially organized in the stomach in vivo and whether it modulates stem cell kinetics and glandular turnover.
Aims & Methods: The aim of the present study was to characterize the cellular and molecular Wnt-network in the stomach and to explore its function in physiological epithelial turnover, as well as upon infection with *H. pylori*. Using in single molecule situ hybridization, different stem cell- and WNT-signaling reporter mice and the murine and as well as human 3D-organoid system we addressed these questions.
Results: We found that Wnt-responsive cells are limited to the base of the antral glands where stem cells reside. However, in addition to previousy descibed Lgr5-positive cells, we found another Wnt-dependent population of highly proliferative Lgr5-negative stem cells in the gland base. We show that the positional identity of these Axin2-positive stem cells relies on R-spondin 3, which is produced by stromal myofibroblasts. Wnt signaling stimulated by exogenous R-spondin induces an expansion and increased proliferation of Axin2-positive stem cells in the stomach antrum while the Lgr5-positive cells remain silenced. Infection of mice with *H. pylori* increases expression of R-spondin 3, which also induces the expansion of Axin2-positive cells and results in gland hyperplasia. By increasing gland turnover following infection, R-spondin counterbalances bacterial gland colonization through increased shedding of cell-attached bacteria.
Conclusion: Thus, stromal R-spondin hierarchically organizes the stem cell compartment producing two Wnt–responsive populations that differ in position within the gland, proliferation kinetics, and sensitivity to R-spondin. In addition to its role in physiological gland homeostasis R-spondin driven regeneration is increased by infection with *H. pylori*, limiting glandular colonization. This establishes a new link between infection, stem cell signaling and epithelial homeostasis.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP046 THE ANTI-APOPTOTIC FACTOR CLUSTERIN IS INVOLVED IN HYPERGASTRINEMIA-INDUCED REMODELING OF THE GASTRIC OXYNTIC MUCOSA

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Introduction: Gastrin is important for normal function and maturation of the gastric oxyntic mucosa. Hypergastrinemia is associated with several premalignant conditions in the stomach and might be involved in gastric carcinogenesis. Previously, we have shown that gastrin regulates expression of the pro-survival factor clusterin (CLU). Expression of CLU is often dysregulated during tumorigenesis and in the stomach, upregulation of CLU marks emergence of spasmolytic polypeptide-expressing metaplasia (SPEM). Here, we study the expression of CLU in gastric oxyntic mucosa of animal models with elevated levels of gastrin and elucidate its role in gastric cells during prolonged stress.
Aims & Methods: Using gastric tissue from humans, rats treated with proton pump inhibitors and/or a cholecystokinin type B receptor (CCK-BR) antagonist, H+/K+-ATPase β-subunit knockout (H/K-β KO) mice and Mongolian gerbils infected with *Helicobacter pylori* and treated with a CCKBR antagonist, we examined the expression pattern and gastrin-mediated regulation of CLU using parallel reaction monitoring mass spectrometry, in situ hybridization and immunohistochemistry. Human gastric cancer cell lines were used to study the gastrin-mediated regulation and biological function of secretory CLU in vitro.
Results: CLU was highly expressed in neuroendocrine cells in normal oxyntic mucosa of humans, rats and mice. In response to hypergastrinemia, expression of CLU was significantly increased and localization shifted from neuroendocrine cells to basal groups of proliferative cells in the mucous neck cell-chief cell lineage in three different animal models. This shift was partly inhibited by antagonizing the CCKBR in rats and Mongolian gerbils. The oxyntic mucosa of H/K-β KO mice contained distinct areas with CLU-positive mucous cell hyperplasia, possibly representing SPEM. In vitro, gastrin increased the secretion of CLU, and both gastrin and secretory CLU promoted survival of gastric cells following starvation- and chemotherapy-induced stress.
Conclusion: Our findings suggest that gastrin and CLU participate in premalignant remodeling of the oxyntic mucosa by influencing the balance between survival and apoptosis in gastric epithelial cells.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP047 THE GREAT MAJORITY OF THE H. PYLORI INFECTED POPULATION HAS REDUCED INTRAGASTRIC ACIDITY WHICH IS MOST MARKED CLOSE TO THE GASTROESOPHAGEAL JUNCTION.

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Introduction: A negative association exists between *H. pylori* infection and both gastroesophageal reflux disease[1] and oesophageal adenocarcinoma[2] and this may be due to the infection reducing intragastric acidity. To exert such a protective effect the reduced acidity would need to be evident in the majority of *H. pylori*-infected subjects. To investigate this we have examined the acid secretory capacity of *H. pylori*-positive and negative volunteers in a Western population.
Aims & Methods: We studied 31 *H. pylori*-positive and 28 *H. pylori*-negative volunteers, matched for age, gender and BMI. Jumbo biopsies were taken at eleven pre-determined locations from the gastroesophageal junction and stomach. High-resolution pHmetry (12 sensors at 11 mm intervals) and manometry (36 sensors at 7.5 mm intervals) was performed for 20 minutes fasted and then for 90 minutes following a standardised meal. The position of the squamocolumnar junction (SCJ), marked with two endoscopically placed radio-opaque clips, was visualised radiologically relative to the probes. The biopsy specimens were scored quantitatively for inflammation and stained with monoclonal antibody to H^+/K^+ATPase and pepsinogen I for calculating parietal cell and chief cell densities respectively.
Results: The mean age of the *H. pylori*-positive group was 55 years (38y–78y) compared to 56 years (24y–74y) for the *H. pylori*-negative group.
Under fasting conditions, the *H. pylori*-positive subjects had less intragastric acidity compared to the *H. pylori*-negatives at all sensors more than 1.1cm distal to the peak lower oesophageal sphincter (LOS) pressure (all $p < 0.01$).
Throughout the three 30-minute postprandial periods, intragastric acidity was significantly less in *H. pylori* positives at the sensors 2.2, 3.3 and 4.4cm distal to the peak LOS pressure (all $p < 0.05$), but there was no significant difference in the sensors 5.5 and 6.6cm distal to peak LOS pressure (Table 1). The postprandial acid pocket was thus attenuated in *H. pylori* positives compared to negatives. The *H. pylori* positives had a significant reduction in density of both parietal and chief cells compared to *H. pylori* negatives, and this was seen in 10 of the 11 gastric locations ($p < 0.01$ for 9 locations). The degree of reduction was similar for the two cell types. The cardia mucosal length was longer in *H. pylori* positives (1.5 mm vs 0.7 mm; $p = 0.013$).
17/31 (54.8%) of the *H. pylori* positives were also CagA seropositive and they showed more a more marked reduction in intragastric acidity and increased mucosal inflammation compared to the CagA negative subjects.

Table 1: Median pH (IQR) detected by sensors relative to the peak LOS pressure during the 30–60 minute postprandial period. NOTE: *p < 0.05, **p < 0.01

Sensor location	*H. pylori* negative Median pH (IQR)	*H. pylori* positive Median pH (IQR)
1.1cm proximal	7.06 (1.42)	7.00 (0.75)
Peak LOS pressure	6.76 (1.02)	6.88 (0.48)
1.1cm distal	5.25 (4.19)	6.40 (1.72)
2.2cm distal	1.95 (1.00)	3.21 (4.46)**
3.3cm distal	1.59 (2.29)	2.07 (2.29)**
4.4cm distal	1.81 (2.09)	2.93 (3.25)*
5.5 cm distal	2.13 (2.02)	3.48 (2.89)
6.6cm distal	3.39 (2.19)	4.10 (2.23)

Conclusion: The majority of *H. pylori*-infected subjects have reduced intragastric acidity compared to the uninfected population and this is most marked close to the gastroesophageal junction. The density of parietal cells and chief cells is reduced in *H. pylori* infected subjects throughout the gastric mucosa. These findings may explain the negative association between *H. pylori* infection and both gastroesophageal reflux disease and oesophageal adenocarcinoma.
Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 10:30–12:00
ABSTRACTS ON FIRE: GORD ON FIRE – HOTSPOT

OP048 ASSOCIATION BETWEEN LUMINAL BILE SALT CONTENT AND DUODENAL MUCOSAL INTEGRITY IN HEALTHY VOLUNTEERS

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Introduction: Functional dyspepsia (FD) is a functional gastrointestinal disorder with a prevalence of up to 15–20% in the general population. Recently, impaired duodenal mucosal integrity was reported as a potential pathophysiological mechanism in FD (Vanheel H, *Gut* 2014). However, the factors controlling duodenal mucosal integrity remain unknown. In this pilot study, we evaluated whether luminal bile salt content is associated with duodenal permeability in healthy volunteers.
Aims & Methods: This study was carried out in 21 healthy volunteers (11 men, 25 ± 6years). Duodenal biopsies were obtained by gastroduodenoscopy and used to measure the in vitro transepithelial resistance (TEER) using Ussing chambers. Meantime, fluorescein isothiocyanate dextran (FITC-dx4, MW 4kDa) was applied to assess paracellular permeability. After the gastroduodenoscopy, an aspiration catheter was placed in the second part of the duodenum under fluoroscopic control. Duodenal fluid aspirates were collected at fixed time points during 1 hour in fasted state and 1.5 hour after a liquid meal (Nutridrink, 200 ml). Concentration and composition of the bile salt pool (including glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, glycoursodeoxycholic acid and tauroursodeoxycholic acid) in these aspirates was evaluated. Correlation analysis was used to look for an association between luminal bile salt content and duodenal mucosal integrity.
Results: Duodenal biopsies of healthy volunteers displayed a paracellular passage of 27.23 ± 7.93 pmol and a TEER of 19.85 ± 2.63 $\Omega.cm^2$. A negative correlation was found between the concentration of tauroursodeoxycholic acid and the duodenal TEER in fasted state as well as at the first bile salt peak after liquid meal and in fed state ($r = -0.6268$, $p = 0.0292$; $r = -0.5154$, $p = 0.0286$; $r = -0.4957$, $p = 0.0364$ respectively). The concentration of glycodeoxycholic acid showed a positive correlation with TEER in fed state ($r = 0.5747$, $p = 0.0126$). The total BA pool showed no correlation with paracellular permeability and TEER in healthy volunteers.
Conclusion: These results imply that the composition of the duodenal bile salt pool may contribute to variations in duodenal mucosal permeability in healthy volunteers. Whether the bile salt concentrations explored in the present study are altered in patients with FD is addressed in ongoing studies.
Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 10:30–12:00
ABSTRACTS ON FIRE: GORD ON FIRE – HOTSPOT

OP049 MUCOSAL AFFERENT NERVES ARE MORE SUPERFICIAL IN THE DISTAL OESOPHAGUS OF PATIENTS WITH NERD COMPARED TO CONTROLS

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Introduction: Patients with gastro-oesophageal reflux disease are more sensitive to painful acid perception than healthy volunteers. This is true even when there is no macroscopic mucosal inflammation. Impaired integrity of the oesophageal mucosa has been heavily implicated in this sensitivity, displaying the presence of dilated intercellular spaces and an impaired barrier integrity in patients with non-erosive reflux disease. Afferent nerves can be found within the oesophageal mucosa, and it is highly likely that these play a role in reflux perception.
We have recently demonstrated that, in healthy volunteers, there is a differential location of afferent nerve fibres within the distal and proximal oesophageal mucosa. In the proximal oesophagus these nerves lie superficially and close to the lumen. In the distal oesophageal mucosa they lie much deeper and closer to the basal epithelium.
Aims & Methods: We aimed to investigate the location of distal and proximal oesophageal mucosal afferent nerves in well-phenotyped patients with non-erosive reflux disease. We investigated mucosa from 10 patients with typical heartburn symptoms, normal macroscopic oesophageal appearances, and all had pathological oesophageal acid exposure on reflux testing (oesophageal pH exposure >4.2%).
In each patient, endoscopic mucosal biopsies were taken from 3 cm above the gastro-oesophageal junction (distal), and at 20 cm from the incisors (proximal). Biopsies were fixed in 4% paraformadehyde, cryoprotected, and 10 µm sections were cut on a cryostat and prepared on slides. Slides were examined immunohistochemically for presence and location of calcitonin gene-related peptide (CGRP)- and protein gene product (PGP) 9.5 - immunoreactive nerve fibres. Where fibres were identified their location in the mucosa was recorded in terms of cell layers from luminal surface.
Results: In the proximal oesophagus of patients with NERD, afferent nerves were found a mean of 7.7 ± 1.3 cell layers from the surface. In the distal oesophagus nerves were found a mean of 8.9 ± 2 cell layers from the surface.
In contrast, in healthy volunteers proximal nerves were found 12.3 ± 0.9 cell layers from the lumen in the proximal oesophagus, and 22.2 ± 2.7 cell layers from the lumen in the distal oesophagus. On ANOVA, the more superficial location of distal oesophageal nerves in patients versus healthy controls was statistically significant ($p < 0.001$). There was a non-significant trend to more superficial proximal nerves in NERD patients versus healthy volunteers.
Conclusion: Distal oesophageal afferent mucosal nerves are significantly closer to the lumen in patients with NERD versus healthy controls, and the usual differential location between proximal and distal fibre location is lost. This may be relevant for symptomatic acid perception in patients with reflux disease, and may be a target for topical treatment of these patients.
Disclosure of Interest: P. Woodland: Research grant from Reckitt Benckiser UK
D. Sifrim: Receives a research grant from Reckitt Benckiser
All other authors have declared no conflicts of interest.

Reference

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OP050 MUCOSAL INTEGRITY AND SENSITIVITY TO ACID OF THE PROXIMAL ESOPHAGUS IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE

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Introduction: Reflux episodes that extend to the proximal esophagus are more likely to be perceived. Our hypothesis is that the enhanced sensitivity of the proximal esophagus is related to more pronounced impairment of mucosal integrity in this part of the esophagus.
Aims & Methods: We aimed to assess acid sensitivity and mucosal integrity of the proximal and distal esophageal segments separately in patients with gastroesophageal reflux disease (GERD) and to investigate the relationship between these parameters. We included patients with heartburn and evidence of GERD on ambulatory pH-impedance measurement. After PPI washout, an esophageal hydrochloric acid perfusion test measuring segmental acid sensitivity proximally and distally in the esophagus (3 and 18 cm above the Z-line) and an upper endoscopy with biopsies at both levels were performed. During endoscopy, electrical tissue impedance spectroscopy was performed at the two levels and biopsies were taken from macroscopically unaffected mucosa. Biopsies were used to measure dilation of intercellular spaces with transmission electron microscopy as a morphological measure of impaired integrity and to investigate transepithelial electrical resistance and transepithelial fluorescein permeability in Ussing Chambers as a functional measure of mucosal integrity.
Results: We included 12 GERD patients (mean age 48 years, range 28–65, M:F 4:8). Lag time to heartburn perception was shorter after proximal acid perfusion (mean (95% CI) 0.8 minutes (0.1–1.5)) than after distal acid perfusion (3.9 minutes (2.4–5.4)); log rank $p = 0.02$. In vivo extracellular tissue impedance was lower in the distal esophagus (median (95% CI) 4563 Ω.m (3640–5429)) compared to the proximal esophagus (8170 Ω.m (7353–10110)); $p = 0.02$. Transepithelial fluorescein permeability was higher in the distal than the proximal segment (median 2051 $nmolcm^{-2}h^{-1}$ (IQR 1201–3708) and 368 $nmolcm^{-2}h^{-1}$ (IQR 0–1389); $p = 0.033$). Intercellular space ratio and transepithelial electrical

resistance were not statistically significant between the proximal and distal esophagus.
Conclusion: The proximal segment of the esophagus in GERD patients off PPI is more rapidly sensitive to acid perfusion, while the distal esophagus shows a more pronounced impairment of mucosal integrity. These findings show that the enhanced sensitivity to acid in the proximal esophagus is not explained by increased mucosal permeability.
Disclosure of Interest: A.J. Bredenoord: Received research funding from Endostim, Medical Measurement Systems, Danone and Given and received speaker and/or consulting fees from MMS, Astellas, AstraZeneca and Almirall. All other authors have declared no conflicts of interest.

OP051 LARYNGOPHARYNGEAL SYMPTOMS IN PRIMARY CARE: USEFULNESS OF SALIVARY PEPSIN MEASUREMENT IN PREDICTING GERD

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Introduction: Incidence of chronic laryngeal symptoms in primary care is about 2%/year and, gastroesophageal reflux disease (GERD) is considered by far the main disorder associated to them, leading to a specific syndrome called Laryngopharyngeal Reflux (LPR). Several studies demonstrated that pepsin measurement in saliva can be adopted as surrogate marker of GERD in LPR patients. Recently, a low-cost, non-invasive salivary pepsin test (PeptestTM, RD Biomed Limited, UK) was found able to measure pepsin in the saliva/sputum and to discriminate with good sensitivity and specificity between patients with typical GERD (i.e. with heartburn and regurgitation), confirmed at impedance-pH monitoring, from those without reflux disease (i.e. functional heartburn). Thus, it has been hypothesized about the utility of using this novel device to diagnose LPR in primary care setting.
Aims & Methods: We aimed to investigate the usefulness of PeptestTM in primary care patients presenting with chronic laryngeal symptoms suggestive of LPR. In a prospective multicenter, controlled, pilot study, consecutive patients presenting with chronic laryngeal symptoms were enrolled by primary care physicians. Uninvestigated individuals with no gastrointestinal symptoms or disease (including GERD or dyspepsia) or history of surgery served as healthy controls (HCs). All subjects completed the validated reflux symptom index (RSI) questionnaire and in case of a score >13, a symptom-based diagnosis of LPR was made. Also the gastrointestinal symptom scale (GIS) questionnaire was completed to investigate reflux symptoms and Quality of Life. All individuals were asked to provide 2 samples of sputum collected one hour after lunch and dinner. A positive PeptestTM was considered in case of a concentration of pepsin higher than 25 mg/mL.
Results: Between February and April 2014 and during August 2015, 86 patients with LPR (37 Male/49 Female, age 54 ± 14; RSI$\geq$13, mean RSI 22 ± 6, mean GSI 22 ± 6.4) and 59 healthy controls (30M/29F, mean age 41 ± 15; RSI<5, mean RSI 0.5 ± 1, mean GSI 33 ± 5.6) were tested. In total 256 samples were examined, whereas 34 samples were discarded because of technical problems (i.e. unclear storage, poor/excessive quantity). At least one positive result was found in 64/86 (74%) LPR patients and in 54/59 (92%) HCs ($p < 0.0095$), whereas two positive results were observed in 34/70 (49%) LPR patients and 26/46 (57%) HCs ($p = 0.4505$). One (in case of a single test) or two negative tests were registered in 22/86 (26%) LPR patients vs 4/59 (7%) of HCs ($p < 0.0039$). PeptestTM had an accuracy of 47% (IC95 39%–55%) a sensitivity of 74% (IC95 65%–84%), a specificity of 7% (IC95 0%–13%), a positive predictive value of 54% (IC95 45%–63%) and a negative predictive value of 2% (IC95 0%–8%) in identifying LPR as diagnosed by RSI.
Conclusion: In this pilot study, PeptestTM was not able to discriminate among primary care patients with LPR from those without and therefore cannot be suggested as preliminary tool to select patients requiring pH monitoring. Further studies including investigated healthy controls are mandatory to elucidate the diagnostic utility of salivary pepsin measurement in primary care setting
Disclosure of Interest: All authors have declared no conflicts of interest.

OP052 INADEQUATE SYMPTOM CONTROL ON LONG-TERM PPI THERAPY IN GERD – FACT OR FICTION? (LOPA II STUDY)

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Introduction: Randomized controlled trials report about 30% of GERD patients complain of bothersome remaining symptoms (heartburn, regurgitation) despite PPI. The LOPA (Lost Patients) I Study of 333 GERD patients seen in general practice revealed 46% of patients experienced heartburn or regurgitation symptoms at least twice per week despite PPI. A total of 20% were dissatisfied with their treatment. Few patients had received specific GERD diagnostics or recommended other options ($<10\%$).
Aims & Methods: The LOPA II study is a prospective, multicenter, observational study conducted in 7 general practice clinics. Patients with chronic GERD, taking PPI therapy for at least 1 year, and not satisfied with their treatment were asked to complete a questionnaire. Patients were asked the duration of their PPI therapy, satisfaction with their current condition, frequency of symptoms in the last week, whether they had previously received diagnostic evaluation or surgical consult related to GERD, whether they plan to consult a reflux specialist for further diagnostics, and reasons for dissatisfaction with their current medication treatment. "Lost Patients" were defined as those with a satisfaction score of 1 or 2 on a 5-point Likert scale (1: very dissatisfied; 2: dissatisfied), GerdQ score at least 8, and have not previously received specialized GERD diagnostics.
Results: 200 consecutive patient responses were collected within one year. Patients suffered from GERD an average of 9.7 years and prescribed PPI therapy for an average duration of 8.2 years. 74% were dissatisfied or very dissatisfied on their current PPI therapy (score of 1 or 2). 89% reported heartburn or regurgitation at least 2 days in the prior week (57% 4–7 days). 53% reported using additional medication other than their prescribed PPI at least 2 days per week (32% 4–7 days). In patients dissatisfied on PPI, most cited insufficient symptom control (91%) as a reason for dissatisfaction. In addition, 26% cited concern with long-term use of drugs and 23% the need for daily medication. 92% of patients had received an upper endoscopy, 8% had a prior pH-metry, 5% manometry, and 7% received prior surgical consult for GERD. The rate of "Lost Patients" in this study was 63%.
Conclusion: Chronic GERD patients who are dissatisfied with their PPI therapy are rarely offered specialized GERD diagnostic procedures or treatment alternatives. Half of the patients took medication in addition to PPI to control their reflux. In addition to persistent symptoms, concerns of long-term PPI use and burden of daily medication play a role in patient dissatisfaction with PPI therapy.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP053 EFFICACY OF ACOTIAMIDE IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE UNRESPONSIVE TO PROTON PUMP INHIBITOR THERAPY

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Introduction: Acid suppression is the mainstay of gastroesophageal reflux disease (GERD) therapy, and proton pump inhibitors (PPIs) are the first choice of drug treatment. Patients with GERD experience persistent heartburn or regurgitation up to 20–30% for PPI therapy. Reflux events are almost always accompanied by transient lower oesophageal sphincter relaxations (TLESRs). Several studies showed that gastric dysmotility such as delayed gastric emptying or impaired gastric accommodation increased TLESRs 1). Acotiamide is a new prokinetic drug that improves gastric motility. We previously reported that acotiamide significantly reduced TLESRs in healthy subjects 2). Our aim was to assess the effect of acotiamide in patients with GERD, who are unresponsive to PPI therapy.
Aims & Methods: This study design was a randomized, placebo-controlled, double-blind, parallel-group study. Patients who had reflux symptoms despite being on PPIs for at least 8 weeks were randomized to receive either acotiamide (10 mg thrice daily) or a matching dose of placebo for 2 weeks. The medicine was administered 30 min before every meal. In addition, patients continued their PPI treatment regimen (maintaining the same dose and type during the study). Symptoms were assessed at baseline and weeks 1 and 2 using questionnaires, and graded as 1 (much improved) to 7 (severely worsened). Grade 1 or 2 (improved) was indicative of treatment efficacy. If possible, 24-h multichannel intraluminal impedance-pH (24-h MII-pH) monitoring was performed at baseline and week 2.
Results: In total, 22 patients were enrolled in this study. The acotiamide and placebo groups consisted of 12 and 10 patients (6 and 7 women; mean age, 56 and 68 years, mean body mass index [BMI], 21 and 23, respectively). There were no significant differences in patient characteristics between both groups. The effective rate was 25 and 10% for acotiamide and the placebo after 2 weeks, respectively, and no statistical significance was observed ($p = 0.368$). Fifteen patients consented to the 24-h MII-pH monitoring at baseline and after 2 weeks. The acotiamide group showed a significant decrease in the number of total reflux events, acid and liquid reflux events (39.6 vs. 25.5, $p = 0.028$; 14.7 vs. 5.4, $p = 0.034$; and 17.6 vs. 8.3, $p = 0.009$, respectively). The placebo group

showed no significant change. In patients with a symptom index > 50% or total reflux events > 40, the effective rate was significantly different ($p = 0.038$) at 60 and 33% for the acotiamide and placebo groups, respectively. These results suggest that acotiamide may be effective in patients with associated reflux events.
Conclusion: Acotiamide significantly reduced the reflux events and improved reflux symptoms in patients whose symptoms were associated with reflux events. Co-administration of acotiamide and PPIs may be a new strategy for PPI-refractory GERD patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP054 A RANDOMIZED CONTROLLED TRIAL TO ASSESS THE CLINICAL EFFICACY OF ESOMEPRAZOLE VS. VONOPRAZAN FOR RESOLUTION OF GASTRO-ESOPHAGEAL REFLUX DISEASE SYMPTOMS IN NEWLY DIAGNOSED PATIENTS

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Introduction: The potassium competitive acid blocker (P-CAB) Vonoprazan (VPZ) has potent acid inhibitory efficacy. We assessed clinical efficacy for Gastro-oesophageal reflux disease (GORD) symptom.
Aims & Methods: This study was a single-center, prospective, randomized controlled, open-label, parallel-group trial conducted to assess the clinical efficacy of Esomeprazole (EPZ) 20 mg once daily vs. VPZ 20 mg once daily for the resolution of GORD symptoms in newly diagnosed patients.
Patients ≥20 years of age with upper gastrointestinal symptoms of at least moderate severity (Global Overall Symptom score [GOS] ≥ 4 on a 7-point Likert scale) were randomized to treatment with EPZ or VPZ.
The primary endpoint was the proportion of patients with sufficient relief of upper gastrointestinal symptoms (GOS ≤ 2) after 4 weeks of treatment.
Secondary endpoints were the proportion of patients with complete overall symptom relief (GOS = 1), Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG) score, and tolerance for both treatment. All patients provided informed consent before enrolment in the trial.
Results: 88 patients were entered and randomly assigned to the EPZ group and the VPZ group.
After 4 weeks, proportion of patients with sufficient relief was achieved by 88.6% in the EPZ group, compared to 58.1% in the VPZ group ($p < 0.01$).
The worsened provability in FSSG Functional Dyspepsia (FD) score were significantly lower in the EPZ group (6.8% / 4.5%) than in the VPZ group (27.9% / 18.6%) after 2 weeks and 4 weeks treatment ($p < 0.05$, $p < 0.01$).
Both treatment were generally well tolerated, but a patient in the VPZ group withdrew because of the adverse events.
Discussion: Despite VPZ has potent acid inhibitory efficacy, EPZ 20 mg once daily provides significant clinical efficacy for the resolution of GORD symptoms beyond that afforded by treatment with VPZ 20 mg once daily. In addition, the probability of worsen FD symptoms were significantly lower in the EPZ group than the VPZ group. The result observed in this study was considered to be caused by the multifactorial pathophysiology of GERD. Various mechanisms may contribute to dyspeptic symptoms, for example, finding that patients with gastric achlorhydria or hypergastrinemia showed impaired gastric motility may be supportive of this point (2).
These findings can suggest that increasing the degree of acid inhibition beyond that already achieved by EPZ 20 mg does not translate into increased clinical efficacy for the resolution of GORD symptoms in newly diagnosed patients.
Conclusion: EPZ 20 mg once daily was more effective than VPZ 20 mg once daily for the resolution of GORD symptoms in newly diagnosed patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP055 EFFICACY AND SAFETY OF THE ENDOLUMINAL MANAGEMENT OF REFRACTORY GASTROESOPHAGEAL REFLUX WITH BAND LIGATION

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Introduction: Gastroesophageal reflux disease is characterized by reflux of the gastric contents causing troublesome esophageal and extraesophageal symptoms that could affect adversely the quality of life. About 10–40% of patients with GERD fail to show adequate symptomatic response to the standard dose of PPI. several mechanisms could explain refractory GERD as improper PPI dosing, patient non-compliance, esophageal hypersensitivity, residual acid reflux,alkaline or bile reflux, nocturnal acid breakthrough. Alternative therapeutic options included laparoscopic fundoplication, lower esophageal magnetic beads which are expensive, and about 10% of patients experience persistanse of heart burn, or develop dysphagia
Aims & Methods: We aimed to evaluate the safety and efficacy of endoluminal rubber band ligation in the management of refractory GERD. 20 patients were enrolled in the study after informed consent was taken. They were treated with rubber band ligation and the cap used for ligation had a diameter of 11 mm and loaded with 6 rings. The main outcome is reduction of reflux symptoms measured by GERD health related quality of life Questionnaire. Patients were included if they were 18 years of age or older with typical symptoms of heartburn or regurgitation refractory or less responsive to maximally optimized dose of PPI therapy (given twice, 30 min before food) and even after adding H2 receptor blocker before bedtime and baclofen 10 mg twice daily to the unresponsive patients. Patients excluded if they had lower esophageal ulcers, pregnancy, red flag signs as loss of weight, fever, dysphagia, odynophagia, bleeding. Large hiatal hernia more than 2 cm, paraesopgageal hernia, active *Helicobacter pylori* infection, eosinophilic esophagitis were also excluded. Band ligation was performed in the four quadrants 5 mm distal to the Z-line which is measured before and after the sessions were completed.
Results: 13 males and 7 females were enrolled in the study. Their mean age 39.5 ± 6.2 with a range (31–49 years). The pre-endoscopic intervention characteristics were mean hemoglobin 10.6 ± 0.9 gm/dl, mean GERD related quality of life questionnaire (GERD-QLQ) value was 35.4 ± 6.9, depth of Z- line 34 ± 1.1cm, frequency of the sessions needed 1.6 ± 0.6 times over 4 months. After 6 months of follow up, GERD-QLQ score had dramatically improved 15.4 ± 4.6 ($t = 11.85$, $p = 0.000$), depth of Z line became 35 ± 0.9 cm ($t = -3.2$, $p = 0.005$), hemoglobin level showed non-significant increase (10.9 ± 0.8 gm/dl, $p = 0.06$). 5 patients experienced mild dysphagia (25%) improved after 6.5 ± 2.2 days, 8 patients (40%) experienced transient epigastric pain which disappeared within 5.4 ± 1.5 days. 13 patients stopped PPI use (65%), 6 patients were on demand therapy (30%), and only one patient needed continuous low dose PPI which was significantly reduced when compared to pre-endoscopic PPI intake.
Conclusion: Endoluminal band ligation is a safe, well tolerated and cost-effective therapeutic option for refractory GERD.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP056 ENDOSTIM® LES STIMULATION THERAPY IMPROVES GERD IN PATIENTS WITH LAPAROSCOPIC SLEEVE GASTRECTOMY (LSG)

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Introduction: LSG is the most commonly performed bariatric procedure in the US /Canada and the Asia-Pacific region. However, LSG can result in new GERD and may worsen preexisting GERD.[i] LSG patients with GERD not well controlled with PPI do not have good treatment options except for more invasive, anatomy-altering gastric bypass surgery. LES electrical stimulation therapy has shown to improve outcomes in GERD patients.[ii-iii]
Aims & Methods: To evaluate the safety and efficacy of LES stimulation in LSG patients with GERD not controlled with maximum dose PPI therapy. Patients with LSG-associated GERD with bothersome symptoms on maximum PPI dose underwent LES stimulator implant procedure and were enrolled in an international patient registry prospectively tracking outcomes in GERD patients treated with LES electrical stimulation. Electrical stimulation was delivered at 5mA, 220uSec pulse in 12, 30 minute sessions daily. GERD outcomes pre and post-stimulation were evaluated.
Results: 12 patients, 66% (8/12) women at 8 centers have been treated. Median age was 46 (IQR = 34–55) years. All (12/12) were on at least daily double-dose PPIs. At their last follow-up (median = 12 months), 75% (6/8) were off-PPIs and one each was using PPIs on < 50% of days and standard dose once a day. The later was on daily PPI for GI prophylaxis for chronic steroid therapy for kidney transplants and not GERD symptoms. Median esophageal pH at baseline was 16.4% (IQR 8.5–22.4), which improved to 1.3% (IQR 0.4–2.2) at last follow-up at least 6 month post-implant ($n = 6$; $p = 0.01$). All patients improved esophageal acid exposure, 83% (5/6) patients had normalized acid exposure and 1/6 patient had >40% improvement in distal esophageal acid exposure. Median GERD-HRQL scores at baseline was 25 (IQR 18–31) which improved to 4 (IQR 3–10) at last follow-up ($n = 6$; $p = 0.015$). No SAEs related to the device or procedure were reported. No dysphagia or other GI side effects were reported.
Conclusion: Preliminary results on patients with LSG and GERD with bothersome symptoms despite maximal medical therapy, treated with LES electrical stimulation, revealed that LES stimulation is safe and results in a significant improvement in GERD symptoms and esophageal acid exposure. Most patients were off their PPI therapy with remaining taking PPI at a reduced dose. Data from a larger patient experience for this indication is being collected using the international registry trial.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP057 ELECTRICAL STIMULATION OF THE LES - AN EMERGING THERAPY FOR GERD PATIENTS WITH FAILED ESOPHAGEAL PERISTALSIS

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Introduction: Antireflux surgery for GERD associated with failed peristalsis, either primary or in patient with prior lung transplant can be a challenge. Traditional antireflux surgery i.e. fundoplication has high rates of dysphagia and Roux-en-y reconstruction is very invasive. Partial fundoplication is traditionally employed but is not as effective in controlling reflux. Electrical stimulation of the LES (LES-EST) has emerged as a new alternative for the treatment of GERD. High-res manometry (HRM) studies reveal no negative effect on esophageal peristalsis or LES relaxation, making it an attractive treatment option for GERD patients with failed peristalsis. We report the outcome of LES-EST in this subgroup patients.
Aims & Methods: Seven patients (6 men; mean age = 58) diagnosed with severe GERD and failed peristalsis ($n = 5$), failed peristalsis and lung transplant ($n = 1$) or lung transplant ($n = 1$) were found eligible for LES-EST and agreed to undergo the procedure. Esophageal body function was assessed with HRM and reflux was diagnosed with Multichannel Intraluminal Impedance-pH testing (MII-pH). The LES Stimulation system (EndoStim, BV, The Hague, The Netherlands) was implanted using standard technique (Surg Endosc. 2013;27:1083–92) and stimulation was delivered in 12, 30 minute sessions of 5mA, 215usec, at 20Hz. Postop follow-up endpoints included clinical symptoms, MII-pH and PPI intake. Mean follow-up was 6 months (2–24).
Results: Surgical implant was completed successfully and electrical stimulation was initiated in all cases. Short and mid-term data was available for 5 patients while 2 patients were recently implanted and data will be included prior to the meeting. At their last follow-up, there was no dysphagia associated with LES-EST reported. Median GERD-HQRL score had improved from 12.5(8.3,20.5) to 6.0(3.0, 8.0). There was an improvement > 50% in pH-exposure showing median esophageal ph at baseline of 25.75(10.2, 54.5) that improved to 9.1(8.4, 25.1). 4/5 patients (80%) were either free of PPI or with a reduced those compared to pre-op and all with good response, 2 of these patients were taking PPI due to chronic immunosuppressant drugs for their lung transplant and not for reflux symptoms. Interestingly, one of the lung transplanted patients improved his FEV1 from 49 to 77 after the procedure while the second one remained stable at ~47 under chronic rejection.
Conclusion: Our preliminary case-series represents the first report of successful use of LES-EST in patients with GERD associated with severe esophageal dysmotility or lung transplant. Our early results suggest that LES-EST maybe a safe and effective treatment in these patients without the risk of new-onset dysphagia. A longer follow-up in a larger group of patients is required to fully establish the role of LES-EST in this difficult group of patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 14:00–15:30
IMPROVING THE ADENOMA DETECTION RATE – ROOM E1

OP058 ENDOCUFF-ASSISTED COLONOSCOPY OUTPERFORMS CONVENTIONAL COLONOSCOPY TO DETECT MISSED-ADENOMAS: EUROPEAN MULTICENTER, RANDOMIZED, BACK-TO-BACK STUDY

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Introduction: Endocuff (ARC Medical Design, Leeds, UK) is a device that mounted on the tip of the scope promises inspection of greater surface of the colonic mucosa as the endoscope is gradually withdrawn by pulling backwards, flattening and stretching the colonic folds. We aimed to compare adenoma miss-rates of Endocuff-assisted colonoscopy (EC) with that of the conventional one (CC).
Aims & Methods: Our study population underwent same-day, back-to-back, (EC as index procedure followed by CC or vice versa, randomly assigned 1:1) colonoscopies by six endoscopists with documented adenoma detection rates >35%, in four tertiary endoscopy facilities. Missed-adenoma detection rate (overall and in the proximal colon) for the two procedures was the study's primary end-point. Secondary endpoints included among others, measurement of missed-advanced adenoma rate, modification of the surveillance schedule according to the second exam, true negative index colonoscopies and early adverse events rate. ClinicalTrials.gov Identifier: NCT02340065.
Results: We randomized 200 patients (aged 61 ± 10 years; 86.4% CRC screening-surveillance cases). There were 7 EC and 1 CC incomplete exams. Scope insertion times were similar for EC and CC (5:44 ± 3:13 min vs. 5:37 ± 0.2:37 min, $p = 0.6$); however, there was a trend for longer EC withdrawal times (7:15 ± 2:52 min vs. 6:50 ± 1:52 min, $p = 0.06$). Overall, we detected one cancer and 194 (EC = 109; CC = 85) adenomas; 84 in the proximal colon. By per-lesion analysis (table), EC showed significant lower overall and proximal colon adenoma miss-rates compared with CC (14.7 [8–21]% vs. 37.6 [27–48]%; $p = 0.0004$ and 10.4 [1.8–19]% vs. 39 [23–55]%; $p = 0.004$, respectively). A similar superiority for EC was not revealed regarding advanced adenomas either overall or in the proximal colon. Index colonoscopy did not miss the cancer. By per-patient analysis, the second exam indicated modification of the surveillance schedule, according to the ASGE guidelines, in 17 and 5 patients who underwent CC and EC index exams (OR = 3.8 [95%CI: 1.4–10.9]; $p = 0.01$), respectively; however no difference in the modification of the surveillance schedule was detected when European guidelines were taken into account. The CC index arm had significantly more false negative (no adenoma) first examinations compared to EC (14 of 100 vs. 3 of 94; $p = 0.01$). There were no adverse events related to EC or CC.
Conclusion: In comparison with conventional colonoscopy, Endocuff-assisted colonoscopy reduces adenoma miss-rate by more than three times, even when highly efficient endoscopists perform the procedures.
Disclosure of Interest: All authors have declared no conflicts of interest.

Abstract No: OP058

	Adenomas overall, N				Proximal colon adenomas, N			
	Found at Index	Missed and found by EC	Missed and found by CC	OR (95%)	Found at Index	Missed and found by EC	Missed and found by CC	OR (95%)
CC Index	53	32	-	3.5 (1.8–7)	22	14	-	5.5 (1.7–17)
EC Index	93	-	16		43	-	5	

OP059 THE DIAGNOSTIC ABILITY OF A COMPUTER-AIDED DIAGNOSIS SYSTEM FOR NARROW-BAND IMAGING ENDOCYTOSCOPY IS COMPARABLE TO THAT OF EXPERT ENDOSCOPISTS

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Introduction: Endocytoscopy (EC) can be used to evaluate not only cell nuclei but also microvessels in vivo. We reported the efficacy of observing the endocytoscopic vascular (ECV) pattern by using EC with narrow-band imaging for diagnosing colorectal lesions (Kudo S, et al. *GIE* 2015.[1]). As the interpretation of the ECV pattern is difficult for novice endoscopists and requires substantial training, we have developed a tentative model of a computer-aided diagnosis (CAD) system for the ECV pattern (ECV-CAD) (Misawa M, et al. Gastroenterology, in press.[2]). However, in our previous study, we did not compare the performance of ECV-CAD with that of human endoscopists. Therefore, it is uncertain whether ECV-CAD can achieve a diagnostic ability as high as that of expert endoscopists.

Aims & Methods: The aim of this study was to compare the diagnostic ability of ECV-CAD with that of human endoscopists in characterization of colorectal lesion. The algorithm of ECV-CAD is based on texture analysis, which can quantify the pattern of endoscopic images, and vessel features. ECV-CAD provides a 2-class diagnosis (neoplastic or non-neoplastic) including its probability value. To validate the diagnostic ability of ECV-CAD, 173 randomly selected EC images (non-neoplasm, 49; neoplasm, 124) that were not used for machine-learning processes were evaluated with ECV-CAD. To compare diagnostic ability between ECV-CAD and manual endoscopy, we selected 4 expert endoscopists (with an experience of >200 cases of EC) and 3 novices (with an experience of <20 cases of EC). The EC images used for the evaluation with ECV-CAD were randomly allocated to the assessors. The assessors recorded their diagnosis (non-neoplasm or neoplasm) with its confidence level (high or low). For ECV-CAD, a probability of $>90\%$ was considered as a high-confidence computed diagnosis. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of distinguishing neoplasms from non-neoplasms, as well as the ratio of high-confidence diagnosis were calculated. Furthermore, the diagnostic ability when the diagnosis was made in high confidence was also calculated.

Results: The overall accuracy of ECV-CAD was 87.8%, whereas the accuracy for high-confidence cases was 93.5%. These values were higher than those for trainees ($P=0.01$, McNemar test) and comparable to those of experts ($P=0.85$, McNemar test). The high-confidence diagnosis ratio of ECV-CAD was 72.0% (124 of 172). The NPV for neoplasms with a high confidence was 94.4%, 84.6%, and 46.3% for ECV-CAD, experts, and novices, respectively. The details of the diagnostic abilities are shown in the Table.

Table: Diagnostic Abilities

	ECV-CAD(%)	Experts(%)	Novices(%)
Overall accuracy (total / high confidence)	87.8 / 93.5	84.2 / 90.8	63.4 / 71.7
Sensitivity (total / high confidence)	94.3 / 99.0	85.6 / 92.9	61.5 / 71.2
Specificity (total / high confidence)	71.4 / 70.8	80.6 / 84.0	68.0 / 73.1
PPV (total / high confidence)	89.2 / 93.3	91.7 / 94.8	82.8 / 88.6
NPV (total / high confidence)	83.3/ 94.4	69.0 / 79.0	41.3 / 46.3
High confidence rate	72.0	70.9	39.7

Conclusion: The overall accuracy of ECV-CAD was comparable to that of experts and significantly better than that of novices. Thus, ECV-CAD could be a powerful decision-making tool for less experienced endoscopists.

Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 14:00–15:30

LONG-TERM MANAGEMENT OF IBD – ROOM G

OP060 LYMPHOMA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A FRENCH NATIONWIDE OBSERVATIONAL COHORT STUDY

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Introduction: Thiopurines are associated with an increased risk of lymphoma. The risk of lymphoma associated with anti-TNFs is uncertain.

Aims & Methods: The aim of this study was to assess the risk of lymphoma in patients with inflammatory bowel disease (IBD) treated with thiopurines, anti-TNFs or the combination of both treatments (combotherapy). Every patient affiliated to the French national health insurance with a diagnosis of IBD, based on listed long-term diseases and/or hospital discharge diagnosis, was included from 1st July 2009 through 31st December 2013, and followed up until December 31st, 2014. A propensity score was built, using a multinomial logistic regression conditional of multiple covariates, to predict the probability to receive thiopurines, anti-TNFs or combotherapy at baseline. Hazard ratios for lymphoma were estimated using Cox proportional hazards regression in which each treatment was introduced as a time dependent covariate.

Results: The cohort included 173 190 patients with IBD, followed for a median time of 4.9 years, accounting for 522 487 persons-years (PY) unexposed to thiopurines or anti-TNFs, 111 113 PY exposed to thiopurines, 60 736 PY exposed to anti-TNFs and 11 514 PY exposed to combotherapy. Among them, 166, 56, 31 and 13 patients developed lymphoma, respectively. In multivariate analysis, patients exposed to thiopurines or anti-TNFs monotherapy had an increased risk of lymphoma as compared to unexposed patients (Hazard ratio and 95% confidence interval ($HR_{95\%}$) 1.64 (1.08–2.26) and $HR_{95\%}$: 1.87 (1.15–3.03), respectively). Patients exposed to combotherapy had a more than four-fold increased risk of lymphoma as compared to unexposed patients ($HR_{95\%}$: 4.83 (2.51–9.16)).

Conclusion: The risk of lymphoma associated with combotherapy is more than two-fold higher than that associated with thiopurines and anti-TNFs monotherapy. This risk should be taken into consideration and weighed against potential benefits of combotherapy.

Disclosure of Interest: F. Carbonnel: Franck Carbonnel had consulting fees from Genentech, Otsuka, Vifor, and lecture fees from Hospira.
All other authors have declared no conflicts of interest.

Abstract No: OP060

Table: Hazard ratio for lymphoma in thiopurines, anti-TNFs monotherapy and combotherapy exposed patients compared to unexposed patients

Treatment	Never exposed to thiopurines or anti-TNFs	Thiopurines monotherapy			Anti-TNFs monotherapy			Combotherapy		
Persons-years	522 487 PY	111 113 PY			60 736 PY			11 514 PY		
	Cases	Cases	Hazard Ratio (95% CI)		Cases	Hazard Ratio (95% CI)		Cases	Hazard Ratio (95% CI)	
			Crude	Adjusted		Crude	Adjusted		Crude	Adjusted
Total	166	56	1.39 (1.02–1.90)	1.64 (1.08–2.26)	31	1.30 (0.88–1.93)	1.87 (1.15–3.03)	13	2.99 (1.69–5.29)	4.83 (2.51–9.16)
Non-Hodgkin lymphoma	150	45	1.19 (0.85–1.68)	1.56 (0.98–248)	25	1.10 (0.71–1.70)	1.94 (1.05–3.05)	9	2.19 (1.11–4.31)	4.09 (1.93–8.64)
Hodgkin lymphoma	16	11	3.32 (1.54–7.18)	2.41 (0.86–6.72)	6	3.31 (1.28–8.54)	2.52 (0.78–8.20)	4	11.50 (3.82–35.59)	9.09 (2.46–33.66)
Adjusted for age and propensity score										

OP061 INCIDENT CANCER IN INFLAMMATORY BOWEL DISEASE: RISK FACTORS IN A LONG TERM MULTICENTER NESTED CASE-CONTROL IG-IBD STUDY AT 4 YEARS

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Introduction: Risk factors for cancer in inflammatory bowel disease [IBD] are debated (1). In a prospective, multicentre, nested case-control study at 3 years (2012–2014), we reported IBD phenotype as a risk factor for cancer (2). The analysis included 44,619 IBD patients (21,953 Crohn's disease (CD), 22,666 ulcerative colitis (UC). Cancer occurred in 174 patients (99 CD [CD-K], 75 UC [UC-K]) (2). A larger study is required to identify risk factors for cancer, including cancer subtypes

Aims & Methods: In a prospective multicenter nested case-control-study, we aimed to assess, in a large IBD population followed up in the long term, risk factors for incident cases of cancer, including cancer subtypes. The role of clinical characteristics of IBD vs immunomodulators (IMM) use as risk factors was also assessed. At this purpose, all IBD patients with incident cancer and their matched controls referring to the same 16 Units involved in the study at 3 years (Jan 2012-Dec 2014) (2) were followed up for additional 15 months (Jan 2015-Mar. 2016: follow up >4 years; 51 months). The study population also included all the additional IBD patients referring to the same Units, with incident cancer from Jan. 2015 to Mar. 2016. Each IBD patient with cancer (IBD-K) was matched with 2 IBD patients without cancer (IBD-C) for: IBD type, gender, age. Risk factors considered: age (at last visit, at diagnosis of IBD, of cancer), IBD extent, CD phenotype [B1-B3], perianal CD, smoking, family history of IBD, IBD-related surgery, current/past use of thiopurines [IS], TNFα antagonists ($\geq$1), any IMM. Data were expressed as median (range),Wilcoxon, Chi-squared test,-multivariate logistic regression analysis as appropriate.

Results: Incident cancer occurred in 208 IBD patients: 117 CD [CD-K], 91 UC [UC-K]. IBD-C included 416 patients: 234 CD [CD-C], 182 UC [UC-C]. IBD-K and IBD-C included 624 patients (351 CD [165 F;47%]; 273 UC [117F;43%]). Cases and controls did not differ in terms of age (CD-K vs CD-C:p = 0.92; UC-K vs UC-C:p = 0.32) and IBD duration (CD-K vs CD-C: p = 0.63;UC-K vs UC-C: p = 0.53). In IBD, cancers (n = 208) involved (n [%]): digestive system (76 [36.5%]: 53 [25.5%] colorectal cancer (CRC), 8 [10.5%] small bowel adenocarcinoma, SBA), skin (28 [13.5%]), urinary tract (23 [11.1%]), breast (17 [8.1%]), lung 14 [6.7%], genital tract (11 [5.2%]), thyroid (8 [3.8%]), lymphoma (7 [3.4%]), others (24 [11.5%]). CRC (n = 53) was more frequent in UC vs CD (n [%]: 31/91 [34%] vs 22/117 [19%]; p = 0.01), while extracolonic cancers (n = 155) in CD vs UC (95/117 [81%] vs 60/91 [66%]; p = 0.01). Lymphoma (n = 7) and SBA (n = 8) occurred only in CD. In CD, risk factors included perianal disease for CRC (3.61 [1.23–10.63]), penetrating (B3) vs non-penetrating non stricturing CD (B1) for extracolonic cancers (OR 2.21 [1–4.99]). IS and anti-TNFα use was at limit of the statistical significance as risk factor for overall cancer in CD (OR 1.59 [0.96–2.66]). In UC, risk factors were: pancolitis and UC-related surgery for cancer overall (OR 1.95 [1.07–3.59] and 3.99 [1.55–11.14]); UC duration (OR 3.74 [1.37–13.17]) for CRC; pancolitis and left-sided vs distal UC (OR 2.11 [1.04–4.4] and 2.47 [1.06–5.73]) and UC-related surgery (OR 3.07 [1.15–8.02] for extracolonic cancers. The same risk factors (extensive UC, penetrating CD, IS and anti-TNFα use) were at limit of the statistical significance for urinary tract and skin cancers.

Conclusion: In a long-term multicentre study, clinical characteristics of IBD (UC extent, penetrating CD, perianal CD). were risk factors for incident cancer. CRC was more frequent in UC and extracolonic cancers in CD.

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All other authors have declared no conflicts of interest.

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OP062 USE OF IMMUNOSUPRESSANTS AND BIOLOGICAL AGENTS IN IBD PATIENTS WITH PAST HISTORY OF CANCER

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Introduction: Conventional immunosuppressants (thiopurines or methotrexate) and anti-TNF agents (IMMs) can influence the immunologic control of cancer and they might ease cancer spread and recurrence. Therefore, a past history of cancer is a relative contraindication for their use in inflammatory bowel disease (IBD).
Aims & Methods: We aimed to describe the risk of incident cancers (recurrent or new) in patients with IBD and a past history of malignancy treated with IMMs, and to identify risk factors. IBD patients included in ENEIDA Project from GETECCU with a past history of cancer were identified and compared between those who were further treated with IMMs and those who never were treated with these drugs (controls).
Results: We identified 947 patients with previous cancer of whom 526 did not received IMMs before the diagnosis of cancer. Of these, 385 were controls and 141 were subsequently treated with IMMs after a median of 60 (23–130) months from cancer diagnosis. After a median follow-up of 68 months (27–126), 52 patients(10%) developed incident cancers (50% recurrent and 50% new). The most frequent recurrent ones were breast (35%) and prostate (20%) cancers. Incident cancers occurred similarly in patients further treated with IMMs and controls (9% vs. 12%p = 0.33), as did regarding the type of the index cancer. However, cancer-related deaths were more frequent among controls (4% vs. 0%;p = 0.013). Cancer-free survival was 99%, 98% and 97% at 1, 2, and 5 years in patients further treated with IMMs and 97%, 96% and 92% at 1, 2 and 5 years in controls, respectively (p = 0.003).
Conclusion: In this large, retrospective cohort, treatment with conventional immunosuppressants or anti-TNF agents in patients with IBD and a past history of cancer was not associated with an increased risk of new or recurrent cancers.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP063 RISK OF SERIOUS AND OPPORTUNISTIC INFECTIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A NATIONWIDE FRENCH COHORT STUDY

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Introduction: Serious and opportunistic infections are a major concern in patients with inflammatory bowel disease (IBD) treated with immunosuppressive agents and biologics.
Aims & Methods: The aim of this study was to assess the risk of serious and opportunistic infections associated with thiopurines monotherapy, anti-TNFs monotherapy and the combination of both treatments (combotherapy). Every patient affiliated to the French national health insurance with a diagnosis of IBD based on listed long-term diseases and/or hospital discharge diagnosis was included from 2009 to 2013, and followed up until 31 December 2014. A propensity score was built to predict the probability to receive a monotherapy with thiopurines, anti-TNFs or combotherapy at baseline. Hazard ratios of infections were estimated based on Cox regression models, stratified on age at cohort entry (aged 18–64 years and $\geq$ 65 years) and with treatments considered as time-dependent variables. Serious and opportunistic infections were classified according to infection sites and pathogens, respectively.
Results: 173 077 IBD patients were included and followed during 4.9 years in median, accounting for 512 805 persons-years (PY) unexposed to anti-TNFs or thiopurines, 108 315 PY exposed to thiopurines monotherapy, 57 464 PY exposed to anti-TNFs monotherapy and 11 089 PY exposed to combotherapy. Among them, a total of 4926, 1144, 1096 and 252 serious infections and 245, 183, 120 and 47 opportunistic infections occurred, respectively. After adjustment (based on propensity score, age, time-varying exposure to corticosteroids and past history of serious infections), exposures to thiopurines monotherapy, anti-TNFs monotherapy and combotherapy were associated with an increased risk of serious and opportunistic infections, compared to unexposed patients. Combotherapy was associated with an increased risk of serious and opportunistic infections compared to anti-TNFs exposure in patients aged 18–64 years (hazard ratio and confidence interval 95% ($HR_{95\%}$) 1.31 (1.14–1.51), $HR_{95\%}$: 2.12 (1.49–3.00), respectively), while exposure to anti-TNFs was associated with an increased risk of serious infections compared to thiopurines in patients aged 18–64 years and $\geq$ 65 years: $HR_{95\%}$: 1.82 (1.67–1.99) and $HR_{95\%}$: 1.83 (1.43–2.35), respectively. Exposure to thiopurines was associated with an increased risk of viral infections compared to anti-TNFs monotherapy in patients aged 18–64 years ($HR_{95\%}$: 1.74 (1.20–2.52)). Similar results were observed in a sensitivity analysis conducted in incident patients.
Conclusion: Thiopurines, anti-TNFs monotherapy and combotherapy are all associated with an increased risk of serious infections in IBD patients compared to unexposed patients. However, the risk of serious infections is higher with anti-TNFs than with thiopurines and the risk of serious and opportunistic infections is higher with combotherapy than with anti-TNFs. The risk of serious and opportunistic infections should be taken into consideration and weighed against potential benefits of anti-TNFs.
Disclosure of Interest: F. Carbonnel: Franck Carbonnel had consulting fees from Genentech, Otsuka, Vifor, and lecture fees from Hospira.
All other authors have declared no conflicts of interest.

OP064 THE COURSE OF HEALTH-RELATED QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE FIVE, TEN AND 20 YEARS AFTER DIAGNOSIS - DATA FROM THE IBSEN STUDY

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Introduction: Previous population-based cross-sectional studies have shown that health-related quality of life (HRQoL) in patients with the inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn's disease (CD) is reduced, especially in association with disease activity. Data describing the course of HRQoL in IBD are scarce.
Aims & Methods: The aim of the present study was to assess the course of HRQoL at three prescheduled time-points during 20 years of follow-up in an inception cohort with IBD patients. IBD patients included in a population-based inception cohort from 1990–93 (Inflammatory Bowel Disease in South-East Norway – IBSEN) were invited to follow-up visits five, ten and 20 years after diagnosis. In addition to structured interviews and clinical examinations at inclusion and follow-up visits, the Short Form 36 (SF-36) and the Norwegian version of the Inflammatory Bowel Disease Questionnaire (N-IBDQ) were completed by the patients at all follow-up visits. The mean N-IBDQ total scores and the mean SF-36 dimensional scores were calculated. In this abstract, we present the total N-IBDQ scores and the dimensional SF-36 scores for general health (GH), stratified by diagnose and sex. Norman et al. (1) defined the difference between HRQoL scores exceeding ½ standard deviation (SD) as clinically relevant. Consequently, we defined patients with changes in scores less than 1/2 SD during follow-up as to have stable HRQoL scores.
Results: Of the initially 756 included patients with confirmed IBD, 599 (79%) were still alive after 20 years. HRQoL questionnaires were answered by 522, 327

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Table: Hazard ratios for any serious or opportunistic infections according to medication exposure

	Exposed to thiopurines versus unexposed to thiopurines or anti-TNFs		Exposed to anti-TNFs monotherapy versus unexposed to thiopurines or anti-TNFs		Exposed to Combotherapy versus unexposed to thiopurines or anti-TNFs		Exposed to anti-TNFs monotherapy versus thiopurines monotherapy		Exposed to Combotherapy versus exposed to anti-TNFs monotherapy	
	Hazard Ratio (95% CI)		Hazard Ratio (95% CI)		Hazard Ratio (95% CI)		Hazard Ratio (95% CI)		Hazard Ratio (95% CI)	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Serious infections, all										
18–64 years	1.29 (1.20–1.39)	1.27 (1.15–1.39)	2.40 (2.23–2.58)	2.31 (2.10–2.53)	3.02 (2.65–3.45)	3.03 (2.62–3.50)	1.86 (1.70–2.03)	1.82 (1.67–1.99)	1.26 (1.09–1.45)	1.31 (1.14–1.51)
≥ 65 years	0.94 (0.81–1.10)	1.19 (0.97–1.47)	1.76 (1.43–2.16)	2.18 (1.73–2.76)	1.82 (1.03–3.22)	2.46 (1.37–4.39)	1.86 (1.45–2.38)	1.83 (1.43–2.35)	1.04 (0.57–1.89)	1.13 (0.62–2.05)
Serious infections, excluding GI infections										
18–64 years	1.31 (1.20–1.42)	1.31 (1.17–1.45)	2.60 (2.39–2.83)	2.54 (2.29–2.83)	3.21 (2.77–3.73)	3.29 (2.79–3.88)	1.99 (1.80–2.20)	1.95 (1.76–2.16)	1.24 (1.05–1.45)	1.29 (1.10–1.52)
≥65 years	0.89 (0.74–1.06)	1.09 (0.87–1.38)	1.86 (1.50–2.32)	2.28 (1.77–2.94)	1.84 (0.99–3.43)	2.45 (1.30–4.63)	2.10 (1.60–2.75)	2.09 (1.59–2.74)	0.99 (0.51–1.90)	1.07 (0.56–2.07)
Opportunistic infections, all										
18–64 years	4.31 (3.48–5.36)	5.04 (3.88–6.55)	5.37 (4.20–6.87)	6.10 (4.56–8.16)	11.3 (8.13–15.8)	12.9 (8.95–18.6)	1.25 (0.98–1.59)	1.21 (0.95–1.54)	2.11 (1.49–2.98)	2.12 (1.49–3.00)
≥65 years	2.38 (1.41–3.99)	1.84 (0.87–3.91)	4.88 (2.55–9.31)	3.92 (1.75–8.78)	7.23 (1.77–29.5)	6.40 (1.45–28.2)	2.05 (0.97–4.36)	2.13 (1.00–4.54)	1.48 (0.33–6.70)	1.63 (0.36–7.38)
Opportunistic infections, excluding mycobacterial infections										
18–64 years	5.30 (4.13–6.81)	6.07 (4.50–8.19)	5.31 (3.95–7.14)	5.91 (4.19–8.34)	10.4 (6.92–15.7)	11.6 (7.44–18.2)	1.00 (0.76–1.33)	0.97 (0.73–1.29)	1.96 (1.28–3.01)	1.97 (1.28–3.02)
≥ 65 years	1.87 (1.00–3.47)	1.17 (0.46–2.97)	4.18 (1.98–8.84)	2.82 (1.07–7.44)	8.59 (2.10–35.1)	6.42 (1.37–30.0)	2.24 (0.91–5.50)	2.40 (0.97–5.91)	2.06 (0.44–9.71)	2.28 (0.48–10.8)

and 438 patients at the five, ten and 20 years follow up, respectively. Of these patients, 199 (139 UC, 60 CD) and 191 (133 UC, 58 CD) answered the N-IBDQ and the SF-36 at every follow-up visit, respectively. We could not register clinically relevant changes between the mean N-IBDQ total scores and the mean GH dimensional scores during the different follow-up visits (Table 1). Of 139 UC patients and 60 CD patients, who answered the N-IBDQ at all follow-up visits, 54 (38.9%) and 17 (28.3%) had stable scores. Of 133 UC patients and 58 CD patients, who answered the SF-36 at all follow-up visits, 31 (23.3%) and 13 (22.4%) had stable scores.

Table 1: N-IBDQ total scores and General Health dimensional scores

		UC Men			UC Women			CD Men			CD Women		
Follow-up year		5	10	20	5	10	20	5	10	20	5	10	20
All patients													
IBDQ	N	180	108	140	168	113	154	88	61	72	86	45	72
	Mean scores	190	191	187	181	180	179	187	186	184	174	180	172
	SD	25	29	23	29	33	28	31	26	26	30	28	26
SF-36	N	178	104	142	165	110	153	86	61	73	86	45	69
GH	Mean scores	68	68	70	64	62	65	66	63	69	57	60	58
	SD	22	24	21	24	23	24	27	25	22	24	22	21
Patients participating in every follow-up													
IBDQ	N	62			77			39			21		
	Mean scores	191	195	191	182	183	181	182	188	181	175	178	180
	SD	23	26	20	29	36	29	30	25	28	28	29	19
SF-36	N	61			76			39			21		
GH	Mean scores	72	73	72	65	64	64	64	69	66	58	62	64
	SD	20	21	21	25	22	24	29	23	22	20	23	16

N-IBDQ: Inflammatory Bowel Disease Questionnaire (Norwegian version). SF-36: Short Form 36. GH: General Health dimension. SD: standard deviation, N: Number of participants

Conclusion: Mean HRQoL scores in our IBD cohort did not vary during follow-up visits five, ten and 20 years after diagnosis. However, only a minority of CD and UC patients had stable HRQoL scores during the 20 years of follow-up. Therefore, a more detailed reporting on changes in subgroups might help to identify factors associated with an unstable course of HRQoL in IBD.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP065 PROGNOSTIC FACTORS FOR LONG-TERM INFLIXIMAB TREATMENT IN CROHN'S DISEASE PATIENTS: A 20-YEAR SINGLE CENTER EXPERIENCE

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Introduction: The long-term efficacy of infliximab (IFX) in Crohn's disease (CD) patients is suboptimal and prognostic factors for real-life long-term efficacy are insufficiently studied.

Aims & Methods: The aim of this study was to identify patient- and disease-related factors influencing the real-life long-term response of infliximab in CD. All consecutive CD patients treated with IFX between December 1994 and January 2016 at a tertiary centre, were retrospectively analysed. Only patients who responded to an induction dose (5 mg/kg on week 0, 2 and 6), followed by scheduled IFX maintenance treatment were included. Exclusion criteria were: prior infliximab use, ever episodic treatment, drug interval (>14 weeks), CD-related surgery during induction therapy and extra-intestinal manifestations as main indication. IFX failure was the primary endpoint, defined as stopping IFX due to one of the following reasons: 1) loss of response (LOR) despite treatment optimization, 2) presence of persistent antibodies towards infliximab (ATI), and 3) the need for IBD related surgery. Since 2010–2011, IFX and ATI serum concentrations at trough were measured in the majority of patients with an in-house-developed and clinically validated drug sensitive bridging enzyme-linked immunosorbent assay (ELISA). Therapeutic drug monitoring (TDM) was defined as the use of serum IFX & ATI concentration measurements to guide treatment decisions and optimization. Patient- and disease-related factors were used to identify independent predictors of IFX failure-free survival using Cox proportional hazards model and Kaplan-Meier analysis. Internal validation of the Cox regression analysis was performed with bootstrapping with 1000 replications. The c-statistic was used to assess the predictive accuracy of the regression model.

Results: A total of 261 CD patients were included in the final analysis. Median time on IFX was 2.4 [IQR 1.4–4.7] years, and 65 (24.9%) patients experienced IFX failure. Median age at start of IFX was 32.8 [22.6–44] years, after a median disease duration of 3.4 [0.7–13.6] years. In total, 39 (14.9%) patients received anti-TNF prior to IFX start (adalimumab or certolizumab pegol). TDM was used in 202 (77.4%) patients. Estimated 1, 5, and 10 year IFX failure-free survival was 93.7% (95% CI 90.7–9i6.7), 65.9% (58.3–73.5) and 58.2% (45.6–70.9), respectively. When combining all available IFX measurements during the follow-up of the study, median IFX concentrations were lower in patients who experienced IFX failure (3.1 [0.3–7.5] μg/mL) compared to patients who did not fail IFX (5.3 [3.1–8.4] μg/mL), $p < 0.0001$). Multivariate Cox regression identified disease duration < 1 year (hazard ratio (HR) 2.5 (95% CI 1.2–5.2), $p = 0.02$), isolated L1 disease location (HR 2.0 (1.1–3.5), $p = 0.02$), prior anti-TNF use (HR 2.3 (1.1–4.8), $p = 0.03$), hemoglobin < 13.5 g/dL (HR 2.3 (1.2–4.4), $p = 0.02$), absence of TDM use (HR 8.0 (4.1–15.6), $p = 1x10^{-9}$), and first IFX dose optimization within first year (HR 3.7 (2.1–6.6), $p = 5x10^{-6}$) as independent predictors of IFX failure-free survival. All these factors remained significant after internal validation with bootstrapping. This final model had a c-statistic of 0.80 which is considered as a well discriminating model. Stratifying patients into risk groups resulted in estimated 3 year IFX failure-free survival rates of 95.3% (95% CI 94.2–96.4) for the low risk group (0 or 1 risk factor), 79.3% (78.4–80.2) for the medium risk group (2–3 risk factors), and 26.3% (8.6–44.0) for the high risk group (≥ 4 risk factors) ($p = 8x10^{-13}$). IFX concentrations at

week 14 were available in 199 (76.2%) patients, and in this subgroup of patients, IFX concentration at week 14 was also a significant predictor of IFX failure-free survival (HR 0.87 (0.80–0.94), p = 0.001).
Conclusion: This study identified several predictors of clinically relevant IFX failure in CD patients. Stratifying patients according to the amount of risk factors can identify patients at high risk for IFX failure. Initiating IFX sooner rather than later and using TDM in this group to proactively strive for adequate drug concentrations may ensure optimal disease outcome.
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M. Ferrante: - Research grant: Takeda - Speakers fee: Abbvie, Boehringer-Ingelheim, Chiesi, Falk, Ferring, Janssen, Mitsubishi Tanabe, MSD, Takeda, Tillotts, Zeria - Consultancy: Abbvie, Boehringer-Ingelheim, Ferring, Janssen, MSD
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All other authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 14:00–15:30
MICROBIOTA AND DIET: FROM BENCH TO BEDSIDE – ROOM K

OP066 CYCLIC ENTERAL NUTRITION FOR THE MAINTENANCE OF REMISSION IN PEDIATRIC CROHN'S DISEASE PATIENTS

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Introduction: Enteral nutrition (EN) is a well-established treatment in pediatric Crohn's disease (CD) for induction of remission as well as disease flares with similar efficacy compared to steroid therapy and no side effects. Some reports indicate a role for EN as maintenance therapy, but usually on top of other treatment or after surgically induced remission. The aim of our study was to test feasibility and efficacy of cyclic EEN as sole maintenance therapy.
Aims & Methods: Nine patients with active luminal paediatric Crohn's disease, L1 (n = 2) or L3 (n = 7), followed at Necker Hospital between 2012 and 2014 were included in this prospective pilot study. After 8 weeks of exclusive enteral nutrition with Modulen IBD, patients who came into complete CRP-negative remission were proposed to continue on cyclic EEN therapy as sole treatment in an open manner. Cyclic EEN consists of a 6 weeks phase of normal feeding followed by a 2 weeks phase of exclusive enteral nutrition, without any concomitant CD-related medication. Patients were followed on a fixed scheme (3 months visits) with collection of anthropometric, clinical and biological data.
Results: At inclusion, all patients were in deep remission (CRP-negative). At month 6 and 12 follow-up visit, 8 of the 9 patients (89%) (wPCDAI 8.4 ± 9.2) and 5 of 6 patients (wPCDAI 5.7 ± 3.2), respectively were in clinical remission. Concomitant to the clinical response, biological scores markedly improved with mean CRP 21.8 ± 14.2 mg/L at M0, 9.8 ± 11.7 mg/L at M6 ($p < 0.05$) and 5.4 ± 2.7 at M12 (n = 6) ($p < 0.05$) and albumin normalization with 33.8 ± 3.8 g/l at M0, 39.9 ± 5.1 g/l at M6 ($p < 0.05$) and 42.8 ± 2.9 at M12 (n = 6) ($p < 0.05$). 3 patients relapsed before M12. Patients presented catch up growth with net improvement of their anthropometric measurements at M2 and stabilization thereafter (Table 1).

	M0 (n = 9)	M2 (n = 9)	M6 (n = 9)	M12 (n = 6)
Z score weight	-0.96 ± 1.13	-0.37 ± 0.97	0.07 ± 0.81	0.30 ± 1.18
Z score height	-0.18 ± 0.84	-0.11 ± 0.80	0.09 ± 1.14	0.35 ± 0.76
Z score BMI	-1.37 ± 1.07	-0.38 ± 0.89	-0.82 ± 1.15	-0.66 ± 1.20

Conclusion: This study demonstrates for the first time prolonged clinical, biological remission and improved growth in pediatric CD patients treated only with cyclic enteral nutrition. Cyclic EN can be an efficacious non pharmacological treatment of Crohn's disease patients potentially acting ahead of the inflammatory cascade in the intestinal mucosa. A sufficiently power randomized controlled trials is currently conducted by the GETAID pédiatrique to confirm these pilot data.
Disclosure of Interest: F. Ruemmele: Nestlé Nutrition Institute, Nestlé Health Science
All other authors have declared no conflicts of interest.

OP067 CHANGES IN MUCOSAL-ASSOCIATED INTESTINAL MICROBIOTA AND FECAL BACTERIA IN INFLAMMATORY BOWEL DISEASE PATIENTS AND HEALTHY SUBJECTS: A PILOT STUDY

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Introduction: The existing literature on intestinal microbiota in inflammatory bowel diseases (IBD) reveals conflicting changes in microbiota composition in all patients, having most of studies been conducted only on fecal microbiota. Microbiota adhering to the gut mucosa might affect epithelial and mucosal function to a greater degree than fecal bacteria.
Aims & Methods: The aim of the present study was to evaluate the mucosal and fecal microbiota composition in healthy controls (CTRLs) and IBD patients, in a case-control study exploited by 16S rRNA targeted metagenomics-based approach (phylotyping, PH). Fecal specimens were collected from 14 IBD patients [10 Crohn's disease (CD), 4 ulcerative colitis (UC)], and from 11 healthy subjects, undergone colonoscopy for screening. Mucosal specimens were obtained during colonoscopy from the terminal ileum, and descending colon. PH was assessed by pyrosequencing as follows. All patients were in wash-out from antibiotics, probiotics and corticosteroids. Genomic DNA was isolated from the entire set of samples. The V1-V3 region of 16S rRNA locus was amplified on a 454-Junior Genome Sequencer. Reads were analyzed by Quantitative Insights into Microbial Ecology (QIIME, v.1.8.0), grouped into operational taxonomic units (OTUs) at a sequence similarity level of 97% by PyNAST for taxonomic assignment, and aligned by UCLUST for OTUs matching against Greengenes database (v. 13.8).
Results: In adult IBD patients colonic biopsies showed a statistically significant increase of *Proteobacteria* and decrease of *Firmicutes* and *Actinobacteria*, compared to CTRLs. The microbiota analysis of stool samples from IBD patient showed an increment of *Proteobacteria* and decrease of *Bacteroidetes*, although the difference was not significant compared to CTRLs. Particularly, a predominant presence of *Enterobacteriaceae* in IBD and a predominant presence of *Ruminococcaceae*, *Rikenellaceae* and *Prevotella* in CTRLs were prevalent ($P < 0.05$). Stratifying patient findings, according to intestinal sampling site, the analysis revealed that only *Ruminococcaceae* resulted statistically increased in the colon. Tacking in account only colon biopsy samples, a significant reduction of *Coprococcus*, *Faecalibacterium prausnitzii*, *Lachnospiraceae*, *Rikenellaceae*, *Roseburia*, *Ruminococcaceae* was observed in patients and an increment of *Enterobacteriaceae* was observed in CTRLs. Finally, stratifying samples on the bases of disease activity a decrease of *Ruminococcus*, *Peptostreptococcus* and *Paraprevotella* and an increase in *Enterococcus* was associated to active disease status ($P < 0.05$).
Conclusion: The present study shows that in the mucosal microbiota of IBD patients, irrespective of disease localization and activity, phylum *Proteobacteria* was significantly more represented, while phylum *Firmicutes* and *Actinobacteria* were reduced. The profiles of fecal microbiota partially replicate those of the mucosal microbiota being not statistically different from controls. It appears that microbiota adhering to the gut mucosa better discriminates patients from controls especially when considering family species. Our data suggest the high diagnostic potential of microbiota profiling with special reference to mucosal biosystem
Disclosure of Interest: All authors have declared no conflicts of interest.

OP068 BACTERIOPHAGE THERAPY: A NEW STRATEGY TO TARGET ADHERENT-INVASIVE ESCHERICHIA COLI BACTERIA IN THE GI TRACT OF CROHN'S DISEASE PATIENTS

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Introduction: Adherent-invasive *Escherichia coli* (AIEC) are abnormally predominant on Crohn's disease (CD) ileal mucosa. AIEC are pathobiont bacteria able to induce inflammatory responses that could initiate or perpetuate the chronic gut inflammation. Antibacterial treatments, such as bacteriophages (viruses infecting bacteria) represent a way to eliminate these bacteria from the GI tract without disturbing the microbiota homeostasis. Here, we evaluated the potential of bacteriophages to reduce AIEC colonization associated to intestinal mucosa.
Aims & Methods: Three bacteriophages were selected to efficiently target AIEC bacteria isolated from CD patient. Efficacy of this bacteriophage cocktail was investigated using two in vivo experimental models: transgenic mice expressing CEACAM6 colonized by AIEC strain LF82 and the DSS chemically-induced colitis model infected with AIEC strain LF82.
Results: In LF82-colonized CEACAM6-expressing mice, 24h after the oral administration of the selected cocktail of three bacteriophages, the fecal

concentration of LF82 bacteria has significantly dropped by two log in the bacteriophage group and stays significantly lower than in control group four days post-treatment, without any additional bacteriophage administration demonstrating the benefit of self-amplification of bacteriophages over time. Furthermore, we found that administration of the cocktail during the first day reduces progressively over a period of five days the colonization level of LF82 bacteria through the entire gut. In addition, bacteriophage treatment reduced colitis symptoms in the DSS-induced model, with a reduction of LF82 bacteria levels in feces, compared to the control group. Then, we showed that bacteriophages were driving a long-term digestive tract decolonization of AIEC LF82 bacteria which in turns reduces colitis symptoms.
Conclusion: Bacteriophages targeting AIEC bacteria with high efficacy in murine models suggest that such a treatment could reduce AIEC-associated symptoms in CD patients, providing an incentive to initiate clinical studies. The use of bacteriophages provides therefore, a new "microbiota friendly" way to efficiently target gut pathogens.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP069 CIPROFLOXACIN RESISTANCE IN INFLAMMATORY BOWEL DISEASE PATIENTS WITH ESBL-PRODUCING ENTEROBACTERIACEAE COLONIZATION

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Introduction: Ciprofloxacin is one of the most frequently used antibiotics in hospitalized inflammatory bowel disease (IBD) patients. In the last few years an emerging resistance to ciprofloxacin, ranging from 43% to 82%, has been described in extended-spectrum beta-lactamase (ESBL)-producing bacteria colonizing the gut [1; 2]. The objective of this study was to evaluate the gut colonization with ESBL-producing *Enterobacteriaceae* in IBD patients, resistance to ciprofloxacin and bacterial plasmid genes associated with that.
Aims & Methods: Rectal swabs from all consecutive patients with confirmed ulcerative colitis (UC) and Crohn's disease (CD) hospitalized in Riga East Clinical University Hospital 2012–2015 were collected, *Enterobacteriaceae* were cultured and analyzed for ESBL presence according to EUCAST guidelines, resistance to ciprofloxacin and bacterial plasmid genes CTX-M, TEM and SHV were detected.
Results: A total of 86 patients with confirmed IBD diagnosis were included in the study – 65 (75%) with UC, 21 (24%) with CD. We found that 7 (11%) of the UC patients and 2 (10%) of the CD patients were colonized with ESBL producing *Enterobacteriaceae*. The isolated ESBL producing strains from UC patients included *Escherichia coli* (n = 5), *Klebsiella oxytoca* (n = 1) and *Escherichia hermanii* (n = 1). The isolated ESBL-producing *Enterobacteriaceae* from CD patients included *Escherichia coli* (n = 2). The isolated bacterial plasmid genes associated with ESBL-production in UC included CTX-M (n = 7; 100%), TEM (n = 2; 29%), SHV (n = 1; 14%), in CD – TEM (n = 2; 100%) and CTX-M (n = 1; 50%). In UC 4 (57%) of the isolated ESBL-producing *Enterobacteriaceae* were resistent to ciprofloxacin. In CD all of the ESBL-producing *Enterobacteriaceae* were sensitive to ciprofloxacin. In 1 case of ESBL resistance CTX-M, TEM and SHV gene combination was observed, in 1 case CTX-M and TEM gene combination was observed and in 2 cases only CTX-M gene was present.
Conclusion: 1. High gut colonization rate (11%) with ESBL-producing bacteria in UC patients, mostly *E. coli*, expressing CTX-M gene. 2. High resistance to ciprofloxacin (57%) in UC patients. 3. CTX-M gene associated with resistance to ciprofloxacin.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP070 CARD9 IMPACTS COLITIS BY ALTERING GUT MICROBIOTA METABOLISM OF TRYPTOPHAN INTO ARYL HYDROCARBON RECEPTOR LIGANDS

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Introduction: Inflammatory bowel diseases (IBD) develop as a result of a combination of genetic predisposition, dysbiosis of the gut microbiota, and environmental influences. Caspase recruitment domain 9 (CARD9), one of the numerous IBD susceptibility genes, encodes an adaptor protein for innate immunity toward a wide range of microorganisms. Card9$^{-/-}$ mice are more susceptible to colitis as a result of impaired of the IL-22 pathway[1]. Our aim was to explore the role of the gut microbiota in the susceptibility of Card9$^{-/-}$ mice to colitis.
Aims & Methods: Germ-free (GF) C57BL/6 wild-type (WT) mice were inoculated by oral gavage with fresh stools from conventional WT (WT—>GF) or Card9$^{-/-}$ (Card9$^{-/-}$—>GF) mice. Colitis was induced by DSS. AHR activity in intestinal content was determined using a reporter cell line. Immune response was assessed at transcripts level, at the protein level and at the cellular level using flow cytometry. Patients with IBD were genotyped for the major IBD-associated SNPs including CARD9. Statistical analysis was performed using parametric or non-parametric tests as appropriate.
Results: Bacterial and fungal gut microbiota of Card9$^{-/-}$ mice (assessed by 16s and ITS2 sequencing) were altered compared to WT mice. Card9$^{-/-}$—>GF mice were more susceptible to colitis than WT—>GF with impaired recovery. Moreover, IL-22 defect was observed in Card9$^{-/-}$—>GF mice at the gene expression and protein levels in the colon and in MLNs. IL-22 production by T helper 22 cells, NKp46^{+} innate lymphoid cells, lymphoid tissue inducer cells, and CD3^{-}CD4^{-}NKp46^{-} cells was decreased in the colon of Card9$^{-/-}$—>GF mice. AHR ligands are known to promote gut IL-22 production[2]. Indeed, the levels of Indole-3-acetic acid (IAA), an AHR ligands, were decreased in stools of Card9$^{-/-}$—>GF and Card9$^{-/-}$ mice. Moreover, feces from Card9$^{-/-}$ and Card9$^{-/-}$—>GF mice were defective in their ability to activate AHR. In Card9$^{-/-}$—>GF mice, susceptibility of colitis, and IL-22 defect were rescued after treatment with AHR agonist (6-formylindolo(3,2-b)carbazole), or inoculation with three *Lactobacillus* strains with strong AHR activity. These effects were abrogated in the presence of AHR antagonist (CH223191). Reduced production of AHR ligands was also observed in the microbiota from patients with IBD, particularly in those with CARD9 risk alleles.
Conclusion: Card9 deletion has an effect on the gut microbiota in mice and its transfer to WT GF recipient is sufficient to recapitulate the defective IL-22 activation and increased sensitivity to colitis observed in Card9$^{-/-}$ mice. These alterations were due to an impaired ability of the microbiota of Card9$^{-/-}$ mice to catabolize tryptophan into AHR ligands. Our results are relevant to humans, as impaired microbial production of AHR ligands was observed in patients with IBD. Thus, defects in expression of factors involved in innate immunity, such as CARD9, can shape an altered microbiota, which can then modify the host immune response. Correcting impaired microbiota functions, such as ability to produce AhR ligands, is an attractive strategy in IBD.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP071 FAECAL MICROBIOTA TRANSPLANTATION (FMT) IN ULCERATIVE COLITIS (UC) IS ASSOCIATED WITH SPECIFIC BACTERIAL CHANGES: STOOL AND COLONIC MUCOSA 16S MICROBIOTA ANALYSIS FROM THE RANDOMISED CONTROLLED FOCUS STUDY

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Introduction: In a randomised placebo-controlled trial, intensive FMT therapy for active ulcerative colitis (UC) was significantly superior to placebo, producing a clinical response in >50% and clinical remission with endoscopic remission or response in 27% of patients (ECCO 2016 & DDW 2016)1. This part of the FOCUS study aimed to characterise the microbial changes underlying FMT in UC, and identify those predictive of, and associated with, response and lack of response.
Aims & Methods: Active UC patients were randomised to intensive FMT or placebo enemas 5 days/week for 8 weeks, with placebo-treated patients subsequently offered 8 weeks of open label FMT. Each FMT enema was derived from 3–7 unrelated donors. Faecal samples were collected from patients at week 0, 4

and 8, open label mid and end of treatment (if applicable), and 8 weeks after FMT; colonic biopsies were collected at week 0 and 8, and end of open label treatment (if applicable). Faecal samples were also collected from individual donors and donor batches. DNA was extracted from faecal samples and 16S ribosomal RNA gene sequencing performed using 2x300 bp Illumina Miseq chemistry (F27 & 519R). Raw sequences were analysed using MOTHUR, and statistical tests performed on counts and relative abundances.

Results: Faecal and colonic samples were collected from 70 study patients. 14 donors contributed to 21 donor batches. 314 patient and 113 donor (individual + batch) faecal samples along with 160 patient colonic samples were analysed. 26976 ± 540 clean sequences per faecal sample and 28093 ± 881 per colonic biopsy were obtained with rarefaction curves suggesting sampling had reached saturation. In both faecal and colonic samples α-diversity significantly increased at all FMT treatment time points relative to baseline ($p < 0.005$); this persisted 8 weeks after FMT in the faecal samples. On PCA, Cluster, and PERMANOVA analyses FMT significantly influenced patient microbial profiles, with the shift towards healthy donor microbiota most notable at the genus and OTU levels. LEfSe analysis of both faecal and colonic samples showed a decrease in patient *Bacteroides* and an increase in donor *Prevotella* with FMT, independent of clinical outcome. A range of other microbial taxa were identified as transplanted or displaced with FMT across all taxanomic levels. Patients receiving FMT who achieved remission had greater baseline faecal and colonic mucosal α-diversity than those who did not achieve remission, and also had greater resultant diversity with and after FMT treatment. Specific taxa were consistently significantly associated with FMT remission across both faecal and colonic samples: taxa within *Barnesiella* were associated with remission, while OTUs within *Fusobacterium* and *Sutterella* were associated with lack of remission.

Conclusion: Baseline patient microbial diversity in UC appears to be predictive of therapeutic response to FMT. Intensive FMT is associated with increased microbial diversity, with the greatest diversity noted in patients achieving remission. Increased diversity persists 8 weeks after cessation of therapy. Specific bacterial taxa are transplanted or displaced by FMT, some of which are associated with treatment outcome. A high level of concordance was observed between the faecal and colonic mucosal microbiota. These findings may be important in both understanding the pathophysiology of the microbiota in UC and shaping future bacterial therapy.

Disclosure of Interest: T.J. Borody: Thomas J. Borody has an interest in the Centre for Digestive Diseases, where faecal microbiota transplantation is a treatment option for patients and has filed patents in this field.
All other authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 14:00–15:30

FREE PAPER SESSION: THE FUTURE OF DIAGNOSTIC IN HBP AND UPPER GI – ROOM N1

OP072 RELAXIN-COATED IRON-OXIDE MAGNETIC NANOPARTICLES AS A NOVEL THERANOSTIC APPROACH FOR DIAGNOSIS AND TREATMENT OF LIVER FIBROSIS

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Introduction: Hepatic fibrosis is a growing health problem with no effective and clinically approved therapy. Hepatic stellate cells (HSCs) are the key cells involved in the pathogenesis of liver fibrosis. Upon activation, HSCs undergo morphological and functional changes, and are transformed into contractile ECM-producing myofibroblasts leading to scar tissue formation. HSCs contraction contributes significantly to the portal hypertension thereby further impairing the liver function. Relaxin (RLN) has been shown to inhibit HSC activation and contraction thereby ameliorate liver fibrosis and portal hypertension. However, RLN has very poor pharmacokinetics and administration of high or frequent doses can lead to detrimental side effects due to vasodilation.

Aims & Methods: In this study, we aimed to develop a nanoparticle-based delivery system to improve pharmacokinetics and therapeutic efficacy of RLN for the diagnosis and treatment of liver fibrosis. We conjugated human RLN-2 to PEGylated magnetic nanoparticles (RLN-MNP) and characterized the size, charge and stability. We examined RLN-MNP for RLN conjugation and HSCs-specific binding/uptake. We analysed RLN receptor (RXFP1) expression on activated HSCs and CCl_4-induced liver fibrosis mouse model. Finally, we assessed the effects of RLN-MNP on human HSCs and CCl_4-induced advanced 8-weeks liver fibrosis mouse model.

Results: RLN-MNP was successfully synthesized and remained stable at 4°C. RLN-MNP showed specific binding and uptake to TGFβ-activated human HSCs while MNP alone showed no binding/uptake. In vitro, RLN-MNP and unconjugated RLN significantly inhibited TGFβ-induced 3D-collagen gel contraction and HSCs migration. Significant up-regulation of RXFP1 in TGFβ-activated HSCs and CCl_4-induced liver fibrosis mouse model was observed. In vivo in established 8 weeks CCl_4-induced liver fibrosis mouse model, both RLN and RLN-MNP strongly attenuated fibrosis by inhibiting HSC activation, ECM production and angiogenesis. Importantly, RLN-MNP, but not unconjugated RLN, increased Nitric oxide release by significant up-regulation of iNOS. On the other hand, unconjugated RLN induced systemic side effects by inducing systemic NO release (in serum) while RLN-MNP did not. In vivo studies for MRI and portal hypertension using relaxin and relaxin magnetic nanoparticles are currently ongoing.

Conclusion: This study presents a novel strategy to deliver RLN specifically to HSCs, key pathogenic cells involved in liver fibrogenesis, for the diagnosis and treatment of liver fibrosis.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP073 A QUANTITATIVE IMAGING PLATFORM TO REAL-TIME MEASURE SPECIFIC ROS LEVELS IN LIVER DISEASES

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Introduction: Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, including hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), singlet oxygen ($^1O_2$), and superoxide (O^{2-}). ROS have been reported to play an important role in the development of liver diseases.[1] For example, H_2O_2 can activate hepatic stellate cells in liver fibrogenesis. During hepatic ischemia-reperfusion injury, HOCl is generated by neutrophils and diffuses into hepatocytes, causing oxidant stress-mediated injury. O^{2-} can react with nitric oxide to form peroxynitrite to modify the cell structure and function of proteins in diseased liver. Various methods have been developed to monitor ROS generation in the liver, but the presence of different cellular sources for ROS as well as the distinct chemical properties of specific ROS may lead to conflicting results.[2] Most developed ROS-detection probes were difficult to be distinguished from endogenous fluorophores and only can be employed under one-photon microscopy. Thus, an optimal strategy for precise real-time ROS detection is highly required to rapidly and accurately reveal the cellular microenvironment in liver diseases in clinic.

Aims & Methods: Four different two-photon fluorescent probes were designed and synthesized for selective detection of chemically reactive molecules of thiols and ROS including glutathione (GSH), H_2O_2, HOCl, and O^{2-}. Mouse models of hepatic steatosis, fibrosis and ischemia-reperfusion injury were developed to mimic human liver diseases.[3] After sacrificing the animals, unfixed live liver tissues were collected and incubated with each probe at the final concentration of 50 to 100 μmol for 10 min, and then imaged using multiphoton microscopy (JenLab GmbH, Jena, Germany).[4]

Results: Each probe exhibited a strong positive fluorescent response only in the presence of its specific chemically reactive molecule, whereas negligible fluorescent signals were observed upon the additions of other reactive oxygen/nitrogen species and metal ions. There was a good linear relationship between the probe responsive fluorescent intensity and the concentration of specific ROS. In the liver with ischemia-reperfusion injury, reduced autofluorescence was detected, indicating the hepatocyte necrosis. Remarkable enhancement of red fluorescence was observed in hepatocytes with decreased autofluorescence, indicating the reaction of with endogenous HOCl. The cellular concentration of GSH decreased and H_2O_2 increased in the liver with fibrosis and steatosis compared to the control. The concentration of each specific ROS was first calculated based on the intensity of images at the cellular level.

Conclusion: We developed a quantitative imaging platform to real-time measure specific ROS changes in liver diseases at the cellular level. This technique can be used to investigate ROS-mediated liver injury and predict treatment response in human liver biopsy, and can be readily extended to examination of diseases and injury of other organs. We anticipate that in the near future this quantitative imaging platform will be evaluated from bench to bedside, leading to real-time monitoring of cellular microenvironment in human diseases.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP074 RANDOMIZED CONTROLLED TRIAL (RCT) OF DOPPLER ENDOSCOPIC PROBE (DEP) FOR BLOOD FLOW DETECTION IN SEVERE NON-VARICEAL UGI HEMORRHAGE (NVUGIH)

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Introduction: For decades, stigmata of recent hemorrhage (SRH) in ulcers & NVUGIH have been used to guide endoscopic hemostasis. Arterial blood flow underlying SRH is rarely monitored, yet determines rebleed risk after treatments.

Aims & Methods: In a RCT, our primary aim was to compare 30-day rebleed rates of index lesions for patients treated with Standard vs. DEP guided endoscopic hemostasis. In a 2-center study, patients were resuscitated & consented. They & managing medical-surgical teams were blinded to endoscopic treatments. Patients with severe inpatient or outpatient start of UGIH (clinical signs, hemoglobin – Hgb - drop of $>$ 2 gms from baseline, & RBC transfusions) were randomized at urgent endoscopy if they had benign appearing ulcers & some SRH (active arterial bleed, non-bleeding visible vessel - NBVV, or adherent clot, oozing without other SRH, or flat spot) or Dieulafoy's lesions or Mallory Weiss tears- MWT (with active bleeding or NBVV). For Standard treatment, hemoclipping &/or multipolar probe electrocoagulation (MPEC-large probe) with or without dilute epinephrine injection was used without DEP & visual end points were control of bleeding, flattening VVs, & a foot-print at the SRH. For the DEP group, SRH & lesion base were interrogated for underlying blood flow at $<$ 4 mm deep settings with an FDA approved control unit & disposable DEP probe (Vascular Technology, Nashua, NH). Then Standard RX was applied on & out from the SRH, where the artery was traced. DEP was used to recheck & if residual blood flow was detected, further hemostasis was performed until no blood flow was detected. Standard group patients with flat spots were not treated endoscopically, but DEP patients were if they had blood flow detected. All patients with ulcers & Dieulafoy's lesions received high dose PPI infusion X 72 hours & then BID for 30 days. MWT patients were treated with anti-emetics & BID PPI. Rebleeding was determined by a $>$ 2 gm decrease of Hgb, with clinical signs of rebleeding, & repeat endoscopy with more hemostasis as needed. Patients were followed prospectively by research coordinators who recorded routine 30 day outcomes.

Results: All blood flow detected by DEP was reproducible & arterial. For 148 patients randomized, see the Table for 30 day rebleed rates by SRH. There was a significant difference in rebleed rates (15.2% higher) in Standard group vs. DEP group ($p = 0.02138$) & surgery (4/76 vs. 0/72 – $p = 0.0484$). 1 perforation occurred in the Standard group & none in the DEP group.

Non-Variceal UGIB Doppler Probe RCT - Primary Outcome of 30 day Rebleeds from the Same Lesion

Stigmata	Standard	DEP
Active Arterial bleed	5/10 (50.0%)	4/14 (28.6%)
NBVV	7/27 (25.9%)	4/26 (15.4%)
Adherent Clot	4/16 (25%)	0/13 (0%)
Flat Spots	3/16 (18.8%)	0/15 (0%)
Oozing bleeding	1/7 (14.3%)	0/4 (0%)
TOTALS	**20/76 (26.3%)**	**8/72 (11.1%)***

*$p = 0.02138$ by Fisher Exact test

Conclusion: In a RCT of patients with severe NVUGIH, use of Doppler probe as a guide to endoscopic hemostasis significantly reduced 30 day rebleed & surgery rates compared to Standard, visually guided hemostasis. We now recommend DEP (along with SRH) as a new guide for risk stratification & definitive endoscopic hemostasis in patients with severe NVUGIH. RCT was supported by a VA Clinical Merit Review Research Grant & in part by NIH-NIDDK AM 41301 CURE DDRC-Human Studies Core. Registered with ClinicalTrials.gov as Project CLIN-013–07F.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP075 ESOPHAGEAL HIGH RESOLUTION MANOMETRY WITH A SOLID TEST MEAL IMPROVES THE DETECTION OF CLINICALLY RELEVANT ESOPHAGEAL DYSFUNCTION AND SYMPTOM REPRODUCIBILITY: A VALIDATION STUDY IN A MULTIRACIAL ASIAN COHORT

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Introduction: The Chicago Classification (CC) of esophageal motility disorders for high resolution manometry (HRM) is based on ten 5 mLs water swallows (WS). We have previously reported the use of a solid test meal (STM) in patients undergoing HRM to improve diagnostic sensitivity(1). We further validate the use of a STM in a multiracial Asian cohort.

Aims & Methods: We aimed to determine if the use of a STM during routine esophageal manometry improves diagnostic yield and symptom reproducibility. Methods: Prospective series of patients referred for esophageal HRM between November 2014-April 2016. All patients had undergone prior endoscopy with findings of normal or mild (LA grade A esophagitis). WS and STM studies were performed in the upright seated position. Diagnosis of major and minor esophageal motility disorders were based on CC version 3.0 for water swallows (2) and modified for solid swallows as appropriate (3). All medications known to interfere with GI motility were stopped for at least one week prior to the study. Symptoms reported by the patients during HRM study were analyzed for any corresponding manometric abnormalities. Symptom associated dysfunction (SAD) was defined as a symptom event reported during or up to 10 seconds after concurrent esophageal dysmotility during STM.

Results: 119 (56 Male [47.1%]; mean age 50.9 ± 16.2) consecutive patients (84 Chinese: 17 Malay:9 Indian:9 others) underwent HRM with WS for evaluation of (i) dysphagia ($n = 56$ [47.4%]), (ii) reflux symptoms ($n = 45$ [38.1%]) and (iii) atypical chest pain ($n = 17$ [14.4%]). HRM with STM was performed in 114 (96%) patients. Compared to WS alone ($n = 2/119$ [1.7%]), more patients were diagnosed with esophago-gastric junction (EGJ) outflow obstruction during a STM ($n = 8/114$ [7.0%]); $p = 0.05$). (Table) Similarly, more patients were diagnosed with esophageal spasm with a STM ($n = 5/114$ [4.4%]) compared to WS (2/119 [1.7%], $p = 0.27$) alone. Upper esophageal dysfunction (UES) was seen only during STM in 3/114 [2.6%] patients. Conversely, more patients were diagnosed with ineffective esophageal motility (IEM) during SWS (16/119 [13.4%]) compared to during STM (6/114 [5.3%], $p = 0.04$) consistent with earlier reports of improved peristaltic contractions in controls and patients with non-erosive reflux disease (4) Symptom associated dysfunction during HRM occurred in significantly more patients during the STM study ($n = 26/114$ [22.8%] compared to SWS alone 1/119 [0.8%], $p < 0.0001$). The study was well tolerated in all patients.

Conclusion: The use of additional physiological stimuli during routine esophageal HRM improves the detection of clinically relevant esophageal dysfunction, including disorders of the upper esophageal sphincter (UES) and the esophago-gastric junction (EGJ). In addition, symptom associated dysfunction occurred more frequently during the solid test meal. The improved diagnostic yield can guide effective treatment.

Disclosure of Interest: All authors have declared no conflicts of interest.

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Abstract No: OP075

Summary of Manometry Findings with Single Water Swallows (SWS) and Solid Test Meal (STM)

Diagnosis on High-Resolution Manometry	Dysphagia (N = 56) SWS	Dysphagia (N = 51) STM	Reflux (N = 46) SWS	Reflux (N = 46) STM	Chest Pain (N = 17) SWS	Chest Pain (N = 17) STM
Achalasia Types I/II/III	15	10				
Esophago-gastric junction (EGJ) outflow obstruction	3	6		1		1
Spasm	1	2	1	2		1
Jackhammer	1	1	1	1	3	4
Aperistalsis	4	0	3	2		
Ineffective esophageal motility	9	5	6	1	1	
Upper esophageal dysfunction		1		2		
Normal	23	26	35	37	13	11

OP076 THE NEW IMAGE ENHANCEMENT TECHNOLOGY USING LINKED COLOR IMAGING WITH ACETIC ACID INDIGOCARMINE MIXTURE FOR DIAGNOSIS OF EARLY GASTRIC NEOPLASM

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Introduction: A value of the combination of magnifying endoscopy of and image enhancement endoscopy (IEE) technology (e.g. NBI, BLI) is reported in a diagnosis for the early gastric neoplasm. This combination is effective, but it is necessary to speculate in real histology from the pattern of a two-dimensional monotone. Therefore, this diagnostic method is still more difficult for general endoscopists. Linked Color Imaging (LCI) was recently developed using a laser endoscopic system (Fujifilm Co., Tokyo, Japan). LCI acquires images by simultaneously using narrow-band short wavelength light and white light in an appropriate balance. This combination of light provides more information about the vasculature and architecture on the mucosal surface than that obtained with typical white-light imaging. When we use acetic acid indigocarmine mixture (AIM) with LCI mode, we discovered that the magnifying images of early gastric cancer are very clear, three-dimensional and near to real histology. So, we examined the examined the utility of this method.

Aims & Methods: This was a prospective observational study performed at a single tertiary referral center. The subjects are 72 lesions of 67 patients with gastric neoplasm. We are indicated of the endoscopic submucosal dissection (ESD), and were given pre-ESD endoscopy in our hospital from September 2014 to February 2016. Firstly we observed the lesions by magnifying endoscopy with the BLI mode and diagnosed using VS classification system1). Secondly we observed the lesions by magnifying endoscopy with LCI+AIM method and diagnosed using VS classification system. Furthermore, we classified the visualization ability of the surface fine structure in Clear, Visible, and Invisible and evaluated it. Finally, we carried out ESD and compared the image with the histopathology.

Results: By the pathology results, 60 lesions were gastric cancer and 12 lesions were gastric adenoma. The differentiation ability of a cancer and the non-cancer (adenoma) did not have the significant difference between the BLI mode and the LCI+AIM methods. In the classification of visualization ability, 12 lesions were Clear, 22 lesions were Visible, 38 lesions were Invisible by BLI mode. On the other hand, 33 lesions were Clear, 34 lesions were Visible, 5 lesions were Invisible by LCI+AIM method. In the visualization ability of the surface fine structure, LCI+AIM method is significantly clearer than BLI mode ($p < 0.05$).

Conclusion: When we use AIM, indigocarmine accumulates in pit of the duct, and duct structures become clear by the acetic acid, By LCI mode, we can observe the vascular pattern of the lesion clearly. So by the combination of AIM and LCI, we can observe the lesion three-dimensionally. By this method, we can compare histopathology with an endoscopic image intuitively, so we believe that a magnifying endoscopy diagnosis of the gastric cancer is enabled even if we do not use various confusing classifications.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP077 EXOSOMES DERIVED FROM GASTRIC CANCER PATIENTS AND CELLS COULD DELIVER MIR-21 TO ELICIT TUMOR PROGRESSION AND METASTASIS AND COULD BE USED AS A POTENTIAL DIAGNOSTIC BIOMARKER

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Introduction: Gastric cancer (GC) remains a global challenge due to high morbidity and mortality rates and poor response to chemotherapy treatment. Increasing evidence suggests that exosomal microRNAs (miRNAs) possess diverse cellular regulatory roles in cancer progression nowadays. The tumor microenvironment is abundant with exosomes that are secreted by the cancer cells themselves. Exosomes are nanosized, organelle-like membranous structures that are increasingly being recognized as major contributors in the progression of malignant neoplasms. For now, little is known about how cancer cell-derived exosomes and miRNAs in exosomes modulate the microenvironment to optimize conditions for tumor progression and metastasis.

Aims & Methods: We aimed to investigate whether cancer cell-derived exosomal miRNA could modulate cancer progression and metastasis and can be used as a diagnostic marker. In this study, we used miRNA microarray technology to identify exosomal miRNAs that were differentially expressed in GC patients and controls. We further examined the biological function of exosomal miR-21 on cell viability, apoptotic death and metastasis in human GC cells and explored the possible downstream mechanism. We also included another 100 GC patients and 100 controls to study whether exosomal miR-21 could be used as a potential biomarker.

Results: We found that exosomes derived from GC patients exhibited significant different miRNA expression patterns compared with those from controls. Of the 233 miRNAs that were differentially expressed, miR-21 stood out as one of the most significantly upregulated miRNAs in cancer patients. miR-21 depletion in GC cells led to decreased miR-21 levels in exosomes and significantly reduced cell proliferation, migration, invasion and increased apoptosis, and the same phenomenon was seen when transfect miR-21 inhibitor into the exosomes from GC cells and co-culture the transfected exosomes with GC cells. Moreover, exosomal miR-21 markedly enhanced snail and vimentin expression in GC cells, while significantly decreasing E-cadherin levels, suggesting that exosomal miRNA might play a role in epithelial-to-mesenchymal transition (EMT) process. Finally, circulating exosomal miR-21 levels were closely associated with TNM stage, and lymph node metastasis in GC patients and could be used as a useful diagnostic biomarker with a sensitivity of 89.2% and specificity of 91.1%.

Conclusion: In conclusion, our findings suggest that GC cells could generate miR-21-rich exosomes that are delivered to surrounding normal cells to promote prometastatic behaviors and prompt further investigation into the therapeutic value of exosome inhibition for cancer treatment and diagnostic marker for cancer diagnosis.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP078 URINARY KALLIKREIN-10 PREDICTS INCURABILITY FOR GASTRIC CANCER

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Introduction: Recent material and technical development enables us to get many therapeutic choices for gastric cancer (GC). Accurate diagnosis is thus needed to choose an optimal treatment for GC, however, the current imaging diagnosis is not enough to identify incurable factors including peritoneal metastasis and local invasion. We have previously reported the usefulness of urinary biomarkers for diagnosis of GC. With the goal of discovering non-invasive biomarkers for progression and incurability of GC, we conducted this study using urine samples from GC patients and healthy control.
Aims & Methods: Urine samples from 189 patients composed of 111 patients with GC and 78 healthy controls were analyzed in this study. According to tumor stage and operability, GC cohort was analyzed.
Results: We conducted a protease protein array analysis to identify potential candidate biomarkers, and three proteins were found to be elevated in the urine of advanced GC patients compared to early GC patients. Among them, urinary kallikrein-10 (KLK10) and proteinase 3 were positively associated with tumor stage progression. Moreover, urinary level of KLK10 (uKLK10) was significantly elevated in the urine of inoperable GC patients compared to operable GC patients (uKLK10: median, 33.5 ng/ml vs. 10.8 ng/ml; P = 0.006), and disease-free survival (DFS) was significantly lower in GC patients with high uKLK10 compared to low uKLK10 (HR: 2.53 (95%CI, 1.23–5.21), P = 0.007). Urinary KLK10 distinguished operability of GC with an area under the curve (AUC) of 0.710 and the combination of uKLK10 with tumor size showed an AUC of 0.835. Immunohistochemical analyses also demonstrated a positive correlation between tumor stage and KLK10 expression in GC tissues. In addition, GC patients with high expression of pathological KLK10 (pKLK10) significantly showed a shorter DFS than those with low pKLK10
Conclusion: uKLK10 is a promising non-invasive biomarker for incurable GC.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 14:00–15:30
FROM SYMPTOMS TO DIAGNOSIS IN IBS – ROOM N2

OP079 POPULATION PREVALENCE OF ROME III AND ROME IV IRRITABLE BOWEL SYNDROME (IBS) IN THE UNITED STATES (US), CANADA AND THE UNITED KINGDOM (UK)

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Introduction: The new Rome IV criteria make several adjustments in diagnostic requirements for IBS compared to Rome III. It is unknown how this will affect the prevalence and demographic distribution of IBS
Aims & Methods: We used data from a large internet survey of the general population in 3 countries to measure and compare Rome IV vs. Rome III IBS rates and the demographics of the disorder. A community sample of 6,300 individuals age 18 and older in the US, UK and Canada (2,100 in each country) completed the secure online survey. Quota-based sampling was used to ensure equal proportion of sex (50%/50%) and age groups (40% aged 18–39, 40% aged 40–64, 20% aged 65+) across countries, and to control education distributions (30% maximum with college degree or equivalent). The survey included the Rome IV Diagnostic Questionnaire for Adults, Rome III diagnostic modules for IBS, and demographic questions. Latest national census figures were used to calculate correction weights for age (in 5-year bins) and gender proportions and obtain census-adjusted IBS prevalence estimates for each country.
Results: Of the 6,300 survey completers, 5,931 were retained for analysis (49.2% female; mean age = 47.4, range 18–92; 1,949 US, 1,994 UK, 1,988 Canada) after 369 inconsistent responders were eliminated. Due to the quota-based sampling, sex or age group proportions did not differ between countries. Rome IV vs. Rome III IBS prevalence rates (census-corrected estimates in parentheses) were 6.1% (6.1%) vs. 10.8% (11.1%) in the US, 5.7 (5.8%) vs. 11.3% (11.7%) in Canada, and 5.5% (5.5%) vs. 10.1% (10.6%) in the UK. There were no IBS prevalence differences between countries, but Rome IV IBS prevalence was significantly lower than Rome III IBS in all countries ($p < 0.0001$ for all comparisons). Women were more likely ($p < 0.0001$) to have IBS than men by both Rome IV (7.1% vs. 4.1%; OR 1.87) and Rome III (14.4 vs. 7.2; OR 2.17) criteria in the combined 3-country sample, and people age 65+ were significantly less likely ($p < 0.0001$) than younger respondents to have IBS according to either criteria. Similar age group and gender difference patterns were seen in the 3 countries (Table). The Rome IV IBS subtype distribution for the combined 3-country sample (27.9% IBS-C, 34.3% IBS-D, 33.3% IBS-M, 4.7% IBS-U) was significantly different ($p < 0.0001$) than with Rome III (16.6% IBS-C, 20.6% IBS-D, 60.1% IBS-M and 2.1% IBS-U).

Table: Population Rome III and Rome IV IBS rates (%) by sex and age groups in the US, UK and Canada survey samples (without census weighting).

ROME III IBS:	Age 18–34	Age 35–49	Age 50–64	Age 65+	All age groups
US Females (n = 962)	15.6	16.6	13.7	9.9	14.2
US Males (n = 987)	7.2	9.3	8.4	5.6	7.6
UK Females (n = 976)	14.2	15.4	15.1	8.9	13.9
UK Males (n = 1018)	4.9	7.2	9.5	3.6	6.5
Canada Females (n = 980)	14.6	16.8	15.4	12.9	15.1
Canada Males (n = 1008)	6.3	10.3	8.2	5.9	7.6
ROME IV IBS:	Age 18–34	Age 35–49	Age 50–64	65+	All age groups
US Females (n = 962)	6.6	10.6	6.9	3.7	7.1
US Males (n = 987)	8.8	3.6	4.2	1.9	5.1
UK Females (n = 976)	6.7	10.2	8.6	3.2	7.5
UK Males (n = 1018)	1.8	5.1	5.5	1.6	3.6
Canada Females (n = 980)	7.1	9.8	8.1	5.3	7.8
Canada Males (n = 1008)	2.5	5.4	5.0	2.1	3.7

Conclusion: These first-ever national population prevalence estimates for Rome IV IBS show that IBS prevalence and demographic distribution is equivalent in the US, UK and Canada, and confirm that the disorder is female-predominant and less common in older individuals. IBS prevalence is significantly lower when Rome IV criteria are used than with Rome III, and the new criteria also change IBS subtype distribution, markedly reducing the IBS-M proportion. [Support: The Rome Foundation]
Disclosure of Interest: O.S.S. Palsson: Salary support from research grants from Salix, Takeda, and Ironwood, and honoraria for participation in educational programs by these companies. Research support from the Rome Foundation.
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A.D. Sperber: Consultant, Takeda-Israel. Rome Foundation Board Member.
W.E. Whitehead: Research grants from Takeda Pharmaceuticals. Educational grants from Takeda and Ferring. Consultant/Advisory Board member for Ono, Ferring, and Biomerica USA. Rome Foundation board member.

OP080 FUNCTIONAL HEARTBURN OVERLAPS WITH IRRITABLE BOWEL SYNDROME MORE OFTEN THAN GERD - DEVELOPMENT OF A PREDICTIVE MODEL FOR CLINICAL PRACTICE

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Introduction: Gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS) are gastrointestinal (GI) disorders affecting a large part of the general population, with relevant impact on quality of life and health care costs. To date, population- and clinical-based studies have reported a certain degree of overlap between GERD and IBS, which cannot be explained solely by chance. By means of multichannel intraluminal impedance and pH (MII-pH) monitoring, patients with proton pump inhibitor (PPI)-refractory heartburn can be distinguished into PPI-refractory GERD and functional heartburn (FH), the latter to be considered a functional GI disorder separate from GERD. Symptoms of IBS have not yet been assessed in patients with reflux symptoms as distinguished into GERD and FH. Recently, it has been reported that patients with GERD as well as patients with IBS have increased levels of anxiety, in turn associated with increased perception of symptoms and reduced quality of life. Again, the prevalence of anxiety in patients with reflux symptoms as clearly distinguished into GERD and FH has not yet been assessed.

Aims & Methods: Our aim was to assess the prevalence of IBS as well as anxiety and depression in patients with typical reflux symptoms subdivided into GERD and FH by means of upper GI endoscopy and MII-pH monitoring. We also aimed to assess the prevalence of various clinical and endoscopic characteristics in GERD and FH patients in order to develop a predictive model for distinguishing FH from GERD in patients presenting with typical reflux symptoms, potentially useful in clinical practice. Patients underwent a structured interview based on questionnaires for GERD (GERDQ), IBS (RIIIAQ), anxiety and depression (HADS). Upper GI endoscopy and 24h MII-pH off-therapy monitoring were performed in all cases. In patients with IBS, fecal calprotectin was measured and colonoscopy was scheduled for values >100 mg/kg to exclude organic disease. Multivariate logistic regression analysis was performed to identify independent risk factors for FH. A predictive model for FH diagnosis based on clinical and endoscopic findings was developed by applying the purposeful selection of covariates. The coefficients estimated in the multivariate logistic regression analysis were used to predict FH diagnosis. The performance of the predictive model was then assessed by examining measures of discrimination and calibration. Discrimination was considered as the ability of the predictive model to differentiate between patients with FH diagnosis and patients with GERD diagnosis and was quantified by calculating the area under the ROC curve (AUC). A calculator to help clinicians in automatically computing the predicted probability of FH versus GERD in patients presenting with heartburn was built.
Results: Of the 701 consecutive heartburn patients who entered the study, 458 (65%) had GERD whereas 243 (35%) had FH. IBS was found in 143/458 (31%) GERD but in 187/243 (77%) FH patients ($P < 0.001$). At multivariate analysis IBS, anxiety, and smoking resulted independent risk factors for FH whereas hiatal hernia resulted protective. We developed a predictive model based on clinical and endoscopic characteristics (IBS. Smoking, Anxiety, Age $\geq$ 45, Hiatal hernia, i.e. ISAAH). The area under ROC curve in an external validation cohort of 51 patients was 0.920. Considering the previously established cut-off, sensitivity and specificity of the predictive model in diagnosing FH against GERD were 84.3% and 78.9%, respectively. A calculator to help clinicians in automatically computing the predicted probability of FH versus GERD in patients presenting with heartburn was built (URL: http://app.calculoid.com/#/calculator/7012).
Conclusion: IBS overlaps more frequently with FH than with GERD, suggesting common pathways and treatment. The score derived from ISAAH predictive model allows a high level of suspicion for FH and can be useful in clinical practice.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP081 IRRITABLE BOWEL SYNDROME: WHICH SYMPTOMS ARE PERSISTENT AND WHICH ARE NOT?

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Introduction: Irritable bowel syndrome (IBS) is characterised by many comorbid symptoms as well as core symptoms, all of which are relevant for the clinical management of this group of patients. However, the evolution of these symptoms over time is poorly understood.
Aims & Methods: The aim of this study was to determine the probability of IBS-related symptoms to persist or subside over time. The study consisted of three parts. First, we addressed the question which factors can determine the probability of a symptom to persist or subside over time. A simulation showed there were five: length of follow-up period, autocorrelation, the interaction between the autocorrelation and symptom severity, the cut-off for symptom severity, and skewness. Second, we used the five factors in a Monte Carlo simulation, generating a reference-table of probabilities for symptoms to persist or subside. Third, our theoretical reference-table was matched with real data from a cohort of 276 IBS patients (70% female; age range 19 to 76 years, median age 39 years). These subjects were thoroughly characterised at baseline, and completed questionnaires annually over a five-year period, covering the following IBS-related symptoms / aspects: gastrointestinal (GI) symptom severity (GSRS), GI-specific anxiety (VSI), quality of life (IBS-QOL), coping resources (CRI), sense of coherence (KASAM), and anxiety/depression (HADS). The cohort was used to retrieve the five factor properties mentioned above (e.g. autocorrelations).
Results: A summary of the main results is shown in table 1. In IBS patients, depression was the most persistent symptom over time, i.e. a 22% chance for depression to persist, versus 23% to subside over a five-year period. Poor coping resources and sense of coherence yielded similar percentages. Values were different for anxiety (12% to persist and 44% to subside) and GI symptom severity (8 and 47%), with no major differences between the different GI symptoms (i.e. diarrhoea, constipation, abdominal pain, satiety, indigestion, and reflux). For IBS-QOL, there were differences between the domains: sexual relations (20% chance to persist, 18% chance to subside) and sleep (20 and 25%), in contrast to the domains mental health (7 and 56%), physical functioning (5 and 64%), and emotional (5 and 57%). The QOL domains physical role, social role, and food were intermediate.

Table 1: Probabilities for IBS-related symptoms to persist or subside over a five-year period.

	Symptom persists		Symptom subsides	
	Probability	95% CI	Probability	95% CI
Depression	22%	18–26%	23%	16–28%
Sense of coherence	21%	18–24%	17%	13–22%
Coping resources	19%	18–21%	20%	17–23%
GI-specific anxiety	16%	14–18%	27%	23–31%
Quality of life	16%	14–18%	27%	23–31%
Anxiety	12%	10–14%	44%	40–50%
GI symptom severity	8%	7–9%	47%	41–50%

Conclusion: For the first time, we show that IBS-related symptoms develop differentially over time. GI symptoms had a high likelihood of subsiding over time, in contrast to depression, sense of coherence, and coping resources. We suggest more attention needs to be paid to the management of depression, and to providing tools for better coping resources in IBS patients.
Disclosure of Interest: J. Tack: Scientific advice to, or speaker bureau for: Abbott, AlfaWasserman, Almirall, AstraZeneca, Danone, Janssen, Menarini, Novartis, Nycomed, Ocera, Ono pharma, Shire, SK Life Sciences, Theravance, Tranzyme, Xenoport, and Zeria Pharmaceuticals.
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M. Simrén: Unrestricted research grants from Danone, and Ferring Pharmaceuticals; Consultant/ Advisory Board member for AstraZeneca, Danone, Nestlé, Chr Hansen, Almirall, Allergan, Albireo, Glycom and Shire; Speaker for Tillotts, Takeda, Shire and Almirall.
All other authors have declared no conflicts of interest.

OP082 SYMPTOMS COMPATIBLE WITH FUNCTIONAL BOWEL DISORDERS IN PATIENTS WITH ULCERATIVE COLITIS IN DEEP REMISSION

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Introduction: Several studies have reported high prevalence of symptoms compatible with irritable bowel syndrome (IBS) in patients with ulcerative colitis (UC) in remission. However, previous studies have not excluded mild inflammatory changes as a cause of these symptoms, and nothing is known about the prevalence of symptoms compatible with other functional bowel disorders (FBD) than IBS in this group of patients and the burden of these symptoms.
Aims & Methods: In a cross-sectional study, patients with UC ($n = 291$) were divided into active disease or deep remission (a total Mayo score$\leq$ 2, physician's global assessment = 0, rectal bleeding = 0 and an endoscopic subscore = 0, with no relapse during the 3-month period prior to visit). The patients completed the Rome III FBD module to define presence of symptoms compatible with FBD, and questionnaires to measure psychological distress (Hospital Anxiety and Depression Scale; HADS), stress (Perceived stress scale; PSS), GI symptom severity (GI Symptom Rating Scale; GSRS), somatic symptoms (Patient Health Questionnaire-15; PHQ-15), disease-specific quality of life (Inflammatory Bowel Disease Questionnaire; IBDQ), and general fatigue (Multidimensional Fatigue Inventory; MFI).
Results: Active UC was present in 159 patients (55%). The 132 patients (45%) in deep remission were assessed by the Rome III diagnostic criteria and 37% fulfilled criteria for a FBD: 18% IBS (11% IBS-M, 4% IBS-C, 3% IBS-D), 12% functional bloating, 4% functional diarrhea, and 3% functional constipation. Additionally, among the UC patients in deep remission who did not meet diagnostic criteria for FBD, a substantial proportion reported some subthreshold symptoms compatible with a functional bowel disorder, and only 18% of patients with UC in deep remission reported no symptoms compatible with FBD (<one day/month). Compared with UC patients in deep remission with symptoms meeting diagnostic criteria for other FBDs (functional bloating, functional diarrhea, functional constipation), or who did not meet diagnostic criteria for a FBD, patients who fulfilled diagnostic criteria for IBS reported more severe psychological distress ($p < 0.0001$), somatic symptoms ($p < 0.0001$), and general fatigue ($p = 0.004$), as well as reduced quality of life ($p < 0.0001$), and they tended to have higher levels of perceived stress ($p = 0.06$). None of these factors differed between patients who met diagnostic criteria for a FBD other than IBS and patients who did not meet diagnostic criteria for FBD. Age, disease duration, fecal calprotectin levels or high-sensitive CRP did not differ between the groups. Overall GI symptom severity (GSRS total score) was highest in patients with symptoms compatible with IBS ($p < 0.0001$ vs no FBD and other FBD groups) and intermediate in patients who fulfilled one of the other FBDs ($p < 0.05$ vs no FBD group).

Conclusion: Symptoms compatible with functional bowel disorders in general, and not only IBS, are common in patients with UC in deep remission. However, the overall disease burden seems to be greater in patients with symptoms compatible with IBS than with the other FBDs. These observations are of great importance when managing patients with IBD to avoid escalating anti-inflammatory treatment, and instead focus on other treatment options to help these patients to manage their symptoms.
Disclosure of Interest: M. Simrén: Unrestricted research grants from Danone, and Ferring Pharmaceuticals; Consultant/ Advisory Board member for AstraZeneca, Danone, Nestlé, Chr Hansen, Almirall, Allergan, Albireo, Glycom and Shire; Speaker for Tillotts, Takeda, Shire and Almirall.
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H. Törnblom: Consultant/Advisory Board member for Almirall, Danone and Shire.
L. Öhman: Unrestricted research grant from AstraZeneca; Consultant/ Advisory Board member for Genetic Analysis; Speaker for Takeda and Abbvie.
H. Strid: Consultant/Advisory Board member for Takeda, Abbvie, Ferring Pharmaceuticals, Tillotts, and MSD; Speaker for Takeda, Abbvie, Ferring Pharmaceuticals, Tilotts, MSD and Shire.

OP083 ENHANCED DIAGNOSTIC PERFORMANCE OF SYMPTOM-BASED CRITERIA FOR IRRITABLE BOWEL SYNDROME BY HISTORY AND DIAGNOSTIC EVALUATION

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Introduction: Symptom-based criteria to diagnose irritable bowel syndrome (IBS) positively perform only modestly. Our aim was to assess whether including other items from the clinical history and diagnostic workup improves their performance.
Aims & Methods: We collected complete symptom, colonoscopy, and histology data from 318 consecutive, unselected adult patients with lower gastrointestinal (GI) symptoms in secondary care. The reference standard used to define presence of true IBS was patient-reported lower abdominal pain or discomfort associated with a change in bowel habit, in the absence of organic GI disease. Sensitivity, specificity, and positive and negative likelihood ratios (LRs), with 95% confidence intervals, were calculated for Rome III criteria, as well as for modifications, incorporating nocturnal symptoms, results of simple blood tests (haemoglobin (Hb) and C-reactive protein (CRP)), measures of somatisation, and/or affect (hospital anxiety or depression scale (HADS) score).
Results: Sensitivity and specificity of Rome III criteria for identifying IBS was 69.6%, and 82.0% respectively, with positive and negative LRs of 3.87 and 0.37. Clinically useful enhancements in positive LRs when combining Rome III criteria with items from the clinical history, and blood tests, are shown in the table.
Conclusion: Incorporating nocturnal symptoms, somatisation, and affect from the clinical history, and haemoglobin and CRP measurements, enhances performance of symptom-based criteria for IBS. Our findings suggest a different approach to the development of future diagnostic criteria should be used.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP084 HEALTHCARE RESOURCE UTILISATION AMONG PATIENTS WITH IRRITABLE BOWEL SYNDROME WITH DIARRHOEA IN THE EU5

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Introduction: Irritable bowel syndrome (IBS) affects an estimated 10–15% of adults, with the diarrhoea subtype (IBS-D) estimated to account for 30–40% of cases. IBS is a chronic, unpredictable disorder associated with increased healthcare-seeking behaviour and significant resource utilisation and costs. However, information on the economic burden of IBS-D in Europe is limited.
Aims & Methods: The objective of this study was to assess healthcare resource utilisation associated with IBS-D among a sample of adults in the EU5 (Spain, France, Italy, Germany, United Kingdom). Respondents were identified from the 2013 National Health and Wellness Survey, a self-administered, internet-based survey. Diagnosed IBS-D patients were defined as those respondents who reported a physician diagnosis of IBS-D; undiagnosed IBS-D patients included respondents who reported experiencing IBS-D symptoms but did not self-report a physician diagnosis. Controls included all respondents without IBS (diagnosed or undiagnosed) or inflammatory bowel disease. IBS-D severity was evaluated based on a single item assessing disease severity (mild, moderate, or severe). Healthcare resource utilisation was evaluated based on the number of patient-reported healthcare provider visits (any healthcare provider, gastroenterologist, or general practitioner [GP]), emergency room (ER) visits, and hospitalisations in the past 6 months. Descriptive statistics were conducted to examine sample characteristics. Bivariate analyses were used to compare resource use by IBS-D severity. To further assess the burden of IBS-D specifically, multivariable generalised linear models compared resource use across groups, controlling for demographic and health characteristics, including age, gender, and comorbidities.
Results: A total of 58,161 respondents were included (859 diagnosed IBS-D; 370 undiagnosed IBS-D; 56,932 controls). Overall, the mean age was 47 years, and 52.6% of respondents were female. Unadjusted analyses revealed that patients (diagnosed and undiagnosed) with moderate ($n = 499$) or severe ($n = 110$) IBS-D had significantly greater healthcare resource utilisation compared with patients with mild IBS-D ($n = 620$), including more visits to any provider (8.65 and 10.10 vs. 6.22; both $p < 0.05$), a gastroenterologist (0.22 and 0.35 vs. 0.08; both $p < 0.05$), the ER (0.37 and 0.46 vs. 0.19; both $p < 0.05$), and a greater number of hospitalisations (0.21 and 0.36 vs. 0.11; both $p < 0.05$). After controlling for demographic and health characteristics, diagnosed IBS-D patients had a significantly greater mean number of visits to any provider, a gastroenterologist, a GP, and the ER, compared with both controls and undiagnosed IBS-D patients (Table).
Conclusion: IBS-D patients utilised significantly greater outpatient healthcare resources compared with controls, with diagnosed patients using more resources than those who are undiagnosed. In addition, patients with moderate or severe IBS-D have the greatest healthcare resource utilisation. The substantial burden imposed by IBS-D patients on healthcare systems highlights the need for treatments to more effectively treat and manage IBS-D symptoms.
Disclosure of Interest: C. Tucker: Catherine Tucker is an employee of Allergan plc.
J.L. Abel: Jessica L. Abel is an employee of Allergan plc and owns stock/stock options in Allergan plc.
R.T. Carson: Robyn T. Carson is an employee of Allergan plc and owns stock/stock options in Allergan plc.
N.M. Flores: Natalia M. Flores is an employee of Kantar Health, which was contracted by Allergan plc for work relating to this study.
R. Liebert: Ryan Liebert is an employee of Kantar Health, which was contracted by Allergan plc for work relating to this study.

Abstract No: OP083

Rome III Criteria and normal Hb and CRP	Sensitivity (95% CI) 49.0% (34.8%–63.4%)	Specificity (95% CI) 89.2% (83.2%–93.6%)	Positive LR (95% CI) 4.53 (2.67–7.64)	Negative LR (95% CI) 0.57 (0.42–0.73)
Rome III criteria and HADS score ≥8	47.2% (35.3%–59.4%)	89.1% (84.2%–92.9%)	4.33 (2.76–6.76)	0.59 (0.46–0.72)
Rome III criteria and high somatisation	37.9% (26.2%–50.7%)	94.8% (90.6%–97.5%)	7.27 (3.74–14.2)	0.66 (0.53–0.77)
Rome III criteria, normal Hb and CRP, and HADS score ≥8	34.0% (20.9%–49.3%)	93.2% (87.9%–96.7%)	5.04 (2.48–10.2)	0.71 (0.55–0.84)
Rome III criteria, normal Hb and CRP, and high somatisation	24.4% (12.4%–40.3%)	96.8% (92.0%–99.1%)	7.56 (2.63–21.7)	0.78 (0.63–0.90)
Rome III criteria, no nocturnal passage of stool, and HADS score ≥8	22.2% (13.3% –33.6%)	95.4% (91.7%–97.8%)	4.84 (2.33–10.0)	0.82 (0.70–0.91)
Rome III criteria, no nocturnal passage of stool, and high somatisation	18.2% (9.8%–29.6%)	99.0% (96.3%–99.9%)	17.3 (4.45–67.6)	0.83 (0.72–0.90)

Abstract No: OP084

Table

Adjusted mean, number in past 6 months (SE)	Diagnosed IBS-D (n = 859)	Undiagnosed IBS-D (n = 370)	Controls (n = 56,932)	p-value: Diagnosed vs. controls	p-value: Diagnosed vs. undiagnosed	p-value: Undiagnosed vs. controls
Any provider visits	7.23 (0.31)	5.17 (0.35)	4.14 (0.02)	**<0.001**	**<0.001**	**0.001**
Gastroenterologist visits	0.19 (0.02)	0.01 (0.01)	0.03 (0)	**<0.001**	**<0.001**	0.146
General practitioner visits	2.69 (0.12)	2.06 (0.15)	1.70 (0.01)	**<0.001**	**0.001**	**0.007**
Emergency room visits	0.27 (0.04)	0.12 (0.03)	0.17 (0)	**0.002**	**0.012**	0.264
Hospitalisations	0.14 (0.03)	0.08 (0.03)	0.11 (0)	0.099	0.148	0.430

MONDAY, OCTOBER 17, 2016 14:00–15:30

WHAT IS NEW IN GASTRIC ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) – ROOM L7

OP085 LONG-TERM OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) AND GASTRECTOMY BASED ON INDICATIONS FOR ESD

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Introduction: Endoscopic submucosal dissection (ESD) has been established as a standard treatment modality of early gastric cancer (EGC), however, long term outcomes between ESD and gastrectomy were rarely reported, especially in terms of ESD criteria.

Aims & Methods: This study aimed to compare long term outcomes between ESD and gastrectomy, and according to the histopathologic ESD criteria; absolute criteria (AC), expanded criteria (EC) and beyond expanded criteria (BEC). Between 2006 and 2012, 925 EGC patients were enrolled; ESD was performed in 468 patients, and gastrectomy in 457 patients.

Results: Recurrence rate was 1.9% in ESD patients, 0.7% in gastrectomy patients ($p = 0.08$); 1.0%, 3.1% and 1.4% in AC, EC and BEC groups in ESD patients, ($p = 0.062$) and 2.0% and 1.4% in the AC+EC and BEC groups in ESD patients ($p = 0.069$), which were not significantly different between criteria groups. In concrete, recurrence rate was 1.1% and 0% in AC group of ESD and gastrectomy patients, respectively, 3.1% and 1.9% in EC group, and 1.4% and 0% in BEC group. 394 of 468 (84.2%) ESD patients were within criteria. (AC+EC group), and 273 of 457 (59.7%) gastrectomy patients were out of ESD criteria (BEC group).

Conclusion: The recurrence rate was neither significantly different between ESD and gastrectomy patients, nor was significantly different between three criteria groups among total patients. Thus, ESD with EC or even BEC might be an alternative option in EGC patients who refuse gastrectomy or with high operation risk.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP086 PREDICTING CLINICAL OUTCOMES OF GASTRIC ENDOSCOPIC SUBMUCOSAL DISSECTION USING A BAYESIAN APPROACH

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Introduction: In patients with gastric superficial neoplasms, the probabilities of success and of adverse events influence the decision process regarding treatment allocation. These probabilities may be predicted using a priori patients' and lesions' factors. However, the knowledge of risk factors alone is not readily and completely usable by patients and clinicians in the decision process since it is difficult to predict the addictive effect of risk factors in the outcome, in a given patient. Bayesian networks are increasingly used for clinical decision support since Bayesian statistical methods allow taking into account prior knowledge when analyzing data and can aid in capturing and reasoning with uncertainty in medicine[1].

Aims & Methods: The aim of this study was to develop a Bayesian model and a computerized tool that can be used in clinical practice to predict outcomes after ESD and aid in the decision-making process. Methods: Data from 245 ESDs performed in our institution was collected, including pre-resection patient factors (age, sex, ASA, antithrombotics) and lesion factors (size, localization, morphology, pre-resection biopsies). The two main endpoints were curative resection and post-procedural bleeding. We defined curative resection as a resection meeting the standard or expanded criteria of the Japanese Gastric Cancer Treatment guidelines. For the analysis and model construction, morphology was recoded into polypoid (0-Is, 0-Isp, 0-Ip), depressed (0-IIa+c, 0-IIc+a, 0-IIc and 0-III) and non-polypoid non-depressed (0-IIa, 0-IIb, 0-IIa+b). Univariate analysis was conducted with chi-squared test to identify associations between pre-treatment factors and the two endpoints, for a significance level of 5%. Logistic regression and Bayesian networks were then built for each outcome. Stratified 10-fold cross-validation was performed to assess the predictive accuracy and discriminative power (ROC curves) of the models. Clinical decision support was then enabled by the definition of risk matrices, direct use of Bayesian inference software and through the use of an online platform.

Results: In our sample, 85% were curative resections and PPB occurred in 8%. In the univariate analysis, age >63 ($p = 0.039$), male sex ($p = 0.027$), ASA status ($p = 0.008$), carcinoma histology ($p < 0.001$), polypoid or depressed morphology ($p = 0.015$) and lesion size greater than 20 mm ($p = 0.006$) were associated with non-curative resection, while age >70 ($p = 0.041$), ASA status ($p = 0.017$), antithrombotic medication ($p < 0.001$) and lesion size greater than >20 mm ($p = 0.026$) were associated with PPB. Logistic regression and Bayesian models presented AUCs above 80% (in-sample) and 75% (cross-validation) on both outcomes. Lesions with cancer at biopsies, >20 mm, proximal and polypoid are more prone to non-curative resection (table 1). Risk matrices for PPB were also defined yielding a posteriori probabilities of PPB <5% in lesions <20 mm in the absence of antithrombotic medications while the risk of PPB increased in greater lesions and in the presence of antithrombotic medications. The Bayesian network can be interactively used in clinical practice to estimate individual probability of outcomes after ESD. Table 1 - Risk (a posteriori probabilities) matrix for curative resection based on morphology, localization, size and pre-resection histology, using a Bayesian model (cross-validation AUC = 78%, 95%CI = [75%,81%]).

		Size <20 mm	Size <20 mm	Size <20 mm	Size ≥20 mm	Size ≥20 mm	Size ≥20 mm
Morphology	Local	LGD	HGD	IMC	LGD	HGD	IMC
Polypoid (0-Is, 0-Ip, 0-Isp)	Middle	85	74	42	66	49	20
	Upper	91	83	56	77	62	30
	Lower	93	86	61	81	67	35
Depressed (0-IIc, 0-IIa+c, 0-IIc+a, III)	Middle	93	87	64	83	70	38
	Upper	96	92	75	89	80	51
	Lower	97	94	79	91	83	57
Non-polypoid, non-depressed (0-IIa, 0-IIa+b, 0-IIb)	Middle	97	94	79	91	83	57
	Upper	98	96	87	95	90	69
	Lower	98	97	89	96	91	74

LGD - Low-grade dysplasia; HGD - High-grade dysplasia; IMC - intramucosal carcinoma

Conclusion: The derived models presented good discriminative power in the prediction of outcomes. Bayesian models and risk matrices can be used to predict individualized probabilities, which can improve the information transmitted to patient regarding a posteriori probabilities and can aid in the decision process regarding allocation for endoscopic or surgical treatment. Additionally, a posteriori probabilities of adverse events can guide management after gastric ESD, namely regarding the timing of discharge from hospital.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP087 LONG-TERM OUTCOMES OF GASTRIC ENDOSCOPIC SUBMUCOSAL DISSECTION: FOCUS ON METACHRONOUS AND NON-CURATIVE RESECTION MANAGEMENT

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Introduction: Endoscopic submucosal dissection (ESD) is an effective treatment for gastric superficial neoplasms, being curative in 80–85%. Identification of risk factors for a non-curative resection is of paramount importance to improve patient selection. Furthermore, it is important to evaluate the management after an unsuccessful treatment in order to assess the clinical outcomes of each option (careful surveillance or surgical treatment). Moreover, patients with an early neoplastic lesion are at risk of developing metachronous lesions and endoscopic surveillance will still be needed after endoscopic resection. The identification of risk factors for metachronous development is also important to adequate surveillance.

Aims & Methods: The aims of this study were to identify risk factors for non-curative resection and metachronous development and to evaluate management and outcomes after non-curative resection. Methods: Single centre assessment of a cohort of consecutive patients submitted to gastric ESD, with a minimum follow-up of 18 months. The Japanese Gastric Cancer Treatment Guidelines criteria were used in clinical practice; resections were also classified according with the recently published European Society of Gastrointestinal Endoscopy guidelines. Univariate analysis (independent samples t-test, Mann-Whitney U test or chi-square test as appropriate) and multivariate logistic regression were performed to identify risk factors. Odds ratio (OR) were computed along with 95% confidence intervals (CI). Survival was analyzed with Kaplan-Meyer curves and log-rank test. Significance level was defined as $p < 0.05$.

Results: ESD was performed in 194 lesions (164 patients) between 2005–2014. The median follow-up time was 40 months. En-bloc and complete resection rates were 95.3% and 93.8%, respectively. Overall adverse events occurred in 13%. Male sex, tumor size ≥20 mm, longer procedural time and more advanced histology in pre-resection biopsies were associated with non-curative resection ($p < 0.05$) but only intramucosal carcinoma on pre-resection biopsies was identified as a significant risk factor on multivariate analysis (adjusted OR 3.04, 95% CI 1.02–9.06). Histological upgrade (from low-grade dysplasia to high-grade dysplasia or from high-grade dysplasia to carcinoma) occurred in 49.5% of the cases. Metachronous lesions occurred in 18.4% and the incidence rate was 4.7 lesions/100 person-years. The median time for metachronous detection was 24 months (interquartile range 9–50.25 months). Older age at diagnosis was identified as the only predictor of metachronous development in logistic regression ($OR_{10\ years}$ 1.68, 95% CI 1.03–2.74). Overall survival was 94.5% and 89.5% at 1 and 3 years, respectively; disease-specific survival was 99.4%, with only one patient dying of gastric cancer. Survival was significantly higher in patients with curative resections (log-rank 4.538, $p = 0.033$). In the non-curative resection group, patients submitted to surgery were significantly younger (mean age 66.7 ± 9.4 versus 73.6 ± 7.5 in the follow-up group, $p = 0.037$) and were less frequently classified as ASA III/IV (23.1% versus 31.3%, $p = 0.62$). However, survival was not significantly different in the two groups (log-rank 0.009, $p = 0.929$). In gastrectomy specimens, there was no residual neoplasia in 75%. Comparing survival according to ESGE criteria, survival in patients with high-risk resection was significantly worse than in patients with low-risk resection (log rank 7.539, $p = 0.006$), while no significant differences were found in the survival of patients with low and local-risk resection (log rank 0.133, $p = 0.715$).

Conclusion: The identified risk factors for non-curative resection help to improve patient selection for endoscopic resection and also patient information regarding probability of success. Metachronous incidence is significant, being older patients at increased risk for its development. In the non-curative resection group, survival did not differ between patients allocated to surveillance and those submitted to gastrectomy. An individualized decision is adequate after a non-curative resection and surveillance seems to be an adequate option in selected cases.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP088 EVALUATION OF METASTATIC POTENTIAL CAUSED BY SUBMUCOSAL OPERATION DURING ENDOSCOPIC SUBMUCOSAL DISSECTION FOR EARLY GASTRIC CANCER IN PATIENTS WHO UNDERWENT ADDITIONAL RADICAL SURGERY: A MULTICENTER RETROSPECTIVE STUDY

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Introduction: In Japan, endoscopic submucosal dissection (ESD) has been a standard option as minimum invasive treatment for early gastric cancer (EGC). According to the current Japanese guideline, radical surgery is recommended in patients who do not meet the curative criteria for ESD. Although the concept of "No-touch isolation techniques" might prevent the spread of cancer cells in colorectal and pancreatic cancer, in the influence of submucosal operation during ESD for gastric cancer is unclear.

Aims & Methods: We aimed to reveal whether metastatic potential increases in patients who underwent radical surgery after having failed to meet the curative criteria. Among 15,838 patients undergoing ESD for EGC at 19 institutions in Japan between 2000 and 2011, we enrolled consecutive patients who did not meet the current curative criteria for ESD and additionally underwent radical surgery. The exclusion criteria were patients merely positive for horizontal margin and those with a follow-up period of <3 years. The overall survival (OS) and disease-specific survival (DSS) were calculated according to the Kaplan-Meier method and analyzed by the log-rank test. In addition, the risk factors for recurrence were calculated using Cox proportional hazards model. The estimated factors were location (lower third or the other), tumor size (>30 or ≤30 mm), tumor depth (submucosal invasion ≥500 μm (SM2) or shallower than SM2), histopathological type (undifferentiated or differentiated), lymphatic invasion, vascular invasion, ulceration (scar), positive vertical margin and lymph node metastasis (LNM). In this study, recurrence was defined as the metastatic one.

Results: A total of 1,064 patients were analyzed with a median follow-up period of 67 months. LNM was found in 89 patients (8.4%) and 14 patients (1.3%) developed recurrence. All recurrent sites at the time of initial diagnosis were distant lymph node or other organs, no regional lymph node. Multivariate analysis showed that the independent risk factors for recurrence were LNM (hazard ratio [95% confidence interval] = 28.2 [7.12–112], $p < 0.001$) and vascular invasion (4.37 [1.25–15.3], $p = 0.021$). The 3-year and 5-year OSs were 96.8% and 92.6%, respectively, and the 3-year and 5-year DSSs were 99.4% and 98.8%, respectively.

Conclusion: This multicenter study with the largest cohort revealed that additional radical surgery for patients who do not meet the current curative criteria for ESD of EGC has a low recurrence rate and excellent prognosis. Submucosal operation during ESD for EGC does not make risk of LNM and prognosis worse.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP089 ENDOSCOPIC FULL-THICKNESS RESECTION WITH DEFECT CLOSURE IN THE STOMACH BY USING A NOVEL GRASP-AND-LOOP (GAL) CLOSURE METHOD (WITH VIDEOS)

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Introduction: Endoscopic full-thickness resection (EFTR) is a minimally invasive method for en bloc resection of GI lesions originating from the muscularis propria layer. Successful closure of the wall defect is a critical step.

Aims & Methods: The aim of this study was to evaluate the feasibility and efficacy of a novel and simplified endoscopic Grasp-and-Loop (GAL) closure method using an endoloop assistant with a grasping forceps for defect closure. From January 2015 to March 2016, 13 patients with SMTs originating from the muscularis propria layer who underwent EFTR were enrolled in this study. After successful tumor resection, an endoloop was anchored onto the circumferential margin of the gastric defect with a grasping forceps assistant and tightened gently (with videos). Patient characteristics, tumor size, en bloc resection, and postoperative complications were evaluated.

Results: Of the 13 lesions in the stomach, 2 were located in the greater curvature of mid-upper body, 11 were located in the fundus. The endoscopic GAL closure method was successfully performed after EFTR in all 13 patients without laparoscopic assistance. The mean procedure time was 43.5 min (range 20–80 min), while the GAL closure procedure took a mean of 9.4 min (range 3–18 min). The mean resected lesion size was 1.5 cm (range 0.5–3.5 cm). Pathological diagnosis of these lesions were 11 gastrointestinal stromal tumors (GISTs) and 2 leiomyomas. No major adverse events occurred during or after the procedure. All patients were discharged after a mean time of 2.4 days (range 1–4 days). No residual lesion or tumor recurrence was found during the follow-up period (median, 5 months; range, 1–15 months).

Conclusion: The endoscopic Grasp-and-Loop closure method is feasible, effective and safe for closing the gastric defect after EFTR in patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP090 A CLINICAL STUDY OF ENDOSCOPIC FULL-THICKNESS RESECTION BY SEROSA SEALING METHOD FOR SUBMUCOSAL INVASIVE GASTRIC CANCER WITHOUT SENTINEL NODE METASTASIS

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Introduction: Endoscopic full-thickness resection (EFTR) and laparoscopic and endoscopic cooperative surgery (LECS) are useful procedures to avoid excessive resection of the gastric wall and postoperative complications, such as stenosis or deformity, because the location of tumor can be confirmed endoscopically to determine an appropriate resection line. However, these methods have some disadvantages, such as loss of endoscopic view caused by collapse of the stomach and peritoneal infection or tumor dissemination by outflow of gastric juice. Thus, we developed new technique of EFTR, we called sealed EFTR, for sealing the serosa of stomach with silicon sheet to prevent collapse of the stomach and outflow of gastric juice.

Aims & Methods: We introduce our sealed EFTR technique and describe a clinical study of EFTR in patients with submucosal invasive gastric cancer who were diagnosed as negative for lymph node metastasis by laparoscopic sentinel lymph node biopsy. Patients: Between December 2012 and April 2016, 9 patients with clinical T1 gastric cancer, who were outside of indication of ESD, were enrolled in this study. Before surgery, written informed consent was obtained from each patient. All procedures were conducted in accordance with the ethical standards of the institution's Committee on Human Experimentation. Laparoscopic sentinel node biopsy. On the day before surgery, indocyanine green solution (5μg/ml) is injected at a volume of 0.2 ml into each of 4 points in the submucosal layer around the lesion. Using an infrared fluorescence laparoscope, sentinel nodes emitting fluorescence are identified. The lymphatic basins containing the bright nodes are dissected laparoscopically and subjected to rapid intraoperative pathological examination. When the sentinel lymph nodes are negative for malignancy, EFTR is performed. On the other hand, when they are positive for tumor cells, standard gastrectomy with D2 lymphadenectomy is performed. Sealed EFTR At first, circumferential mucosal incision is performed in the same manner as ESD. Continuously, silicon sheet and polyglycolic acid (PGA) sheet are put on the serosa of the lesion and pasted with fibrinogen, thrombin solution. Then, full-thickness incision is performed by Hook knife and/or IT knife. The tumor, silicon sheet and PGA sheet are removed through oral cavity. Finally, the defect of gastric wall is closed laparoscopically using hand-sewn sutures.

Results: Seven patients (78%) were negative for sentinel node metastasis, and were performed EFTR. Four patients who were enrolled after 2014 were performed EFTR using serosa sealing method (sealed EFTR). In sealed EFTR, it was possible to incise all-layer of the stomach with keeping good endoscopic view without collapse of the stomach by covering the serosa using silicon sheet and PGA sheet. Postoperative diet intake was almost the same as before surgery. All patients were preserved QOL without postoperative complications such as small stomach syndrome or early satiety. During follow-up of 1 to 4 years, all patients except one, who died of other cancer, are alive without recurrence or metastasis.

Conclusion: Serosa sealing method (Sealed EFTR) was considered to be useful technique as one of the minimally invasive surgeries for lymph node negative gastric cancer, because it was possible to incise all-layer of the stomach while confirming the incision line from the inside of the stomach without exposure the tumor to the abdominal cavity.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP091 CALORIC AND NON-CALORIC ARTIFICIAL SWEETENERS HAVE DISSOCIABLE EFFECTS ON ANTRAL MOTILITY AND PLASMA MOTILIN LEVELS IN HEALTHY VOLUNTEERS

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Introduction: Activation of gastrointestinal (GI) sweet taste receptors by caloric sweeteners such as glucose or fructose induces the secretion of GI peptides to regulate food intake. The effect of non-caloric sweeteners on GI peptide secretion and satiation is controversial. We have recently shown that motilin-induced gastric phase III contractions of the migrating motor complex (MMC) signal hunger feelings. The mechanism underlying interruption of the MMC by specific sweet tastants has not yet been studied. It is conceivable that this requires sweet taste receptor activation and accompanying changes in the release of GI peptides.

Aims & Methods: The aim was to determine the effect of caloric and non-caloric sweeteners on GI motility and GI peptide secretion as well as on hunger feelings in healthy volunteers. The study was a randomized, double-blind, cross-over trial. 12 healthy volunteers were included. Participants underwent gastroduodenal manometry recording for the occurrence of one phase III contraction followed by the intragastric administration of 250 mL tap water (control), or equisweet caloric (50g glucose, 25g fructose) and non-caloric sweeteners (220 mg acesulfame-K (ace-K)) dissolved in 250 mL tap water. Measurement was continued until at least one subsequent phase III occurred. Recording of antroduodenal pressures was performed using a Manoscan® high resolution manometry catheter. Blood samples were collected for determination of plasma glucose and motilin concentrations. Visual analogue scales were used to rate hunger and satiety feelings. Data were analyzed using mixed model analysis. Post-hoc analyses were corrected using Bonferroni.

Results: Antral motility was significantly reduced in response to the caloric sweeteners (glucose: $p = 0.004$ and fructose: $p = 0.010$, respectively); antral motility after ace-K administration did not differ significantly from placebo. Glucose induced a significant reduction in antral motility compared to ace-K ($p = 0.010$). In contrast, duodenal motility was significantly reduced by both the caloric as well as non-caloric sweeteners compared to placebo (glucose: $p = 0.043$, fructose: $p = 0.006$ and ace-K: $p = 0.032$, respectively). The change over time of plasma glucose concentrations was significantly increased after glucose and fructose compared to placebo administration ($p = 0.026$ and $p = 0.002$, respectively); ace-K had no effect on plasma glucose concentrations. The change over time of plasma motilin concentrations was significantly decreased after fructose ($p = 0.001$) administration; ace-K administration induced no difference compared to placebo. Plasma motilin levels were significantly decreased after the caloric sweeteners compared to the non-caloric sweetener ace-K (glucose: $p = 0.005$ and fructose: $p = 0.008$, respectively). The time course of satiation scores differed significantly between glucose and ace-K ($p = 0.041$) with a slower decrease in satiation scores after glucose compared to ace-K administration.

Conclusion: Caloric and non-caloric sweeteners have dissociable effects on antral but not duodenal motility; the reduction in antral motility after glucose and fructose administration parallels changes in motilin secretion. These findings provide an important contribution to the current discussion about possible physiological effects of non-caloric sweeteners on appetite metabolism.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP092 XYLITOL AND ERYTHRITOL INDUCE SATIATION PEPTIDE RELEASE AND RETARDATION IN GASTRIC EMPTYING IN HEALTHY HUMANS

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Introduction: With the increasing prevalence of obesity and its possible association with increasing sucrose consumption, non-nutritive sweeteners are gaining popularity. Artificial sweeteners might have adverse effects and alternative solutions are sought. Polyols such as xylitol and erythritol have been known for a long time and their beneficial effects on caries prevention and potential health benefits in diabetic patients have been demonstrated in several studies. Incretins such as glucagon-like peptide-1 (GLP-1) and gastrointestinal peptides such as cholecystokinin (CCK) are released from the gut in response to food intake, promote satiation, reduce gastric emptying (GE) and modulate glucose homeostasis. While glucose ingestion stimulates sweet taste receptors in the gut, and leads to incretin and gastrointestinal peptide release, the effect of xylitol and erythritol has not been studied.

Aims & Methods: The aim was to study gastrointestinal peptide and incretin release as well as effects on gastric emptying in response to xylitol and erythritol intake. The study was conducted as a randomized, double-blind, parallel-group trial. A total of 10 healthy lean and 10 non-diabetic obese (BMI > 30) participants were included. Subjects received intragastric equisweet loads of 50 g xylitol or 75 g erythritol dissolved in 300 mL tap water; 75 g glucose solution and 300

mL tap water were control treatments. Solutions were enriched with ^{13}C-sodium acetate (for determination of gastric emptying). We measured plasma GLP-1 and CCK, as well as plasma insulin and glucose levels. GE was measured by a ^{13}C-sodium acetate breath test.
Results: i) xylitol and erythritol lead to a marked increase in CCK ($p < 0.001$, respectively) and GLP-1 ($p = 0.001$ and $p < 0.001$, respectively); ii) plasma insulin and glucose are not (erythritol) or minimally (xylitol) affected; iii) xylitol and erythritol induce a significant retardation in gastric emptying rates ($p < 0.001$, respectively).
Conclusion: There is emerging evidence to indicate a beneficial role for dietary polyols: erythritol and xylitol are low in calories, have no or only a small effect on plasma glucose and insulin release, yet stimulate gastrointestinal satiation peptides. A potential therapeutic application requires further studies.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP093 INFLUENCE OF LIRAGLUTIDE, A GLUCAGON-LIKE PEPTIDE-1 ANALOG, ON HUNGER AND SATIETY, INTERDIGESTIVE MOTILITY, GASTRIC ACCOMMODATION AND GASTRIC EMPTYING IN HEALTHY VOLUNTEERS

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Introduction: Liraglutide (LG) was recently approved for the treatment of obesity. However, the mechanism by which it induces weight loss is incompletely understood and involvement of altered gastrointestinal motility has been implicated. Recent studies have implicated gastric phase III of the interdigestive migrating motor complex (MMC), gastric accommodation (GA) and gastric emptying (GE) in the control of hunger and food intake.
Aims & Methods: The aim of this study was to investigate the effect of LG on MMC, GA, GE and hunger or satiation in healthy volunteers (HVs). The study was an open-label, crossover trial conducted in 10 lean HVs. Liraglutide (Victoza®, Novo Nordisk, Belgium, 0.6 mg) was administered subcutaneously 14 hours before the start of the study protocol. No administration was done in the placebo arm. The study consisted of protocol 1 (MMC) and protocol 2 (GA/GE); in both protocols a high-resolution manometry probe was advanced via the nose to the duodenum. **Protocol 1:** Gastroduodenal motility was registered for the duration of 1 MMC cycle. Antral and duodenal motility index (MI) were calculated as (number of contractions*average amplitude contractions*average duration contractions)/5 min. Average MI was calculated by averaging 6 consecutive antral or duodenal channels. Occurrence of antral or duodenal phase III contractions was evaluated. **Protocol 2:** After a stabilization period, HVs ingested a liquid test meal (200 ml, 300 kcal; 89% carbohydrate, 11% protein) labeled with 100 mg ^{13}C-sodium octanoate. GA was measured as the intragastric pressure (IGP) drop in the first 30 min after the drink and was calculated as the average pressure over 5 channels in the fundus compared to baseline 5 minutes before the drink. GE rates were determined from breath test samples collected before the meal and at 15-min intervals for 4 hours. Occurrence of antral or duodenal phases III within the 4 hours was evaluated. In both protocols feelings of hunger, satiation and epigastric symptoms were measured using 100 mm visual analogue scales (VAS). All data are expressed as mean ± SEM. Outcomes were analyzed using mix-model analysis (MI, IGP, symptoms), paired t-test (half GE time ($t_{1/2}$) or chi square test (phase III occurrence and origin). $p < 0.05$ was considered significant
Results: LG was well tolerated by all HVs[AR1]. **Protocol 1:** LG significantly reduced the number of phase III contractions with a gastric origin from 65% (placebo) to 5% (LG) ($p = 0.0001$). The antral MI of both first and second phase III contractions was significantly lower after LG ($p = 0.01$ and 0.002 respectively). Similarly, the duodenal MI was also lower after LG for both phases III ($p = 0.007$ and 0.005 respectively). **Protocol 2**: LG administration did not affect the IGP drop but it significantly delayed the $GEt_{1/2}$ ($p = 0.005$) (Table). In the control condition all volunteers had a phase III within 4 hours after the meal. After LG this number decreased to 70 [AR2]% (ns). LG administration completely switched the origin of phase III contractions with a gastric origin from 90% (control) to 0% (LG) ($p = 0.0004$). Antral and duodenal motility were significantly lower in the LG arm compared to control ($p = 0.002$ and $p = 0.05$, respectively). Hunger or satiation ratings [JT3] were not affected by LG treatment in both protocols.

Parameter	placebo	LG	p value
Average IGP drop 30 min from the drink (mmHg)	−7.7 ± 1	−6.6 ± 0.6	0.6
GE $t_{1/2}$ (min)	69.6 ± 5.1	119.4 ± 18.4	0.005

Conclusion: Acutely administered LG decreases both antral and duodenal motility during the interdigestive state and delays gastric emptying after a standard liquid meal. However, at this dose it does not seem to influence gastric accommodation or hunger and satiation feelings.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP094 INFLAMMATORY AND ANTIOXIDANT RESPONSE FOLLOWING STANDARD MEAL CONSUMPTION IN PATIENTS WITH FUNCTIONAL DYSPEPSIA AND HEALTHY VOLUNTEERS

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Introduction: The Rome III criteria recognize two distinct subgroups of functional dyspepsia (FD): the postprandial distress syndrome (PDS) and the epigastric pain syndrome (EPS). The underlying pathophysiological mechanisms of these syndromes are partially known. Recently, the worsening of hypersensitivity in the postprandial period was shown in PDS (1–2) and an impairment of gastric compliance was detected in EPD (2). Moreover, in FD patients an altered permeability of intestinal mucosa, an altered expression of cell adhesion proteins and the presence of mucosal infiltration of mast cells and eosinophils were shown (1), suggesting a role for inflammation and permeability alterations in the pathogenesis of this condition.
Aims & Methods: Our aim was the evaluation of postprandial modification of both inflammatory and antioxidant markers in a group of PDS patients in comparison with healthy volunteers (HV). 14 consecutive, non-smoking patients (9 females, mean age 42.8 ± 11.2 yrs) affected by FD, subtype PDS, according to Rome III criteria and a group of 13 HV comparable for age and gender were enrolled. Chronic inflammatory and autoimmune diseases were excluded. Serum levels of inflammatory cytokines (IL-1, IL-6 and TNFα), insulin, glucose, uric acid (UA) and lipopolysaccharide (LPS) were evaluated at fast and every 30 minutes after the ingestion of a standard meal (proteins 15.7%, lipids 28.3%, carbohydrates 56%) for a 4-hour period. The presence and severity of symptoms (abdominal pain, abdominal distension, bloating, flatulence, nausea, vomiting, belching, heartburn, regurgitation, diarrhea, headache) were evaluated while fasting and in the postprandial period by VAL.
Results: Mean fasting values of TNFα, IL-1 and insulin were significantly higher in PDS patients (1.62 ± 1.21, 0.37 ± 0.24, 15.4 ± 10.24, respectively) in comparison with HV (0.26 ± 0.15, 0.13 ± 0.11 and 7.45 ± 6.08, respectively; $p < 0.05$ for all). Similarly, postprandial values of TNFα, IL-1 and insulin were significantly higher in PDS (2.65 ± 1.76, 0.64 ± 0.59, 30.39 ± 12.60, respectively) than in HV (0.23 ± 0.17, 0.19 ± 0.11, 21.04 ± 7.02 respectively) ($p < 0.05$ for all). In FD but not in HV, mean postprandial levels of TNFα were significantly higher than fasting values ($p < 0.05$). As far as the antioxidant system is concerned, mean postprandial values of UA were significantly higher in PDS (52.94 ± 19.16) than in HV (34.46 ± 5.61) ($p < 0.05$). Serum levels of LPS and IL-6 did not show significant differences between PDS and HV. As expected, only in PDS and not in HV was there a significant increase of postprandial symptoms. Finally, the severity of symptoms was significantly correlated with the postprandial serum levels of both inflammatory and antioxidant markers.
Conclusion: Our results show that in PDS the ingestion of a standard meal induces an inflammatory response and a secondary activation of the endogenous antioxidant system, strictly correlated with symptom occurrence. Further studies are needed to confirm the pathogenetic role of postprandial inflammatory response in a condition characterized by low-grade inflammatory alterations.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP095 A DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER STUDY USING BACLOFEN IN THE TREATMENT OF RUMINATION SYNDROME

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Introduction: Rumination syndrome and supra-gastric belching are two conditions with limited treatment options. Baclofen, a γ-aminobutyric acid agonist, increases lower oesophageal sphincter (LOS) pressure. We previously demonstrated, in an open-label study, that baclofen reduces pressure flow events in patients with clinically suspected rumination and/or supra-gastric belching.
Aims & Methods: To study the effect of baclofen in a placebo-controlled, double-blind, cross-over study in patients with clinically suspected rumination and/or supra-gastric belching. Consecutive patients with clinically suspected rumination and/or supra-gastric belching were randomized in a double-blind fashion to receive baclofen (10 mg, 3 t.i.d) or placebo for 2 weeks with cross-over to the alternative intervention after 1 week wash-out. At the end of each treatment period, patients underwent a solid state high resolution impedance manometry (HRiM) measurement. After positioning of the probe, 10 wet swallows were performed to assess oesophageal function. After 30 min recording, patients received a 1000 kcal solid meal and recordings continued for 1 hour. Patients filled out daily diaries, questionnaires at the end of each treatment period (i.e. overall treatment evaluation (OTE) on -3 to +3 scale) and registered symptoms during the HRiM using an event marker. The number of symptoms registered and number and type of flow events during the HRiM were compared between placebo and baclofen.

Results: We enrolled 20 patients (mean age 42y (range 18–61), 13f). Lower oesophageal sphincter (LOS) pressure was significantly higher in the baclofen treatment arm compared to the placebo arm (17.8±1.4 vs. 12.8 ± 1.4 mmHg, p = 0.001). The number of transient LOS relaxations was lower (6 ± 1 vs. 8 ± 2, p = 0.05) and the integrated relaxation pressure was higher (11.8 ± 1.0 vs. 8.1 ± 1.2 mm Hg, p = 0.003) after baclofen compared to placebo. The number of reflux events did not differ between both arms (4 ± 1 vs. 3 ± 1, NS). The number of rumination episodes was significantly lower in the baclofen treatment arm (15 ± 3 vs. 9 ± 2, p = 0.018), but the number of supra-gastric belching episodes was similar in both treatment groups (43 ± 18 vs. 65 ± 32, NS). In the placebo arm 60% of rumination episodes were classified as primary rumination, 20% as secondary rumination and 20% as supra-gastric belch associated rumination. In the baclofen arm, distribution was similar, with 66% being primary rumination, 11% secondary rumination and 22% supra-gastric belch associated rumination. There was no difference in straining episodes between placebo and baclofen arm, but the percentage of straining episodes associated with rumination was significantly lower in the baclofen arm (14.64 ± 3.84 vs. 31.29 ± 5.96, p = 0.0005). The number of postprandial regurgitation symptoms marked by the patients tended to be lower in the baclofen treatment arm (p = 0.09). OTE was superior after baclofen compared to placebo (1 (0–2) vs. 0 (−1–0), p = 0.04).
Conclusion: This study confirms that baclofen is an effective treatment option for patients with rumination syndrome, probably through its effect on LOS pressure.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP096 GASTRIC ELECTRICAL STIMULATION (GES) FOR REFRACTORY VOMITING: RESULTS OF A PROSPECTIVE MULTICENTER DOUBLE-BLINDED RANDOMIZED CONTROLLED CROSS-OVER TRIAL

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Introduction: Open trials have suggested that GES could be effective for the relief of refractory vomiting, associated or not with delayed gastric emptying (GE). But, short randomized trials carried out in gastroparetic patients led to negative results. Our aim was to perform a large multicenter randomized double-blind controlled trial in patients with refractory vomiting associated or not with gastroparesis, to confirm or not the efficacy of GES.
Aims & Methods: Any patient, aged 18 to 70, with chronic (>12 months) refractory vomiting, either idiopathic or associated with a type 1 or 2 diabetes mellitus or possurgical, was eligible. After a screening period of 4 months to assess symptoms prospectively, patients were implanted with an ENTERRA (R) device with 2 electrodes sewn in the antrum. During the first month post surgery, the device was not activated. Then each subject was randomized in a masked fashion to one of 2 treatment arms: 4 months "ON" then 4 months "OFF" or 4 months "OFF" then 4 months "OFF". During the cross-over phase, both patients and physicians were blinded to the stimulation status. When the device was "ON", stimulation parameters were 14 Hz, 5mA, pulses of 330 µsec. Two follow-up visits were scheduled at 5 and 9 months after implantation. The primary end-points were the vomiting score ranging from 0 (daily vomiting) to 4 (no vomiting) and the QoL assessed by the GIQLI score.
Results: In 19 centers, 172 patients (women:66%), 45+/−12 years old, with symptoms lasting from 5.1+/−5.9 years, associated with gastroparesis in 133, were implanted. Among the 172 patients, 149 patients were evaluated at 9 months. Vomiting score was significantly better during the "ON" than during the "OFF" period (median score: 2 vs 1, p < 0.001), without any carry-over effect. The greater symptomatic benefit during the "ON" period was observed both in diabetic and non diabetic patients and was more important in case of gastroparesis (p < 0.009) than when GE was normal (p:0.05). GE was not significantly faster during the "ON" period. The greater symptomatic effect with an effective GES, was not associated with a better QoL.
Conclusion: An effective GES reduced significantly the frequency of refractory vomiting both in diabetic and non diabetic patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP097 BCL-3 ACTS AS A PROTO-ONCOGENE IN PANCREATIC CANCER IN HUMANS AND MICE

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Introduction: Despite numerous efforts to develop novel therapies, pancreatic ductal adenocarcinoma (PDAC) has remained one of the most devastating and lethal malignancies worldwide. B-cell chronic lymphatic leukemia protein 3 (Bcl-3) is an atypical member of the ankyrin repeat-containing IκB family of NF-κB inhibitors that was first identified as a candidate proto-oncogene in chronic lymphocytic leukemia. Accumulating evidence reveals that elevated Bcl-3 expression results in increased cell proliferation, cell survival and malignant potential. However, the functional role of Bcl-3 in pancreatic cancer has not been elucidated so far. In this study, we aim to identify whether Bcl-3 impacts pancreatic cancer development and progression in humans and mice.
Aims & Methods: PDAC tissues and cell lines obtained from humans and a $Kras^{G12D}$ mouse model (**KC**) of pancreatic cancer were investigated for Bcl-3 expression. The overall survival of human PDACs expressing high and low levels of Bcl-3 was compared. Further, Bcl-3 was deleted in a $Kras^{G12D}$ mouse model (**KCB**) and tumor incidence, metastases as well as proliferation, and apoptosis in tumor tissues and primary tumor cells of **KC** and **KCB** mice were investigated. Pancreatic Intraepithelial Neoplasia (PanIN) in **KC** and **KCB** mice at 13 and 24 weeks was analyzed.
Results: We show that Bcl-3 is highly expressed in human PDACs and in a **KC** mouse model of pancreatic cancer, correlating with prognosis and overall survival. Bcl-3 promotes cell growth and cell survival in vivo and in vitro. Further, Bcl-3 leads to acceleration in PanIN progression, tumor development and metastases in a **KC** mouse model of pancreatic cancer.
Conclusion: In summary, our data provide the first insights into the function of Bcl-3 in pancreatic cancer, and indicate that Bcl-3 has an important pro-tumorigenic role in pancreatic cancer development and progression.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP098 INTEGRIN ALPHA5 AS A NOVEL PROGNOSTIC AND THERAPEUTIC TARGET IN PANCREATIC TUMOR STROMA

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Introduction: Pancreatic cancer is the deadliest tumor type with less than 5% survival rate, characterized by the presence of abundant stroma. Pancreatic stellate cells (PSCs) are the main precursor of myofibroblasts (cancer-associated fibroblasts; CAFs) in tumor stroma and therefore become key target in pancreatic tumor stroma (1). CAFs secrete growth factors, exosomes and extracellular matrix (ECM) and thereby aggravate tumor growth and metastasis (2). This is of paramount importance to find out new targets in stromal myofibroblasts which could be used for developing novel prognostic, diagnostic and therapeutic strategies.
Aims & Methods: In this study, we investigated integrin α5 (ITGA5), a receptor for the ECM protein fibronectin, for its prognostic and therapeutic significance in pancreatic tumor stroma. The ITGA5 expression was investigated using immunohistochemical staining on tissue microarray consist of 137 patient samples of pancreatic tumors. In vivo, Panc-1 and PSCs were co-injected subcutaneously into the flank of SCID mice and investigated the expression of ITGA5 versus Panc-1 tumor alone. To elucidate the role of ITGA5, we knocked down the expression of ITGA5 in PSCs using shRNA-ITGA5. We investigated the phenotypic changes in ITGA5-KD PSCs after TGFβ activation, using immunostainings, quantitative PCR and RT2 profiler human fibrosis array. We also examined the paracrine effect of TGF-β activated ITGA5-KD PSCs on the proliferation of pancreatic tumor cells (Panc-1).
Results: In human patient tumor samples, a total of 85% and 66% of patients were positive for stromal α-SMA and ITGA5, respectively and well co-localized, shown with double immunostaining. The ITGA5 expression was positively correlated with α-SMA in 72% patients. Overall, clinical data analysis reveals that the overexpression of ITGA5 (log-rank p = 0.022) and α-SMA (log-rank p = 0.006) are linked to significant decreased overall survival. In vivo, in mice co-injected with Panc-1 and PSCs showed a significant increase of tumor growth and a higher ITGA5 expression compared to Panc-1 tumors. Next, we studied the effect of ITGA5 knockdown in PSCs on their phenotypic characteristics. Knockdown (60%) of ITGA5 led to a dramatic reduction of several ECM molecules and integrin receptors, shown with RT2 human profiler array. ITGA5-KD PSCs had morphological changes, as they became flattened and lost FAK, Rac, Cdc4 signaling, indicating the loss of lamelopodia and filopodia formation. Furthermore, functional assays showed that ITGA5-KD PSCs had a substantial decrease in cell adhesion, migration (wound healing assay), proliferation and 3D spheroid formation compared to control shRNA-PSCs. Also, knockdown of ITGA5 abolished the tumor cell proliferation induced by TGF-β activated PSCs. These data indicated that ITGA5 induces differentiation and phenotypic behavior of PSCs as well as PSC-induced paracrine effects on tumor cells.

Conclusion: In conclusion, the present study reveals ITGA5 as a novel prognostic and therapeutic target in pancreatic tumor stroma. These data make a strong base to utilize this target for developing novel diagnostic and therapeutic strategies against pancreatic tumor.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP099 MICRORNA-622 INHIBITS EPITHELIAL-MESENCHYMAL TRANSITION BY TARGETING LONG NON-CODING RNA HULC IN HUMAN PANCREATIC CANCER

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Introduction: Transforming growth factor (TGF)-b-induced epithelial-mesenchymal transition (EMT) is a trigger of invasion and metastasis in pancreatic cancer. Although long non-coding RNAs (lncRNAs), which are defined as non-coding RNAs (ncRNAs) more than 200 nucleotides in length, have been implicated in disease pathogenesis, their contributions to pancreatic cancer are not well understood. Recently, the inter-relationship between two classes of ncRNA, microRNAs (miRNAs) and lncRNAs, has been reported to contribute to the epigenetic regulation of gene expression in several cancers.
Aims & Methods: Our aims were to investigate the involvement and functional roles of TGF-β induced lncRNA during EMT and reveal contributions of the inter-relationship between the TGF-β induced lncRNA and miRNA to the regulatory mechanisms of EMT in human pancreatic cancer. We used human pancreatic cancer (Panc-1, BxPC-3, MiaPaCa-2, QGP-1 and KP-3) and non-malignant pancreatic ductal epithelial (hTERT-HPNE) cells. Expression profiling of 90 lncRNAs and 2565 miRNAs were performed using qPCR and miRNA microarray. miRNA targets were predicted by miRanda. Cells were treated with 10 ng/ml of TGF-b for 72 hours to induce EMT. siRNA or miRNA mimic were used to modulate RNA expression. Cell viability was assessed by MTS assay and trypan blue. Cell invasion and migration were examined by transwell and wound healing assay. Expression of RNA was assessed by qPCR and of protein by Western blot.
Results: LncRNA expression profiling identified 22 lncRNAs that were induced by TGF-b in Panc-1 cells by >1.4-fold. Of these, HULC was amongst the top most significantly up-regulated. HULC expression was induced by TGF-b by 1.5 to 2.7-fold in a panel of pancreatic cancer cells and up-regulated by 2.4 to 8.9-fold in pancreatic cancer cells compared to hTERT-HPNE cells. In Panc-1 cells, knockdown of HULC by siRNA significantly increased expression of E-cadherin and decreased expression of N-cadherin, Snail and Vimentin ($p < 0.05$). Moreover, siRNA to HULC decreased cell viability, invasion and migration. Furthermore, to identify miRNAs that can target HULC and suppress EMT, miRNA microarray and bioinformatics analysis were performed. Microarray identified 187 miRNAs that were decreased by < 0.87 fold in Panc-1 cells treated with TGF-β compared to control. Of these, miR-622 was predicted to target HULC by miRanda. miR-622 expression was reduced by TGF-β by 0.5 to 0.9-fold in a panel of pancreatic cancer cells. Overexpression of miR-622 using miRNA mimic significantly decreased expression of HULC, increased expression of E-cadherin and decreased expression of Snail, N-cadherin and Vimentin ($p < 0.05$). In addition, miR-622 overexpression significantly reduced cell invasion and migration.
Conclusion: These findings provide mechanistic insights into EMT in pancreatic cancer by (a) identifying HULC as a highly induced lncRNA by TGF-b, (b) demonstrating that HULC promotes EMT, (c) identifying that miR-622, as a down regulated miRNA by TGF-β, can target HULC, and (d) showing a functional role for miR-622 in EMT via targeting HULC. These observations implicate miR-622 would suppress invasion and metastasis by inhibiting EMT signaling through targeting HULC and suggest potential strategies to inhibit invasion and metastasis in human pancreatic cancer.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP100 ESSENTIAL ROLE OF THE NON-RECEPTOR TYROSINE-PHOSPHATASE PTPN11/SHP-2 IN ORGAN DEVELOPMENT AND HOMEOSTASIS OF THE MURINE EXOCRINE PANCREAS

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Introduction: The Src-homology-2 (SH2) domain containing protein tyrosine phosphatase SHP-2 is expressed ubiquitously and is involved in an array of intracellular signal transduction processes (Ras-Raf-MAPK, JAK-STAT, Pi3K-Akt-mTOR, NFκB,...). Thus, for instance, SHP-2 plays a role in cellular responses to growth factors (PDGF, EGF, FGF, IGF-1,...), cytokines (IL6, IL3, IL5, GM-CSF,...) and extracellular matrix (via integrins, focal adhesion complex). Via these pathways SHP2 mediates transcriptional regulation of mitogenic activation, cell proliferation, survival, differentiation, migration and metabolism. The role of SHP-2 in organ development and homeostasis of the pancreas has so far not been explored.
Aims & Methods: Mouse models with pancreas specific deletion of SHP-2 (Ptf1a-Cre^{ex1}/$Ptpn11^{fl/fl}$) with or without mutated Kras (LSL-$Kras^{G12D}$) and/or lineage tracing allele (ACTB-TdTomato;-EGFP) were used for analysis.
Results: Early embryologic Deletion of SHP-2 in the pancreas via Ptf1a-Cre preserves organ architecture and endocrine function. However, adequate expansion of the exocrine compartment in the growing pancreas is impaired. In adult mice, organ weight is reduced by about 50%, compared to unrecombined littermate-controls. In the organ growth phase, (centro-)acinar cells display enhanced cell death (necrosis and apoptosis) which is accompanied by markedly reduced proliferation. In aged SHP-$2^{\Delta panc}$ mice acinar lobuli are consecutively replaced by adipocytes. Lineage-tracing experiments provide insight into the origin of this cell population (invasion vs. transdifferentiation) and will be presented. Interestingly, introduction of mutated Kras (LSL-$Kras^{G12D}$) into the model fully compensates for the deletion of SHP-2. Finally, in the pancreas, we not only observe an essential role of SHP2 in adequate activation of the RTK-Ras-Raf-MEK-ERK-signaling axis but also in positive regulation of RTK-expression levels.
Conclusion: The central role of the non-receptor tyrosine phosphatase SHP-2 in organ development and homeostasis of the murine pancreas is linked to the RTK-Ras-Raf-MEK-ERK-signaling axis. SHP-2 is essential for adequate transmission of growth factor signals and thereby influences proliferation and survival of the acinar cell.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP101 RELA CONTROLS KRAS-DRIVEN PANCREATIC CARCINOGENESIS BY MEDIATING ONCOGENE-INDUCED SENESCENCE VIA THE CXCL1/KC/CXCR2 AXIS

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Introduction: The IKK/NF-κB pathway has been shown to be a crucial mediator of tumour growth and progression, exhibiting both tumour-promoting and tumour-suppressive properties. How IKK/NF-κB possesses these opposite activities during tumor development remains elusive.
Aims & Methods: In this study, we aimed to elucidate mechanisms by which IKK/NF-κB mediates its tumorigenic functions in pancreatic carcinogenesis. To determine the role of RelA/p65, the functional subunit, which is responsible for the transcriptional activity of NF-κB, we used a mouse model of pancreatic ductal adenocarcinoma (PDAC). We generated compound mutants $Kras^{G12D}$ mice with specific deletion of the p65 gene in the pancreas. Pancreata were investigated histologically and biochemically.
Results: Our data clearly demonstrate a dual role of NF-κB/RelA activation in pancreatic carcinogenesis. In early stages of tumorigenesis, the tumor-suppressive function of NF-κB is beneficial because it controls oncogene-induced senescence (OIS) by regulating the CXCL1/KC-CXCR2 axis. However, as soon as OIS is bypassed during late stages of tumorigenesis, NF-κB supports tumor progression by enhancing proliferation of the transformed pancreatic cancer cells.
Conclusion: Examining these context-dependent activities of RelA will be important for effective clinical use of NF-kB inhibitors. Furthermore, these findings underscore that caution should be exercised, when exploring the use of pharmaceuticals targeting the CXCR2 receptor as a therapeutic option for the treatment of various solid tumors.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP102 MODELLING TUMOR CELL NERVE INTERACTIONS IN PANCREATIC CANCER

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Introduction: Neural invasion (NI) has emerged as a key pathologic feature of pancreatic ductal adenocarcinoma (PDAC) and represents a distinct route of tumour cell spread independent from lymphatic and haematogenous tumour cell dissemination. NI is associated with an unfavourable course of the disease and also constitutes a major cause of neuropathic pain, thus limiting the quality of life. NI is considered as a mutual interaction between tumour cells and nerves and involves both, the unidirectional tracking and invasion of tumour cells along neural routes but also implicates tumour mediated changes in neural plasticity resulting in nerve hypertrophy and increased nerve density in PDAC.
Aims & Methods: Here we describe several applicable tools, using live cell and time-lapse microscopy, co-cultures of tumour cells or ex vivo PDAC xenograft tissues with freshly isolated dorsal root ganglia (DRG), primary DRG neurons and F11 hybridoma neurons to investigate the reciprocal interaction at the tumour cell-nerve interface.
Results: To study the invasion of tumour cells along neurites we have combined 3D co-culture assays of dorsal root ganglia (DRG) and tumour cells with time-lapse microscopy and specifically track the unidirectional movement of individual tumour cells along neurites extending from DRGs. Quantification of the dynamic process revealed that neuronal scaffolds provide the infrastructure for an accelerated and consistent migration of tumour cells towards the DRG as the source of chemotactic gradients. In another approach, using explanted PDAC xenograft tissues instead of tumour cell colonies, it occurred that neurite outgrowth from DRGs is skewed towards the tumour tissue. Thus, neurites facing the tumour were more elongated than neurites at the opposite site of the DRG, suggesting that tumour gradients stimulate and/or attract neurite outgrowth and elongation. In support of a tumour-derived chemotactic effect, supernatants from different tumour cell lines displayed varying neurotrophic effects on the outgrowth of freshly isolated primary neurons in transwell assays. In order to gain a more dynamic representation on how neurites explore a chemoattractant gradient, F11 hybridoma neurons were co-cultured with PDAC cell lines in separate patches divided by a 500 µm gap. These assays use time-lapse imaging and endpoint analysis in order to track the locomotion of individual neurite extensions, monitor their outgrowth from neurons and elongation towards the tumour cell front, and allow to quantitate length, velocity, forward migration index, and directness of each protruding trajectory in response to different PDAC cell lines. Moreover, the extent of growth cone formation and collapse can be scored by determining dynamic changes in circumferential size and area of growth cones.
Conclusion: These in vitro and ex vivo models emulate several important aspects of nerve-tumour interactions and allow pharmacological or gain and loss-of-function manipulations. In addition, semi- to fully-automated quantification for high-throughput screening may offer investigators reliable tools to test their candidate target genes or drugs.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 15:45–17:15
FUTURE DRUGS IN IBD – ROOM C

OP103 SELECTIVE IL-23 INHIBITION BY RISANKIZUMAB MODULATES THE MOLECULAR PROFILE IN THE COLON OF ACTIVE CROHN'S DISEASE PATIENTS

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Introduction: IL-23 contributes to the activation, maintenance and proliferation of Th17 cells, and the IL-23 pathway has been implicated in the pathogenesis of Crohn's disease (CD). Risankizumab is a humanized IgG1 monoclonal antibody that binds the p19 subunit of IL-23 and inhibits binding of IL-23 to its receptor. In a Phase II trial (NCT02031276), risankizumab was more effective than placebo for inducing clinical and endoscopic remission in patients with active CD through 12 weeks.
Aims & Methods: We investigated the underlying mechanism of risankizumab in this Phase II trial by characterising the molecular profile in the colon and/or ileum tissue in a subset of patients with CD, who received either 200 mg ($n = 26$), 600 mg ($n = 27$) risankizumab or placebo ($n = 26$). From each patient, 6–9 biopsy samples were obtained from inflamed lesions in the colon or ileum at baseline and at 12 weeks post-treatment. Biopsy samples from ileum and from colon were separately analysed by transcriptome-wide RNA-Seq profiling. Univariate associations were assessed using linear regression. Effect size, p-values and FDR were calculated for significant genes. CDEIS response ($> 50\%$ reduction from baseline) and CDEIS remission (≤ 4; for patients with isolated ileitis of ≤ 2) were evaluated at Week 12 by an independent blinded reviewer.
Results: Risankizumab treatment significantly decreased the expression of 1146 genes from baseline to Week 12 in the colon tissue of CD patients vs placebo ($p < 0.05$). Of note, risankizumab treatment was associated with a significant reduction in the expression of genes associated with the IL-23 pathway (IL-23A, IL-26, IL-21R, IL-17A, STAT3), innate immunity (IL6, IL7, IL7R, IL8, ICAM1, IL1, IL11, IL13RA2, IL15RA, IL18R1, TNF), tissue turnover (S-100A8, A9, A12, MMP1, MMP3, MMP9, MMP12, ADAM8, ADAM12, ADAM33) and solute carrier family (SLC11A1, SLC1A3, SLC2A3, SLC2A6, SLC6A14, SLC7A11, SLC7A5). These overall changes in gene expression in the risankizumab-treated cohort reflected the molecular changes observed in patients achieving CDEIS response and remission at Week 12. A comparison of gene expression changes in the colon significantly modulated by risankizumab at Week 12 vs anti-TNF treatment at Week 14 in a published patient cohort highlighted larger decreases in suppression of pathways associated with epithelial biology (cell–cell adhesion, morphogenesis, intracellular signal transduction, second messenger signalling) following risankizumab treatment. In contrast, no significant changes were observed in the molecular profile in the ileum from patients treated with risankizumab vs placebo from baseline to Week 12.
Conclusion: The superior efficacy observed with risankizumab in active CD patients at Week 12 was associated with significant molecular changes in the

colon of CDEIS responding patients. The molecular profile appears to be differentiated from anti-TNF treatment.

Disclosure of Interest: S. Visvanathan: Sudha Visvanathan: Employee of Boehringer Ingelheim.
P. Baum: Patrick Baum: Employee of Boehringer Ingelheim.
R. Vinisko: Richard Vinisko: Employee of Boehringer Ingelheim.
R. Schmid: Ramona Schmid: Employee of Boehringer Ingelheim.
W. Boecher: Wulf Boecher: Employee of Boehringer Ingelheim.
S. Padula: Steven Padula: Employee of Boehringer Ingelheim.
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J.S. Fine: Jay S. Fine: Employee of Boehringer Ingelheim.
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OP104 EFFICACY OF USTEKINUMAB FOR INDUCTION AND MAINTENANCE OF ENDOSCOPIC HEALING IN PATIENTS WITH CROHN'S DISEASE

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Introduction: Ustekinumab (UST) has been shown to induce & maintain clinical response & remission in 2 induction (UNITI-1&2) & 1 maintenance (IM-UNITI) trials in moderate-severe Crohn's disease (CD). A substudy evaluated the efficacy of UST in the induction & maintenance of endoscopic healing.

Aims & Methods: Patients in the substudy had up to 3 colonoscopy evaluations (i.e. at UNITI-1 or 2 baseline [BL] and Wk8, and IM-UNITI Wk44) in 5 ileocolonic segments (i.e. ileum, right colon, transverse colon, left colon, rectum) within the 52-Wk study period. A single central reader blindly scored all video endoscopies for ulcerations and simplified endoscopic activity score for CD (SES-CD). At induction Wk0, patients received a single IV dose (UST 130 mg, UST ~6 mg/kg, or PBO). At maintenance Wk0 (i.e. induction Wk8), UST induction responders [Primary randomized maintenance population] were re-randomized to subcutaneous (SC) PBO, UST 90 mg every 12 wks (q12w), or UST 90 mg every 8 wks (q8w). For the 3 non-randomized maintenance groups: (1)UST induction non-responders received SC UST 90 mg, then continued SC UST 90 mg q8w if CDAI decreased ≥100 after 8wks; (2)PBO induction nonresponders received UST IV 130 mg, then continued SC UST 90 mg q12w if CDAI decreased ≥100 after 8wks; and (3)PBO induction responders received PBO throughout. Patients with SES-CD ≥3 (i.e. ulceration in any segment) at induction BL were eligible for analysis. The primary endpoint was change in SES-CD from BL at induction Wk8 in the integrated UST group (data across induction studies & dose groups) vs PBO. Efficacy at IM-UNITI Wk44 was evaluated in the primary randomized maintenance population and the post-hoc pooled maintenance population (i.e. randomized & nonrandomized IM-UNITI populations combined). Additional induction & maintenance endpoints included clinically meaningful endoscopic improvement, endoscopic response, endoscopic remission & mucosal healing; in both combined and individual treatment groups.

Results: The substudy primary endpoint was met, as UST induced significantly greater reduction in SES-CD from BL at Wk8 vs PBO. Results were similar by induction study & UST dose. Other induction endoscopic endpoints also consistently favored UST vs PBO (Table 1a). At IM-UNITI Wk44, trends for greater efficacy with UST vs. PBO maintenance, especially UST 90 mg q8w, was observed in the primary randomized maintenance population, but small sample sizes (UST n = 46; PBO n = 24) precluded definitive conclusions. In the larger post-hoc pooled maintenance population (Table 1b), consistent trends in support of UST maintenance, especially UST 90 mg q8w, were observed across endoscopic endpoints at Wk44.

Table 1a: Induction Week 8 (UNITI-1&2)

	PBO (N = 97)	UST (N = 155)
SES-CD Change from BL, mean (SD)[8]	−0.7 (4.97)	−2.8 (8.10)*
Clinically meaningful endoscopic improvement[1]	29.9%	47.7%*
Endoscopic Response[2]	13.4%	20.6%
Endoscopic Remission[3]	4.1%	7.7%
Mucosal Healing[4]	4.1%	9.0%

(Table 1b) Maintenance Week 44 (IM-MUNITI)

	PBO (N = 51)	90 mg q12w (N = 47)	90 mg q8w (N = 74)
SES-CD Change from BL, mean (SD)	−2.0 (5.35)	−1.5 (4.22)	−3.8 (6.02)
Clinically meaningful endoscopic improvement[1]	27.5%	29.8%	48.6%*
Endoscopic Response[2]	4.2%	5.9%	24.1%*
Endoscopic Remission[3]	9.8%	12.8%	20.3%
Mucosal Healing[4]	9.8%	12.8%	21.6%

*P < 0.05 [8]Primary endpoint [1]SES-CD reduction ≥3 from induction BL [2]SES-CD reduction ≥50% from induction BL [3]SES-CD total score ≤2 [4]Complete absence of ulcers

Conclusion: The endoscopy substudy primary endpoint was met; a single IV dose of UST induced significantly greater reduction in endoscopic disease activity vs PBO, despite a relatively early evaluation at Wk8. Results in the small primary randomized maintenance population were supported by the larger post-hoc pooled maintenance population; greater proportions of subjects receiving UST maintenance, especially UST 90 mg q8w, achieved maintenance endoscopic endpoints vs PBO. Together, these data support the efficacy of UST in inducing & maintaining endoscopic healing of the mucosa in CD.

Disclosure of Interest: P. Rutgeerts: Investigator for Janssen Research and Development, LLC
C. Gasink: Employee of Janssen Research and Development, LLC
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OP105 FILGOTINIB, A SELECTIVE JAK1 INHIBITOR, INDUCES CLINICAL REMISSION IN PATIENTS WITH MODERATE-TO-SEVERE CROHN'S DISEASE: FINAL ANALYSIS OF THE PHASE 2 FITZROY STUDY

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Introduction: Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor, which has demonstrated high efficacy in patients with rheumatoid arthritis. This 20-week Phase 2 study was designed to evaluate the efficacy and safety of filgotinib in patients with active Crohn's disease (CD).

Aims & Methods: 174 patients with moderate-to-severe CD (CDAI: 220 to 450, endoscopic evidence of active disease) were randomized 3:1 to receive 200 mg filgotinib (FIL) or placebo (PBO) QD for 10 weeks. Based on Week 10 clinical response, patients continued to receive filgotinib (200 mg or 100 mg QD) or placebo for an additional 10 weeks. Patients who demonstrated clinical response (CDAI-100) underwent corticosteroid tapering after Week 10. Anti-TNF-naïve as well as anti-TNF non-responders were included. Immunosuppressants were to be discontinued prior to treatment initiation. Final data for the primary endpoint of clinical remission (CDAI < 150) at Week 10 are presented.

Results: Baseline characteristics were comparable in both groups, including mean disease duration (8.3 y), mean CDAI score (293), mean CRP (15.6 mg/L, 41% > 10 mg/L), oral corticosteroids (51%, mean daily dose 21.6 mg/day). Primary endpoint of the study was met: Filgotinib induced clinical remission in 47% of the patients, compared to 23% in placebo recipients (p = 0.0077), and led to improvement in PRO2 score, and quality of life (IBDQ changes from baseline) compared to placebo (table 1). Numerically more patients on filgotinib normalized CRP (FIL:27%, PBO:14%) and showed an improvement of at least 50% in SES-CD endoscopy score (FIL:25%, PBO:13.6%), Histopathology overall total score was decreased more significantly in the filgotinib group compared to placebo (p < 0.05).

Table 1: Key efficacy parameters

Variable/unit/population	Placebo n = 44	filgotinib n = 128	p-value
Clinical remission (CDAI < 150), %, ITT-NRI	23	47	0.0077
PRO2, mean change from baseline, ITT-LOCF	−15.6	−21.9	0.0321
	17.6	33.8	0.0045

(continued)

Table 1 Continued

Variable/unit/population	Placebo n = 44	filgotinib n = 128	p-value
Total IBDQ score, mean change from baseline, ITT-LOCF			
SES-CD improvement by at least 50%, %, ITT-LOCF	13.6	25	NS
overall total histopathology score, mean change from baseline, ITT-LOCF	–0.6	–3.5	0.0359

CDAI: Crohn's Disease Activity Index; ITT: Intent-to-treat; NRI: Non-responder imputation; LOCF: Last observation carried forward; PRO2: Patient Reported Outcome = 7x (mean daily number of liquid or very soft stools) + 7x (mean daily abdominal pain score); IBDQ: Inflammatory Bowel Disease Questionnaire; SES-CD: Simple Endoscopic Score for Crohn's Disease; Histopathology score = Adaptation from histopathology score D'haens Overall, filgotinib was safe and well tolerated. Similar incidences in early discontinuations, SAEs and AEs including infections were observed, with the majority of the SAEs related to worsening of CD. An increase in mean haemoglobin concentration was observed, without difference between filgotinib and placebo. No clinically significant changes from baseline in mean neutrophil counts or liver function tests were observed. Filgotinib showed a favourable lipid profile with an increase in HDL and no change in LDL, resulting in an improved atherogenic index.

Conclusion: Inhibition of JAK1 with filgotinib induces clinical remission, supported by CRP, endoscopy and histopathology results, and improves quality of life in patients with moderate to severe CD. The efficacy and safety data of filgotinib suggest a favourable risk/benefit profile, showing its potential as an oral treatment with a novel mechanism of action for the treatment of CD.

Disclosure of Interest: S. Vermeire: Grant support: Abbvie, MSD, Takeda Lectures: Abbvie, MSD, Takeda, Ferring, Falk Pharma, Hospira, Tillotts Consultancy: Abbvie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, J&J
S. Schreiber: Paid consultancies to AbbVie, Galapagos, Pfizer, Takeda
T. Kuehbacher: Advising and /or speaking fees for Abbvie Takeda MSD Shire Falk
X. Hebuterne: Educational activities: ARARD, Abbvie, Ferring, MSD, Nutricia Educational activities and consultancy: Takeda Member of board: Janssen, Fresenius-Kabi
X. Roblin: MSD, Abbvie, Takeda, Hospira, Janssen, Theradiag
M. Klopocka: Payment for lectures/ Royalty- Abbvie, Alvogen, Takeda, Polish Foundation for Gastroenterology Travel/accommodations/ meeting expenses Ferring, Alvogen, Abbvie, Polish Foundation for Gastroenterology
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P. Harrison: employee of Galapagos NV
All other authors have declared no conflicts of interest.

OP106 TOFACITINIB HAS INDUCTION EFFICACY IN MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS, REGARDLESS OF PRIOR TNF INHIBITOR THERAPY

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Introduction: Tofacitinib is an oral, small molecule JAK inhibitor that is being investigated for ulcerative colitis (UC). Two Phase 3 randomised placebo (PBO)-controlled studies (OCTAVE Induction 1, NCT01465763; OCTAVE Induction 2, NCT01458951) demonstrated efficacy of tofacitinib 10 mg twice daily (BID) vs PBO as induction therapy for patients (pts) with moderate to severe UC.[1]

Aims & Methods: We investigated the effect of prior tumour necrosis factor inhibitor (TNFi) therapies or disease activity (baseline Mayo score) on clinical efficacy endpoints and patient-reported outcomes (PROs) in pooled data from OCTAVE Induction 1 and 2. Adults with moderately to severely active UC (baseline Mayo score ≥6, rectal bleeding subscore ≥1 and endoscopic subscore ≥2) and prior failure/intolerance to ≥1 of corticosteroids, thiopurines or TNFi were randomised (4:1) to receive tofacitinib 10 mg or PBO BID for up to 9 weeks (wks). Efficacy endpoints at Wk 8 included: remission (primary endpoint; Mayo score ≤2, no subscore >1 and rectal bleeding subscore of 0), mucosal healing at Wk 8 (Mayo endoscopic subscore ≤1), clinical response (decrease from baseline Mayo score of ≥3 points and ≥30%, plus decrease in rectal bleeding subscore ≥1 or absolute subscore ≤1). All endoscopic scores were read centrally. PROs at Wk 8 included Inflammatory Bowel Disease Questionnaire (IBDQ) remission (total score ≥170) and IBDQ response (≥16-point increase from baseline). For binary endpoints, the comparison of tofacitinib 10 mg BID vs PBO was assessed using the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by study, prior TNFi treatment, corticosteroid use at baseline and geographic region. Within each subgroup, the CMH chi-square test stratified by study was used.

Results: At Wk 8, significantly more pts achieved remission, mucosal healing and clinical response with tofacitinib 10 mg BID vs PBO (all $p < 0.0001$, Table). The difference generally remained significant regardless of prior TNFi exposure, prior TNFi failure, reason for TNFi failure (primary or secondary) or disease severity (based on baseline Mayo score ≥9 or <9; Table). For all three endpoints, greater effects were observed when comparing secondary vs primary TNFi failure subpopulations and baseline Mayo score <9 vs baseline Mayo score ≥9. IBDQ remission and response were significantly greater with tofacitinib 10 mg BID vs PBO at Wk 8 regardless of prior TNFi exposure/prior TNFi failure.

Conclusion: Tofacitinib demonstrated efficacy vs PBO, regardless of prior TNFi therapy in pts with moderately to severely active UC. PRO results were similar in pts with/without prior TNFi exposure or failure.

Table: Summary of efficacy endpoints in OCTAVE Induction 1 and OCTAVE Induction 2 at Wk 8

10 mg BID N = 905	Tofacitinib Placebo N = 234	Difference (95% CI)	
Remission, n (%)[i]	159 (17.6)	14 (6.0)	11.6 (7.7, 15.5)***
Prior TNFi exposure[a]	60 (12.3)	1 (0.8)	11.5 (8.2, 14.8)***
No prior TNFi exposure[b]	99 (23.7)	13 (12.5)	11.2 (3.7, 18.8)*
Prior TNFi failure[c]	53 (11.4)	1 (0.8)	10.6 (7.3, 13.9)**
No prior TNFi failure[d]	106 (24.1)	13 (11.8)	12.3 (5.0, 19.5)*
Prior TNFi failure (primary non-responder)[e]	19 (7.5)	1 (1.4)	6.2 (2.0, 10.3)*
Prior TNFi failure (secondary non-responder)[f]	31 (16.6)	0 (0.0)	16.6 (11.2, 21.9)*
Baseline Mayo score <9[g]	91 (28.3)	6 (7.3)	21.0 (13.5, 28.5)***
Baseline Mayo score ≥9[h]	68 (11.7)	8 (5.3)	6.4 (2.0, 10.8)*
Mucosal healing, n (%)[i]	271 (29.9)	32 (13.7)	16.3 (11.0, 21.6)***
Prior TNFi exposure[a]	112 (23.0)	8 (6.2)	16.8 (11.2, 22.4)***
No prior TNFi exposure[b]	159 (38.1)	24 (23.1)	15.1 (5.7, 24.4)*
Prior TNFi failure[c]	103 (22.2)	8 (6.5)	15.7 (10.0, 21.4)***
No prior TNFi failure[d]	168 (38.2)	24 (21.8)	16.4 (7.4, 25.3)*
Prior TNFi failure (primary non-responder)[e]	38 (15.0)	5 (6.8)	8.3 (1.0, 15.5)NS
Prior TNFi failure (secondary non-responder)[f]	57 (30.5)	2 (4.7)	25.8 (16.7, 34.9)**
Baseline Mayo score <9[g]	145 (45.2)	17 (20.7)	24.4 (14.1, 34.8)***
Baseline Mayo score ≥9[h]	126 (21.6)	15 (9.9)	11.7 (5.9, 17.5)*
Clinical response, n (%)[i]	521 (57.6)	72 (30.8)	26.8 (20.1, 33.5)***
Prior TNFi exposure[a]	254 (52.0)	29 (22.3)	29.7 (21.3, 38.2)***
No prior TNFi exposure[b]	267 (64.0)	43 (41.3)	22.7 (12.2, 33.2)***
Prior TNFi failure[c]	237 (51.0)	29 (23.4)	27.6 (18.9, 36.3)***
No prior TNFi failure[d]	284 (64.5)	43 (39.1)	25.5 (15.3, 35.6)***
Prior TNFi failure (primary non-responder)[e]	116 (45.8)	19 (25.7)	20.2 (8.5, 31.9)*
Prior TNFi failure (secondary non-responder)[f]	102 (54.5)	9 (20.9)	33.6 (19.5, 47.7)**
Baseline Mayo score <9[g]	205 (63.9)	30 (36.6)	27.3 (15.6, 39.0)***
Baseline Mayo score ≥9[h]	316 (54.3)	42 (27.8)	26.5 (18.3, 34.7)***

Full analysis set, non-responder imputation [NS]Not significant; *$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$ vs placebo 95% confidence interval was based on normal approximation for the difference in binomial proportions [a]N = 488 for tofacitinib 10 mg BID and N = 130 for placebo; [b]N = 417 for tofacitinib 10 mg BID and N = 104 for placebo;[c]N = 465 for tofacitinib 10 mg BID and N = 124 for placebo; [d]N = 440 for tofacitinib 10 mg BID and N = 110 for placebo; [e]N = 253 for tofacitinib 10 mg BID and N = 74 for placebo; [f]N = 187 for tofacitinib 10 mg BID and N = 43 for placebo; [g]N = 321 for tofacitinib 10 mg BID and N = 82 for placebo; [h]N = 582 for tofacitinib 10 mg BID and N = 151 for placebo; [i]statistical significance based on the Cochran-Mantel-Haenszel chi-squared test stratified by study, prior treatment with tumour necrosis factor inhibitors, corticosteroid use at baseline and geographic region BID, twice daily; CI, confidence interval; TNFi, tumour necrosis factor inhibitor; Wk, week

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W.J. Sandborn: Study-related disclosures: Dr Sandborn received grant support, personal fees and non-financial support from Pfizer during the conduct of the study; grant support from Pfizer
T. Hibi: Grants, personal fees: Mitsubishi Tanabe Pharma, Ajinomoto Phama, JIMRO, Zeria Pharma Grants: Abbvie Personal fees: Eizai, Takeda Pharma

C. Su: Employee and shareholder: Pfizer Inc
W. Niezychowski: Employee and shareholder: Pfizer Inc
S. Ghosh: Consultant: Abbott, Pfizer Inc, Merck, Shire, Centocor, BMS Research grants: Merck, Abbott Lectures: Abbott, Merck, Shire, Millenium, Centocor and Ferring Development of educational presentation: Abbott.
H. Zhang: Employee and shareholder: Pfizer Inc
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D. Woodworth: Employee and shareholder: Pfizer Inc
P. Healey: Employee and shareholder: Pfizer Inc
A. Marren: Employee and shareholder: Pfizer Inc
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Reference

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OP107 CLINICAL DISEASE ACTIVITY INFLUENCES THE THERAPEUTIC EFFICACY OF THE TOLL LIKE RECEPTOR-9 AGONIST COBITOLIMOD IN PATIENTS WITH MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS

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Introduction: In the COLLECT study the Toll like receptor (TLR-) 9 agonist cobitolimod (formerly known as DIMS0150, Kappaproct®) was evaluated for its therapeutic efficacy in ulcerative colitis (UC) patients refractory to conventional therapy.
Aims & Methods: In this post hoc analysis the therapeutic effects were analysed with respect to disease activity of the patients at baseline. Cobitolimod was studied in a randomized, double blind, placebo-controlled, multicentre, pan-European trial named COLLECT in 131 patients with moderate to severe active ulcerative colitis. Patients were on mandatory steroid therapy and could be taking sulphasalazine, aminosalicylates, or thiopurines at stable doses. Patients were randomly assigned to receive two single doses of cobitolimod (30 mg) or placebo (in a 2:1 ratio) topically through the endoscope to the inflamed mucosa at baseline (week 0) and after 4 weeks (week 4). For this post-hoc analysis efficacy was studied using the secondary endpoint symptomatic remission (SR) (absence of blood in stool and mean weekly stools < 35) at week 4, 8 and 12. As endoscopic examination was performed at week 4 and 12 symptomatic remission in combination with mucosal healing (MH) defined as endoscopic Mayo score of ≤ 1 were assessed at week 4 and 12. Disease activity was measured using the CAI score, which ranges from 0–23. In the FAS (full analysis set) population 28% of the patients had moderate disease (CAI = 9), 46% had moderate to severe disease setting (CAI = 10–11), while 26% had severe disease (CAI $\geq$ 12) at baseline.
Results: In the moderate UC patient population (CAI = 9) symptomatic remission was achieved in 50/64/59% of the cobitolimod vs. 15/23/23% of placebo-treated patients at week 4/8/12, respectively. In the moderate to severe UC patient population (CAI = 10–11) symptomatic remission was evident in 32/40/46% of the cobitolimod vs. 15/35/40% in placebo-treated patients at week 4/8/12, respectively. In the severe UC patient population (CAI = 12 and more) 14/31/22% of the cobitolimod vs. 10/20/30% of the placebo-treated patients showed symptomatic remission at week 4/8/12. With respect to the endpoint symptomatic remission plus mucosal healing the patients with moderate disease showed remission rates of 32/40% for cobitolimod vs. 8/8% for placebo-treated patients at week 4/12, respectively. In patients with moderate to severe disease rates for SR plus MH were 22/35% in the cobitolimod vs. 0/35% in placebo-treated patients at week 4/12, respectively. In patients with severe disease these rates were 9/18% in the cobitolimod vs. 0/20% in placebo-treated patients for week 4/12, respectively.
Conclusion: The results of the COLLECT study demonstrate that the TLR-9 agonist cobitolimod is able to induce clinical remission in UC patients both with moderate and severe disease activity. The concept of TLR-9 activation represents a promising and well-tolerated novel therapeutic option for ulcerative colitis patients with active disease and warrants further trials.
Disclosure of Interest: R. Atreya: Consultancy for Index Pharmaceuticals
L. Peyrin-Biroulet: Consultancy for Index Pharmaceuticals
W. Reinisch: Consultancy for Index Pharmaceuticals
F. Scaldaferri: Consultancy for Index Pharmaceuticals
C. Admyre: Employment at and stock options of Index Pharmaceuticals
T. Knittel: Consultancy for and share holding of Index Pharmaceuticals
J. Kowalski: Consultancy for and share holding of Index Pharmaceuticals
M.F. Neurath: Consultancy for Index Pharmaceuticals
C.J. Hawkey: Consultancy for Index Pharmaceuticals

OP108 SAFETY AND EFFICACY OF LONG-TERM TREATMENT WITH OZANIMOD, AND ORAL S1P RECEPTOR MODULATOR, IN MODERATE TO SEVERE ULCERATIVE COLITIS: TOUCHSTONE EXTENSION

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Introduction: Ozanimod (RPC1063) is an oral, selective sphingosine 1-phosphate (S1P) 1 and 5 receptor modulator in clinical development for the treatment of Inflammatory Bowel Disease (ulcerative colitis [UC] and Crohn's disease) and relapsing multiple sclerosis. The objective of the open-label extension (OLE) of the TOUCHSTONE trial is to evaluate the long-term efficacy and safety of daily 1 mg ozanimod in patients with moderate to severe UC who had initially participated in the TOUCHSTONE trial.
Aims & Methods: A total of 197 patients were randomized (1:1:1) and treated with daily ozanimod at 0.5 mg, 1 mg (n = 67), or placebo in the TOUCHSTONE trial. Of the initial 197 patients randomized 170 (86%) entered the OLE and received daily 1 mg ozanimod with 109 (64%) remaining in the OLE as of the data cut-off (March 2016). At the data cut-off, all remaining patients had received treatment in the OLE for $\geq$ 1 year.
Results: At entry into the OLE, the partial Mayo Score (pMS) for patients on placebo, ozanimod 0.5 mg, and 1.0 mg was 4.6, 4.5, and 3.3 respectively. At the time of the data-cut in the OLE, the pMS had improved in all groups (1.7, 1.7, and 1.9) at Week 44. The greatest improvement was reported in patients who received placebo or ozanimod 0.5 mg in the TOUCHSTONE trial with a change in pMS at Week 44 of –2.6, –2.7 and –1.3 in the placebo, 0.5 mg and 1 mg groups. Improvement occurred rapidly, in the first 4 to 8 weeks of the OLE. The greatest improvement was reported for patients who received placebo or ozanimod 0.5 mg in the TOUCHSTONE trial with a change in pMS at Week 4 of –1.8, –1.5 and –0.8 and a change in pMS at Week 8 of –2.4, –1.9 and –1.1 in the placebo, 0.5 mg and 1 mg groups. At the Week 44 visit in the OLE, 119/131 (90.9%) had little or no active disease based on the physician global assessment (PGA 0 or 1), 129/131 (98.4%) had little or no blood in their stools (rectal bleeding subscore [RBS] 0 or 1), 111/131 (84.7%) had no blood in the stools (RBS 0), and 105/131 (80.2%) had little or no increase in their number of stools (Stool Frequency subscore of 0 or 1). The most common adverse events (AEs) (>2.0%) during OLE were UC flare, anemia, upper respiratory tract infection, nasal pharyngitis, back pain, arthralgia, headache, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation. The only serious AEs in $\geq$2 patients were anemia, and ulcerative colitis flare. ALT and AST > 3x upper limit of normal occurred in 4 (2.4%) of the 170 patients in the OLE. All elevations were asymptomatic, <5xULN, transient, and resolving while receiving continued treatment.
Conclusion: Long-term treatment with ozanimod continues to be safe and well tolerated with good compliance and evidence of durable efficacy.
Disclosure of Interest: W.J. Sandborn: William J. Sandborn receives financial support for research and consultancy fees from Celgene, Inc.
B.G. Feagan: Brian G. Feagan receives consulting fees from Celgene, Inc.
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P.A. Frohna: Paul A. Frohna is an employee of Celgene, Inc.
R. Aranda: Richard Aranda is an employee of Celgene, Inc.

MONDAY, OCTOBER 17, 2016 15:45–17:15

NON-BLEEDING EMERGENCIES OF THE OESOPHAGUS – ROOM E1

OP109 SELF ASSEMBLING PEPTIDE MATRIX FOR THE PREVENTION OF ESOPHAGEAL STRICTURE AFTER ENDOSCOPIC RESECTION: A RANDOMIZED CONTROLLED TRIAL IN A PORCINE MODEL

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Introduction: Esophageal stricture formation after extensive endoscopic resection remains a major limitation of endoscopic therapy for early esophageal neoplasia.

We assessed a recently developed self-assembling peptide matrix as a wound dressing after endoscopic resection for the prevention of esophageal stricture.
Aims & Methods: Ten pigs were randomly assigned to the self-assembling peptide RADA-16 (4 [Arg-Ala-Asp-Ala]) or the control group after undergoing a 5 cm long circumferential endoscopic submucosal dissection of the lower esophagus. Esophageal diameter on endoscopy and esophagogram, weight variation, and histological measurements of fibrosis, granulation tissue, and neoepithelium were assessed in each animal.
Results: The rate of esophageal stricture at day 14 was 40% in the group treated with self-assembling peptide vs. 100% in the control group ($p = 0.04$). Median (IQR) esophageal diameter at day 14 was 8 mm (2.5–9) in the self-assembling peptide group vs. 4 mm (3–4) in the control group ($p = 0.13$). The median (IQR) stricture indexes on esophagograms at day 14 were 0.32 (0.14–0.48) and 0.26 (0.14–0.33) in treated and control groups, respectively ($p = 0.42$). Median (IQR) weight variation during the study was +0.2 (−7.4; +1.8) and −3.8 (−5.4; +0.6) in the treated and control groups, respectively ($p = 0.9$). No differences were observed between the groups in terms of histological outcomes. All animals eventually developed esophageal strictures at day 28.
Conclusion: The application of a self assembling peptide matrix on esophageal wounds after circumferential endoscopic submucosal dissection is safe and feasible, and prevents early esophageal stricture occurence in our model.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP110 INTRALESIONAL STEROID INJECTION COMBINED WITH ORAL STEROID ADMINISTRATION TO PREVENT ESOPHAGEAL STRICTURE AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION OF LESION NO LESS THAN A HALF OF CIRCUMFERENCE

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Introduction: Endoscopic submucosal dissection (ESD) is becoming an important and main therapy for early esophagus carcinoma or precancerous lesion. However, stricture ofter occurs when the mucosal defects created by ESD are larger than a half of circumference. It's an urgent task to find out a safe and effecient method to prevent stenosis.
Aims & Methods: To investigate the safety and efficiency of local steroid injection combined with oral steroid administration in preventing esophageal stricture after ESD of esophagus carcinoma or precancerous lesion which are no less than a half of circumference. A single-center randomized controlled trial was designed to examine the effects and safety of intralesional steroid injection combined with oral steroid administration in preventing stricture after esophageal ESD. 43 patients with mucosal defects no less than a half of circumference following esophageal ESD were randomized to receive intralesional triamcinolone injection immediately after ESD and oral prednisone administration for consecutive 12 weeks, which starting at a dose of 30 mg daily, tapered gradually at a speed of 5 mg in every two weeks ($n = 20$, treatment group) or to be treated conventionally ($n = 23$, control group). The primary endpoint was the frequency of stricture. Secondary endpoints were the number of balloon dilatation, rate of other complications and hospital stays.
Results: The frequency of stricture (20% vs. 69.6%) and the number of balloon dilatation (mean 0.5 vs. 1.3) were less in treatment group, and the former one had a significant difference. The hospital stays and rate of complications were similar between two groups. One patient suffered perforation of stomach in the treatment group, which was not a direct result of steroid injection or ESD.

Frequency of stricture formation, number of endoscopic balloon dilations (EBDs) performed, hospital stays after ESD and other complications in two groups.

	Treatment group (n = 20)	Control group (n = 23)	p-value
Frequency of stricture, n (%)	5(20)	16(69.6)	0.004*
Number of EBDs, n mean ± SD (range)	0.5 ± 1.1 (0–3)	1.3 ± 2.0 (0–8)	0.241
Perforation by procedure, n per session (%)	1/30 (3.7)	0/53(0)	0.361
Bleeding by procedure, n per session (%)	0/30(0)	1/53(1.9)	1.0
Hospital stays after ESD, days mean ± SD (range)	4.1 ± 4.4 (1–22)	3.3 ± 2.0 (1–8)	0.469

*Significant difference

Conclusion: Intralesional steroid injection combined with oral steroid administration appears to be safe and effective in preventing esophageal stricture following ESD of lesions no less than a half of circumference.
Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 15:45–17:15
HOT TOPICS IN ERCP – ROOM K

OP111 CLINICAL UTILITY OF SINGLE OPERATOR CHOLANGIOSCOPY USING SPYGLASS™ DS COMPARED WITH SPYGLASS™ LEGACY – RESULTS FROM A LARGE MULTI-NATIONAL REGISTRY

J.H. Moon[1], M. K. Ramchandani[2], A. Maydeo[3], T. Itoi[4], R. Rerknimitr[5], D. Seo[6], J. Y. w. Lau[7], M.K. Goenka[8], A. Aljebreen[9], S. Niaz[10], J. Lee[11], T. Ang[12], N. Q. Nguyen[13], J. Reichenberger[14], R. Sud[15], R. Kochhar[16], B. Devereaux[17], I. Yasuda[18], A. J. Kaffes[19], M. Kitano[20]
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Introduction: Addition of single operator cholangioscopy (SOC) to endoscopic retrograde cholangiography (ERC) may improve diagnostic accuracy and increase therapeutic efficiency in bile duct diseases. Indications for SOC, procedural success and impact on subject management are investigated in a multinational prospective registry.
Aims & Methods: SOC registry using the SpyGlass™ Legacy (Spy Legacy) or new SpyGlass DS™ (Spy DS) system and SpyBite™ biopsy forceps (Boston Scientific Corp, Marlboro, MA, USA) at 20 centers in 10 countries. The registry was not designed as a comparative study. Procedural success defined as: Group A: Indeterminate strictures/filling defects: ability to visualize lesions, provide visual impression of malignancy, and, when applicable, obtain biopsies adequate for histology. Group B: Biliary stones: ability to achieve stone clearance in one or more SOC procedures. Group C: Other indications: ability to establish diagnosis and/or complete therapy as intended.
Results: Total of 504 patients (pts) have completed primary endpoint information, 207 (41%) pts using Spy DS. Average age 61 years, 54% male. Indications for SOC were Group A in 278 (55%) pts, Group B in 190 (38%) pts and Group C in 62 (12%) pts, principally including pre-operative assessment of tumor margins (20), confirmation of stone clearance (15), selective guidewire placement (8), extraction of migrated stent (5) assessment of cause of occluded self-expanding metal stent (3), unexplained hemobilia (3), dilated left hepatic duct (2), and presence of residual IPNB after photodynamic therapy (1). Investigators rated image quality as "Excellent or Good" in 98% Spy DS cases and 78% of Spy Legacy cases ($P < 0.0001$). Procedural success was reached in 504 (84%) procedures overall, namely in 279 (85%) procedures in Group A, 190 (82%) in Group B, and 56 (89%) in Group C. Thirteen (7%) pts in Group B required 2 or more SOC procedures to reach stone clearance. Failures were inability to provide impression of malignancy (31 Group A), intraductal biopsies not yielding determinate histopathology (8 Group A), inability to reach stone clearance (33 Group B), inability to assess ductal tumor (3 Group C) and failed guidewire placement (3 Group C). Overall procedural success trended to be higher in Spy DS than in Spy Legacy group namely 86% (178/207) versus 82% (244/297) ($p = 0.262$). SOC

altered diagnosis/therapy and/or influenced management in 417 (85%) pts. Malignant visual impression as a predictor for malignant pathology of SpyBite biopsies is better for Spy DS than Spy Legacy ($p = 0.014$). Adverse events in 7 (1%) pts: 2 mild pancreatitis, 2 mild and 1 moderate cholangitis, 1 moderate bleeding and 1 micro perforation.
Conclusion: SOC, especially using Spy DS, has high procedural success and provides important impact on diagnosis, therapy and/or management in a wide range of indications, with excellent safety profile.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP113 PROPOSAL OF A MACROSCOPIC CLASSIFICATION FOR TISSULAR LESIONS OF THE BILE DUCT DETECTED DURING PER ORAL CHOLANGIOSCOPY (POCS)

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Introduction: The macroscopic aspects to determine malignancy of the bile duct during per oral cholangioscopy (POCS) are: presence of irregular surface with bleeding and drooling or tortuous vessels. For benign lesions the typical aspects are lesions with smooth surface ''without vessels or mass''. However, many misdiagnosis are made due to a lack of correlation between the macroscopic aspects and histology. Moreover, masses are many times benign, and reported data shows 78% of sensitivity for visual impression diagnosing malignancy.
Aims & Methods: Propose a macroscopic classification of bile duct tissular lesions for differentiation between benign and malignant lesions.
A retrospective study from Sept-2013 to Sept-2015 was made at our institution in patients evaluated by POCS (using SpyGlass® legacy and DS). Inclusion criteria: tissular lesions detected by POCS. Exclusion criteria: absence of histology confirmation (either biopsy or surgical resection for malignancy) and/or absence of POCS at 6 months follow-up (for benign lesions). To determine the macroscopic classification all patients' records were evaluated. 315 images were analyzed and classified as benign or malignant by an expert with more than 140 POCS cases, and compared to histology. Based on the morphological and vascular pattern the lesions were classified as follows:
Benign lesions: Type 1 ''Villous pattern'' (micronodular or villous pattern without vascularity), Type 2 ''Polypoid pattern'' (adenoma or granuloma pattern without vascularity) and Type 3 ''Inflammatory pattern'' (regular or irregular fibrous and congestive pattern with regular vascularity). Malignant lesions: Type 1 ''Flat pattern'' (flat and smooth or irregular surface with irregular or spider vascularity); Type 2 ''Polypoid'' (polypoid or mass with fibrosis and irregular or spider vascularity), Type 3 ''ulcerated'' (irregular pattern ulcerated and infiltrative with or without fibrosis with irregular or spider vascularity) and type 4 ''honey-comb pattern'' (fibrous honey-comb pattern with or without irregular or spider vascularity). Inter-observer and intra-observer agreement was calculated using 40 random images of lesions for 1 expert and 2 non-expert in POCS. Finally a prospective, non randomized, double blind evaluation of diagnostic accuracy, sensitivity, specificity, PPV, NPV using the new classification was performed for consecutive tissular lesions detected from Oct-2015 to April-2016 correlated with histology.
Results: 130 patients were studied, (retrospective: 87 / prospective: 43); 30 female, mean age 61 (50–74). Absence of statistical difference in genre (p value = 0.606) or age ($p = 0.107$) between groups. For retrospective evaluation 46/87 patients were evaluated, 21 female, mean age 61 (52–73). 18/46 cases were malignant and 28/46 benign. The overall interobserver agreement was substantial when lesions were classified as benign or malignant ($K = 0.75$ – CI 0.46–0.89) and when lesions were classified by sub-types ($K = 0.71$ – CI 0.39–0.88).The intraobserver agreement was almost perfect when lesions were classified as benign and malignant ($K = 0.88$ – CI 0.66–1.0) and when lesions were classified by sub-types ($K = 0.90$ – CI 0.71–1.0). For the prospective evaluation 23/43 patients were evaluated, 9 female, mean age 61 (48–72) years old. 13/23 cases were malignant and 10/23 benign. The accuracy was 86.9%, sensitivity 100%, specificity 70%, PPV 81.3%, NPV 100%.
Conclusion: The proposed macroscopic classification could help physicians to distinguish benign from malignant lesions with a good inter and intra-observer concordance.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP114 RECTAL INDOMETHACIN MAY NOT DECREASE THE INCIDENCE OF POST-ERCP PANCREATITIS IN CONSECUTIVE PATIENTS: A META-ANALYSIS OF RANDOMIZED AND CONTROLLED TRIALS

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Introduction: Data on the efficacy of prophylactic rectal indomethacin to prevent post-ERCP pancreatitis in consecutive patients is inconsistent. We therefore conducted a meta-analysis of high-quality randomized clinical trials specifically studying rectal indomethacin in prevention of post-ERCP pancreatitis in consecutive patients.
Aims & Methods: Relevant studies for the meta-analysis were identified through search of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases. Randomized controlled clinical trials employing rectal indomethacin for the prevention of post-ERCP pancreatitis were included. The primary outcome was the overall rates of post-ERCP pancreatitis.
Results: A total of 2473 patients from 6 studies were included. The incidence of post-ERCP pancreatitis across all 2473 patients was 7% (95% CI, 6%–9%). We found that there was no significant difference in overall rates of post-ERCP pancreatitis in consecutive patients between rectal indomethacin and placebo (OR, 0.67; 95% CI, 0.46–1.00, $p = 0.050$). There was also no difference in rates of moderate to severe (OR, 0.66; 95% CI, 0.28–1.56, $p = 0.345$) or mild (OR, 0.71; 95% CI, 0.45–1.10, $p = 0.127$) post-ERCP pancreatitis between indomethacin and placebo.
Conclusion: In a contemporary meta-analysis of available randomized controlled trials of consecutive patients undergoing ERCP, rectal indomethacin did not show significant prevention effect of post-ERCP pancreatitis.
Disclosure of Interest: U. Navaneethan: Udayakumar Navaneethan is a consultant for AbbVie, Janssen and Takeda.
S. Varadarajulu: Shyam Varadarajulu is a consultant for Boston Scientific and Olympus.
R. Hawes: Robert Hawes is a consultant for Olympus and Boston Scientific.
All other authors have declared no conflicts of interest.

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Table (OP114)

Characteristics of Included Trials

	Montano Loza, 2007	Sotoudehmanesh, 2007	Dobronte, 2012	Dobronte, 2014	Patai, 2015	Levenick, 2016
Methodology						
Intervention	100 mg PR before ERCP	100 mg PR before ERCP	100 mg PR before ERCP	100 mg PR before ERCP	100 mg PR before ERCP	100 mg PR during ERCP
Location	Mexico-multicenter	Iran-single center	Hungary-single center	Hungary-multicenter	Hungary-single center	US-single center
Definition of post-ERCP pancreatitis	Clinical, amylase	Clinical, amylase	Pain, amylase, pro-longed admission	Clinical, amylase, pro-longed admission	Pain, amylase, pro-longed admission	Pain, amylase, pro-longed admission
Pancreatic stent used?	Yes (10 cases in indo-methacin group; 9 cases in placebo group)	No	N/A	No	No	Yes (36 cases in indo-methacin group; 35 cases in placebo group)
Randomization						
Total randomized	150	490	228	686	539	449
Total analysed	150	442	228	665	539	449
Indomethacin	75	221	130	347	270	223
Placebo	75	221	98	318	269	226
Baseline demographics						
Mean age (y)						
Indomethacin	55	58	66	66	66	65
Placebo	51	58	67	68	65	64
% Female						
Indomethacin	65	56	63	62	67	53
Placebo	68	53	70	67	67	52
Procedure demographics						
% Difficult cannulation						
Indomethacin	N/A	N/A	N/A	18	29	21
Placebo	N/A	N/A	N/A	16	30	19
% Pancreatic duct injection						
Indomethacin	7	20	63	71	23	22
Placebo	8	19	68	68	30	22

OP115 PREVENTION OF POST-SPHINCTEROTOMY BLEEDING BY PROTON PUMP INHIBITOR: A PROSPECTIVE RANDOMIZED TRIAL

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Introduction: Bleeding after endoscopic sphincterotomy (EST) is one of the most frequent complications of therapeutic ERCP. Although the use of proton pump inhibitor (PPI) has been shown to reduce the risk of rebleeding in patients with peptic ulcer bleeding after endoscopic hemostasis, the role of acid suppression in preventing EST bleeding has not been evaluated. We hypothesized that preemptive high dose PPI could reduce the risk of post-EST bleeding.

Aims & Methods: The aim of this study was to study the role of high-dose PPI in patients undergoing EST. It was a prospective randomized open-label study performed in the endoscopy centre of a university teaching hospital. Consecutive patients who were scheduled to have ERCP and EST were enrolled. We excluded patients who had previous EST, prior gastric surgery, or were taking PPIs. Antiplatelet therapies were continued as usual. Anti-coagulants (warfarin or heparin) were stopped with coagulopathy corrected prior to ERCP. Eligible patients were randomized to receive either PPI or standard care (SC). PPI group would receive esomeprazole given intravenously at 80 mg every 12h for Day 1, starting 4 hours prior to ERCP, and followed by oral esomeprazole 40 mg bid from Day 2 to 10. Standard care arm would receive usual care without any acid suppressive therapy. Endoscopists were unaware of the treatment allocation of the patients. Primary outcome was the proportion of patients with immediate or delayed post-EST bleeding. Immediate bleeding was defined as bleeding that occurred during the procedure and required endoscopic hemostasis. Delayed bleeding was defined as bleeding after the completion of ERCP which manifested as overt GIB with melena or hematemesis. All patients were followed up for 30 days. Secondary outcomes included drop in hemoglobin >2 g without overt bleeding, transfusion requirement and all-cause mortality at 30 days. Analysis was based on modified intention-to-treat, which included only randomized patients who had undergone EST.

Results: 196 patients were enrolled and 71 patients did not have EST. The analysis included 125 patients who had undergone EST with 60 in the PPI group and 65 in SC group. The mean age was 70.9 (SD = 14.8) years with 62 (49%) men. The baseline characteristics of the two groups including indications for ERCP, use of anti-platelet agents or anti-coagulants, and comorbidity were comparable. Immediate bleeding was noted in 9 (15%) patients in the PPI group and 4 (6.2%) in the SC groups (P = 0.14). Overt delayed ES bleeding was respectively seen in 2 (3.3%) and 5 (7.7%) patients in PPI and SC arms (P = 0.44). There was also no significant difference in the proportions of patients with hemoglobin drop of >2 g without overt bleeding (Day 10: 13.3% in PPI group and 9.2% in SC group; P = 0.57). Other outcomes including hospital stay (13.1 vs 11.8 days; P = 0.69), transfusion requirement (5% vs 7.7%; P = 0.72) and 30-day mortality (3.3% vs 1.5%; P = 0.61) were also comparable between the PPI and SC groups.

Conclusion: The use of high-dose PPI did not appear to significantly reduce the risk of both immediate and delayed bleeding in patients undergoing EST.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP116 IMPACT OF INTENSIVE HYDRATION ON THE INCIDENCE OF POST-ERCP PANCREATITIS: DOUBLE-BLINDED RANDOMIZED CONTROLLED TRIAL

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Introduction: Pancreatitis is the most frequent complication following endoscopic retrograde cholangiopancreatography (ERCP), with an estimated incidence of 1.6% to 15.7%, depending on patient and procedure-related factors. Intensive hydration with lactated Ringer's solution has been shown in small studies to reduce post-ERCP pancreatitis (PEP) incidence and severity.

Aims & Methods: We aimed to assess whether intensive hydration impacts on the incidence and severity of PEP. We performed a prospective, double-blinded randomized controlled trial, including consecutive patients submitted to ERCP in our institution. Patients with previous sphincterotomy, chronic pancreatitis, heart failure (NYHA $\geq$3), chronic kidney disease (stage$\geq$3) and shock were excluded. Patients were randomized (1:1) to either intensive hydration with lactated Ringer's solution (3 mL/kg/h during the procedure, 20 mL/ kg bolus after the procedure, and 3 mL/kg/h for 8 hours after the procedure), or standard hydration (1.5 mL/kg/h of lactated Ringer's solution during and for 8 hours after the procedure). A blood panel including serum levels of amylase and lipase was obtained at 4 and 24 hours after ERCP. Primary outcome was the incidence of PEP (defined as epigastric pain plus either amylase or lipase levels >3 times the upper limit of normal at 24h). Secondary outcomes were severity of PEP, incidence of volume overload, patient and procedure-related factors associated with PEP, and the predictive values of serum amylase/lipase at 4 hours after ERCP for PEP development.

Results: Included were 75 patients, 38 in the intensive hydration arm, and 37 in the standard hydration arm. Both groups were homogeneous for patient and procedure-related factors. PEP incidence was 9.3% (n = 7), and was lower in the intensive hydration arm (5.3% versus 13.5%, p = 0.204). Additionally, both PEP in the intensive hydration arm were mild, while out of the 5 PEP in the normal hydration arm, two patients presented with moderate and severe PEP, respectively. Contrast injection of the Wirsung was significantly associated with PEP (28.6% versus 7.1%, p = 0.016), while no other patient or procedure-related factors associated with PEP incidence. Finally, both amylase levels <2 times and lipase levels $<$ 3 times the upper limit of normal at 4 hours demonstrated a

negative predictive value of 100% for the development of PEP. No complication was observed as a consequence of intensive hydration.
Conclusion: In our series, the incidence of PEP was 9.3%, and a non-significant risk reduction trend was observed in patients undergoing intensive hydration, with no severe pancreatitis being observed in this group. Wirsung contrast injection significantly increased the risk of PEP. Lower serum amylase and lipase levels at 4 hours after ERCP were excellent predictors for absence of PEP at 24 hours, displaying a negative predictive value of 100%.
Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 15:45–17:15
UPPER GI NERVE-GUT INTERACTIONS – ROOM N2

OP117 INTRAGASTRIC BITTER TASTANT ALTERS BRAIN ACTIVITY IN HOMEOSTATIC AND HEDONIC REGIONS AND DECREASES OCTANOYLATED GHRELIN LEVELS AND HEDONIC FOOD INTAKE

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Introduction: Intragastric administration of bitter tastants decreases hunger ratings in the fasted state. Activation of bitter taste receptors can alter ghrelin levels, a gut hormone which increases hunger in between meals and becomes active after octanoylation. This indicates a potential role for bitter agonists in the regulation of appetite and food intake, putatively via interference with gut-brain signals to regions involved in homeostatic (brainstem, hypothalamus) and hedonic (mesolimbic reward system) control of feeding.
Aims & Methods: The aim of this project was to study the effect of intragastric administration of the bitter tastant Quinine Hydrochloride (QHCl) on brain activity in homeostatic and hedonic regions and on circulating ghrelin plasma levels. Furthermore, to test the hypothesis of lower hunger and prospective food consumption ratings, and lower hedonic food intake after QHCl administration compared to placebo. Fifteen healthy women were studied after an overnight fast. Brain activity before and up to 50 minutes after infusion of QHCl (10 μmol/kg) or distilled water (placebo) was recorded using functional magnetic resonance imaging (MRI). Hunger and prospective food consumption scores were assessed every 10 min using Visual Analogue Scales. Blood samples were taken at the same time points. Hedonic food intake was measured immediately after scanning using an ad libitum chocolate milkshake drink test. MRI preprocessing and analysis was conducted using SPM12. Brain responses over time to QHCl versus placebo infusion were compared in a priori defined regions of interest (ROI) at both voxel- and cluster-level threshold of $p_{FWEcorrected} < 0.05$. The infusion-by-time interaction effect was tested on hunger and prospective food consumption scores with mixed models. Hedonic food intake was compared between infusions using a one-tailed paired T-test. Blood plasma was analysed for circulating ghrelin levels using radioimmunoassays.
Results: Compared to placebo, intragastric QHCl infusion significantly increased neural activity in 5 different clusters within the ROIs, with local maxima in the putamen, insula, caudate, amygdala, anterior cingulate cortex, medial prefrontal cortex, medial orbitofrontal cortex and hippocampus. A decrease of neural activity was observed in the brainstem. Significantly lower prospective food consumption scores were observed after QHCl administration compared to placebo ($p = 0.02$), but no significant differences were observed for hunger scores. Milkshake intake was significantly lower after QHCl administration, compared to placebo ($p = 0.04$; Cohen's $d = 0.50$). A significant decrease of octanoylated ghrelin plasma levels was observed post-infusion after bitter administration compared to placebo ($p = 0.05$).
Conclusion: Intragastric administration of the bitter tastant QHCl significantly altered activity in homeostatic and hedonic brain regions. Prospective food consumption ratings, circulating octanoylated ghrelin levels and hedonic food intake were decreased after QHCl. These observations indicate a potential role for bitter agonists in the treatment of obesity.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP118 TRANSDIAGNOSTIC COGNITIVE BEHAVIOUR THERAPY SHOW PROMISE FOR BOTH MOOD AND GASTROINTESTINAL SYMPTOMS IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL DISORDERS

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Introduction: Irritable Bowel Syndrome (IBS) is a heterogenous disorder characteristised by recurrent abdominal pain combined with alteration in bowel habit. It is associated with reduced quality-of-life and significant economic cost to society. IBS sufferers also have elevated scores for anxiety and depression which have been speculated to be part of the disease etiology [1]. Indirect evidence for the role of mood in IBS prevalence comes from studies showing that a proportion of patients show improvement in abdominal symptoms with antidepressants [2] but also in response to psychological therapies including cognitive behaviour therapy (CBT) [3]. Newer forms of CBT including internet-delivered CBT (iCBT) have shown similar effect sizes to conventional CBT in patients with mood disorder [4]. iCBT provides access to therapy for patients who are geographically or culturally isolated from qualified psychologists and has been shown to be cost-effective [5]. The eCentreClinic at Macquarie University (Australia) has developed a transdiagnostic model of CBT which is applied via distance mode, primarily via internet but also by telephone.
Aims & Methods: This study sought to pilot a new form of iCBT designed for chronic health conditions, including functional gastrointestinal disorders, with respect to: 1. Reduction in abdominal symptom burden, anxiety and depression 2. Identify changes in psychological factors that correlate with improvements in abdominal symptom burden. These aims were addressed using a single arm design with measurements of psychological factors and symptoms pre, mid and post-therapy. $n = 27$ individuals from across Australia were recruited at the eCentreClinic at Macquarie University (Australia) which specialises in online psychological threapies. Abdominal symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS) while anxiety was measured via the GAD-7 and depression via the PHQ-9. Aim 1 was addressed via change from pre- to post-treatment in scores while aim 2 was addressed by correlating change in GSRS scores with change in anxiety, depression and pain catastrophising scores.
Results: Of 27 patients who commenced therapy 22 completed the entire course and provided post-therapy measures. There was no difference in baseline scores for any measure between completers and non-completers. Scores for both abdominal symptom and psychological traits were substantially and statistically significantly improved at the end of therapy (Table 1).

Table 1: Baseline and change in scores for abdominal symptoms and psychological factors

Score	Baseline	Change	Cohen's d
GSRS	44.2 (11.0)	−7.6 (10.5)	−0.72
Anxiety	10.0 (5.2)	−5.1 (4.4)	−1.16
Depression	9.7 (4.8)	−4.1 (5.3)	−0.78
Catastrophising	19.8 (11.3)	−11.5 (11.9)	−0.97

At end of therapy 77% of patients had reduced GSRS scores and 95% reported the program was worth the effort expended. The percentage change in GSRS score was positively correlated with percentage change in pain catastrophising ($\rho = 0.53$, $p = 0.01$) and depression ($\rho = 0.53$, $p = 0.01$) and to a lesser extent with change in anxiety ($\rho = 0.36$, $p = 0.1$).
Conclusion: Based on this pilot trial, a transdiagnostic iCBT program developed specifically for functional gastrointestinal disorders shows considerable promise with improvements in both gastrointestinal symptoms as well as psychological functioning. The correlation between change in both mood scores and catastrophizing with change in abdominal symptoms opens avenues for further understanding of the mechanisms by which iCBT improves the gastrointestinal sufferings of these patients. The low cost of iCBT compared with conventional face-to-face therapy is attractive given challenges to public health budgets and its modality makes therapy accessible to potential patients who are not able to travel to a psychologist. Further, the transdiagnostic model on which this particular iCBT treatment is based is readily adaptable to other functional somatic syndromes so offers hope to a wide range of disorders.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP119 DYSBIOSIS INDUCES GUT INFLAMMATION AND DEPRESSIVE-LIKE BEHAVIOR ASSOCIATED WITH BRAIN BIOCHEMICAL AND FUNCTIONAL ALTERATIONS WHICH ARE RESTORED BY PROBIOTIC TREATMENT

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Introduction: The gut-brain axis has been indicated as major substrate of pathophysiological mechanisms in psychiatric comorbidities associated with chronic inflammatory bowel disorders. In particular, intestinal microbiota alterations may play a role in communication between these two systems[1]. However, such communication is not fully understood and probably involves multiple mechanisms.
Aims & Methods: In the present study we examined the presence of gut inflammation, the behavior, as well as, the brain biochemical and functional alterations in an antibiotic-induced dysbiosis animal model. Young male mice received a mixture of nonabsorbable antimicrobials (ampicilline, streptomicin and clyndamicin), which has been associated to the microflora composition alteration[2], for 2 weeks. Afterwards, animals were treated with probiotic (Lactobacillus Casei DG, 10^9 cells) or vehicle up to 7 days. Whereupon, various behavioral testing were performed. After sacrifice, mice intestine was cut in segments (duodenum, jejunum, ileum and colon) and expression of pro-inflammatory markers (IL-1β,

TNFα and iNOS) was evaluated by Western Blot analysis. Extracellular recording from CA3 region of dorsal hippocampus was performed. Astrocytes and microglial cells markers (GFAP and Iba-1, respectively) expression was evaluated by immunohistochemistry.
Results: Biochemical evaluations indicated that dysbiosis induced an overall gut inflammatory condition (significant increase in IL-1β, TNFα and iNOS expression), associated with a depressive-like behavior and a reduced social interaction. Altered behavior was accompanied by significant changes CA3 pyramidal neurons firing activity. Moreover, the number of GFAP and Iba-1 positive cells was significantly increased by dysbiosis. Very intriguingly, probiotic treatment significantly decreased IL-1β, TNFα and iNOS expression, normalized mice behavior, restored the spontaneous ongoing activity of CA3 pyramidal neurons and reduced the GFAP and Iba-1 positive cells number.
Conclusion: We found that, in mice, dysbiosis induced gut inflammation and sickness behaviours associated with biochemical and electrophysiological alterations in hippocampus. Probiotic treatment counteracted the gut inflammation and restored the behavioural phenotype as well as the biochemical and functional changes occurring in the brain of dysbiotic mice. These data suggest that intestinal dysbiosis, via the gut-brain axis, might contribute to the psychiatric comorbidity in patients with bowel disorders associated with an altered microflora and that probiotic treatment may improve this condition.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP120 QUORUM SENSING MOLECULES OF GUT MICROBIOTA AFFECT INTESTINAL TASTE RECEPTORS AND ANOREXIGENIC PEPTIDES TO CONTROL SATIETY IN THE HOST

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Introduction: Accumulating evidence suggests that the gut microbiota controls host satiety and hungry (1). Even if quantitative modifications of the gut microbiota have been described in obesity, bacterial derived soluble factors are likely involved in host dietary habits.
Aims & Methods: In this study we investigated the role of quorum sensing molecules (the autoinducers, AI) used for communication within gut microbial communities (2), in modifying food intake in the host. Adults CD1 male mice were fed a high-fat diet (HFD, 35% energy by fat) or a normal diet (4% energy by fat) and then daily rectally dosed with vehicle or 30 ng/g body weight of purified AI namely N-(3-oxododecanoyl)-L-homoserine lactone (AHL-12) or 2-Heptyl-3-hydroxy-4(1H)-quinolone (PQS). Two weeks later we determined: a) gut microbiota composition by quantitative PCR (qPCR) on fecal DNA; b) enteroendocrine cells (EECs) density in colonic mucosa by immunohistochemistry (IHC) for synaptophysin; c) mRNA levels specific for taste receptors and for anorectic or orexigenic peptides by qRT-PCR on colon and hypothalamus; d) food intake, body weight gain, oral glucose tolerance test.
Results: In HFD-fed mice rectally administration of AHL-12 or PQS restored the gut microbiota composition and normalized EECs density in colonic mucosa, altered by fat diet. AI administration increased the mRNA levels of Tas2r5, Tas2r38 and Tas2r105 whereas did not affect Tas2r131 and Tas1r3 allelic variants of bitter taste receptors. Moreover, AHL-12 and PQS significantly increased mRNA levels of anorectic peptides namely Cholecystokinin, Leptin and Neurotensin in the gut and Brain-Derived Neurotrophic Factor in the hypothalamus. Intraperitoneal administration of AHL-12 or PQS had no effects, supporting an intestinal direct action. Accordingly, the rectal but not the peritoneal administration of PQS and to a lesser extent AHL-12 significantly reduced food intake, decreased fat-diet induced body weight gain and improved oral glucose tolerance test.
Conclusion: We speculate that gut microbial AI mediate satiety through activation of taste receptors expressed by EECs and the release of gut peptides involved in food intake.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP121 OXIDATIVE STRESS ACTIVATES NLRP3 INFLAMMASOME AND IMPAIRS GASTRIC ANTRUM SMOOTH MUSCLE ACTIVITY IN OBESE PATIENTS

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Introduction: Obesity is associated to oxidative stress and chronic inflammation. Oxidative stress activates NLRP3 inflammasome with recruitment of ASC and pro caspase-1, leading to caspase-1 (CASP) activation and subsequent interleukin-1β (IL-1β) secretion. Motor disorders of the gastric antrum are observed in obese patients (OB) with in vitro impairment of VIP-induced relaxation both of smooth muscle cells (SMC) and strips
Aims & Methods: Our aim was to evaluate in vivo obese antral smooth muscle impairment and to study in vitro the roles for oxidative stress and inflammation on SMC motor alterations. Antral scans were obtained by Magnetic Resonance Imaging (MRI) before and after a liquid meal in OB and normal weight (NW) patients. SMC were isolated from human gastric antrum from 19 OB ($40.9 < BMI < 52.0$ kg/m^2) submitted to sleeve gastrectomy and 9 NW patients submitted to gastrectomy for gastric cancer ($19.0 < BMI < 25.0$ kg/m^2). Antioxidant capacity was evaluated by ELISA; qPCR analysis was performed for mRNA for NLRP3, ASC, CASP, IL-1β, TNFα and COX-2 and the data were normalized to β-actin mRNA levels. The effect of NADPH inhibitor Apocynin (APO:1μg/ml) in reverting OB SMC alterations was tested both on mRNA expression and on VIP (1μM) induced antral relaxation. Data are expressed as mean ± SE, $p < 0.05$ considered significant.
Results: In respect to NW, RMI scans showed a reduced antral motility, both during fasting and post-prandial periods, in OB consisting in a significant reduction of the width of antral contraction waves and magnitude of antral diameters variations. OB SMC presented a statistically significant decrease in antioxidant capacity (%59.02 ± 0.13) associated to a stronger increase of mRNA encoding for the inflammatory proteins TNFα (%46.60 ± 0.80), COX 2 (%348.18 ± 0.63) and NLRP3 inflammasome-related molecules. Pretreatment of OB gastric SMC with APO restored by 84.71 ± 0.2 antioxidant capacity and completely inhibited the expressions in OB NLRP3 (26.25 ± 0.35), ASC (34.52 ± 2.18), CASP-1 (31.80 ± 1.50) and IL-1β transcripts (3.58 ± 0.86), all undetermined after APO treatment. Associated to inhibition of the inflammasome components expression, APO completely restored VIP-induced relaxations in obese SMC (OB: %79.60 ± 11.84 vs NW: %79.96 ± 5.78).
Conclusion: Our study indicates a role for ROS in activation of NLRP3 inflammasome in obese gastric smooth muscle leading to a significant dysmotility that could be restored by the use of antioxidants
Disclosure of Interest: All authors have declared no conflicts of interest.

OP122 ACOTIAMIDE-SENSITIVE IMPAIRED RECEPTIVE RELAXATION OF LOWER ESOPHAGEAL SPHINCTER IN PATIENTS WITH ESOPHAGOGASTRIC JUNCTION OUTFLOW OBSTRUCTION

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Introduction: The pathogenesis and treatment of esophagogastric junction outflow obstruction (EGJOO) are not fully understood. The lower esophageal sphincter (LES) reportedly exhibits accommodation responses, and LES pressure is suppressed by swallowing and pharyngeal water stimulation (PWS) (Mittal, RK et. al. *Gastroenterology*. 1996;111:378–384); PWS-induced LES relaxation appears to be analogous to gastric receptive relaxation. We have previously reported that acotiamide was effective for patients with EGJOO.
Aims & Methods: This study aimed to evaluate the physiologic characteristics of acotiamide-sensitive LES relaxation in patients with EGJOO. High-resolution manometry was performed according to a standard protocol with the participant in the supine position, while swallowing ten 5-mL liquid boluses. 13 patients with EGJOO (mean age 65.5 ± standard deviation 4.1 years, eight of whom were women) and 19 participants with normal esophageal pressures (mean age 50.0 ± 3.0 years, 11 of whom were women) were enrolled. Basal LES pressure (BLESP) and the integrated relaxation pressure (IRP) were measured. The extent of PWS-induced LES relaxation (mmHg) was calculated as the difference between BLESP and the mean LES pressure in the 5-s period before PWS.
Results: There was no difference in BLESP between normal subjects (34.6 ± 2.1 mmHg) and patients with EGJOO (32.7 ± 1.8 mmHg), but IRP was significantly higher in patients with EGJOO (20.3 ± 1.4 mmHg) than normal subjects (10.8 ± 0.6 mmHg). In normal subjects, LES pressure immediately declined from 34.6 ± 2.1 mmHg to 25.6 ± 1.4 mmHg when the fluid bolus stimulated the mouth and pharynx on the first swallow. Mean PWS-induced LES relaxation was 9.0 ± 1.7 mmHg in normal subjects, but was absent in patients with EGJOO.

The mean LES pressure induced by PWS was 33.0 ± 1.6 mmHg, and did not differ significantly from the BLESP 32.7 ± 1.8 mmHg). Acotiamide was administered to address severe symptoms in six out of 13 patients with EGJOO. Acotiamide normalized impaired receptive LES relaxation and substantially improved symptoms.
Conclusion: Normal subjects have receptive LES relaxation, but this is impaired in EGJOO. Acotiamide normalizes IRP in EGJOO, mainly by restoring LES receptive relaxation.
Disclosure of Interest: All authors have declared no conflicts of interest.

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MONDAY, OCTOBER 17, 2016 15:45–17:15
ENDOSCOPIC MANAGEMENT OF UPPER GASTROINTESTINAL CANCER – ROOM L7

OP123 EFFICACY AND SAFETY OF ESD FOR SUPERFICIAL CANCER OF THE CERVICAL ESOPHAGUS

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Introduction: It is a difficult to observe a lesion in the cervical esophagus because of the difficulty in spreading the lumen. It is a challenge not only to find esophageal cancers at an early stage, but also to successfully treat them by ESD compared with lesions located at the thoracic esophagus.
Aims & Methods: The aim of this study was to clarify the safety and efficacy of ESD for superficial cancer located at the cervical esophagus. Patients who met the following criteria (case group) were enrolled in this retrospective study: 1) ESD was performed from January 2006 to December 2015; 2) the lesion was located at the cervical esophagus; and 3) squamous cell carcinoma (SCC) was proven histologically. Forty-five patients met those criteria. As a control group, 379 patients with 405 lesions of SCC which were located at the middle thoracic esophagus were enrolled. The lesions with entire circumferential mucosal defect, recurrent lesions after radiotherapy, and the lesions located near the scar were excluded in both groups. We evaluated adverse events including stricture and pneumonia, procedure time, en bloc resection rate, and frequency of local recurrence.
Results: In the case group, the average age was 67.3 years old, and the male-to-female ratio was 38:7. The average maximum size of lesions was 20.7 mm, and the histological depth of invasion was EP/LPM, MM, and SM2 in 39, 5, and 1 cases, respectively. The en bloc resection rate and R0 resection rate was 100% and 91.1%, respectively, and the mean procedure time was 57 min. ESD was performed under general anesthesia in 32 patients (71.1%). Damage of the muscle layer during treatment was observed in 5 patients, for which clipping was performed in 2 patients. Esophageal stricture was observed in 9 patients (41%), for which local injection of steroid was administered in 6 patients. No post-ESD bleeding was observed. Although perforation was identified in one patient, he recovered with conservative treatment. Chemoradiotherapy as additional treatments were conducted in 1patient. No local recurrence was observed during an average duration of follow-up of 34.1 months. In the control group, the average age was 67.3 years old, and the male-to-female ratio was 334:45. The average maximum size of lesions was 24.2 mm, and the histological depth of invasion was EP/LPM, MM/SM1, and SM2 in 306, 67, and 32 cases, respectively. The en bloc resection rate and R0 resection rate was 100% and 96%, respectively, and the mean procedure time was 54 min. ESD was performed under general anesthesia in 45 patients (11.1%). Damage of the muscle layer during treatment was observed in 91 patients (22.5%), for which clipping was performed in 38 patients. Esophageal stricture was observed in 14 patients (6.6%) of 213 patients with more than half of mucosal defect, for which local injection of steroid or PGA sheet were administered in 38 patients. No post-ESD bleeding was observed. Although perforation was identified in three patients, they recovered with conservative treatment.Surgery or chemoradiotherapy as additional treatments were conducted in 19 or 49 patients respectively. Local recurrence was observed in one patient during an average duration of follow-up of 41.8 months.
Conclusion: Safe ESD for superficial esophageal cancer in the cervical esophagus could be achieved under an appropriate management and successful local control was also confirmed. The stricture after ESD in the cervical esophagus developed significantly higher than those in the middle esophagus.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP124 SUBMUCOSAL TUNNELING ENDOSCOPIC RESECTION VS. THORACOSCOPIC SURGERY FOR LARGE SYMPTOMATIC SUBMUCOSAL TUMORS IN THE ESOPHAGUS AND ESOPHAGOGASTRIC JUNCTION

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Introduction: Small gastrointestinal submucosal tumors (SMTs) are asymptomatic and undetectable, while patients with larger tumors have symptoms, and require intervention. Previously, thoracoscopic surgery (TS) is the gold standard for these large SMTs in esophagus and esophagogastric junction (EGJ). We described a new technique, submucosal tunneling endoscopic resection (STER), for the resection of upper gastrointestinal SMTs. Recently, reports about STER are increasing. However, it is unclear whether STER is feasible for large SMTs. Moreover, studies about comparasion of STER and surgery for upper gastrointestinal SMTs are still little known.
Aims & Methods: The aim of this study is to compare the clinical outcomes of STER and thoracoscopic surgery for large symptomatic SMTs in esophagus and esophagogastric junction, as well as to analyze the clinicopathological factors that effect the feasiblilty of STER. Patients with large SMTs originating from the MP layer in esophagus and EGJ were enrolled in this retrospective study between May 2011 and December 2013. The clinicopathological data of a total of 145 patients were collected and analyzed.
Results: Among the 145 patients, 39 patients (26.9%) complained specific symptoms, while 106 patients (73.1%) had non-specific complaints. In the STER group, the mean tumor long and transverse diameters were 5.8 cm and 2.2 cm. Meanwhile, in the TS group, the mean tumor long and transverse diameters were 6.5 cm and 3.1 cm, respectively. Among all SMTs, 64 had regular shapes (44.1%) and 81 had irregular shapes (55.9%). All of the tumors were located in esophagus (84, 57.9%), and EGJ (61, 42.1%). There was no significant difference between the two groups in age, gender, symptom, tumor size, tumor location, tumor shape, and tumor histopathology. No recurrence was found in both groups during the follow up period. In this study, en bloc resection was achieved in 84.1% of the cases in the STER group and 85.7% of the cases in the TS group, and there was no significance ($p = 0.794$). In addition, the incidence of complications in this study was 8.5% in STER group and 4.8% in TS group. There was no significant difference in complications rates of the 2 groups. However, the procedure time and the hospital stay in the STER group were significantly shorter than those of the TS group. Based on statistical analysis, tumors with long diameter larger than 7.0 cm, transverse diameter lager than 3.5 cm and irregular shape were 3 significant risk factors for STER-related piecemeal resection, while tumor with transverse diameter lager than 3.5 cm was the risk factor for STER-related complications.
Conclusion: STER is feasible and safe for large symptomatic SMTs in esophagus and EGJ. It is associated with a shorter procedure time and hospital stay compared with TS. Besides long diameter and irregular shape, transverse diameter of SMTs is the critical factor for en bloc resection. STER for tumors with large transverse diameter and irregular shape is feasible, but associated with a relatively high risk of difficulty in retrieval of tumors.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP125 CHARACTERISTICS OF METACHRONOUS GASTRIC NEOPLASMS OCCURRING AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION FOR GASTRIC ADENOMAS AND CANCERS

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Introduction: With the progress of endoscopic diagnosis and treatment, endoscopic treatment has come to be used for gastric adenomas and early gastric cancers (EGCs). Endoscopic submucosal dissection (ESD) has become accepted as a minimally invasive treatment for superficial gastric neoplasms. However, the development of metachronous gastric neoplasms has been occasionally detected during follow-up after ESD. The clinicopathologic characteristics of these lesions occurring after ESD were investigated.
Aims & Methods: From August 2006 to December 2015, stomach ESD was performed for 375 patients with 426 lesions of gastric adenoma and differentiated-type EGC at Aichi Cancer Center Aichi Hospital. Periodic upper gastrointestinal endoscopy, blood tests, and chest and abdominal computed tomography were performed every 6 to 12 months after treatment. During the follow-up period, 31 metachronous lesions (27 patients) were discovered at endoscopy more than 1 year after initial ESD. The characteristics of these lesions were examined retrospectively.
Results: The median age at initial ESD was 72 (range, 56–82) years. The male to female ratio was 23:4. On endoscopy, all patients were found to have atrophic gastritis of the open-type according to the Kimura-Takemoto classification. *Helicobacter pylori* testing was positive in 18 patients (66.7%), negative in 8 patients (29.6%), and unknown in 1 patient (3.7%). Of these 18 *H. pylori*-positive patients, 17 underwent *H. pylori* eradication therapy after initial ESD, and it was successful in 16(94.1%). The median duration from initial ESD to the detection of a metachronous lesion was 25.9 (range, 12.4–83.8) months. The locations of the lesions were classified as follows: upper third (U), middle third (M), and lower third (L). Of 29 primary lesions (27 patients), 1 lesion (3.4%) was U, 11 lesions (37.9%) were M, and 17 lesions (58.6%) were L. The gross type was 0-I in one lesion (3.4%), 0-IIa in 15 lesions (51.7%), 0-IIc in 12 lesions (41.4%), and 0-IIa+IIc in one lesion (3.4%). The median tumor size was 10 (range, 2–50) mm. En bloc resection was performed for 28 lesions (96.6%). Aspiration pneumonia occurred in one patient after ESD, but the patient was successfully treated by intravenous antibiotics. There were no treatment-related deaths. On pathological examination, 21 were tubular adenocarcinoma, and 8 were tubular adenoma. Histologically, curative resection was obtained in 27 lesions (93.1%). In contrast, the location of 31 metachronous lesions was U in 9 lesions (29%), M in 8 lesions (25.8%), and L in 14 lesions (45.2%). The gross type was 0-IIa in 16 lesions (51.6%), 0-IIb in 1 lesion (3.2%), 0-IIc in 13 lesions (41.9%), and 0-IIa+IIb in 1 lesion (3.2%). The median tumor size was 9 (range, 1.5–38) mm. En bloc resection was performed for 28 lesions (90.3%). Aspiration pneumonia occurred in one patient after ESD, but the patient was successfully treated by intravenous

antibiotics. There were no treatment-related deaths. On pathological examination, 20 were tubular adenocarcinoma, and 11 were tubular adenoma. Histologically, curative resection was obtained in 26 of the 31 lesions (83.9%). There were no differences in gross type (elevated type/flat and depressed type), tumor size, or histology between primary and metachronous lesions. However, location (U/M/L) was significantly different (P = 0.029). Furthermore, there were significant differences in U/M (P = 0.016) and U/L (P = 0.014). Therefore, there was a slightly higher frequency of metachronous lesions in the U area.
Conclusion: Metachronous lesions tended to develop in the U area. These results suggest that it is necessary to carefully observe the U area by surveillance endoscopy after ESD for gastric neoplasms.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP126 A SIMPLE SCORING SYSTEM TO STRATIFY CURABILITY AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION FOR EARLY GASTRIC CANCER WHICH HAS PATHOLOGICAL FACTORS HIGHLY RELATED WITH LYMPH NODE METASTASIS: DEVELOPMENT AND VALIDATION OF "ECURA SYSTEM"

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Introduction: According to the European and Japanese guidelines for endoscopic submucosal dissection (ESD) of early gastric cancer (EGC), radical surgery is recommended for patients after ESD that does not meet the curative criteria because of the potential risk of lymph node metastasis (LNM). However, as LNM occurs in only 5–10% of patients who undergo radical surgery, this recommendation for all such patients may be overestimated.
Aims & Methods: This multicenter study aimed to establish a scoring system (eCura system) for deciding the potential risk of LNM after ESD with pathological factors related with LNM. Of the 15,785 consecutive patients who underwent ESD for EGC from January 2000 to August 2011, we retrospectively reviewed 2,006 patients who did not meet the curative criteria for ESD of EGC. This study consisted of two stages. First, the risk-scoring system for LNM was developed using multivariate logistic regression analysis in 1,101 patients who underwent radical surgery after having failed to meet the curative criteria. The estimated factors were tumor size (>30 mm), tumor depth (submucosal invasion ≥500 μm: SM2), histopathological type (undifferentiated-type), lymphatic invasion, venous invasion, ulceration (scar), and positive vertical margin (VM). We assigned weighted points proportional to β regression coefficient values for the factors determined in the multivariate analysis. Second, for validating the risk-scoring system, the validity by survival analysis was evaluated in 905 patients without additional treatment.
Results: In the development stage, based on accordant regression coefficients, five risk factors for LNM were weighted with point values: 3 points for lymphatic invasion and 1 point each for tumor size >30 mm, positive VM, venous invasion, and SM2. Then, the patients were categorized into three LNM risk groups: low (0–1 point: 2.5% risk), intermediate (2–4 points: 6.7%), and high (5–7 points: 22.7%). The C statistic (95% confidence interval (CI)) of the system for LNM was 0.74 (0.62–0.87) and the bootstrapping analysis showed similar results (95% CI, 0.62–0.86). In the validation stage, cancer-specific survival differed significantly among these groups (99.6%, 95.5%, and 90.1%, respectively, at 5 years; p < 0.001). Cox proportional hazards regression analysis showed that the high-risk [hazard ratio (95% CI) = 15.5 (4.03–59.4), p < 0.001] and intermediate-risk [6.63 (1.75–25.1), p = 0.005] groups had significantly higher cancer-specific mortality compared with the low-risk group. Moreover, the C statistic of the system for cancer-specific mortality was 0.78.
Conclusion: This scoring system predicted cancer-specific survival, which may be helpful to value the risk of LNM in patients after ESD that does not meet the curative criteria.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP127 COMPARISON OF EMR AND ENDOSCOPIC SUBMUCOSAL DISSECTION FOR RESECTION OF EARLY STAGE GASTROINTESTINAL CANCER

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Introduction: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are now being increasingly used for the treatment of gastrointestinal neoplasia. However, their efficacies (en-bloc and curative resection) have not been compared. EMR is associated with local recurrences, especially when lesions larger than 20 mm are resected in a piecemeal manner (1). In piecemeal-resected specimens, histologic assessment becomes difficult, because of the effects of burning on the lesion. ESD permits a larger resection of the tissue over the muscularis propria, including large lesions and positive non-lifting sign lesions, with its major advantage being the ability to achieve a higher en-bloc resection rate due to submucosal dissection with a direct view. This results in enhanced curability and more accurate histopathological assessment. However, this procedure is known to have several disadvantages such as greater technical difficulty, longer procedure time and increased risk of related complications.
Aims & Methods: The aim of this study is to find the best method for treating early gastrointestinal neoplasia. Fifty-one patients (mean patient age 71, range 32–92 years, male: female ratio 25/26) including 19 involved adenoma with low-grade dysplasia, 21 intraepithelial cancers with high-grade dysplasia, 3 minute submucosal cancers, 6 submucosal deep cancers and 2 carcinoid tumors submitted to ESD, were compared to 98 patients (mean patient age 62.7, range 20–88 years, male: female ratio 52/46) who underwent EMR (20 involved adenoma with low grade dysplasia, 42 intraepithelial cancers with high-grade dysplasia, 24 minute submucosal cancers, 3 submucosal deep cancers, 4 carcinoid tumors, 3 granular cell tumors and 2 Brunner's adenoma). In ESD group, the mean operation time was 1.6 hrs and the mean size of resected specimen was 25.5 mm (range 10–80 mm); in EMR group, the mean operation time was 0.5 hrs and the mean size of resected specimen was 26.2 mm (range 10–100 mm). En-bloc resection rate, curative resection rate, piecemeal resection, recurrence rate, postoperative bleeding and perforation rate were compared with the use of the chi-square test.
Results: En-bloc resection rate (ESD: 82.4%, 42/51 vs EMR: 51%, 50/98; p < 0.01) and curative resection rate (ESD: 88.2%, 45/51 vs EMR: 72.9%, 71/98; p < 0.05) were significantly higher in ESD group in comparison with EMR group. Piecemeal resection was significantly lower in ESD (17.7%, 9/51) when compared to EMR group (49.9%, 48/98) (p < 0.01). In the EMR group, 6 patients developed local recurrences (6.1%): five were successfully treated by additional EMR and one by surgical resection; in contrast, there was no recurrence in the ESD group (p = NS). The post-operative bleeding rate was 3.92% (2/51) in ESD and 3.1% (3/98) in EMR group (p = NS). Perforation rate for ESD was 3.9% (2/51) when compared to conventional EMR (2%, 2/98) (p = NS).
Conclusion: In the present study, we evaluated the efficacy of 2 endoscopic resection methods from the perspectives of the en-bloc and curative resection rates. Based on these aspects, an ESD was found to be the best method for early gastrointestinal cancers; EMR would be a good alternative to an ESD, especially in poor-risk patients or when performed by less experienced endoscopists.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP128 LONG-TERM OUTCOME OF THE INCIDENCE RATE OF METACHRONOUS GASTRIC CANCERS AFTER HELICOBACTER PYLORI ERADICATION – A FOLLOW-UP AND ANALYSES OF JAPAN GAST STUDY GROUP ENROLLED PATIENTS

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Introduction: The author and Japan Gast Study Group (JGSG) reported that the eradication of *Helicobacter pylori* reduced the incidence of metachronous gastric cancers (GC) after endoscopic mucosal resection significantly in the Lancet 2008[1].
Aims & Methods: We analyse long-term outcomes of the incidence rate of metachronous GC for JGSG enrolled patients at Yamagata Prefectural Central Hospital. Out of 89 enrolled patients, 6 patients died by other diseases and 43 patients were introduced to other clinics and hospitals, therefore 40 patients (the eradication group 21, the non-eradication group 19) were followed-up at Yamagata Prefectural Central Hospital. After this Lancet study, non-eradication patients were recommended to receive an eradication therapy. Patients have been followed-up once a year endoscopically. Among 40 patients the longest follow-up case is in 15th observation year. A long-term incidence rate of metachronous GC was analysed and compared between the two groups.
Results: Out of the eradication group, 1 metachronous GC was detected (9 years 7 months after the enrollment). Out of the non-eradication group, 4 metachronous GC were detected (5 years 3 months, 6 years 7 months, 10 years 2 months, 13 years 10 months after the enrollment). When these 4 lesions were detected, 3 cases were not yet eradicated and 1 case was eradicated unsuccessfully. The incidence rate of metachronous GC of the eradication group was 4.8% but that of the non-eradication group was 21.1%.
Conclusion: The incidence rate of metachronous GC of the non-eradication group was about four times higher than that of the eradication group even in 15th observation year. All 4 cases of metachronous GC of the non-eradication group were persistent infected cases. The earlier eradication of *Helicobacter pylori* is recommended.
Disclosure of Interest: All authors have declared no conflicts of interest.

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Table (OP130)

Risk factors for enterococcal cholangitis	Enterococcus spp. isolation (N = 109)	Non-enrerococcus spp. isolation (N = 82)	Univariate analysis Odds ratio (95% CI)	P value	Mutivariate analysis Adjusted odds ratio (95% CI)	P value
Age(years)	76.4(42–97)	71.4(34–97)				
age≧75	65(60%)	35(43%)	1.984(1.109–3.548)	0.028	1.637(0.844–3.191)	0.144
Male gender	72(66%)	55(67%)	0.955(0.520–1.754)	1		
Onset after 48 h admission	21(19%)	19(23%)	0.791(0.393–1.593)	0.591		
Biliary tract malignancies	54(50%)	38(46%)	1.137(0.640–2.018)	0.77		
Diabetes mellitus	22(20%)	19(23%)	0.838(0.419–1.679)	0.722		
Prior cholecystitis	12(11%)	4(4.9%)	2.412(0.749–7.774)	0.187		
CBD stone	48(44%)	38(46%)	0.911(0.512–1.620)	0.77		
Gallstone or biliary sludge	63(58%)	52(63%)	0.790(0.439–1.423)	0.458		
Prior PTCD	12(11%)	9(11%)	1.003(0.401–2.508)	1		
Prior EST	51(47%)	11(13%)	5.676(2.713–11.87)	<0.0001	4.480(1.907–11.26)	0.0005
Presence of device in biliary tract	45(41%)	15(18%)	3.141(1.595–6.183)	0.0009	1.442(0.600–3.419)	0.408
Biliary tract reconstruction	14(13%)	2(2.4%)	5.895(1.301–26.71)	0.015	8.945(2.247–60.12)	0.001
Prior cholecystectomy	24(22%)	10(12&)	2.033(0.912–4.532)	0.088		
Stay in ICU in present admission	53(49%)	35(43%)	1.244(0.698–2.218)	0.467		
Stay in ICU in past admission	44(40%)	17(21%)	2.588(1.342–4.992)	0.005	1.731(0.826–3.675)	0.146
Any antibiotic treatment within previous 14 days	25(23%)	11(13%)	1.921(0.884–4.175)	0.134		
Cephalosporins	17(16%)	10(12%)	1.330(0.574–3.081)	0.537		
Penicillins	9(8.1%)	1(1.2%)	7.29(0.905–58.74)	0.045	3.157(0.461–64.83)	0.269

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HEPATIC CYSTS AND HEPATO-BILIARY TRACT DISORDERS – ROOM L8

OP129 THE EFFECT OF PASIREOTIDE IN CYST REDUCTION OF ASPIRATION SCLEROTHERAPY IN PATIENTS WITH LARGE SYMPTOMATIC HEPATIC CYSTS, A RANDOMIZED CONTROLLED TRIAL

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Introduction: Aspiration sclerotherapy is a therapeutical option for large symptomatic hepatic cysts. However, inadequate cyst reduction is frequently reported. Somatostatin analogues are able to curtail cyst volume. We hypothesized that combining the long-acting somatostatin analogue pasireotide (SOM230) with aspiration sclerotherapy would enhance hepatic cyst reduction.

Aims & Methods: Our aim was to test whether pasireotide could improve the efficacy of aspiration sclerotherapy of large symptomatic hepatic cysts. We conducted a single-center, randomized (1:1 ratio), double-blind, placebo-controlled trial in patients with a large (> 5 cm) symptomatic hepatic cyst. All patients underwent aspiration sclerotherapy. In addition, we randomized patients between two arms: (1) pasireotide 60 mg long-acting release (LAR) injection or (2) placebo (saline) injection. Injections were administrated two weeks prior and two weeks after aspiration sclerotherapy. Primary endpoint was proportional cyst diameter reduction after six weeks, as measured by ultrasonography. Secondary outcomes included long-term diameter reduction at 26 weeks, symptomatic change at 26 weeks, and safety during the study. Symptomatic change was evaluated using the polycystic liver disease-questionnaire (PLD-Q) that assesses frequency and severity of 14 disease-specific symptoms leading to a total PLD-Q sum score.

Results: Thirty-four patients (32 females (94%); mean age 53.6 ± 7.8 years) were randomized between pasireotide (n = 17) and placebo (n = 17). Pasireotide did not improve efficacy of aspiration sclerotherapy at six weeks compared to controls (23.6% [IQR 9.6–31.8%] versus 21.8% [IQR 9.6–31.8%], respectively; $p = 0.96$). Long-term cyst diameter reduction was similar in both groups (49.1% [IQR 27.0–73.6%] and 45.5% [IQR 29.2–59.6%]; $p = 0.90$). Mean PLD-Q scores improved significantly in both groups ($p < 0.01$) indicating symptomatic relief, but there were no differences between groups ($p = 0.92$). Transient hyperglycaemia was seen in all patients allocated to pasireotide.

Conclusion: Aspiration sclerotherapy is a highly effective treatment option of large symptomatic hepatic cysts, spiking with pasireotide does not further improve efficacy.

Disclosure of Interest: J.P.H. Drenth: Novartis provided the study drug and partially funded this investigator-initiated study. Novartis did not have any influence on the execution of the trail or the preparation of the manuscript.
All other authors have declared no conflicts of interest.

OP130 A STUDY TO INVESTIGATE RISK FACTOR FOR ENTEROCOCCUS SPECIES ISOLATION FROM BILE AND /OR BLOOD CULTURE OBTAINED FROM PATIENTS WITH CHOLANGITIS

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Introduction: Knowledge of pathogenic spectrum for cholangitis is important for adequate empiric therapy. *Enterococcus* species, which come well equipped with a variety of intrinsic antibiotic resistances, are sometimes isolated. However, little is known of risk factors for this organism's isolation in patients with cholangitis. We conducted a study to investigate them on the basis of single-center experience in Japan.

Aims & Methods: Consecutive 191 hospitalized patients with cholangitis with positive bile and /or blood culture between January 2009 and October 2015 were enrolled. Diagnosis of cholangitis was based on clinical symptoms, blood chemistry and radiological imaging. Potential risk factors for *Enterococcus* species isolation such as patient attributes (Age, sex, underlying conditions, and past history) were retrospectively investigated. Univariate and multivariate analyses to identify risk factors were performed using a proportional hazards model.

Results: 127 patients were men (67%). The average age was 74.2(34–97) years. *Enterococcus* species were isolated in 128 episodes from bile and /or blood culture. Age over 75 years old(Odds Ratio [OR]=1.984; 95% Confidence Interval [CI] 1.109–3.548; P = 0.028), prior endoscopic sphinterotomy(OR = 5.676; CI 2.713–11.87; P < 0.0001), presence of device in biliary tract(OR = 3.141; CI 1.595–6.183; P = 0.0009), biliary reconstruction(OR = 5.895; CI 1.301–26.71; P = 0.015), stayed in Intensive Care Unit in past admission(OR = 2.588; CI 1.342–4.992; P = 0.005), administration of penicillins(OR = 7.29; CI 0.905–58.74; P = 0.045) were identified as risk factors for *Enterococcus* species isolation by the univariate analysis. Multivariate analysis revealed that prior endoscopic sphinterotomy (OR = 4.480; 95%CI 1.907–11.26; P = 0.0005) and biliary reconstruction(OR = 8.945; CI 2.247–60.12; P = 0.001) were independent significant risk factors.

Conclusion: We found prior endoscopic sphinterotomy and biliary reconstruction were independent risk factors for *Enterococcus* species isolation in cholangitis. We should consider empirial therapy with anti-enterococcal antibiotics when managing patients with these attributes.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP131 MENOPAUSAL HORMONE THERAPY AND RISK OF BILIARY TRACT CANCER

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Introduction: The risk of developing biliary tract cancer, including cancers of the gallbladder and the extra-hepatic bile ducts, may be influenced by estrogen

exposure.[1] Exogenous estrogens are used extensively to alleviate symptoms of menopause, but the effect on biliary tract cancer risk is not known.[2]
Aims & Methods: This was a population-based cohort study conducted in Sweden between July 2005 and December 2011 aiming to investigate the risk of biliary tract cancer after menopausal hormonal therapy (MHT). The National Prescribed Drug Register was used to identify MHT exposed women during the study period. For each exposed woman, three unexposed women were randomly selected from the same study base. Unexposed individuals were exactly matched for history of delivery, thrombotic events and hysterectomy, creating 8 strata. Furthermore, additional matching (nearest neighbor) was performed for age, smoking status, alcohol use, obesity and diabetes within each stratum. Record linkage to the Swedish Patient Register allowed collection of potential confounding factors and status of the matching variables. The cohort was followed-up for biliary tract cancer and death by linkage to The Swedish Cancer Register and the Cause of Death Register. Logistic regression models were estimated to calculate odds ratios and matching 95% confidence intervals for the association between MHT exposure and biliary tract cancer. All analyses were stratified according to MHT regimen (estrogen or estrogen/progestogen combinations). All matching variables were included in the logistic models. Additionally, the risk of developing symptomatic gallstone disease was evaluated using a similar logistic regression model.
Results: The final cohort included 290,186 MHT exposed, and 870,165 unexposed, women. The resulting total cohort consisted of more than 1.1 million women and follow-up was performed over 7 years. The odds of gallbladder cancer was decreased in MHT-exposed women (OR 0.6, 95% CI 0.4–0.8), whereas no clear association between MHT-exposure and cancers of the extrahepatic bile ducts was seen (OR 0.8, 95% CI 0.6–1.2). There were no clear differences when the analyses were stratified for estrogen or estrogen/progesterone-combinations. Adjusting for clinically manifest gallstone disease attenuated the odds of gallbladder cancer in MHT-exposed women (OR 0.8, 95% CI 0.6–1.2). Additionally, MHT exposure significantly increased the risk of gallstone disease (OR 7.0, 95% CI 6.6 – 7.3).
Conclusion: In conclusion, this large cohort study did not support a clear association between MHT and BTC. Furthermore, the reduced risk of GBC after MHT exposure is likely to be explained by increased risk of symptomatic gallstone disease resulting in cholecystectomy. Thus, this study supports the role of gallstones as an intermediate step in the development of GBC.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP132 MUCIN3A, A PROMISING TUMOR MARKER FOR DIAGNOSIS OF EXTRAHEPATIC CHOLANGIOCARCINOMA

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Introduction: The prognosis of extrahepatic cholangiocarcinoma (ECC) was poor for the difficulty of early diagnosis due to their anatomical location and insidious onset, and little effective tumor markers. Our previous study showed Mucin3A (MUC3A) was the main differential protein in bile with proteomics technology using isobaric tags for relative and absolute quantitation (iTRAQ) in 20 patients with ECC and 20 patients with sphincter of oddi dysfunction (SOD).
Aims & Methods: Aim: To validate the histologic expression of MUC3A in ECC and explore diagnosis value of serum MUC3A as the potential tumor marker for diagnosis of ECC. Methods: (1) The expression of MUC3A was detected in 15 specimens of ECC and 20 normal bile duct tissues specimens by immunohistochemistry method. The relationship between MUC3A and the clinicopathologic features of ECC were investigated. (2) Serum MUC3A were detected in 16 preoperative patients with ECC and 15 preoperative patients with SOD, Serum MUC3A in 16 patients with ECC were compared preoperative with postoperative one month. (3) The clinical diagnosis application of serum MUC3A was compared with CEA, CA19–9 in 20 patients with ECC and 20 patients with SOD.
Results: (1) The positive cells rates of MUC3A in ECC specimens were significant higher than in normal bile duct tissues specimens (83.3% vs. 35.0%, $P < 0.01$). The expression of MUC3A was significant correlated with metastasis of lymph node, infiltration and UICC stage of carcinoma, differentiation grade of carcinoma ($P < 0.05$). (2) The preoperative serum values of MUC3A in patients with ECC were significant higher than patients with SOD (57.8 ± 19.6 vs. 25.1 ± 9.2ng/ml, $P < 0.01$). Compared with the preoperative results, postoperative one month serum MUC3A in patients with ECC were significant decreased (26.8 ± 4.6 vs. 57.8 ± 19.6ng/ml, $P < 0.01$). ROC curve analysis showed serum MUC3A could distinguish ECC with SOD while 40.7 ng/ml as the cut-off value (AUC = 0.907, 84.6% sensitivity, 90% specificity). (3) The serum MUC3A has much higher sensitivity (84.6%, 38.5%, 76.9%), specificity (90%, 95%, 85%), diagnostic accuracies (86.6%, 63%, 80.4%) and less false positive rates (10%, 5%, 15%) than serum CA19–9, CEA in diagnosing ECC.
Conclusion: MUC3A is high expression in tumor tissue of ECC, and related to the differentiation grade and stage of tumor. The MUC3A in peripheral blood is valuable to preoperative diagnosis of ECC. MUC3A is expected to become one of diagnosis and detection indicator of ECC.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP133 KINETICS OF PULMONARY ANGIOGENESIS IN MOUSE COMMON BILE DUCT LIGATION-INDUCED LIVER FIBROSIS

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Introduction: Hepatopulmonary syndrome (HPS) is a severe pulmonary complication of liver disease for which no medical treatment is available. In rats, common bile duct ligation (CBDL) has been documented as a model for human HPS, which is characterized by pathological pulmonary angiogenesis. Studies in genetically modified mice could offer opportunities for further research, however, in this species the development of pulmonary angiogenesis in biliary cirrhosis has not been outlined yet.
Aims & Methods: We aimed to elucidate the temporal changes in proangiogenic signature of hepatic and pulmonary vasculature after CBDL in mice and in addition identify potential proangiogenic factors contributing to the pathogenesis of HPS. Male Swiss mice underwent CBDL or sham surgery and were sacrificed at a weekly basis for 6 consecutive weeks. Pulmonary inflammation was studied by cytology on broncho-alveolar lavage fluid, myeloperoxidase assay and luminex bead based assay on lung tissue. Liver and lungs were collected for protein analysis and histology to assess liver fibrosis and hepatic and pulmonary angiogenesis. Scanning electron microscopy was performed on vascular corrosion casts to visualize pulmonary vasculature during cirrhosis ex vivo.
Results: CBDL progressively induced liver fibrosis from week 1 (F0–1) to week 6 (F4). This was accompanied by a gradual increase in hepatic immunopositivity for Endoglin and von Willebrand Factor, two markers of endothelial cell activation ($P < 0.0001$). Hepatic levels of vascular endothelial growth factor (VEGF), VEGF receptor 1 and 2 were significantly increased at week 6, whereas placental growth factor (PlGF), which is exclusively involved in pathological angiogenesis, was already upregulated at week 2 ($P < 0.0001$). In the pulmonary compartment, CBDL resulted in neutrophil infiltration and increased pro-inflammatory mediators from week 2 to 6 (all $P < 0.001$). Pulmonary immunoreactivity for Endoglin and von Willebrand Factor progressively increased from week 4 to 6, while PlGF was already increased from week 2 onwards (all $P < 0.0001$). Scanning electron microscopy revealed regions of abnormal vascular architecture, mainly located at the pleural side, decreased intercapillary distance ($P < 0.001$) and increased capillary density ($P < 0.05$) in lungs of cirrhotic mice.
Conclusion: CBDL in mice is associated with pathological pulmonary angiogenesis and may represent a model for human HPS. In addition, we point to PlGF as an early indicator of pathological hepatic and pulmonary angiogenesis.

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H. Van Vlierberghe: Hans Van Vlierberghe is senior clinical investigator of the Research Foundation Flanders.
All other authors have declared no conflicts of interest.

OP134 EPIDEMIOLOGY OF GALLBLADDER POLYPS ON HISTOLOGICAL ASSESSMENT AFTER CHOLECYSTECTOMY

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Introduction: Gallbladder polyps can be divided in neoplastic polyps (adenoma, dysplastic polyp, and carcinoma) and nonneoplastic polyps (eg. cholesterol polyp, inflammatory polyp or adenomyoma).[1] Cholecystectomy is only indicated for neoplastic polyps, as they are (pre)malignant.[2] Annually, over 23,000 cholecystectomies are performed in the Netherlands.[3] However, there is scarce pathology data on the prevalence of gallbladder polyps and attribution of neoplastic and nonneoplastic polyps.
Aims & Methods: We aimed to assess nationwide pathology data on gallbladder polyps over a 10-year period. Methods: The PALGA database, the Dutch Pathology Registry,[4] was used to identify all histopathologically proven gallbladder polyps over the period 2003–2013. The search was restricted to histological samples of patients $\geq$ 18 years of age. Biopsies, and cholecystectomies performed as part of primary non-gallbladder surgery (e.g. whipple or hepatectomy), were excluded. All excerpts concerning primary gallbladder surgery containing a polyp or (focal) wall thickening $>$ 5 mm were included. These excerpts were rated as neoplastic (adenoma, dysplasia, carcinoma or other malignancies) or nonneoplastic (all other types of polyp). If both neoplastic and nonneoplastic lesions were present, the excerpt was classified as neoplastic. Prevalence of gallbladder

polyps and the attribution of neoplastic polyps and nonneoplastic polyps was calculated. To determine prevalence of gallbladder polyps, we obtained the total number of cholecystectomies between 2003–2013 from PALGA.
Results: In total 220,612 cholecystectomies were performed over the period 2003–2013. The PALGA search identified 4532 excerpts, representing 4349 patients. A total of 337 patients were excluded due to primary non-gallbladder surgery, leaving 4012 unique cholecystectomies. In 2083 cholecystectomies (0.9%), a polypoid leasion was present. Which results in a calculated prevalence of polyps in 944/100,000 patients who undergone cholecystectomy. Of the polyps, 1172 (56.3%) were neoplastic; 278 (13.3%) adenomas (incl. cystadenoma), 190 (9.1%) dysplastic polyps, 647 (31.1%) adenocarcinomas, and 57 (2.7%) other malignancies. Nine hundred and ten (43.7%) polyp were nonneoplastic; 375 (18%) cholesterol polyps, 334 (16%) adenomyoma's, 70 (3.7%) hyperplastic polyps, 54 (2.6%) mucosal polyps, 42 (2.0%) inflammatory polyps, 18 (0.9%) papiloma's and 17 (0.8%) other types of polyps.
Conclusion: Approximately one percent of gallbladders contain a polyp on histopathological assessment after cholecystectomy. Fifty-six percent of the polyps after cholecystectomy are neoplastic.
Disclosure of Interest: All authors have declared no conflicts of interest.

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MECHANISMS OF LIVER CANCER AND PORTAL HYPERTENSION – ROOM 1.86

OP135 CHANGES IN CIRCULATING MICRORNA AFTER TREATMENT: MICRORNA SIGNATURES TO PREDICT THERAPY RESPONSE AND DISEASE FREE SURVIVAL IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide. Although treatment options have improved in the past 30 years, prognosis remains unfavorable in many patients. The lack of effective models for outcome prediction prevents the opportunity for individualized treatment protocols. The potential role of microRNAs (miRNA) as prognostic biomarker has witnessed an increasing interest, owing to the non-invasive nature of miRNA-based screening assays. While many studies have suggested several miRNAs as biomarker candidates, dynamic variations over extended time period have not been assessed until now.
Aims & Methods: To identify potential circulating miRNA signatures for the prediction oftherapy response and patient follow-up. Methods: 15 consecutive patients with early/intermediated stage HCC were enrolled and treated according to the ESSL/AASLD practice guidelines. Patients were staged (CT scan and/or MRI) at time 0 (T0, before treatment), 1 month (T1) and 6 months (T6) from therapy. Pax-gene Blood RNA tubes and Vacuette tubes where used to collect total blood and serum at T0,T1,T6. Small RNAs were isolated and hybridized on Affymetrix GeneChip miRNA arrays 3.0. qRT-PCR was used for miRNA validation in an independent cohort of 15 matched patients. The Kaplan-Meier model was used to estimate disease-free survival (DFS).
Results: 80 single miRNA profiles have been analyzed using a microarray approach. We analyzed 1733 miRNas over the 6 months period. The analysis yielded different profile in serum and blood identifying the two biofluids as two distinctive sources of miRNA carrying the same message. Only a small portion of the circulating mirnome remained significant in all time points indicating a dynamic variation in the miRNA expression. Blood mir-3179, 373, 4773 significantly increased from T0 to T6 while mir-2277–5p, 106b, 202 decrease. In serum, mir-4649–3p, 3148, 371 increase while mir-103b decrease. The hierarchical clustering of the most 150 variable miRNAs on log scale clearly differentiated T0 profiles from T1 and T6 both in blood and serum. Interestingly at T1 two main clusters distinguished patient with a complete response from whose having only a partial response to therapy. Further validation of miR-106b showed a correlation between mir-106b levels and treatment response ($P < 0.001$), and the longer DFS ($P < 0.0038$). MiRNA-106b was also significantly correlated with the with BCLC staging A1 and A2 ($P < 0.001$).
Conclusion: This study underlines the importance of the different information provided by miRNA profiles during the follow-up of a single patient. Circulating mir-106b detection offers a promising non-invasive analysis tool to identifyg patients with the longest disease-free survival in response to anticancer therapies.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP136 HEPATITIS B VIRUS GENOTYPE, ZINC RIBBON DOMAIN-CONTAINING 1 ANTISENSE RNA 1 POLYMORPHISMS AND THEIR INTERACTIONS IN HEPATOCELLULAR CARCINOMA: A MULTI-CENTER CASE-CONTROL STUDY

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Introduction: Zinc ribbon domain-containing 1 antisense RNA 1 (ZNRD1-AS1) genetic polymorphisms have been associated with hepatocellular carcinoma (HCC) development. We aimed to determine impacts of ZNRD1-AS1 polymorphisms and their interactions with HBV genotypes on the risk of HCC.
Aims & Methods: We conducted a large multi-center case-control study with a total of 1,507 HBV-related HCC cases and 1,560 HBV persistent carriers. Three single nucleotide polymorphisms (SNPs) in ZNRD1-AS1 (rs3757328, rs6940552 and rs9261204) were genotyped using TaqMan allelic discrimination assay, and HBV genotypes were identified by multiplex PCR.
Results: We found consistently significant associations between ZNRD1-AS1 rs6940552/rs9261204 and increasing risks of HCC (dominant genetic model: adjusted OR = 1.16, 95% CI = 1.03–1.32 for rs6940552; adjusted OR = 1.20, 95% CI = 1.06–1.35 for rs9261204), and a borderline significant association of rs3757328 with HCC risk. Besides, a dose-dependent manner was observed between the increasing number of variant alleles of the three SNPs and the risk for HCC (P for trend < 0.001). Moreover, a strong combined effect of three SNPs was observed among the subjects infected with non-B groups (adjusted OR = 1.26, 95% CI = 1.05–1.50) on HCC risk, compared with those in HBV B-related genotype groups (adjusted OR = 0.89, 95% CI = 0.69–1.15) (P= 0.029 for heterogeneity test). We also detected a significant multiplicative interaction between the variant alleles and HBV genotype on HCC susceptibility (P = 0.030).
Conclusion: ZNRD1-AS1 SNPs (rs3757328, rs6940552 and rs9261204) and their interaction with HBV genotypes may serve as susceptibility biomarkers for risk of HBV-related HCC.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP137 HMGB1-DEPENDENT AUTOPHAGY: A NEW PATHWAY TO MAINTAIN REGULATORY T CELL FUNCTION IN PATIENTS WITH CHRONIC HEPATITIS B

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Introduction: Recent studies suggest autophagy is highly active in regulatory T (Treg) cells. High-mobility group box-1 protein (HMGB1), enriched in the microenvironment of damaged and injured livers, is critical for T cell autophagy.
Aims & Methods: This study is designed to determine whether and how HMGB1-dependent autophagy maintains the immunesuppressive features of Treg cells during chronic hepatitis B virus (HBV) infection. Blood samples from patients with chronic hepatitis B (CHB, n = 36), at immune-tolerant stages (IT, n = 25) and healthy controls (n = 50) were collected. By flow cytometry, $CD4^+CD25^+CD127^-$ (Treg) cells were purified from peripheral blood mononuclear cells (PBMCs) for further analysis. Serum samples were prepared to determine HMGB1 levels. The autophagy in Treg cells were in vitro determined with Lysotracker Green probes in the presence or absence of HMGB1, rapamycin and 3-methyladenine. HMGB1-dependent autophagy pathway and its effects on Treg functions were determined by both western blot and quantitive real-time PCR. The microtubule-associated protein 1 light chain 3 (LC3)-GFP mice were injected with AAV-1.3HBV to further determine HMGB1-dependent autophagy in Treg cells in the microenvironment of livers during chronic HBV infection.
Results: Treg cells from patients in IT group had significantly up-regulated baseline autophagy levels compared to both CHB and HC groups, reflected by increased intracellular mass of lysosomes. The mean fluorescence intensity (MFI) of lysosomes in Treg cells significantly and positively correlated with serum HMGB1 levels. In vitro, HMGB1 mainly acted through the receptor for advanced glycation end-products (RAGEs) of Treg cells to up-regulate the autophagy levels, with significantly decreased phosphorylation of mTOR and increased Beclin-1/Vps34 proteins. Besides, HMGB1-RAGEs induced autophagy was indispensible to maintain Foxp3, CTLA-4, IL-10 and TGF-beita mRNA levels of Treg cells. In HBV-infected mouse models, the intra-hepatic HMGB1, RAGEs and LC3 expressions were significantly increased. Moreover, down-regulated p-mTOR and up-regulated Beclin-1/Vps34 proteins were detected in the intra-hepatic Treg cells.
Conclusion: HMGB1-dependent autophagy is a new mechanism to maintain the immunosuppressive features of Treg cells during chronic HBV infection.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP138 RIOCIGUAT, A STIMULATOR OF THE GUANYLYL CYCLASE, REDUCES LIVER FIBROSIS AND PORTAL PRESSURE IN CIRRHOTIC RATS

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Introduction: Intrahepatic nitric oxide (NO) signaling including activation of its receptor guanylyl cyclase (GC) is impaired in cirrhosis. The GC stimulator riociguat (RIO) is approved for treatment of pulmonary hypertension. Experimental studies suggest antifibrotic effects of RIO. We investigated the effects of RIO in cirrhotic rats with portal hypertension (PHT).

Aims & Methods: Two early and advanced cirrhotic rat models were used to assess changes in hemodynamics and fibrosis after RIO treatment. Cirrhosis was induced by i.p. carbontetrachloride ("early": 1 mL/kg - "advanced": 2 mL/kg 50%CCl4, 8 weeks) or by bile duct ligation (BDL, "early": 3 weeks - or "advanced": 5 weeks) in 100 male Sprague Dawley rats. Controls received olive-oil (OO) or underwent sham operation (SO), respectively. RIO (1 mg/kg/d) or vehicle was gavaged from weeks 5–8 in CCl4/OO and from weeks 2–3 [or 4–5] in BDL/SO animals. Systemic hemodynamics, portal pressure (PP), superior mesenteric blood flow (SMABF) and porto-systemic shunting (PSS) were measured. Hepatic fibrosis was quantified by hydroxyproline content (HP) and chrome aniline blue (CAB) staining. Expression of TNFα, endothelial nitric oxide synthase (eNOS) and inducible NOS (iNOS) were quantified in liver tissue by western blotting.

Results: BDL and CCl4 rats presented with cirrhosis, elevated PP, SMABF and PSS, which was more pronounced in the advanced setting. In early BDL cirrhosis, preventive RIO treatment (W2–3) reduced PP (13.2 ± 2.5 vs. 10.1 ± 2.4 mmHg; $p = 0.048$), HP content (286 ± 147 vs. 144 ± 74 µg/g; $p = 0.039$) and CAB area (24.7 ± 4.6 vs. $13.3 \pm 2.1\%$; $p < 0.001$) without affecting systemic hemodynamics, SMABF or PSS. When RIO was given to BDL rats with advanced disease, PP (15.5 ± 1.6 vs. 11.9 ± 2.1 mm Hg; $p = 0.002$), HP content (354 ± 169 vs. 233 ± 45µg/g; $p = 0.044$) and CAB area (29.9 ± 2.2 vs. $19.3 \pm 5.7\%$; $p < 0.001$) all significantly improved. Further, in BDL-RIO animals, hepatic eNOS and iNOS content increased, while TNFα expression was significantly reduced. In early CCl4-rats, RIO treatment reduced CAB area (33.5 ± 4.9 vs. $25.8 \pm 2.8\%$; $p = 0.028$) while the reduction in HP was not significant. The increase in PP (8.13 ± 1.31 vs. 6.43 ± 0.40 mm Hg; $p = 0.042$) and SMABF (52 ± 5 vs. 42 ± 4 mL/min; $p = 0.010$) observed in early CCl4 cirrhosis was significantly blunted in RIO treated animals. In advanced CCl4 rats only a SMABF reduction (75 ± 11 vs. 43 ± 6 mL/min; $p = 0.036$) and a trend towards lower CAB area (43.8 ± 6.1 vs. $28.9 \pm 7.5\%$; $p = 0.056$) was notable. RIO had no effects in control animals (SO and OO rats).

Conclusion: RIO treatment significantly reduced liver fibrosis and portal pressure in early biliary and toxic cirrhosis. Even in advanced biliary cirrhosis, RIO treatment ameliorated liver fibrosis and portal hypertension.

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All other authors have declared no conflicts of interest.

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OP139 MECHANISM OF LIVER ATROPHY DUE TO PORTAL VEIN EMBOLIZATION - ASSOCIATION WITH AUTOPHAGY AND APOPTOSIS

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Introduction: The mechanism of liver atrophy due to portal vein embolization was still unclear. With regard to the liver, autophagy has been reported to be caused by starvation and related to hepatocellular atrophy[1]. Using pig models of percutaneous transhepatic portal vein embolization (PTPE) with absolute ethanol, we have previously observed temporary elevation of serum levels of liver enzymes immediately after ethanol injection and macroscopic liver atrophy accompanied by an increased future liver remnant /total estimated liver volume ratio 2 weeks after PTPE[2]. The other literature have reported that the relative lobule size in the embolized lobe of the pig had gradually decreased to 23% of the normal pig liver at 12 days after PTPE with a combination of coils and polyvinyl alcohol particles; thereafter, the size did not change[3]. Therefore, in order to clarify the mechanisms responsible for liver atrophy, pathological analysis should be carried out within this time period. However, to the best of our knowledge, these time-course studies have not yet been carried out[4–5].

Aims & Methods: We attempted to investigate the mechanism of liver atrophy by portal vein obstruction and clarify the role of autophagy and apoptosis. As pig lobule structures were well-defined as compared with human specimen, we performed percutaneous transhepatic portal embolization (PTPE) in 5 pigs. And then sacrificed them at day 0, week 2, 4 or 6 (d0, w2, w4 and w6, respectively). In specimens of embolized lobe (E) and non-embolized lobe (control, Cont), we measured the distance between portal vein and central vein (PV-CV), area and hepatocyte number per lobule and apoptotic activity. Immunohistochemical reactivates of microtubule-associated protein-light chain 3 beta (LC3) as autophagy and glutamine synthetase (GS) and cytochrome 2E1 (CYP2E1) as zonation were evaluated.

Results: PV-CV and lobule area showed no significant difference between E and Cont at d0, but were lower in E than in Cont at w2, w4 or w6 ($P \leq 0.001$). Hepatocyte number was not significantly reduced in E at d0 and w2 but was reduced at w4 and w6 ($P \leq 0.01$). Apoptotic activity was higher in E than in Cont at d0 and w4. LC3 staining peaked in E at w2, with no significant difference between E and Cont at w4 and w6. GS and CYP2E1 areas in E at w2, w4 and w6 were narrower than those in Cont.

Conclusion: Our morphological study focused on changes in the lobules over time, and we observed two distinct phases of liver atrophy following portal blood flow disruption. The first (the autophagic phase) was characterized by lobular shrinkage without hepatocytes loss and high LC3 expression, and lasted for the first two weeks following PTPE. The second phase, termed the apoptotic phase, was characterized by reduced hepatocyte number without reduced lobular size but with reduced LC3 expression and increased TUNEL staining, and lasted 2–4 weeks.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP140 EFFECT OF CHRONIC THIOACETAMIDE TREATMENT ON HEPATIC HEMODYNAMIC PARAMETERS IN RATS: EVALUATION BY MAGNETIC RESONANCE IMAGING

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Introduction: For the investigation of hepatic hemodynamics in animal models invasive methods are conventionally used. This study seeks to evaluate a non-invasive Magnetic Resonance Imaging (MRI) method as a reliable diagnostic tool in the widely used model of Thioacetamide (TAA)-induced liver injury.

Aims & Methods: (1) To quantitatively assess hepatic hemodynamic parameters (portal vein area, portal blood flow velocity and portal blood flow volume) and aortal blood flow volume using MRI technique in rats; (2) To investigate the influence of the hepatotoxic agent TAA on these hemodynamic parameters. 54 male Wistar rats were studied. 15 of which were left untreated and 39 received TAA in their drinking water (0.03g TAA / 100 ml H_2O). The TAA dosage was adjusted weekly based on the body weight changes. From the 39 treated rats 15 received TAA for 12 weeks and 24 for 16 weeks. The following parameters were measured by a 9.4 Tesla preclinical MR scanner: portal vein area, portal blood flow velocity, portal blood flow volume and aortal blood flow volume. Specifically gradient-echo fast phase contrast sequences were used with both cardiac and respiratory gating. All MRI measurements were performed under continuous Isoflurane anesthesia. The degree of liver injury was estimated by standard histological criteria. Histological evaluation was performed in all 54 rats while hemodynamic measurements could be evaluated in 50 rats. For statistical analysis Kruskal-Wallis test was used.

Results: From the rats which received TAA for 12 weeks 100% (15/15) developed liver fibrosis with a Desmet score of 1–3 (group 12w/fib). From the rats which

received TAA for 16 weeks, 46% (11/24) developed liver fibrosis with a Desmet score of 1–3 (group 16w/fib) and 54% (13/24) had liver cirrhosis with a Desmet score of 4 (group 16w/cir). The untreated rats (15/54) served as control group (group con). Mean portal vein area showed no significant differences among all groups. However mean portal flow velocity was reduced by 15% in group 12w/fib, 19% in group 16w/fib and 12% in group 16w/cir compared to group con. In group 16w/cir mean weight was significantly lower than that of group con. Thus flow volumes were adjusted according to the body weight in order to eliminate weight-induced changes in hemodynamics. Mean aortal flow volume per body weight showed no significant differences among all groups. In contrast mean portal flow volume per body weight was significantly reduced in group 12w/fib by 23% compared to group con. On the other hand, in group 16w/fib and group 16w/cir there was no further reduction of mean portal flow volume per body weight. These results indicate that in the model of TAA-induced liver injury the development of fibrosis is sufficient to cause a significant decrease in portal flow volume. There were no significant differences between group 12w/fib and 16w/fib in terms of all parameters, in particular portal flow volume.

Conclusion: In conclusion the non-invasive MRI technique can be a reliable diagnostic tool to investigate the hepatic hemodynamics in different experimental models of liver injury. In this particular animal model even the TAA-induced liver fibrosis led to a significantly reduced portal liver perfusion. The molecular mechanisms of this finding need to be further investigated.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30–10:00

OPTIMISING ANTI-TNF THERAPY – ROOM G

OP141 CORRELATION OF ENDOSCOPIC FINDINGS WITH SERUM DRUG CONCENTRATIONS AND NEED FOR RESCUE THERAPY: SUBANALYSIS OF THE TROUGH CONCENTRATION ADAPTED INFLIXIMAB TREATMENT (TAXIT) TRIAL

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Introduction: The Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial [1] showed that targeting patients' infliximab trough concentrations to a 3–7 μg/mL window resulted in a more efficient use of the drug in patients with inflammatory bowel disease. Following dose optimization, continued concentration-based dosing was not superior to clinically-based dosing for achieving clinical and biochemical remission (primary endpoint) after 1 year maintenance treatment. This subanalysis of TAXIT aimed to explore the correlation between drug level-based dosing and endoscopic healing.

Aims & Methods: This was a retrospective analysis of all endoscopies performed at the end of TAXIT. For Crohn's disease (CD), mucosal healing was defined as absence of ulcerations (complete mucosal healing) or clear improvement in ulcerations (partial mucosal healing) when compared to baseline. For ulcerative colitis (UC), healing was defined as a Mayo endoscopic subscore of 0 or 1. Rates of mucosal healing were compared for both arms in TAXIT (clinically-based arm 1 and concentration-based dosing arm 2) and infliximab trough concentrations were correlated to the degree of healing.

Results: Of the 226 patients completing the TAXIT maintenance phase, 125 (55%) underwent endoscopy after one year ($n = 55$ in arm 1 and $n = 70$ in arm 2). In the clinically-based dosing arm 1, 50/55 (91%) patients had mucosal healing at the end of the study, as compared to 63/70 (90%) patients in the concentration-based dosing arm 2 ($p = 1$). The rates of mucosal healing were also comparable between both arms in CD patients (35/38 in arm 1 vs. 49/52 in arm 2; $p = 0.69$) and in UC patients separately (15/17 in arm 1 vs. 14/18 patients in arm 2; $p = 0.66$). Patients who reached the primary endpoint of TAXIT more frequently had complete mucosal healing (73/84 or 87%) compared to patients who did not reach the primary endpoint (28/41 or 68%) ($p = 0.02$). Numerically more patients who needed rescue therapy during maintenance phase of TAXIT had not achieved mucosal healing (3/12 or 25%) compared to patients who did not need rescue therapy (9/113 or 8%) ($p = 0.09$). The mean serum trough concentrations during the maintenance phase of TAXIT were 5.31 μg/mL in patients with mucosal healing and 4.26 μg/mL in patients without mucosal healing ($p = 0.07$).

Conclusion: The primary endpoint of TAXIT, clinical and biochemical remission, correlated with endoscopic mucosal healing. Similar rates of mucosal healing were observed in patients after clinically-based dosing compared to concentration-based dosing. A trend towards less mucosal healing was seen if rescue therapy was needed during TAXIT. Mean serum trough concentrations during the maintenance phase of TAXIT were higher in patients with mucosal healing.

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A. Gils: Lecture fees from MSD, Janssen Biologicals, Abbvie, Pfizer, Takeda. Consultancy for UCB. Conflict with license of infliximab, anti-infliximab and adalimumab ELISA from Institution to apDia and with lateral flow infliximab to R-Biopharm AG.

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All other authors have declared no conflicts of interest.

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OP142 FREQUENCY AND CHARACTERISTICS OF INFUSION REACTIONS DURING BIOSIMILAR INFLIXIMAB TREATMENT IN INFLAMMATORY BOWEL DISEASES: RESULTS FROM CENTRAL EUROPEAN NATIONWIDE COHORT

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Introduction: Safety data of the immunogenicity coming from the 'real life' use of CT-P13, the first biosimilar to infliximab, in inflammatory bowel disease (IBD) are still lacking.

Aims & Methods: Our aim was to assess the frequency and characteristics of infusion reactions during CT-P13 therapy in 13 Hungarian and 1 Czech IBD centres. Demographic data were collected and a harmonized monitoring strategy was applied. Trough level (TL) and anti-drug antibody (ADA) concentration were regularly measured by ELISA at baseline and before every subsequent CT-P13 therapy in the Hungarian cohort. Predictors, characteristics, therapy and outcomes of infusion reactions were prospectively evaluated.

Results: 384 consecutive IBD patients were included in the present cohort. Twenty-eight Hungarian IBD patients (9.6%) developed infusion reaction during the treatment. Infusion reaction did not occur in the Czech population thus predictors were assessed only in the Hungarian patients. Infusion reaction occurred most frequently during the 2nd and 3rd infusion. The most frequent symptoms of infusion reactions were flushing, dyspnoea and chest pain. CT-P13 therapy had to be stopped in 78.6% of the cases and was switched to adalimumab in 42.8% of the patients. However in 21.4% CT-P13 therapy was continued with the use of supplementary intervention. Previous anti-TNF exposure and ADA positivity during the induction therapy were predictive factor for infusion reaction. Concomitant azathioprine therapy showed borderline protective effect on infusion reaction.

Conclusion: Patients with previous exposure to anti-TNFs and ADA positivity during the induction therapy were more likely to develop infusion reactions. CT-P13 biosimilar is safe with low rate of infusion reaction.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP143 AZATHIOPRINE DOSE REDUCTION INFLAMMATORY BOWEL DISEASE PATIENTS ON COMBINATION THERAPY: A PROSPECTIVE STUDY

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Introduction: Combination therapy with infliximab (IFX) and azathioprine (A) is the most effective strategy in patients with Crohn's disease (CD) and ulcerative colitis (UC) naive to both therapies. However the optimal dose of AZA which is needed is still controversial. We assessed the impact of AZA dose reduction on the risk of clinical relapse and pharmacokinetics of IFX in inflammatory bowel disease (IBD) patients on combination therapy.

Aims & Methods: This prospective study included three cohorts of IBD patients treated for at least one year with IFX-AZA and being in deep remission (clinical

Table (OP144): Clinical and serological evolution after dose de-escalation

	T-1 (n = 33)	T0 (n = 43)	T1 (n = 43)	T2 (n = 26)
Median (IQR) time from T0	18.0 weeks (13.5–26.1)		14.0 weeks (12.3–19.0)	30.5 weeks (26.8–34.5)
Median (IQR) ADA serum level	11.6 μg/mL (9.1–15.1)	11.5 μg/mL (9.3–14.3)	7.5 μg/mL (5.8–9.8) *p < 0.001*	7.2 μg/mL (5.4–8.6) *p < 0.001*
Median (IQR) C-reactive protein	1.6 mg/L (0.4–4.9)	1.4 mg/L (0.6–3.3)	1.3 mg/L (0.6–5.1) *p = 0.217*	1.7 mg/L (0.6–4.1) *p = 0.139*
Median (IQR) serum albumin	44.5 g/L (42.6–47.0)	44.1 g/L (42.2–47.0)	43.7 g/L (41.6–47.2) *p = 0.893*	42.4 g/L (40.9–45.0) *p = 0.330*
Median (IQR) PRO2 UC	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0) *p = 1.000*	
Median (IQR) PRO2 CD	0.0 (0.0–7.0)	0.0 (0.0–6.0)	2.0 (0.0–9.0) *p = 0.048*	4.5 (0.0–9.8) *p = 0.021*

p-values: relative to T0, Wilcoxon Signed Rank test; IQR: interquartile range During a median follow-up of 24 months, 39% of patients needed dose escalation to ADM 40 mg every other week due to clinical relapse (23%), ADM serum levels <3 μg/mL (7%) or both (9%). The only independent factor associated with dose escalation free survival was a baseline CRP < 3 mg/L [Odds ratio 3.76 (1.41–10.05), p = 0.008]. We were not able to define a minimal ADM serum level at T0 or T1 to consider or maintain dose de-escalation. In 52% of patients dose de-escalation was associated with a complete disappearance of AE and this after a median of 4 months (8/17 skin manifestation, 3/7 arthralgia, 2/7 recurrent infections).

and endoscopic and/or biomarkers remission) for at least 6 months. All patients had an IFX trough level over 2 μg/mL and were on stable doses of AZA (2 to 2.5 mg/kg/d) and IFX (5 mg/kg every 8 weeks). In cohort A, AZA and IFX were continued unchanged; In cohort B, the dose of AZA was halved, with a minimum dose of 50 mg/d; in cohort C, AZA was stopped and IFX continued as monotherapy. Primary endpoint was failure defined as a clinical relapse (CDAI > 220 with fecal calprotectin > 450 μg/g stools) and/or need to change the original therapeutic regimen because of adverse events. Trough levels of IFX (TRI) and antibodies (ATI) were measured before each infusion.
Results: 81 patients (45 CD and 36 CD, mean age: 29.7 years, mean disease duration: 24 months)were included (28 in Cohort A; 27 in Cohort B; 26 in Cohort C). The clinical characteristics, duration of combination therapy, biomarkers levels and TRI were similar in the three cohorts at the time of inclusion. Five patients (17.8%) in Cohort A, three in Cohort B (11.5%), and 8 in Cohort C (30.7%) experienced failure at one year (p = 0.1 across group). Three patients in Cohort A had to stop AZA or to reduce the dose due to myelotoxicity or digestive intolerance. In cohort A, The mean TRI concentrations were similar at the time of inclusion (3.65 vs 3.45 μg/ml, respectively). In Cohort B, the mean TRI remained stable after the reduction of AZA dose (3.95 vs 3.6 μg/mL, respectively) while there was a significant reduction in the mean 6-TGN levels (310 pmoles vs 128 pmoles, respectively; p = 0 .03) at one year whereas in cohort C, there was a significant reduction in TRI (4.2 vs 2.1 μg/mL; p = 0.02). Four patients (14.2%) in Cohort A, four patients in Cohort B (14.8%), and 11 in Cohort C (42.3%) experienced an unfavourable evolution of IFX pharmacokinetic defined by a decrease of TRI < 1 μg/mL or undetectable TRI with positive ATI (p = 0.022 between A and C, p = 0.039 between B and C, p = 0.87 between A and B). By ROC analysis (AUROC: O.93), a threshold of 6-TGN < 105 pmoles was associated with an unfavourable evolution of IFX pharmacokinetic (sensitivity: 67%; specificity: 92%; Likelihood ratio: 7.67).
Conclusion: AZA dose reduction in IBD patients on combination therapy is as effective as the maintenance of AZA at the same dose and may improve AZA safety profile. A threshold of 6-TGN < 105pmoles was associated with an unfavourable evolution of IFX pharmacokinetics.
Disclosure of Interest: E. Del Tedesco: MSD
S. Paul: Theradiag, MSD
X. Roblin: MSD, Theradiag, HAC Pharma
All other authors have declared no conflicts of interest.

OP144 DOSE DE-ESCALATION TO ADALIMUMAB 40 MG EVERY THREE WEEKS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A RETROSPECTIVE COHORT ANALYSIS

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Introduction: Although dose escalation is widely used to optimize biological therapy in case of clinical relapse, less is known about possibilities to de-escalate therapy in patients with inflammatory bowel disease (IBD) who are in clinical remission. Dose de-escalation may not only have beneficial economic repercussions, it may possibly also decrease the occurrence of adverse events.
Aims & Methods: In this retrospective cohort analysis, the outcome of dose de-escalation to adalimumab (ADM) 40 mg every three weeks (ETW) in patients with IBD was studied. Out of 898 patients treated with ADM for Crohn's disease (CD) or ulcerative colitis (UC) in a tertiary referral center, we selected all patients who had received maintenance therapy with ADM 40 mg ETW with serum levels available before and after dose de-escalation. Serum was collected 4 months prior to dose de-escalation (T-1, n = 33), at dose de-escalation (T0, n = 43), 4 months after dose de-escalation (T1, n = 43) and 8 months after dose de-escalation (T2, n = 26). ADM serum levels were measured using RIDASCREEN® monitoring kit (R-biopharm AG). In addition, patient reported outcome (PRO2), C-reactive protein (CRP) and serum albumin were collected for each time-point. Other baseline variables included disease behavior, disease location, smoking behavior, concomitant therapy, body weight, and body mass index. Mann-Whitney U, Wilcoxon Signed Rank test, and Cox regression were performed using SPSS 23.0.
Results: We identified 43 patients with dose de-escalation to ADM 40 mg ETW (32 male, 39 CD, 4 UC, median age 37 years). All patients received monotherapy with ADM every other week, which was initiated a median of 28 months prior to dose de-escalation. Median PRO2 was 0, and median CRP level 1.4 mg/L. Reasons for dose de-escalation were ADM associated adverse events (AE, n = 1), serum levels above 7 μg/mL (n = 9), or a combination of both (n = 33). Most frequently reported AE were skin manifestations (52%), arthralgia (24%) and recurrent infections (21%). While ADM serum level dropped significantly 4 and 8 months after dose de-escalation, CRP levels remained stable (Table). In patients with CD a significant increase in PRO2 was observed.
Conclusion: In this retrospective cohort analysis, 61% of patients were able to continue ADM therapy at a dose of 40 mg ETW. Furthermore, in half of the patients who experienced ADM related AE at baseline, the AE disappeared completely. Regardless of ADM serum levels, disease remission should be objectively assessed prior to dose de-escalation, since an elevated baseline CRP predicted the relapse following de-escalation with subsequent need for increase of ADM dose.
Disclosure of Interest: S. Vermeire: Grants from MSD, Takeda and Abbvie, lecture fees from Abbvie, MSD, Falk, Tillotts, Ferring, Centocor, Takeda, Hospira; consultancy for Ferring, Abbvie, Shire, Genentech/Roche, Celgene, Janssen, MSD, Takeda, Galapagos, Hospira, Mundipharma, Pfizer.
G. Van Assche: Gert Van Assche receives financial support for research from Abbvie and MSD, lecture fees from Janssen, Takeda, Ferring, MSD, and Abbvie and does consultancy for Abbvie, MSD, and Takeda.
A. Gils: Ann Gils has been a consultant for Merck, Janssen Biologics, and Abbvie
M. Ferrante: Research grant from Janssen Takeda, lecture fees from Tillotts, Ferring, Boehringer-Ingelheim, Janssen, Chiesi, Falk, Zeria, Mitsubishi Tanabe, MSD, Takeda, and Abbvie and does consultancy for Abbvie, Ferring, MSD, Boehringer-Ingelheim and Janssen.
All other authors have declared no conflicts of interest.

OP145 EFFICACY AND SAFETY OF BIOSIMILAR INFLIXIMAB AFTER ONE-YEAR: RESULTS FROM A PROSPECTIVE NATIONWIDE COHORT

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Introduction: Biosimilar infliximab CT-P13 received positive CHMP recommendation in June 2013 for all indications of the originator product. It has been previously shown that CT-P13 is effective and safe in inducing remission in inflammatory bowel diseases (IBD). However, prospective, long-term data on the efficacy and safety of the biosimilar infliximab in IBD are lacking.
Aims & Methods: A prospective, nationwide, multicentre, observational cohort was designed to examine the efficacy and safety of CT-P13 infliximab biosimilar in the induction and maintenance treatment of Crohn's disease (CD) and ulcerative colitis (UC). Demographic data were collected and a harmonized monitoring strategy was applied. Clinical remission, response and biochemical response was evaluated at week 14, 30 and 54. None of the patients had received infliximab within 12 months prior to initiation of the biosimilar infliximab. Safety data was registered.
Results: 291 consecutive IBD (184 CD and 107 UC) patients were included in the present cohort, of which 100 patients reached the week 54 endpoint. The age at disease onset was 23/28 years (median, IQR: 19–34 and 22–39) in CD and UC patients, respectively. 32/49% of CD patients had colonic/ileocolonic disease location, 41% had complicated disease behaviour, 35% had perianal disease and 23% had gone through previous surgery. 8/33/59% of UC patients had proctitis/left-sided colitis/extensive colitis. 25/14% of patients had received previous anti-TNF therapy in CD and UC, respectively. 60/52% of CD/UC patients received concomitant immunosuppressives at baseline. 55, 57 and 47% of CD patients reached clinical remission by week 14, 30 and 54. Clinical response was 83, 77 and 58%, respectively. 59, 46 and 53% of UC patients reached clinical remission by week 14, 30 and 54. Clinical response was 78, 69 and 64%, respectively. Previous anti-TNF exposure was associated with lower response and remission rates in both CD ($p < 0.001/0.01$, $p = 0.014/0.05$ and $p = 0.002/0.04$) and UC ($p = NS/0.06$, $p = 0.1/0.1$ and $p = 0.048/0.03$) at weeks 14, 30 and 54. Mean CRP decreased significantly both in CD and UC patients by week 14, which was maintained throughout the 1-year follow-up. (CRP level decreased from 20.5 to W14: 8, W30: 8.7 and W54: 12.1 mg/ L in CD and from 29.5 to W14: 8.5, W30: 13 and W54: 12.3 mg/L in UC). 21 (6.6%) patients had infusion reactions, 23 (7.9%) patients had infections and 1 death occurred.
Conclusion: This prospective nationwide cohort shows that CT-P13 is effective and safe in inducing and maintaining remission in both CD and UC. Efficacy was influenced by previous anti-TNF exposure.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP146 COST-UTILITY OF BIOSIMILAR INFLIXIMAB (INFLECTRA©) FOR THE TREATMENT OF LUMINAL CROHN'S DISEASE IN NINE EUROPEAN COUNTRIES

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Introduction: Biosimilar infliximab (Inflectra©) has been approved by the European Medicines Agency for the treatment of luminal Crohn's disease (CD) since 2013. Currently biosimilars offer a massive price reduction in most European countries. Nevertheless, no study has yet compared the cost-effectiveness of originator and biosimilar agents in luminal CD patients. (Furthermore, there are no published studies reporting between-biologicals cost-effectiveness for luminal CD in European countries.)
Aims & Methods: We aim to compare cost-effectiveness of adalimumab, infliximab, vedolizumab and biosimilar infliximab for the treatment of luminal CD in nine European countries (Belgium, France, Germany, Hungary, Italy, the Netherlands, Spain, Sweden and the UK). A probabilistic Markov model was developed to analyse the cost-effectiveness of selected biological treatment sequences compared to the standard care or to other biological sequences in patients with moderate to severely active luminal CD unresponsive to conventional treatment. Transition probabilities of moving between health states were estimated based on randomised controlled trials and cohorts. Country-specific unit costs, including drugs, monitoring, administration, hospitalization and surgical costs were considered. The model applied a third-party payer perspective and a five-year time horizon. Discount rates for both costs and benefits complied with the national pharmacoeconomic guidelines.
Results: The incremental cost-utility ratio (ICUR) of the biosimilar infliximab-standard care treatment sequence vs. standard care varied between €35,170/QALY (Hungary) and €71,624/QALY (Sweden). Over the five years, the average undiscounted health gain was 0.3 QALY per patient. In all countries, biosimilar infliximab was dominant relative to originator infliximab-standard care strategy. The inclusion of additional biologicals to the treatment sequence resulted in a higher cost-utility ratio. ICURs of biosimilar infliximab-adalimumab-vedolizumab sequences ranged from €77,305/QALY to €125,643/QALY compared to the standard care. The biosimilar infliximab-adalimumab-vedolizumab sequence dominated the originator infliximab-adalimumab-vedolizumab sequence. The results were most sensitive to changes in the perspective of the analysis, utility values and time horizon (10-year).
Conclusion: Biosimilar infliximab is a cost-effective alternative to the originator product for the treatment of adults with luminal CD, and it may contribute to increasing the affordability of biological treatments throughout Europe.
Disclosure of Interest: F. Rencz: F Rencz received funding from Hospira Pfizer.
V. Brodszky: V Brodszky received funding and support for research on biosimilars from EGIS Pharma, and Hospira Pfizer.
P. Baji: P Baji received funding and support for research on biosimilars from EGIS Pharma, and Hospira Pfizer.
M. Pentek: M Pentek received funding and support for research on biosimilars from EGIS Pharma, and Hospira Pfizer.
L. Gulacsi: L Gulácsi has been paid as a consultant by Celltrion and received funding, and support for research on biosimilars from EGIS Pharma and Hospira Pfizer.
K.B. Gecse: KB Gecse has served as a consultant for Pfizer/Hospira and Sandoz and received speaker's honoraria from Pfizer/Hospira.
P.L. Lakatos: PL Lakatos has served as a consultant for Celltrion, EGIS and Pfizer/Hospira and received speaker's honoraria from Celltrion, EGIS and Pfizer/Hospira and unrestricted research funding from Pfier/Hospira.
All other authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30–10:00
DRUG-INDUCED UPER GI BLEEDING – ROOM K

OP147 IDARUCIZUMAB FOR EMERGENT REVERSAL OF DABIGATRAN-RELATED ANTICOAGULATION DURING SEVERE GASTROINTESTINAL HEMORRHAGE: INTERIM RESULTS (N = 123) FROM THE REVERSE-ADTM STUDY

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Introduction: Gastrointestinal bleeding (GIB) is a feared complication of anticoagulation therapy. Idarucizumab (IDA) is a rapid-onset specific reversal agent for the direct thrombin inhibitor dabigatran. IDA should benefit management of dabigatran users experiencing severe GIB.
Aims & Methods: The on-going REVERSE-AD™ study evaluates the safety and efficacy of IDA 5 grams intravenously in dabigatran users with (A) life-threatening haemorrhage or (B) requirement for emergency surgery. Here, we analyze the clinical characteristics and outcomes of REVERSE-AD™ enrolees presenting with severe GIB. Our study is performed on an interim analysis cohort of 123 patients; centralized laboratory coagulation data are available for 90/123 (20/27 patients with major GIB).
Results: Of the 66 patients enrolled in REVERSE-AD™ due to severe bleeding, 27 (41%) bled in the GI tract. The mean age of GIB patients was 77.5 years (range, 60–93), 15 (56%) were male, and renal impairment was present in 22 of the 23 patients with creatinine clearance measurements (96%). Atrial fibrillation was the indication for anticoagulation in 93%; 74% took their most recent dabigatran dose <24 hours before presentation. Ten patients (37%) bled from the upper GI tract, 8 (30%) from the lower GI tract, and 9 (33%) from an unknown level of the GI tract. IDA achieved immediate reversal of dabigatran-related anticoagulation, and its effect lasted for up to 24 hours in the majority of patients. Hospital admission was required for 25 patients (93%, median length of stay = 6.0 nights); 8 patients required ≥1 day in intensive care unit (ICU) (30%, median length of ICU stay = 3.5 days). Patients with lower GI bleeding had shorter time to cessation of bleeding (median 1.5 hours vs. 7.3 hours). No adverse events attributable to IDA were reported. A total of 24 patients received ≥1 unit packed red cells (mean 4.5 units); 9 received fresh frozen plasma (mean 2.6 units); 2 received platelets (mean 1.5 units); and 1 received prothrombin complex concentrate prior to IDA treatment. There were 3 deaths by 90 days, but none directly attributable to GIB. Antithrombotic therapy was resumed in 20 patients (74%) prior to study termination, within a median of 6.1 days (range 0–41 days) after IDA administration. Dabigatran was resumed in 6 patients (22%).
Conclusion: The GI tract is the most common site of anticoagulant-associated haemorrhage meeting clinical criteria for emergent reversal. IDA achieves immediate reversal of dabigatran-induced anticoagulation, an effect that is sustained for up to 1 day in the majority of patients. Overall, GIB outcomes in this setting are favourable; antithrombotic therapy can be resumed promptly in most patients.
Disclosure of Interest: J. Aisenberg: James has provided consultancy to Boehringer Ingelheim.
P. Reilly: Paul Reilly is an employee of Boehringer Ingelheim Pharmaceuticals
F. Gruenenfelder: Fredrik Gruenenfelder is an employee of Boehringer Ingelheim Pharmaceuticals
E. Kleine: Eva Kleine is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG
S. Glund: Stephan Glund Pharma is an employee of Boehringer Ingelheim GmbH & Co. KG

J. van Ryn: Joanne van Ryn is an employee of Boehringer Ingelheim GmbH & Co. KG
C.V. Pollack: BI, Bristol-Myers Squibb (BMS)/Pfizer, Daiichi Sankyo (DS), Janssen, AstraZeneca (AZ).
All other authors have declared no conflicts of interest.

OP148 ROLE OF MELATONIN RECEPTORS, SURVIVIN, INSULIN GROWTH FACTOR-1 AND ITS RECEPTOR IN PROTECTIVE ACTION OF MELATONIN AGAINST INDOMETHACIN DAMAGE OF GASTRIC EPITHELIAL CELLS

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Introduction: Melatonin is a major pineal gland hormone involved in the control of sleep and circadian rhythm but present also in large quantities in the gut. This indoleamine is a potent free radical scavenger and exerts protective action against mucosal injury induced by gastric corrosive substances (ethanol, bile) and stress but the possibility that melatonin directly protects in vitro gastric epithelial cells (cytoprotection) against injury under conditions independent of systemic (e.g. neural, vascular) factors has not been explored before. Likewise, the expression of melatonin receptors (MT1 & MT2) in gastric epithelial cells; and, their spatial relation to factors promoting cell survival such as survivin, insulin like growth factor (IGF-1) and its receptor 1 β (IGFR-1β) has not been so far elucidated.
Aims & Methods: We studied whether the pretreatment with melatonin results in protection of cultured rat gastric epithelial cells against indomethacin-induced gastric mucosal injury and whether it affects the expression of MT1 and -2, survivin, IGF-1 and IGFR-1β in these cells. In in vitro study, the cultured normal rat gastric mucosal epithelial cells (RGM1) were pretreated with vehicle or melatonin (10 μM) for 24 hrs and then exposed to either: medium alone (controls), or indomethacin (IND–0.25 mM) for 4 hrs. In these cells the following were assessed: 1) cell injury under confocal microscopy, 2) survival and apoptosis using Calcein AM live cell tracking dye and MTT assay; 3) cell proliferation using BrdU assay; 4) quantitatively expression of MT1 & 2, and survivin, IGF-1 and IGFR-1β by Western blotting and immunostaining. For comparison, the quantitative expression of MT1 and MT2 in gastric epithelial and submucosal structures from full thickness wall specimens of a normal rat stomach was evaluated.
Results: Rat gastric mucosa expressed both MT1 and MT2 (1.8-fold more MT1 than MT2; $p < 0.01$) in gastric epithelial progenitor cells, endothelial cells of blood vessels, and in enteric neural elements. RGM1 cells expressed both MT1 and MT2, which were co-localized with survivin, IGF-1 and IGFR-1β. IND treatment produced extensive cell injury and reduced RGM1 cell viability by 3.8-fold ($p < 0.001$ vs. control). In cells pretreated with melatonin, IND-induced cell injury and death was dramatically reduced by $82 \pm 4\%$ ($p < 0.001$) reflecting a direct protective action of melatonin.
Conclusion: 1) Melatonin directly protects the gastric mucosal epithelial cells against IND- induced injury and this effect is independent of systemic and neural factors, 2) rat gastric epithelial RGM1 cells express melatonin receptors MT1 and MT2 that are co-localized with survivin, IGF-1 and IGFR-1β indicating local autocrine interactions, and 3) besides the systemic hormonal action of melatonin derived from pineal gland, this indoleamine can protect the gastric epithelial cells possibly due to its local autocrine and paracrine actions and interactions with survivin, IGF-1 and its receptor.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP149 RISK OF REBLEEDING, VASCULAR EVENTS AND DEATH AFTER GASTROINTESTINAL BLEEDING IN ANTICOAGULANT AND/OR ANTIPLATELET USERS

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Introduction: Patients who develop gastrointestinal (GI) bleeding during anticoagulant (AC) and/or antiplatelet (AP) therapy represent a clinical challenge. Clinical decisión of either long-term interruption or short-term resumption of these treatments will have important clinical implications concerning the risk of vascular, GI bleeding and death events. Differences on the risks between AP or AC users after drug resumption are not well established.
Aims & Methods: We aimed to determine the rate of rebleeding, vascular events and death in a cohort of patients treated with AP or AC agents who developed a major GIB (upper or lower) event. To compare these risks depending on the treatment adopted after the GIB event. Methods: Retrospective long-term observational cohort study of patients who developed GIB while on AP and/or AC treatment from March 2008 to August 2013. Drug use information was prospectively collected during the GIB event. Data concerning the follow-up period, which ended on December 31st 2013 were obtained from databases from 2 different Spanish Health care areas. Primary outcomes were vascular event, GI rebleeding and death from any cause. Statistical analyses were performed using SPSS software version 22.0.
Results: 774 patients were included (mean age 78.7 ± 8.9; 56.6% males); 52.8% (409/774), 38.5% (298/774), 8.7% (67/774) were on AP, AC or AP+AC therapy respectively. 22.6% of patients presented rebleeding, 17.1% ischemic event and 26.0% death during the follow up (median 23 months). Following the index GIB, therapy was interrupted in 92.2% (714/774) of patients, although 80.1% (572/714) resumed afterwards (median time 6 days (1–370). Resumption of therapy was associated with higher risk of rebleeding (3.5% vs 24%;$p < 0.001$) but lower risk of death (43.7% vs 19.9%;$p < 0.001$). Early resumption of therapy (≤7 days) vs delayed (>7) was associated with a higher rate of ischemic events (13% vs 20.4%;$p = 0.020$), with no statistical differences in GI events. AC users had higher death risk (OR 1.5; 95%CI: 1.1–2.2) compared to AP users. Dual AP users had higher risk of ischemic events (OR 2.1; 95%CI: 1.1–3.7). Rebleeding event rates were 85 and 120 events per 1000 pt-year with AP and AC users respectively. The corresponding event rates were 71 and 82 per 1000 pt-year for vascular events, and 93 and 144 respectively for deaths.
Conclusion: Nearly 40% of patients presented a new adverse event related with AP/AC treatment during the follow-up. The risk of death is higher in patients on AC therapy compared with AP users. Resumption of AC/AP therapy is associated with higher risk of rebleeding and lower risk of death without any influence on ischemic events. Resumption of AP or AC agents later than 7 days is associated with significant higher risk of ischemic events.
Disclosure of Interest: A. Lanas: Professor Lanas has been advisor for AstraZeneca, Bayer and Pfizer.
All other authors have declared no conflicts of interest.

OP150 NOVEL 4-THIAZOLIDINONE DERIVATIVES AS CYTOPROTECTIVE AGENTS AGAINST NSAID-INDUCED INJURY

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Introduction: Hydrogen sulfide (H_2S) and prostaglandins are an important mediator of mucosal defense and suppression of its synthesis by NSAIDs leads to increased susceptibility to enteropathy. H_2S also exerts a number of anti-inflammatory effects. Thus, the ability of H_2S to promote the healing of the damage tissue and to resolution of inflammatory response has been exploited in the development of novel therapeutic agents.
Aims & Methods: The purpose of our study was to investigate the role of 4-thiazolidinone derivatives (compounds Les-5054 [5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-2-thioxo-thiazolidin-4-one] and Les-5055 [3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-mercapto-acrylic acid]) as a novel H_2S donors in promoting the resolution of inflammation and injury in small intestine. The studies were conducted on 40 white rats weighing 180–250 g according to the ethical requirements concerning the work with the laboratory animals. Animals were divided into 4 groups: I – control; II – small intestinal injury produced by indomethacin (IM) in the ulcerogenic dose (35 mg/ kg, subcutaneously) per 72 h; III, IV – compounds Les-5054 and Les-5055 were administered three times per 72 h intragastrically at a single dose 10 mgkg-1 on the background of NSAID-induced injury. Then the rats were sacrificed and in small intestinal mucosa were measured the NOS and arginase activity, concentration of nitrite anion and MDA, activity of enzymes of the antioxidant protection system (SOD and catalase) and MPO activity; the concentration of L-arginine and H_2S in blood plasma.
Results: IM injection manifested by erosions and hemorrhages and leads to the following changes: the activity of iNOS increased more than threefold ($P < 0.01$) as well as the content of nitrite enhanced in two times while arginase activity decrease more than 4 fold ($P < 0.01$); enhanced activity of lipid peroxidation processes manifested by a steep rise of MDA concentration – by 56% ($P < 0.01$), MPO activity enhanced more than 4 fold ($P < 0.01$) and catalase activity – by 32% ($P < 0.01$). Compound Les-5054 displayed significant cytoprotective effect and decreased the total area of hemorrhagic lesions for 63% ($p < 0.05$). The administration of Les-5054 on the background of IM decrease the activity of iNOS for 35% ($P < 0.01$), and activity of eNOS increased for 52% ($P < 0.01$), MDA concentration declined for 32% ($P < 0.01$), H_2S concentration increased for 24% ($P < 0.05$) as compared with indices of the second group. Compound Les-5055 decreased the total area of hemorrhagic lesions for 37% ($p < 0.05$) as compared with independent action of indomethacin. Parameters of NO-synthase system in Les-5055-treated group showed the same tendency as under the effect of Les-5054.
Conclusion: Administration of 4-thiazolidinone derivatives on the background of indomethacin induced injury reduce the activity of iNOS, myeloperoxidase, intensity of lipid peroxidation and increase generation of H_2S, that may be linked with the structure of this compounds. However compound Les-5054 showed more efficacious effect and antioxidant properties than compound Les-5055. Thus, the novel 4-thiazolidinone derivatives, particularly compound

Les-5054 demonstrated a remarkable anti-inflammatory and cytoprotective ability against experimentally NSAID-induced damage in small intestine.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP151 BACTERICIDAL/PERMEABILITY INCREASING FOLD-CONTAINING FAMILY B MEMBER 4 (BPIFB4) ASSOCIATED WITH NSAID-INDUCED SMALL INTESTINAL MUCOSAL INJURY

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Introduction: There was considerable individual variability in NSAID-induced small intestinal injury in previous studies on healthy subjects. Several studies reported that several single nucleotide polymorphisms (SNPs) were associated with gastrointestinal bleeding and/or ulceration. However, the studies investigated only a few candidate SNPs in the enzymes of metabolizing NSAIDs and arachidonic acid cascade. Therefore, a comprehensive analysis was necessary to identify other unknown SNPs having a stronger effect on NSAID-induced small intestinal injury than the reported SNPs.
Aims & Methods: The aim of the study was to identify the SNP most significantly involved with NSAID-induced small intestinal mucosal injury. One-hundred fifty healthy subjects were enrolled from an RCT which compared small intestinal mucosal breaks after 14-day treatment between celecoxib monotherapy and concomitant treatment with loxoprofen and lansoprazole. Details of the RCT were reported by Fujimori S et al (1). After the RCT, subjects were divided into three groups on the basis of numbers of increasing small intestinal mucosal breaks after NSAIDs treatment with zero (No injury group), one to four (Mild injury group), and five and more mucosal breaks (Severe injury group). A genome-wide association study (GWAS) was conducted among the three groups to detect the SNP which was the most associated with NSAID enteropathy.
Results: After RCT and GWAS analysis, 70 subjects receiving the loxoprofen treatment and 69 subjects receiving the celecoxib treatment were determined to eligible for analysis. The minimum p-value was detected in the analysis between 16 cases with five or more mucosal breaks (severe injury group) and 123 controls with zero to four mucosal breaks (no injury group combined with mild injury group). In the GWAS, five SNPs in bactericidal/permeability-increasing fold-containing family B member 4 (BPIFB4) gene showed the lowest p-value ($p = 2.69 \times 10^{-7}$ with an odds ratio of 40.91). Among the five SNPs, four were nonsynonymous SNPs (rs2070325: V268I, rs2889732: T320N, rs11699009: F527L, rs11696307: T533I, rs11696310: intronic).
Conclusion: Although SNPs that surpassed the genome-wide significance level ($p < 5 \times 10^{-8}$) could not be identified through GWAS, results seemed to indicate that the SNPs of BPIFB4 were associated with NSAID-induced small intestinal mucosal injury. (UMIN: 000007936: The GWAS was financially supported by grants from the Project for Development of Innovative Research on Cancer Therapeutics and from the Tailor-made Medical Treatment Program (BioBank Japan) funded by Ministry of Education, Culture, Sports, Science and Technology of Japan.)
Disclosure of Interest: S. Fujimori: Dr. Fujimori has received grant/research support from Astellas Pharma Inc., Covidien Co, Ltd., Daiich-Sankyo Co. Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Pfizer Japan Inc., and, Zeria Co., Ltd.
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C. Sakamoto: Dr. Choitsu Sakamoto has received speaker fees from Pfizer, Astellas, and AstraZeneca.
All other authors have declared no conflicts of interest.

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OP152 RISK OF GASTROINTESTINAL BLEEDING AND BENEFIT FROM COLORECTAL CANCER REDUCTION. A 10-YEAR POPULATION-BASED STUDY FOR LONG-TERM USE OF LOW DOSE ASPIRIN

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Introduction: Aspirin is a potent anti-platelet agent used for the prevention of cardiovascular and cerebro-vascular diseases. It has also been proven to be effective in reducing the incidence of colorectal cancers (CRC) in many previous studies. However, gastrointestinal (GI) bleeding is the most frequently reported serious adverse events for the long term use of aspirin.
Aims & Methods: The objective of this study is to investigate whether the risk of aspirin usage on increasing ulcer bleeding would outweigh its benefit on the prevention of CRC. The present study investigated the electronic medical records from 42 publically funded hospitals, which serves a 7 million population in Hong Kong. All hospital admissions from 2000 to 2004 and their outcome in the follow-up period were extracted until 2014. Aspirin users were matched with age and gender in a ratio of 1:2 to non-aspirin users in the study period. Incidences of CRC and GI bleeding were the primary outcomes. Logistic regression was used to compare incidence rates and Cox-proportional hazard regression model was used to compare the mortality rates. Subgroup analyses were performed for those with ulcer bleeding, or for those with regular aspirin prescribed.
Results: A total of 4,564,100 subjects were identified in the system between year 2000 and 2004, and 254,887 of them (5.6%) were prescribed aspirin for at least one month. Among the subjects who were never prescribed aspirin, 491,852 subjects (10.8%) were identified in the system. The total sample size of this study was 746,739. The baseline characteristics of aspirin and non-aspirin users are described in Table 1. The mean ages of aspirin users and non-aspirin users were 68.4 (SD = 13.1) and 66.4 (SD = 13.2) respectively. In the aspirin group, 78,316 patients (30.7%) had aspirin prescribed for 10 years or more, and 54,011 of them (69.0%) were routinely prescription during the years of clinic visits. Median dose of aspirin used among the patients were 80 mg with interquartile range from 80 mg to 100 mg. Average duration of aspirin prescribed was 6.3 years. Patients in aspirin group showed significantly lower incidence of CRC (OR = 0.82; 95% CI = 0.80 to 0.85), and showed significant reduction in overall mortality (HR = 0.89; 95% CI = 0.86 to 0.92). Whereas, patients in aspirin group showed significantly higher incidence of GI bleeding (OR = 1.77; 95% CI = 1.74 to 1.80), and showed marginally significant higher mortality among those diagnosed with GI bleeding (HR = 1.03; 95% CI = 1.02 to 1.05). The results remained consistent in the subgroup analyses.
Conclusion: This is a population-based study to concurrently compare the risk and benefit of long-term use of aspirin. We concluded that long-term use of low-dose aspirin will increase the incidence of GI bleeding, and moderate increase the overall mortality among the patients with GI bleeding. On the other hand, the long-term use of aspirin showed benefit to reduce CRC on both incidence and overall mortality.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30–10:00
OUTCOMES IN PERORAL ENDOSCOPIC MYOTOMY (POEM) – ROOM M

OP153 COMPREHENSIVE ANALYSIS OF ADVERSE EVENTS ASSOCIATED WITH PER ORAL ENDOSCOPIC MYOTOMY (POEM) IN 1826 PATIENTS: AN INTERNATIONAL MULTICENTER STUDY

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Introduction: POEM was introduced as a minimally invasive and effective therapeutic modality for the treatment of achalasia and spastic esophageal disorders (SEDs). Data largely from single-center studies and small case series suggest

POEM as a safe alternative to Heller Myotomy. However, the safety of POEM is still debated since comprehensive analysis of adverse events (AEs) associated with POEM in large cohort studies has not been performed.
Aims & Methods: We aimed to study (1) the rate of AEs and (2) factors associated with occurrence of AEs in patients undergoing POEM. Methods: Patients who underwent POEM performed for the treatment of achalasia and SEDs at 12 tertiary-care centers (5 US, 4 Europe, 2 Asia and 1 Australia) between 2011 and 2015 were used in a case-control study. Cases were defined by the occurrence of any AEs related to POEM procedure. Control patients were selected for each AE case by matching for age, gender, disease classification (type I&II vs. type III/SEDs). All pertinent data including AEs were collected and their severity was graded according to the ASGE lexicon's severity grading system.
Results: A total of 1826 patients underwent POEM during the study period. Overall, 153 AEs occurred in 137 patients (7.5%). A total of 48 inadvertent mucosotomies occurred and represented the most common AE of POEM (31% of all AEs, overall incidence 2.8%). Mild, moderate and severe AEs occurred in 102 (74.5%), 26 (19%) and 9 (6.5%) patients, respectively. Among the 9 severe AEs, 2 were esophageal leaks, 1 perforation, 1 aspiration pneumonia, 1 empyema, 1 pneumomediastinum, 1 cardiac arrhythmia and 2 delayed bleeding). There were no deaths related to POEM. When patients with AEs were compared with a control group (case-control analysis), there was no difference between the 2 groups in terms of Charlson comorbidity index/ASA class, prior therapy, sigmoid esophagus, operator specialty, direction of myotomy (anterior vs. posterior), type of knife used, extent and length of myotomy, and operator experience. However, time of procedure was significantly longer in cases as compared to controls (123 min $\pm$ 49 vs. 103 min $\pm$ 38, $p = 0.002$). Length of stay was significantly higher in patients who experienced AEs (4.9d vs. 2.7d, $p < 0.001$).
Conclusion: This is the largest study that comprehensively assessed safety of POEM. It highly suggests POEM as a safe therapeutic modality with an overall 7.5% incidence of AEs. Severe AEs are rare. AEs result in prolongation of hospital stay. Longer procedural times (indicative of technically complex procedures) are associated with increases occurrence of AEs.
Disclosure of Interest: M. Khashab: Consultant of Boston Scientific and Xlumena
All other authors have declared no conflicts of interest.

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OP154 LONG TERM OUTCOMES OF PERORAL ENDOSCOPIC MYOTOMY (POEM) IN ACHALASIA PATIENTS WITH A MINIMUM FOLLOW-UP OF 2 YEARS: AN INTERNATIONAL MULTICENTER STUDY

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Introduction: Peroral endoscopic myotomy (POEM) aims to palliate symptoms of achalasia by reducing pressure at the lower esophageal sphincter (LES). Current data demonstrates high short-term clinical response in 82–100% of patients. However, long term data is very limited.
Aims & Methods: We aimed to study (1) clinical outcome of patients with a minimum post-POEM follow-up of 2 years and (2) factors associated with long term clinical failure after POEM. Methods: We conducted a retrospective review of consecutive patients with achalasia who underwent POEM with a minimum follow-up of 2 years at 10 tertiary-care centers (3 US, 4 Europe, 3 Asia). Clinical response was defined by decrease in Eckardt score to ≤ 3.
Results: A total of 179 patients (82 males (45.8%); mean age 49 yr) underwent POEM for the treatment of achalasia (type I 11, type II 51, type III 6, unspecified type 111). Of these, 16 patients (8.9%) had prior Heller myotomy, 65 (36%) had prior pneumatic dilatation (PD) and 6 (3%) had prior botulinum injection. POEM was successfully completed in all patients. A total of 18 adverse events occurred in 8 (4.4%) patients (8 mucosotomies, 1 delayed bleeding, 1 esophageal leak, 2 DVT/PE, 1 pneumothorax, 2 symptomatic pleural effusion, 2 aspiration pneumonia, and 1 mediastinitis). The median follow-up was 30 months (IQR 26–37). Clinical success was achieved in 97.5% (159/163), 99.8% (124/125), 90% (161/179) in patients with follow-up within 6 months, at 12 months, and $\geq$24 months, respectively. Of 159 patients with clinical response at 6 months, 11 (7%) experienced recurrent symptoms at 2 years. Mean Eckardt score decreased from 6.7 ± 2.2 before POEM to 1.5 ± 1.4 at the time of last follow-up ($p < 0.001$) and 4sIRP pressure improved, 23.3 ± 8.7 to 7.1 ± 4.4 mmHg ($p < 0.001$). As compared to patients with clinical response, the non responders were more likely to be younger (44 ± 8 vs 49 ± 16 yr, p 0.03) and had history of prior PD (11 (61%) vs 54 (33%), p 0.03). In a multivariate analysis, history of prior PD was independently associated with long-term treatment failure (OR 2.99; 95%CI 1.09–8.22, p 0.03). Three patients with clinical failure underwent treatment with repeat

Table (OP154)

	Aspirin Group (n = 254,887)	Non-Aspirin Group (n = 491,852)
Age < 50 50–64 65–79 > = 80	24,067 (9.4%) 59,289 (23.3%) 121,671 (47.7%) 49,860 (19.6%)	57,690 (11.7%) 129,196 (26.3%) 232,319 (47.2%) 72,647 (14.8%)
Sex – Male	136,534 (53.8%)	260,933 (53.1%)
Duration of Aspirin Prescribed 1 month to < 6 months 6 months to < 3 years 3 years to < 5 years 5 years to < 10 years 10 years or more	48,591 (19.1%) 44,516 (17.5%) 34,013 (13.3%) 49,451 (19.4%) 78,316 (30.7%)	NA*

*Not Applicable for the Patients in Non-Aspirin Group.

POEM (n = 1) and Heller myotomy (n = 2) and clinical response was noted in 2 of them. Of 171 patients with available data, 24% patients reported reflux symptoms after POEM. Reflux esophagitis was noted in 26 patients of 144 (18%) who had EGD after POEM. 15% of asymptomatic patients had reflux esophagitis.
Conclusion: POEM is safe and provides high initial clinical success and excellent long-term outcomes. Less than 10% of patients who had clinical response at 6 months had recurrent symptoms at 2 years. History of prior pneumatic dilatation is associated with clinical failure. Post-POEM symptomatic reflux occurs in quarter of patients and esophagitis is found in 15% of asymptomatic patients.
Disclosure of Interest: S. Roman: Sabine Roman is a consultant for Medtronic and Sandhill Scientific
F. Mion: Francois Mion is a consultant for Medtronic
M. Khashab: Mouen Khashab is a consultant for Boston Scientific
All other authors have declared no conflicts of interest.

OP155 A 5-YEAR LONG POEM EXPERIENCE. IS IT TIME TO DRAW CONCLUSIONS?

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Introduction: Peroral Endoscopic Myotomy (POEM) has been recently developed for the treatment of achalasia and other esophageal motility disorders. Despite being widely used in many centers, data on the long-term efficacy of POEM are still lacking. We report on a large consecutive series of patients treated with POEM, with mid- and long-term follow-up.
Aims & Methods: All the patients who underwent POEM between May 2011 and April 2016 at our endoscopy unit were retrospectively identified on a prospectively collected database. Analyzed data included demographics, clinical history, previous treatments, manometry and procedure data, complications and clinical outcomes. Follow-up visits were scheduled at 3, 6, 12, 24, 36, 48 and 60 months after POEM. EGD, manometry and barium swallow were regularly performed during follow-up. pH-monitoring study was performed once, usually between the 6- and 12-month follow-up visit. Clinical success was defined by an Eckardt score ≤ 3.
Results: A total of 347 patients underwent POEM (mean age 47 years, 48% males). Seventy-eight patients (22.5%) had type I achalasia, 174 type II (50.1%), 40 type III (11.5%), 2 Jackhammer esophagus (0.6%), 4 distal esophageal spasm (1.1%), 1 nutcracker esophagus (0.3%); in 48 patients (13.8%) achalasia type was not classified (ie: standard manometry or incomplete examination). Before POEM, 52 patients had undergo pneumatic dilation (PD), 8 surgical myotomy, 8 botulinum toxin injection. The procedure was effectively completed in 338 cases (97%). Mild complications occurred in 3 patients (0.8%): a delayed bleeding, a covered esophageal perforation, and a esophageal stricture following a large ulceration. All the above mentioned complications were treated conservatively. Four patients were lost at follow-up. A minimum 6-month follow-up was available for 274 patients (mean follow-up 19 months). Clinical success was achieved in 95% of patients. Thirteen patients had symptoms recurrence: 7 underwent successful PD, 3 surgery, 3 received no treatment because of mild symptoms. Clinical success slightly decreased with time, being 97%, 97%, 93%, 85%, 72% and 67% after 6, 12, 24, 36, 48 and 60 months, respectively. However, almost 50% of recurrences (6/13) occurred during the first 25 cases (learning curve). No associations were found between preoperative manometric pattern and clinical outcomes: the success rate of POEM was similar in patients with type I, type II and type III achalasia (94%, 96% and 91%, respectively. $p > 0.05$). A total reflux time > 5% was diagnosed in 50% of the patients (111/223) who underwent pH-study. Esophagitis was seen in 28% of patients, 22% of patients receive PPI because of heartburn. Esophagitis healed completely with proton pump inhibitors (PPI) in all the patients. GERD symptoms were effectively controlled with PPI in all the patients but 2 who complained with heartburn and regurgitations.
Conclusion: Our mid-term and long-term follow-up analysis confirms the safety and efficacy of POEM for the management of achalasia and other motility disorders. The vast majority of initial clinical failure can be solved with endoscopic re-treatment. Iatrogenic GERD-rate remains the only possible drawback of the procedure.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP156 MAJOR PERI-OPERATIVE ADVERSE EVENTS OF PERORAL ENDOSCOPIC MYOTOMY (POEM): 5 YEARS' EXPERIENCE, 1680 PATIENTS

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Introduction: Peroral endoscopic myotomy (POEM) is now a widely used treatment for esophageal achalasia, supported by several large cohort studies. Although major perioperative adverse events (mAE) are rare, in-depth investigations of related risks and preventive measures are lacking.
Aims & Methods: Hence, mAE during POEM were systematically assessed in terms of incidence, risks, prevention, and management. This retrospective single-center analysis included all patients (N = 1680) undergoing POEM between August, 2010 and July, 2015 at our facility. Major adverse events were defined as follows: vital-sign instability, required ICU stay, hospital readmission, conversion to open surgery, invasive postoperative procedure, blood transfusion, or hospitalization > 5 days due to functional impairment.
Results: A total of 55 patients (3.3%, 95% confidence interval [CI] 2.5–4.2%) suffered mAE, distributed as follows: delayed mucosal barrier failure, 13 (0.8%, 95% CI 0.4–1.3%); delayed bleeding, 3 (0.2%, 95% CI 0.04–0.5%); hydrothorax, 8 (0.5%, 95% CI 0.2–0.9%); pneumothorax, 25 (1.5%, 95% CI 1.0–2.2%); and miscellaneous, 6 (0.4%, 95% CI 0.1–0.8%). Four patients (0.2%) required ICU admissions. No surgical conversions occurred, and 30-day mortality was zero. In stepwise multivariate regression, experience <1 year (OR = 3.85, 95% CI 1.49–9.95), air insufflation (OR = 3.41, 95% CI 1.37–8.50), and mucosal edema (OR = 2.01, 95% CI 1.14–3.53) were identified as related risk factors. After introducing CO_2 insufflation, mAE rate declined to 1.9% (95% CI 1.2–2.7%) and seemed to plateau after 3.5 years at ~1%.
Conclusion: In general, POEM is a safe procedure. Major adverse events are rare and usually may be prevented or anticipated and conservatively managed.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP157 COMPARATIVE EVALUATION OF PERORAL ENDOSCOPIC MYOTOMY (POEM) FOR THE TREATMENT OF ACHALASIA IN PATIENTS WITH FAILED HELLER MYOTOMY VS PATIENTS WITHOUT A HISTORY OF SURGICAL MYOTOMY: A MULTICENTER RETROSPECTIVE COHORT STUDY

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Introduction: In patients with persistent symptoms after Heller myotomy (HM), treatment options include repeat HM, pneumatic dilation (PD) or peroral endoscopic myotomy (POEM). The data on efficacy and safety of POEM for patients who failed prior HM are limited to small series.

Aims & Methods: We aimed to compare technical success, clinical response and safety of POEM in achalasia patients with and without prior HM. Methods: We conducted a retrospective review of achalasia patients who underwent POEM at 11 tertiary centers (4 US, 4 Europe, 3 Asia). Patients were divided into two groups: (1) patients who had prior HM (HM group) and (2) those without prior HM (control group). Control patients were selected for each HM case by matching for age, achalasia subtypes (type I&II vs type III), and baseline Eckardt scores (ES) [Stage II (ES 4–6) or Stage III (ES > 6)]. Clinical response was defined by decrease in ES to ≤3. Adverse events (AEs) were graded according to the ASGE lexicon. Technical success, clinical success and AEs were compared between the two groups.

Results: A total of 181 patients (91 HM, 90 controls) were included. There was no difference between the groups in baseline demographics, ES and 4sIRP. The HM group had higher proportion of patients with prior PD (44% vs 26%; p 0.01). The length of myotomy was similar between the two groups. Technical success rates were comparable between HM group (89/91; 98%; 2 failures due to extensive submucosal fibrosis) and control group (100%) in control group (p 0.49). Procedure time was similar between the two groups. The mean follow-up was 8.5 months (IQR 3.2–14.7) and was similar in both groups. 20 AEs occurred in 19 patients [7 (8%) in HM group and 12 (13%) in control group, p 0.23]. For HM and control respectively, the rate of mild (5% vs 10%, $p = 0.28$) and moderate (1% vs 3%, $p = 0.34$) AEs were similar. One severe AE (mediastinitis) occurred in the HM group. Follow-up data were available in 153 patients. Clinical response was significantly lower in the HM group as compared to the control (80% vs 94%, p 0.02). Mean post-POEM ES was also higher in the HM group (2.09 ± 2.5 vs 1.08 ± 1.2, p 0.002). On univariate analysis, prior HM (OR 3.54, p 0.02) and prior PD (OR 3.36, p 0.01) were significantly associated with clinical failure. Multivariate analysis demonstrated prior HM (adjusted OR 2.91, p 0.05) was marginally associated with clinical failure after POEM. Post-POEM symptomatic reflux, presence of reflux esophagitis and abnormal pH acid exposure were similar between the two groups.

Conclusion: In this large multicenter study, POEM was safe and effective for achalasia patients who failed prior HM. Although rate of clinical success in patients with prior HM is lower than those without prior HM, the safety profile of POEM is comparable to that of patients with no prior HM.

Disclosure of Interest: S. Roman: Sabine Roman is a consultant for Medtronic and Sandhill Scientific
F. Mion: Francois Mion is a consultant for Medtronic
M. Khashab: Mouen Khashab is a consultant for Boston Scientific
All other authors have declared no conflicts of interest.

OP158 GASTRIC PERORAL ENDOSCOPIC ANTRO-PYLORO-MYOTOMY (G-POEM) FOR THE TREATMENT OF REFRACTORY GASTROPARESIS: LARGEST SERIES WITH CLINICAL AND SCINTIGRAPHHIC FOLLOW-UP

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Introduction: Gastroparesis is an invalidating motility disorder and the available treatments remain disappointing. Recently, a novel approach has been described by performing a myotomy of the pylorus after creating a tunnel, with promising results [1–3]. We report the largest retrospective clinical experience in 23 consecutive patients treated by gastric peroral endoscopic myotomy (G-POEM). The aim was to evaluate the results of this new technique.

Aims & Methods: This is a case consecutive report on 23 patients operated for severe refractory gastroparesis, between January 2014 and April 2016, with a rigorous prospectively designed follow-up. The inclusion criteria were patients with a disturbed gastric emptying scintigraphy (GES) and elevated GCSI score > 2. The procedures were performed under general anesthesia in an intubated patient, with large channel gastroscope using CO2 and the Triangle knife (Olympus, Japan) as dissection device. The steps were: sub-mucosal injection and mucosal incision 5 cm upstream the pylorus; submucosal tunnel by dissection (Swift Coag, 35W, Effect 2) until reaching the pyloric arch, which had a consistent aspect; retrograde antro-pyloro-myotomy of 3cm length; closure of the mucosal flap with clips. The primary objective was to document, at 5 days, one month and 3 months, the efficacy based on GCSI score and gastroparesis symptoms (vomiting, nausea, abdominal pain and gastric fullness), and the improvement of quality of life (visual analogic scale /5), The secondary objectives were to document the GES evolution at 2 months and the procedure complications.

Results: The procedure was completed on all the patients. We observed a significant improvement of GCSI score at POD 5, 1 month and 3 months (3.5 ± 0.8 vs. 0.8 ± 0.8; 0.9 ± 0.9; 1.1 ± 1.5; $p < 0.001$). Regarding the severity of symptoms analyzed separately, it was observed a significant improvement of each of them, except anorexia. The overall clinical efficacy was 80%, with a mean overall quality of life improvement > 65%. The GES normalized in 75% of cases, showing a significant improvement of the mean half emptying time (222 ± 90 min vs. 133 ± 90; $p = 0.03$) and of retention at 2 hours ($76 \pm 20\%$ vs. $44 \pm 26\%$; $p = 0.009$). Two patients underwent complications related to the procedure: one was a bleeding due to an ulceration along the tunnel path (coagulation necrosis) treated by endoscopy, who then worsened a renal insufficiency and was transferred to intensive care unit; the second had a secondary perforation of an unseen fundic ulcer, which was managed endoscopically by a naso-cystic drain and fasting, with excellent outcomes. All the other patients could be reefed at POD2–3, and discharged at POD5–6, with PPI treatment.

Conclusion: Per-oral endoscopic pyloromyotomy seems to be an effective approach for treating patients with documented severe refractory gastroparesis. This procedure is also highly reproducible, when applying some tips to increase the technical success rate, and safe with complication that could be managed endoscopically. It could be a new hope for a many patients whom have a poor quality of life. More data, especially in prospective studies are needed to confirm these very promising results.

Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 08:30–10:00
LIVER FIBROSIS: FROM MECHANISM TO THERAPY – ROOM 1.61/1.62

OP159 EXPRESSION OF CONSTITUTIVELY ACTIVE IKK2 LEADS TO LIVER FIBROSIS AND INCREASED CARCINOGENESIS IN THE BACKGROUND OF LIVER SPECIFIC TRP53 DELETION

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Introduction: Liver carcinoma is of particular importance, since it is a leading cause of cancer-related deaths worldwide. Most frequently liver tumors are arising in an inflammatory milieu as a consequence of liver fibrosis and cirrhosis, which primarily develop subsequently due to chronic liver diseases. Another circumstance contributing to liver cancer formation is the disruption of the p53 signaling pathway. In human liver tumors, p53 mutations are associated with a poor prognosis. In this study, we analyze the cooperation between loss of p53 and inflammatory response in the liver.

Aims & Methods: To investigate the sequence of inflammation and Trp53 deletion, we combined two transgenic mouse models. For modulation of an inflammatory response, we used an inducible mouse model (Tet-Off system) with a permanent expression of a constitutively active IKK2 isoform (CAIKK2). The expression of CAIKK2, starting from birth, leads to a continuous activation of the NF-kB pathway, simulating chronic inflammation. For the modulation of a p53 loss, the inducible Cre-recombinase expressing transgenic mouse line AlfpCre-ERT2 was crossed with a conditional Trp53 knockout mouse. Tamoxifen treatment at the age of four weeks induces liver-specific deletion of Trp53.

Results: Expression of the constitutively active IKK2 isoform leads to liver fibrosis development, increased proliferation in the liver and elevated expression of inflammatory markers independent of the p53 status. During ageing, the CAIKK2 expression and the inflammatory response decreased, the liver fibrosis was reversible. The tumor incidence at the age of 9–12 month in CAIKK2 Trp53Δ/Δ mice is significantly higher (67%) compared to CAIKK2 mice with wild-type Trp53 (25%). Mice with induced liver-specific Trp53 deletion did not exhibit liver tumor formation at the same age. The majority of liver tumors in CAIKK2 Trp53Δ/Δ mice show intrahepatic cholangiocarcinoma (ICC) (81%) next to hepatocellular carcinoma (2%) and combined HCC/ICC (17%). In contrast, CAIKK2 mice with wild-type Trp53 developed mainly HCC (50%), but also ICC (25%) and HCC/ICC (25%) at lower level.

Conclusion: The study shows that liver-specific Trp53 deletion in combination with an inflammatory background results in elevated tumor incidence and leads to an increased occurrence of ICCs in the liver.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP160 EXPRESSION OF CD161 ON CD4+ T CELLS PROMOTES HEPATITIS B VIRUS RELATED LIVER FIBROSIS THROUGH ACID SPHINGOMYELINASE AND CD161-LECTIN-LIKE TRANSCRIPT-1 INTERACTION

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Introduction: Hepatitis B virus (HBV)-related liver fibrosis always progresses from inflammation to fibrosis. $CD4^+$ T cell immune responses play a pivotal role in the process. Recently, CD161 is considered to be a costimulatory molecule on T cells and an important phenotypic marker of human Th17 cells.

Aims & Methods: This study was designed to investigate the roles of CD161 in the pathogenesis of HBV-related liver fibrosis. Methods: A total of 54 CHB patients who underwent liver biopsy and 20 healthy controls (HC) were enrolled. CHB patients were further categorized according to the disease phase: immune-tolerant (IT, n = 12), immune-active (IA, n = 30), or inactive CHB (n = 12). Peripheral blood mononuclear cells (PBMCs) and flow cytometry sorted $CD4^+CD161^+$ and $CD4^+CD161^-$ T cells were prepared for further flow cytometric and real-time PCR analyses. Flow cytometry sorted $CD4^+CD161^+$ and $CD4^+CD161^-$ T cells were also cultured alone or co-culture with primary hepatic stellate cells (HSCs) in in vitro experiments.

Results: Compared to HC, the percentage of $CD4^+CD161^+$ T cells significantly increased among IA patients while dramatically decreased among IT patients, but there was no significant difference between inactive CHB patients and HC. Besides, CD161 showed a positive correlation with histological inflammation grades and advanced histological fibrosis stages. In the PBMCs of CHB patients, $CD4^+CD161^+$ T cells exhibited a $CD45RO^+$ memory phenotype and secreted more IFN-gamma, TNF-alpha, IL-17, IL-21 and IL-4 whereas produced less IL-10 and IL-22 than $CD4^+CD161^-$ T cells. In comparison with $CD4^+CD161^-$ T cells, in vitro culture of $CD4^+CD161^+$ T cells revealed that CD161 expression increased the activity of acid Sphingomyelinase (aSM) and subsequent PI3K/Akt, MAPK and mTOR pathways of $CD4^+$ T cells. Both knocking down of CD161 and using imipramine to inhibit aSM could down-regulate $CD4^+$ T cell-proliferation and production of IFN-gamma and IL-17, especially for IL-17. HSCs express lectin-like transcript-1 (LLT1), the only ligand of human CD161. HBcAg-stimulated HSCs upregulated LLT1 expression. In the co-culture system of HSCs and $CD4^+CD161^+$ T cells, CD161-LLT1 interaction not only promoted the proliferation and activation of HSCs, but increased IL-17 and IFN-gamma production of $CD4^+CD161^+$ T cells as well. Knocking down of CD161 on $CD4^+$ T cells or LLT1 on HSCs could partly reverse the aforementioned effects. In HSCs-$CD4^+CD161^-$ T cells co-culture system, expression of pro-fibrotic genes in HSCs were inhibited. However, when CD161 was overexpressed on $CD4^+CD161^-$ T cells, we detected a reactivated HSCs phenotype.

Conclusion: Our data revealed that the expression of CD161 on $CD4^+$ T cells might promote HBV-related liver fibrosis through CD161-LLT1 interaction to activate HSCs and through raising aSM to enhance the proinflammatory functions of $CD4^+$ T cells.

Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 08:30–10:00

FREE PAPER SESSION: NOVEL DIAGNOSTIC TOOLS: GOING DEEPER AND DEEPER INTO THE BOWEL – ROOM N1

OP161 FULL SPECTRUM ENDOSCOPY (FUSE) IN THE DETECTION OF INFLAMMATORY BOWEL DISEASE NEOPLASIA (FUSION): A RANDOMIZED CROSSOVER TANDEM STUDY VERSUS CONVENTIONAL COLONOSCOPY

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Introduction: Inflammatory bowel diseases (IBD) are the most significant acquired risk factors of colorectal cancer and therefore surveillance colonoscopy is widely endorsed. Conventional forward-viewing colonoscopy (FVC), however, lacks acceptable sensitivity in IBD dysplasia identification and the addition of dye-based chromoendoscopy is recommended. Full Spectrum Endoscopy (FUSE) is a novel colonoscope that incorporates 2 additional cameras to the forward camera and provides 330- degree panoramic view of the colonic mucosa. Whether FUSE can decrease dysplasia miss rate in IBD surveillance has never been tested previously.

Aims & Methods: This study aims to assess FUSE versus FVC in dysplasia surveillance in an IBD population. The dysplasia yield of targetted versus random colonic biopsies will also be assessed. Methods: A prospective, single-center, randomized-order, back-to-back crossover tandem colonoscopy study was conducted comparing FVC versus FUSE in an IBD- surveillance population. Crohn's disease (CD) and ulcerative colitis (UC) subjects were recruited from the IBD Sydney Cohort population-based database, all of whom met the inclusion criteria of published IBD surveillance guidelines. Subjects not due their surveillance colonoscopy were excluded. The primary outcome was the per-lesion dysplasia miss rate of the first colonoscopy identified by the second colonoscopy with chromoendoscopy. Secondary outcomes were per-subject dysplasia miss rate, mean dysplasia lesions found, procedural times, and dysplasia yield of targeted- versus random colonic biopsies. The trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12616000047493).

Results: In total 104 tandem (52-paired) colonoscopies were conducted with 27 subjects randomized to FVC first and 25 to FUSE first. Both arms were not statistically significantly different for age, IBD duration, CD versus UC, and additional dysplasia risk factors. The dysplasia prevalence rate of the cohort was 30.8%. The dysplasia miss rates for FVC and FUSE were 71.4% versus 25.0% respectively ($P = 0.0001$). On per-subject analysis, the dysplasia miss rate was 75.0% using FVC and 25.0% using FUSE ($P = 0.046$). FUSE identified a mean of 0.37 dysplastic lesions versus 0.12 for FVC ($P = 0.007$). Targeted biopsies increased dysplasia identification (26/163, 16.0%) versus random biopsies (2/687, 0.3%, $P < 0.0001$). Chromoendoscopy identified 10/28 (35.7%) of dysplastic lesions. The total colonoscopy times were similar (21.2 minutes versus 19.1 minutes, $P = 0.32$) but colonoscope withdrawal time was significantly longer (15.8 minutes versus 12.0 minutes, $P = 0.03$) for FUSE and FVC respectively.

Conclusion: Full Spectrum Endoscopy outperformed conventional forward viewing colonoscopy in inflammatory bowel disease subjects undergoing dysplasia surveillance. A high dysplasia prevalence was identified most likely due to multiple colonoscopy passes and the use of multiple advanced imaging modalities comprising of high-definition white-light colonoscopy, FUSE and chromoendoscopy. Improved dysplasia identification rates may reduce colorectal cancer mortality and increase interval colonoscopies. Improved dysplasia yield of targetted biopsies versus random colonic biopsies was confirmed.

Disclosure of Interest: R.W. Leong: Endochoice USA investigator-initiated grant All other authors have declared no conflicts of interest.

OP162 THE ACCURACY OF WAVSTAT VERSION 4 OPTICAL BIOPSY FORCEPS IN CHARACTERIZING COLORECTAL POLYPS LESS 10 MM: A PROSPECTIVE BLINDED STUDY

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Introduction: Optical biopsies of colonic polyps < 10 mm in size could potentially replace standard histological assessment. WavSTAT version 4 is a novel optical biopsy system designed by Spectrascience Inc, San Diego, California, USA. for prediction of histology based on laser induced autofluorescence spectroscopy.

Aims & Methods: The primary aim of this study was to demonstrate the accuracy of WavSTAT version 4 in characterizing colorectal polyps <10 mm that can be resected and discarded (or left in-situ) without adverse clinical impact. The secondary aim was to compare the real time diagnostic performance of WavSTAT version 4 with NBI and a combination of endoscopic and WavSTAT assessments. Patients attending the endoscopy unit for lower gastrointestinal endoscopy as requested by their responsible physician were approached to participate in the study. Adult patients aged above 18 years were included.

Table (OP162): Diagnostic performance of Wavstat4, Endosocpic assessment and combined alogithmic assessment for characterization fo colorectal poylps less than 10 mm in size and prediction of surveillance intervals

	WavSTAT alone	WLE+NBI assessment	Combination of WavSTAT + endoscopic assessment (algorithmic approach)
Sensitivity	97.6% (95% CI 0.88–0.95)	85.0% (95% CI 0.77–0.89)	95.8% (95%CI 0.89–0.96)
Specificity	46.9% (95%CI 0.44–0.98)	77.2% (95%CI 0.61–0.82)	78% (95%CI 0.66–0.79)
NPV	96.8% (95%CI 0.85–0.91	91% (95%CI 0.73–0.84)	98.5% (95% CI 0.89–0.95)
PPV	54.7% (95%CI 0.28–0.77)	66% (95%CI 0.44–0.79)	89.3% (95%CI 0.76–0.92)
Surveillance interval (% of patients coded correctly)	81.2%	97%	100%
Surveillance interval (% of patients called earlier)	18.8%	3%	0%

Patients known to have inflammatory bowel disease or colorectal cancer were excluded from the study. Polyps sized <10 mm were assessed in real time by high definition white light, NBI and WavSTAT version4 optical biopsy forceps. Standard techniques were used for polypectomy. Histopathological specimens were read separately by two expert GI pathologists blinded to the results of the NBI and WavSTAT assessments. The primary outcome measure was the negative predictive value in distinguishing adenomatous from non-adenomatous colorectal polyps. The secondary outcome measure was the accuracy of on-site recommended surveillance intervals.
Results: 156 polyps (146 were <10 mm and 10 were >10 mm) were found in 70 patients (Males-44, females-27). Average age of the patients was 65 years (range 29–95 years). 16 polyps were not included in the final analysis due to discrepancy in histological analysis between two pathologists. We failed to retrieve 5 polyps. 26 patients were excluded from the study (No polyps seen in 17 patients, polyps <10 mm were not seen in 3 patients, and device failure in 4 patients). A total of 126 polyps <10 mm were included in final analysis. The diagnostic performance for WavStat version 4 and endoscopic assessment is detailed in the table. Wavstat4 had a NPV of 96.8% but lacked specificity. Endoscopic assessment had a NPV of 91% and was more specific. Since the specificity of WavSTAT was poor mainly for hyperplastic recto-sigmoid polyps we evaluated an algorithmic approach where we classified the polyps according to the WavSTAT4 result when proximal to the recto-sigmoid junction. We classed them according to the endoscopic classification only if Wavstat4 prediction was as as an adenomatous polyp in the recto-sigmoid area. This combined algorithmic approach met the PIVI thresholds and had a NPV of 95.8% and predicted 100% of surveillance intervals correctly.
Conclusion: WavSTAT version 4 has a high NPV for characterizing colorectal polyps less than 10 mm in size but only predicts surveillance intervals correctly in 81.2% of patients.. An algorithmic approach combining Wavstat4 and endoscopic assessment had a high NPV with accurate prediction of surveillance intervals.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP163 DEEPER AND DEEPER INTO THE SMALL BOWEL IN PEDIATRIC CROHN'S DISEASE: PROSPECTIVE COMPARATIVE STUDY BETWEEN SMALL INTESTINE CONTRAST ULTRASONOGRAPHY (SICUS) AND MAGNETIC RESONANCE IMAGING

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Introduction: Small bowel (SB) assessment is essential for the proper management of pediatric Crohn's disease (CD). Magnetic resonance imaging (MRI) is considered the gold-standard for the evaluation of small bowel (SB). However, MRI is expensive, it requires a strong compliance and a considerable amount of oral contrast to adequately distend the intestinal lumen. Small intestine contrast ultrasonography (SICUS) is non-invasive, low cost and generally well-tolerated by pediatric patients (pts).
Aims & Methods: We aimed to compare the diagnostic accuracy of SICUS and MRI in detecting presence, site and extension of SB disease and in assessing strictures in pediatric CD. Children with suspected CD or relapse of a known CD were prospectively enrolled. All underwent SICUS, MRI and ileo-colonoscopy, performed by different operators blinded to other results. The SB was subdivided into: jejunum, ileum, terminal ileum (TI). The concordance (k) between the two techniques for presence and site of lesions was calculated according to Landis and Koch criteria*. For the TI, sensitivity (SE) and specificity (SP) were also assessed, with ileo-colonoscopy as reference standard. One-way ANOVA with Kruskal-Wallis post-test was applied to compare the extension (cm) of disease in the different segments.
Results: 66 pts (median age 13; range 7–18), 23 suspected, 43 known CD were included. The overall concordance (k) between SICUS and MRI for presence of SB lesions was 0.94 (ES 0.06; 95%CI 0.8–1). The k for segments was: jejunum 0.67 (ES 0.1, 95%CI 0.4–0.8), ileum 0.91 (ES 0.06, 95% CI 0.76–1), TI 0.91 (ES 0.06; 95%CI 0.8–1). SE and SP (%) of SICUS and MRI for TI lesions were 98, 100 and 93, 92, respectively. There was no difference in the assessment of disease extension between SICUS and MRI (p ns). The overall k for strictures was 0.62 (ES 0.1, 95% CI 0.4–0.8). SE and SP(%) of SICUS and MRI for TI strictures were 100, 100 and 92, 87, respectively. MRI provided 7 false positive results, not detected at SICUS nor confirmed at endoscopy.
Conclusion: The diagnostic performance of SICUS is comparable to that of MRI in pediatric CD. SICUS is useful in assessing SB strictures, probably with higher accuracy than MRI. SICUS might represent a first-line tool in pediatric CD, able to reduce costs and to post-pone or even avoid more invasive and expensive investigations.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP164 A ROLE FOR T CELL CLONAL EXPANSIONS IN THE POST-OPERATIVE RECURRENCE IN CROHN'S DISEASE: A STUDY FROM THE REMIND GROUP

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Introduction: Operative resection in Crohn's disease is not curative. Indeed, a majority of CD patients undergoing ileocecal resection have an endoscopic recurrence in the neo-terminal ileum as soon as six months after surgery. T cells are major players in the intestinal immune response. We previously demonstrated the persistence of T cell clonal expansions over time in the inflamed mucosa of CD patients (1). The presence of T cell clonal expansions at time of surgery could play an important role in the post-operative recurrence.
Aims & Methods: The aims of the study were to explore the impact of the presence of T cell clonal expansions in the inflamed tissue at time of surgery on the risk of post-operative endoscopic recurrence, and to analyse the correlation between the persistence of these T cell clones in the neoterminal ileum and inflammation. The REMIND Post-OPerative study has been performed in 9 centers, collecting data at time of surgery (M0) and of endoscopy (performed at M6), associated with an extensive bio-banking. Clinical, biological and endoscopic parameters were collected at month 6. Endoscopic recurrence was defined by a Rutgeerts score≥1. Biopsies of ileal mucosa were collected on surgical specimen and by endoscopy six months after surgery. T cell Receptor (TCR) analysis was performed on DNA extracted from biopsies by next generation sequencing (Adaptive Biotechnology Inc., Seattle, Washington, USA). The TCR repertoire was analyzed in biopsies obtained on the surgical specimen and during the control endoscopy at six months. Sequences, numbers, frequencies and clonality indexes were assessed; and further analyzed to determine TOP100 clone frequencies and persistent clonal expansions present at both M0 and M6 in each patient.
Results: Fifty-seven patients from the REMIND cohort were analyzed: 33 (58%) were male; median age at surgery was 38 years old (±14). We found that the TCR repertoire in biopsies from CD patients display a large number of unique TCR sequences (mean 10000 unique sequences) suggesting a high variety of T cell specificities. However, measures of diversity of the TCR repertoire showed an important range of clonality within the cohort (0.001 to 0.5). Importantly, the frequency of the 100 most represented clones in the tissue at M0 was significantly increased in patients with endoscopic recurrence (Rutgeerts score≥1) at M6, showing that increased clonality at time of surgery was predictive of disease recurrence. Furthermore, the presence and frequency of persistent clones (present at M0 and M6) was significantly increased in patients who had an endoscopic recurrence. High or low proportion of persistent clones could define two subgroups of patients with endoscopic recurrence in regard to their TCR repertoire. Interestingly, expanded clones could be found in different T cell subsets.
Conclusion: T cell clonal expansions in the inflamed tissue at time of surgery and their persistence in the neoterminal ileum after surgery are both associated with post-operative endoscopic recurrence in Crohn's disease.
Disclosure of Interest: M. Allez: I received honoraria from MSD, Abbvie, Janssen, Novo Nordisk, Novartis, Takeda, Genentech, UCB, Pfizer, Ferring
All other authors have declared no conflicts of interest.

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OP165 TARGETED CHEMICAL ANALYSIS OF THE COLON CANCER MICROBIOME USING DESORPTION ELECTROSPRAY IONISATION MASS SPECTROMETRY IMAGING (DESI-MSI)

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Introduction: The gut microbiome is an important modulator of colorectal (CRC) cancer risk. Here we describe a novel methodology for the targeted analysis of the

colon cancer microbiome using mass spectrometry imaging in a prospective cohort of CRC patients.
Aims & Methods: A prospective, multi centre observational study was performed on patients undergoing elective resections for colorectal cancer at Imperial Healthcare NHS Trust and the Royal Marsden Hospital. Fresh mucosal tissue was sampled under aseptic conditions from cancers and adjacent normal tissue and frozen at –80°C. Using 16S rRNA sequencing analysis of corresponding tissue samples (performed in Mothur and Stamp), target bacteria including *Fusobacterium* spp, *E.Coli* and *Bifidobacteria* were identified. A chemical database of these bacteria was created using Rapid Evaporative Ionisation Mass Spectrometry (REIMS) from pure cultures of the target microbes. Desorption Electrospray Ionisation Imaging Mass Spectrometry (DESI-MSI) was then performed to provide a spatially resolved map of the mucosal microbial lipidome. Taxon specific data were mapped onto these images using chemical spectra identified by REIMS. Candidate microbial lipids were validated using cell co-culture experiments and analysis with REIMS. Multivariate analysis was performed using Matlab (Mathworks) and R. Both unsupervised Principle Component Analysis and supervised Linear Disciminant Analysis were performed. ANOVA was used to perform statistical analysis of single lipid species.
Results: 26 patients with sporadic colorectal cancer were recruited (17 women, median age 68, range 35–84, median BMI 27 kg/m^2). Eight tumours were right sided, eleven were left sided and seven were rectal. Two patients had neo-adjuvant chemoradiotherapy. Histology showed six adenomas, one T1, six T2, ten T3 and three T4 cancers. Using DESI-MSI it was possible to geographically identify distinct anatomical regions based on co-registration of the chemical data with independently validated H+E stained tissue. Using leave one patient out cross validation, DESI-MSI was able to diagnose cancer from normal colonic mucosa with ROC AUC = 97.5. Increased long chain fatty acids were seen in malignant tissue and increased glycerophospholipids were seen in healthy mucosa (both $p < 0.001$). Target spectra just specific to the mucosa were then extracted for analysis. This revealed 102 lipid species that differentiated colon cancer from normal adjacent mucosa, including 24 attributable to taxon-specific markers for *Bacteroidetes*, *Bifidobacteriales* and *Enterobacteriales*. These were positively validated using cell culture REIMS.
Conclusion: Chemical mapping of the colonic lipidome permits spatially resolved analysis of the cancer microbiome and its metabolic functions, and this has diagnostic value. DESI-MSI provides a completely novel methodology for studying microbial-host interactions critical to the aetiology of inflammation and cancer.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP166 UNSUPERVISED, TRANSCRIPTOMICS-BASED CLUSTERING OF ULCERATIVE COLITIS PATIENTS REVEALS MARKED HETEROGENEITY THAT RELATES TO ANTI-TNF TREATMENT RESPONSE

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Introduction: Heterogeneity in IBD patient populations is widely cited as the main barrier to efficient clinical trials and development of therapies with high clinical efficacy. We and others hypothesize that phenotypic heterogeneity is a direct result of molecular heterogeneity in disease-driving molecular pathways. We present an approach not extensively explored for defining molecular heterogeneity in a manner independent of known biology.
Aims & Methods: Whole-genome transcriptomic data was generated for colonic biopsies from 217 moderately to severely active ulcerative colitis subjects and 21 healthy normal controls. Subjects were scored based on enrichment of 113 co-expression modules, or lists of correlated genes, derived from colonic biopsies from both UC and CD biopsies. Scores for each subject and co-expression module were computed using the gene set variation analysis algorithm. Co-expression modules were then hierarchically clustered into 4 module clusters and annotated with pathways using the union of genes within each of the 4 module clusters. Each subject was then reclassified based on the 4 module clusters by taking the median enrichment score of the modules within each module cluster. IBD subjects and normal controls were then hierarchically clustered into 4 subgroups using the 4 module clusters and assessed for relationship to anti-TNF response.
Results: The 4 module clusters represented distinct pathway sets which we summarized as inflammation/monocytes, mucosa/pro-regulatory, T cells/metabolism and mitochondria/metabolism. Patients belonging to the subgroup characterized by the highest enrichment for the inflammation/monocyte module cluster trended towards lower response rates to anti-TNF therapy. Conversely, the highest response rates to anti-TNF therapy were observed in the subgroup characterized by the lowest enrichment for the inflammation/monocyte module cluster. These subgroups also contained normal healthy controls. Enrichment values for the mucosa/pro-regulatory module cluster anti-correlated ($r = -0.49$) with enrichment values for the inflammation/monocyte module cluster.
Conclusion: We find that there is pronounced molecular heterogeneity in the pathways present in colonic biopsies from UC patients. We also show that this heterogeneity may be related to the ability of patients to respond to anti-TNF therapy. This suggests that molecular stratification may be a key step towards designing smaller clinical trials and identifying meaningful personalized medicine approaches for IBD patients.
Disclosure of Interest: C. Monast: Employee of Janssen Research and Development, LLC
A. Stojmirovic: Employee of Janssen Research and Development, LLC
R. Dobrin: Employee of Janssen Research and Development, LLC
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OP167 COMPREHENSIVE CIRCULATORY TRANSCRIPTOME AND PROTEOMIC PROFILING IN NEWLY DIAGNOSED INFLAMMATORY BOWEL DISEASES: A MULTI-CENTRE COHORT STUDY

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Introduction: There is an unmet need to gain functional insights into pathways that are relevant in Inflammatory Bowel Diseases (IBD). By performing transcriptome and proteome profiling in newly diagnosed IBD, we can gain an understanding into the molecular mechanisms that may be relevant in disease.
Aims & Methods: Gene expression patterns from whole blood RNA and proteomic profiles from serum were assessed from patients using targeted RNA-seq (Ion AmpliSeq Transcriptome Human Gene Expression platform) and Olink multiplex protein panels (Olink Proteomics). Treatment-naïve newly diagnosed IBD and healthy symptomatic controls were included in the study. Phenotypic data were captured including demographics and disease classification. Statistical analysis was performed using R. Differentially expressed transcriptomes were correlated with serum protein expression to obtain a circulating profile at diagnosis.
Results: RNA expression profiles were available in 639 patients (351 IBD, 288 controls). A total of 5678 genes were differentially expressed between IBD and controls. Using hsCRP to adjust for inflammatory status, 1440 remained significant. The most differentially expressed genes were CD-177 (Bonferroni corrected $p = 2.3\times10^{-36}$), VBP1 ($p = 2.90\times10^{-32}$) and S100 proteins (S100A9, $p = 3.3\times10^{-26}$ and S100A12, $p = 6.8\times10^{-26}$). Proteomic profiles were available in 635 patients (152 CD, 159 UC, 26 IBD-U, 298 non-IBD) Multivariable analysis identified 59 protein markers that were significantly associated with IBD. The top significant proteins upregulated in IBD included MMP12 (Holm-adjusted $p = 4.1\times10^{-26}$) and CXCL9 ($p = 1.7\times10^{-20}$). Matched serum protein profiles were available and correlated with RNA expression. 39 proteins showed significant correlation with gene expression including OSM ($rho = 0.51$, Holm-adjusted $p = 1.4\times10^{-40}$) and S100A12 ($rho = 0.33$, $p = 3.4\times10^{-14}$) while other markers such as CXCL9 show poor correlation ($rho = 0.16$, $p = 0.04$). As biomarkers, top 2 serum markers were able to discriminate IBD from controls with a similar area under the receiver operator characteristics curve (AUC) of 0.75 and 0.74 respectively. Individually these markers outperformed hsCRP ($n = 619$, AUC 0.64, p for comparison $= 2.7\text{x}10^{-4}$ vs. MMP12) and albumin (AUC 0.66, $p = 0.004$ vs MMP12). 6 proteins differentiated UC from CD including MMP12 ($p = 4.6\times10^{-4}$). In CD, MMP12 levels were lower in those with small bowel involvement(Montreal Classification L1, L3 and L4 vs L2; $p = 0.009$) while in UC, MMP12 levels were significantly higher in extensive disease (Paris classification E1 and E2 vs. E3, $p = 5.8\text{x}10^{-7}$).
Conclusion: This is the largest integrative multicentre characterisation of the circulating expression profile studied in IBD at diagnosis. These data identify key pathways that may be relevant in IBD pathogenesis and demonstrate the translational potential of these markers in diagnosing and classifying IBD.
Disclosure of Interest: R. Kalla: Funded by IBD Character Ferring Speaker Fees
J. Jahnsen: JJ has served as a speaker, a consultant and a advisory board member for MSD, Tillot, Ferring, AbbVie, Celltrion, Orion Pharma, Takeda, Napp Pharm, Meda, AstroPharma, Hikma and Pfizer.
F. Gomollon: Advisor: Grifols, Abbvie, MSD. Travel Grants: Abbvie, MSD. Research funding (Department) MSD
J. Satsangi: JS has served as a speaker, a consultant and an advisory board member for MSD, Ferring Abbvie and Shire, consultant with Takeda, speaking fees from MSD and has received research funding from Abbvie
All other authors have declared no conflicts of interest.

Table 1 (OP168): Demographics, procedural outcomes, bowel cleanliness and adenoma detection.

				P value			
Demographics	WE N = 408	WI N = 408	AI N = 408	WE vs WI	WE vs AI	WI vs AI	ANOVA
Females, n (%)	184 (45.1)	185 (45.3)	183 (44.9)				
Males, n (%)	224 (54.9)	223 (54.7)	225 (55.1)	1†	1†	0.888†	0.990
Age, mean (SD)	61.4 (6.2)	61.0 (6.3)	60.9 (6.2)	0.261‡	0.173‡	0.822‡	0.350
Body Mass Index, mean (SD)	26.4 (4.1)	26.4 (4.4)	26.6 (4.4)	0.751‡	0.473‡	0.696‡	0.775
Indications for colonoscopy, n (%)							
Screening FIT+	242 (59.3)	242 (59.3)	222 (54.4)	1†	0.157†	0.157†	0.263
Screening FOBT+	18 (4.4)	19 (4.7)	19 (4.7)	0.863†	0.863†	1†	0.982
Family history of colorectal cancer	47 (11.5)	47 (11.5)	45 (11.0)	1†	0.823†	0.823†	0.968
Primary colonoscopy	101 (24.8)	100 (24.5)	122 (29.9)	0.920†	0.099†	0.084†	0.143
Procedural outcomes							
Cecal intubation rate (final), n (%)	402 (98.5)	400 (98.0)	399 (97.8)	0.590†	0.435†	0.807†	0.734
Cecal intubation time, mean (SD), min	10.1 (5.4)	9.4 (5.7)	9.7 (6.7)	0.050‡	0.364‡	0.390‡	0.188
Withdrawal time without polypectomy, mean (SD), min	9.5 (3.2)	9.5 (3.6)	8.9 (3.1)	0.870‡	0.074‡	0.128‡	0.084
Total procedure time, mean (SD), min	24.8 (11.7)	24.6 (12.0)	23.3 (11.0)	0.842‡	0.059‡	0.098‡	0.128
Withdrawal endoscopists' correct guesses of insertion method	119 (29.2)	135 (33.1)	116 (28.4)	- -	- -	- -	- -
Overall Boston Bowel Preparation Scale (BBPS) score, mean (SD)	7.9 (1.5)	7.4 (1.6)	7.5 (1.7)	<0.0005‡	<0.0005‡	0.924‡	<0.0005
Right colon BBPS score (SD)	2.6 (0.6)	2.4 (0.6)	2.4 (0.7)	<0.0005‡	<0.0005‡	0.815‡	<0.0005
Infused water during insertion, median (range), mL	550 (50–6500)	400 (50–2000)	0 (0–1000)	- -	- -	- -	- -
Aspirated water during insertion, median (range), mL	500 (0–6500)	50 (0–1000)	100 (0–900)	- -	- -	- -	- -
Adenoma detection							
Overall ADR, n (%)	201 (49.3)	177 (43.4)	165 (40.4)	0.395†	0.011†	0.092†	0.036
Overall advanced adenoma detection rate, n (%)	79 (19.4)	70 (17.2)	58 (14.2)	0.4137†	0.049†	0.249†	0.145
Right colon ADR, n (%)	98 (24.0)	78 (19.1)	69 (16.9)	0.089†	0.012†	0.413†	0.034
MAP+, mean (SD)	1.79 (1.2)	1.98 (1.9)	1.79 (1.3)	0.265‡	0.981‡	0.245‡	0.365
At BBPS 9–8 (entire colon)	**WE n = 275**	**WI n = 227**	**AI, n = 227**				
Adjusted overall ADR, n (%)	148 (53.8)	94 (41.4)	88 (38.8)	<0.0005†	<0.0005†	0.566†	0.001
At BBPS 3 (right colon)	**WE n = 243**	**WI n = 186**	**AI n = 190**				
Adjusted right colon ADR, n (%)	63 (25.9)	32 (17.2)	26 (13.7)	0.0007†	<0.0005†	0.346†	0.004

SD, standard deviation; FIT+, positive at fecal immunochemical testing; FOBT+, fecal occult (guaiac-based) blood testing; Advanced adenomas: adenomas ≥10 mm in diameter, or high grade dysplasia, or with ≥20% villous components. †Chi-squared; ‡t test; ANOVA, analysis of variance.

TUESDAY, OCTOBER 18, 2016 08:30–10:00

IMPROVING DETECTION OF POLYPS – ROOM N2

OP168 A RANDOMIZED, CONTROLLED TRIAL COMPARING AIR INSUFFLATION, WATER IMMERSION AND WATER EXCHANGE FOR ADENOMA DETECTION IN SCREENING COLONOSCOPY PATIENTS

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Introduction: Adenoma detection rate (ADR, proportion of patients with at least one adenoma) is the primary quality indicator of colonoscopy, due to its correlation with the risk of post-colonoscopy interval cancer and mortality [1,2]. Data from U.S. male veterans [3,4], patients in Taiwan [5] and Europe [6], suggest that water exchange (WE, infusion of clean water in an airless lumen and removal of dirty water during insertion), but not water immersion (WI, infusion of water as adjunct to insufflation and removal of residual water during withdrawal) significantly increases ADR in the proximal (cecum-splenic flexure) and right (cecum-ascending) colon, when compared with standard air insufflation (AI). Limitations of these studies were their retrospective analysis and/or investigators unblinded to the insertion method.

Aims & Methods: In a prospective, multi-site randomized controlled trial we tested the hypothesis that WE, but not WI, significantly increases ADR (primary outcome measure) compared with AI. The study population was represented by 50–70 years-old asymptomatic subjects, undergoing colonoscopy as primary screening test or after positive fecal occult blood test. A total of 1224 (672 males) patients were enrolled at three centers and randomly allocated 1:1:1 to WE, WI and AI. Split-dose bowel preparation was adopted to ensure optimal pre-procedure cleansing. To overcome the limitation of previous reports of unblinded colonoscopist performing withdrawal inspection, after reaching the cecum another investigator blinded to the insertion technique used performed the withdrawal. To assess adequacy of blinding the withdrawal, the second endoscopist was asked to guess the insertion technique.

Results: All results are reported in Table 1. Demographics, clinical features, indications, cecal intubation rates and procedure times were comparable. Compared with AI (40.4%), WE (49.3%) but not WI (43.4%) achieved significantly higher overall ADR (p = 0.011 and 0.092, respectively). Compared with AI (14.2%), WE (19.4%) but not WI (17.2%) achieved significantly higher advanced ADR (p = 0.049 and 0.249, respectively). In the right colon, WE (24%) but not WI (19.1%) achieved significantly higher ADR than AI (16.9%) (p = 0.012 and 0.413, respectively). Even after split-dose preparation, WE was associated with higher overall and right colon BBPS scores. The impact was most notable in patients with excellent BBPS, adjusted entire and right colon ADR of WE were significantly higher than those of WI and AI. Multivariate logistic regression showed that WE, compared with AI, was an independent predictor of adenoma detection in the entire colon [OR (95% CI), 1.18 (1.03–1.36)] and in the right colon [1.24 (1.04–1.47)], respectively. Comparable correct guesses of insertion method (<32%) suggest adequate investigator blinding. Similar withdrawal times without polypectomy suggested withdrawal technique was comparable. Equal mean adenoma per positive colonoscopy (MAP+) suggest ADR was not negatively impacted by the one-and-done approach. Volumes of water infused and suctioned suggested that WE, WI and AI methods were correctly used.

Conclusion: The current study shows that in European screening patients, WE increased adenoma detection by 18% in the entire colon and by 24% in the right colon. Moreover, compared with the two other methods, WE improves the quality of colon cleansing. A type II error could account for the absence of statistical significance between unadjusted ADR in the WE and WI groups, further direct comparisons between WE and WI are required.

Disclosure of Interest: S. Cadoni: Recipient of the 2013 ESGE Research Grant All other authors have declared no conflicts of interest.

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OP169 EFFICACY OF ENDOCUFF-ASSISTED COLONOSCOPY IN THE DETECTION OF COLORECTAL POLYPS

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Introduction: Colonoscopy is the gold standard for detecting colorectal adenomas and cancers. Endoscopic surveillance has been shown to be effective for preventing colorectal cancer. Although the detection of colorectal polyps at an early stage is important, the endoscopic visualization of early neoplasia can be difficult.
Aims & Methods: The Endocuff is a new device that can be attached to the tip of the colonoscope to hold the colonic folds away from the field of view during withdrawal. The aim of this study was to compare the polyp and adenoma detection rates between Endocuff-assisted colonoscopy and standard colonoscopy. This randomized prospective study was conducted at two academic endoscopy departments in Japan. The subjects were 446 patients who underwent a complete colonoscopic examination from April 2015 to September 2015. The Endocuff group included 239 patients. Cecal intubation rate, insertion time, withdrawal time, pain score, complications, polyp detection rate, and adenoma detection rate were assessed.
Results: There were no differences between the groups in cecal intubation rate, insertion time, withdrawal time, or pain score. Cecal intubation was achieved in 235 patients (98.8%) in the Endocuff group. In four patients, the Endocuff-assisted examination had to be stopped in the sigmoid colon due to severe stenosis caused by diverticula or cancers. These examinations were completed with a standard colonoscope. Superficial mucosal erosions occurred in 54 patients (23.0%) during withdrawal in the Endocuff group but no major complication occurred. The polyp detection rate in patients increased by 12% (62% vs. 50%, $P = 0.013$) and the adenoma detection rate increased by 15% (55% vs. 40%, $P = 0.001$) with the use of Endocuff. The advanced adenoma detection rate was higher in the Endocuff group but no statistically significant difference was found (6.1% vs. 3.2%, $P = 0.17$).
Conclusion: Endocuff-assisted colonoscopy enabled a significantly higher polyp and adenoma detection rate than standard colonoscopy. This attachment improved important quality measures used for screening colonoscopy.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP170 DEVELOPMENT AND VALIDATION OF A SIMPLE CLASSIFICATION SYSTEM FOR IN VIVO DIAGNOSIS OF COLORECTAL POLYPS USING THE NEWLY INTRODUCED OPTICAL ENHANCEMENT (OE) TECHNOLOGY

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Introduction: Optical enhancement (OE) will be introduced at UEGW 2016 as a novel endoscopic imaging technique that adjusts emitted light to enhance mucosal vascular pattern and surface pattern morphology. This study assessed for the first time the utility of OE to predict colorectal polyp histology.
Aims & Methods: Primary objective was to develop and validate a simple classification system allowing differentiation of hyperplasic and adenomatous colorectal lesions by using OE. In the first phase, the capacity of experienced endoscopists to predict the histology of colorectal polyps was assessed. In the second phase, a simplified classification was developed allowing histologic prediction. Thirdly, the validity of the classification was evaluated among inexperienced raters, including medical students, nurses and GI fellows. At least, a pilot clinical evaluation was performed during real-time colonoscopy.
Results: A simple classification system for differentiating hyperplasic and adenomatous colorectal lesions by using OE was developed and validated. Diagnosis was made in 85% to 90% of polyps with high-confidence. Sensitivity ranged from 92% to 96% and specificity ranged from 86% to 93%, respectively. During real-time colonoscopy, diagnosis was made with high-confidence in 90% of polyps with sensitivity of 96%, specificity of 92%, and accuracy of 95%. Positive and negative predictive values were 96% and 93%, respectively.
Conclusion: We developed and validated for the first time a simple and effective classification system for differentiating hyperplasic and adenomatous colorectal lesions by using the newly introduced OE-technology during real-time colonoscopy. These findings need to be evaluated in future prospective, controlled, and blinded clinical trials.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP171 FREQUENCY AND PREDICTORS OF ADVANCED HISTOLOGY IN LARGE NON-PEDUNCULATED COLORECTAL POLYPS: EXPERIENCE-BASED DATA AT A UNIVERSITY HOSPITAL

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Introduction: Endoscopic resection of large non-pedunculated colorectal polyps (LNPCPs) is challenging, with a significant proportion of them containing malignancy. Diagnostic work-up has the potential to improve clinical outcomes. The aims of this study were to examine the frequency of LNPCPs in clinical practice, endoscopic and histopathologic features and predictors for advanced histology.
Aims & Methods: We previously trained all endoscopists (9 faculty and 14 trainees) at Maastricht UMC+ on detection, diagnosis and endoscopic resection of colorectal neoplasms using a stepwise training program: Phase 1: Training on detection and diagnosis of colorectal neoplasms, with special attention for non-polypoid (flat and depressed) colorectal neoplasms using lectures, videos and individual feedback. Phase 2: Training in endoscopic resection techniques using videotraining and hands-on training with experienced colonoscopists. Then, we embarked in a prospective study of all consecutive colonoscopies performed at our institution from February 2008 to February 2012. Quality indicators (cecal intubation rate, adenoma and polyp detection and resection rate) were monitored. We recorded patient characteristics (age, gender) and lesion characteristics, i.e. location, size, shape using Paris classification (including photo documentation) and histopathology. We defined LNPCPs as large (≥20 mm) non-pedunculated (i.e. sessile, flat, depressed, combinations) colorectal neoplasms (Rutter et al, Gut 2015). We paid special attention to laterally spreading tumors (LSTs), defined as superficially growing lesions along the mucosa instead of growing up- or downwards. We conducted a logistic regression analysis to identify predictors for advanced histopathology, defined as high-grade dysplasia or early colorectal cancer (pT1).
Results: A total of 7166 neoplasms were identified in 9353 patients (mean age 58.9 years, 46.0% male), of which 205 (2.9%) in 176 (1.9%) patients (mean age 68.3 years, 56.3% male) were LNPCPs. The majority (65.9%) of LNPCPs were located in the proximal colon. Mean size was 30 mm (20–100 mm). Ninety-six LNPCPs (46.8%) were sessile and 109 (53.2%) LSTs. LNPCPs contained low-grade dysplasia adenoma (29.8%), high-grade dysplasia adenoma (37.1%), early colorectal cancer (17.1%), sessile serrated adenoma/polyp (6.6%), hyperplasia (8.8%), and traditional serrated adenoma (0.5%). Sessile-LNPCPs more often contained advanced histopathology than LST-LNPCPs (61.5% vs. 34.9%, $p < 0.001$). After adjusting for age and gender, distal location (OR 3.1, 95%-CI 1.6–6.0, $p < 0.001$), size of lesion (OR 2.7 for LNPCP ≥40 mm compared to 20–29 mm, 95% CI 1.1–6.2, $p = 0.023$) and sessile shape (OR 2.3, 95%-CI 1.2–4.4, $p < 0.001$) were all independent predictors for advanced histopathology. The overall referral rate to surgery ($n = 45$) decreased from 30.4% in the first half of the study period to 16.7%. Delayed bleeding occurred in 6 (5.6%) cases after endoscopic resection, none requiring surgical intervention. No perforations occurred.
Conclusion: In this real-life prospective cohort, 1.9% of all patients undergoing a colonoscopy had a LNPCP. Lesion size, sessile shape and distal location were independent predictors of advanced histology. Careful case selection which considers both patient-related factors and endoscopic predictors of advanced histology is critical to optimize the outcomes of endotherapy for LNPCPs.
Disclosure of Interest: S. Sanduleanu: Consultancy: Pentax Europe
All other authors have declared no conflicts of interest.

Reference

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OP172 HEALTH EFFECTS AND COSTS DUE TO POST-COLONOSCOPY COLORECTAL CANCER

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Introduction: Colorectal cancers (CRC) detected shortly after a colonoscopy are referred to as a post-colonoscopy colorectal cancer (PCCRC), and has been reported to represent 2–9% of all CRCs, depending on the definition, setting and methods for estimating its incidence. The delay in detection of the CRC might imply higher mortality, effect on the quality of life of the diagnosed individuals, and association with extra costs for health services.
Aims & Methods: The aim of this study was to estimate the loss of health and health care costs following delay in CRC-diagnosis due to PCCRC in Sweden. A

Table 1 (OP172): Logistic regression model adjusted for age and gender to identify predictors for advanced histopathology in LNPCPs. LGD: low-grade dysplasia; HGD: high-grade dysplasia; early CRC: early colorectal cancer (pT1).

Feature	Total (n = 205)	Histopathology		Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
		LGD (n = 108)	HGD or early CRC (n = 97)		
Location				**p < 0.001**	**p < 0.001**
Proximal	135 (65.9%)	87 (64.4%)	48 (35.6%)	1.0	1.0
Distal	70 (34.1%)	21 (30.0%)	49 (70%)	4.2 (2.3–7.9)	3.1 (1.6–6.0)
Size				p = 0.191 & **0.001**	p = 0.131 & **0.023**
20–29 mm	109 (53.2%)	67 (61.5%)	42 (38.5%)	1.0	1.0
30–39 mm	57 (27.8%)	29 (50.9%)	28 (49.1%)	1.5 (0.8–2.9)	1.7 (0.9–3.5)
≥40 mm	39 (19.0%)	12 (30.8%)	27 (69.2%)	3.6 (1.6–7.8)	2.7 (1.1–6.2)
Shape				**p < 0.001**	**p < 0.001**
LST	109 (53.2%)	71 (65.1%)	38 (34.9%)	1.0	1.0
Sessile	96 (46.8%)	37 (38.5%)	59 (61.5%)	3.0 (1.7–5.3)	2.3 (1.2–4.4)

*Logistic regression model adjusted for age and gender

recent register study of colonoscopies in Sweden during 2001–2010 revealed that 18,244 individuals were diagnosed with CRC within 0–36 months after a colonoscopy. A CRC was defined as a PCCRC if it was detected within 6–36 months after a colonoscopy in which no cancer was detected. A total of 1,473 (8.1%) PCCRCs were found in the register study and included in this study. A lifelong mathematical Markov model was employed to calculate the lifelong health effects and resource usage for PCCRC. The effects were calculated by simulating the hypothetical lives of the individuals diagnosed with PCCRC if their condition had instead been diagnosed at the time of colonoscopy. These lives were then compared with simulated lives of individuals diagnosed with PCCRC, in terms of life expectancy, quality of life and costs. The simulation model was constructed by using Swedish registry data, supplemented with data from the published scientific literature and databases.

Results: Our simulation indicated that if the CRC of the individuals diagnosed with PCCRC had been diagnosed at the prior colonoscopy, there would have been a down-staging of the cancer. The proportion of patients at each cancer stage shifted from 53% in stage I-II, 35% in stage III and 9% in stage IV at the time of the index colonoscopy, to; 47% in stage I-II, 31% in stage III and 22% in stage IV, respectively, when diagnosed as a PCCRC. Additionally, based on our simulations 3% of the PCCRC was expected to be at an adenoma stage at the time of the colonoscopy and were, thus, theoretically able to prevent. The 1,473 PCCRCs were associated with a loss of 1551 life-years or, expressed differently, 1275 quality-adjusted life-years, compared to being ones detected at colonoscopy. Additionally, the delay in detection was also associated with higher lifetime costs due to an increased need of health care services related to CRC. The cumulative cost was estimated to be €1,922, 000 less if the patients had been diagnosed at the time of the prior colonoscopy. The extra cost per case is €1305.

Conclusion: Our simulation results imply that false negative colonoscopies cause significant loss of life-years and quality of life in the affected individuals. This, together with higher costs, motivates further efforts to improve the quality of colonoscopies.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP173 COMPARISON OF COLONOSCOPY, SIGMOIDOSCOPY AND MULTIPLE ROUNDS OF FIT-BASED COLORECTAL CANCER SCREENING: LONG-TERM FOLLOW-UP

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Introduction: Several methods for colorectal cancer (CRC) screening are available; the most often used include colonoscopy, sigmoidoscopy and fecal immunochemical testing (FIT). To date, comparison between these screenings methods was mainly focused on one-time endoscopic screening to one-time FIT screening. A fair comparison of diagnostic yield (DY) of FIT would comprise cumulative DY after multiple rounds of FIT screening. The aim of our study is to compare the DY of multiple rounds of FIT-screening to one-time screening by sigmoidoscopy and colonoscopy.

Aims & Methods: Demographic data of 30,007 randomly chosen individuals aged 50–74 were obtained from municipal population registers (June 2006 – August 2010); of these 15,046 were invited for four rounds of FIT, 8,407 for one-time sigmoidoscopy, and 6,600 for one-time colonoscopy screening. We compared 2 rounds of FIT to one-time sigmoidoscopy and 4 rounds of FIT to one-time colonoscopy. Cumulative (cum.) participation rate, positivity rate, number of colonoscopies, and diagnostic yield were calculated for each method. The DY was calculated relative to eligible invitees and participants. Between-group differences for participation, number of colonoscopies and DY were evaluated using multivariable logistic regression analysis adjusted for age and gender.

Results: In total, 28,515 eligible persons (median age 60 years, IQR 55–66; 50% males) were invited. Cum. participation was significantly higher for FIT (77%) than for sigmoidoscopy (31%; $p < 0.001$) and colonoscopy (24%; $p < 0.001$). Number of colonoscopies performed relative to eligible invitees was highest for colonoscopy (24%) compared to FIT (13%; $p < 0.001$) and sigmoidoscopy (3%; $p < 0.001$). For invitees the DY for advanced neoplasia (AN) was significantly higher after two rounds of FIT compared to one-time sigmoidoscopy (3.1% vs 2.3%; $p < 0.001$) and after four rounds of FIT compared to one-time colonoscopy (4.5% vs 2.2%; $p < 0.001$). For participants, DY for AN was significantly higher for endoscopic screening; 4.7% for 2 rounds of FIT compared to 7.3% for sigmoidoscopy ($p < 0.001$), and 6.1% for 4 rounds of FIT compared to 9.1% colonoscopy ($p < 0.001$).

Conclusion: In this population-based CRC screening cohort, we demonstrated that multiple rounds of FIT screening detects significantly more advanced neoplasia per invitee compared to one-time sigmoidoscopy and colonoscopy screening, and with significantly fewer colonoscopies needed. Colonoscopy detected more advanced neoplasia per participant. However, due to low participation in colonoscopy screening, FIT seems most effective in population-based CRC screening.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30–10:00
SURGERY IN IBD – ROOM L7

OP174 OUTCOMES OF EMERGENCY ADMISSIONS WITH CROHN'S DISEASE IN ADULTS IN ENGLAND BETWEEN 2004 AND 2014

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Introduction: Between 2006 and 2010, the UK national audit of adult inflammatory bowel disease admissions revealed a small but non-significant fall in mortality in Crohn's disease (CD) from 1.3 to 0.8%, an increase in the rate of prescription of anti-TNF therapy on admission from 3.9 to 8% and a fall in surgery from 23 to 18%.

Aims & Methods: Hospital Episode Statistics (HES) is an administrative database of data on all elective and emergency care episodes in hospitals in England. Using HES, patients aged between 18 and 60 years coded with a first emergency admission with CD were identified. The influence of demographic factors, comorbidity and infused anti-TNF therapy on mortality, surgery and emergency readmissions was examined using multivariate logistic regression.

Results: Between 2004 and 2014, 24,830 patients (55% female, mean age of 35 (IQR 25–44)) were identified. Mortality was 0.22% at 30 days, 0.29% in hospital and 0.81% within 1 year. During admission, 19.2% of patients underwent surgery (median time to surgery 2 days (IQR 1–6)) and 1.9% received infused anti-TNF therapy. Surgery during admission rose from 16.1 to 22.9% (OR 1.52 (95% CI 1.32–1.75), $p < 0.001$) between 2004 and 2014, and infused anti-TNF therapy rose from 1.8 to 2.8% between 2006 and 2014. In-hospital and 1-year mortality fell from 0.51 and 1.03% in 2004 to 0.10 and 0.57% in 2013 (0.18 (95% CI 0.04–0.77), p = 0.021 and 0.46 (0.23–0.91), p = 0.026 respectively). Patients aged 35–60 had a higher 30-day (3.99 (1.97–8.05), $p < 0.001$) and 1-year mortality (4.57 (3.14–6.65), $p < 0.001$) than those aged 18–34. Increasing comorbidity (15.38

(7.33–32.23), $p < 0.001$) and deprivation (3.14 (1.06–9.31), $p = 0.039$) was associated with a higher 30-day and 1-year mortality, but not gender. Females were less likely to have surgery during their admission (0.71 (0.67–0.76), $p < 0.001$) or within 1 year (0.82 (0.77–0.97), $p < 0.001$) and surgery within 1 year was more common in younger (35–60 years 0.87 (0.81–0.93), $p < 0.001$) and non-white patients (1.18 (1.08–1.28), $p < 0.001$). Anti-TNF therapy during admission was associated with less surgery immediately (0.39 (0.28–0.54), $p < 0.001$) and within 1 year (0.55 (0.41–0.73), $p < 0.001$). Emergency readmissions within 30 days were associated with male gender (females 0.74 (0.55–0.98), p 0.039), younger age (35–60 years 0.85 (0.79–0.91), $p < 0.001$), non-white ethnicity (1.25 (1.13–1.38), $p < 0.001$) and not having anti-TNF therapy during admission (0.74 (0.55–0.98), p0.039).

Conclusion: For patients with a first emergency admission for CD, in-hospital and 1-year mortality fell considerably over the study period. Surgery and anti-TNF therapy during admission has increased between 2004 and 2014. Surgery during admission was associated with men and at 1 year with men, younger age and non-white ethnicity.

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All other authors have declared no conflicts of interest.

OP175 IS THE 'RESET' SURGERY EFFECTIVE FOR CROHN'S DISEASE PATIENTS REFRACTORY TO ANTI-TNFA THERAPY?

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Introduction: Anti TNF-alpha agents (anti-TNFα) are currently the most effective therapeutics for Crohn's disease (CD). Some of CD patients under anti-TNFα therapy, however, need surgery because of disease progression. Surgical resection ('Reset') usually leads to the elimination of the intestinal regions with the most severe activity. However, little is known about whether retreatment with anti-TNFα is effective for patients who underwent 'Reset' surgery. The aim of this study was to evaluate the efficacy of anti-TNFα therapy for CD patients who underwent surgery due to the refractoriness to previous anti-TNFα.

Aims & Methods: From July 2005 to November 2015, 65 CD patients underwent intestinal resection at Okayama University Hospital. Of these, 34 patients received anti-TNFα therapy after surgery: 19 refractory to preoperative anti-TNFα (TNFα-refractory group), and 15 anti-TNFα naïve (TNFα-naïve group). The efficacy of post-surgical treatment with anti-TNFα was compared according to the status of pre-operative anti-TNFα therapy. In addition, clinical factors predicting relapse in patients with anti-TNFα retreatment after precedent surgery were evaluated. The evaluated factors were clinical backgrounds, duration of TNFα therapy, concomitant medications before and after surgery, laboratory data before surgery, and the residual of the affected intestine after surgery, etc. The relapse was defined as intensification of medical therapy, hospitalization, or surgery due to worsening of abdominal symptoms, CRP elevation with the evidence of endoscopic recurrence.

Results: Patients of the TNFα-refractory group showed significantly higher rate of relapse than those of the TNFα-naïve group (12/19 (63%) vs. 3/15 (20%), $p < 0.05$). In the evaluation of factors predicting relapse in patients with retreatment of anti-TNFα after surgery, only the residual of the affected intestine after surgery is the significant predictor of relapse (patients with vs. without residual the affected intestine: 11/12 (92%) vs. 3/7(43%), $p < 0.05$).

Conclusion: The 'Reset' surgery was not so effective for CD patients refractory to anti-TNFα therapy. In particular, patients with the residual of the affected intestine after surgery had higher risk of relapse despite retreatment with anti-TNFα after surgery. Those patients may need additional treatment besides anti-TNFα therapy or increase in the dosage amount of the anti-TNFα agent.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP176 IMPACT OF MINIMALLY INVASIVE SURGERY ON QUALITY OF LIFE AFTER SURGERY FOR CROHN'S DISEASE TERMINAL ILEITIS

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Introduction: Crohn's disease (CD) is a chronic illness that interferes with the daily life of those affected. Surgical treatment is required in about 70% of CD patients during the course of disease and risk of surgery is among the highest rated concerns among them. Quality of life is often worsened by intestinal surgery.

Aims & Methods: The aim of the study is to assess the impact of minimally invasive surgery on quality of life after surgery for Crohn's disease terminal ileitis. From June 2010 to December 2015, one hundred twelve consecutive CD patients who underwent surgery for Crohn's disease terminal ileitis were enrolled. They were interviewed by telephone and responded to the generic Cleveland Global Quality of Life (CGQL) questionnaire and the Body Image Questionnarie (BIQ). Their disease activity was defined as Harvey-Bradshaw Index (HBI). Comparisons and correlations were carried out with non-parametric tests. Survival analysis was performed with log rank test.

Results: In our study group 46 patients had minimally invasive surgery for terminal ileum CD while 66 had open surgery for the same indication. Twenty seven patients had a recurrent CD. The total CGQL score and its single items (quality of health, quality of life and energy levels) were significantly higher (and thus, better) in the laparoscopy group patients. Similarly, all the BIQ items were significantly better in patients who had a minimally invasive surgery compared to those who had open surgery. At univariate analysis, total CGQL score was directly correlated with minimally invasive surgery ($rho = 0.40$, $p < 0.001$) and inversely correlated with disease activity at the moment of the interview ($rho = -0.44$, $p = 0.001$), the use of steroids ($rho = -0.20$, $p = 0.02$) and recurrent CD as indication for surgery ($rho = 0.19$, $p = 0.05$). At multivariate analysis, only minimally invasive surgery and disease activity at the moment of the interview revealed to be independent predictors of quality of life. Finally, minimally invasive surgery tended to be associate to a less frequently CD recurrence ($p = 0.08$)

Conclusion: Minimally invasive surgery was associated to a better quality of life and body image perception. This results is probably due in part to the beneficial effect of minimally invasive surgery on body image but also by the less severe disease of these patients (less recurrent Cd as indication for surgery or simpler surgery). Quality of life is essentially predicted by current disease activity and minimally invasive surgery. Finally, minimally invasive surgery tended to be associate to a less frequent CD recurrence.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP177 CLOSE RECTAL DISSECTION VERSUS TOTAL MESORECTAL EXCISION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE UNDERGOING PROCTECTOMY

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Introduction: Proctocolectomy or completion proctectomy in inflammatory bowel disease patients is frequently complicated by disturbed perineal wound healing and presacral abscess formation. Close rectal dissection (CRD) has been regarded as an improved surgical technique for benign conditions that could reduce this complication by leaving the rectal mesentery in situ to minimize dead space cavity compared to total mesorectal excision (TME).

Aims & Methods: The aim of this study was to compare perineal wound healing in ulcerative colitis (UC) and Crohn's disease (CD) patients undergoing TME or CRD. Since it has been suggested that Crohn's mesenteric adipose tissue is involved in CD pathology with reduced regulatory potential of wound healing macrophages, differences in macrophage populations between UC and CD patients were assessed. Adult patients undergoing proctocolectomy or completion proctectomy without reconstruction for UC or CD (2005–2015) were included. Endpoints were postoperative perineal complications, and healing at 6 and 12 months. Rectal mesentery was cultured and walk-out cells were analysed by flow cytometry. CD45+ immune cells were identified, with phenotyping of wound healing macrophages by regulatory markers CD206 and CD14.

Results: Fifty-nine patients (17 UC/42 CD) were included (46.4% male, mean age 45.5 (±14.5)). CRD was performed in 8 UC (47.1%) and 32 CD patients (76.2%). In UC, significantly less perineal complications (17.6% versus 47.6%, $p = 0.033$) and a higher healing rate at 6 months (87.5% versus 64.3%, $p = 0.066$) were seen. No significant differences in outcome between the techniques in UC. Perineal complications occurred less frequently in CD patients who underwent TME compared to CRD, (20.0% versus 56.3%, $p = 0.045$), with higher healing rates at 6 months after TME (90.0% versus 53.3%, $p = 0.052$). Perineal healing rate at 12 months was 87.5% in the TME group versus 65.5% in the CRD group ($p = 0.443$). Analysis of rectal mesentery showed an enhanced infiltration of CD45+ immune cells in CD patients with the balance between CD3+ lymphoid T cells and CD14+ myeloid cells skewed significantly towards the myeloid population (UC vs CD median 24% versus 53%, $p < 0.01$ In addition, macrophages in CD patients showed significantly less expression of the wound healing marker CD206, in line with a more pro-inflammatory and less wound healing profile of CD rectal mesentery. Strikingly, these alterations were maintained in patients with a defunctioning stoma.

Conclusion: In UC, significantly less perineal complications were seen after proctocolectomy or completion proctectomy, compared to CD with higher healing rates. >50% of CD patients had perineal complications and impaired healing, which was seen more frequently after CRD. These findings can probably be explained by the increased pro-inflammatory myeloid cell population with decreased wound healing macrophages, irrespective of the presence of a

defunctioning stoma. These findings suggest that excision of the mesorectum is of crucial importance in CD.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP178 LONG-TERM FOLLOW-UP AFTER ILEORECTAL ANASTOMOSIS IN ULCERATIVE COLITIS (UC): A GETAID/ GETAID CHIRURGIE MULTICENTER RETROSPECTIVE COHORT OF 343 PATIENTS

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Introduction: Colectomy is frequently performed in ulcerative colitis (UC) patients. Although ileal pouch-anal anastomosis is recommended after colectomy, ileorectal anastomosis (IRA) is still performed. The main objective of our study was to determine the cumulative incidence of IRA failure and its prognostic factors.
Aims & Methods: This was a multicenter retrospective cohort study, which included patients with IRA for UC performed between 1960 and 2014. IRA failure was defined as secondary proctectomy and/or rectal cancer occurrence. Uni- and multivariate survival analyses were performed using a Cox-proportional hazards model.
Results: 343 patients from 13 French centers were included. Median follow-up after IRA was 10.6 years. IRA failure rates were estimated at 27.0% (95CI [22–32]) and 40.0% (95CI [33–47]) at 10 and 20 years, respectively. Median survival time without IRA failure was estimated at 26.8 years. Two-thirds of secondary proctectomies were performed for refractory proctitis, and 20% for rectal neoplasia. Univariate analysis identified factors associated with IRA failure: IRA performed after 2004, a longer duration of disease at the time of IRA and having received immunomodulative agents prior to IRA. In multivariate analysis, treatment with both immunosuppressant (IS) and anti-TNF before colectomy was independently associated with IRA failure (HR = 2.9, 95CI [1.21–7.10]). Conversely, colectomy for severe acute colitis was associated with decreased risk of IRA failure (HR = 0.6, 95CI [0.41–0.97]).
Conclusion: Patients with UC have a high risk of IRA failure, particularly when performed for refractory disease. However, IRA could be discussed after colectomy for severe acute colitis, in patients naive to both IS and anti-TNF.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP179 THERAPY REFRACTORY UC PATIENTS MAY BENEFIT FROM APPENDECTOMY; EARLY RESULT FROM THE PASSION STUDY

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Introduction: Evidence has been accumulating indicating that the appendix has an immunomodulatory role in patients with ulcerative colitis (UC) potentially reducing the need for medication and colectomy. However, prospective data are limited and the therapeutic mechanism is not yet understood. The objective of this study was to examine the effect of an appendectomy to modulate the disease course of therapy refractory UC patients.
Aims & Methods: Patients with therapy refractory UC, and referred for proctocolectomy were invited to undergo laparoscopic appendectomy first. The primary endpoint was clinical response at 3 months and after 12 months. Secondary endpoints were remission, improvement in IBDQ score and failure. Results were measured by the Mayo score (partial clinical 0–9 and endoscopic 0–3) and IBDQ score (32 to 224). Clinical response was defined as a decrease in the partial Mayo of ≥3 points. Remission was defined as an endoscopic Mayo ≤1 point. Improvement in IBDQ was defined as an increase of >20 points. Failure was defined as when patients underwent colectomy or prescribed trial medication (eg. Vedolizumab, Etrolizumab).
Results: In total, 30 patients (57% female) with a median age of 40 (IQR, 33–47) underwent appendectomy with a mean preoperative total Mayo score of 9 (SD 2). The mean baseline IBDQ was 125 (SD 34). After 3 months, clinical response was seen in 16 (53%) patients of whom 7 (30%) were in remission (7 patients refused endoscopy at this time point). Improvement in IBDQ was seen in 14 (47%) patients with a mean of 120 (SD 29) that increased to 168 (SD 29). After 12 months, 11 patients failed (7 colectomy, 4 trial medication) and 5 did not yet reach the endpoint. In the remaining 14 patients, 9 (36%) had lasting clinical response of whom 5 (23%) were in remission (3 patients refused endoscopy).
Conclusion: Appendectomy was effective in at least 30% of therapy-refractory UC patients. These early results suggests that UC patients may benefit from appendectomy and that this effect is maintained for a longer period of time. However, follow up of at least 2 years is warranted to exclude a possible placebo effect.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30–10:00
GI INFECTIONS FROM MECHANISMS TO TREATMENT – ROOM L8

OP180 THE RISK OF CLOSTRIDIUM DIFFICILE INFECTION IN PATIENTS WITH PERNICIOUS ANAEMIA: A RETROSPECTIVE COHORT STUDY USING PRIMARY CARE DATABASE

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Introduction: Previous studies have shown an association between proton pump inhibitor use and *Clostridium difficile* infection[1]. One suggested mechanism of this association is the very low stomach acid levels caused by these drugs, since gastric acidity is an important host defence against ingested pathogens. If acid suppression is the true cause of *Clostridium difficile* infection in patients receiving proton pump inhibitors, then this effect should be manifested in patients with achlorhydia (no acid production), a condition associated with pernicious anaemia. Elucidating this association would provide a clear understating of the acid-suppression hypothesis underlying the increased risk of infection in patients who have received gastric acid suppressive therapy.
Aims & Methods: The aim of this study was to determine the risk of *Clostridium difficile* infection in patients with pernicious anaemia. We conducted a population based cohort study using English linked primary (Clinical Practice Research Datalink) and secondary (Hospital Episode Statistics) care records (1998–2012). The exposed group consisted of patients with a diagnosis of pernicious anaemia who had been treated with vitamin B12 therapy. Each exposed patient was matched by age (within 5 years), gender and general practice to non-pernicious anaemia patients, with the follow-up start date of the control being as their matched exposed patient. Cox regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval for the association between *Clostridium difficile* infection and pernicious anaemia, adjusted for potential confounders.
Results: We identified 20,058 patients with pernicious anaemia receiving vitamin B12 therapy and 196,895 controls. The crude incidence rate of *Clostridium difficile* was 3.3/1000 person-years for those with pernicious anaemia while it was 1.7/1000 person-years for controls. Patients with pernicious anaemia had a greater risk of *Clostridium difficile* infection than controls (adjusted HR 1.52, 95% confidence interval 1.33 to 1.73).
Conclusion: Individuals with pernicious anaemia have an increased risk of *Clostridium difficile* infection. This study supports severe hypochlorhydria as the mechanism for the increased *Clostridium difficile* infection in people who have received long-term acid suppression medication.
Disclosure of Interest: F. Othman: This study has been carried out as part of my PhD program at University of Nottingham-UK, funded by Scholarship Award from King Saud bin Abdulaziz University for Health Sciences Saudi Arabia. There is no other potential conflicts of interest
All other authors have declared no conflicts of interest.

Reference

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OP181 CONSISTENT AND REPRODUCIBLE PRODUCTION OF A MICROBIOTA-BASED DRUG FOR RECURRENT C. DIFFICILE INFECTION: APPLICATION OF A NOVEL DIAGNOSTIC FOR DYSBIOSIS

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Introduction: Antibiotics are the first-line treatment for *C. difficile* infection (CDI). However, the most commonly prescribed antibiotics for CDI are associated with high recurrence rates. Antibiotics have been shown to disrupt the intestinal microbiota. Restoration of the intestinal microbiota to its pre-disease state protects against recurrence. There is an unmet need for a standardised, reproducible, microbiota-based therapy for recurrent CDI. RBX2600, a

microbiota-based drug candidate targeted at recurrent CDI, is sourced from human-derived microbes from extensively screened donors and manufactured using standardised, quality controlled processes.

Aims & Methods: To compare the bacterial abundance in the source material for RBX2660 (DS) with the bacterial abundance in the finished drug product (DP) used in the Phase 2B PUNCH CD 2 study. A total of 70 DS samples sourced from 17 unrelated donors (mean age 27; range 18 to 57 years; 94% male) from August 2014 to February 2016 were compared with 70 matched DP samples using the GA-map Dysbiosis Test (GA-test), Genetic Analysis AS, Oslo, Norway. The GA-test uses 54 probes targeting V3 to V7 of the bacterial 16s rRNA gene to characterise and identify bacteria present. Approximately 300–400 bacteria at different taxonomic levels are covered, providing for an assessment of the microbial community using multiple variable regions. The GA- test enables serial assessment of the faecal bacterial abundance profile as well as potentially clinically relevant alterations in the microbiome over time. These capabilities of the GA-test were used to assess the production processes for RBX2660. The differences in bacterial abundance between the DP and DS were calculated from log10 of the probe values (DP-DS); averaging the differences.

Results: The GA-test found that the bacterial abundance in the RBX2660 DP was lower than in the DS in 38 of the 54 probes; equal in number in 6 of the probes; and higher in 10. More specifically, *Firmicutes* and *Actinobacterium* showed reduced signal strength in the DP compared with the DS. *Bacteroidetes* showed increased signal strength in the DP compared with the DS, while *Proteobacteria* demonstrated equal signal strength in both samples. The comparative abundance in the DP vs. the DS is shown in Table 1. Accuracy was as high as 83.4% at cross-validation. Principal component analysis found that the bacterial profiles in the RBX2660 DP, though lower than in the donor source material, were largely kept intact during the production process for all 17 donors.

Table 1: Comparative Signal Strength of Bacteria

Bacteria	Signal Strength in DP vs. DS	Mean Difference (95% CIM)
Bacteroidetes		
Bacteroides fragilis	Increased	0.07 (0.03, 0.11)
Parabacteroides	Increased	0.12 (0.07, 0.17)
Alistipes	Increased	0.17 (0.11, 0.23)
Firmicutes		
Lachnospirae	Decreased	−0.13 (−0.15, −0.11)
Streptococcus	Decreased	−0.16 (−0.20, −0.13
Negativicutes	Increased	0.03 (0.01, 0.06)
Clostridia	Decreased	−0.18 (−0.20, −0.16)
Actinobacteria		
Bifidobacterium	Decreased	−0.33 (−0.38, −0.28)
DP = drug product	DS = drug source	CIM = confidence interval of mean

Conclusion: GA-test analysis confirmed that RBX2660 can be manufactured in a consistent and reliable manner with the preservation of key bacterial diversity believed critical for protection from recurrent CDI.

Disclosure of Interest: C. Jones: Employee of Rebiotix Inc., Roseville, MN USA

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OP182 A METHYL DONOR MOLECULES-SUPPLEMENTED DIET ERADICATES E. COLI POPULATION AND METHYLATES CEACAM6 PROMOTER DECREASING ITS EXPRESSION IN COLONIC EPITHELIAL CELLS IN MICE

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Introduction: Adherent-invasive *E. coli* are clearly involved in triggering and maintaining ileal CD. AIEC bacteria adhere to the enterocytes through high affinity interaction between their variant type one pili and abnormally expressed CEACAM6 protein on host cells. We previously reported an original mechanism of CEACAM6 regulation depending on DNA methylation of transcription factor HIF-1 binding site (HRE, Hypoxia responsive element) in the promoter of the gene. We observed that an unmethylated HRE site allows HIF-1 to bind the promoter and to induce CEACAM6 expression in intestinal epithelial cells (IEC). Decreasing CEACAM6 expression in CD intestinal cells is one strategy that could prevent AIEC bacteria colonization of the intestinal mucosa and subsequent inflammation. This work aims at studying the effect of a methyl-donor enriched diet (HMD: High Methyl Diet) on the intestinal physiology, on microbiota composition, on DNA methylation and on genes expression with a specific focus on CEACAM6.

Aims & Methods: CEABAC10 female mice were fed a HMD (supplemented in folate, biotin, B12 vitamin, zinc, methionine) for 2 weeks before pregnancy. After weaning, the colonic epithelial cells from offspring were purified using EDTA. We analyzed different physiological parameters such as the lipocalin-2 in stools. *E. coli* population was quantified using a qPCR approach. DNA methylation was measured at a global level and on the CEACAM6 promoter using bisulfite-sequencing. qPCR was used to quantify CEACAM6 mRNA. RNA-seq was also used to highlight transcriptomic changes in colonic cells in the both conditions tested.

Results: We observed that mice fed a HMD show a significant decrease in basal lipocalin-2 level in stools compared to mice receiving a conventional diet suggesting a beneficial effect on global intestinal inflammation. No significant changes were observed on histological sections following HMD. Microbiota analysis revealed a 1000-fold decrease in *E. coli* population in mice fed HMD compared to mice receiving a conventional diet. As expected, global DNA methylation analysis revealed a global increase in cytosine methylation in mice fed a HMD compared to mice fed a conventional diet. Bisulfite sequencing revealed a hyper-methylation of the CEACAM6 promoter, especially on the HRE sites. This hypermethylation of the promoter was associated with a significant decrease in CEACAM6 expression as measured by qPCR and Western-blot. RNA-seq data confirmed the decrease in CEACAM6 expression and highlighted many mis-regulated genes following HMD, among them, many genes involved in adaptive immunity.

Conclusion: This work shows that the addition of a few vitamins and oligo-elements to the diet could interfere with the DNA-methylation metabolism leading to changes in genes expression such as a decrease in CEACAM6 and modify microbiota composition leading to eradication of the *E. coli* population in the intestine. A diet-based strategy could help decreasing AIEC colonization in CD patients by modulating CEACAM6 expression.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP183 COMPARATIVE GENOMICS AND SINGLE NUCLEOTIDE POLYMORPHISM DISTRIBUTION BETWEEN ADHERENT-INVASIVE ESCHERICHIA COLI (AIEC) AND NON-AIEC STRAINS FROM THE HUMAN INTESTINE

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Introduction: The molecular basis of Adherent-invasive *Escherichia coli* (AIEC) pathogenicity, a pathotype associated with Crohn's disease, still needs to be well resolved. Nowadays the identification of the pathotype is performed with time-consuming techniques based in phenotypic screening of cultured bacteria; obtaining new molecular tools would therefore be of great significance.

Aims & Methods: Our aim was to identify putative genetic elements involved in AIEC phenotype to gain insight into the mechanisms of its pathogenicity and to find molecular targets for its identification. To achieve this objective we performed comparative genomics of three *E. coli* strain pairs consisting in one AIEC and one non-AIEC of identical pulsed field gel electrophoresis fingerprint. Each pair belonged to a distinct phylogroup. This approach was designed in order to increase the chance of finding sequences AIEC-specific and not strain-specific. The six strains' genomes were sequenced de novo by combining paired-end libraries of HiSeq Illumina and PacBio. Two different approaches for comparative genomics were used: i) assembly with Velvet and genome comparison between pairs with Differences software, ii) SPAdes for assembly and comparative genomics between pairs in relation to a genome of reference (AIEC UM146) with Mauve. Only non-synonymous Single Nucleotide Polymorphisms (SNPs) in coding regions were selected. Sanger sequencing was performed to confirm the presence of SNPs and to evaluate the distribution of the SNPs in a collection of 22 AIEC and 29 non-AIEC isolates. Nucleotides for each SNP were analysed taking into account AIEC phenotype, adhesion and invasion indices of isolates by χ^2 test or ANOVA as required.

Results: Genome sizes of Velvet assemblies for AIEC strains ONT:HNT-D, O6:H1-B2 and O22:H7-B1 were 4.86, 5.16 and 4.79Mb respectively. When SPAdes was used, they presented +95,362bp, +47,933bp and +30,178bp respectively. Comparative genomics of the first approach reported 114, 80 and 31 SNPs, whereas the second resulted in 19, 27 and 31 SNPs respectively. Six SNPs were found with both strategies. From all, 23 SNPs were confirmed by Sanger and analysed among the study collection. These SNPs were comprised in 14 genes from which 3 were involved in metabolic processes, 2 in stress tolerance and 3 in adhesion and invasion pathways. Most of the SNPs were strain-specific, except from one found in a gene putatively implicated in adhesion/invasion, that was differentially distributed among AIEC and non-AIEC strains ($p = 0.029$). Interestingly, this SNP plus 3 other SNPs positions located in the same gene were associated with invasion ($p < 0.024$) and one of them also with adhesion ($p = 0.04$).

Conclusion: To conclude, we have detected SNP variations in a single gene that could be associated with AIEC phenotype. However, further studies with site-specific mutations are needed to confirm the implication of this gene in the AIEC pathogenicity and the SNP effects. Our study indicates that there is not an AIEC-specific genetic marker and widely distributed in all AIEC.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP184 ENTEROHEMORRHAGIC ESCHERICHIA COLI TROPISM TO PEYER'S PATCHES: ROLE OF LONG POLAR FIMBRIAE AND INHIBITION BY A PROBIOTIC YEAST

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Introduction: Enterohemorrhagic *Escherichia coli* (EHEC) are food-borne pathogens associated with diarrhea, hemorrhagic colitis and life-threatening complications such as hemolytic-uremic syndrome. EHEC interact with the Follicule-Associated Epithelium (FAE) of Peyer's patches of the distal ileum in humans and translocate across the intestinal epithelium via M cells. Molecular mechanisms are still unknown but Long Polar Fimbriae (Lpf), which contribute to intestinal colonization, may be involved. Currently no specific treatment is available in EHEC infections and use of antibiotics remains controversial. Probiotic could be an alternative strategy.
Aims & Methods: The objectives of the study were to investigate the role of Lpf in EHEC tropism to Peyer's patches, and to explore the influence of probiotic yeasts on EHEC interactions with intestinal mucosa. The expression of lpf genes (encoded by two lpf operons) of EHEC O157:H7 strain EDL933 was analyzed using in vitro models of the human upper gastrointestinal tract and large intestine. To investigate the involvement of Lpf in the ability of EDL933 to target Peyer's patches, we generated the DlpfA1, DlpfA2, DlpfA1-DlpfA2 isogenic mutants and trans-complemented them with lpf genes. Lpf interaction with M-like cells was investigated using an in vitro model of specialized M cells. In vivo interactions of EHEC with murine Peyer's patches were analyzed in ileal loop assays. Mice were infected with a mixture of two bacterial strains, and the numbers of Peyer's patches-interacting bacteria were determined using a competitive index analysis. To investigate the effect of probiotic yeasts, mice were given the probiotic for 7 days before ileal loops assays were conducted with O157:H7 wild type.
Results: Lpf isogenic mutants (i) were not able to interact with ileal biopsies containing Peyer's patches compared to the wild type strain in competitive colonization assays and (ii) translocated across M cells at levels significantly lower than those observed for the wild type strain. Trans-complementation of the mutants with the cloned lpf genes restored their ability to interact with Peyer's patches and M cells, indicating that expression of lpfA1 or/and lpfA2 genes is required for interactions with Peyer's patches. Bloodshot Peyer's patches were macroscopically observed following EHEC infection of murine ileal loops. We showed that or pre-treatment with yeasts significantly inhibited O157:H7 interactions with Peyer's patches and reduced the number of hemorrhagic Peyer's patches in murine ileal loops. Since yeast cell surface is rich in mannose, the role of carbohydrates in EHEC interactions with Peyer's patches was investigated. Among the carbohydrates tested, only mannose specifically limited the interactions of EHEC with Peyer's Patches.
Conclusion: We conclude that Lpf are involved in the interactions of EHEC with murine Peyer's patches and are needed for an active translocation across M cell monolayer. Tropism of EHEC to Peyer's patches can be limited by probiotic yeasts and by specific carbohydrates.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP185 CURRENT OR PAST CLOSTRIDIUM DIFFICILE INFECTION IS ASSOCIATED WITH INCREASED MORTALITY, MORBIDITY AND RESOURCE UTILIZATION AMONG PATIENTS HOSPITALIZED FOR CROHNS' DISEASE: RESULTS OF A NATIONWIDE ANALYSIS

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Introduction: Multiple factors have been associated with an acute flare of Crohn's disease, including cigarette smoking and non-steroidal anti-inflammatory drug use. Recently, *Clostridium difficile* infection (CDI) has been added to this list. CDI can become chronic or recurrent in 20% of patients. To date, the impact of CDI on patients' mortality and other outcomes among patients with Crohn's disease has not been investigated.
Aims & Methods: The aim of this study is to explore the impact of past or current CDI on mortality, morbidity and resource utilization among patients hospitalized for Crohn's disease. This was a retrospective cohort study using the 2012 National inpatient sample, the largest publically available inpatient database in the United States. The inclusion criteria were: 1- a principal diagnosis of Crohn's disease 2- A principal diagnosis of intestinal hemorrhage, obstruction, fistula, or abdominal abscess with a secondary diagnosis of Crohn's disease. There were no exclusion criteria. The primary outcome was in-hospital mortality. The secondary outcomes were morbidity as measured by shock, intensive care unit (ICU) admission, colectomy or intestinal resection rate and resource utilization as measured by length of hospital stay (LOS), abdominal CT scan, total parenteral nutrition (TPN) use and total hospitalization charges. Odds ratios and means were adjusted for the following confounders using multivariate regression analyses: age, sex, race, median income in the patient's zip code, Charlson Comorbidity Index, hospital region, rural location, size and hospital teaching status.
Results: 74,515 patients with Crohn's disease were included in the study, 1,465 (2%) of whom had CDI. The mean age was 43 years and 42% of patients were female. Patients with CDI had higher mortality rate (adjusted odds Ratio (OR):5.84, 95% confidence interval (CI):1.79–19.07, $p < 0.01$) compared with patients without CDI. Looking at morbidity, patients with CDI had similar a colectomy rate (OR:1.16, CI: 0.75–1.77, $p = 0.5$), ICU admission rate (OR: 2.77, CI: 0.93–8.29, $p = 0.07$) and shock rate (OR: 3.06, CI: 0.94–9.97, $p = 0.06$) but a lower intestinal resection rate (OR: 0.26, CI: 0.08–0.82, $p = 0.02$) compared with patients without CDI. When resource utilization was examined, patients with CDI had longer LOS (adjusted mean (mean): 2.54 days, CI: 1.78–3.30 days, $p < 0.01$), higher TPN use (OR: 2.71, CI: 1.92–3.82, $p = 0.02$), higher total hospitalization charges (mean: $14,250, CI: $8,473–$20,026, $p < 0.01$) and similar abdominal CT scan use (OR: 1.41, CI: 0.78–2.59, $p = 0.25$) compared with patients without CDI.
Conclusion: Current or past CDI is associated with increased mortality among hospitalized patients with Crohn's disease. However, patients with CDI have similar colectomy rates, shock or ICU admission rate compared with patients without CDI. Finally, CDI has a profound effect on resource utilization with longer length of stay, increased TPN use and substantially higher total hospitalization charges.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30–10:00
COLON CANCER: FROM SCREENING TO PALLIATION – ROOM 1.86

OP186 SELF-EXPANDABLE METALLIC STENT AS BRIDGE TO SURGERY IS MORE SUPERIOR THAN TRANSANAL DRAINAGE TUBE AT QUALITY OF LIFE FOR THE PATIENTS WITH PRIMARY MALIGNANT COLORECTAL OBSTRUCTION

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Introduction: Self-expandable metallic stent (SEMS) or transanal drainage tube (TDT) is endoscopic decompression for malignant colorectal obstruction. SEMS is said to be superior to TDT at quality of life (QOL) for the patients, but the comparison between SEMS and TDT for malignant colorectal obstruction was few reported include the clinical efficiency, safety and prognosis.
Aims & Methods: The aim of this study is to evaluate QOLs, clinical efficiency and safety between SEMS and TDT for the patients with malignant colorectal obstruction. We retrospectively analyzed 69 patients who underwent SEMS or TDT insertion for malignant colorectal obstruction from April 2009 to March 2016 on the basis of single-center experience in Japan. SEMS was inserted for bridge to surgery (BTS) or palliation, and TDT was inserted for BTS or bridge to SEMS insertion.
Results: There were 27 patients in SEMS group (male 37.0%, median age 73 ± 17.0years) and 42 patients in TDT group (male 54.8%, median age 65 ± 15.2 years). Technical success rate was 100% of SEMS group and 95.2% of TDT group ($p = 0.15$). The endoscopic decompression as BTS for primary colorectal cancer was performed in 57.1% of SEMS group and 85.7% of TDT group ($p = 0.02$). Among these patients, the duration for surgery after decompression was longer in SEMS group (14.9 ± 7.0 days vs 10.5 ± 6.6 days, $p = 0.04$), because the rate of temporary discharge was significantly higher in SEMS group (41.7% vs 0.0%, $p < 0.001$). No significant difference was shown about the hospitalization in both group (36.1 ± 23.5 days vs 46.4 ± 36.0 days, $p = 0.36$). The rate of oral intake (at least soft solids) was significantly higher in SEMS group (88.9% vs 25.0%, $p < 0.001$). The Colonic Stent Safe Procedure Research Group ColoRectal Obstruction Scoring System (CROSS) score before decompression had no significant difference in both group (1.1 ± 0.9 vs 1.2 ± 0.7, $p = 0.49$), but CROSS score after decompression was significantly improved in SEMS group (3.7 ± 0.8 vs 2.3 ± 0.5, $p < 0.001$). The complications after procedure, such as perforation, migration, re-obstruction, had no significant difference in both group.

Table: Patients characteristics and results

	SEMS (n = 27)	TDT (n = 42)	p value
Sex (male)	10 (37.0%)	23 (54.8%)	N.S.
Age (median, years)	73 ± 17.0	65 ± 15.2	N.S.
-Age > = 85years	9 (33.3%)	3 (7.1%)	p = 0.005
Obstructed location (left side)	23 (85.2%)	38 (90.5%)	N.S.
Primary colorectal cancer	21 (77.8%)	28 (70.0%)	N.S.
-BTS	12	24	p = 0.02
-Bridge to SEMS insertion	-	2	
-Palliation	7	-	
-Emergent surgery	2	1	
Metastatic colorectal cancer	6 (22.2%)	12 (30.0%)	N.S.
-BTS	0	5	
-Bridge to SEMS insertion	-	2	
-Palliation	5	-	
-Emergent surgery	1	1	
-Technical Success	27 (100%)	40 (95.2%)	N.S.
Complications			
-Perforation	2 (7.4%)	6 (14.3%)	N.S.

(continued)

Table Continued

	SEMS (n = 27)	TDT (n = 42)	p value
-Re-obstruction	5 (18.5%)	1 (2.4%)	N.S.
-Migration	2 (7.4%)	2 (4.8%)	N.S.
QOLs			
-Temporary discharge	5/12 (41.7%)	0/24 (0.0%)	$p < 0.001$
-Duration for surgery (days)	14.9 ± 7.0	10.5 ± 6.6	N.S.
-Hospitalization (days)	36.1 ± 23.5	46.4 ± 36.0	$p = 0.36$
-Oral intake (at least soft solids)	11/12 (88.9%)	6/24 (25.0%)	$p < 0.001$
-CROSS score (before procedure)	1.1 ± 0.9	1.2 ± 0.7	N.S.
-CROSS score (after procedure)	3.7 ± 0.8	2.3 ± 0.5	$p < 0.001$

Conclusion: SEMS has the equivalent safety, clinical efficiency and is more superior at QOLs for the patients with malignant colorectal obstruction, comparing TDT.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP187 EVALUATION OF CLINICAL FACTORS ASSOCIATED WITH THE TECHNICAL DIFFICULTY OF SELF-EXPANDABLE METALLIC STENT PLACEMENT FOR MALIGNANT COLONIC OBSTRUCTION

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Introduction: In January 2012, the National Health Insurance began covering endoscopic self-expandable metallic stent (SEMS) placement for malignant colonic obstruction, and now this procedure is widely used in Japan. However, the clinical factors affecting the technical difficulty of SEMS placement are unclear.
Aims & Methods: This study aimed to clarify the clinical factors associated with the technical difficulty of SEMS placement for malignant colonic obstruction. We established the Colonic Stent Safe Procedure Research Group to provide instructions on how to safety perform SEMS placement, and we then conducted tis prospective, observational, single-arm, multicenter clinical trial between March 2012 and October 2013 in Japan. Forty-six facilities participated in this study. An uncovered WallFlex Enteral Colonic Stent (Boston Scientific Corporation) was placed in each patient. Technically difficult cases of SEMS placement were defined as those that had a procedure time longer than 45 min (i.e., 1.5-fold longer than the median procedure time). We evaluated the clinical data and extracted risk factors associated with the technical difficulty of SEMS placement by using univariate and multivariate analyses.
Results: A total of 518 consecutive patients were enrolled in this study. Seven patients were excluded and the remaining 511 patients constituted the per-protocol cohort. Of these, 289 were men (57%), and the mean age was 70.6 years. Three hundred eleven patients (61%) underwent stenting as a bridge to surgery, and 200 (39%) underwent stenting for palliation. Technical success was achieved in 501 patients (98%). The median (range) procedure time in the cohort with technical success was 30 min (4–170 min). One hundred thirty-six patients (27%) were defined as technically difficult cases of SEMS placement. Clinical risk factors independently associated with the technical difficulty in SEMS placement were metastasis of peritoneal carcinomatosis (odds ratio [OR], 2.24; 95% confidence interval [CI], 1.26–3.96; $p < 0.01$), a Colorectal Obstruction Scoring System (CROSS) [1]score of 0 before SEMS placement (OR, 2.00; 95% CI, 1.18–3.40; $p < 0.01$), tumor site in the right colon (OR, 3.33; 95% CI, 2.06–5.42; $p < 0.001$), stricture length >5 cm (OR, 1.65; 95% CI, 1.01–2.70; $p = 0.04$), the placement of >1 stent (OR, 5.96; 95% CI, 1.39–29.72; $p = 0.02$), and a length of >6 cm for the first stent (OR, 2.21; 95% CI, 1.38–3.56; $p < 0.01$). However, the clinical risk factors independently negatively associated with technical difficulty were a history of chemotherapy before SEMS placement (OR, 0.47; 95% CI, 0.22–0.98; $p = 0.04$), digestive tract decompression (OR, 0.45; 95% CI, 0.25–0.81; $p < 0.01$), and a diameter of 25 mm for the first placed stent (OR, 0.32; 95% CI, 0.12–0.76; $p = 0.02$).
Conclusion: This large study demonstrated the high technical success rate of SEMS placement for malignant colorectal obstruction. However, clinicians should perform this procedure very carefully in cases with metastasis of peritoneal carcinomatosis, severe stenosis with a CROSS score of 0, and/or long strictures treated with a long stent.
Disclosure of Interest: M. Shimada: personal fees:Century Medical Inc., Boston Scientific Japan
T. Kuwai: personal fees: Boston Scientific Japan
S. Yoshida: personal fees: Century Medical Inc., Boston Scientific Japan, ZEON
H. Isayama: Donation & Lecture fees:Century Medical Inc. Boston Scientific Corp., Taewoong Medical Co, Ltd
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T. Sasaki: personal fees: Boston Scientific Japan., Piolax Medical Device
K. Koizumi: Lecture fee: Century medical inc.personal fees: Olympus Medical Syste ms
I. Maetani: Lecture fee: Century medical inc., Boston Scientific Japan., Piolax M edical Device, MC Medical
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All other authors have declared no conflicts of interest.

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OP188 17 YEARS OF SINGLE CENTER EXPERIENCE WITH SELF-EXPANDABLE METAL STENTS IN COLONIC OBSTRUCTION

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Introduction: Since 1991, self-expandable metal stents (SEMS) has been used in the treatment of malignant colonic obstruction (1). In 1997, Bispebjerg Hospital was the first hospital in Denmark to initiate the use of SEMS in the treatment of malignant colonic obstruction. This study represents the largest material from a single centre ever published.
Aims & Methods: This is a prospective registration of all patients who underwent SEMS at our institution, in the period from January 1st 1997 to October 1st 2014. No patients were excluded. The indications were predominantly malignant, but a few were performed at benign indications. All procedures were performed with a combined endoscopic and fluoroscopic technique. Relevant patient characteristics, the postoperative course, complications and follow-up data, were gathered by retrospective patient chart review.
Results: In the period, 521 SEMS procedures was performed in 455 patients, 402 of these had colorectal cancer. Mean age was 74 ± 13 years, and 50.3% were male. The indications for SEMS placement were malignant colonic obstruction in 418 patients, including 158 as bridge to surgery (BTS), 237 as palliation, three with malignant anastomotic stricture and 20 patients with obstruction due to external tumor compression. The benign indications in 37 patients were respectively diverticulitis stricture in 15, diverticulitis fistula in two and benign anastomotic stricture in 20. Two hundred and seventy-seven patients had manifested total colonic obstruction and 121 had small bowel dilatation at the time of the procedure. The placement of the SEMS was 111 in rectum, 221 in sigmoid colon, 52 in descending colon, 30 in splenic flexure, 30 in transverse colon, 6 in hepatic flexure and 5 in ascending colon. Mean length of stenosis was 4.5 ± 1.9 cm and mean days of obstruction was 5.2 ± 3.4 days. There was an overall technical success rate at 90.3% and clinical success rate of 87.7%. Stent procedure related complications was 4.2%, mainly guidewire perforations, and none of these patients died within 30 days. A second stent intervention was performed in 5.9% in the BTS group, 11.9% in the palliative group and in 27.3% in the group of benign indications, external tumor compression and malignant anastomotic stricture. Very few patients required additional re-interventions. The overall 30-day mortality rate was 13.4%, 5.8% for BTS group and 17% for palliative group. Follow up time for BTS group was mean 79 ± 70 months and at last follow up 35.3% (36/102) showed clinical signs of recurrence. 5-year survival in BTS group was 32.3% and 2.5% in the palliative group.
Conclusion: Our data shows that routine use of SEMS insertion is a safe and effective technique for colonic decompression in the setting of malignant large bowel obstruction, as either a palliative measure or as a bridge to subsequent resection. SEMS for benign conditions is feasible but with less favourable outcome.
Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

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OP189 LONG-TERM SURVIVAL AFTER ENDOSCOPIC STENTING AS A BRIDGE TO SURGERY IN OBSTRUCTIVE COLON CANCER: A SINGLE CENTER STUDY

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Introduction: Self-expandable metallic stents are increasingly used in the treatment of obstructive colorectal cancer. Although endoscopic stenting is widely accepted in a palliative setting, disagreement exists about its role in a curative setting (1). The main advantage of this approach is the elective, and thereby less invasive, character of the surgical resection. It offers the opportunity for an adequate pre-operative assessment of the patient and a good preparation of the colon (2).
Aims & Methods: This study aims to describe the long-term survival data in a large patient group, treated with a stent as a bridge to surgery (BTS) for colon cancer. Ninety-seven patients, who presented in a Belgian secondary hospital between June 1998 and November 2013 with a large bowel obstruction due to colon cancer, were included. All patients underwent endoscopic stenting as a BTS in a potentially curable disease. Procedure-related complications and long-term follow-up survival data were collected and compared with the colon cancer mortality in Belgium in the same era (3).

Results: Overall survival in this observational cohort did not differ significantly from survival in all Belgian colon cancer patients in the same period (p = 0.14). One-, five- and ten-year survival was not statitiscally different in both groups (95.9% vs 79.0%; 54.7% vs 51.2%; 41.0% vs 35.6% respectively). Additionally, for tumour stage II, III and IV no statistical differences between both cohorts were found (p = 0.21, p = 0.58, p = 0.10 respectively). Technical success rate was 94.8%. Seventy patients did not experience any complication. Stent migration occurred in 9 patients, whereas stent-related micro- and macro perforations were observed in 14 patients, without influencing survival. Incidence rates of peritoneal metastases did not differ significantly between patients with and without any type of perforation (22.2% vs 15.2% respectively, p = 0.47). On average, surgery took place 16.6 days after colonic stenting, ranging from an operation on the same day as the endoscopic procedure, to an interval of maximal 124 days. In 82.5% of the cases a laparoscopic resection of the tumor was performed. Five point two per cent of the patients got primarily open surgery. In 5.2% of the patients a laparoscopic procedure was converted to laparotomy, because of adhesions or peritonitis. Stoma rates were low (5.2%).
Conclusion: These data indicate that stenting before surgery is effective and safe in the treatment with curative intent of patients with obstructive colon cancer and reinforce the debate on stenting as a BTS.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP190 IMPACT OF MORTALITY FROM SURGICAL ADENOMA REMOVAL ON THE EFFECTIVENESS OF COLORECTAL CANCER SCREENING

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Introduction: Implementation of colorectal cancer (CRC) screening programs results in an increase in the number of adenoma diagnoses. Some of the advanced adenomas (AADs) cannot be endoscopically removed and patients may then be referred for surgery. However these surgical resections have an associated mortality risk and will have a negative impact on the effectiveness of CRC screening. So far, the size of this impact is unknown. Therefore the objective of this study is to estimate the size of this perioperative mortality in relation to AAD removal on the effectiveness of CRC screening.
Aims & Methods: We used the MISCAN-Colon microsimulation model to simulate the Dutch population, aged 50 years and older in 2013 and followed them lifetime. The population was offered biennial FIT (FOB-Gold at a cut-off of 46 mg/g feces) screening between ages 55 and 75. Gradual roll-out was simulated from 2014 to 2020 according to implementation. To assess the impact of perioperative mortality in relation to AAD removal, we simulated a scenario with and without perioperative mortality within the screening program. In the scenario with perioperative mortality, we assumed that 3.9% of all AADs diagnosed during diagnostic colonoscopy need to be surgically removed, based on findings in Dutch pilot studies. The perioperative mortality rate is estimated at 2.1%, based on reports of Dutch surgeons. This leads to an overall mortality risk of 0.08% for every AAD diagnosis. The primary outcomes were the size of perioperative mortality per year, the number of prevented CRC deaths, life years gained (LYG), quality adjusted life years (QALYs) and costs. Sensitivity analyses were performed with a mortality risk of 0.05% and 0.11%.
Results: During the roll out of the Dutch screening program between 2014 and 2020, perioperative mortality caused up to 18 deaths every year. After 2020 the number of AAD screen detected decreased and thus perioperative mortality decreased gradually through approximately 11 per year in 2033. Between 2014 and 2033, a total of 251 individuals died from perioperative complications. This corresponded with a decrease in prevented CRC deaths of 1.5% (22135 without operation mortality vs 21928 with), a decrease in LYG from screening of 2.5% and in QALY's of 1.0%. The impact on costs of the screening program was negligible. With higher and lower perioperative mortality assumptions, the outcomes altered proportionally.
Conclusion: Mortality due to surgical AAD resection has a negative impact on the effectiveness of CRC screening, although the impact is modest. Benefits of CRC screening as a whole are maintained. However, deaths due to surgical AAD resection are an order of magnitude larger than deaths due to complications of colonoscopy. Future studies into the effectiveness of CRC screening should therefore incorporate the harms of surgical AAD removal.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP191 SCREENING COLONOSCOPIES IN SENIORS OVER 70 YEARS OF AGE

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Introduction: The recomended age for colonoscopy screening in average risk population is 50–55 years, but there is no upper age limit. Many patients are addressed for screening in advanced age. Although the prevalence of neoplastic lesions increases with age, life expectancy decreases. The aim of or study was to evaluate the outcomes of screening colonoscopies in population over 70 years of age.
Aims & Methods: The data from all screening colonoscopies performed in one non-university gastroenterology center from january 2012 to december 2015 were recorded to database in MS Excel. The main parts of the database comprise of epidemiologic data about the patient, data about examination, histologic results and complications. The data of population aged 70 years and over and under 70 years were compared, the chi-square and Student t test were used to compare dichotomous and continous variables considering level od significance of .05.
Results: 1677 screening colonoscopies were performed in total, 333 in group 70 years and more, 1344 in group under 70 years. Polyp detection rate (PDR) and and quality of bowel preparation in both groups were comparable. There were significantly more neoplasias (ADR), advanced neoplasias (advanced adenoma and carcinoma) and carcinomas in older group and also adenoma per colonoscopy rate (APCR) was higher in seniors. Caecal intubation rate was significantly lower. The numer of colonoscopies after positive FOBT was significantly higher than primary colonoscopies in seniors. See the table. There were no bleeding complications or perforations during screening examinations in both groups.

	≥70 years (333)	<70 years (1344)	p
Men	160 (48%)	706 (53%)	0.139
FOBT/primary col.	**213/120**	**660/684**	**<0.005**
PDR	237 (71%)	911 (68%)	0.240
ADR	**174 (52%)**	**616 (46%)**	**0.037**
Advanced ADR	**74 (22%)**	**200 (15%)**	**0.001**
Carcinoma	**10 (3%)**	**17 (1%)**	**0.024**
APCR	**1.102**	**0.875**	**0.006**
Caecal intubation	**313 (94%)**	**1304 (97%)**	**0.006**
Inadequate preparation	24 (7%)	74 (5%)	0.237

Conclusion: Screening colonoscopies in population over 70 years of age in our study were safe, with higher detection of neoplasias, but with lower completion rate. There was higher number of colonoscopies after positive FOBT than primary colonoscopies among seniors.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 10:30–12:00
COMPLICATIONS IN IBD – ROOM F2

OP192 THE OCCURENCE OF ANAEMIA AND ANAEMIA SUBTYPES DURING THE FIRST YEAR OF DISEASE IN AN EAST-WEST EUROPEAN INCEPTION COHORT – AN ECCO-EPICOM COHORT STUDY

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Introduction: The EpiCom-cohort is a European prospective population-based cohort of unselected patients uniformly diagnosed with inflammatory bowel disease (IBD) in 2010 in 31 Western and Eastern European centres[1]. Previously, this cohort has demonstrated differences in the treatment strategy of IBD patients between Eastern and Western European centre including that significantly more patients in Western Europe receive biological therapy[2]. Despite these differences in treatment no differences regarding disease outcomes including surgery and hospitalization rates and quality of life between the two regions have been found. Anaemia is a common systemic complication and/or extra-intestinal manifestation to IBD as well as an indicator of the level of global IBD care and inflammation control.

Aims & Methods: The aim of the current study was to investigate the occurrence of anaemia as well as differences between Eastern and Western Europe during the first year of disease. Incident patients were followed prospectively from the time of diagnosis. Clinical data on surgery, medical treatment, hospitalization, and blood samples were captured throughout the follow-up period. Anaemia and its subtypes were defined according to the World Health Organisation and ECCO guideline.

Results: A total of 827 patients aged 15 years or older from 29 centres (20 Western, 9 Eastern European) were eligible for analysis of whom 433 (52%) had ulcerative colitis (UC), 300 (37%) had Crohn's disease (CD), and 94 (11%) had IBD unclassified (IBDU). The proportion of patients with anaemia and its subtypes at diagnosis and follow-up is shown in table 1. Overall, anaemia was more frequent in Eastern than in Western European patients for both CD and UC. After 1 year of follow-up significantly more patients in Eastern Europe who were anaemic at diagnosis remained anaemic (23% UC, 24% CD) compared to Western Europe (8% UC 9% CD), while a similar proportion in both regions changed from the anaemic state to normal (20% UC and 35% CD in both regions) during follow-up. More IBD patients receiving biological therapy during the first year of disease changed status from anaemia at diagnosis to no anaemia at follow-up (83%) compared to patients not having received biological therapy (70%), while fewer patients receiving biological therapy remained anaemic during follow-up (17% vs 30%). These differences did, however, not reach statistical significance (p = 0.09).

Table 1: Prevalence of anemia at diagnosis and at 1-year follow up.

	Ulcerative colitis				Crohn's disease			
	Eastern Europe		Western Europe		Eastern Europe		Western Europe	
	Diagnosis	Follow-up	Diagnosis	Follow-up	Diagnosis	Follow-up	Diagnosis	Follow-up
Anaemia - overall	43%	26%	29%	13%	58%	25%	45%	12%
Iron deficiency	6%	3%	3%	2%	7%	4%	1%	0%
Anaemia of chronic disease	9%	3%	3%	1%	13%	0%	12%	1%
Mixed anaemia	6%	1%	1%	1%	24%	7%	17%	1%
Other anaemia	6%	4%	4%	2%	2%	0%	6%	2%
Unclassified	14%	16%	16%	6%	13%	15%	10%	9%

Conclusion: In this unselected, population-based inception cohort the frequency of anaemia was high at the time of diagnosis, especially for CD, but decreased during the first year of follow-up. More Eastern than Western European patients remained anaemic after 1 year of follow-up. These geographic differences could be caused by differences in awareness of anaemia or they might reflect differences in global care and inflammation control of IBD patients in Europe. Geographic variations in the use of biological therapy might contribute to the observed differences in anaemia frequency.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP193 INCIDENCE AND RISK FACTORS OF SERIOUS VIRAL INFECTIONS IN INFLAMMATORY BOWEL DISEASE

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Introduction: Use of immunosuppressants in IBD is associated with an increased risk of serious infections that varies considerably according to infection and immunosuppressant subtypes. This study aimed to determine the incidence rate and risk factors for serious viral infection (SVI) according to drug exposure and IBD activity in patients with IBD.

Aims & Methods: Using MICISTA registry, a prospective observational cohort of IBD patients treated at our tertiary care hospital, we identified between Jan 2005 and Dec 2014 patients who developed SVI as defined by need for hospitalization, definite organ damage or disabling sequelae. Cases of CMV colitis without systemic manifestations were excluded. We first estimated incidence rates of SVI, overall and according to maximal yearly treatment. Additionally, we performed a case-control study (4 controls for 1 case matched for age, gender, IBD subtype and duration) assessing risk of SVI according to IBD drug use and IBD clinical activity in the 3 months preceding the SVI (data extracted from individual health records).

Results: We identified 31 patients with SVI among 2645 patients, followed for a median period of 6.2 years and a total observational time of 16922 patient-years. We identified 13 cases of CMV systemic infection (primary infection (n = 6), reactivation (n = 7)), 10 cases of EBV infection (primary infection (n = 6) including 2 haemophagocytic syndromes, reactivation (n = 4)), 5 cases of VZV infection (varicella (n = 3), shingles (n = 2)) and 3 cases of HSV infection (severe esophagitis, facial nerve paralysis, severe refractory cutaneous manifestation). Most patients required hospitalization (94%) and received IV anti-viral therapy (52%), while no death occurred. The incidence rate of SVI in patients with IBD was 1.83 per 1000 patients-years. Table 1 shows the incidence rate of SVI according to the maximal treatment received during the year. In the case control study, risk of SVI was associated with exposure to thiopurine (adjusted odds-ratio (aOR), 5.1; 95% CI, 1.9–13.4; p = 0.001) and methotrexate (aOR, 4.1; 95%CI, 1.0–16.8; p = 0.05), and active clinical disease (aOR, 3.2; 95% CI, 1.3–8.1; p = 0.02). Odds-ratios for corticosteroids and anti-TNF did not reach statistical significance (1.1 and 1.2, respectively).

	Exposure to medication (patients-years)	Incidence rate for SVI (per 1000 patients-years)	P value	95% Confidence interval
No treatment or 5ASA	7922	0.50	ref	0.01–1.00
Steroids	1582	0.63	0.68	0–1.87
Immunomodulators	6236	3.2	0.0002	1.80–4.61
Anti-TNF ± immunomodulators	5173	1.16	0.31	0.23–2.09

Conclusion: SVI are rare events in patients with IBD who do not receive immunosuppressants. Exposure to thiopurines or methotrexate, and IBD clinical activity increases substantially the risk. Among 100 patients treated with thiopurines for 10 years, 3 will develop SVI.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP194 COLORECTAL CANCER RISK IN A NATIONWIDE INFLAMMATORY BOWEL DISEASE COHORT WITH LOW GRADE DYSPLASIA

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Introduction: Patients with long-standing colonic inflammatory bowel disease (IBD) bear an increased colorectal cancer (CRC) risk. Endoscopic surveillance allows early detection and removal of precancerous lesions such as low-grade dysplasia (LGD), and may subsequently prevent CRC. However, the long-term outcome after LGD and the subsequent risk to develop CRC remains uncertain,

since most available studies are small and cover a relatively short follow-up period. To this end, we established a nationwide cohort of IBD patients with a history of LGD to 1) determine the cumulative CRC incidence, and 2) identify risk factors for developing CRC.
Aims & Methods: Using the Dutch National Pathology Registry (PALGA) we identified all IBD patients diagnosed with LGD between 1991 and 2005 in the Netherlands. Subsequently, follow-up data were extracted until 2016. We determined the cumulative CRC incidence with Kaplan Meier curves censuring patients at the end of colorectal surveillance or colectomy. A case control study, comparing IBD patients with LGD who developed CRC (cases) versus patients who did not develop CRC (controls), was performed to identify risk factors for developing CRC. Demographic data, including gender, IBD type, age and duration, and LGD age and recurrence, were extracted from PALGA. Subsequently univariable and multivariable Cox regression analyses with backward elimination were used to identify independent risk factors.
Results: We identified 1177 IBD patients with colonic LGD with a median follow-up time of 9.8 years per patient after LGD diagnosis (total follow-up time: 11741 patient years). 825 (70.1%) patients had ulcerative colitis, 216 (18.4%) Crohn's disease and 136 (11.6%) indeterminate colitis. Hundred nine out of 1177 (9.3%) patients underwent colectomy. CRC developed in 86 out of 1177 patients resulting in a cumulative incidence of 2.9%, 5.8%, 11.1%, and 18.7% after respectively 5, 10, 15 and 20 years. Patients with an IBD duration of more than 5 years before LGD development had a significantly higher cumulative CRC incidence (14.7% after 15 years) compared to those with a shorter IBD duration (9.4% after 15 years; log rank $p = 0.001$). Furthermore, patients with recurrent LGD had a higher CRC risk compared to patients with single LGD (10.5% after 15 years versus 4.5% after 15 years; log rank $p = 0.026$). Multivariable Cox regression identified both a longer IBD duration (hazard ratio 2.5, 95% confidence interval 1.5–4.3) and recurrent LGD (hazard ratio 1.9, 95% confidence interval 1.1–3.4) as independent factors associated with increased CRC risk.
Conclusion: We showed a cumulative CRC risk of 18.7% after 20 years in a large nationwide cohort of IBD patients with a history of LGD. Both a longer IBD duration and recurrent LGD were identified as independent risk factors for CRC development following LGD. These findings may aid in risk stratification following a diagnosis of LGD in IBD patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP195 ROLE OF DIFFUSION-WEIGHTED IMAGING (DWI) IN MRI-ENTEROGRAPHY FOR THE EVALUATION OF SURGICAL RISK IN PATIENTS WITH CROHN'S DISEASE

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Introduction: In Crohn's disease (CD) it's useful to discriminate inflammatory from fibrotic lesions. MRI-Diffusion Weighted Imaging (DWI) is able to identify active inflammation in most pathological tissues.
Aims & Methods: We aimed to define the role of DWI in evaluating the risk of surgery in CD. We performed an observational prospective study including all consecutive CD patients with active CD undergone MRI. MRI study included: measurement of bowel wall thickness (BWT), CD extension, enhancement pattern, pre-stenotic dilation, presence of oedema and/or comb-sign, presence of fistulas/abscesses, T2 and T2 sequences. Furthermore, all patients were studied by DWI sequences defining: visual analysis of iperintensity and analysis of Apparent Diffusion Coefficient (ADC) maps. Statistical analysis was performed dividing all patients in 2 groups (operated vs not operated) using T-student and X-square test when indicated. To identify the variables associated to surgical risk, we performed a logistic multiple regression expressing the risk in terms of Odd Ratio. Finally, the diagnostic accuracy was tested by a ROC curve.
Results: 110 patients were enrolled and 127 bowel segments resulted pathologic at MRI. 26 patients (23.6%) and 31 segments were resected during the follow-up period. At all pathological segments, the iperintensity in DWI sequences, the reduction of ADC max, ADC medium and the presence of fistulas/abscesses were significantly associated with a subsequent surgical intervention ($p < 0.05$). In particular, the presence of CD complication was the variable with the highest risk of surgery ($p = 0.008$; OR 3.9; 95% CI 1.4–10.7). When excluding the patients with complications, we reported a significant correlation of DWI iperintensity, ADC max and medium with surgical intervention. The reduction of ADC medium was the variable with the highest risk of surgery ($p = 0.03$; OR 2.0; 95% CI 0.79–0.92). The cut-off value for discriminating patients at risk of surgery was 1.081×10^{-3} mm^2/s (sensibility 55.6%, specificity 70.3%, PPV 33.3%, NPV 85%).
Conclusion: The presence of fistulas/abscesses remains the variable most associated with surgical risk in CD. In not complicated CD, DWI sequences at MRI-Enterography correlates with the need of surgery. High value of ADC medium shows high NPV for surgery in CD patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP196 PREDICTORS OF FIRST COLONIC EPITHELIAL NEOPLASIA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE UNDERGOING COLONOSCOPIC SURVEILLANCE

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Introduction: Patients with inflammatory bowel disease (IBD) are at increased risk for developing colorectal neoplasia (CRN). Little is known about risk factors of first CRN in IBD patients after a surveillance colonoscopy negative for neoplasia.
Aims & Methods: The aim of our study was to identify predictive factors of first CRN in IBD patients after a surveillance colonoscopy negative for neoplasia. All consecutive patients who underwent at least two colonoscopies at Saint-Antoine Hospital between 01/01/1996 and 01/03/2015 and whose first procedure was a surveillance colonoscopy were included. A nested case-control study was performed to assess risk factors of CRN in inflamed mucosa. Information on treatments, endoscopic and histologic inflammation was collected. The identified CRN risk factors were used to build a predictive score that was then tested in the whole study population.
Results: Among 404 patients who underwent 1236 colonoscopies, 38 patients who developed CRN in inflamed mucosa and 92 matched controls were included in a nested case-control study. Independent factors significantly associated with CRN were primary sclerosing cholangitis (PSC) (Odds ratio (OR), 6.26; CI 95% 1.07–36.8, $p = 0.04$), presence of neutrophils, crypt abscess or histological ulcerations (OR, 8.77; CI 95% 1.71–45, $p = 0.009$) and presence of crypt architectural irregularities without neutrophils or ulcerations (OR, 8.09; CI 95% 1.21–54.3, $p = 0.03$) on more than half of procedures during follow-up, exposure to thiopurines (OR, 0.18; CI 95% 0.047–0.698, $p = 0.01$) and 5-aminosalicylates (OR, 0.27; CI 95% 0.084–0.876, $p = 0.03$) at the time of neoplasia or last colonoscopy. We developed a score based on these five items at the time of the surveillance colonoscopy negative for neoplasia. Among patients with a score of 0, the negative predictive value in predicting any CRN was 100% in patients with colonoscopies performed 1 and 3 years after the first surveillance colonoscopy.
Conclusion: In IBD patients undergoing endoscopic surveillance, the risk of first CRN is increased in case of PSC, persistence of histological acute inflammation and quiescent disease, and decreased by concurrent treatment with thiopurines and 5-aminosalicylates. The use of a predictive score derived from these factors could be considered for making decisions on optimal intervals between two surveillance colonoscopies.
Disclosure of Interest: A. Bourrier: Anne Bourrier has received lecture fees from UCB
H. Sokol: Harry Sokol received consulting fees from Enterome, Astellas, Roche, Merck, Maat and Danone.
P. Seksik: Philippe Seksik had consulting fees from Abbvie, Merck-MSD and Biocodex and grants from Biocodex.
J. Cosnes: Jacques Cosnes has received lecture fees from Abbvie, consulting fees from Vifor Pharma
L. Beaugerie: Laurent Beaugerie has received consulting fees from Abbott, lecture fees from Abbott, Abbvie, MSD, Ferring Pharmaceuticals, Janssen, and research support from Abbott, Biocodex and Ferring Pharmaceuticals.
All other authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 10:30–12:00
COLORECTAL CANCER SCREENING: STATE-OF-THE-ART – ROOM K

OP198 PREDICTORS AND TRENDS IN FECAL HEMOGLOBIN CONCENTRATION: LONG-TERM FOLLOW-UP OF FIT-NEGATIVE SCREENEES IN POPULATION-BASED COLORECTAL CANCER SCREENING

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Introduction: Quantitative fecal immunochemical tests (FITs) are invariably used in a qualitative manner using pre-specified cut-offs in colorectal cancer (CRC) screening. To optimize FIT-based screening programs, it makes sense to explore if participants with a negative FIT result at first participation and subsequent participations can be categorized according to fecal Hb ($_f$Hb) concentration to predict risk of developing future colorectal advanced neoplasia (AN).
Aims & Methods: In this population based screening cohort, average-risk subjects aged 50–74 years, were invited for four rounds of FIT screening (cut-off of 10 μg Hb/g, corresponding to 50 ng Hb/ml buffer). For this study all subjects with a negative FIT at first participation were included. Baseline $_f$Hb was divided into 3

categories (0 μg Hb/g, >0–5 μg Hb/g and, >5–10 μg Hb/g) to calculate cumulative incidence of AN. To identify factors associated with AN a Cox proportional hazard regression analysis was performed to calculate hazard ratios (HRs). Consecutive FIT results were analyzed using logistic regression analyses to calculate relative risks of AN. Risks were visualized by generating heat plots for men and women.

Results: A total of 13,566 subjects were invited for screening of whom 9,561 (70%) participated at least once. Of those, 7,663 (92%) had a negative FIT at first screen. Median follow-up was 4.7 years (IQR 2.0–6.1 years). Screenees with a baseline $_f$Hb of more than 5 μg Hb/g had a 23% higher cumulative incidence of AN than those with a baseline $_f$Hb of 0 μg Hb/g ($p < 0.001$). In multivariate Cox regression analysis HRs increased from 1.7 (95% CI 1.2–2.2) to 6.0 (95% CI 4.0–9.0) for a $_f$Hb concentration of more than 0 to 5 μg Hb/g and more than 5 up to 10, respectively ($p < 0.0001$; Table 1). In logistic regression analysis of two consecutive negative FIT results, RRs increased with $_f$Hb concentration, with up to a 14-fold risk increase for two consecutive FITs with both a $_f$Hb concentration of 8 μg Hb/g feces compared to twice a $_f$Hb concentration of 0 μgHb/g ($p < 0.001$).

Table 1: Time-dependent cox-regression analysis of baseline FIT of advanced neoplasia.

	Advanced neoplasia					
	Univariate			Multivariate		
	HR	95% CI	p-value		95%CI	p-value
Gender (male)	1.7	1.3–2.3	<0.001	1.6	1.2–2.1	<0.001
Age (years)	1.1	1.0–1.1	<0.001	1.1	1.0–1.1	<0.001
Baseline $_f$Hb conc.						
0 μg Hb/g	Ref.		<0.001	Ref.		
>0–5 μg Hb/g	1.8	1.3–2.4		1.7	1.2–2.2	<0.001
>5–10 μg Hb/g	7.0	4.6–10.5		6.0	4.0–9.0	
Socioeconomic status						
High	Ref.		0.08			
Average	1.0	0.7–1.3				
Low	0.6	0.4–1.0				

Conclusion: Among FIT negative screenees, baseline $_f$Hb concentration is an independent predictor for the risk of future AN. Moreover, $_f$Hb concentrations of two consecutive negative FITs are a strong predictor of the risk of AN with up to a 14-fold risk increase. These findings suggest a role for $_f$Hb in personalized screening strategies in population-based screening policies. In addition, the use of $_f$Hb of negative FITs may permit alteration of screening intervals. Such strategies could decrease unnecessary burden for screenee and optimize the use of program related resources.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP199 MASS SCREENING FOR COLORECTAL CANCER BY USING A FECAL IMMUNOCHEMICAL TEST IN COMBINATION WITH FEXIBLE SIMOIDOSCOPY

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Introduction: To date, there have only been a few large-scale community-based studies that examined the efficacy of using a fecal immunochemical test (FIT) in combination with flexible sigmoidoscopy (FS) for colorectal cancer (CRC) screening. Since 1983, we have been conducting community-based mass screening for CRC using fecal occult blood testing in combination with FS in Kyushu, Japan. In 1988, we designed special buses with the necessary equipment to perform FS mass screening in order to test as many people as possible. The two-day FIT method combined with small caliber electronic endoscopes for FS have been in use since 1992.The aim of this study was to investigate the efficacy of combining FIT with FS to detect CRC and then analyze the CRC detection rates.

Aims & Methods: A large sample of 1,597,734 subjects that underwent the FIT procedure to detect CRC and who exhibited a cut-off value of 100 ng/ml were enrolled in this study from 1992 to 2014. Colorectal cancers that were detected using FIT in conjunction with follow-up examinations were classified as two-day FIT-detected cancers. When lesions (i.e. polyps) were found using FS despite a negative two-day FIT outcome or when CRC was detected using colonoscopy the cancers were classified as FIT-negative and FS-detected, respectively. Out of the cases with a negative two-day FIT outcome, 180,779 of them underwent FS.

Results: The positive rate for the negative two-day FIT and FS cases was 8.6% and 90.9% of them underwent work-up examinations. The work-up examinations resulted in a CRC detection rate of 0.15% (mucosal cancer, 0.12%; invasive cancer, 0.03%). In first-time negative two-day FIT and FS cases (33,469), the cancer detection rates were as high as 0.27% (mucosal cancer, 0.22%; invasive cancer, 0.05%). On the other hand, 7.1% of all the subjects were detected as positive using only the two-day FIT procedure and 78.0% of them underwent work-up examinations. This resulted in a detection rate of 0.16% (mucosal cancer, 0.07%; invasive cancer, 0.09%). Among first-time subjects (417,352), the cancer detection rate using only the two-day FIT procedure was 0.32% (mucosal cancer, 0.14%; invasive cancer, 0.17%). The CRC detection rate was significantly higher in males than in females and the rates increased with age in both genders. Moreover, the detection rates were significantly higher in males that were 50 years of age or older. Adverse events included 15 cases of ischemic colitis that occurred after FS (incidence rate, 0.0082%). There were no cases of perforation after endoscopy.

Conclusion: Although there are some problems in introducing FS into mass screening for CRC, (i.e. cost-effectiveness, speed of examinations and lack of manpower), FS is easier to prepare and it is a shorter and safer procedure than colonoscopy. The findings suggest that using FIT in combination with FS is effective for detecting CRC in first-time subjects that are 50 years of age and older. However, this same procedure provides limited benefit for those who are below 50 years of age.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP200 GASTROINTESTINAL EVENTS AFTER A NORMAL COLONOSCOPY IN FIT-POSITIVE PARTICIPANTS IN AN ORGANIZED, POPULATION-BASED COLORECTAL CANCER SCREENING PROGRAM

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Introduction: Positive fecal immunochemical test (FIT) is associated to colorectal neoplasia and/or bleeding from non-neoplastic lesions. However, a considerable proportion of individuals with a positive FIT have a normal colonoscopy.

Aims & Methods: We aimed 1) to identify possible causes of positive-FIT result in subjects with normal colonoscopy 2) to ascertain the rate of post-colonoscopy colorectal cancer (CRC) in this cohort. Methods: All individuals from the first round of the Barcelona's CRC Screening Program (January 2010–December 2012) with a positive FIT(≥20 μg/g) and complete negative colonoscopy (i.e. no neoplastic lesion) were included. Subsequent gastrointestinal events that implied a medical consultation and/or procedure were recorded at the National Health Service electronic database. Attribution of causality for positive FIT was ascertained according to time of presentation of the event: certain (at baseline colonoscopy), probable (≤6 months after colonoscopy), possible (6–12 months after colonoscopy), uncertain (>12 months after colonoscopy). Post-colonoscopy CRC were defined as any invasive CRC detected after colonoscopy until the end of follow-up (median, 50.6 months [range, 36–69]).

Results: From 2659 individuals who underwent colonoscopy after a positive FIT, 811 (30.5%; age 59.1 ± 0.4 years; 60.7% women) had a negative colonoscopy. In 102 (12.6%) individuals a cause of positive FIT was identified at the colonoscopy (angiodisplasia, 50; inflammatory lesions, 52). Of those 709 individuals with a normal colonoscopy, 32 (4.5%) had subsequent gastrointestinal events classified as probable cause in 2 (gastric adenocarcinoma and Los Angeles' grade D esophagitis), possible cause in 4 (invasive CRC, small bowel lymphoma, diverticular hemorrhage, and gastric antral vascular ectasia), and uncertain cause in 26 (2 invasive CRC, 4 advanced adenomas, 2 non-advanced adenomas, 15 inflammatory lesions, and 3 anorectal disorders). Age, sex, FIT levels, comorbidities (hepatic, renal, coagulopathy) or chronic antiplatelet/anticoagulant/NSAID treatments were not associated with a higher prevalence of gastrointestinal events. On the other hand, 3 (0.36%) post-colonoscopy CRC were detected (age, 56.3 ± 7.5 years; 66% men; TNM stage: 2 were IIIA and 1 was IIIB) within 11–28 months after screening. There were no significant differences regarding age, sex and FIT level among subjects with or without post-colonoscopy CRC.

Conclusion: Most individuals (83%) with a positive FIT and negative colonoscopy do not have any lesion that may explain this result. Of these, 96% do not present subsequent gastrointestinal events. Importantly, the rate of post-colonoscopy CRC in these subjects is very low (0.36%).

Disclosure of Interest: All authors have declared no conflicts of interest.

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Table (OP202)

	Screen-detected cancer	FIT interval cancer	Colonoscopy interval cancer	CRC in non-participants	p-value
Total CRCs	116	27	13	109	
Age diagnosis (%(n))−50–59−60–69–>70	24.1 (28) 43.1 (50) 32.8 (38)	22.2 (6) 40.7 (11) 37 (10)	7.7 (1) 61.5 (8) 30.8 (4)	19.3 (21) 45 (49) 35.8 (39)	p = 0.803
Sex (male;%(n))	62.9 (73)	59.3 (16)	53.8 (7)	63.3 (69)	p = 0.904
SES (%(n))–Low–Average–High	11.2 (13) 70.7 (82) 18.1 (21)	7.4 (2) 77.8 (21) 14.8 (4)	15.4 (2) 76.9 (10) 7.7 (1)	—	p = 0.814
Tumor location (%(n))–Proximal–Distal–Unknown	29.3 (34) 70.7 (82) 0 (0)	37 (10) 63 (17) 0 (0)	69.2 (9) 23.1 (3) 7.7 (1)	34.9 (38) 61.5 (67) 3.6 (4)	p = 0.010
Stage–I–II–III–IV–Missing	51.7 (60) 13.8 (16) 31.9 (37) 2.6 (3) 0 (0)	29.6 (8) 22.2 (6) 33.4 (9) 14.8 (4) 0 (0)	38.5(5) 7.7(1) 7.7(1) 38.5(5) 7.7(1)	15.6 (17) 28.5 (31) 33.0 (36) 21.1 (23) 1.8 (2)	p < 0.001
Survival (% (n))	88 (102)	81.5 (22)	61.5 (8)	59.6 (65)	p < 0.001

OP201 CHANGES IN HEALTH BEHAVIOUR ONE-YEAR AFTER TESTING NEGATIVE AT COLORECTAL CANCER SCREENING – A RANDOMIZED CONTROLLED STUDY

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Introduction: Nine out of ten participants in colorectal cancer (CRC) screening have a negative screening test result. It has been hypothesized that getting a negative screening test result may reduce incentives to strive for a healthy lifestyle.

Aims & Methods: The aim of the present study was to investigate potential differences in changes of health behavior at one-year follow-up between screen-negative attendees to two different screening modalities and controls not invited to screening. Participants of both gender, aged 50–74, were invited to complete a self-reported lifestyle questionnaire (LSQ) on smoking, body weight, physical activity, alcohol intake and selected dietary items at baseline and at one-year follow-up. Participants were randomly assigned to five biennial rounds of fecal immunochemical test (FIT), one round flexible sigmoidoscopy (FS) or no screening (controls). In total, 1809 and 1327 individuals with a negative screening test result in the FIT and FS group, respectively, completed the LSQ, as did 1029 controls. ANCOVA and logistic regression were used to calculate differences in changes of health behavior (and 95% confidence intervals (CI)) between the arms at follow-up.

Result: Participants with a negative CRC screening test result in the first round of the FIT arm reduced their alcohol consumption significantly more than controls (−0.29 glass/week, (95%CI; −0.54 to −0.04)) during one-year follow-up. Body weight decreased more in participant with a negative screening test result in the FS arm than in the FIT arm during the one-year follow-up (−0.31 kg, (95%CI; −0.55 to −0.08)).

Conclusion: The present study does not suggest unfavorable short-term consequences in health behavior after getting a negative CRC screening test result whether this is from once only FS or first round of FIT screening.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP202 SCREEN-DETECTED AND NON-SCREEN-DETECTED COLORECTAL CANCERS AFTER FOUR ROUNDS OF FECAL IMMUNOCHEMICAL TEST-BASED COLORECTAL CANCER SCREENING

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Introduction: Fecal immunochemical test (FIT)-based colorectal cancer (CRC) screening aims to detect CRC in an early stage, thereby reducing morbidity and mortality from this disease. Whereas data on interval CRCs in screening programs based on guaiac fecal occult blood testing are available in literature, few data exist on cancers in FIT-screening programs.

Aims & Methods: The aim of our study was to compare patient demographics, tumor site, stage and survival between patients with screen-detected CRCs (SD-CRC) and non-screen-detected CRCs (non-SD-CRC). Between 2006 and 2014, asymptomatic persons aged 50 to 74 were invited to take part in four consecutive biennial FIT-screening rounds. CRC cases were identified through linkage with the Netherlands Cancer Registry and were classified into four groups: SD-CRC, FIT interval cancers (diagnosed between screening rounds after negative FIT), colonoscopy interval cancers (diagnosed after negative colonoscopy after a positive FIT) and CRC in non-participants (the latter three representing non-SD-CRC). Information on gender, age, socioeconomic status (SES), tumor site, stage and survival were collected and compared between patients in the four CRC groups using Chi-square-test.

Result: A total of 27,340 people were invited for FIT-screening, of whom 18,752 (68,6%) participated at least once. Median follow-up time was 46,4 months (IQR 18.5–72.4). Among participants, 3,009 (16%) had a positive FIT in one of the 4 screening rounds. In total, 265 patients were diagnosed with CRC: 116 were SD-CRCs, 27 FIT interval CRCs, 13 colonoscopy interval CRCs and 109 CRCs detected in non-participants. There were no differences between the groups regarding age, gender and SES distribution. Screen-detected CRCs, FIT interval cancers and CRCs in non-participants were mostly located in the distal colon (70.7%, 63%, 61.5% of cases, respectively), whereas colonoscopy interval CRCs were mainly located in the proximal colon (69.2%)(p = 0.010). Stage distribution was significantly different between the four groups, with more favorable stages in patients with SD-CRCs (p < 0.001). Stage distribution in patients with FIT interval CRC and CRCs in non-participants was similar (p = 0.361). Survival-rates were significantly higher among patients with SD-CRCs and FIT interval cancers compared to non-participants and patients with colonoscopy interval CRCs.

Conclusion: In this population-based CRC screening cohort, 0.14% of all participants were diagnosed with a FIT interval CRC during follow-up. The patients with SD-CRCs had the most favorable stages and highest survival rates. Our results support the effectiveness of FIT-screening programs.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP203 THE ADDED BENEFIT OF SURVEILLANCE IN COLORECTAL CANCER SCREENING

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Introduction: Although the impact of colorectal cancer (CRC) screening on CRC burden is well studied, the added benefit of surveillance in the context of an implemented screening programme is unclear.

Aims & Methods: Using the Adenoma and Serrated pathway to Colorectal CAncer model, we simulated the Dutch faecal immunochemical test (FIT) - based screening programme and combined this with a colonoscopy surveillance strategy based on the Dutch guideline. In this strategy, individuals considered at low risk return to screening after ten years whereas surveillance with a three or five-year interval is recommended for high- and intermediate-risk individuals, respectively. Furthermore, we evaluated three strategies in which the surveillance intervals as recommended in the Dutch guideline were prolonged to a) five years for all individuals at increased risk, b) five and ten years for respectively high- and intermediate-risk individuals and c) ten years for all individuals at increased risk. The comparator strategy was no screening and no surveillance. In addition, we simulated a screening only strategy without surveillance. Outcomes were CRC incidence and mortality, number of colonoscopies per detected CRC, life-years lived and costs per individual in the lifetime of 20,000,000 individuals.

Result: FIT screening without a surveillance programme reduced CRC incidence and mortality with respectively 25.4% and 39.0% compared to a no screening and no surveillance strategy. CRC incidence and mortality reductions increased to 28.1% and 40.8% when surveillance based on the Dutch guideline was added to FIT screening. Prolonging surveillance intervals slightly reduced surveillance effectiveness (incidence reductions 26.6%–27.2%, mortality reductions 39.6%–40.8% compared to no screening and no surveillance). In screening, 21 diagnostic colonoscopies were required to detect one CRC. The burden of surveillance was considerably higher; in the Dutch guideline strategy, 572 colonoscopies were required to detect one CRC by surveillance. Prolonging surveillance intervals decreased this burden to 129–366 colonoscopies per surveillance-detected CRC. All screening plus surveillance strategies were equally or more effective (0–0.0011 life-years gained) and less costly (€−2.45-€−8.24) than screening only. The strategy in which all surveillance intervals were set at five years dominated all other screening plus surveillance strategies.
Conclusion: Adding surveillance to FIT screening reduces CRC burden and is cost-effective compared to screening without surveillance. However, the colonoscopy burden in surveillance is markedly higher than this burden in a screening programme. Through modelling, we showed that this burden can be substantially lowered, without substantial loss of effectiveness, if surveillance intervals are lengthened to five years.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 10:30–12:00
VIRAL HEPATITIS: NATURAL HISTORY AND TREATMENT – ROOM M

OP204 SUSTAINED VIROLOGIC RESPONSE TO INTERFERON-FREE THERAPIES AMELIORATES HCV-INDUCED PORTAL HYPERTENSION

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Introduction: Portal pressure, assessed by hepatic venous pressure gradient (HVPG) measurement, drives the development of liver-related complications and mortality in patients advanced chronic liver disease. Since a decrease in HVPG translates into a clinically meaningful benefit, it is an acceptable surrogate endpoint.
Aims & Methods: We aimed to investigate the impact of sustained virologic response (SVR) to interferon (IFN)-free therapies on portal hypertension in patients with paired HVPG measurements. One hundred and four patients with portal hypertension (HVPG $\geq$ 6 mmHg) who underwent HVPG and transient elastography (TE) before IFN-free therapy (baseline [BL]) were retrospectively studied. The effect of SVR on portal pressure was investigated in patients with SVR who also underwent follow-up (FU)-HVPG and TE after IFN-free therapy (group A; n = 60). To demonstrate the generalizability of our results, we included a second group (group B; n = 40), comprising all patients who achieved SVR, but did not undergo FU-HVPG measurement. In these patients, only information on FU-TE was available. Moreover, we also included 4 patients who did not achieve SVR.
Result: SVR to IFN-free therapies significantly decreased HVPG across all BL-HVPG strata: 6–9 mmHg (BL:7.37 ± 0.28 vs. FU: 5.11 ± 0.38 mmHg; −2.26 ± 0.42 mmHg; $P < 0.001$), 10–15 mmHg (BL:12.2 ± 0.4 vs. FU:8.91 ± 0.62 mmHg; −3.29 ± 0.59 mmHg; $P < 0.001$) and $\geq$ 16 mmHg (BL:19.4 ± 0.73 vs. FU:17.1 ± 1.21 mmHg; −2.3 ± 0.89 mmHg; $P = 0.018$). In the subgroup of patients with BL-HVPG of 6–9 mmHg, portal hypertension resolved in 63%(12/19), while no patient had an increase in HVPG at FU. Among patients with a BL-HVPG of 10–15 mmHg, portal hypertension resolved in 14%(3/21), 29%(6/21) had a FU-HVPG of 6–9 mmHg, while no patient showed a progression of portal hypertension at FU. Finally, in the subgroup of patients with a BL-HVPG $\geq$ 16 mmHg, 5%(1/20) and 35%(7/20) of patients had a regression to a FU-HVPG of 6–9 mmHg or a FU-HVPG of 10–15 mmHg, respectively. However, portal hypertension did not resolve in any patient and 20%(4/20) of patients showed an increase in HVPG at FU. Patients with Child-Pugh stage B were less likely to have a HVPG-decrease (HR:0.103; 95%CI:0.02–0.514; P = 0.006), when compared to Child-Pugh A patients. In the subgroup of patients with a BL-HVPG $\geq$ 10 mmHg, the relative change in liver stiffness (per %; HR:0.972; 95%CI:0.945–0.999; P = 0.044) was a predictor of a HVPG-decrease $\geq$10%. The area under the receiver operating characteristic curve for the diagnosis of FU-HVPG $\geq$10 mmHg by FU liver stiffness was 0.931(95%CI:0.865–0.997). The liver stiffness values at FU for ruling-in and ruling-out FU-HVPG $\geq$ 10 mmHg were 12.4 (negative predictive value:100%) and 25.3 kPa (positive predictive value:94%), respectively. Changes in liver stiffness, platelet count, and liver function tests were comparable between patients with (group A) and without FU-HVPG measurement (group B), providing an argument for the generalizability of our results. Among the 4 patients without SVR, one patient underwent FU-HVPG and TE (HVPG increased from 18 to 20 mmHg; liver stiffness increased from 45 to 75 kPa), while 3 patients only underwent FU-TE (16.5 to 14.8 kPa, 72 to 72 kPa and 10.2 to 10.5 kPa).
Conclusion: SVR to IFN-free therapies ameliorates portal hypertension across all BL-HVPG strata. However, amelioration of portal hypertension was less likely in patients with more advanced liver dysfunction. TE might be useful for the non-invasive evaluation of portal hypertension after SVR. In contrast, patients who did not achieve SVR showed either no significant improvement or even worsening of liver disease.
Disclosure of Interest: M. Mandorfer: M.M. received honoraria for consulting from Janssen, payments for lectures from Boehringer Ingelheim, Bristol-Myers Squibb, Janssen and Roche, as well as travel support from AbbVie, Gilead, MSD and Roche.
K. Kozbial: K.K. received travel support from AbbVie, Bristol-Myers Squibb and Gilead.
P. Schwabl: P.S. received payments for lectures from Roche and travel support from Janssen and Roche.
C. Freissmuth: C.F. received travel support from Gilead and Janssen.
R. Stern: R.ST. received travel support from AbbVie.
A.F. Stättermayer: A.F.S. received honoraria for consulting from Gilead, payments for lectures from Boehringer Ingelheim, Janssen and Roche, as well as travel support from Gilead, Bristol-Myers Squibb, Janssen and Roche.
T. Reiberger: T.R. received payments for lectures from Roche, as well as travel support from Gilead, MSD and Roche.
S. Beinhardt: S.B. received honoraria for consulting from AbbVie, payments for lectures from Bristol-Myers Squibb, as well as travel support from Gilead, MSD and Roche.
M. Trauner: M.T. received grants from MSD, honoraria for consulting from AbbVie, Gilead, Janssen and MSD, payments for lectures from Gilead, MSD and Roche, as well as travel support from Gilead.
H. Hofer: H.H. received payments for lectures from AbbVie, Gilead, Janssen, MSD and Roche.
A. Ferlitsch: A.F. received grants from Janssen and payments for lectures from Gilead, MSD and Roche.
P. Ferenci: P.F. received grants from Gilead, MSD, and Roche, as well as honoraria for board membership and consulting from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Idenix, MSD and Roche.
M. Peck-Radosavljevic: M.P. received grants from Gilead, MSD and Roche, honoraria for board membership and consulting from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen and MSD, as well as payments for lectures from AbbVie, Boehringer Ingelheim.
All other authors have declared no conflicts of interest.

OP206 RISK OF AND PREDICTORS FOR CLINICAL EVENTS FOLLOWING VIROLOGICAL RELAPSE IN CHRONIC HEPATITIS B PATIENTS AFTER CESSATION OF NUCLEOS(T)IDE ANALOGUE THERAPY

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Introduction: Clinical hepatitis may follow virological relapse in chronic hepatitis B (CHB) patients after discontinuing nucleos(t)ide analogue (NAs), but the incidence and risk predictors remained elusive.
Aims & Methods: Between July 1, 2011 and July 1, 2015, this multicenter study prospectively enrolled 140 consecutive CHB patients with negative HBeAg and undetectable viral DNA at the cessation of NAs after a minimum of 3 years on therapy. In those who experienced virological relapse (viral DNA >2,000 IU/mL), the incidences of clinical relapse (virological relapse plus ALT >80 IU/mL) and persistent/severe hepatitis (clinical relapse lasting for 3 months or accompanied with jaundice) were estimated by the Kaplan Meier method. Predictors were explored by the Cox proportional hazard modelling.
Result: Following virological relapse that took place in 94 patients, clinical relapse and persistent/severe hepatitis occurred in 49 and 34 patients, respectively. The 2-year cumulative incidences were 61.5% (95% CI, 50.1 ~ 73.0%) and 56.2% (95% CI, 42.2 ~ 71.2%), respectively. Multivariate-adjusted analyses revealed clinical relapse was associated with serum concentration of viral DNA (hazard ratio [HR], 1.26 per log/mL; 95% CI, 1.04 ~ 1.53) and alanine aminotransferase (ALT) at virological relapse (HR, 1.003 per IU/L; 95% CI, 1.0 ~ 1.004), as well as ALT at NA cessation (HR, 1.008; 95% CI, 1.002 ~ 1.01), whereas persistent/severe hepatitis was associated with viral DNA (HR, 1.41; 95% CI, 1.16 ~ 1.71), ALT (HR, 1.004; 95% CI, 1.001 ~ 1.01), and α-fetoprotein (HR, 1.13 per ng/ml; 95% CI, 1.02 ~ 1.26) at virological relapse.
Conclusion: Clinical hepatitis frequently occurs following virological relapse in CHB patients after NA cessation, and may be predicted by serum viral load, ALT, and α-fetoprotein at the viral resurgence.
Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

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OP207 COMBINATION THERAPY WITH DACLATASVIR AND ASUNAPREVIR IN CIRRHOTIC AND NON-CIRRHOTIC PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1B IN JAPAN

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Introduction: Combination therapy with daclatasvir (DCV; NS5A inhibitor) and asunaprevir (ASV; second-generation HCV-NS3/NS4A protease inhibitor) was approved for patients with HCV genotype 1 in Japan since September 2014. Now, elderly patients and those with advanced hepatic fibrosis including chronic liver cancer were administered IFN-free therapy. Our objective was to assess the efficacy and tolerability of DCV/ASV combination therapy in patients with hepatic cirrhosis.

Aims & Methods: In total, 153 consecutive patients with HCV 1 b initiating DCV/ASV therapy were enrolled. The cohort comprised 52 patients with compensated cirrhosis and 101 patients without cirrhosis (67 males and 86 females; median age, 71 years; 9 patients were >80 years old). NS5A resistance-associated variants (RAV) were examined using direct sequencing. The patients were treated with 60 mg of DCV once daily and 100 mg of ASV twice per day for 24 weeks. Clinical, biological, and virological data, including adverse effects, were recorded at baseline and during follow-up.

Result: Only 10 (6.5%) patients had L31M or Y93H RAVs. There was no statistically significant difference in age, sex, IL28B genotypes, HCV viral load at baseline, ALT level, creatinine level, or NS5A RAVs between patients with and without cirrhosis. On the other hand, those with cirrhosis showed significantly lower levels of platelets, white blood cells, and hemoglobin and higher levels of alpha fetoprotein. The rapid viral response rate (HCV-RNA < 25 IU/ml at week 4) was the same between patients with and without cirrhosis (80% and 84%, respectively). One of 52 patients with cirrhosis, and two of 101 patients without cirrhosis who did not have NS5A RAVs at baseline developed viral breakthrough. The rate of SVR12 was 94% (49/52) in patients with cirrhosis and 97% (96/99) in patients without cirrhosis. Grade 3/4 complications frequently occurred in 21% of patients with cirrhosis ($p = 0.04$), of whom two had an elevated ALT level, two progressed to decompensated cirrhosis without ALT elevation, one developed interstitial pneumonia, one had severe bronchitis, one had arterial fibrillation, two had gastrointestinal bleeding, and two developed edema. Of the patients without cirrhosis (9%), ALT elevation was observed in five patients, coagulation abnormality developed in two patients, gastrointestinal bleeding occurred in one, and high fever occurred in one patient. After DCV/ASV therapy, HCC developed in two cirrhotic patients, and one non-cirrhotic patient.

Conclusion: DCV/ASV therapy achieved a high anti-HCV effect in patients both with and without cirrhosis. However, careful management is necessary in patients with cirrhosis.

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N. Kawada: Dr. Norifumi Kawada has received research funding from MSD K.K., Chugai Pharmaceutical Co., Ltd. Bristol-Myers Squibb, and a lecturer's fee from Janssen Pharmaceutical K.K.
All other authors have declared no conflicts of interest.

OP208 EXPERIENCE IN THE MANAGEMENT OF DECOMPENSATED HCV CIRRHOTIC PATIENTS WITH LOW DOSE SOFOSBUVIR AND RIBAVIRIN COMBINED WITH DACLATASVIR

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Introduction: With the introduction of oral direct-acting antiviral (DAA) therapy in the management of chronic active HCV, sustained response rates occurred in more than 95% of patients with compensated liver disease with improvement in their survival and the risk of decompensation that necessitates liver transplantation. The postulated explanation of reduced rates of sustained virological response in decompensated cirrhosis was explained by extensive portosystemic collaterals, advanced fibrotic parenchyma which are difficult to be penetrated, and provide dormant foci for viral reactivation. It was claimed that achieving SVR will improve MELD and CPT scores with improvement in clinically significant portal hypertension and hepatic venous pressure gradient.

Aims & Methods: Evaluation of the efficacy and safety of managing chronic active HCV in patients with decompensated cirrhosis and if SVR will improve CTP, MELD scores and quality of life of these patients Forty patients with decompensated cirrhosis with frequent hepatic encephalopathy or difficult to treat ascites were included if they had chronic active HCV proved by the positivity of HCV RNA, elevated transaminases. Patients were excluded if they had hepatocellular carcinoma, other causes of liver diseases or mixed causes (excessive alcohol consumption, autoimmune liver disease), previous liver transplantation. The patients were given sofosbuvir 200 mg, ribavirin 200 mg, and daclatasvir 60 mg for 6 months and evaluated for the development of sustained virological response (SVR), the occurrence of complications and the effects of SVR on the rate of development of hepatic encephalopathy, improvement in ascites control.

Result: Forty patients (31 males, 9 females) presented with chronic active HCV were enrolled, all showed difficult to treat cirrhotic ascites. 29 patients showed chronic recurrent episodes of hepatic encephalopathy (62.5%, 2.1 ± 0.6 episodes/2 months). The mean age was 51.4 ± 6.3 years, albumin 2.3 ± 0.4 gm/dl, total bilirubin 1.9 ± 0.5 mg/dl, Hemoglobin 9.9 ± 0.9 gm/dl, platelet count $83.9 \pm 15.4 \times 103$ cell/ul, creatinine 1.3 ± 0.2 mg/dl, AST 77.4 ± 22.4 IU/dl, ALT 66.5 ± 15.2 IU/dl, AFP 29.8 ± 10.8 ug/dl, MELD score 22.6 ± 2, Child Turcotte Pugh (CTP) score 9 ± 0.9. After six months of therapy; all the patients were compliant, with no reported major complications. Mean platelet count was significantly increased after treatment ($88.6 \pm 13.9 \times 103$ cell/ul, $p = 0.000$), with significant improvement in serum albumin (2.7 ± 0.02 gm/dl, $p = 0.000$), total bilirubin (1.4 ± 0.2 mg/dl, $p = 0.000$), AFP (16.3 ± 0.9 ug/dl, $p = 0.000$), CTP score (8.4 ± 0.5, $p = 0.002$) and MELD score (21.2 ± 1.04, $p = 0.000$). After treatment a significant reduction in the episodes of HE was noted; only 8/29 still experiencing HE ($\chi 2 > 14.312$, $p = 0.0002$, 1.4 ± 0.2 episodes/2 months). SVR was achieved in 36 patients (90%). Ascites became completely controlled in 10 patients (25%) and partially controlled in 23 patients (57.5%) and not changed in 7 patients (17.5%)

Conclusion: Treatment of decompensated cirrhotic patients with a 6-month low dose DAA had led to SVR in 90% with improvement in CTP, MELD scores and a significant reduction in hepatic encephalopathy episodes with better control of ascites.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP209 INTERFERON-FREE DAA TREATMENS DECREASE PORTAL PRESSURE AND HALT HISTOLOGICAL NECROINFLAMMATION IN HIV/HCV - COINFECTED PATIENTS WITH PORTAL HYPERTENSION

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Introduction: Patients with HIV/HCV confection show increased fibrosis progression and are at risk for complications of portal hypertension (PHT). We measured changes in liver stiffness and portal pressure and evaluated liver histology after successful interferon (IFN)-free DAA therapy.

Aims & Methods: HIV/HCV patients undergoing IFN-free DAA treatment and had paired hepatic venous pressure gradient (HVPG) and liver stiffness (LS) measurements at baseline and three months after end of treatment (SVR12) were included. LS and HVPG were measured in a fasted, non-sedated state. Concomitant beta-blocker treatment was stopped for all measurements. Post-treatment liver biopsies were assessed by METAVIR score.

Result: Of 19 patients (56% male, age: 53.4 ± 6.7 years, 95% concomitant antiretroviral therapy), 16 received SOF/DCV, 2 SOF/ RBV, and 1 SOF/LDV. Seven (37%) patients were treatment experienced and HCV genotype (GT) distribution was: GT-1a: 12, GT-1b: 2 and GT-3a: 5. All patients had portal hypertension (HVPG > 5 mmHg) and 14 patients (74%) presented with liver cirrhosis (LS > 12 kPa). DAA treatment resulted in 100% SVR12. LS decreased significantly from 23.0 ± 16.5 to 16.9 ± 16.1 kPa (mean change (Δ): -6.1 ± 5.2 kPa; $p < 0.001$). Also, HVPG decreased from 10.4 ± 4.0 to 7.6 ± 4.3 mmHg (Δ: -2.8 ± 2.4 mmHg; $p < 0.001$). In patients with clinically significant portal hypertension (HVPG ≥ 10 mmHg, $n = 9$), HVPG decreased from 13.8 ± 3.0 to 10.9 ± 3.8 mmHg (Δ: -2.9 ± 2.8 mmHg; $p = 0.015$) – resulting in a hemodynamic response of ≥10% in 6/9 (66%) patients. In the subgroup of patients with baseline HVPG < 10 mmHg ($n = 10$), a reduction from 7.3 ± 1.3 to 4.6 ± 1.8 mmHg (Δ: -2.7 ± 2.2 mmHg; $p = 0.003$) was noted – resulting in cure of PHT (< 5 mmHg) in 6/10 (60%). Posttreatment liver biopsies were available in 15 patients, of which the majority (66%) did not show any hepatic necroinflammatory activity (METAVIR A0). 8 of 14 (57%) patients with cirrhosis at baseline, presented a post-treatment histological METAVIR ≤F3. Serum transaminases were normalized after therapy (AST: 66 ± 34 vs. 33 ± 20, $p < 0.001$; ALT: 60 ± 37 vs. 24 ± 15, $p < 0.001$), while hemoglobin, WBC and CD4 cell counts remained stable.

Conclusion: Virological response to IFN-free DAA therapies decreases LS and ameliorates portal hypertension. SVR12 seems to abolish histological necroinflammatory activity in most HIV/HCV coinfected patients. It remains to be explored if these improvements result in decreased liver-related mortality in the setting of HIV/HCV coinfection.

Disclosure of Interest: P. Schwabl: received payments for lectures from Roche and Böhringer Ingelheim, and travel support from AbbVie, Gilead, Janssen, and Roche

M. Mandorfer: received honoraria for consulting from Janssen, payments for lectures from Boehringer Ingelheim, Bristol- Myers Squibb, Janssen, and Roche, as well as travel support from AbbVie, Gilead, MSD, and Roche
B. Scheiner: received travel support from Gilead.
T. Bucsics: received payments for lectures from Roche and travel support from Bristol-Myers Squibb
K. Grabmeier-Pfistershammer: received honoraria for consulting from Gilead, payments for lectures from Bristol-Myers Squibb and ViiV, as well as travel support from Bristol-Myers Squibb, Gilead, and GlaxoSmithKline
A. Ferlitsch: reveived travel support from AbbVie and Gilead
M. Trauner: received grants from MSD, honoraria for consulting from AbbVie, Gilead, Janssen, and MSD, payments for lectures from Gilead, MSD, and Roche, as well as travel support from Gilead
M. Peck-Radosavljevic: received grants from Gilead, MSD, and Roche, honoraria from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, and MSD, and payments for lectures from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, MSD, and Roche
T. Reiberger: received payments for lectures from Roche, as well as travel support from Gilead, MSD, and Roche.
All other authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 10:30–12:00

IMPROVING DETECTION AND TREATMENT OF COLONIC POLYPS – ROOM N2

OP210 RANDOMIZED, BACK-TO-BACK TRIAL OF NEW GENERATION OF NBI (HQ 290) FOR THE DETECTION OF COLORECTAL POLYPS

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Introduction: The benefits of narrow band imaging (NBI) for improving the detection of colorectal polyps remain questionable. The newly available second generation of NBI using 290 system (290-NBI) privides an at least two folds brighter image compared with the previous version.

Aims & Methods: The aim of this study was to compare polyp miss rates between 290-NBI and high-resolution white light endoscopy (HR-WLE). Methods: From June 2015 to September 2015, 102 patients were randomized to undergo either HD-WLE or 290-NBI colonoscopy. In HD-WLE group, we performed colonoscopic examination as first inspection with HR-WLE followed by a second inspection with NBI. In 290-NBI group, colonoscopic examination were performed first inspection with NBI followed by a second inspection with HR-WLE. The primary outcomes were polyp miss rates.

Result: A total of 127 polyps of 102 patients were detected. In HD-WLE group, 39 polyps were detected during the first inspection. A second inspection with NBI added 20 polyps, resulting in polyp miss rate of 33.9% with HR-WLE. In the NBI group, 54 polyps were detected during the first inspection. Subsequent inspection with HR-WLE added 14 polyps, resulting in polyp miss rate of NBI of 20.6% (33.9% vs 20.6%, $p = 0.068$). In subgroup analysis, the polyp miss rates of flat type of HR-WLE and NBI showed significant difference (18.6% vs. 5.9%, $p = 0.029$).

Conclusion: New generation of NBI (HQ290) may reduce polyp miss rates and be more effective in reducing polyp miss rates of flat type.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP211 DIAGNOSTIC CHARACTERISTICS OF DEPRESSED TYPE COLORECTAL NEOPLASMS IN MAGNIFYING ENDOSCOPY AND ENDOCYTOSCOPY

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Introduction: Colorectal cancers are generally recognized to develop from"polyps". This "adenoma-carcinoma sequence" theory has been in the mainstream of development of colorectal cancers. But recently the existence of many depressed-type cancers has been revealed, which are considered to emerge directly from normal epithelium, not through the adenomatous stage. This theory is called "de novo" pathway. Now, it is possible to presume the histology of colorectal lesions using magnifying endoscopy (pit pattern classification) and endocytoscopy (EC).We can observe not only the structural atypia but also the cellular atypia in living colorectal lesions. The aim is to clarify the diagnostic characteristics of depressed-type colorectal neoplasms, demonstrating the validity of pit pattern diagnosis and EC classification.

Aims & Methods: A total of 27599 colorectal neoplasms excluding advanced cancers were resected endoscopically or surgically in our unit from April 2001 to December 2015. Of these, 16075 lesions were low-grade dysplasia, 5241 were high-grade dysplasia and 1097 were submucosally invasive (T1) carcinomas. According to the developmental morphology classification, they were divided into 3 types: depressed, flat and protruded type. We investigated the rate of T1 carcinomas and the characteristics of depressed-type neoplasms concerning pit pattern and EC classification.

Result: The rate of T1 carcinomas in depressed-type lesions reached to 62.1%, meanwhile that in flat-type and protruded-type lesions was 3.3% and 2.8%, respectively. Within less than 5 mm in diameter, that was 10.6%, 0% and 0%, respectively. Most (90.1% and 91.5%) of the flat-type and protruded-type lesions showed type III_L or IV pit pattern corresponding to adenomas, whereas 94.6% of the depressed-type lesions were characterized by type III_S, V_I or V_N pit pattern corresponding to carcinomas. As for endocytoscopy, most of the flat-and protruded-type lesions showed EC2 corresponding to adenomas. In contrast, the depressed-type lesions were observed as EC3a (38.9%) and EC3b (58.0%) corresponding to invasive carcinomas.

Conclusion: This study revealed the diagnostic characteristics of depressed-type lesions. They show typically type III_S,V_I or V_N pit patterns in magnifying endoscopy and type EC3a or EC3b in endocytoscopy. These lesions tend to invade the submucosal layer even when they are small. Therefore, it is important to consider deeply and examine the developmental morphology of colorectal neoplasms.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP212 ASSOCIATION OF CHROMOSOMAL INSTABILITY AND MICROSATELLITE INSTABILITY PATHWAYS WITH POSTCOLONOSCOPY COLORECTAL CANCER IN A RETROSPECTIVE COHORT STUDY

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Introduction: Over 50% of the postcolonoscopy colorectal cancers (PCCRCs) (i.e. CRC diagnosed after a colonoscopy that excluded cancer) originate from missed precursor lesions, in particular the subtle appearing non-polypoid (flat and depressed) adenomas and sessile serrated lesions. The biologic pathway of these lesions is unclear. We hypothesized that PCCRCs and subtle appearing precursors may share molecular features. In a retrospective, cohort study, we examined the occurrence of chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) in PCCRCs and prevalent CRCs.

Aims & Methods: We identified all PCCRCs diagnosed from 2001 to 2010 in a large gastroenterology practice from the Netherlands (le Clercq et al, *Gut* 2014). PCCRCs were defined as cancers occurring within 5 years after a complete index colonoscopy, which excluded CRC. We applied a clinical algorithm to assign the most likely explanation of PCCRC (incomplete colonoscopy/ insufficient bowel preparation, missed lesion, incompletely resected lesion or new cancer). PCCRCs attributable to technical factors (insufficient bowel preparation/ incomplete

Table 1. (OP213)

Subject #	Age	Sex	Indication(s)	BMI	ASA Grade	Insertion Time (min)	Procedure Time (min)	Point of Deepest Insertion	Complications	Final Diagnosis
1	24	M	Abdominal pain; video capsule findings of ulcerated mucosa in mid small bowel	40	III	33	41	Distal Jejunum	None	None
2	22	M	CT scan finding of intussusception	21	II	32	43	Cecum	None	None
3	61	F	Gastrointestinal bleeding; video capsule finding of angioectasia	27	III	61	94	Cecum	None	None
4	58	F	Iron deficiency anemia; video capsule finding of angioectasia	23	II	47	70	Distal Ileum	None	None
5	67	F	Iron deficiency anemia	23	II	48	66	Cecum	None	None
6	33	M	Gastrintestinal bleeding	28	III	59	78	Cecum	Bleeding	Meckel's diverticulum
7	29	M	Suspected crohn's; video capsule findings of a bleeding angioectasia and a small bowel polyp	28	II	49	72	Cecum	None	Crohn's

colonoscopy or incomplete resection) were excluded. We reviewed clinical and pathological records. Whole-genome DNA copy number changes and mutation status of genes commonly affected in CRC (APC, KRAS, BRAF, FBXW7, PIK3CA, NRAS, SMAD4 and TP53) were examined by shallow whole-genome sequencing and targeted sequencing, respectively, using Illumina next generation sequencing platforms. MSI and CIMP status were examined using the pentaplex marker panel from Promega and the Weisenberger CIMP panel using methylation-specific PCR, respectively.
Result: In total, 120 PCCRCs and 100 prevalent CRCs were examined. Regarding clinicopathological features, PCCRCs are more often located proximally in the colon ($p < 0.001$), non-polypoid appearing ($p = 0.001$), early stage tumors ($p = 0.008$), and poorly differentiated ($p = 0.001$) compared to prevalent CRCs. Regarding DNA copy number alterations, PCCRCs contain less often 17p ($p = 0.002$) and 18q ($p = 0.003$) deletions than prevalent CRCs. Furthermore, PCCRCs contain less frequently APC ($p = 0.04$), NRAS ($p = 0.03$), and TP53 mutations ($p = 0.03$) than prevalent CRCs. In contrast, MSI ($p = 0.004$), CIMP ($p = 0.02$) and BRAF mutations ($p = 0.04$) are more frequent in PCCRCs than prevalent CRCs.
Conclusion: Both CIN and MSI pathways are associated with the occurrence of PCCRC. PCCRCs contain less often deletions of chromosomes 17p and 18q, APC, NRAS and TP53 mutations and more often MSI, CIMP and BRAF mutations than prevalent cancers. Such molecular profiles are similar to those previously described in non-polypoid (flat and depressed) adenomas and sessile serrated lesions. Taken together, our results support the hypothesis that non-polypoid adenomas and sessile serrated lesions are in the origin of PCCRCs.
Disclosure of Interest: S. Sanduleanu: Consultancy: Pentax Medical Systems Europe
All other authors have declared no conflicts of interest.

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OP213 MOTORIZED SPIRAL ENTEROSCOPY: A NEW TECHNIQUE FOR ONE-STAGE COMPLETE ENTEROSCOPY

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Introduction: Three different platforms have been developed to perform deep enteroscopy; namely, single balloon, double balloon, and spiral enteroscopy. None of these devices permits routine evaluation of the entire small intestine, even with a combination of antegrade and retrograde enteroscopy. We report our early clinical experience with a motorized spiral enteroscope, which may provide a modality for one-stage complete enteroscopy.
Aims & Methods: We report early experience with a prospective multi-center efficacy and safety trial. The study was approved by the institutional review boards of each of the participating centers. Patients referred for evaluation of small bowel disease at one of the three participating centers requiring antegrade enteroscopy were offered participation in the study, and then screened for exclusion criteria. If enrolled, informed consent was obtained. Under general endotracheal anesthesia, the motorized spiral enteroscope (SIF-Y0019, Olympus, Japan) is inserted through the mouth. The rotational advancement and withdrawal is controlled by the endoscopist using a foot pedal. The primary outcome of the study was the depth of insertion of the enteroscope.
Result: Demographics of the study patients are summarized in Table 1. Of the first 7 completed procedures, we were able to accomplish complete enteroscopy in 5 (71%) patients. In the other two instances, the distal jejunum and distal ileum were reached. The average insertion time was 47 minutes [range: 32–61] with an average total procedure time of 66 minutes [range: 41–94]. A bleeding event requiring hospitalization occurred within 7 days of one of the procedures but that was due to the underlying lesion rather than a complication of the procedure. No other significant adverse events were reported.
Conclusion: We present our initial experience of a safety and efficacy data trial for the motorized spiral enteroscope. We were able to safely accomplish full enteroscopy in 71% of cases with a single antegrade deep enteroscopy using the motorized spiral enteroscope. This percent achievement of complete enteroscopy in a time typically reported for unidirectional deep enteroscopy suggests that this device is a significant development in design of small bowel enteroscopes. One patient experienced bleeding requiring hospitalization within 7 days of the procedure. This was a significant adverse event (SAE) by protocol. However on further review it was determined that the patient bled from a Meckel's diverticulum, identified during deep enteroscopy. Subsequent surgery was curative.
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D. Demarco: Consulting for Spirus
All other authors have declared no conflicts of interest.

OP214 THE AER-O-SCOPE COLONOSCOPE PROVIDES SUCCESSFUL ENDOSCOPIC THERAPY IN AN EX VIVO SWINE COLON MODEL

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Introduction: The Aer-O-Scope Colonoscope System (GI View Ltd., Ramat Gan, Israel) is a self-propelled, joystick controlled, disposable colonoscope that provides panoramic (360°) endoscopic visualization of the colon and includes two working channels compatible with standard endoscopic tools [1,2].
Aims & Methods: We aimed to demonstrate the success of the self-propelled Aer-O-Scope colonoscope in providing endoscopic therapeutic access. Therapeutic endoscopic access was a priori defined as the ability to reach a pre-defined target of interest, a pseudo-polyp, within an ex vivo swine colon and deliver "simulated" endoscopic therapy including: polypectomy with snare or biopsy forceps, submucosal injection, or thermal coagulation using argon plasma coagulation (APC). This was a prospective cohort study ($n = 12$ ex vivo swine colons each housed in four different models that simulated variants of a human colon). Varying sized pseudo-polyps ($n = 8$ in each ex vivo swine colon) were created using colored thread and were randomly distributed throughout each ex vivo swine colon. Thus, $n = 96$ pseudopolyps in total were created: 1 mm–5mm ($n = 77$, 80%); 6 mm–9mm ($n = 13$, 14%); ≥10 mm ($n = 6$, 6%). Following one day of Aer-O-Scope training for joystick utilization and endoscopic therapeutic access, two endoscopists (IMG and SB) performed all the colonoscopies ($n = 12$ colonoscopies per each endoscopist) on three separate procedure dates, in random order, and blinded to the type of colon model. The study's primary endpoint was a success rate of at least 90% in providing simulated endoscopic therapy and the study's secondary endpoint was endoscopist-perceived usability of the Aer-O-Scope for endoscopic therapy. We planned on performing a total of 240 simulated endoscopic therapies ($n = 192$ biopsy forceps, snare polypectomy, or combination injection/snare polypectomy and $n = 48$ APC applications). This sample size allowed up to a 10% pseudo-polyp miss rate with a two-sided

statistical precision of 5%. This study protocol was reviewed and approved by an animal ethics committee.
Result: There were 5 (5.2%) pseudo-polyps dislodged, thus 235 simulated endoscopic therapies were able to be attempted. The success rate of the Aer-O-Scope colonoscope simulated endoscopic therapy was: 234/235 = 99.6% (95%CI 0.976–1.00). The overall success rate was 234/240 97.6% ($p < 0.001$). The below Table shows the number of successful simulated endoscopic therapies per endoscopic tool. All endoscopic tools had a success rate >95%. There were only 2 failures, both during use of a polypectomy snare. Endoscopist-rated subjective usability of the Aer-O-Scope for simulated endoscopic therapy (easy to perform or only slightly complicated to perform) was very high (98%–100%) for all endoscopic tools.

Endoscopic Tool	n	Therapeutic Successes	95%CI
Snare	140	138 (98.6%)	0.95–1.00
Biopsy Forceps	47	47 (100%)	0.92–1.00
Injection Needle	60	60 (100%)	0.94–1.00
APC	48	48 (100%)	0.93–1.00

Conclusion: In an ex vivo swine colon model, the Aer-O-Scope Colonoscope System demonstrated the ability to easily provide simulated endoscopic therapeutic access using standard endoscopic tools while having very high usability ratings.
Disclosure of Interest: S. Bezobchuk: I am a consultant for GI View Ltd.
I.M. Gralnek: I am a consultant for GI View Ltd.

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OP215 OUTCOME OF ENDOSCOPIC MUCOSAL RESECTION OF 424 LARGE SESSILE COLONIC POLYPS (≥20MM) OVER A 9 YEAR PERIOD: A SINGLE CENTRE EXPERIENCE AND ANALYSIS OF CHANGE WITH TIME

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Introduction: Endoscopic mucosal resection (EMR) has become the standard technique for resection of large sessile and flat colonic polyps. We aimed to assess the clinical outcome of colonic EMR of polyps 2 cm and greater in size at University Hospital of Leicester NHS Trust and to assess changes over a 9-year period.
Aims & Methods: Data was collected for all sessile colonic polyps ≥20 mm removed by EMR between 2006 and 2014 by 3 endoscopists (PW, JDC, RJR). Patient demographics, resection technique, completeness of initial resection, recurrence rate at first surveillance (SC1), polyp eradication at 2nd surveillance after at least 1 year (SC2) and complication rates were analysed.
Result: 564 patients were assessed for EMR, among which there were 424 completed EMRs (BCSP 138, Symptomatic 286) by three operators. Of the 140 not proceeding to complete EMR, in 65 EMR was not attempted and patients were referred for surgical resection (cancer 31, technical difficulty 34). In a further 32, EMR was attempted but abandoned; all were referred for surgery (cancer 18, benign polyp 14). Finally, 43 had no intervention (13 declined, 22 non-adenomatous or pseudo polyps, 8 moved away). The mean age was 68.7 years (range 25–93), male 226 (53%), female 198 (47%). Mean polyp size was 33 mm (median 30 mm). Site of polyp was right colon 27%, transverse colon 5%, left colon 68% (rectum 58%, sigmoid 4%, descending 6%). Piecemeal EMR was done in 381 (90%), and 'en bloc' in 43 (10%). Of those who have undergone surveillance so far, recurrence was found in 56/284 (19.7%) at initial SC1 (mean 7 month; range 2–36) and was endoscopically treated in 53/56 (94.6%); 3/56 (5.4%) referred for surgical resection (2 cancer, 1 non lifting). Complete eradication after one year SC2 (mean 16 months, range 5–51) 211/234 (90.2%) with recurrence in 23 (9.8%) – but in 22/23 this was endoscopically resected. Overall complication rate 17/424 (4%): immediate perforation 1/424 (0.2%) post-caecal EMR required conservative medical treatment; post polypectomy pain syndrome 14/424 (3.3%) required admission for overnight conservative medical treatment. Delayed bleeding 2/424 (0.5%) required endoscopic therapy to achieve haemostasis. There were no procedure-related deaths. For each 3-year period (2006–8, 2009–11, 2012–14), there was a consistent reduction in number of polyps not treated endoscopically or requiring surgery (overall decrease of 15.7%), incomplete EMR referred for surgical resection (overall decrease of 2.3%) and recurrence rate at first SC1 (overall decrease 16.3%). There were increases in numbers of EMRs performed annually (overall increase 26%), mean polyp size resected (+7 mm), level 3 & 4 polypectomies (3.7 and 7%) and complete eradication rate at SC1 (16.3%).
Conclusion: This is a large single-centre series of EMR of 424 sessile colonic polyps >2 cm performed by 3 operators over a 9 year period; almost 20% had recurrence at initial surveillance, most managed endoscopically, with eradication rate at 1 year of over 90% (22/23 one year recurrences treated endoscopically). Examination of time trends over this period showed progressive reduction in recurrence and a trend for larger, more complex polyps to be resected endoscopically, with a corresponding drop in surgical management, demonstrating improvement in outcome with time.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP216 DEVELOPMENT AND VALIDATION OF A CLASSIFICATION SYSTEM TO IDENTIFY BARRETT'S NEOPLASIA USING ACETIC ACID CHROMOENDOSCOPY: THE PREDICT CLASSIFICATION

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Introduction: Neoplasia in Barrett's can be very subtle and difficult to identify. Acetic acid chromoendoscopy (AAC) has been demonstrated to highlight neoplastic areas allowing for earlier treatment. Although the technique of AAC is very simple, lesion recognition with acetic acid (AA) remains a challenge and therefore hampering its widespread usage.
Aims & Methods: We aim to develop a simple and easy to use classification system for AAC to allow easy identification of Barrett's neoplasia. Three expert AAC endoscopists (PB, GLW, OP) formed a working group to identify AAC component criteria of non-dysplastic and dysplastic Barrett's using a modified Delphi Method. Following this, a panel of 7 advanced endoscopists assessed the performance of each individual criterion by reviewing a bespoke online database of 40 images and 40 videos of non-dysplastic and dysplastic Barrett's lesions. Finally, we assessed the diagnostic reproducibility of the validated criteria by asking 13 non-AAC expert endoscopists to complete an assessment tool of 40 images and 20 videos using this newly developed classification system.
Result: The component criteria identified by the expert AAC endoscopists were as follows: - Early focal loss of acetowhitening - Present: Indicates presence of neoplasia - Absent: Indicates the absence of neoplasia - Surface pattern - Normal (Large uniformly distributed pits): Indicates non-neoplastic Barrett's - Abnormal (Compact, irregular or absent pits): Indicates neoplasia A total of 560 observations were undertaken to validate these criteria. The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) is shown in Table 1.

Table 1: Validation results of the classification criteria

Criteria	Sensitivity	Specificity	NPV	PPV
Loss of acetowhitening	96.2% (93.4–97.9%)	93.8% (88.9–96.9%)	90.9% (85.5–94.8%)	97.5% (95.4–98.8%)
Surface pattern	77.0%	99.0%	91.4%	96.9%
Normal	(69.7–83.3%)	(97.5–99.7%)	(88.4–93.9%)	(92.2–99.1%)
Abnormal	99% (97.5–99.7%)	77.0% (69.7–83.3%)	96.9% (92.2–99.1%)	91.4% (88.4–93.9%)

When the AAC validated criteria are applied by the 13 endoscopists, the sensitivity, specificity, NPV and PPV of detecting neoplastic Barrett's are 98.5%, 64.0%, 97.5% and 72.5% respectively.
Conclusion: We have developed and established the validity of a simple classification system to identify Barrett's neoplasia using AAC. When non-AAC trained endoscopists apply these criteria, the sensitivity and NPV meet the recommended PIVI threshold.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP217 STEPWISE DEVELOPMENT OF A VOLUMETRIC LASER ENDOMICROSCOPY PREDICTION SCORE FOR BARRETT'S NEOPLASIA USING MATCHED VLE-HISTOLOGY IMAGES OF ENDOSCOPIC RESECTION SPECIMENS

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Introduction: Endoscopic detection of early neoplasia in Barrett's esophagus (BE) is difficult. Volumetric laser endomicroscopy (VLE) is an advanced imaging system incorporating 2nd generation optical coherence tomography in a balloon-based system, providing a 6-cm long circumferential scan of the esophageal wall up to 3 mm deep, with near-microscopic resolution. Several VLE features of early BE neoplasia have been determined previously (1,2).
Aims & Methods: Aims of this study were to determine (additional) VLE features of neoplasia, based on precise VLE-histology correlations ex vivo, and to develop and validate a VLE prediction score for early BE neoplasia.
A unique database of VLE images from endoscopic resection specimens and corresponding histology from BE patients +/- neoplasia was used. Precise

VLE-histology correlation methodology has been described previously (3). In the orientation phase, 25 VLE-histology images were evaluated in an unblinded manner by a GI pathologist, BE endoscopist and VLE researcher. Features potentially predictive for early BE neoplasia were identified and subsequently discussed in consensus with 2 VLE experts. In the learning phase, VLE images corresponding with neoplasia ((high-grade dysplasia (HGD) or early adenocarcinoma (EAC); n = 10) and non-dysplastic (ND)BE tissue (n = 10) were scored by the 2 VLE experts – blinded to histology – for presence of neoplasia and VLE features identified in the orientation phase. After a consensus meeting, a prediction score was created based on multivariable logistic regression analysis using learning phase results. This score was validated by expert scoring of 40 additional VLE images (20 HGD/EAC; 20 NDBE) using area under receiver operating characteristic (ROC) curve (AUC) analysis.

Result: Four VLE features potentially predictive for BE neoplasia were identified: 1) lack of layering; 2) higher surface signal than subsurface signal; 3) presence of irregular, dilated glands/ducts; 4) homogeneity. In the learning phase, features 1, 2 and 3 were significantly and independently associated with neoplasia. The VLE neoplasia prediction score was developed with: feature 1 (6 points), 2 (6 or 8 points for equal or higher surface signal) and 3 (5 points). ROC curve of this prediction score showed an AUC of 0.83 (95% CI 0.69–0.96) in the learning and 0.81 (95% CI 0.71–0.90) in the validation phase. A cut-off value of ≥8 was associated with a sensitivity and specificity of 85% and 68% in the learning and 83% and 71% in the validation phase, respectively.

Conclusion: This study, using high-quality ex vivo VLE-histology correlation, confirms that the VLE features layering, surface signal, and irregular glands/ducts are independently and significantly associated with early BE neoplasia. Using these features, we developed and validated a VLE prediction score for BE neoplasia, with promising accuracy.

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All other authors have declared no conflicts of interest.

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OP218 DETECTION OF DYSPLASIA IN BARRETT'S OESOPHAGUS USING LECTIN-BASED NEAR INFRA-RED MOLECULAR IMAGING: AN EX-VIVO STUDY ON HUMAN TISSUE

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Introduction: Detection of early neoplasia in Barrett's oesophagus by white-light endoscopy is challenging due to the inconspicuous nature of dysplasia. Molecular imaging using fluorescently labelled wheat-germ agglutinin (WGA) is a promising tool for detecting dysplasia as this topically applied imaging agent shows lower binding to dysplastic versus non-dysplastic oesophageal glandular mucosa (1). However in an endoscopy setting, the detection of fluorescence in the blue/green range is limited by high levels of tissue autofluorescence. This limitation can be overcome by using near infra-red (NIR) imaging.

Aims & Methods: The aim of this study was to assess in an ex-vivo model the feasibility of WGA-based NIR imaging for detection of dysplasia in Barrett's. To this end, we studied patients with early Barrett's-related neoplasia undergoing endoscopic mucosal resection (EMR). Freshly collected EMR specimens were sprayed with WGA-IR800CW (10 µg/mL; 10 min, room temperature); washed with PBS buffer and then imaged with a high-sensitivity NIR camera (Fluobeam™, Fluoptics). Planar fluorescence images were captured and up to two punch biopsies (2 mm diameter) were collected from each EMR specimen, under fluorescence guidance. The EMRs were then formalin fixed and paraffin embedded (FFPE), cut every 2 mm and processed for histopathological assessment. Each section was scored by an expert GI pathologist every 1 mm to construct a pathology grid, which was manually co-registered with the fluorescence image. Targeted punch biopsies, taken from areas of interest within the EMR specimen, were also scored by the pathologist. The mean fluorescence intensity (MFI) of cells in dysplastic and non-dysplastic areas was compared by the Wilcoxon matched-pairs signed rank test. The MFI of punch biopsies taken from dysplastic and non-dysplastic areas was compared by Mann-Whitney test. The correlation between the fluorescent contrast and spatial extent of dysplasia was analysed by linear regression.

Result: Ten patients were recruited at a single centre. We included in the analysis 19 EMR specimens with at least one dysplastic gland and 45 punch biopsies, of which 16 were dysplastic. In the whole EMR analysis, we found a significantly lower mean fluorescence intensity (MFI) in dysplastic versus non-dysplastic areas ($P < 0.0001$), in accordance with the reported reduced binding of WGA to neoplastic Barrett's epithelium (1). Similarly, the MFI of punch biopsies taken from dysplastic regions was significant lower compared to that of non-dysplastic areas ($P = 0.0002$). Finally, we found that the fluorescent contrast between dysplastic and non-dysplastic areas was higher in EMRs with wider extent of neoplasia (R^2 0.58, $p = 0.0002$).

Conclusion: WGA-based NIR imaging is an effective method for differentiating dysplastic from non-dysplastic Barrett's mucosa ex vivo, which reduces the effects of tissue autofluorescence. In-vivo studies are now required to test the efficacy of this method for detecting dysplasia during endoscopic surveillance.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP219 RESULTS OF A PROSPECTIVE MULTICENTER BELGIAN REGISTRY OF RADIOFREQUENCY ABLATION FOR BARRETT'S ESOPHAGUS

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Introduction: Radiofrequency ablation (RFA), combined with endoscopic resection (ER) of visible lesions, can be used as a primary treatment for low-grade dysplasia (LGD), high-grade dysplasia (HGD) and early adenocarcinoma (EAC) in Barrett's esophagus. In prospective multicenter controlled trials, high rates of complete remission of dysplasia (CR-D) and intestinal metaplasia (CR-IM) has been reported.

Aims & Methods: The aim of this study is to monitor outcome and efficacy of RFA in a setting of absence of reimbursement in a multicenter national prospective registry. Between February 2008 and August 2015, data from 7 centers performing RFA were collected in the Belgian RFA registry. All procedures were monitored for indication, treatment before RFA, short/long-term complications and prospective long-term pathological outcome. Primary endpoint was CR-D and CR-IM. Secondary endpoints was safety.

Result: 538 RFA procedures were registered in 279 different patients (mean age 65; 84.5% men). In 60% a previous EMR/ESD was performed. Baseline worst histology prior to RFA (including ER) was: 2% SIM (5), 8% LGIN (22), 52% HGIN (146), 37% adenocarcinoma (102), 1% unknown (4). At the time of analysis 44 patients were still under treatment. In an intention to treat analysis (ITT), 83% (194/235) patients achieved CR-IM and 87% (204/235) CR-D after a median of 2 RFA sessions. 18 patients discontinued treatment, giving a per protocol(PP) CR-IM in 89% (194/217) and CR-D in 94% (204/217). 185 and 193 patients with CR-IM respectively CR-D entered follow-up. Recurrence of disease was limited to IM in 38 patients and recurrent neoplasia occurred in 24 patients: 7 LGD, 17 HGIN/Ca. With a median FU time of 735 days, the ITT and PP analysis for durability of CR-IM is 63% and 66% respectively. The results of durability of CR-D with a median FU time of 670 days in an ITT and PP analysis are 82% and 87% respectively. Immediate complications occurred in 4% of the procedures in 21 different patients (7.5%): 16 small mucosal lacerations (9 after sizing), 7 bleedings, no perforations. Late adverse events occurred in 8% of the procedures in 42 different patients (15%): 19 stenosis (mean 4 dilatations), 7 bleedings, 3 poor healing, 9 prolonged hospitalization for general symptoms, 4 fever without prolonged hospitalization, 2 pneumonia. Comparison of the Belgian RFA registry with the EURO II trial and with the UK RFA registry revealed that there was no significant difference for CR-IM, CR-D and complication rate. Remarkably, there were significantly more rescue treatments ($p < 0.0001$) in Belgium before achieving remission in comparison to the UK.

Conclusion: Our data confirm that combined ER- RFA is an efficient treatment for Barrett's associated neoplasia. In the absence of reimbursement, more escape treatments were performed in comparison to published controlled trials. Outside clinical trials, meticulous follow-up appears to be even more important to detect and treat early recurrence. We suggest a systematic registration of RFA practice to monitor long term outcome and efficacy.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP220 LONG-TERM FOLLOW-UP RESULTS OF STEPWISE RADICAL ENDOSCOPIC RESECTION FOR BARRETT'S ESOPHAGUS WITH EARLY NEOPLASIA

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Introduction: Stepwise radical endoscopic resection (SRER) allows for complete endoscopic resection of Barrett's esophagus (BE) with early neoplasia. This approach has been shown very effective in reaching complete eradication of high-grade dysplasia (HGD) or early cancer (EC) (CE-neo) in 98% and all intestinal metaplasia (CE-IM) in 85% of patients.

Aims & Methods: The aim of this study was to report the long-term follow-up (FU) results after successful SRER for BE with early neoplasia. We screened all patients treated with SRER in two centers between 2001–2014, for BE $\leq$5 cm with HGD/EC, without signs of invasion >T1sm1, G3/G4 differentiation, lymph-vascular invasion or irradical deep resection margins in ER specimens. All patients who had reached endoscopic and histologically confirmed CE-neo and CE-IM after SRER were included for evaluation of long-term FU. All information from FU endoscopies and histological outcomes were collected and entered in a dedicated database. Duration of FU was calculated from last treatment till last FU endoscopy. Primary outcomes: recurrence of HGD/EC and recurrence of IM combined with visible BE islands or tongues. Secondary outcomes: Buried Barrett's (BB) in neosquamous biopsies, and IM in biopsies obtained distal to the neo-z-line.

Result: Seventy-three patients were included (64 men, mean age 66 yrs, median BE C2M3). Worst baseline pathology: HGD, n = 50; EC, n = 23. Median FU was 76 months (IQR 55–102) with a median of 6 (IQR 4–8) endoscopies. Recurrence of HGD/EC was observed in 1 patient (1.4%) after 129 months FU (T1bN0M0 treated with curative surgery). Recurrence of IM in endoscopically visible BE was observed in 16 patients (of which 2 had LGD) after a median FU of 31 months. In all cases the extent of recurrence was limited to small (<1 cm) islands or tongues. Histological recurrence without visible BE was found in 25 patients: 3 patients had BB in neosquamous biopsies (4% overall, 0.7% per patient year); 24 patients (33%) showed IM in biopsies just distal to a normal appearing neo-z-line. A finding of IM of the neo-Z-line was reproduced in 50% of patients and BB in none of the patients. Additional treatment was performed in 8 patients: esophagectomy for T1b-cancer, ER of small island with LGD (n = 1), APC for small islands (n = 5), RFA for LGD in the neo-z-line (n = 1). CE-neo and CE-IM (excluding IM in the neo-z-line) at the last FU endoscopy (after additional treatment) was seen in 100% and 96% respectively.

Conclusion: This study presents the longest published follow-up data on SRER to date. The 6-year outcomes show that after successful SRER of BE $\leq$5 cm recurrence of HGD/EC is rare (1% overall, 0.2% per patient year). Recurrence of endoscopically visible BE with IM or LGD was found in 22% of patients and was generally confined to small islands or tongues. Buried glands were rare (0.7% per patient year) and just as IM of the neo-z-line (33% of cases) of insignificant importance.

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All other authors have declared no conflicts of interest.

OP221 SPECIFIC BMP4 INHIBITION AS A POTENTIAL THERAPEUTIC STRATEGY FOR SMAD4 DEFECTIVE ESOPHAGEAL ADENOCARCINOMAS

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Introduction: BMP4 is a growth factor with a key role in carcinogenesis and metastasis. We previously found that BMP4 is aberrantly expressed in Barret's esophagus and that together with CDX2 drives the intestinalization of epithelial metaplasia. Its role in the progression and development towards esophageal adenocarcinoma remains uncertain. In colorectal cancers that present mutations in the canonical transcription factor SMAD4, BMP4 induces tumorigenic characteristics in epithelial cells through activation of its SMAD-independent signaling pathways. SMAD4 mutations or deletions are also found in 10% of esophageal adenocarcinoma (EAC) patients and are associated to poor prognosis (1).

Aims & Methods: The aim of this project is to elucidate whether BMP4 is involved in malignancy in EAC. We have recently developed unique low molecular weight Llama derived antibodies that specifically and effectively target BMP4 and therefore present less off-target effects, which renders them more apt for clinical purposes (2–3). These antibodies were used to study the effect of specific inhibition of BMP4 on both in vitro as well as in vivo models of Esophageal Adenocarcinoma.

Result: We have found that 70% of EAC tumors express BMP4 at the protein levels. When the analysis was restricted to SMAD4 negative EAC tumors about 90% of those were BMP4+. Using an antibody that recognizes the pro-domain of BMP4, and therefore identifies the cells producing BMP4, we found that epithelial as well as some stromal cells, produce BMP4. We validated these results by generating an RNAseq database of 56 EAC biopsies, and confirmed that approximately 80% of those samples expressed BMP4 at the RNA levels. We next investigated the correlation of BMP4 expression and found that patients with high levels of BMP4 expression tend to have a poorer recurrence-free survival than patients with low BMP4 expression, which suggests a more aggressive tumor behavior in BMP4 expressing EAC tumors. Inhibition of BMP4 function in SMAD4 negative EAC cells by the anti-BMP4 antibodies leads to an increase in chemosensitivity and a decrease in invasive and migratory capabilities in vitro. Analyses of the signaling pathways showed that inhibition of the BMP4-mediated non-canonical pathways was responsible for these effects. Next, we made use of a patient-derived tumor xenograft (PDTX) mouse model of a SMAD4 negative EAC tumor (4). Preclinical in vivo studies with these mice confirmed that anti-BMP4 antibodies can effectively reduce tumor growth and synergistically act with chemotherapy agents.

Conclusion: Our studies support a role of BMP4 as a positive regulator of chemoresistance and invasiveness in EAC, and suggest that inhibition of BMP4 with highly specific antibodies has the potential to ameliorate the malignant behavior of aggressive SMAD4 negative esophageal cancers.

Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 10:30–12:00

ACCURACY IN UPPER GI ENDOSCOPY – ROOM L8

OP222 PREMEDICATION WITH SIMETHICONE AND N-ACETYLCYSTEINE IN IMPROVING MUCOSAL VISIBILITY DURING UPPER ENDOSCOPY – A PROSPECTIVE DOUBLE-BLINDED RANDOMIZED CONTROLLED TRIAL

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Introduction: Upper endoscopy is the most common method for the diagnosis of upper gastrointestinal tract diseases. Our aim was to determine if pre-medication with simethicone or N-Acetylcysteine improves mucosal visualization during upper endoscopy.

Aims & Methods: Randomized double-blinded, placebo controlled trial of 297 patients scheduled for upper endoscopy, pre-medicated 15–30 minutes before with: A–100 mL of water (placebo); B–water plus 100 mg simethicone; C–water plus simethicone plus 600 mg N-acetylcysteine. Primary outcome was the quality of mucosal visualization (score: 1-excellent; 2-adequate; 3-inadequate). Trial registered in http://clinicaltrials.gov (NCT02357303). Statistical analysis with X^2 and one-way ANOVA with Tukey's correction.

Result: Visualization scores between groups B and C (versus A) were significantly better in the oesophagus 1.09 and 1.15 vs. 1.31 ($p < 0.05$) and stomach 1.26 and 1.30 vs. 1.67 ($p < 0.01$) and better without significance in the duodenum 1.07 and 1.09 vs. 1.20 (p = NS). ''Excellent'' scores versus others provided similar results (B and C vs. A): oesophagus 91% and 87% vs. 71% ($p < 0.001$), stomach 76% and 75% vs. 39% ($p < 0.001$) and duodenum 85% and 82% vs. 73% (p = NS). There were no significant differences in scores between groups B and C or between gastric scores if previous subtotal gastrectomy (B and C vs. A): 1.45 and 1.68 vs. 1.86 (p = NS). The rate of reported lesions was higher in group B (without statistical significance).

Conclusion: Pre-medication with simethicone leads to better mucosal visibility, might improve diagnostic yield and should be considered standard practice. Addition of N-acetylcysteine had no benefit over simethicone alone.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP223 DIAGNOSIS OF TUMOR EXTENT OF EARLY GASTRIC CANCER BY MAGNIFYING NARROW BAND IMAGING VS. CHROMOENDOSCOPY: A MULTICENTER PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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Introduction: Accurate diagnosis of lateral extent of early gastric cancer (EGC) is important in terms of deciding treatment indication and achieving complete resection by endoscopy or surgery. Magnifying narrow band imaging (M-NBI) has been suggested to increase yield of endoscopic diagnosis for determining extent of EGC.

Aims & Methods: To compare diagnostic ability of M-NBI for determining lateral extent of EGC with that of chromoendoscopy (CE). This study was conducted as a multicenter prospective randomized controlled trial including one university hospital, one cancer referral center and three general hospitals. Inclusion criteria were patients with EGC sized 1 cm or over who underwent endoscopic or surgical treatment. Exclusion criteria were history of gastric resection and high risk of bleeding for biopsy. After stratification by institution, tumor location, and histological type, patients were randomly assigned to M-NBI or CE groups. In each group, tumor extent was firstly evaluated by white light endoscopy according to difference of mucosal height and color, then oral margin of the tumor was determined by the assigned method. Diagnostic criteria of M-NBI were 1) demarcation line and 2) irregular microvessel/microsurface patterns; and that of CE were 1) abrupt change of mucosal structure of the surrounding mucosa and 2) irregular structure patterns. Biopsy specimens were taken from 5-mm-outside and -inside of the oral boundary of the tumor and sent for histological evaluation. When the outside specimen was non-cancer and the inside specimen was cancer in histology, it was defined as ''successful delineation''. Primary endpoint was difference of proportion of successful delineation between the two groups. A study protocol was approved by institutional review board in each institution and written informed consent for study participation was obtained from all patients.

Result: A total of 382 patients were enrolled and were assigned to the M-NBI group (n = 191) and the CE group (n = 191). Eight patients in the M-NBI group and 12 in the CE group were excluded remaining 183 in the M-NBI and 179 in the CE group for analysis. Successful delineation rates (95% CI) in the M-NBI and CE groups were 86% (81–91%) and 84% (78–89%), respectively (p = 0.498).

Conclusion: This prospective randomized controlled trial revealed M-NBI and CE were equally accurate for determining extent of EGC, thus both methods are adequate to perform in clinical practice (UMIN000014628).

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP224 FEASIBILITY OF A COMPUTER ALGORITHM FOR DETECTION OF EARLY BARRETT'S NEOPLASIA USING VOLUMETRIC LASER ENDOMICROSCOPY

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Introduction: Volumetric laser endomicroscopy (VLE) incorporates 2nd generation optical coherence tomography technology in a balloon-based system, which is capable of scanning the esophagus circumferentially over 6 cm, up to a depth of 3 mm with near-microscopic resolution. VLE has the potential to improve detection of early neoplasia in Barrett's esophagus (BE). However, interpretation of VLE images is complex due to subtle differences in architecture and gray-scale color and the large amount of images that needs to be scrutinized by the endoscopist (a 6-cm VLE scan contains 1200 frames). A recently developed clinical prediction model of VLE features for BE neoplasia showed a reasonable accuracy (AUC of 0.81).

Aims & Methods: The aim of this study was to investigate the feasibility of a computer algorithm to identify early BE neoplasia on ex vivo VLE images. Sixty VLE images from a database of high-quality one-to-one VLE-histology correlations were used (30 non-dysplastic (ND)BE and 30 neoplastic images; high-grade dysplasia and early adenocarcinoma), consisting of VLE scans from endoscopic resection specimens of Barrett's patients +/- neoplasia. VLE images were normalized to a height of 400 pixels in order to obtain a standardized zoom factor. Previously identified VLE features predictive for BE neoplasia served as clinical input for the algorithm: 1) higher VLE surface signal than subsurface signal in tissue, 2) lack of layering. From these VLE features an algorithm feature was developed analyzing both top layers and surface signal. A signal intensity histogram using 8 intensity categories was calculated over the first 4 layers of 50 pixels, starting at the top of the image. Linear support vector machine was used to classify the images according to the used VLE texture features. Leave-one-out cross-validation was employed for validation of the algorithm.

Result: Using the correlated histology as the reference standard, sensitivity, specificity and accuracy for the algorithm to detect BE neoplasia were 93%, 70% and 82%, respectively. The performance of the algorithm was good, with an area under the receiver operating curve (AUC) of 0.91 to detect BE neoplasia in ex vivo VLE images. Most distinctive features of the algorithm are the top layers and mid-range intensities of the histogram.

Conclusion: This is the first study in which a computer algorithm for BE neoplasia was developed based on VLE images with direct histological correlates. The algorithm showed good performance to detect BE neoplasia in ex vivo VLE images (AUC 0.91). Compared to the performance of a recently developed clinical VLE prediction score (AUC 0.81), this study suggests that an automatic detection algorithm seems to perform at least as good as assessment by VLE experts in detecting early neoplasia on VLE. Future studies on in vivo VLE scans are needed to further validate the algorithm.

Disclosure of Interest: J.J. Bergman: - Research support: Olympus Endoscopy, Fuji-film, Cook Medical, Boston Scientific, Covidien, Erbe, Ninepoint Medical, C2-therapeutics, Cernostics, Interpace - Training programs: Covidien, Boston Sc. - Consultancy-speaker: Cook, Boston Sc.,Covidien
All other authors have declared no conflicts of interest.

OP225 OPTICAL ENHANCEMENT SYSTEM ™ PLUS OPTICAL MAGNIFICATION UTILITY IN THE IDENTIFICATION OF NORMAL GASTRIC MUCOSA, HELICOBACTER PYLORI ASSOCIATED GASTRITIS, AND GASTRIC ATROPHY

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Introduction: It has been proposed that high-resolution zoom endoscopes (optical zoom up to 115 times) could predict gastric pit pattern for gastric pathology. Recently an image-enhanced endoscopic technology called Optical Enhancement system (OE System™) was introduced, improving visualization of microvessels. In addition to this, new high-definition zoom scopes called Magniview™ are available allowing an optical zoom up to 136 times with a better evaluation of the mucosa and superficial vascular aspects.

Aims & Methods: The aim of this study was to evaluate the utility OE System™ plus Magniview™ in the diagnosis of normal gastric mucosa, *Helicobacter pylori* associated gastritis, and gastric atrophy. Methods: Prospective, non-randomized and double blind study. All of the participants enrolled had functional dyspepsia according to the Rome III criteria and were tested for Helicobacter Pylori (HP) using stool antigen test. After this phase two groups were selected, dyspeptic HP (+) and dyspeptic HP (-) patients (control group). Finally an upper endoscopy using OE system™ plus Magniview™ scopes was performed and the gastric body evaluated using a previously described classification of four patterns, based on the combination of the parameters subepithelial capillary network (SECN), collecting venules and round pits. Type 1 pattern predicts normal

Table 1. (OP225): Overall accuracy of the four patterns predictions

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, %
Type I[a]	90.00 (55.50–99.75)	79,03 (66.82–88.34)	40.91 (20.70–63.65)	90.00 (89.35–99.95)	80.55
Type II–III[b]	91.43 (76.94–98.20)	78.38 (61.79–90.17)	80.00 (64.35–90.95)	90.62 (74.98–98.02)	84.72
Type IV[c]	66.67 (9.43–99.16)	88.41 (78.43–94.86)	20.00 (2.52–55.61)	98.39 (91.34–99.96)	87,50

a) Ability to predict normal mucosa. b) Ability to predict *Helicobacter pylori* infection. c) Ability to predict mucosa atrophy.

gastric mucosa, types 2 and 3 HP related gastritis and the type 4 gastric atrophy. (1) Images were photographically recorded and biopsies taken in order to correlate the images with the histology

Result: A total of 72 patients were included, 35 in the dyspeptic HP (+) group and 37 in the control dyspeptic HP (-) group. The average age was 46.3 (37–58.5) years old and 69.4% were women. The images were analyzed and classified into the four patterns after the agreement of three endoscopists. There were 22 (30.6%) patients with type I, 13 (18.1%) with type II, 27 (37.5%) with type III and 10 (13.9%) with type IV pattern. Almost all patients (90%) with normal mucosa were Type I. Most type II and III patterns had active chronic gastritis, which correlates with HP infection. In fact, 32/34 (91.5%) of patients with HP (+) were Type II-III. The 66% of patients with atrophy had Type IV pattern. The Table 1 shows the overall accuracy of the four patterns predictions. Type I predicts normal mucosa, Type II-III HP infection, and Type IV atrophy with a sensitivity of 90%, 91% and 66.7% respectively and an accuracy of 80.5%, 84.7% and 87.5% respectively. Finally the intra and inter-observer agreement was calculated with a kappa value of 0.91 and 0.89 respectively

Conclusion: OE chromoendoscopy plus optical magnification has proved to be useful in the diagnosis of normal gastric mucosa and HP associated gastritis with high accuracy, unlike gastric atrophy evaluation

Disclosure of Interest: C. Robles-Medranda: Key Opinion Leader for Pentax Medical

All other authors have declared no conflicts of interest.

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OP226 FIRST-IN-MAN PILOT STUDY: FEASIBILITY OF LASER MARKING IN BARRETT'S ESOPHAGUS WITH VOLUMETRIC LASER ENDOMICROSCOPY

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Introduction: Volumetric laser endomicroscopy (VLE) is an advanced imaging system that provides a 6-cm long, circumferential scan of the esophageal wall subsurface layers with near-microscopic resolution. VLE has the potential to improve the detection of neoplasia during Barrett's esophagus (BE) surveillance. A new feature of the VLE system is a laser marking tool that enables direct marking of suspicious areas during VLE scanning, which subsequently can be targeted for histological sampling. We herein describe the first in human use of the VLE laser marking tool in BE patients.

Aims & Methods: The aim is to evaluate visibility and positional accuracy of VLE laser marks in different esophageal tissue types on white light endoscopy (WLE) and VLE. BE patients with and without neoplasia were imaged with VLE. In a learning phase protocol refinements were practiced. In the second phase, visibility of laser marks (LMs) was assessed by randomly marking 4 quadrants in squamous, BE and gastric tissue. LMs were automatically placed in offset mode; 2 LMs 6 mm apart horizontally. In the third phase, positional accuracy of LMs was tested, whereby previously placed electrocoagulation markers (ECMs) were targeted on VLE and laser marked (2 ECMs per tissue type). In the final phase, in each patient the most suspicious areas for neoplasia were identified on VLE, targeted by laser marks and subsequently biopsied.

Result: In total 17 BE patients were included (15 males, median age 67): 11 patients with non-dysplastic (ND)BE, 6 patients with high-grade dysplasia (HGD) or early esophageal adenocarcinoma (EAC). Median BE length: C2 (IQR 1–9) M4 (IQR 4–11). In total 222 LMs were placed, of which 207 (93%) were visible upon WLE and 192 (86%) on VLE, see table for visibility per tissue type. In total in 25/33 of targeted ECMs (76%) the LMs were confirmed to be positioned accurately. Three ECMs were not accurately targeted due to a system error and 5 due to difficult visualization on VLE. In the final phase (5 patients), 18 areas identified on VLE as most suspicious were successfully targeted by LMs (3 areas contained EAC, 3 HGD, 1 LGD and 11 NDBE). Mean VLE procedure time was 22 minutes (SD 6) – with a mean total endoscopy time of 56 minutes (SD 17). No adverse events were reported.

Visibility of laser marks in esophageal tissue types

	Gastric mucosa	Barrett's mucosa	Squamous mucosa	TOTAL
Upon WLE	49/62 (79%)	96/96 (100%)	62/64 (97%)	207/222 (93%)
Upon VLE	43/62 (69%)	88/96 (92%)	61/64 (95%)	192/222 (86%)

Conclusion: The first in human use of VLE laser marking in 17 BE patients was found to be feasible and safe. The majority of the LMs was visible upon WLE and VLE, although appearance on VLE can be subtle. Targeting VLE areas of interest proved to be highly successful and VLE laser marking may thus improve the clinical value of VLE in BE surveillance in the future.

Disclosure of Interest: B.L.A.M. Weusten: - Research support for IRB approved studies: Covidien GI Solutions Erbe Medical C2Therapeutic - Consultancy: Boston Scientific C2Therapeutic

All other authors have declared no conflicts of interest.

OP227 ROAD MAP FLUOROSCOPY FOR SUCCESSFUL GUIDANCE OF ENDOSCOPIC INTERVENTIONS IN THE ESOPHAGUS

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Introduction: Digital subtraction angiography is a method to enhance the contrast of anatomic structures after opacification with contrast media. Therefore structures that are not of interest are deleted from the image by subtraction of image information. A variation of this technique is called Road Map Fluoroscopy (RMF) where an image at peak opacification is used as the mask for subsequent subtraction images. With this technique the advancement of guidewires, stents or catheters can be viewed without additional marking or contrast injection. In summary, the opacification is only performed once but the information remains on the image throughout the investigation. In this way anatomic structures such as length or diameter of stenosis can be measured with high accuracy (1–4). Although esophageal stent placement has been reported to be safe also without fluoroscopic guidance most endoscopists prefer to use fluoroscopy during stent deployment (5–7). Mucosal marking using the injection of lipoidol for stent implantation is widely used among endoscopists but may no longer be necessary if RMF is used as guidance of the procedure. The use of RMF has so far not been evaluated for endoscopic procedures.

Aims & Methods: We aimed to evaluate the usefulness of Road Map Fluoroscopy to guide endoscopic interventions in the esophagus. Patients with esophageal strictures were consecutively enrolled in a monocentric observational trial. After identification of the stenosis, a Road Map (Philips Multidiagnost Eleva, Philips Healthcare, Netherlands) scan was performed using 20–40 ml of water soluble contrast media that was applied through the working channel of a gastroscope (Fujifilm EG530NW or Olympus GIF-Q 180). RMF recording requires stable fluoroscopy of the region of interest to generate a mask for consecutive subtraction. Thereafter contrast medium is injected. After RMF application all further fluoroscopy images contain the information of the subtraction as steady overlay. Directly after the RMF was finished, the complete fluid was removed from the esophagus to avoid aspiration. Patients were all investigated in recumbent position under sedation with midazolam or propofol. All further interventions and measurements were performed by using the RM images.

Result: 21 investigations were performed in 18 patients (age:71 ± 13 years male:12 female:6). Indications for interventions were: balloon dilatation of benign strictures: n = 9 including 1 pneumatic balloon dilatation for the treatment of achalasia, bouginage of benign stricture: n = 3 and diagnostic radiography without intervention: n = 1. In addition 8 stents, 5 partially covered and 3 fully covered, were placed using RMF as a guide for exact determination of stent length and diameter. Stents were also deployed under RMF guidance (figure). Endoscopic control revealed desired stent position in all cases. The choice of stent was made by measurement of the length of the stenosis as well as diameter of healthy esophagus adjacent to the stricture. Available stents that fitted best to the measured dimensions were implanted. In all procedures RMF successfully guided the intervention. The feeling of resistance during bouginage was exactly matching the location for RMF projection of the stenosis. With the help of RM imaging dilatation balloons could easily be centered inside the stenosis to avoid slipping of the balloon. Complications did not occur.

Conclusion: RMF provides the possibility of permanent radiographic illustration of stenosis or anatomic changes throughout the intervention by using contrast medium only at the beginning of the intervention. RMF is feasible and safe to guide radiology based interventions in the esophagus. RMF directs the selection of stents better than endoscopy because all relevant dimensions can be measured exactly.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 10:30–12:00

SMALL BOWEL DISEASE AND NUTRITIONAL THERAPY – ROOM 1.86

OP228 GASTROINTESTINAL DISEASES IN COMMON VARIABLE IMMUNODEFICIENCY

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Introduction: Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency in adults. CVID is a combination of humoral and cell-mediated deficiency, and the cornerstone of its treatment is intravenous or subcutaneous immunoglobulin therapy. However, while this treatment prevents infections, many CVID patients may still develop a broad spectrum of gastrointestinal disorders including autoimmune and inflammatory diseases such as atrophic gastritis, small bowel villous atrophy and inflammatory bowel disease (IBD).

Aims & Methods: Aim of the study: To investigate in detail the gastrointestinal phenotype of CVID patients living in southern Finland. Patients and Methods: Our study cohort consisted of 105 adult CVID patients followed up between 2007–2015 in Helsinki University Hospitals Adult Immunodefiency Unit and the respective outpatient clinics of Carea and Eksote. CVID patients were diagnosed with the strict vaccine response criteria and lived within these 3 hospital districts of southern Finland (1.9 million inhabitants). Adult patients of this cohort were diagnosed from the year 1960 to 2015 when recruitment stopped. We investigated retrospectively their medical records, laboratory results, endoscopy (over 300 endoscopies) ja histology reports and data was collected to an electronic database designed for the study. Of this patient cohort, 12 patients died and 11 were lost to follow up.
Result: Upper endoscopy and ileo-colonoscopy were done at least once to 83 (79%) and 77 (73%) patients, respectively. 1. Gastric: *Helicobacter pylori* was found in 7 patients, was negative in 74 and unknown in 23 patients. Eradication was succesful in all *Helicobacter*-positive patients. *Helicobacter*-negative chronic gastritis without marked atrophy, but ranging from mild to severe inflammatory activity, was found in 11 patients (11%). In addition, atrophic gastritis was found in 10 patients (10%). 2. Small bowel: All tested patients were seronegative for coeliac disease. Of patients with increased intra-epithelial lymphocytes and villous atrophy of duodenum, 2 had complete histological and clinical response to gluten-free diet and all 4 others were unresponsive but had no enterocyte antibodies. 3 of the patients with refractory duodenal villous atrophy and inflammation had also inflammatory changes in colon as well. 3. Hepatobiliary: Primary sclerosing cholangitis or CVID-associated cholangitis was diagnosed in 5 patients. 3. Large Bowel: Inflammatory changes of mucosa ranged from unspecific colitis and microscopic colitis (including lymphocytic colitis and collagen colitis) to crypt-desctructive and/or graft-versus-host like severe inflammation. Colonic enteropathy included IBD-like phenotypes: colitis ulcerosa was diagnosed in 5 patients (2 colectomies) and one patient had stricturing ileocolonic Crohńs disease. Altogether, inflammation of colon was more common than small bowel enteropathy and it was found in 20 patients (19%). Prior to ileocolonoscopy, bacterial and parasitic infections were ruled out by standard laboratory methods including fecal sample screening. Nodular lymphatic hyperplasia was detected from gastric mucosa to rectum, and ranged from asymptomatic enhanced ileal nodularity to major changes of the gastric and bowel mucosal appearance and function. It was relatively common finding and noted in 36 patients (34%). 4. Mortality and gastrointestinal malignancies: 12 patients died during the follow up and in 3 patients it was directly due to metastatic malignancies of gastrointestinal tract: 2 patients with gastric adenocarcinoma and one patient with adenocarcinoma of the colon. Small bowel enteropathy had been found also in other 2 patients that died due to the cardiovascular disease. Meanwhile, one patient with unspecific inflammatory nodularity of colon eventually developed ceacal large B-cell lymphoma which was timely diagnosed, and treated successfully.
Conclusion: Gastrointestinal and hepatobiliary manifestations are common among patients with CVID and the risk malignancies are increased.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP229 BILE ACID DIARRHOEA: EVIDENCE FOR LOWER SEHCAT RETENTION IN TYPE 3 PATIENTS FOLLOWING CHOLECYSTECTOMY

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Introduction: Bile Acid Diarrhoea (BAD) is an under-recognised cause of chronic diarrhoea and can be assessed by measuring SeHCAT retention. BAD can relate to terminal ileal disease or resection (designated as Type 1), be considered as idiopathic (type 2), or be linked to other underlying conditions (Type 3). Its prevalence is increased following cholecystectomy, but the clinical profile and severity of bile acid malabsorption are poorly characterised.
Aims & Methods: A prospective study evaluated SeHCAT usage across the United Kingdom was undertaken, capturing data from 38 centres and 1,036 patients. Aims were to investigate SeHCAT retention rates according to the type of BAD suspected, and to evaluate centre-defined abnormal results.
Result: Of the 1,036 patients, 752 had information on suspected BAD type, of whom 310 had suspected Type 3 BAD (71% female, mean age 49 years). A large subset were identified as post-cholecystectomy (n = 98, 82% female, mean age 52 years) and non post-cholecystectomy (n = 212, 67% female, mean age 48 years). Suspected Type 3 are hereon referred to as BAD Types 3a (all except post-cholecystectomy) and 3b (post-cholecystectomy only). Patients with suspected BAM Type 3a had the largest mean retention of 25% (95% CI: 22.3–28.0%, median = 20, while post-cholecystectomy patients (BAD Type 3b) had a mean retention of 15% (95% CI: 11.7–18.3%, median = 9). These compare to mean retentions of 9% in suspected Type 1 and 21% in Type 2 (1). Centre-defined abnormal results were higher amongst suspected Type 3b patients (56%) than Type 3a (30%), with correspondingly higher bile acid sequestrant prescriptions for Type 3b patients (49%) than Type 3a (25%) at the time of the survey.
Conclusion: Subdivision of BAD Type 3 patients suggest (although not conclusively given the limitations of this survey) that post-cholecystectomy patients have a physiologically different profile compared to non post-cholecystectomy Type 3a patients, with more severe bile acid malabsorption. This warrants separate analysis in future research.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP230 EVALUATING THE UTILITY OF AMINO ACID CITRULLINE AS A METABOLOMIC SIGNATURE IN PREDICTIVE AND FOLLOW UP VALUE IN CELIAC DISEASE; SUGGESTING IT TO BE A MARKER OF ENTEROCYTE VILLOUS DAMAGE

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Introduction: Amino acid citrulline is a non-essential amino acid which does not corporate into proteins and small intestine (gut enterocyte) is the main endogenous source of circulating citrulline in blood. Since celiac disease is thought to be a highly heterogeneous spectrum ranging from classic malabsorptive form to atypical potential or latent form. It is envisaged that citrulline could be an important metabolomic or proteomic signature to assess silent and potential forms of the disease, compliance of the disease after institution of gluten free diet and it may add predictive value for closer surveillance of high risk groups such as first degree relatives of CD.
Aims & Methods: We aimed to evaluate the baseline and six months follow up plasma citrulline levels in patients with celiac disease and in their first degree relatives and to establish a correlation between histopathological findings and the amino acid levels as a biomarkers for villous atrophy. Materials and Method: The procedure adopted for measuring plasma citrulline was Tendem Mass Spectrometery (LC-MS/MS) & RP-HPLC. Disease state was confirmed by histopathology findings including Marsh score and HLA typing(DQ2 & DQ8) BY SSP-PCR
Result: Mean plasma citrulline levels in 54 serology positive subjects was 9.0 ± SD umol/L whereas the mean citrulline levels in 124 serology negative subjects (first degree relatives) was 24.3umol/L. This difference was statistically highly significant with p value of 0.0001. Correlations between biopsy grades of Subjects with their citrulline levels were established & found to be significant. For Marsh 3c grade lesions, mean citrulline levels were 5.6 ± SD umol/L. For Marsh 3b, mean citrulline levels were 15.0 ± SD umol/L with p value 0.006. Understandably the patients with total villous atrophy had a lower citrulline levels even if they were asymptomatic. All the patients were on stringent six month follow up and the mean levels were 12.8 ± SD umol/L. DQ2 heterodimer were collectively found in 71.63% high risk subjects. A total of 8.69% subjects found negative for HLA DQ2 heterodimer. HLA type DQ8 was not found in any of the subject.
Conclusion: Citrulline alone is a very important metabolomic signature of initial damage of gut enterocytes in celiac disease and also when correlated with Marsh score. Citrulline estimation on dried blood spots using tandem mass spectrometry is a minimally invasive and promising test in near future which could be transported from the remotest place in the country to suggest improvement in gut enterocyte mass. Plasma citrulline estimation assures detection of potential celiac disease and may be use for monitoring of compliance and recovery in CD which is likely to be of immense benefit in the diagnosis of celiac disease and analyzing citrulline on dried blood spot by a highly sensitive technique of liquid chromatography mass spectrometry may ease follow up and diagnosis of CD
Disclosure of Interest: All authors have declared no conflicts of interest.

OP231 CELLULAR ZINC IS REQUIRED FOR INTESTINAL EPITHELIAL BARRIER MAINTENANCE VIA THE REGULATION OF CLAUDIN-3 AND OCCLUDIN EXPRESSION

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Introduction: Intracellular zinc is required for a variety of cell functions. Previous studies suggest that the intracellular zinc has an essential role in the maintenance of the intestinal tight junction (TJ) barrier, however, the underlying mechanisms remain unclear (1, 2). The present study investigated the essential roles of intracellular zinc in the preservation of intestinal TJ integrity and the underlying molecular mechanisms in human intestinal Caco-2 cells and mouse colons.
Aims & Methods: Depletion of intracellular zinc in Caco-2 cells and mouse colons was achieved by the application of a cell permeable zinc chelator, N, N,N',N'-Tetrakis(2-pyridylmethyl)ethylenediamine (TPEN). Caco-2 cells grown in Transwell inserts were incubated with TPEN. The TJ barrier function was assessed by measuring transepithelial electrical resistance (TER) and dextran flux. The TJ proteins expression and distribution (ZO-1, ZO-2, occludin, JAM-1, and claudin-1-4) were evaluated by immunoblot, immunofluorescence and qPCR analyses. To confirm specificity of the TPEN effects, $ZnSO_4$ was supplemented to the culture media in the presence of TPEN. The TPEN-induced proteolysis of occluidn was examined by biotinylation of cell surface proteins. To examine the mechanisms underlying for the zinc depletion-induced occludin proteolysis, selective inhibitors of calpain, proteasomes, autophagy, matrix metalloprotease and cathepsin were used. The effect of zinc depletion on claudin-3 promoter activity was examined by means of a reporter gene assay. Roles of transcription factors, sp1 and egr1, for the zinc-mediated claudin-3 promoter

activity were examined by a mutagenesis technique in the promoter assay and RNA interference technology. The effects of TPEN on occludin and claudin-3 expression in mouse colons were also examined in combination with the calpain inhibitor.
Result: Intracellular zinc depletion by TPEN impaired the TJ barrier of intestinal Caco-2 cells, indicated by decreased TER and increased dextran flux. The TPEN-induced TJ disruption is associated with downregulation of 2 TJ proteins, occludin and claudin-3. These changes induced by TPEN were completely restored by supplemental zinc. Biotinylation of cell surface proteins revealed that the zinc depletion induced the proteolysis of occludin, but not claudin-3. Occludin proteolysis was sensitive to the inhibition of calpain activity, and increased calpain activity was observed in the zinc-depleted cells. Although qPCR analysis and promoter reporter assay have demonstrated that the zinc depletion-induced claudin-3 downregulation occurred at transcriptional levels, a site-directed mutation in the egr1 binding site in the claudin-3 promoter sequence induced loss of both the basal promoter activity and the TPEN-induced decreases. Reduced egr1 expression by a specific siRNA also inhibited the claudin-3 expression and barrier maturation in cells. In mouse colons, the calpain inhibitor restored the TPEN-induced decrease in occludin, but not claudin-3.
Conclusion: This study shows that intracellular zinc has an essential role in the maintenance of the intestinal epithelial TJ barrier through regulation of occludin proteolysis and claudin-3 transcription. Intracellular zinc seems to physiologically suppress occludin proteolysis by robust calpain activity. Further, zinc finger-containing egr1 was shown to be critical for the transcriptional regulation of claudin-3.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP232 EVALUATING THE QUALITY OF LIFE OF ADULT PATIENTS ON HOME PARENTERAL NUTRITION IN NORTHERN AND NORTHEAST ENGLAND

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Introduction: Home parenteral nutrition (HPN) is an established treatment for the management of patients with Type 3 intestinal failure (IF). A Quality of Life (QOL) assessment tool (HPN-QOL version 1.0) was developed and validated in 2009 specifically for this patient population (1). Little data exist in literature on the QOL of HPN patients. We incorporated this tool into local clinical practice to evaluate the QOL of our HPN cohort in Northern and Northeast England.
Aims & Methods: The HPN-QOL was discussed with all patients in clinic and sent by post with a prepaid return envelope and a letter explaining how information will be used. Participation was voluntary. Responses were collected between February and July 2015. Data were anonymised for analysis and reporting.
Patients scored themselves in 45 questions relating to 10 domains of function and 9 domains of symptoms. 3 further questions asked for a global numerical rating of QOL. A final question allowed free text comments. Scores were computed if at least half of the questions in each domain were answered as per the validated process in HPN-QOL. Raw patient responses were scaled to a score of 0–100 for each domain. The QOL global numerical ratings had a scale of −60 to 65. Based on the rating descriptors in the HPN-QOL we interpreted a scaled score of more than 50 in domains relating to function as good functioning ability. A scaled score exceeding 50 in symptom domains were interpreted as frequent symptoms impairing QOL. For the QOL global numerical ratings, a scaled score of 23 or more was interpreted as good overall QOL.
Patients were grouped according to the following 4 criteria for further analysis: gender, age (>55 and ≤ 55), presence of stoma, and aetiology of IF. Within each group, QOL scaled scores were compared in every domain using the Kruskal-Wallis test.
Result: 55 responses were received from 67 patients. Two responses were excluded due to insufficient information to perform any form of analysis. 22 patients (41.5%) were male and 31 female. Median age was 55 years (range 19–85). 27 patients (50.9%) were 55 years and younger and 26 patients were older than 55 years. The aetiologies of intestinal failure were mesenteric ischaemia, 16 (30.2%); inflammatory bowel disease (IBD), 15 (28.3%); surgical complications, 8 (15.1%); motility disorder and radiation enteritis, 5 each (18.9% in total); and malignancy, 4 (7.5%). 37 patients (69.8%) had a stoma and 16 had no stoma.
There was no significant difference between patients with and without a stoma in all domains except gastrointestinal (GI) symptoms ($p=0.01$). This is in keeping with findings by Baxter, et al (1). In gender analysis, males reported better ability to eat and drink ($p=0.027$), better perceived support from the MDT ($p=0.027$), and better sexual function ($p=0.046$). However, they also reported more GI symptoms ($p=0.006$). In age group analysis, patients over 55 had lower employment scores ($p=0.004$) and more GI symptoms ($p=0.014$). The lower employment scores may be confounded by advancing age alone. In analysis of aetiology, patients with motility disorders reported significantly reduced ability to eat and drink compared to those with other causes of IF except malignancy ($p=0.034$). Regardless of gender, age, or presence of stoma, patients generally rated their ability to travel/holiday, physical function, employment, and sexual function poorly. Fatigue was a major limiting symptom. The global QOL numerical rating was also poor in all groups.
Conclusion: As part of the holistic clinical care of patients on HPN, their QOL should be considered. Results of this study show that the majority of our HPN patients experience problems that impair their QOL. It is not possible to establish how much this relates to the underlying condition or HPN itself. This is an area that would benefit from further study.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP233 EARLY ENTERAL VERSUS TOTAL PARENTERAL NUTRITION IN PATIENTS UNDERGOING PANREATICODUODENECTOMY: A RANDOMIZED MULTICENTER CONTROLLED TRIAL (NUTRI DPC)

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Introduction: Current nutritional guidelines recommend the use of enteral over parenteral nutrition in patients undergoing gastrointestinal surgery. However, the NJEEN remains controversial in patients undergoing PD.
Aims & Methods: To compare nasojejunal early enteral nutrition (NJEEN) with total parenteral nutrition (TPN), after pancreaticoduodenectomy (PD), in terms of postoperative complications. Multicenter, randomized, controlled trial was conducted between 2011 and 2014. Nine centers in France analyzed 204 patients undergoing PD to NJEEN ($n=103$) or TPN ($n=101$). Primary outcome was the rate of postoperative complications according to Clavien-Dindo classification. Successful NJEEN was defined as insertion of a nasojejunal feeding tube, delivering at least 50% of nutritional needs on PoD 5, and no TPN for more than consecutive 48 hours.
Result: Postoperative complications occurred in 77.5% (IC 95% [68.1–85.1]) patients in the NJEEN group versus 64.4% (IC 95% [54.2–73.6]) in TPN group ($p=0.040$). NJEEN was associated with higher frequency of postoperative pancreatic fistula (POPF) (48.1% vs. 27.7%, $p=0.012$) and higher severity (grade B/C 29.4% vs. 13.9%; $p=0.007$). There was no significant difference in the incidence of post-pancreatectomy hemorrhage, delayed gastric emptying, infectious complications, the grade of postoperative complications and the length of postoperative stay. A successful NJEEN was achieved in 63% patients. In TPN group, average energy intake was significantly higher ($p<0.001$) and patients had an earlier recovery of oral feeding ($p=0.0009$).
Conclusion: In patients undergoing PD, NJEEN was associated with increased overall postoperative complications rate. The frequency and the severity of POPF were also significantly increased after NJEEN. In term of safety and feasibility, NJEEN should not be recommended.
Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 10:30–12:00

ABSTRACTS ON FIRE: GI: ALL ABOUT MICROBIOTA? – HOTSPOT

OP234 DIETARY EMULSIFIERS DIRECTLY IMPACT THE HUMAN GUT MICROBIOTA INCREASING ITS PRO-INFLAMMATORY POTENTIAL

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Introduction: We recently demonstrated that, in mice, consumption of dietary emulsifiers, detergent-like components of many processed foods, results in a disturbed gut microbiota, including alterations in species composition, elevated pro-inflammatory potential (i.e. higher levels of bioactive LPS and flagellin) and microbiota encroachment (1). Such disturbance of the microbiota promotes a range of chronic inflammatory diseases including metabolic syndrome and colitis. However, the underlying mechanism by which emulsifiers induce such effects, including whether they act directly upon the microbiota or the host, remains unclear.

Aims & Methods: Our aim in the current study was to investigate if, and how, emulsifiers directly impact upon the microbiota in the absence of a host response The M-SHIME® (Mucosal Simulator of the Gastrointestinal Microbial Ecosystem) model was used to examine the effects of emulsifiers on the microbiota in vitro. After a stabilization period of 7 days, this dynamic human gut model was treated with emulsifiers (Carboxymethylcellulose (CMC) or Polysorbate-80 (P80), 1%). Microbiota composition, meta-transcriptomic and pro-inflammatory potential (Flagellin and LPS loads) were analyzed. Microbiota metagenome was predicted using PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States). Human microbiota from the SHIME system was transferred to Germfree recipient mice, with subsequent intestinal inflammation analysis.

Result: Both P80 and CMC treatment increased the pro-inflammatory potential of human microbiota, as revealed by a dramatic increase in bioactive flagellin within one day for CMC and 5 days for P80. P80 induced drastic alteration of the human gut microbiota composition, associated with an increased proportion of genes involved in bacterial motility. Both P80 and CMC treatment did not significantly alter branched or short chain fatty acid compositions, but significantly increased the proportion of microbiota mRNAs encoding motility related proteins. When transferred to germfree recipient mice, P80 and CMC-treated human microbiota was sufficient to drive low-grade intestinal inflammation and metabolic syndrome.

Conclusion: Both emulsifiers directly acted upon the microbiota to increase its pro-inflammatory potential, indicating that at least a portion of the effects of emulsifiers in vivo results from direct action of these compounds on the microbiota. The mechanisms by which P80 and CMC act are distinct, with P80 altering the composition of the microbiota, favoring species expressing high level of flagellin, whereas CMC increase the pro-inflammatory potential of the microbiota in a composition independent manner, by inducing expression of motility genes.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP235 THE CENTRAL ROLE OF THE GUT MICROBIOTA IN CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

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Introduction: Chronic Intestinal Pseudo-Obstruction (CIPO) is a chronic severe disorder of gastrointestinal (GI) motility leading to clinical features of intestinal obstruction without mechanical occlusion. The intestinal microbiota is a key factor determining gut motility. We hypothesized that dysbiosis may be found in CIPO and that it contributes to clinical features of the disease.

Aims & Methods: 1) To characterize the gut microbiota of patients with CIPO. 2) To determine whether this microbiota is responsible for clinical features typical of CIPO using a gnotobiotic mouse model. 3) To evaluate whether faecal microbiota transplantation (FMT) improves symptoms of CIPO. The faecal microbiota of 3 patients with CIPO (1 female, median age 38.6 ± 11 years) and 3 healthy volunteers (2 females, 39.5 ± 9 years) was analyzed by 16S rRNA based Illumina sequencing. Stool samples from 1 patient with CIPO and 1 healthy control were used to colonize germ-free NIH Swiss mice ($n = 15$ mice per donor, mixed gender) by oral gavage. GI transit was determined at 2 weeks using a validated in vivo videofluoroscopic technique[1]. Caecum and stomach size, and maximal bowel diameter, were determined using oral contrast-enhanced abdominal CT scan. The faecal microbiota of recipient mice was analyzed 48 hours and 2 weeks after colonization by Illumina and inferred metagenomic profiles were assessed by PICRUSt. The CIPO patient was then treated with FMT by jejunal infusion from a healthy donor at regular intervals for 20 weeks. GI symptoms, overall health and quality of life were assessed using standardized questionnaires.

Result: The microbiota of patients with CIPO exhibited marked dysbiosis with predominance of *Proteobacteria* species, especially *Enterobacteriaceae* and *Enterococcaceae*. In contrast, healthy volunteers showed a predominance of *Firmicutes* and *Bacteroidetes*. Bacterial richness and diversity were lower in CIPO patients. The faecal microbiota profiles of gnotobiotic mice resembled that of human donors. Mice colonized with microbiota from the CIPO patient had a slower GI transit than mice with healthy control microbiota (mean transit score 1 ± 2 vs. 12 ± 5, $p < 0.001$). Furthermore, CIPO microbiota colonized mice had a larger caecum size (2.39 ± 0.32 cm^3 vs. 1.56 ± 0.22 cm^3, $p < 0.001$) and a higher maximal bowel diameter (3.3 ± 0.2 mm vs. 2.9 ± 0.2, $p = 0.003$) compared to control microbiota colonized mice. Bacterial genes related to bile acid metabolism and disaccharide fermentation were differentially expressed in the faeces of recipient mice. Importantly, FMT led to a rapid and sustained improvement in GI symptoms and overall quality of life in our CIPO patient. His microbiota dramatically changed after FMT and resembled that of the donor.

Conclusion: The faecal microbiota composition and its metabolic activity are altered in patients with CIPO. This dysbiotic microbiota has the ability to induce clinical features reminiscent of this disorder in a gnotobiotic mouse model. Finally, faecal transplantation may be an effective treatment for patients with CIPO.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP236 MICROBIOTA DIVERSITY AT TIME OF SURGERY PREDICTS ENDOSCOPIC RECURRENCE IN CROHN'S DISEASE: A STUDY FROM THE REMIND GROUP

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Introduction: Operative resection in Crohn's disease (CD) is not curative. After ileocecal resection, endoscopic recurrence is frequently observed on the anastomosis and/or on the neo-terminal ileum.

Aims & Methods: The aim of this study was to analyze the mucosa associated microbiota at time of surgery and to look for predictors of post-operative endoscopic recurrence within the microbiota. This is a prospective study performed in 9 centers of the REMIND group, collecting clinical and biological data at time of

Table (OP237)

Specific aim	Study groups	Control groups
1) Role of microbiota in the etiopathogenesis of PSC	Early disease (ERC score $\leq$5), n = 37	Healthy controls (C), n = 46
2) Role of microbiota in disease progression	Advanced bile duct disease (ERC score $\geq$ 6), n = 36	Early disease, n = 37
3) Role of microbiota in biliary dysplasia and CCA (DC)	Patients with biliary dysplasia/CCA, n = 11	Early and advanced PSC, n = 73

surgery and of endoscopy (performed at 6 months). Bacterial composition of the ileal mucosa associated microbiota was analyzed at time of surgery using 16S (MiSeq, Illumina) sequencing. The obtained sequences (rarefied to 5000 read/sample) were analyzed using the Qiime pipeline to assess composition, alpha and beta diversity. Bacterial taxa associated with clinical parameters were identified using Multivariate association with Linear Models (MaAsLin) taking into account disease phenotype, clinical parameters and treatments.
Result: 146 patients were included: 73 (50%) were male, median age at surgery was 32 years (IQR 26–42). Median disease duration was 6 years (IQR 2–12). 44 patients (30%) were active smoker at time of surgery. Thirty patients (21%) had a previous resection, and 35 patients (24%) had perianal lesions. Indication for surgery was stricturing disease (n = 95), penetrating disease (n = 53). At time of surgery, 67 patients (46%) had received anti-TNF therapy within the last 3 months. After surgery, 31 patients received thiopurines, and 52 patients received anti-TNF therapy. The microbiota was mainly composed of bacteria from the *Firmicutes* (Mean 53%, range 0.3–99%), *Proteobacteria* (Mean 36%, range 0.5–99%), *Bacteroidetes* (Mean 3%, range 0–52%) and *Actinobacteria* (Mean 6%, range 0–81%) phyla. As expected, antibiotics treatment within one month before surgery had a dramatic impact on microbiota composition (Anosim, $p < 0.0001$) and diversity (mean observed species: 302 ± 17 vs 236 ± 14, $p = 0.005$). In multivariate analysis (MaAsLin), antibiotics treatment was notably associated with an increase in Enterococcus sp. ($q < 0.0001$) and with a decrease in Lachnospiraceae family ($q = 0.004$). Taking into account only the patients who did not received antibiotics within a month before surgery, we then looked for predictive factors of endoscopic recurrence. Patients with endoscopic recurrence, defined by a Rutgeerts score $\geq$1 (n = 27), had a lower bacterial diversity at time of surgery compared to patients in endoscopic remission (n = 65) (mean observed species: 276 ± 14 vs 365 ± 45, $p = 0.015$).
Conclusion: Ileal mucosa associated microbiota of CD patients at time of surgery is dominated by bacteria belonging to *Firmicutes*, *Proteobacteria*, *Bacteroidetes* and *Actinobacteria phyla*. Antibiotics given during the last month prior to surgery induce major perturbations of the microbiota. Reduction in bacterial diversity at time of surgery is predictive of endoscopic recurrence.
Disclosure of Interest: H. Sokol: Consulting fee: danone, Roche, Enterome, Maat, MSD, Astellas
All other authors have declared no conflicts of interest.

Reference

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OP237 BILE MICROBIOTA IN PRIMARY SCLEROSING CHOLANGITIS: EFFECTS ON DISEASE STAGE AND RISK FOR BILIARY DYSPLASIA

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease leading to strictures in intra- and extrahepatic bile ducts and finally to cholestasis and secondary biliary cirrhosis (1). The chronic inflammation is associated with increased proliferation of biliary epithelial cells and a markedly increased risk of development of biliary dysplasia and cholangiocarcinoma (2). The etiopathogenesis of PSC is unknown, but the frequent association with inflammatory bowel disease, in 62–83% of PSC patients, and increased intestinal permeability in PSC has suggested a role for microbiota or microbial metabolites or derivatives, e.g. pathogen-associated molecular patterns, PAMPs) such as lipopolysaccharide (LPS), lipoteichoic acid, and peptidoglycan in the etiopathogenesis of the disease (3–5). It has been proposed that the association between PSC and IBD can be due to increased enterohepatic circulation of PAMPs (“leaking gut”), or abnormal PAMPs (as a result of enteric microbial dysbiosis, described in IBD). Moreover, 16S ribosomal ribonucleic acid (rRNA) has been detected in bile and also in cholangiocytes in PSC patients. The microbiota in bile have also been shown to be modified by genetic factors such as FUT2 (2-α-L-fucosyltransferase 2) polymorphism, a gene involved in protein glycosylation.
Aims & Methods: To study the possible role of biliary microbiota in ethiopathogenesis, disease progression and risk of dysplasia and cholangiocarcinoma (CCA). The clinical part of the study was conducted at Helsinki University, Clinic of Gastroenterology. The patients were recruited from the PSC registry of the Clinic of Gastroenterology. The indication for ERCP examination was the documentation of diagnosis of PSC due to: 1) constantly elevated or fluctuating serum alkaline phosphatase (ALP) levels in conjunction with IBD, or 2) magnetic resonance cholangiography findings, or 3) liver biopsy suggestive of PSC, or dysplasia surveillance. During patient’s ERCP and before injecting contrast media a bile sample was aspirated from extrahepatic bile ducts using balloon catheter, whenever possible. Brush cytology was routinely performed during ERC. ERC findings were scored according to the modified Amsterdam score (mAm score) and the number of ERC examination were recorded in each patient group. Isolation, amplification and sequencing of the bacterial 16S rRNA gene were performed. The resulting data was analyzed with negative binomial generalized linear models, PERMANOVA, and non-parametric tests.
Result: 1) A very low abundance OTU (“species”) belonging to the family *Neisseriaceae* was reduced in abundance in the early disease group. 2) Increase in *Streptococcus* from early disease to long disease progression. *Streptococcus* also correlates with increase in ERC severity score and potentially with the number of ERCP examinations. More robust are the findings regarding overall community diversity, which decreases in long progression and dysplasia/CCA. 3) A low abundance *Prevotella* OTU disappears in patients with dysplasia or CCA. *Streptococcus* seems to again increase.
Conclusion: The data in our exploratory study suggests that the etiology of the disease is not connected with changes in biliary microbiota. However, Streptococcus seems to be connected with disease progression and risk of dysplasia and CCA. It may also be related to the number of ERC examinations and therefore a role, at least partially, for nosocomial infection cannot be ruled out at this stage. Overall microbial diversity decreases in long progression and further more in dysplasia/CCA.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP238 INCREASED FAECAL LEVELS OF GRANINS IN IRRITABLE BOWEL SYNDROME ARE ASSOCIATED WITH LUMINAL MICROBIOTA COMPOSITION AND SYMPTOM SEVERITY

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Introduction: Chromogranins (Cg) and secretogranins (Sg) are acidic gut hormones, which are secreted from the neuroendocrine system and may regulate immune activation. We have previously shown increased levels of faecal Cg and Sg in IBS patients (1). However, the consequences and cause of increased levels of luminal granins in IBS are still undefined.
Aims & Methods: In this study we aimed to quantify faecal granin levels in IBS patients and evaluate potential relationships between granin levels, microbiota composition and immune activation. Levels of CgA, CgB, SgII, SgIII and calprotectin were analysed with radioimmunoassay and ELISA, respectively, in faecal samples from IBS patients (n = 143) and healthy subjects (n = 43). mRNA expression of interleukin (IL)-8, IL-10, tumour necrosis factor (TNF) and forkhead box P3 (FOXP3) in mucosal biopsies from the sigmoid colon was determined with qRT-PCR. Faecal (n = 111 subjects) and mucosal-associated microbiota (n = 50 subjects) were analysed by 16S rRNA targeted pyrosequencing. IBS symptom severity and psychological distress were evaluated with the Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) and the Hospital Anxiety and Depression Scale (HADs), respectively.
Result: IBS patients demonstrated higher levels of faecal CgA (8.1 (3.3–17.4) pmol/L) compared to healthy subjects (4.7 (2.9–9.0), $p < 0.02$ pmol/L). The levels of SgII (0.8 (0.1–3.6) pmol/L) and SgIII (2.0 (0.8–4.8) pmol/L) in IBS patients were also increased compared to healthy subjects ((0.1 (0.0–0.2), $p < 0.01$) respectively (0.7 (0.4–2.4), $p < 0.001$, pmol/L)). Faecal microbial diversity was negatively correlated with CgA ($r = -0.29$, $p < 0.005$), CgB ($r = -0.21$,

Table 1. (OP239): Dysbiosis status

Dysbiosis	Patients	Age [med.]	Female	IBD	CD	UC	IBDU	Non-IBD	Healthy control	Unknown
No	72	28 (19–68)	43	22 [18%]	7 [16%]	11 [18%]	4 [31%]	21 [17%]	27 [56%]	2 [100%]
Low	96	33 (19–66)	49	33 [28%]	14 [31%]	15 [24%]	4 [31%]	50 [40%]	13 [27%]	0
High	126	32 (18–69)	80	65 [54%]	24 [53%]	36 [58%]	5 [38%]	53 [43%]	8 [17%]	0
Total	294	NA	172	120	45	62	13	124	48	2

$p < 0.05$) and SgIII ($r = -0.28$, $p < 0.005$). In addition, SgII showed a tendency to be negatively correlated with faecal microbial Shannon diversity ($r = -0.19$, $p = 0.05$). No correlations were found between any of the granins (CgA, CgB, SgII and SgIII) and mucosal-associated microbiota Shannon diversity or mucosal immune activity (i.e. calprotectin or expression of IL-8, IL-10, TNF and FOXP3). A positive correlation between total GI symptom severity (GSRS-IBS) and levels of CgB was detected ($r = 0.22$, $p < 0.001$). General psychological distress measured with total HAD score was positively correlated to CgA ($r = 0.24$) and CgB ($r = 0.34$, both $p < 0.05$).

Conclusion: This study confirms that IBS patients have increased faecal levels of CgA, SgII and SgIII as compared to healthy subjects. Negative associations were found between levels of luminal granins and luminal microbiota diversity, but not with either mucosal immune activity or mucosal-associated microbiota. GI symptom severity and psychological distress were also associated with increased levels of chromogranins in the lumen.

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M. Derrien: Employee at Danone
B. Le Nevé: Employee at Danone
H. Törnblom: Consultant/Advisory Board member for Almirall, Allergan, Danone and Shire, Speaker for Tillotts, Takeda, Shire and Almirall
L. Öhman: Unrestricted research grants from AstraZeneca; Consultant/ Advisory Board member for Genetic Analysis; Speaker for Genetic Analysis, Takeda and Abbot
M. Simrén: Unrestricted research grants from Danone, and Ferring Pharmaceuticals; Consultant/ Advisory Board member for AstraZeneca, Danone, Nestlé, Chr Hansen, Almirall, Allergan, Albireo, Glycom and Shire; Speaker for Tillotts, Takeda, Shire and Almirall.
All other authors have declared no conflicts of interest.

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OP239 MICROBIOTA ALTERATIONS IN TREATMENT NAÏVE IBD AND NON-IBD PATIENTS - THE EU IBD-CHARACTER PROJECT

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Introduction: The microbiota is considered important for development of intestinal diseases. In order to create a molecular snapshot of IBD in its early manifestation, one part of the IBD-Character project identified faecal microbiota profiles among the strictly treatment naïve IBD and symptomatic non-IBD patients, and a healthy control group.

Aims & Methods: Patients where characterized by international criteria including endoscopy and biopsies. Faecal samples collected during five days prior to diagnosis where stored at –80°C before examination on GA-map™ Dysbiosis Test (1), a 16S rRNA DNA test utilizing DNA probes to recognize gut bacteria profiles. In total 54 probes have been selected (1) for recognition of dysbiosis.

Result: In total 294 adult patients and healthy individuals were investigated for microbiota profiling. Table 1 shows the distribution and frequency of dysbiosis in the diagnose groups, subgroups and healthy controls. Comparing the bacteria profiles of IBD, non-IBD and control groups, the abundance of *Proteobacteria* was increased in IBD and non-IBD as compared to the controls ($p < 0.02$), while the abundance of *Bifidobacterium* and *Faecalibacterium prausnitzii* was decreased ($p < 0.02$ and < 0.07, respectively). Concerning the CD and UC subgroups, a significantly reduced abundance of *Firmicutes*, *Streptococcus* and *Clostridia* was found in UC patients ($p < 0.05$ for all) as compared to CD. Looking at the microbiota profiles of the Montreal classified subgroups of the UC patients, as compared to the healthy controls in a PLS analysis, the healthy controls ($n = 48$) and E1 ($n = 22$) patients clustered together, while the combined group of E2 ($n = 17$) and E3 ($n = 23$) patients made a separate cluster. Among 10 bacteria groups contributing to the clustering we looked into three of the groups in details; *Bifidobacterium* and *Eubacterium* were significantly reduced ($p < 0.01$), and *Escherichia/Proteobacteria* were significantly increased ($p < 0.01$) in the E2/ E3 group as compared to E1/ healthy controls group. Frequency of high dysbiosis among the healthy individuals was higher than observed in other studies (1).

Conclusion: The present results support that alterations in microbial composition is important in both IBD and symptomatic non-IBD patients. The result demonstrated: 1) Differences in microbiota profiles between IBD and symptomatic non-IBD patients and healthy individuals; 2) Equal levels of dysbiosis frequency in CD and UC, however the bacteria profiles differed; 3) In subgroups of UC, microbiota profiles were dependent upon the localization of the inflammation.

Disclosure of Interest: E. Ciemniejewska: Employee of Genetic Analysis
M.H. Vatn: Member of Genetic Analysis' Scientific Advisory Board
M. Sekelja: Former employee of Genetic Analysis AS
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All other authors have declared no conflicts of interest.

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OP240 METABOLIC SYNDROME CORRELATES WITH MICROBIOTA ENCROACHMENT IN HUMAN INTESTINE

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Introduction: The intestinal tract is inhabited by a large and diverse community of bacteria collectively referred as gut microbiota. Mucoid structures coating the epithelium, largely devoid of bacteria, are central to maintaining intestinal-microbiota homeostasis. Our recently published work has led to the hypothesis that, in mice, bacterial encroachment of the epithelium, as a consequence of an innate immune deficiency or ingestion of substances that alter host-microbiota interactions, promotes low-grade inflammation that can drive metabolic disease (1–2).

Aims & Methods: The aim of the current study was to study microbiota localization in human subjects with metabolic syndrome. Subjects were enrolled at the Veteran's Administration Hospital (Atlanta, GA, USA). A review of the patient medical record was conducted to determine control and diabetic patients, as shown by their glycosylated hemoglobin and fasted serum glucose levels. During the colonoscopy procedure, two mucosal biopsies were taken in the left colon approximately 40 cm from the anus using a regular forceps. The biopsies were immediately placed in Carnoy fixative and mucus immunostaining was paired with fluorescent in situ hybridization in order to analyze bacteria localization at the surface of the intestinal mucosa.

Result: We found that bacterial encroachment of the epithelium correlates with central features of metabolic syndrome in humans. Specifically, confocal microscopic analysis of biopsies from middle-aged persons revealed an inverse correlation between bacterial-epithelial distance and body mass index, fasting blood glucose, and hemoglobin A1C level. Ethnicity or antibiotic use did not significantly correlate with microbiota-epithelial distance.

Conclusion: These observations support the notion that microbiota promotion of low-grade inflammation may play a causative role in metabolic diseases in human. Those findings are important advances that will significantly impact our understanding of the epidemic of metabolic syndrome.

Disclosure of Interest: All authors have declared no conflicts of interest.

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Table 1. (OP241): The taxa numbers of IBS-P, IBS-N and HC in genus levels [M (Q1, Q3)]

Phylum	Genus	Taxa Numbers			
		IBS-P (n = 31)	IBS-N (n = 39)	HC (n = 20)	P
Actinobacteria	*Collinsella*	95(34, 146)b	21(2, 155)	47(19, 133)	<0.05
Bacteroidetes	*Prevotella_9*	726(9, 14813)a	17(1, 9272)	4(1, 5677)	NS
	Alistipes	434(131, 1064)b	155(13, 467)a	579(70, 849)	<0.05
	Barnesiella	35(0, 217)b	3(0, 45)	23(0, 142)	NS
	Butyricimonas	22(4, 80)b	5(0, 15)	9(0, 49)	<0.05
	Parabacteroides	242(152, 683)b	108(45, 245)a	225(145,538)	<0.05
	Paraprevotella	6(0, 312)a	1(0, 23)	0(0, 28)	<0.05
	Odoribacter	35(1, 88)b	5(0, 47)	33(1, 73)	NS
Firmicutes	*Faecalibacterium*	3387(1778, 6294)b	2174(449, 4175)	2860(1290, 4699)	NS
	Pseudobutyrivibrio	3524(1284, 5860)b	1245(269, 3360)	1911(1163, 3133)	<0.05
	Subdoligranulum	1101(621, 2182)b	544(77, 1666)	1245(316, 1962)	NS
	Lachnospiraceae_NK4A136	234(82, 672)b	85(22, 468)a	406(169, 1446)	<0.05
	Eubacterium_coprostanoligenes	197(46, 571)b	90(3, 197)	139(10, 810)	NS
	Ruminococcus_1	145(35, 523)b	7(1, 111)a	291(4, 436)	<0.05
	Eubacterium_hallii	313(132, 636)b	118(44, 367)	141(61, 620)	NS
	ChristensenellaceaeR-7	104(4, 209)b	5(1, 81)a	61(6, 357)	<0.05
	Enterococcus	7(3, 13)	11(4, 30)a	3(0, 16)	NS
	Family_XIII	18(2, 28)b	3(0, 16)a	15(4, 31)	<0.05
	Incertae_Sedis	156(54, 426)b	53(10, 267)	77(15, 515)	<0.05
	Lachnospiraceae_NC2004	25(7, 60)a	16(2, 37)	13(2, 28)	NS
	Lachnospiraceae	1020(595, 1971)b	598(289, 1131)	863(409, 2232)	<0.05
	Romboutsia	86(15, 201)b	156(46, 478)	127(40, 284)	NS
	Ruminococcaceae	968(337, 1803)b	321(85, 905)a	804(266, 1183)	<0.05
Proteobacteria	*Escherichia_Shigella*	49(31, 471)b	338(65, 1458)a	27(9, 216)	<0.05
	Klebsiella	43(4, 130)b	106(11, 494)	40(1, 172)	NS
	Raoultella	7(3, 11)a	11(4, 28)a	2(0, 9)	<0.05
	Sutterella	7(1, 136)	2(0, 57)a	50(4, 163)	NS

Indication: IBS-P, IBS with SIBO; IBS-N, IBS without SIBO; HC, health controls; NS, no significance; a, compared with HC, $p < 0.05$; b, compared with IBS-N, $p < 0.05$

OP241 CLINICAL FEATURES AND FECAL MICROBIOTA PROFILE IN IRRITABLE BOWEL SYNDROME PATIENTS WITH SMALL INTESTINAL BACTERIAL OVERGROWTH

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Introduction: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, but the relationship between diarrhea-predominant IBS (IBS-D) and small intestinal bacterial overgrowth (SIBO) is unclear.

Aims & Methods: We aimed to investigate the clinical features and fecal microbiota profiles of IBS-D patients with SIBO by hydrogen and methane lactulose breath test (LBT), and compare them with IBS-D patients without SIBO and healthy controls. IBS-D patients who met Rome II criteria were divided into IBS-D with SIBO (IBS-P) and without SIBO (IBS-N) by hydrogen and methane LBT, while healthy controls with negative LBT (HC) were recruited. All subjects underwent colonoscopy to exclude organic diseases, and barostat for visceral hypersensitivity, intestinal permeability test [lactulose (L), mannitol (M) and L/M in 6-hour urine], systematic inflammation severity (IL-10, IL-12 and IL-10/IL-12 in supernate of peripheral blood mononuclear cells), fecal short chain fatty acids(SCFA) evaluation, and fecal microbiota profiles analysis by Illumina MiSeq high throughput sequencing.

Result: 22 HC and 84 IBS-D patients were enrolled. 35 of patients were with SIBO (41.67%) and 49 patients were IBS-N. (1) The body mass index of IBS-P was lower than IBS-N [(21.61 ± 0.57) vs. (23.44 ± 0.54) kg/m^2, $P < 0.05$]. (2) The IL-12 was higher in IBS-N than IBS-P and HC [2306.24(927.85, 3168.88) vs. 1263.40(482.55, 1965.99)pg/mL, 2306.24(927.85, 3168.88) vs. 1087.04(884.53, 1740.47) pg/mL, $P < 0.05$, respectively]. (3) The L and M in IBS-P were higher than that in HC ($P > 0.05$), with similar L/M. While the L of IBS-N was higher than that in HC [2.85(1.35, 6.40)vs.1.47(0.97, 2.62) μg/mL, $P < 0.05$], with higher M and L/M($P > 0.05$). (4) The initial defecation threshold of IBS-P was lower than HC [16.00(12.00, 20.00) vs. 20.00(18.00, 28.00) mmHg, $P < 0.05$], while both thresholds for initial sensory and defecation in IBS-N were lower than HC [8.00(6.00, 12.00) vs. 12.00(8.00, 14.00) mmHg, 16.00(14.00, 18.00) vs. 20.00(18.00, 28.00) mmHg, $P < 0.05$]. (5) The fecal SCFA, include acetate, propionate, butyrate, isobutyrate and isovalerate in IBS-P were higher than that in HC, while valerate was lower. In IBS-N, the fecal propionate was higher than in HC [51.90(37.58, 70.82) vs. 35.26(30.48, 42.39) μmol/g, $P < 0.05$], while the other SCFA were lower compared with HC. (6) There were significant differences in Shnnon index and Simpson index between IBS-P and IBS-N [3.57(3.20, 3.70) vs. 3.22(2.75, 3.45), 0.051(0.068, 0.093) vs. 0.094(0.065, 0.140), $P < 0.05$, respectively]. (8) The microbiota abundance of IBS-P was different from IBS-N and HC (table 1). Besides, the fecal microbiota profile of IBS-P was more similar to HC than IBS-N, according to Pcoa and Hcluster tree-bar.

Conclusion: (1) According to Rome II criteria, approximately 41.67% IBS-D patients present SIBO, which can be better screened by hydrogen and methane LBT. (2) SIBO can cause malnutrition and worsen nutritional status. (3)The intestinal permeability, systemic inflammation and visceral hypersensitivity of IBS-P are better than IBS-N. (4) Differences are observed in fecal SCFA between IBS-P and IBS-N. (5) Both IBS-P and IBS-N are different from HC in microbiota abundance and community diversity, in which IBS-P is also different from IBS-N. As a consequence, IBS-P is different from IBS-N in many physiological parameters and fecal microbiota profile, so IBS-P may be just SIBO which should be screened before diagnosis of IBS-D according to Rome II criteria.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP242 FECAL MICROBIOTA TRANSPLANTATION FOR RECURRENT C. DIFFICILE INFECTION: ANALYSIS OF FACTORS ASSOCIATED WITH THE NEED FOR MULTIPLE FECAL INFUSIONS

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Introduction: Fecal microbiota transplantation (FMT) from healthy donors is considered a highly effective treatment against recurrent *Clostridium difficile* infection (rCDI). A single fecal infusion is usually sufficient to resolve symptoms and eradicate rCDI, but a subgroup of these patients need multiple infusions to cure the disease. In our previously published randomized controlled trial of FMT versus vancomycin for rCDI,[1] we observed that patients with pseudomembranous colitis (PMC) needed repeat fecal infusions to be cured; further reports confirmed our findings.[2] To date, however, neither PMC nor other factors have been clearly proven to be associated with the need for multiple FMT.

Aims & Methods: Therefore, our aim was to identify predictive factors for the need for repeated fecal infusions in a series of patients treated with FMT for rCDI. We identified prospectively and included in the analysis all patients treated with FMT by colonoscopy for rCDI in our Centre. Demographic, clinical, endoscopic, and follow-up data were collected. Repeat fecal infusions were administered if the patient recurred or failed to improve after first infusion. Gender, age, inpatient status, number or CDI recurrences (>3), poor/inadequate bowel preparation (according to Ottawa Scale), endoscopic evidence of colonic oedema, presence of PMC, use of external donors, infusion of frozen material, and infused grams of faeces were analysed as potential impact factors. Univariate associations between possible predictors and the need for repeated fecal infusions were investigated, using t-test for continuous variables and Fisher's chi-square for dychotomous variables. Multivariate associations between all candidate predictors and the need for repeated fecal infusions were investigated using logistic regression analysis. P-values of <0.05 were considered statistically significant.
Result: A total of 54 patients with rCDI (Males = 24; mean age = 71 years old, range = 29–94) received FMT from healthy donors by colonoscopy. Fifteen patients received multiple infusions, for a total of 81 procedures. Resolution of rCDI occurred in 52 of 54 patients (96%); of them, none experienced further recurrences after FMT. Univariate analysis showed that both poor/inadequate bowel preparation ($p = 0.024$) and PMC ($p < 0.001$) were significantly associated with the need of repeated fecal infusions; also colonic oedema was more common among patients who needed repeated FMT, albeit nonsignificantly ($p = 0.083$). On multivariate analysis, both the presence of PMC (OR = 2257; 95% CI = 25.17–>1000, $p = 0.014$) and poor/inadequate bowel preparation (OR = 64.80; 95% CI = 3.43–>1000, $p = 0.021$) were identified as significant predictors of the need of repeated infusions. Additionally, the need for repeated infusion was more common among patient who experienced a number or CDI recurrences higher than 3 than among those who did not, although without reaching statistical significance (OR = 26.80; 95% CI = 1.69–>1000; $p = 0.054$). The large confidence interval observed for most predictors could be explained presumably by the relatively low number of cases in our sample. Finally, the infusion of frozen material was significantly associated with lower need of multiple FMT (OR = 0.01; 95% CI = 0.0–>0.19, $p = 0.033$).
Conclusion: Among patients treated with FMT for rCDI, both PMC and poor/inadequate bowel preparation appear to be significant predictors of the need for repeated fecal infusions. Additionally, frozen FMT appears to be significantly associated with a decreased need of multiple FMT. As the small sample size represents a limitation of our analysis, our findings, although promising, should be confirmed by further, larger studies.
Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 14:00–15:30

ENDOSCOPIC TREATMENT OF COMPLICATIONS AFTER UPPER GI SURGERY – ROOM E2

OP243 ENDOSCOPIC BALLOON DILATION FOLLOWED BY STEROID INJECTION IN ANASTOMOTIC STRICTURES AFTER ESOPHAGECTOMY: A MULTICENTER RANDOMIZED, DOUBLE-BLIND CONTROLLED TRIAL

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Introduction: Esophageal cancer is the fifth most common cause of cancer-related death for men and the eighth for women worldwide. Although the effectiveness of chemotherapy or chemoradiotherapy for the treatment of esophageal cancer has been reported, esophagectomy remains the standard treatment to cure esophageal cancer. Anastomotic stricture, a major complication after esophagectomy, substantially decreases patients' quality of life, and requires treatment with multiple sessions of endoscopic balloon dilation (EBD).
Aims & Methods: We conducted a multicenter randomized controlled trial to evaluate the usefulness of administration of local steroid injections to prevent the recurrence of anastomotic stricture. Patients were randomized to receive either triamcinolone or placebo immediately after EBD. The primary endpoint was the number of dilations required to resolve the stricture. Secondary endpoints were restricture-free survival and adverse events. Restricture-free survival is defined as the number of days from randomization to performing EBD for any reason or death from any cause. Patients with a dysphagia symptom score of two or more after esophagectomy with anastomotic stricture confirmed by endoscopy were included. Patients and investigators were blinded to the type of agent injected. The syringe containing triamcinolone or placebo was prepared by nursing staff unconnected to the trial. Patients underwent EBD with a standard through-the-scope balloon dilator. The balloon was inflated with water, aiming for a luminal diameter of maximum 15 mm for 3 min. After EBD, a second endoscopist who was not involved in the follow-up evaluation of the patients performed the injections into the mucosal laceration. A total of 50 mg of triamcinolone acetonide (50 mg/5 mL; Bristol-Myers Squibb) or an identical volume of normal saline solution as a placebo was injected per single site using a 25-gauge needle. Neither the patient nor the treating physician knew which treatment was given. Esophagogastroduodenoscopy (EGD) was performed on demand whenever patients reported dysphagia. In patients without dysphagia, EGD was performed within 3 months after EBD to evaluate the stricture. EBD was performed when the stricture was confirmed. Stricture was defined as dysphagia to some solids (dysphagia score 2) and an inability to pass an endoscope of at least 9.2-mm diameter.
Result: Over a 4-year period, 68 patients met the inclusion criteria and were screened. Three patients declined to participate. Sixty-five consecutive patients were therefore recruited to the study and randomized: 33 to receive steroid and 32 to receive placebo. The median number of EBD sessions required to resolve stricture in the steroid group was 2 (range, 1–7), significantly smaller than the median of 4 EBD sessions (range, 1–29) required by the control group ($p < 0.001$). After 6 months of follow-up, 39% of patients who received steroid injections remained recurrence-free compared with 19% of those injected with saline ($p < 0.01$). There were no adverse events during follow-up.
Conclusion: Steroid injection showed promising results for the prevention of stricture recurrence in patients who underwent EBD for anastomotic stricture.
Disclosure of Interest: N. Hanaoka: The Japan Foundation for Research and Promotion of Endoscopy Grant
All other authors have declared no conflicts of interest.

OP244 THE "TUNNEL + CLIP" METHOD FACILITATES OESOPHAGEAL ESD PROCEDURES: A PROSPECTIVE, CONSECUTIVE BI-CENTRIC STUDY

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Introduction: ESD is the treatment of choice for superficial neoplasms of the oesophagus due to its oncological efficiency and the morbidity associated with the surgical alternative. ESD requires a high level of skill and is technically challenging and time consuming. Therefore, it is often reserved to experts. Combining the tunnel technique and the clip-line counter-traction may enable optimisation of oesophageal ESDs.
Aims & Methods: From January 2014 to April 2016 we performed a prospective bi-centre case series of consecutive "tunnel + clip" oesophageal ESDs. Four young operators (fewer than 50 ESDs and fewer than 5 oesophageal ESDs) performed consecutively the ESD using the tunnel + clip method: generation of a classic tunnel beneath the lesion followed by constant counter-traction thanks to a clip with line dropped at the oral side of the tunnel.
Results: Thirty-three lesions (14 SCC and 19 ADK/HGD complicating Barrett's oesophagus) were resected consecutively. En bloc, R0 and curative resection rates were 100% (33/33), 87.8% (29/33) and 75.8% (25/33), respectively. No perforation occurred. The mean speed of ESD was 22.3 mm^2/min for a mean lesion size of 61,6 mm. The clip provided considerable assistance in performing the procedure. No pathological damage caused by the clipping was reported.

n = 33		Mean	Min	Max
Age (years)		63,9,8	36	85
Male		22 (84.6%)		
Procedure duration (min)	131	25	350	
Large diameter (mm)	61.6	30	105	
Small diameter (mm)	44	20	78	
Surface (mm^2)	2418	471	6300	
Speed (mm^2/min)	22,3	7.0	79	
Circumference (%)	60.0%	30.0%	100%	
Monobloc resection	33 (100%)			
R0 resection	29 (87.8%)			
Curative resection	25 (75.8%)			
Periprocedural bleeding	14 (42.0%)			
Perforation	0 (0.0%)			
Post-procedural bleeding	2 (6%)			
Stenosis		5 (15.1%)		

(continued)

Continued

n = 33		Mean	Min	Max
Pathologic analysis				
	SCC	14 (42.4%)		
	ADK/DHG	19 (57.6%)		
Residual disease (3 months)	0 (0.0%)			

Discussion: First study of the strategy "tunnel + clip". Our en bloc and R0 resection rates confirmed the usefulness of this technique, despite the relative inexperience of the operators. Our resection results were similar to those reported in large series by international experts, including those in Japan and our absence of perforation highlighted the safety of this strategy.
Conclusion: The tunnel + clip method for oesophageal ESD is effective and safe, in particular for physicians with little experience. This strategy standardizes the ESD procedure for superficial oesophageal neoplasia and increases of the speed of dissection. Thus, it will help to widespread oesophageal ESD performed in Western countries.
Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 14:00–15:30

WHAT TO DO WITH SMALL COLORECTAL POLYPS? – ROOM F1

OP245 DEVELOPMENT AND VALIDATION OF A SIMPLE CLASSIFICATION SYSTEM FOR IN VIVO DIAGNOSIS OF COLORECTAL POLYPS USING THE NEWLY INTRODUCED BLUE LIGHT IMAGING (BLI)

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Introduction: BLI is a novel endoscopic imaging technique for enhancement of subtle mucosal and vascular details. The potential of this novel technology for in vivo diagnosis of colorectal polyps has yet to be established.
Aims & Methods: Primary study objective was to develop a simple classification for in vivo differentiation of hyperplasic and adenomatous colorectal lesions by using the novel BLI technology. Second study endpoint was to validate the classification among experienced and non-experienced users. In the first phase, the capacity of experienced endoscopists to predict the histology of colorectal polyps was assessed. In the second phase, a simplified classification was developed allowing histologic prediction. Thirdly, the validity of the classification was evaluated among inexperienced raters, including medical students and GI fellows. At least, a pilot clinical evaluation was performed during real-time colonoscopy.
Result: A simple classification system for differentiating hyperplasic and adenomatous colorectal lesions by using the novel introduced BLI technology was developed and validated. Diagnosis was made in 80% to 88% of polyps with high-confidence. Sensitivity and specificity ranged from 93% to 100% and 83% to 92%, respectively. During real-time colonoscopy, diagnosis was made with high-confidence in 88% of polyps with sensitivity of 96%, specificity of 92%, and accuracy of 95%. Positive and negative predictive values were 96% and 92%, respectively.
Conclusion: This is the first study evaluating the novel BLI technology for in vivo prediction of colorectal polyps. The proposed classification allowed for adequate in vivo diagnosis of hyperplastic and adenomatous lesions. Further prospective multicenter trials should now confirm these preliminary results.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP246 MANAGEMENT OF DIMINUTIVE, RECTOSIGMOID POLYPS BY USING COMPUTER-AIDED DIAGNOSTIC SYSTEM

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Introduction: The PIVI initiatives propose that a "leave in place" approach is acceptable for a diminutive (≤5 mm), rectosigmoid hyperplastic polyp when endoscopist's optical diagnosis provides over 90% negative predictive value (NPV) for adenomas in high confidence predictions [1]; however, expertise is required to achieve a high accuracy and some studies conducted in community-based hospitals have been disappointing [2]. Recently, we have reported the usefulness of computer-aided diagnosis (CAD) in supporting endoscopists' decision making during colonoscopy [3,4]. The present study was aimed to validate the efficacy of the latest CAD model for endocytoscopy (380-fold ultra-magnifying endoscopy) in management of diminutive, rectosigmoid polyps.
Aims & Methods: The present study was aimed to validate the efficacy of the latest CAD model for endocytoscopy (380-fold ultra magnifying endoscopy) in management of diminutive, rectosigmoid polyps. The CAD for endocytoscopy comprises image acquisition, nuclear segmentation, feature extraction, and classification into three pathological groups (non-neoplastic, adenoma, and invasive cancer). The classification algorithm was programmed based on 296 features of each image (e.g., area, circularity, diameter, and perimeter of nuclei, and over 250 variables calculated by texture analysis of a whole image). We used a support vector machine to help classify these many features; 6051 endocytoscopic images were used for machine learning in the process of construction of the model. In order to validate this CAD model, the pilot study using a test set was undertaken between August and November 2015. The test set comprised endocytoscopic images of 65 diminutive, rectosigmoid polyps from the database of Showa University Northern Yokohama Hospital. Each image was automatically allocated to the CAD, and the predicted pathology was immediately output by the CAD in 0.2 seconds. The main outcome measure was NPV of the CAD for adenomatous histology for diminutive, rectosigmoid colon polyps when they had been diagnosed with high confidence.
Result: Of the 65 diminutive rectosigmoid polyps (mean size, 3.6 + −1.0 mm), the CAD diagnosed 55 (19 neoplastic and 36 non-neoplastic) with high confidence. Details of the diagnostic performance by the CAD for these 55 polyps were shown in the Table. The CAD correctly predicted neoplastic histology in 18 of the 20 neoplastic polyps (positive predictive value of 90% [95% CI, 68–99]) and non-neoplastic histology in 34 of the 35 non-neoplastic polyps (NPV of 97% [95% CI, 85–100]). This performance of the CAD met the "leave in situ" criteria proposed by the PIVI initiative.

Table: Details of the diagnostic performance by the CAD

	neoplastic in pathology	non-neoplastic in pathology
Diagnosis of neoplastic by CAD	18	2
Diagnosis of non-neoplastic by CAD	1	34

Conclusion: The CAD applying endocytoscopy can be a powerful and quick support tool in management of diminutive, rectosigmoid polyps.
Disclosure of Interest: K. Mori: Cybernet System Corp.
All other authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 14:00–15:30

BIOMARKERS IN IBD – ROOM K

OP247 IBDOC – FIRST SMARTPHONE BASED CALPROTECTIN HOME TEST – 18 MONTHS EXPERIENCE

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Introduction: Inflammatory Bowel Disease (IBD) is a chronic inflammation of the gut presenting with phases of active inflammation, remission and relapses. IBD treatment goals are mucosal healing and persistent remission. Calprotectin measured in patients' stool samples is a well-established biomarker to measure the inflammatory activity in the gut. Periodical assessment of calprotectin levels is important to measure effectiveness of the treatment as well as predicting relapses. Until now this meant that patients send in their stool sample for laboratory analysis, leading to long delays between sample collection, final test result and potential adaptations of therapies.
Aims & Methods: We have developed a smartphone-based calprotectin home test, called IBDoc®, that allows real-time information about the inflammatory activities in the gut for both, the patient and the health care provider. The IBDoc® consists of a stool collection and extraction device (CALEX® Valve) and an immunochromatographic calprotectin rapid test, which is measured using a smartphone App (CalApp®), controlling the phone's camera. Once the test is

measured the result is instantly sent to a webserver (IBDoc® Portal) allowing the treating physician immediate access to the test result. IBDoc® has achieved CE/IVD mark for self-testing in March 2015 and has since then been in routine use by patients throughout Europe and overseas. We have gathered data concerning technical performance of the device in the hands of both professional and lay users as well as usability aspects for patients.
Result: In a direct method comparison with an existing point-of-care test (Quantum Blue®) and a laboratory based ELISA method (BÜHLMANN fCAL® ELISA) IBDoc® correlated very well with both methods with a mean bias below 10%. In regard to repeatability and precisions the smartphones as measuring devices alone showed a coefficient of variability of below 10%, while the entire method including pre-analytical steps showed a coefficient of variability between 16% and 24%. IBDoc® displays results as Normal/green (below 100 µg/g mean bias at cut-off, –7.0 to 5.4%), Moderate/amber (100–300 µg/g) and as High/red (above 300 µg/g, mean bias at cut-off, 1.1–6.5%). No false positive or false negative results (Normal/green instead of High/red and vice versa) were observed when lay-users performing the test were compared to professional users. There was a 97% within-class agreement observed. Patients judged the entire IBDoc® system as extremely user friendly with a mean of 93 points (out of 100) on a standardized System Usability Scale (SUS) score[1,2,3].
Conclusion: IBDoc® is the first Calprotectin Home Test available for patients. IBDoc® is well accepted by patients and health care providers and correlates well to existing calprotectin point-of-care and laboratory based methods and has proven to be a supportive tool in daily clinical routine.
Disclosure of Interest: C. Reinhard: Christian Reinhard is an employee of BÜHLMANN Laboratories AG
A. Ritz: Alicja Ritz is an employee of BÜHLMANN Laboratories AG
M. Überschlag: Marie-Eve Überschlag is an employee of BÜHLMANN Laboratories AG
J. Weber: Jakob Weber is an employee of BÜHLMANN Laboratories AG
All other authors have declared no conflicts of interest.

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OP248 A COMBINATION OF THE MONITOR IBD AT HOME QUESTIONNAIRE AND A CALPROTECTIN HOME TEST AS EXCELLENT SCREENING TOOL FOR MUCOSAL INFLAMMATION IN IBD PATIENTS

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Introduction: Telemedicine programmes are of interest for inflammatory bowel diseases (IBD), but should include adequate monitoring of mucosal inflammation to prevent long-term complications. Different clinical activity questionnaires are available, however, none are patient-reported, clear and easy to fill out and validated against endoscopy. For this reason we previously developed the Monitor IBD At Home questionnaire (MIAH) (1). The score does not include laboratory tests or physical examination. The objective of this study was to investigate whether a combination of the MIAH questionnaire and a calprotectin home test yields higher diagnostic accuracy.
Aims & Methods: Between September 2015 and April 2016 all consecutive IBD patients with a scheduled endoscopy in the Maastricht University Medical Centre+ were eligible for inclusion. Patients with an ileostomy, colostomy, ileoanal pouch anastomosis or ileorectal anastomosis were excluded. Patients were invited to fill out the 5-item MIAH-UC questionnaire for UC, regarding blood loss, number of stools, urgency, abdominal pain and general well-being, or the 6-item MIAH-CD questionnaire for CD, including questions on blood loss, mucus, number of stools, urgency, fatigue and general well-being. In addition, patients were asked to collect a stool sample prior to bowel cleansing. Fecal calprotectin was determined with a calprotectin home test. Mucosal inflammation was assessed with the simple endoscopic activity score (SES-CD) for Crohn's disease (CD) and the Mayo endoscopic subscore (MES) for ulcerative colitis (UC). Sensitivity, specificity, positive predictive value (PPV) and negative predicted value (NPV) of the MIAH-UC and MIAH-CD in combination with the calprotectin home test were calculated.
Result: Thirty-two CD patients (50.0% male, mean age 51.4 ± 15.2 years, 43.8% active disease) and 28 UC patients (50.0% male, mean age 57.3 ± 10.4 years, 39.3% active disease) were included. The combination of the MIAH-CD and the calprotectin home test showed a sensitivity of 100.0%, a specificity of 61.1%, a NPV of 100.0% and a PPV of 67.0%. The combination of the MIAH-UC and the calprotectin home test yielded a sensitivity of 91.7%, a specificity of 68.8%, a NPV of 91.7% and a PPV of 68.8%.
Conclusion: The MIAH is the first patient-reported questionnaire developed to predict endoscopic inflammation in IBD patients. A combination of this questionnaire and a calprotectin home test shows a high sensitivity and thus excellent diagnostic accuracy for use in telemedicine programmes to screen for patients who need further assessment of disease activity with biochemical markers, imaging or endoscopy.
Disclosure of Interest: M.J. de Jong: Non financial support Immundiagnostik
All other authors have declared no conflicts of interest.

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OP249 ACCURACY OF NON-INVASIVE TESTS IN THE INITIAL DIAGNOSTIC WORK-UP OF PEDIATRIC INFLAMMATORY BOWEL DISEASES

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Introduction: Upper and lower endoscopy with histology together with imaging of the small bowel is the gold standard for the diagnosis of inflammatory bowel disease (IBD) in children. Due to high costs and invasive nature of these techniques, accurate selection of patients is mandatory.
Aims & Methods: We aimed to assess the accuracy of non-invasive tests including fecal calprotectin (FC), blood inflammatory markers (BIM) and bowel ultrasound (US) alone or in combination as first level investigations in children with suspected IBD. Consecutive patients referred to our Unit for a clinical history compatible with IBD were enrolled during a 3-year period. All underwent FC (Calprest®, Eurospital), C-reactive protein [CRP], erythrocyte sedimentation rate [ESR] and bowel US as first investigations. Endoscopy with biopsies was the gold standard for diagnosis. At US pathological findings were: BWT > 3 mm, BW vascularity, loss of stratification, enlarged mesenteric nodes. Multiple logistic analysis with stepwise method considering IBD diagnosis as dependent variable was conducted. Sensitivity (SE), specificity (SP), positive and negative predictive values (PPV and NPV) of laboratory and US parameters alone or in combination were analyzed according to the final diagnosis.
Result: 100 patients (58 males, median age 12) were enrolled. The final diagnosis was IBD in 69 (57 CD, 12 CU) other than IBD in 31. The mean values of CRP, ESR, FC and BWT were higher in IBD vs non-IBD patients ($p < 0.001$). Multiple logistic analysis showed that independent variables predictive of IBD were: FC (OR 44.8; $p < 0.01$), BWT (OR 20.4, $p < 0.001$) and ESR (OR 9; $p < 0.05$). The combination of 3 or 2 parameters was more frequent in IBD patients ($p < 0.01$). Table 2 shows SE, SP, PPV, NPV of these parameters alone or in combination.

Parameters	SE %	SP %	PPV %	NPV %
FC (ug/g)	94	89	94	89
ESR (mm/h)	75	89	93	65
BWT (mm) >3 mm	94	83	88	57
2 (at least 2 of 3)	96	84	97	92
2 (FC + BWT)	91	100	100	86
3 (FC + BWT + ESR)	71	100	100	64

Conclusion: the combination of FC, BIM and bowel US may help to select children needing further invasive procedures and allow to avoid or delay endoscopy in patients with negative initial diagnostic work-up.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP250 THE SEROLOGIC MARKERS ASCA AND PANCA SHOW BETTER PREDICTABILITY THAN CRP, ESR AND CALPROTECTIN FOR ANTI- TNF TREATMENT AMONG PEDIATRIC IBD PATIENTS

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Introduction: Serologic nuclear and anti microbial antibodies have been recognized as predictive markers of disease course and complications in ulcerative colitis (UC) and Crohn's disease (CD). The significance of serological markers from onset of the disease, their ability to predict disease outcome and their stability over time is not fully explored in IBD patients.
Aims & Methods: To study the prevalence of serological markers in treatment-naïve pediatric patients with newly diagnosed inflammatory bowel disease and prospectively evaluate the antibody and titer-variations related to disease subgroups, treatments and disease course. We also wanted to compare the value of

serological markers with the biochemical markers C-reactive protein (CRP), elevated sedimentation rate (ESR) and fecal calprotectin. Patients aged < 18 years, (n = 58) diagnosed with IBD were included between 2005–2007 as a part of a prospective population based study in South-Eastern Norway (IBSEN- II). Fecal samples were analyzed for calprotectin (Bühlmann, Basel, Switzerland) and blood specimens were analyzed for antibodies (Prometheus labs, San Diego), CRP and ESR at diagnosis and after 1–2 years of treatment. Treatment was decided at the courtesy of the treating pediatrician. Tumor necrosis factor (TNF) blocker treatment was regarded as aggressive treatment compared to treatment with immunomodulators.

Result: Among the UC patients, 13 (72%) were perinuclear anti-neutrophil cytoplasmic antibody (pANCA) positive, versus 13 (35%) of the CD patients. None of the UC patients harbored anti–Saccharomyces cerevisiae (ASCA) antibodies, whereas 20 (54%) of CD patients were ASCA IgA or IgG positive ($p < 0.0001$), 18 (49%) were positive for ASCA IgA, 14 (38%) for ASCA IgG, and 12 (33%) for both. There were no statistically significant differences between CD and UC patients in the prevalence of antibodies against *Pseudomonas fluorescens* associated sequence (I2) (41% vs. 33%), the outer membrane porin of *Escherichia coli* (OmpC) (8% vs. 6%) or flagellin expressed by Clostridial phylum (CBir) (22% vs. 0%, respectively). The 18 (49%) CD patients who received aggressive therapy with TNF blockers had higher presence of antibodies against ASCA IgA ($p = 0.05$) and ASCA IgG ($p = 0.045$) as well as higher titers of ASCA IgG ($p = 0.046$) compared to the 19 (51%) CD patients who received conventional treatment. If ASCA antibodies were present at baseline the probability of receiving infliximab treatment in CD patients was 70%, with OR 8.8 (2.0–37.7), $p = 0.004$. The presence of pANCA antibodies was less frequent at diagnosis in TNF blocker treated CD patients compared to conventionally treated CD patients. The OR of receiving aggressive therapy being pANCA negative was 5.2 (1.11–24.13), $p = 0.02$. CD patients who were given infliximab had significantly higher levels of fecal calprotectin, CRP and ESR at diagnosis compared to conventionally treated CD patients with median values of fecal calprotectin (mg/kg) 1506 vs. 501 ($p = 0.01$), CRP (mg/l) 28 vs. 7.5 ($p = 0.02$) and ESR (mm/h) of 32 vs. 18 ($p = 0.01$) respectively. Being pANCA negative and/ or ASCA IgA or ASCA IgG positive was associated with the need for TNF blocker therapy, even after adjustment for CRP, ESR and fecal calprotectin levels. After treatment there was no difference in antibody prevalence for ASCA IgA, ASCA IgG, I2, OmpC or CBir in the CD and UC patients, regardless of treatment modality. Fewer UC patients, 9 (64%), tested positive for pANCA after treatment, compared to at baseline, 13 (72%), $p = 0.013$. Only one of the 18 UC patients received TNF blocker treatment.

Conclusion: ASCA and pANCA status was associated with the need for early aggressive therapy with TNF blockers in our CD patients. We found that being pANCA negative and/ or ASCA IgA or ASCA IgG positive were more predictive of needing aggressive treatment than CRP, ESP or fecal calprotectin levels. ASCA serology was stable, regardless of treatment modality, and might be a prognostic tool at any time in the disease course.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP251 INTRA- AND INTER-VARIABILITY OF FECAL CALPROTECTIN IN INFLAMMATORY BOWEL DISEASE PATIENTS: A PROSPECTIVE OBSERVATIONAL CASE-CONTROL STUDY

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Introduction: Fecal Calprotectin (FC), a calcium binding protein in neutrophils, indirectly reflects intestinal inflammation and is today widely used in the management of inflammatory bowel disease (IBD) patients. FC values appears to vary according to disease type, activity and location. FC seems more sensitive in assessing disease activity in ulcerative colitis (UC) than in Crohn's disease (CD). Several factors may affect FC values. However, few studies have looked at the intra- and inter-variability of FC in IBD patients.

Aims & Methods: We aimed to assess the robustness of using a single stool punch for the measurement of FC and prospectively evaluated the intra- and inter-variability of FC in a cohort of IBD and irritable bowel syndrome (IBS) patients. 72 IBD patients (49 CD and 23 UC) and a control group of 7 IBS patients were enrolled. Disease location and disease activity were determined using endoscopic and clinical activity scores (Crohn's disease activity index and Harvey–Bradshaw score in CD and Mayo score in UC), as well as C-reactive protein levels. Stool samples were collected twice (within 1 to 5 days interval) in 62 patients and FC was measured on both punches (100 mg stool per punch) and homogenates (5–8 g per stool) by fluorometric enzyme immunocapture assay (ELiA Calprotectin, ThermoFischer). Intra-stool FC variability defined as the variability between 3 punches in the same stool sample and intra-individual FC variability defined as the variability between 2 stool samples of the same patient a few days apart were both examined. Intra-stool variability was assessed by measuring the coefficient of variation (CV) between the 3 punches of a stool sample. Inter-variability of FC was also measured.

Result: Inter-variability is reported in Figure according to disease type, location and activity. The highest FC values were found in active UC patients while IBS and quiescent ileal CD patients had the lowest ($p < 0.05$). Colonic location just as active disease seemed to affect FC values, as it has already been described. Nevertheless, these results were not significant probably due to small sample size. Concerning intra-stool variability, the average CV between the punches was 32%, showing a wide intra-stool variability. The largest CV were observed for low FC measurements (< 50µg/g). However, this resulted in clinical significance for only 7 IBD patients (9,70%) or 3 IBD patients (4,20%) when using a FC cut-off of respectively 50 µg/g or 250 µg/g. A significant correlation was demonstrated between FC measurements of 2 stool samples at 1–5 days intervals in 62 patients with correlation coefficient of 0.78 ($p < 0.0001$). Statistical analysis (T-test) could not show difference between the 2 stool samples ($p > 0,05$).

Conclusion: These results suggest that there are variations in FC values within the same stool but with little clinical significance in IBD patients. Thus, a single stool punch appears to be reliable for FC measurement. This study confirms that disease type, location and activity influence the inter-individual FC variability, while intra-stool and intra-individual FC variability, regardless of disease activity, remains low.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP252 ANALYTICAL PERFORMANCE OF A NEW IPHONE-BASED PATIENT MONITORING SYSTEM COMPARABLE TO ELISA FOR MEASURING FECAL CALPROTECTIN IN IBD PATIENTS

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Introduction: Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory disorder presenting with phases of active inflammation, remission and relapse. Fecal calprotectin (fcalpro) measurement has become established for the monitoring of inflammation activity. Periodical assessment of fcalpro levels has been demonstrated to be an important non-invasive indicator of treatment efficacy and predictor of relapse. However, until now, fcalpro determination required patients to send stool samples in for laboratory analysis, resulting in a long delay between sample collection and final test results. We developed a simple home-based calprotectin test system called QuantOnCal to allow patients to regularly monitor their own inflammatory status by testing fcalpro levels in the comfort of their own home.

Aims & Methods: QuantOnCal consists of a stool extraction device (IDK® Extract) and an immunochromatographic rapid test performed by an iPhone App via the phone camera. Results are automatically sent to a webserver (QuantOnCal website), where they are displayed for monitoring by the consulting physician or IBD nurse. The objective of this study was to validate the QuantOnCal test system by comparing its quantitative performance with a standard ELISA-based method. Stool samples from 157 IBD and non-IBD patients containing various levels of calprotectin (95 IBD: CU/CD/active/remission, 42/43/48/47; 33 IBS: 23 Chm: 6 Div) were either loaded onto immunochromatographic test cassettes (TCs) or analysed with a commercial ELISA test (Immundiagnostik, Bensheim, Germany). The QuantOnCal app was installed on 4 different iPhone models (iPhones 4, 4s, 5c, 6). Agreement between QuantOnCal testing versus ELISA was assessed by Analyse-it for Microsoft Excel.

Result: The QuantOnCal system produces a quantitative test result between 25–2000 mg/g fcalpro/g of stool, covering the clinically relevant range of this biomarker. The total agreement (TA) was 94.6% with 0% false positive and 0% false negative rates. The TA for fcalpro between the 4 different iPhone models was 91.3%.

Conclusion: QuantOnCal is a new, complete and validated test system which allows the IBD patient to monitor and follow his inflammatory status by measuring the IBD biomarker, faecal calprotectin, using his/her own smartphone. The performance of the QuantOnCal test system was shown to be comparable to the professional, ELISA-based method.

Abbreviations IBD, inflammatory bowel disease; Chm, Carbohydrate malabsorption; CU, colitis ulcerosa; CD, Crohńs disease; Div, Diverticulitis; IBS, irritable bowel syndrome; TA, total agreement

Disclosure of Interest: K.F. Wintgens: Karl Florian Wintgens is an employee of Immundiagnostik AG, Bensheim, Germany
J. Stein: Jürgen Stein has received payment for lectures and consultancy from Immundiagnostik AG, Bensheim, Germany
All other authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 14:00–15:30
CLINICAL TRIALS IN FUNCTIONAL GI DISORDERS – ROOM M

OP253 RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF BIOFEEDBACK FOR THE TREATMENT OF ABDOMINAL DISTENSION

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Introduction: Abdominal distension is the most bothersome complaint in patients with functional gut disorders and has no effective treatment. In a previous study we showed that abdominal distension is produced by diaphragmatic contraction and descent with protrusion of the anterior abdominal wall, and we developed an original biofeedback technique 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 abdominal distension. We performed a randomized, placebo controlled in a referral center (Clinical Trials Gov Registration Number 01205100). Forty-eight consecutive patients complaining of episodes of visible abdominal distension who fulfilled the Rome III criteria for functional intestinal disorders (47 women, 1 men; 21–74 yr age range) were recruited and randomly allocated to biofeedback and placebo treatment. Abdomino-thoracic muscle activity was recorded by EMG during basal conditions (no distension) and during an episode of distension to prove the abdomino-phrenic origin of their distension. Each patient underwent three treatment sessions over a 10-day period. In each session abdomino-thoracic muscle activity was recorded by electromyography. The patients in the biofeedback group were shown the signal and instructed to control muscle activity; the patients in the control group were given and oral placebo. The main outcome was subjective sensation of abdominal distension scored by a 0–6 graphic rating scale daily for 10 days before and after treatment
Results: Patients on biofeedback, but not on placebo, effectively learned to reduce intercostal activity (by $45 \pm 3\%$ vs $5 \pm 2\%$ on placebo; $p < 0.001$) and to increase anterior wall muscle activity (by $101 \pm 10\%$ vs $-4 \pm 2\%$). Biofeedback treatment resulted in a $56\% \pm 1\%$ reduction of abdominal distension (from 4.6 ± 0.2 to 2.0 ± 0.2 score after intervention) vs $13 \pm 8\%$ on placebo; $p < 0.001$ (from 4.7 ± 0.1 to 4.1 ± 0.4 score after intervention).
Conclusion: Abdominal distension can be effectively corrected by biofeedback-guided control of abdomino-thoracic muscular activity.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP254 LOW FODMAP DIET ALTERS SYMPTOMS, MICROBIOTA, SHORT-CHAIN FATTY ACIDS AND CYTOKINE PROFILES IN PATIENTS WITH IBS: A RANDOMIZED CONTROLLED TRIAL

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Introduction: Irritable bowel syndrome (IBS) is the most common gastrointestinal (GI) disorder worldwide. In the lack of cures, different management strategies have been purposed, including a diet low in FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols). Although being increasingly accepted and recommended as one of the most effective therapies, there is insufficient high-quality evidence of its efficacy as well as uncertainties regarding long-term consequences on gut microbiota composition and function.
Aims & Methods: In the present study we aimed to investigate the effect of a low versus high FODMAP diet on symptoms, gut microbiota, short-chain fatty acids (SCFAs) and pro-inflammatory cytokine profiles in a randomized, double-blinded, crossover trial of Norwegian patients with IBS. Twenty patients with IBS (15 female/5 male, mean age 34.6 y) were instructed to follow a low FODMAP diet (LFD) throughout a study period of 9 weeks. After 3 weeks they were randomized and double-blindly assigned to receive a daily supplement of either high (16 g fructo-oligosaccharides (FOS)) or low (16 g maltodextrin (=placebo)) FODMAP for the next 10 days, followed by a 3-week washout before crossing-over to the alternative supplementation for 10 new days. IBS Severity Scoring System (IBS-SSS) was used to evaluate symptoms. Blood samples were collected to analyse serum cytokines (IL-6, IL-8, TNF-α), and faeces samples for gut microbiota (s16r RNA) and SCFAs.
Result: IBS symptoms consistently and significantly improved after 3 weeks of LFD, with a mean overall reduction of 163.8 points ($p < 0.0001$). On average, 4 of 5 symptoms were significantly worsened in response to FOS compared with placebo, with an overall difference of 65.1 points ($p = 0.014$). Serum levels of IL-6 and IL-8, but not TNF-α, significantly decreased on the LFD ($p = 0.001$ and $p < 0.0001$, respectively). The same did apply to luminal *Faecalibacterium prausnitzii* and *Bifidobacterium* ($p = 0.0084$ and $p = 0.0094$, respectively). Levels of total SCFAs and butyric acid were also significantly decreased on the LFD ($p = 0.04$ and $p = 0.01$, respectively). Ten days of FOS supplementation normalized the level of bacteria, but did not change the levels of cytokines nor SCFAs.
Conclusion: FODMAP content was related to IBS symptoms, cytokine levels and microbiota composition and function. Our results provide evidence to support the efficacy of a LFD in reducing functional GI symptoms. Further studies are warranted to explore the link between FODMAPs, gut microbiota and immune activation.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP255 PREDICTORS FOR THE OUTCOME OF THE FODMAP DIET IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL DISORDERS

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Introduction: The reduction of poorly fermentable carbohydrates collectively termed FODMAPs (fermentable oligo-, di-, monosaccharides and polyols) is increasingly being advocated in patients with functional gastrointestinal disorders (FGID). At present, selection criteria or response predictors for dietary intervention are poorly defined.
Aims & Methods: In this study the predictive associations between clinical characteristics, breath test results and the global outcome measure advocated in FGID were examined. Clinical characteristics and breath test results from 580 successive patients presenting to our clinic with FGID (Rome III) and fructose or lactose intolerance, and completing a standardized FODMAP dietary program were analyzed. Intolerance was defined by a positive symptom index and malabsorption by increases in H2 (>20 ppm) or CH4 (>10 ppm) values during breath testing. The response to the dietary program was assessed using a standard adequate global symptom relief question. Predictive associations were assessed by uni- and multivariate analyses.
Result: Adequate symptom relief was achieved in 81% of the 580 FGID patients, with similar response rates in patients with fructose (82%) or lactose (79%) intolerances and across all FGID subtypes (IBS-diarrhea: 80%, IBS-constipation: 71%, IBS-mixed: 89%, FD: 79%). A positive history of chronic diarrhea or pruritus predicted adequate symptom relief with the FODMAP diet (univariate analysis OR (95% CI): 2.96 (1.83–4.79) and 2.50 (1.27–4.92), respectively, both $p < 0.01$), while nausea predicted inadequate relief (0.55 (0.34–0.89), $p = 0.01$). Multivariate analysis confirmed the associations between adequate symptom relief and a history of diarrhea (positive predictor: 2.74 (1.52–4.94, $p = 0.001$) and nausea (negative predictor: 0.45 (0.25–0.81), $p = 0.07$). There were no significant associations between the H2 or CH4 breath concentrations and the attainment of adequate relief. A positive dietary response in patients with fructose intolerance was associated with the development of diarrhea during breath testing (univariate analysis 1.7 (1.03–2.81, $p = 0.04$). No other significant associations between symptoms experienced during fructose or lactose breath testing and dietary outcome were demonstrated.
Conclusion: Adequate global symptom relief with a FODMAP diet is achieved in a large majority of all FGID patients with fructose or lactose intolerance, and is predicted by a few clinical and breath-test associated symptoms and not by the presence of malabsorption. Consequently, a reduction of FODMAPs appears to modulate multiple physiological processes across the spectrum of FGIDs. Furthermore, adequate relief likely reflects a complex constellation of psychological and physical factors, rather than a reduction in individual symptoms, explaining the few significant associations with clinical or provoked symptoms.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP256 A RANDOMIZED TRIPLE BLIND CONTROLLED TRIAL ASSESSING THE EFFECTS OF DOXEPIN AND NORTRIPTYLINE ON DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME

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Introduction: Tricyclic antidepressants tend to be constipating and, therefore, may be of most benefit in diarrhea-predominant IBS (IBS-D). The aim of this study was to compare the effects of low doses of doxepin and nortriptyline on IBS-D.
Aims & Methods: Seventy-five patients with IBS according to Rome III criteria were treated for two months. All possible organic diseases responsible for bowel symptoms were excluded. The patients were randomly assigned to one of three groups treated with doxepin(10 mg), nortriptyline(10 mg) or placebo. Subjects were assessed clinically weekly. The symptoms and adverse effects of the drugs were recorded in the questionnaire. The primary outcome was the responder rate for treatment at the end of treatment.

Result: Abdominal pain and bloating were the most common symptoms before initiation of treatment, occurring in 62 (82.7%) patients. The frequency of the symptoms was decreased significantly after treatment in doxepin and nortriptyline groups compared with pre-treatment. The responder rate was 80%, 52%, and 36% for doxepin, nortriptyline, and placebo groups, respectively($p = 0.007$). The responder rate for doxepin group was superior to nortriptyline and placebo groups($p = 0.037$ and $p = 0.002$, respectively) but there was no significant difference in responder rates of nortriptyline and placebo groups($p = 0.254$). There were no significant differences in improvement rates in individual symptoms between doxepin and nortriptyline groups(all $p > 0.05$).
Conclusion: Treatment of diarrhea-predominant IBS with low dose of doxepin or nortriptyline could be effective. Improvement rates of the symptoms are similar in doxepin and nortriptyline groups but doxepin has a better response rate than nortriptyline.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP257 TREATMENT OF IRRITABLE BOWEL SYNDROME WITH FECAL MICROBIOTA TRANSPLANTATION: A CASE SERIES OF 10 PATIENTS

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Introduction: Irritable bowel syndrome (IBS) is commonly diagnosed gastrointestinal disease worldwide. The pathogenesis of IBS cannot be explained by a simple mechanism, but alterations in the intestinal microbiome are increasingly a focus of interest. Traditional treatments of IBS, including psychological therapies, dietary change, probiotics, have had only limited success, underscoring the need for additional therapeutic options. We hypothesized that fecal microbiota transplantation (FMT) may be beneficial in managing IBS by restoring the intestinal homeostasis. The purpose of this study is to prospectively examine the symptomatic response of FMT in patient with moderate IBS.
Aims & Methods: Patients with IBS who were not responsive to traditional treatment were enrolled prospectively in this study. Diagnosis of IBS was based on Rome III Criteria and nonresponsive IBS was defined as failure to achieve symptomatic relief with traditional therapeutic modalities. The healthy donors from patient's family were screened and tested for infectious diseases before FMT. Patients were questioned with IBS severity score before and 1 month and 3 month after FMT. IBS severity score consist of 5 questions. Total score is 500. As the score is lower, their general condition is considered to be better. Study outcomes included the length of symptom-free intervals, abdominal pain, bloating, flatus, dyspepsia, frequency of bowel movements, and overall well-being before and after FMT.
Result: A total of 10 patients (mean age of 55 years; 60% male) were identified and completed the study questionnaire. Mean time from initial diagnosis of IBS until FMT was 3.6 years. In our study, 80% of the patients experienced resolution or improvement of symptoms after FMT. There were no long-term side effects, and none of the participants developed any new diseases. Clinically significant improvements in IBS severity scores were observed one month after FMT (132 ± 100) comparing to baseline (252 ± 121.7) ($p = 0.027$). However, their symptoms tended to return to their pre-FMT state at 3 month after FMT (231 ± 110).
Conclusion: This study showed that FMT may be helpful for one month. However, their effect seemed to decrease over time. FMT may be used as an adjuvant therapy with standard medication for managing IBS. Further large prospective population study is needed.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP258 1-MONTH TREATMENT WITH ELUXADOLINE FOR IBS-D PREDICTS SUSTAINED RESPONSE: CONTINUATION ANALYSES OF RESPONSE IN TWO PHASE 3 STUDIES

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Introduction: Eluxadoline (ELX), a mixed μ-opioid receptor (OR) and κ-OR agonist and δ-OR antagonist that is locally active in the gastrointestinal tract, is approved for the treatment of irritable bowel syndrome with diarrhoea (IBS-D) in adults. In two Phase 3 studies, ELX significantly improved symptoms of IBS-D based on a composite endpoint, defined by simultaneous improvement in stool consistency and reduction in abdominal pain scores, and the historical 'adequate relief' endpoint. Given the potential long-term use of eluxadoline treatment, it is important to understand the time course of clinical benefits as experienced by patients and clinicians, including time to onset and the sustainability over time, to establish reasonable expectations about the effectiveness of treatment.
Aims & Methods: The efficacy of ELX over longer treatment intervals was evaluated in patients who were responders or non-responders for the composite endpoint or adequate relief endpoint over the first month of treatment in the Phase 3 studies. Two double-blind, placebo-controlled, Phase 3 clinical trials (IBS-3001 and IBS-3002) randomised patients meeting Rome III criteria for IBS-D to twice-daily treatment with ELX (75 or 100 mg) or placebo. Patients rated IBS symptoms daily, including worst abdominal pain (WAP; 0–10 scale) and stool consistency (Bristol Stool Scale [BSS]). The primary efficacy endpoint was composite response, based on simultaneous daily improvement of ≥30% in WAP score vs. baseline and BSS score <5, with ≥50% of days demonstrating a response, evaluated over 12 and 26 weeks. Composite endpoint response rates over Weeks 1–12 and 1–26 were calculated for patients who were responders and non-responders over Month 1 (Weeks 1–4) using a pooled analysis of the intent-to-treat (ITT) population. Comparable analyses for adequate relief were conducted, for which a responder was defined as reporting a "yes" response to the question "Over the past week have you had adequate relief of your IBS symptoms?" for ≥50% of weeks in the treatment interval.
Result: The pooled ITT analysis set included 2423 patients with IBS-D. Over Month 1, 12.5% (101/809), 22.8% (184/808), and 24.6% (198/806) of patients were composite responders in the placebo, ELX 75 mg, and ELX 100 mg groups, respectively. Over Month 1, 49.3% (399/809), 59.9% (484/808), and 61.8% (498/806) of patients were adequate relief responders in the placebo, ELX 75 mg, and ELX 100 mg groups, respectively. For both ELX doses, the majority of patients who were composite or adequate relief responders over Month 1 showed sustained response over Weeks 1–12 and 1–26 (Table). Of the patients who were not composite or adequate relief responders in Month 1, approximately 13–18% subsequently achieved response over 6 months of treatment.
Conclusion: Approximately two-thirds of patients who achieved either the composite or adequate relief endpoint over the first month of ELX treatment demonstrated sustained response over 6 months.
Disclosure of Interest: W.D. Chey: Dr Chey: Research support: Ironwood, Nestle, Prometheus; consultancy: Allergan plc, Ironwood, Nestle, Prometheus, Valeant, Sucampo, Takeda; patents: My GI Health, My Nutrition Health; co-founder: My Total Health.
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C.R. Gutman: Dr Gutman: employee of Allergan plc.
P.S. Covington: Dr Covington: former employee of Furiex Pharmaceuticals, an Allergan affiliate.

Table (OP258): Composite response rates over longer treatment intervals in ELX-treated patients who were composite or adequate relief responders over Month 1

	Placebo (n = 809)		ELX 75 mg BID (n = 808)		ELX 100 mg BID (n = 806)	
Patients, n (%)	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Composite endpoint: Weeks 1–4	101 (12.5)	708 (87.5)	184 (22.8)	624 (77.2)	198 (24.6)	608 (75.4)
Composite endpoint: Weeks 1–12[a]	78 (77.2)	23 (22.8)	150 (81.5)	34 (18.5)	154 (77.8)	44 (22.2)
Composite endpoint: Weeks 1–26[a]	67 (66.3)	34 (33.7)	136 (73.9)	48 (26.1)	140 (70.7)	58 (29.3)
Adequate relief: Weeks 1–4	399 (49.3)	410 (50.7)	484 (59.9)	324 (40.1)	498 (61.8)	308 (38.2)
Adequate relief: Weeks 1–12[b]	329 (82.5)	70 (17.5)	405 (83.7)	79 (16.3)	419 (84.1)	79 (15.9)
Adequate relief: Weeks 1–26[b]	278 (69.7)	121 (30.3)	341 (70.5)	143 (29.5)	364 (73.1)	134 (26.9)

BID, twice daily; ELX, eluxadoline
[a]Percentage calculated based on number of patients who were composite responders over Weeks 1–4
[b]Percentage calculated based on number of patients who were adequate relief responders over Weeks 1–4

TUESDAY, OCTOBER 18, 2016 14:00–15:30
HOT TOPICS IN PANCREATOLOGY – ROOM N2

OP259 HUMAN PLURIPOTENT STEM CELL-DERIVED EXOCRINE/DUCTAL ORGANOIDS GENERATE HUMAN PANCREAS UPON ORTHOTOPIC TRANSPLANTATION AND ALLOW DISEASE MODELLING

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Introduction: Exocrine/ductal pancreatic differentiation from human pluripotent stem cells is a poorly understood process albeit various diseases arise from this compartment.
Aims & Methods: We designed a straightforward approach to direct human pluripotent stem cells (PSC) toward pancreatic organoids resembling exocrine and ductal progeny.
Result: Extensive phenotyping of the organoids not only shows the appropriate marker profile but also ultra-structural and functional hallmarks of human pancreas in the dish. Upon orthotopic transplantation into immunodeficient mice, these organoids form normal pancreatic ducts and acinar tissue resembling fetal human pancreas without any evidence of tumour formation or transformation. Finally, we implemented this unique phenotyping tool as a model for pancreatic facets of cystic fibrosis (CF) but also other inherited pancreatic disorders. We provide for the first time evidence that pancreatic commitment occurs generally unhindered in CF. Importantly, CFTR-activation in mutated pancreatic organoids mirrors the CF-phenotype in a series of functional assays. We also conducted a scalable proof-of concept screen in CF-pancreatic organoids using a set of CFTR correctors and activators. Finally, we did orthotopic transplantation of CF-organoids to generate diseased human pancreata in mice and established a mRNA-mediated gene repair approach in CF-organoids. Similar assays were applied to another inherited pancreatic disorder.
Conclusion: Thus, our platform provides novel opportunities to model pancreatic disease and development but also to screen for disease rescuing agents.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP260 CANCER ASSOCIATED FIBROBLASTS (CAFS) SEQUESTER GEMCITABINE TO INCREASE INTRATUMORAL DRUG DELIVERY IN MURINE PANCREAS CANCER

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Introduction: The pronounced tumour stroma in pancreatic cancer has recently been appreciated as physical barrier impeding delivery of therapeutic agents. Herein, we aim to investigate the delivery of gemcitabine metabolites in primary pancreas tumours and matched liver metastases and dissect stromal and neoplastic compartments.
Aims & Methods: The cellular and acellular tumour stroma was assessed in human and mouse primary tumours and matched liver metastases. Gemcitabine metabolites were analysed in LSL-$Kras^{G12D/+}$;LSL-$Trp53^{R172H/+}$; Pdx-1-Cre (KPC) tumours and matched liver metastases, primary tumour cell lines, cancer associated fibroblasts (CAFs), and pancreatic stellate cells (PSCs) by liquid chromatography- mass spectrometry/mass spectrometry (LC-MS/MS). Expression analysis of gemcitabine metabolism pathways was performed in vitro and in vivo. Viability of CAFs was assessed in vivo following a preclinical trial in the KPC model.
Result: Fibroblast density and collagen deposition were significantly reduced in human and murine liver metastases as compared to matched primary tumours. Gemcitabine (dFdC) and its activate metabolite dFdCTP were significantly higher in stroma rich tumours compared to stroma poor liver metastases and normal liver. Mean vessel density did not correlate with gemcitabine delivery at pharmacodynamically relevant endpoints. In cell culture, significantly increased concentrations of activated dFdCTP and greatly reduced levels of the inactive gemcitabine metabolite dFdU were detected in PSCs and CAFs. Importantly, key metabolite enzymes for gemcitabine inactivation such as deoxycytidylate deaminase (Dctd), cytidine deaminase (Cda) and hydrolytic cytosolic 5'-nucleotidases (Nt5c1A, Nt5c3) were differentially expressed in PSCs and CAFs. Moreover, treatment of KPC mice revealed intrinsic resistance of CAFs to gemcitabine.
Conclusion: Our findings suggest that CAFs sequester gemcitabine and thus may contribute to the clinical failure of this drug in desmoplastic pancreatic cancer. Therefore, metabolic engineering of CAFs may constitute a promising new avenue to enhance the cytotoxic effects of gemcitabine in patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP261 CIRCULATING CELL-FREE DNA IS A RELIABLE TOOL TO DETECT HOT SPOT MUTATIONS IN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is the most common cancer type of the pancreas. The three PDAC precursor lesions are: (i) pancreatic intraepithelial neoplasia (PanIN), (ii) mucinous cystic neoplasm (MCN), and (iii) IPMN. In contrast, serous cystadenomas are strictly benign cystic neoplastic lesions and rarely require surgery.
Aims & Methods: Frequently, differential diagnosis of neoplastic cysts remains cumbersome. Thus, non-invasive diagnostic stratification would be welcome. Such a test should allow both discrimination of (i) IPMN from strictly benign pancreatic cysts but also (ii) low- from high-grade IPMN.
Result: Little is known about the molecular alterations of IPMN, but GNAS mutations have been described to promote IPMN formation. A tumor-derived fraction of cell-free DNA (cfDNA) circulating in the bloodstream represents the mutational makeup of tumors and could be a tool for non-invasive monitoring. We demonstrate that cfDNA levels discriminate controls from a cohort of Fukuoka-negative branch-duct IPMN but also from pancreatic cancer. Furthermore, GNAS mutations were detected in IPMN patients but were absent in serous cystadenoma (SCA) and in controls. Moreover, we observed relevant concordance between tissue and liquid biopsies-based GNAS mutations in an independent cohort of resected IPMN patients.
Conclusion: These findings establish cfDNA and targeted genotyping as a diagnostic tool for IPMN, which may aid differential diagnosis and risk stratification of cystic pancreatic lesions.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 14:00–15:30
INTESTINAL FAILURE: FROM PATHWAYS TO TREATMENT – ROOM L7

OP262 NOVEL GENE MUTATIONS IN NEUROGENIC CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

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Introduction: Chronic intestinal pseudo-obstruction (CIPO) is a severe gut dysmotility mimicking an intestinal sub-occlusion without demonstrable mechanical causes. Several genes have been identified in familial cases, suggesting a genetic heterogeneity. We identified a novel mutation in the RAD21 gene in a recessive form of familial CIPO[1]. RAD21 is a transcription factor essential for a number of functions including sister chromatid division during cell replication.
Aims & Methods: This study aimed to identify other mutated genes in a selected subset of CIPO, i.e. those cases associated with peripheral small fiber neuropathy (SFN), a condition affecting peripheral neurons including those of the autonomic system. Whole exome sequencing (WES) was performed on genomic DNA of n = 6 patients (3 trios and 3 sporadic cases) with clinical, radiological and manometric well-defined CIPO. A neurological work-up established SFN in each of them. Libraries were enriched with the Nimblegen SeqCap EZ v3.0 and sequenced via paired-end 50 bp reads on HiSeq2500 sequencer. Variants were annotated with the SeattleSeq137 Annotation Server. Additional 77 patients were collected for replication study. Target resequencing on selected genes was performed using the TruSeq amplicon panel designed with Design Studio software. Data analysis and variant calling was performed with the TruSeq Amplicon application in BaseSpace.
Result: WES analysis was performed considering pathogenic variants present as autosomal recessive (compound heterozygotes), X-linked or de-novo in the affected probands, since all the parents were healthy. We identified novel/rare missense mutations in FAT1 and in CROCC genes, inherited in an autosomal recessive way (compound heterozygous) in two trios, and a de-novo variant in B3GAT2 in the affected individual of the other trio analyzed, in combination with two rare/novel variants in Lipoprotein Related Receptor 2 (LRP2), that binds APOB which we have previously related to CIPO[1]. Analysis of these genes in 77 additional CIPO patients is currently ongoing. All the identified pathogenic variants were absent in our in-house database of 1,000 Italian chromosomes.
Conclusion: We identified three novel gene defects in three different CIPO patients with SFN. FAT1 is an unconventional cadherin, B3GAT2 is a glucuronyl transferase implicated in neuronal cellular migration and adhesion, while CROCC encodes for rootletin, a protein crucial for centrosome cohesion and separation during the cell cycle. Similarly to RAD21, also rootletin is related to chromosome structural maintenance suggesting that recessive defects in these genes may severely impair autonomic, including enteric, neurons. WES implementation can contribute to decipher complex genetic mechanisms underlying neurogenic CIPO.
Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

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OP263 PROTEASE SIGNALING IN HUMAN SENSORY NEURONS

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Introduction: IBS is a functional bowel disorder characterized by abdominal pain, associated with constipation and/or diarrhea. Among the mediators studied in IBS, increased colonic proteolytic activity appears as a common feature in all IBS sub-groups. Through Protease-Activated Receptors (PARs) activation, proteases can activate primary afferents and act on visceral pain pathways in rodents, but the relevance of PAR activation in human sensory neurons still has to be determined. Thus, the objective of our study was to decipher the PAR pharmacology in human sensory neurons.
Aims & Methods: Cryo-protected or fresh human thoracic dorsal root ganglia (DRG) were obtained from the national disease resource interchange (NDRI). Expression of PAR_1, PAR_2 and PAR_4 was studied on slices of DRG (DRG T12, n = 3) by co-staining immunochemistry with a pan-neuronal marker (pgp9.5) and PAR antibodies. Calcium signaling responses to PAR agonist peptide (PAR_1-AP (TFLLR; 1, 10 and 100 μM), PAR_2-AP (SLIGRL; 100 μM) and PAR_4-AP (AYPGKF; 100 μM), their irrelevant peptides (PAR-IP; 100 μM) or proteases: trypsin (1 and 10 U) and thrombin (1 and 10 U) were studied in cultured human DRG neurons, which were fixed thereafter, to study PAR expression.
Result: In fixed human DRG, PAR_1, PAR_2 and PAR_4 were expressed in 20, 40 and 40% of human sensory neurons respectively. PAR expression was not modified after culture. PAR_1-AP increased intracellular calcium concentration in a dose-dependent manner. This increase was inhibited by PAR_1 antagonist (SCH79797, 10 μM). In contrast, PAR_2-AP, PAR_4-AP and PAR-IP did not cause calcium mobilization. Thrombin (PAR_1 and PAR_4 agonist) but not trypsin (PAR_2 and PAR_4 agonist) increased calcium flux in human sensory neurons. PAR_1-AP-induced calcium mobilization was significantly reduced by pre-incubation with PAR_4-AP, but not with PAR_2-AP or any of the PAR-IP.
Conclusion: Our study demonstrates that PAR_1, PAR_2 and PAR_4 are expressed in human sensory neurons. In contrast to PAR_2 and PAR_4, PAR_1 activation induced calcium increase in human sensory neurons. PAR_4 activation reduced PAR_1 induced calcium mobilization. Thus, in Human PAR_1 and PAR_4 seem to play an important role in neuronal activation and may be relevant in IBS research.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP264 DIFFERENTIAL BASELINE CHARACTERISTICS IN SHORT BOWEL SYNDROME DUE TO VASCULAR CATASTROPHES ARE ASSOCIATED WITH VARYING RESPONSE TO TEDUGLUTIDE TREATMENT: POST HOC ANALYSIS

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Introduction: Vascular catastrophes are an underlying condition for massive intestinal resection and failure associated with short bowel syndrome (SBS–IF).
Aims & Methods: This post hoc analysis of data reported in patient e-case forms compared baseline characteristics of patients with SBS–IF due to vascular catastrophes (SBS–Vasc) vs patients with nonvascular causes of SBS–IF (SBS–non-Vasc), including the clinical response to teduglutide (TED). STEPS (NCT00798967; EudraCT2008-006193-15) was a 24-week, placebo (PBO)–controlled study of TED 0.05 mg/kg/day in patients with SBS–IF. Response was defined as ≥20% reduction from baseline in weekly parenteral support (PS) volume at Week 20 that was maintained at Week 24. Vascular catastrophes were intestinal ischaemia or mesenteric vessel thrombi or emboli. Descriptive summary statistics are presented with standard deviations (SD) or 95% confidence intervals (CI); this post hoc analysis was not powered for statistical significance.
Results: The patient characteristics for the SBS–Vasc (n = 32) and SBS–non-Vasc (n = 53) groups are detailed in the **Table**. The reason for the majority of the intestinal resections was Crohn's disease (SBS–non-Vasc) or mesenteric vessel thrombi or emboli (SBS–Vasc), **Table**. At baseline, more SBS–Vasc patients were older (55 vs 48 years) and male (53% vs 41%) than SBS–non-Vasc patients. SBS–Vasc patients had shorter bowel length (55 vs 92 cm), were more likely to have colon-in-continuity (78% vs 43%), and were less likely to have stoma present (19% vs 61%) compared with SBS–non-Vasc patients. SBS–Vasc patients had lower PS volume at baseline (11.2 vs 14.3 L/week) compared with SBS–non-Vasc patients. After 24 weeks, 53% (CI, 27%–79%) of SBS–Vasc patients and 70% (CI, 50%–86%) of SBS–non-Vasc patients were responders to TED. In the PBO groups, 35% (CI, 14%–62%) of SBS–Vasc patients and 27% (CI, 11%–48%) of SBS–non-Vasc patients met the response criteria. In the TED groups, reduction in mean PS volume (change and percentage change) took longer in the SBS–Vasc group (Week 12: 1.9 [CI, 0.3–3.5], 12% [CI, 3%–20%]; Week 24, 3.6 [CI, 1.5–5.7], 25% [CI, 15%–35%]) compared with the SBS–non-Vasc group (Week 12: 4.0 [CI, 2.0–5.9], 24% [CI, 16%–33%]; Week 24: 5.5 [CI, 3.4–7.6], 36% [CI, 29%–43%]). The overall TED safety profile was generally similar between the 2 groups. Specifically, >15% of SBS–Vasc patients reported abdominal pain, dyspnoea, fatigue, nausea, and peripheral oedema, whereas ≥15% of SBS–non-Vasc patients reported nausea, abdominal distension, abdominal pain, stoma complication, and peripheral oedema.
Conclusion: To our knowledge, this post hoc analysis is the first to compare baseline characteristics and response to treatment in patients with SBS resulting from vascular catastrophes and nonvascular diseases. In this group of patients, SBS-IF patients with vascular catastrophes were more likely to have colon-in-continuity, less likely to have stoma present, and had less baseline PS volume than in patients with nonvascular causes of SBS–IF. SBS-IF patients with vascular catastrophes look longer to respond to teduglutide in the observed PS volume reduction.

Table: Demographic and Baseline Characteristics

	SBS–Vasc	SBS–Vasc	SBS–non-Vasc	SBS–non-Vasc
Parameter	PBO (n = 17)	TED (n = 15)	PBO (n = 26)	TED (n = 27)
Age, y	56.6 (13.8)	52.3 (13.5)	45.2 (15.3)	50.8 (12.0)
Sex, n%				
-Male	8 (47)	9 (60)	11 (42)	11 (41)

(continued)

Table Continued

	SBS–Vasc	SBS–Vasc	SBS–non-Vasc	SBS–non-Vasc
-Female	9 (53)	6 (40)	15 (58)	16 (59)
Body weight, kg	66.6 (12.9)	63.9 (11.2)	58.5 (11.5)	62.1 (11.7)
BMI, kg/m^2	23.3 (3.4)	22.6 (3.4)	21.5 (2.8)	22.4 (3.1)
SBS history				
-Vascular catastrophe categories, n				
–Intestinal ischaemia	4	5		
–Mesenteric vessel thrombi or emboli	13	9	–	–
–Unknown vascular cause	0	1		
-Nonvascular causes of SBS-IF, n				
–Crohn's disease			8	10
–Injury			4	4
–Volvulus	–	–	6	3
–Cancer			2	1
–Other			6	9
-Colon-in-continuity, n (%)	13 (76)	12 (80)	10 (38)	13 (48)
-Stoma presence, n (%)	2 (12)	4 (27)	15 (58)	17 (63)
–Jejunostomy	1 (50)	2 (50)	4 (26)	9 (53)
–Ileostomy	0	1 (25)	9 (60)	5 (29)
–Colostomy	0	1 (25)	1 (7)	3 (18)
–Other	1 (50)	0	1 (7)	0
-Ileo-cecal value presence, n (%)	9 (53)	4 (27)	5 (19)	6 (22)
–Yes	6 (67)	1 (25)	4 (80)	2 (33)
-Estimated remaining small bowel length, cm	40.2 (29.9)*	70.9 (57.8)	87.6 (73.6)*	95.8 (67.8)*
PS history				
-PS duration at baseline, y	6.1 (6.2)	5.4 (4.7)	5.8 (5.5)	7.2 (7.0)
-PS L/week at baseline	10.2 (5.4)	12.4 (5.5)	15.5 (7.3)	13.3 (8.3)
-PS days per week at baseline	5.4 (1.8)	5.6 (1.6)	6.3 (1.2)	5.6 (1.8)

Data are expressed as mean (SD) unless otherwise noted.
BMI = body mass index; PBO = placebo; PS = parenteral support; SBS-IF = intestinal resection and failure associated with short bowel syndrome; TED = teduglutide.
*SBS–Vasc n = 16 PBO; Nonvascular, n = 24 PBO, n = 24 TED.

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K. Iyer: Has received grant/research support and served as an advisory board member and consultant for NPS Pharmaceuticals, Inc and Shire plc.
H. Lee: Employee and stockholder of Shire plc.
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OP265 NUTRITIONAL OUTCOME IN SMALL BOWEL AND MULTIVISCERAL TRANSPLANT PATIENTS

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Introduction: There has been an increase in the numbers of small bowel and multivisceral transplants performed in the UK over the past 10 years. Despite successful transplants, these patients require close monitoring long-term and currently there is limited data on their nutritional outcome.
Aims & Methods: Our primary end points are to examine 1) the percentage of patients who achieved nutritional autonomy (without oral nutritional supplement ONS, enteral nutrition EN, intravenous IV fluid or parenteral nutrition PN) post-transplant and 2) the change in their weight and body mass index (BMI) in the immediate and long term. Secondary end points include 1) the duration on nutritional support post- transplant; 2) change in anthropometry and 3) difference in nutritional outcome in patients who have colon-containing graft or received continuity surgery. Data was collected prospectively on all patients who underwent small bowel or multivisceral transplants at Addenbrooke's Hospital, Cambridge, UK. There were 54 patients in total from January 2006 to April 2015. Patients with survival less than 6 months post-transplant (n = 9) and with incomplete data (n = 1) were excluded. This resulted in 44 eligible patients whose weights, BMI and grip strengths (in non-dominant hand) were analysed. Grip strengths were performed by one of two dedicated dietitians.
Result: Patient characteristics: Transplants included 12 isolated small bowel (SBT), 5 liver and small bowel (LSBT), 12 modified multivisceral (small bowel, stomach, pancreas-MMVT) and 22 multivisceral (small bowel, stomach, pancreas, liver-MVT). 7 patients were re-transplanted. Recently, donor colon has been included in the graft to help with fluid balance. Mean age at transplant was 43.9 years. Patients were followed up for a median of 30 months, to April 2016 or death (n = 14). Primary outcomes: Out of the 30 long-term survivors, 73.3% (22) of them are maintained on oral diet alone at the end of follow up. The other 5 patients require ONS, 2 require IV fluids and 1 patient continues on PN. Most patients (95.5%; 21/22) who achieved nutritional autonomy were previously dependent on nutritional support (2 ONS; 1 EN; 18 PN) except for one patient who was listed super-urgently. Of the patients who died, 3 out of 14 were requiring PN. The mean BMI pre-transplant was 21.7 (SD = 3.5). Post-operatively, the majority of patients (86.7%) lost weight (mean 14.3%; range 1–30%) with their nadir weight occurring at a mean of 10.7 months. 11 lost ≥20% of their pre-transplant weight. However more than half (26/44) of the patients weights improved over time. Compared to the time of assessment, their BMI improved by 0.9 kg/m^2 (SD = 4.3) in the first year (median = 11 months) and increased further by 1.4 kg/m^2 (SD = 4.3) at the end of the follow up. The most recent mean BMI in 30 survivors were 23.3 kg/m^2 (SD = 5.2). Further analysis revealed 20 patients have healthy weight (BMI 18.5–25), 4 underweight (BMI < 18.5), 3 overweight (BMI > 25) and 3 obese (BMI > 30). Secondary outcomes: Post-transplant, PN was given for a median of 22 days (range 2–241) and 39.5 days (range 11–262) of EN. At the end of the follow up, those who have nutritional autonomy required a considerably shorter duration of nutritional support post-transplant compared to those who are nutrition dependent (mean of 65.3 vs 120.7 days). This suggests that the duration on nutritional support post-transplant may predict nutritional autonomy. Of the patients who have colon (graft or continuity), 64% have nutritional autonomy. However those without functioning colon are less likely to (47.4%) (P = 0.36). Handgrip strength was measured in 31 patients pre and post-transplant. At median of 9 months (range from 2–32), there was a slight reduction by 6% of expected value which correlates with their weight loss. 18 patients had further handgrip strength test and they improved with a mean of 7% at last follow up (median 16 months).
Conclusion: The majority of patients achieved nutritional autonomy post-transplant and a colon-containing graft may be beneficial. It is common for patients to lose a moderate amount of weight, up to 30% post-operatively. Therefore timely referral is crucial to allow optimisation of perioperative nutritional status.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP266 SUBANALYSIS OF TEDUGLUTIDE EFFICACY AND SAFETY DATA FROM PATIENTS WITH CROHN'S DISEASE AND ULCERATIVE COLITIS IN THE STEPS STUDY

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Introduction: Inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis) is a major underlying condition for massive intestinal resection leading to intestinal failure associated with short bowel syndrome (SBS–IF).
Aims & Methods: This post hoc subgroup analysis compared response to teduglutide (TED) in patients with SBS–IF due to IBD (SBS–IBD) vs those with noninflammatory causes of SBS–IF (SBS–non-IBD). STEPS (NCT00798967, EudraCT2008-006193-15) was a 24-week, phase III, placebo-controlled study of 0.05 mg/kg/day TED in patients with SBS–IF. Patients with CD were in clinical remission for ≥12 weeks at baseline. Response was a ≥20% reduction from baseline in weekly parenteral support (PS) volume at Week 20 that was maintained at Week 24. Descriptive summary statistics are presented with 95% confidence intervals (CIs); this post hoc analysis was not powered for statistical significance.
Result: The **Table** details patient characteristics (SBS–IBD, n = 19; SBS–non-IBD, n = 67). Patients with SBS–IBD had lower colon-in-continuity, higher stoma presence, and higher baseline PS volume than those with SBS–non-IBD. After 24 weeks, 73% (95% CI, 39%–94%) of patients with SBS–IBD and 59% (95% CI, 41%–76%) with SBS–non-IBD were responders to TED. In the TED patients, mean PS volume was reduced by 45% (95% CI, 31%–59%) in patients with SBS–IBD and 29% (95% CI, 22%–35%) in those with SBS–non-IBD. Two of 9 (22%) patients with SBS–IBD and 6/30 (20%) patients with SBS–non-IBD achieved a PS reduction of ≥2 days per week. Overall safety profile was similar in both groups (SBS–IBD, n = 19; SBS–non-IBD, n = 66). Among patients receiving TED, treatment-emergent adverse events (TEAEs) were reported by 100% of patients with SBS–IBD and 77% of those with SBS–non-IBD. Serious adverse events among those receiving TED occurred in 27% of patients with SBS–IBD and 39% of those with SBS–non-IBD. No TEAEs of CD were reported in either

subgroup. No patients with SBS–IBD and 1/47 (2%) with SBS–non-IBD with a colon experienced 1 TEAE (TED) of colitis.
Conclusion: In this analysis, the subgroup of patients with inflammatory bowel disease (SBS–IBD) had evidence of more severe disease based on a higher frequency of stoma presence, higher PS requirements, and lower colon-in-continuity. Despite this, clinical responses to TED were equally strong.

Table: Demographic and Disease History Data

	SBS–IBDPlacebo (n = 8)	SBS–IBDTED (n = 11)	SBS–Non-IBDPlacebo (n = 35)	SBS–Non-IBDTED (n = 32)
Age, mean (SD), y	48 (7)	48 (7)	50 (17)	52 (14)
Women, n (%)	5 (63)	5 (46)	19 (54)	17 (53)
Body mass index, mean (SD), kg/m^2	22.6 (3.6)	23.3 (4.1)	22.2 (3.1)	22.2 (2.8)*
Stoma present, n (%)	7 (88)	11 (100)	10 (29)	10 (32)*
Colon-in-continuity, n (%)	1 (13)	1 (9)	22 (63)	24 (77)*
Estimated small bowel length, mean (SD), cm	128 (98)	129 (77)†	54 (43)‡	73 (56)§
Baseline PS, mean (SD), L/wk	21.6 (8.1)	15.9 (10.4)	11.5 (5.9)	11.2 (6.4)*
Baseline PS duration, mean (SD), y	7.2 (7.4)	8.1 (8.0)	5.6 (5.3)	6.1 (5.7)*

*n = 31, †n = 9, ‡n = 32, §n = 30.

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H. Lee: Employee and stockholder of Shire plc.
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OP267 INDICATIONS AND OUTCOMES OF INTESTINAL AND MULTIVISCERAL TRANSPLANT

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Introduction: Despite a reduction in numbers worldwide, we have seen an increase in adult Intestinal and Multivisceral transplants in the UK in the past 3 years. Some recent transplants have been performed 'superurgently' for acute widespread splanchnic ischaemia. Longstanding indications include complications of parenteral nutrition in patients with type 3 Intestinal Failure (IF-associated liver disease (IFALD), recurrent catheter-related infections and loss of vascular access), cirrhosis with extensive portomesenteric venous thrombosis precluding an isolated liver transplant and the need for extensive evisceration due to benign tumour. Re-transplantation is indicated for loss of previous graft due to rejection, ischaemia or primary non-function.
Aims & Methods: We describe here the indications and outcomes for Intestinal and Multivisceral transplant at Addenbrooke's Hospital, Cambridge, UK Data was collected prospectively on an internal database of all patients transplanted from January 2006 to April 2016. All patients considered for an intestine-containing graft require ratification at a national forum (NASIT). Grafts which include liver or kidney are also discussed at local listing committees. Induction immunosuppression is with Campath (Alemtuzumab) and maintenance initially with tacrolimus and steroids. If complications related to tacrolimus occur, patients are switched to ciclosporin or sirolimus. An antimetabolite is added to aid steroid withdrawal post discharge.
Result: In the study period, 66 transplants were performed in 61 patients (33 Multivisceral, MVT; 7 Liver/small bowel, LSB; 9 Modified multivisceral, MMV; 17 small bowel, SB). Grafts can also contain colon and pancreas. 26 patients (39%) received a transplant for complications relating to intestinal failure (overt IFALD = 11, impending IFALD = 4, recurrent sepsis = 1, loss of vascular access = 10). 14 patients (21%) received a multivisceral graft because an isolated liver transplant was not possible due to extensive portomesenteric venous thrombosis. An increasing indication is that of 'acute abdominal catastrophe' – 9 patients were transplanted for this including 5 with widespread splanchnic ischaemia. Less frequent indications included desmoid tumours (4), re-transplant (6), short bowel and renal failure (2). The median length of hospital stay post transplant is 77 days. 7 patients had a proven episode of acute cellular rejection (ACR) within 90 days, 12 patients had an episode between 90 days and 1 year and 7 had ACR after 1 year. The vast majority of episodes were treated with pulsed methylprednisolone (23/26, 88%). Subsequent treatments given were Alemtuzumab (n = 9), Infliximab (n = 1), second pulse of steroids (n = 6) anti-thymocyte globulin (ATG, n = 4). 3 grafts required removal due to rejection and all 3 patients have been re-transplanted. Within our cohort, there have been 5 cases of graft versus host disease (GVHD) and 6 cases of post-transplant lymphoproliferative disorder (PTLD). Infections continued to be a problem. We have seen increasing rate of vancomycin resistant enterococcus (VRE) and carbapenem resistant pseudomonas. Cytomegalovirus is the most common viral infection. Overall rates are 37.5% but this increases to 91% when seropositive donor is given to a seronegative recipient. 1 year patient survival for SB recipients is 91%, for MMV is 89% and for MVT/LSB is 69%. 3 year patient survival for SB recipients is 81%, for MMV is 89% and for MVT/LSB is 52%.
Conclusion: Transplantation of intestinal-containing grafts is technically challenging and recipients have a higher rate of complications compared to other solid organ transplants. However, with advances in surgical techniques and increasing experience of the management of medical complications, survival is improving. Intestinal or Multivisceral transplant should be considered for certain patients who have suffered an abdominal catastrophe, are unable to have a liver transplant due to extensive portomesenteric thrombosis, or have complications arising from intestinal failure. Timely referral to a transplant centre and careful follow-up is essential to continue improvement in outcomes.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 14:00–15:30
PROGNOSTIC FACTORS IN LOWER GI CANCER – ROOM L8

OP268 EXPRESSION OF DDR2 CORRELATES WITH HIGH FREQUENCY OF PERITONEAL DISSEMINATION AND POOR PROGNOSIS IN COLORECTAL CANCER

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Introduction: In the previous study, our colleagues identified that discoidin-domain receptor 2 (DDR2) is a promising driver gene of peritoneal disseminations in gastric cancer by a comprehensive expression assay. We found DDR2 expression was associated with high frequency of peritoneal dissemination and poor prognosis in gastric cancer, and also revealed that the DDR2 was upregulated by the loss of DNA methylation and that DDR2 knockdown reduced peritoneal dissemination in a xenograft. Furthermore, we found dasatinib, an inhibitor of the DDR2 signaling pathway, suppressed peritoneal dissemination. In colorectal cancer, peritoneal dissemination is second popular site for colorectal cancer metastasis, next to the liver. Its frequency is estimated to be 4–7% of patients with colorectal cancer at primary surgery, and approximately 4–19% of patients during follow-up after curative surgery. Peritoneal dissemination is one of most frequent non-curative clinical factors also in colorectal cancer.
Aims & Methods: In this study, we analyzed correlations of DDR2 expression with clinicopathological factors in colorectal cancer, especially peritoneal dissemination. We selected 63 cases with colorectal cancer who had an operation in our hospital between 2009 and 2014. Among them, 13 cases had synchronous or metachronous peritoneal dissemination. We performed immunohistochemical examinations for 63 primary colorectal cancers and 12 peritoneal dissemination lesions in 11 cases with anti-DDR2 antibody. We evaluated histological localization of DDR2 expressions, divided 63 cases into two groups by the degree of DDR2 expressions, and compared various clinicopathological factors and overall survival between these two groups.
Result: In primary lesions, DDR2 was expressed more preferentially in cancer cells at invasive front of tumors. The group with high DDR2 expression had significantly more proportion of T4, lymph node metastasis, and peritoneal dissemination than the group with low DDR2 expression (p = 0.0025, 0.012, and 0.012, respectively), and the prognosis of the former was significantly poorer than the prognosis of the latter (p = 0.0164). In peritoneal dissemination lesions, 11 out of 12 exhibited intense DDR2 expressions.
Conclusion: High DDR2 expression correlates with peritoneal expression and poor prognosis in colorectal cancer as well as in gastric cancer. DDR2 might be one of promising driver genes of peritoneal dissemination universally in gastrointestinal peritoneal dissemination.
Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

1. Kurashige J, et al. Integrated Molecular Profiling of Human Gastric Cancer Identifies DDR2 as a Potential Regulator of Peritoneal Dissemination. *Sci Rep* 2016 Mar 3; 6: 22371doi: 10.1038/srep22371.

OP269 GENETIC SUSCEPTIBILITY AND FAMILY HISTORY OF COLORECTAL CANCER. RELEVANCE OF SINGLE NUCLEOTIDE POLYMORPHISMS IN THE DEVELOPMENT OF COLORECTAL PRENEOPLASTIC LESIONS

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Introduction: First-degree relatives (FDR) of patients with colorectal cancer (CRC) have been shown to have a 2- to 3-fold increased risk of developing CRC compared with the overall population. It is likely that CRC susceptibility in these individuals results from common variants in low-penetrance genes. However, very little is known about the relevance of genetic variants in the development of colorectal preneoplastic lesions according to the family history of CRC

Aims & Methods: We aimed to evaluate the role of certain single nucleotide polymorphisms (SNPs) associated with CRC risk in the development of colorectal adenomas depending on the family history of CRC. We carried out a case-control study comprising 750 FDR of patients with non-syndromic CRC (cases), and 750 sex- aged- and histological lesion- matched individuals with no family history of CRC (controls). Cases and controls were selected from the Spanish CRC screening registries in Aragon and The Canary Islands. All subjects underwent at least one colonoscopy and diagnosis of adenoma was confirmed by histological study. Genomic DNA from cases and controls was genotyped by the MassArray™(Sequenom) platform for a panel of 99 SNPs previously associated with CRC risk. Genetic analysis was performed using the SNPassoc package implemented in R. To address the issue of adjustment for multiple testing, the false discovery rate method and Bonferroni's correction were applied.

Result: Average age of participants was 54.5 ± 9.4 years with a slight predominance of women (51.7%). In 57% of patients, no preneoplastic lesions were found. By contrast, 288 patients (144 cases and 144 controls) showed non advanced adenomas (NAA), and 354 patients (177 cases and 177 controls) had advanced adenomas (AA). Concerning gene analysis, 2 SNPs (rs10505477 A > G and rs6983267 G > T) located in the CASC8 gene were associated with the development of adenomas. Thus, the rs10505477G and the rs6983267T alleles were significantly associated with a reduced risk of adenomas in patients with no family history of CRC (controls) (log-additive models, OR: 0.67, 95% CI:0.54–0.83 and OR: 0.66, 95% CI:0.54–0.84, respectively). However, such a protective effect was not observed in FDR of patients with CRC (cases). In the stratified analysis by histological lesion, the rs10505477G and the rs6983267T variants were significantly associated with a reduced risk of both, NAA and AA in controls, although this effect was stronger on the risk of developing NAA (recessive models, OR:0.38, 95% CI:0.21–0.67 for rs10505477, and OR: 0.32, 95% CI: 0.17–0. 61 for rs6983267), suggesting their possible implication in early stages of CRC development. Finally, 2 SNPs (rs10795668G > A and rs11255841T > A) located in the lncRNA gene LINC00709 were significantly associated with a reduced risk of NAA in both, FDR of patients with CRC (recessive models, OR: 0.22, 95% CI: 0.06–0.72 for rs10795668, and OR: 0.08, 95% CI: 0.03–0.61 for rs11255841) and patients with no family history of CRC (dominant models, OR: 0.50, 95% CI: 0.34–0.75 for rs10795668, and OR:0.52, 95% CI: 0.35–0.78 for rs11255841), suggesting their possible implication in early stages of CRC development.

Conclusion: Family history of CRC and some specific variants associated with CRC risk (rs10505477 and rs6983267 in CASC8 gene and rs10795668 and rs11255841 in LINC00709 gene) are involved in the development of colorectal adenomas or specific histological subtypes.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP270 A NOVEL AMPLIFICATION GENE PCID2 PROMOTES TUMORIGENICITY OF COLORECTAL CANCER THROUGH DIRECTLY DEGRADING A TUMOR SUPPRESSOR PML AND IS ASSOCIATED WITH DISEASE RECURRENCE

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Introduction: PCI Domain Containing 2 (PCID2) located at 13q34 was identified to be amplified in colorectal cancer (CRC) by genome sequencing. We evaluated its amplification, overexpression, biological functions and clinical implication in CRC.

Aims & Methods: The PCID2 gene amplification status in CRC tissues was evaluated by Copy Number Assay. The biological effects of PCID2 overexpression and knockdown were determined by in vitro and in vivo tumorigenicity assays. The PCID2 interaction partner was identified by immunoprecipitation followed by mass spectrometry. PCID2 downstream effectors and signaling pathways were elucidated by promoter luciferase assay and co-immunoprecipitation. The clinical impact of PCID2 overexpression was assessed in three cohorts of 114 CRC patients from Beijing (cohort I), 46 CRC patients from Hong Kong (cohort II) and 376 CRC cases from TCGA dataset (cohort III).

Result: Amplification of PCID2 was detected in 32.5% (37/114) of CRC patients from cohort I and 62.0% (233/376) of CRC patients from cohort III by Copy Number Assay. The copy number gain was positively correlated with its mRNA overexpression both in cohort I ($r\ sq = 0.327$, $p < 0.0001$) and in cohort III ($r\ sq = 0.619$, $p < 0.0001$). Biological functional investigation of PCID2 revealed that ectopic expression of PCID2 in colon cancer cell lines (DLD1 and HT29) significantly increased cell proliferation ($p < 0.01$ in DLD1 and $p < 0.001$ in HT29), G1-S cell cycle transition ($p < 0.01$ and $p < 0.05$, respectively), invasion ($p < 0.01$ and $p < 0.01$, respectively) and migration ($p < 0.01$ and $p < 0.05$, respectively) abilities, and suppressed cell apoptosis ($p < 0.01$ and $p < 0.05$, respectively). In addition, PCID2 significantly promoted xenograft tumor growth as well as lung metastasis in nude mice. On the other hand, knockdown PCID2 in colon cancer cell lines (HCT116 and SW480) showed opposite effects. We further revealed that the oncogenic effect of PCID2 was mediated through degrading its interaction partner promyelocytic leukemia (PML) by ubiquitination. PML played a tumor suppressive role in CRC. PCID2 induced Wnt signaling pathway and inhibited p53/p21 pathway activity. PCID2 expression level was evaluated by quantitative PCR in cohort I and cohort II patients. Multivariate analysis revealed that patients with PCID2 overexpression were significantly correlated with CRC recurrence ($p < 0.05$ for cohort I, $p < 0.05$ for cohort II). Recurrence curves showed that PCID2 overexpression was a prediction marker for recurrence of patients with CRC ($p = 0.004$ for cohort I, $p = 0.03$ for cohort II).

Conclusion: PCID2 plays a pivotal oncogenic role in colorectal carcinogenesis by degrading its downstream effector PML. PCID2 overexpression is an independent recurrence prediction marker for CRC patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP271 PREDICTION OF COMPLETE RESECTIONS AFTER CYTOREDUCTIVE SURGERY BASED ON THE EXTENT OF COLORECTAL PERITONITEAL CARCINOMATOSIS

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Introduction: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is the treatment of choice for colorectal peritoneal carcinomatosis (PC). Prior to surgery abdominal computed tomography (CT) was performed to gain insight into the extent of PC and the presence of distant metastases.

Aims & Methods: Our objective was to evaluate the relation between the completeness of cytoreduction and the Dutch seven region count evaluated with CT and during surgery. Patients who underwent abdominal CT-imaging for PC prior to CRS-HIPEC were eligible. The seven-point region count was assessed with CT by an experienced radiologist and peroperative evaluation was performed by the operating surgeon, based on the Dutch region count. The completeness of cytoreduction was scored after CRS. Survival analyses were performed.

Result: Two hundred thirty-four patients were included. Patients with incomplete cytroductive surgery had more often PC in five to seven regions during surgery ($p < 0.001$). This result was not found using de CT-related region count ($p = 0.06$). Regarding disease free survival and overall survival significant differences were found with medians of 21.9 months (IQR 19.1–24.7) and 44.6 months (IQR 35.8–53.5) in patients with complete cytoreduction compared to 12.1 months (IQR 9.7–14.6) and 19.0 months (IQR 14.2–23.8) in patients with incomplete cytoreductive surgery ($p < 0.001$ and [$p < 0.001$).

Conclusion: Patients with four or less involved abdominal regions with PC peroperative were more likely to have a complete resection. CT assessment of the region score could not accurately predict a complete resection. Patients with a complete resection showed better survival than patients with an incomplete cytoreduction.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP272 PREVALENCE OF LYMPH NODE METASTASIS AND LONG TERM SURVIVAL OF T1 RECTAL CARCINOID TUMORS: AN ANALYSIS OF SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) DATABASE

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Introduction: Rectal carcinoids are the most common neuroendocrine tumors of the gastrointestinal tract and their incidence is increasing due to colorectal cancer screening. Several previous studies have suggested that local excision (endoscopic or transanal excision) is effective for ≤10 mm lesions but data on long-term

outcomes are very limited. In addition, management of 11–19 mm tumors is not well defined because of variable estimates of risk of lymph node (LN)/ distant metastasis.
Aims & Methods: The aims of this study were: 1) to determine the prevalence of metastasis of resected T1 rectal carcinoid tumors using a large national cancer database, 2) to identify risk factors for metastasis, 3) evaluate the long-term survival of patients with T1N0M0 rectal carcinoid tumors after local resection as compared to radical surgery. The SEER 18 database was used to identify patients aged 18–80 years with T1 histologically confirmed rectal carcinoids <2 cm in size diagnosed between 1998 and 2012. T1 was defined as tumor invading lamina propria or submucosa. Prevalence of LN (N1) /distant metastases (M1) at initial diagnosis and risk factors for metastases were analyzed. Cancer-specific survival (CSS) and overall survival were calculated using Kaplan-Meier's estimate and compared with log-rank test.
Result: A total of 788 patients with T1 rectal carcinoids were identified [mean age: 54.8 (SD 11.3); 49.5% men; 57% white]. Of these, 727 (92.3%) patients had tumors <10 mm in diameter and 61 (7.7%) had tumors 11–19 mm. Submucosal involvement was noted in 54.9%. Overall, 12 patients (1.5%) had N1/M1 at the time of diagnosis with prevalence of 1.1% in lesions $\leq$10 mm and 6.6% in lesions 11–19 mm in size ($p=0.01$). Tumor size (OR 6.31; 95%CI 1.8 – 21.5; $p=0.003$) and submucosal invasion ($p=0.03$) were associated with LN/ distant metastasis. Median follow-up of the entire cohort was 23 months (range 0–172). Survival of patients with T1 rectal carcinoids without N1/M1 was significantly better than those with N1/M1 with 5- yr CSS of 100% and 78%, respectively ($p<0.001$). Of 559 patients with T1N0M0 rectal carcinoids <10 mm in size and follow >6 months, 527 (94.5%) underwent local excision and 32 (5.7%) had radical surgery. 5-yr CSS was 100% and 10-yr CSS was 98% (SE 0.01). For 46 patients with T1N0M0 rectal carcinoids 11–19 mm in size [39 (84.8%) who underwent local excision and 7 (15.2%) underwent radical surgery], there were no carcinoid tumor-related deaths after a median follow up of 28 months (range 8–122). The overall survival of T1N0M0 rectal carcinoids treated by local excision versus radical surgery were comparable.
Conclusion: Larger T1 rectal carcinoid tumors (11–19 mm) are at increased risk of LN metastases compared those $\leq$10 mm. Survival is worse with regional or distal metastatic disease. Hence, thorough evaluation for metastatic disease should be considered for these lesions. Local therapy is adequate for T1 rectal carcinoids <10 mm and 11–19 mm N0M0 with excellent long term outcomes.
Disclosure of Interest: V. Singh: Vikesh Singh is a consultant for Abbvie, D-Pharm, and Santarus.
M. Khashab: Mouen Khashab is a consultant for Boston Scientific
All other authors have declared no conflicts of interest.

OP273 LONG-TERM FOLLOW-UP FEATURES ON RECTAL MRI DURING 'WATCH-AND-WAIT' IN CLINICAL COMPLETE RESPONDERS AFTER CHEMORADIOTHERAPY: AN UPDATE OF 68 PATIENTS

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Introduction: Non-operative treatment with stringent follow-up ('watch-and-wait') is emerging as an alternative to surgical resection in rectal cancer patients who show a clinical complete response after chemoradiotherapy. An important question is how (how frequently and with what modalities) to monitor patients once surgery is omitted. In addition to clinical examination and endoscopy, imaging – mainly MRI – plays an important role. Given the novelty of the 'watch-and-wait' approach, limited data exists yet on what we can expect to see on MRI during long-term follow-up after chemoradiotherapy. A pilot study described various patterns of a complete response during watch-and-wait in a small group of 19 patients.[1]
Aims & Methods: Aim of this study was to follow-up on this previous research in a larger patient cohort. Objectives are to describe the morphology of the rectal wall in patients with a complete response after chemoradiotherapy and study the evolution in rectal wall morphology during long-term clinical follow-up in these patients.
68 patients with a sustained complete response (i.e. no evidence of recurrence on sequential imaging and endoscopy ±biopsy examinations) were analysed during long term follow-up within the scope of a watch-and-wait protocol. Patients underwent MRI (as well as corresponding clinical examination and endoscopy) 3-monthly in the first year and 6 monthly during the second to fifth year. Two readers in consensus analysed the rectal wall morphology on the initial post-chemoradiotherapy MRI scan and studied the evolution in morphology on the various sequential follow-up MRIs. MRIs were performed at 1.5 T. Routine T2-weighted sequences in sagittal, trasverse and coronal plane were analysed.
Result: Median follow-up time was 30 months (range 6–98). A total of 512 MRIs was analysed (median 7, range 3–15/patient). In 7% of patients the rectal wall completely normalised post-CRT. The other 93% showed a fibrotic remnant (60% minimal fibrosis limited to the bowel wall; 21% thick/mass-like fibrosis and 12% irregular/spicular fibrosis). In 94% the rectal wall morphology remained unchanged during long-term follow-up, in 2% initial fibrosis later developed into a normalised wall, in 3% the fibrosis slightly thickened (without evidence of recurrence).
Conclusion: In the majority of patients with a complete response residual fibrosis is present post-chemoradiotherapy which remains unchanged during long-term follow-up in almost all patients. A completely normalised wall is observed in approximately 1 in 10–20 patients. The findings of this study may serve as a reference and provide teaching for radiologists involved in the clinical follow-up of patients selected to undergo a watch-and-wait policy.
Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 14:00–15:30
GENERAL HEPATOLOGY – ROOM 1.86

OP274 ACCURACY OF A POINT SHEAR WAVE ELASTOGRAPHY TECHNIQUE (ELASTPQ) IN THE NON-INVASIVE ASSESSMENT OF LIVER FIBROSIS IN A LARGE COHORT OF LIVER PATIENTS

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Introduction: ElastPQ is a novel point shear wave elastography (PSWE) technique that assesses liver fibrosis by measuring liver stiffness (in kPa) with few studies published so far. The aim of this study was to determine the accuracy and the feasibility for the assessment of liver stiffness in a large cohort of patients undergoing liver biopsy (LB) for various etiologies.
Aims & Methods: Consecutive patients scheduled for LB were studied by using the iU22 Philips ultrasound system with ElastPQ technique. The correlations between laboratory findings, liver stiffness and the Metavir score were analyzed using Spearman correlation and ROC curve analyses were performed to calculate AUC for $F\geq 2$, $F\geq 3$ and $F=4$.
Result: We enrolled 289 patients (176/113 males/females) who underwent LB for viral or non-viral chronic hepatitis (HCV 49%; NASH 20%; AIH/PBC 18%; other 13%). Liver stiffness measurements performed on the right lobe were reliable in all cases but eight patients (due to morbid obesity and narrow intercostal spaces). After univariate and multiple regression analysis PSWE showed a strong correlation with the fibrosis stage; no significant correlation was found with the degree of necroinflammation or steatosis. Mean kPa values in the whole cohort were 3.7 (range 2.3–4.9) for F0, 4.9 (range 2.6–9.6) for F1, 7.6 (2.8–20.7) for F2, 10.2 (6.1–19.9) for F3 and 20.4 (10.9–38.4) for F4 in the right lobe. AUROCs were 0.92 (±0.02), 0.93 (±0.02) and 0.96 (±0.01), when comparing F0-F1 vs F2-F4, F0-F2 vs F3-F4 and F0–3 vs F4, respectively. The optimal cut-off values for different levels of fibrosis were 6.0, 7,7 and 10.9 kPa for $F\geq 2$, $F\geq 3$ and F4, respectively. When analyzing PSWE values according to different etiologies, AUROCs were 0.89 (±0.04), 0.93 (±0.29) and 0.96 (±0.03) for $F\geq 2$; 0.88 (±0.04), 0.85 (±0.03) and 0.95 (±0.03) for $F\geq 3$; 0.90 (±0.01), 0.95 (±0.01) and 0.96 (±0.01) for F4 in HCV, NASH and AIH/PBC patients, respectively.
Conclusion: To date this is the largest case series evaluating the accuracy of ElastPQ technique. This novel PSWE system appears to be a very useful tool for non-invasive evaluation of liver fibrosis not only in patients with viral chronic hepatitis, but also for patients with different liver diseases. In order to validate such a non-invasive technique these findings need to be confirmed in larger studies comparing different elastography devices.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP275 COMPARATIVE STUDY BETWEEN TWO 2D-SHEAR WAVES ELASTOGRAPHY TECHNIQUES FOR THE ASSESSMENT OF LIVER STIFFNESS: 2D-SWE.SSI VS. 2D-SWE.GE

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Introduction: Chronic liver diseases are quite frequent encounterd in daily practice and are due to chronic viral infections (B or C viruses) and other conditions such as chronic alcohol abuse (ASH) and NAFLD. In this conditions, the evaluation of chronic liver disease's severity is mandatory, for prognosis, for management and for decision regarding therapy.
Aims & Methods: The aim of this study was to compare the feasability of two 2D-Shear Waves Elastography (2D-SWE) methods for the assessment of Liver Stiffness (LS) and also to compare the methods with a validated one-Transient Elastography(TE). Our study included 130 consecutive patients with chronic hepatopathies (HCV–90%, HBV–6%, other–4%), in which Liver Stiffness (LS) was evaluated in the same session by means of two 2D-SWE tehniques: 2D-SWE.GE(LOGIQ E9, GE Healthcare) and 2D-SWE.SSI (Aixplorer® ultrasound system, SuperSonic Imagine) and also by an

elastographic refference method: Transient Elastography (TE)- FibroScan, EchoSens (M and XL probes). Reliable LS measurements were defined as follows: for 2D-SWE.GE: the median value of 10 measurements acquired in a homogenous area and an interquartile range (IQR) $<30\%$ (1), for 2D-SWE.SSI: the median value of 3 measurements acquired in an homogenous area (2) and for TE- the median value of 10 measurements with a success rate of $\geq 60\%$ and an interquartile range $<30\%$ (3). Spearman's rank correlation coefficient (r) was used to assess the correlation of LS measurements by means of 2D-SWE.GE, 2D-SWE.SSI and TE.

Result: Valid measurements were obtained in **94.6%** (123/130) for 2D-SWE.GE, **90.7%** (118/130) for 2D-SWE.SSI, **89.2%** (116/130) for TE ($p > 0.05$). Reliable liver stiffness results were obtained in 107 subjects by means of 2D-SWE.SSI, 2D-SWE.GE and TE. The values ranged from 4.17 to 20.48 kPa for 2D-SWE.GE and from 3.4 to 82.4 kPa for 2D-SWE.SSI. The mean LS values by 2D-SWE.SSI were significantly higher than for 2D-SWE.GE: 19 ± 12.3 kPa vs. 12.1 ± 3.7 kPa ($p < 0.0001$). There was a significant correlation between 2D-SWE.GE and 2D-SWE.SSI LS values ($r = 0.712$, $p < 0.0001$). The correlation between 2D-SWE.GE and TE was $r = 0.746$, $p < 0.0001$, and between 2D-SWE.SSI and TE was $r = 0.604$, $p < 0.0001$ with no significant differences between them ($p = 0.0565$). Taking TE as the refference method, both 2D-SWE.SSI and 2D-SWE.GE had a good value to differentiate between other stages of liver fibrosis and liver cirrhosis. For 2D-SWE.SSI the best liver stiffness cut-off value to differentiate between liver cirrhosis and other stages of fibosis was >13.7 kPa with 88.57 Se, 75.68 Sp, 87.3 positive predictive value (PPV) and 77.8 negative predictive value (NPV) (AUROC $= 0.831$, $p < 0.0001$). For a liver stiffness cut-off value >10.7 kPa, 2D-SWE.GE had 91.43 Se, 78.38 Sp, 88.9 PPV, 82.9 NPV (AUROC $= 0.904$, $p < 0.0001$) for differentiating liver cirrhosis. The AUROCs of 2D-SWE.SSI and 2D-SWE.GE for predicting the presence of liver cirrhosis were similar ($p = 0.09$).

Conclusion: Both 2D-SWE techniques have a very good feasibility for the non-invasive liver fibrosis assessment and both have a strong correlation with TE. Liver stiffness values obtained by 2D-SWE.GE are significantly lower than those obtained by 2D-SWE.SSI. Both methods have good performance for predicting liver cirrhosis.

Disclosure of Interest: I. Sporea: Ioan Sporea participated in an Advisory Board for Siemens and received speaker fees from Philips, Siemens and General Electric
R.L.D. Sirli: Roxana Sirli received speaker fees from Philips
A. Popescu: Alina Popescu received speaker fees from Philips
All other authors have declared no conflicts of interest.

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OP276 UTILITY OF REAL-TIME SHEAR WAVE ELASTOGRAPHY FOR ASSESSING LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS C

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Introduction: Real-time shear wave elastography (SWE) is a newly developed method of evaluating liver stiffness, which previously had limited comparability with other non-invasive fibrosis biomarkers.

Aims & Methods: This study aimed to compare the utility of SWE, magnetic resonance elastography (MRE), M2BPGi, Fibrosis-4 index (FIB-4), and platelet count (PLT) for diagnosing liver fibrosis. One hundred thirty-seven patients with biopsy-proven chronic hepatitis C (73 men and 64 women; mean age, 64.6 ± 10.6 years; mean body mass index, 23.6 ± 5.08 kg/m^2) were enrolled. Fibrosis was staged from liver biopsies according to the MATAVIR score. We compared the diagnostic performances of SWE (GE Healthcare, USA), MRE (GE Healthcare, USA), M2BPGi, FIB-4, and PLT. SWE, MRE, and liver biopsy were performed on the same day, when we also collected blood samples for M2BPGi, FIB-4, and PLT. Data analysis included Mann-Whitney U test, non-parametric correlation analysis (Spearman), and the area under the receiver operating characteristic curve (AUROC).

Result: All patients completed all examinations except MRE, which could not be performed in 51 patients, primarily due to the presence of metal parts in the body. Fibrosis severity was F0/F1/F2/F3/F4 in 7/50/33/24/23 patients, respectively. The median SWE (m/s), MRE (kPa), M2BPGi (COI), FIB-4, and PLT ($\times 10^4/\mu$L) in patients with F0/F1/F2/F3/F4 were 1.37/1.53/1.71/1.95/1.96, 1.97/2.78/3.43/5.46/6.15, 1.00/1.25/2.20/6.30/6.40, 1.64/2.25/2.94/4.58/6.56, and 20.0/17.1/14.4/10.6/9.4, respectively. Significant differences were observed between F1/F2 and F2/F3 in SWE, F0/F1, F1/F2, and F2/F3 in MRE, F1/F2 and F2/F3 in M2BPGi, F1/F2 and F2/F3 in FIB-4, and F2/F3 in PLT. The AUROCs for SWE, MRE, M2BPGi, FIB-4, and PLT for detecting considerable fibrosis ($\geq$F2) were 0.86 (95% CI, 0.78–0.92; cut-off, 1.75 m/s), 0.88 (CI, 0.80–0.95; cut-off, 3.40 kPa), 0.87 (CI, 0.81–0.93; cut-off, 2.2 COI), 0.81 (CI, 0.74–0.88; cut-off, 2.83) and 0.78 (CI, 0.70–0.86; cut-off, $14.5 \times 10^4/\mu$L), respectively. Similarly AUROCs for SWE, MRE, M2BPGi, FIB-4, and PLT for detecting severe fibrosis ($\geq$F3) were 0.93 (95% CI, 0.89–0.98; cut-off, 1.81 m/s), 0.92 (CI, 0.86–0.97; cut-off, 4.21 kPa), 0.89 (CI, 0.83–0.95; cut-off, 2.99 COI), 0.84 (CI, 0.77–0.91; cut-off, 4.11) and 0.85 (CI, 0.79–0.92; cut-off, $12.6 \times 10^4/\mu$L), respectively. There was a strong correlation between SWE and MRE ($r = 0.77$, $p < 0.001$).

Conclusion: The AUROC for SWE for diagnosing severe fibrosis in patients with chronic hepatitis C was similar to that for MRE and higher than those for other fibrosis biomarkers (M2BPGi, FIB-4, and PLT). Compared to MRE, SWE demonstrated greater utility in its feasibility, with fewer contraindications, greater ease of performance, and lower cost.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP277 ASSOCIATIONS OF TOLL LIKE RECEPTORS (TLR-2) & (TLR-4) ALLELES WITH THE HEPATITIS C VIRUS INFECTION OUTCOME IN EGYPTIAN POPULATION: A MULTICENTRE FAMILY BASED STUDY

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Introduction: The human Toll like receptors (TLRs) family consists of ten receptors that are critically important for innate immunity. TLRs recognize and respond to diverse microbial molecules and enable the innate immune system to discriminate among groups of pathogens and to induce an appropriate cascade of effector responses. HCV has different effects upon TLR pathway stimulation in various cellular compartments and in this way is able to both stimulate proinflammatorycytokine production leading to liver damage and evade immune responses to establish viral persistence.

Aims & Methods: The aim of this work is to investigate the association of TLR SNPs with the outcome of the HCV infection. Four SNPS of TLR2 and TLR4 were genotyped by real time PCR using Taq^{Man}allelic discrimination kit (Applied Biosystems) according to the manufacturer's protocol. A total 392 families (1176 individuals) were recruited in this study from upper & lower Egypt (east & west delta), we compared the risk of allele carriage of selected markers in different groups. These groups included spontaneous virus clearance (SVC) (108 subject), chronic HCV patients (549), and negative control (519) individuals. The rs 121917864 (C/T) and rs5743708 (G/A) were genotyped for TLR2 while rs4986791 (C/T) and rs62522600 (G/A) were genotyped for TLR4.

Result: As regard TLR2, The T allele of rs 121917864 (C/T) is significantly higher in HCV group compared to that control group and spontaneous(SVC) group ({OR 2.960 (95% CI 1.95 to 3.45 $P = 0.0005$) and 2.635 (95%CI 2.14 to 4.15 $P = 0.0001$)} respectively. While A allele of rs5743708 (G/A) is highly significant associated with HCV group compared to that control group and spontaneous (SVC) group {OR = 2.2071 (95% CI 1.2056 to 4.0404 $P = 0.007$) and 2.1321 (95% CI 1.5528 to 2.9274. $P = 0.0001$)} respectively**.** On the other hand the TLR4 genotyping revealed that the carriages of C allele of rs4986791 was significantly higher in negative and spontaneous (SVC) group compared to that of chronic HCV group (OR:0.4843 95% CI :0.388–0.646 and 0.4449 and 95% CI: 0.2917–0.6787) simultaneously indicating that the C allele act as protective allele against HCV infection and development of chronic HCV. Linkage Disequilibrium of rs4986791 and rs62522600 SNPs indicating that the carriage of TA haplotype was significantly higher in chronic HCV compared to that of negative group (OR = 3.8 95% CI: 2.95–4.95). No one of spontaneous group was carriage for TA haplotype, this revealing the role of TA haplotype as a risk indicator for HCV infection.

Conclusion: Current study demonstrated that spontaneous clearance of HCV was associated with The allele C ofrs4986791 of TLR-4 and chronicity of HCV infection is associated with the risk haplotype (TA) of TLR-4& T allele of rs121917864 & A allele of rs5743708 of TLR-2.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP278 USEFULNESS OF MULTIPOLAR BIPOLAR RADIOFREQUENCY SYSTEM AND VALUE OF 3D SIM-NAVIGATOR

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Introduction: Fusion imaging technology is reportedly useful for radiofrequency ablation (RFA), and various types of ultrasound equipment with integral fusion imaging systems have been developed. Several RFA devices have also become available in Japan. CelonPOWER (Olympus Surgical Technology), a multipolar and bipolar RFA device, was approved for use in Japan in 2012. A single procedure using several applicators simultaneously can ablate an extensive area and reduce treatment time. A sufficiently wide area of ablation requires the optimal placement of multiple applicators. The accurate positioning of two applicators can be quite easily visualized by ultrasonography, whereas precise three-dimensional (3D) positioning of three applicators cannot. The 3D Sim-Navigator (HITACHI) is a new navigation system that can be used during real-time virtual sonography (RVS) by simulating the 3D positions of multiple applicators, which can facilitate their ideal 3D positioning. We evaluated local hepatocellular carcinoma (HCC) recurrence rates after treatment using a multipolar RF system and determined the applicability of the 3D Sim-Navigator to the system.
Aims & Methods: We compared the local recurrence rates of 209 HCC treated using multipolar or monopolar RF systems between January 2013 and October 2015 using propensity-score matching analysis. We evaluated 77 nodules from 63 patients treated using a bipolar RFA system with multiple applicators and compared complete necrosis rates (CNR) generated with or without the 3D Sim-Navigator.
Results: Propensity-score matching analysis showed that the mean tumor diameter was 24.7 ± 5.9 mm, and the cumulative annual local recurrence rates were 0% and 14.9% for the multipolar and monopolar RF systems, respectively ($p = 0.228$). Thirty-two and 45 nodules with mean diameters of 28.1 ± 11.5 and 22.2 ± 5.7 mm ($p = 0.011$) were treated with and without the 3D Sim-Navigator, respectively, with CNR of 68.8% and 66.6%, respectively, indicating that the two groups did not significantly differ ($p = 0.847$).
Conclusion: Case matching analysis of local recurrence rates of HCC after RFA showed that that the multipolar RF system is more effective than the monopolar RF system against tumors with a diameter >25 mm. Although tumor diameter was significantly larger in the group with, than without the 3D Sim-Navigator, CNR did not significantly differ between the two groups, because multiple applicators could be placed in ideal 3D positions using the 3D Sim-Navigator. Therefore, HCC with a tumor diameter >25 mm should be ablated using a multipolar RF system with ideal 3D positioning facilitated by the 3D Sim-Navigator.
Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

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OP279 ASSOCIATION BETWEEN ADIPOQ GENE POLYMORPHISMS AND THE RISK OF NEW-ONSET DIABETES MELLITUS AFTER LIVER TRANSPLANTATION

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Introduction: New-onset diabetes mellitus (NODAT) is a common metabolic complication after liver transplantation (LT). The prevalence of NODAT stays high and has been reported as 17–36%.[1] NODAT contributes to an increased risk of infections, cardiovascular disease, chronic rejection and renal failure, which subsequently lead to a reduced life quality and high mortality.[2,3] Recent findings suggest a tight link between ADIPOQ gene polymorphism and glucose metabolism and diabetes mellitus. Several studies have found that serum adiponectin levels are lower in diabetic patients than healthy people.[4] In addition, reduced pretransplantation serum adiponectin levels are also correlated with new-onset diabetes mellitus after kidney transplantation.[5] From previous studies we can reasonably infer that adiponectin would be an important protein in the development of NODAT. However, there have been no report to describe the association between ADIPOQ gene polymorphism and new-onset diabetes mellitus after liver transplantation.
Aims & Methods: In the current study, we aim to investigate whether single nucleotide polymorphisms of ADIPOQ were correlated with the NODAT and also to compare the overall survival and graft survival between NODAT group and non-NODAT. The study included 256 patients who underwent liver transplantation in our center from January 2009 to December 2011. They were divided into two groups: NODAT group and Non-NODAT group. We screened independent risk factors of NODAT with univariate and multivariate analyses. We further built three NODAT prediction models containing the risk factors and got optimized model with AUROC curve method. In addition, the association between metabolic syndrome and NODAT was also examined. Overall survival and graft survival were determined by the Kaplan-Meier method and tested by the log-rank statistics.
Result: The incidence rate of NODAT within 6 months post liver transplantation was 29% (75/181). There were 214 men and 42 women in the study and the average age was 48.0 ± 9.9 y. Age (54.0 ± 4.1 vs 45.4 ± 6.9, $P < 0.001$), BMI (23.1 ± 3.0 vs 22.3 ± 3.0, $P < 0.014$), blood tacrolimus level at 1 month post liver transplantation (10.23 ± 3.30 vs 8.76 ± 1.74, $P < 0.001$), ADIPOQ rs1501299 ($P < 0.007$) and rs822396 ($P < 0.013$) were significantly correlated with NODAT with univariate analyses. Dominant model and recessive model confirmed these risk factors further. Three NODAT prediction models were built containing these risk factors and we finally found the optimized model (AUROC = 0.743). Metabolic syndrome was also associated with NODAT (21% vs 8%, $P < 0.003$). The overall survival rate ($P < 0.015$) and graft survival rate ($P < 0.011$) of NODAT were significantly lower than that of Non-NODAT.
Conclusion: This study is the first to provide evidence of the association between recipient rs1501299 genotype polymorphism and new-onset diabetes mellitus after liver transplantation on large samples. Our findings demonstrate that recipient rs1501299 is associated with higher risk of NODAT and would be a potential genetic factor to improve the predictive ability of NODAT. we also confirm age, BMI, blood tacrolimus level at 1-month after LT are independent risk factors of NODAT. These findings may be beneficial in helping to estimate the risk of NODAT development in liver transplantation and thereby in controlling modifiable risk factors.
Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 15:45–17:15

MANAGEMENT OF REFRACTORY CROHN'S DISEASE – ROOM A

OP280 DISAPPEARANCE OF ANTI-DRUG ANTIBODIES TO INFLIXIMAB AND ADALIMUMAB AFTER ADDITION OF AN IMMUNOMODULATOR IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Introduction: Since therapeutic options for patients with inflammatory bowel disease (IBD) who lose response to anti-TNF therapy are limited, optimal use of these agents is crucial. Loss of response can be caused by anti-drug antibody (ADA) formation and subsequent neutralization of the effect of the drug. Addition of an immunomodulator (IM) to anti-TNF therapy has been proposed as an approach to reduce antibody formation, increase serum concentrations and to regain clinical response.
Aims & Methods: We investigated whether addition of an IM to anti-TNF monotherapy can lead to a decrease of ADA levels and regained clinical response. Therefore, we retrospectively collected measurements of infliximab (IFX) and adalimumab (ADL) serum concentrations together with ADA levels from 602 patients at our IBD centre (September 2005-September 2015). ADA levels were determined with a drug sensitive assay by Sanquin Biologicals Laboratory. As a next step, we identified all ADA positive patients with secondary loss of response to IFX or ADL who received an IM in an attempt to eliminate ADA and to

regain clinical response. Detailed documentation of disease activity was registered.
Result: In 98/376 patients ADA directed against IFX and in 61/226 patients ADA against ADL were detectable. From all 159 ADA positive patients, 17 patients had received an IM, either a thiopurine or MTX, because of secondary loss of clinical response. Seven patients received MTX, ten a thiopurine (4 azathioprine, 4 mercaptopurine and 2 6-TG). In 7 out of 8 patients treated with IFX, addition of an IM resulted in an increase of serum drug levels accompanied with a decrease of ADA till they were undetectable. The median time for ADA to IFX to become undetectable was 11 months (IQR 6–28). For patients treated with ADL, an increase of the serum drug concentrations, together with a decrease of ADA levels, was reached in 6 out of 7 patients after addition of an IM. The median time for the ADA levels to be undetectable was also 11 months (IQR 2–37). All patients receiving MTX responded clinically which resulted in continuation of the ongoing anti-TNF treatment.
Conclusion: Addition of an IM to IFX or ADL monotherapy in IBD patients with secondary loss of response due to ADA formation, led to a decrease of ADA levels and an increase in serum drug concentrations in the majority of the patients. Patients who regained response due to this strategy could continue the current anti-TNF treatment and switching to another agent was not necessary.
Disclosure of Interest: G.R. van den Brink: G. van den Brink has received consulting and lecture fees from Abbott laboratories, Merck Sharp & Dohme and Ferring Pharmaceuticals. He has received research grants from Abbott laboratories, Crucell and Ferring Pharmaceuticals.
M. Lowenberg: M. Löwenberg has served as speaker for AbbVie, Covidien, Dr. Falk, Ferring Pharmaceuticals, Merck Sharp & Dohme, Receptos, Takeda, Tillots and Tramedico. He has received research grants from AbbVie, Merck Sharp & Dohme, Achmea healthcare and ZonMW.
G. D'Haens: G. D'Haens reports having received consulting fees from AbbVie, Boehringer, Ferring, Jansen Biologics, Merck Sharp and Dohme, Takeda, Pfizer, Tillotts Pharma and reports receiving research grants from Abbott Laboratories, Jansen Biologics, MSD, DrFalk Pharma
All other authors have declared no conflicts of interest.

OP281 POST-OPERATIVE COMPLICATIONS IN ELDERLY-ONSET INFLAMMATORY BOWEL DISEASE: A POPULATION-BASED STUDY

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Introduction: Inflammatory Bowel Diseases (IBD) diagnosed after the age of 60 are increasing and seems to have a milder course compared to younger patients. However, the intestinal surgery rates are similar to those in the young adult population. Data on post-operative complications (POC) in elderly-onset IBD are scarce. We reported the incidence and factors associated with POC in general population.
Aims & Methods: Among 841 elderly-onset population-based EPIMAD Cohort (1), 139 patients underwent surgery. Among those, 100 had Crohn's Diseases (CD) and 39 Ulcerative Colitis (UC). Medical charts for early (within 30 days of surgery) and late (>30 days of surgery) POC (POC) have been reviewed according to Dindo's classification (2). Associated factors have been tested by Cox regression models.
Result: After a median follow-up of 7.3 years [Q1 = 3-Q3 = 12], 50 patients (36%) had at least one POC. No significant difference was observed for POC frequency between UC and CD. Thirty-two early POC were found in 23 patients (16.5%); 52% were severe (defined by a Dindo's grade >2) and 47% infectious. Among the 37 late complications observed in 33 patients (23.7%), 42 were severe (grade > 2) and 56% were mechanical (bridle, eventration, anastomotic stricture). The cumulative probability of POC was 7.4% at 6 months (95% CI: 3.9–13.7), 10.9% at 1 year (6.5–18.1), 22.8% at 5 years (16.0–32.0) and 30.5% at 10 years (21.8–41.4). In multivariate analysis, emergency surgery (HR = 4.46 [1.75–11.36]) and acute severe ulcerative colitis (HR = 7.84 [2.15 – 28.52]) were significantly associated with early POC while recent steroid exposure and co morbidities (Charlson's index) were not independently associated with an increased risk. Female gender (HR = 2.10 [1.01 – 4.37]) and time between diagnosis and surgery >3 months (HR = 2.09 [1.01 – 4.31]) were significantly associated with late POC.
Conclusion: In elderly onset IBD patient who underwent surgery, POC were frequent. The early POC were more severe than the late POC. Emergency surgery and acute severe ulcerative colitis were significantly associated with early complications when female gender and delay between diagnosis and surgery were associated with late POC. These results reinforce the need for specialized and dedicated management of these at-risk elderly patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 15:45–17:15
FROM GUIDELINES TO CLINICAL PRACTICE: H. PYLORI – ROOM D

OP282 PAN-EUROPEAN REGISTRY ON H. PYLORI MANAGEMENT (HP-EUREG): INTERIM ANALYSIS OF THE SINGLE-CAPSULE BISMUTH QUADRUPLE TREATMENT (PYLERA®)

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Introduction: The most novel treatment used in *H. pylori* management in Europe is the single-capsule bismuth quadruple treatment (Pylera®), but there is still very little evidence of its efficacy and safety on routine clinical practice. Pylera® is still non-commercially available in most countries in Europe and, in most of those available, it has just recently reached pharmacies.
Aims & Methods: We aimed to evaluate the use and outcomes of Pylera® in the European Registry on *H. pylori* Management (Hp-EuReg). Methods: A systematic prospective registry of the clinical practice of European gastroenterologists regarding *H. pylori* infection and treatment (31 countries and 280 recruiting investigators). A local coordinator was selected from each country. Each coordinator selected a representative group of recruiting investigators from its country. An electronic clinical research file (e-CRF) was created on AEG-REDCap to systematically register all adult patients infected with *H. pylori*. Variables included: Patient's demographics, previous eradication attempts, prescribed eradication treatments, adverse events, and outcomes (cure rates, compliance, follow up, etc.). Patients with both eradication confirmatory test and with less than one-year follow-up have been considered ongoing and were excluded from the analysis.
Result: Up to now, 15,660 patients have been included, and 12,921 have finished follow up (59% females, 88% Caucasian). Mean age was 55 years. Pylera® was used in 175 patients (1.2% of all treatments registered: 44% in first-line, 27% in second, 22% in third, and 8% in following rescues). Omeprazole was used in 69% of cases and esomeprazole in 24%. Overall efficacy was 76% (95%C.I. = 66–86%) by ITT and 78% (69–87%) by PP. In first line, efficacy was 93% (84–100%) both by ITT and PP. Second line efficacy was 68% (51–85%) by ITT and 74% (58–90%) by PP. Compliance with treatment was 98%. Adverse events were reported in 14% of cases and did not cause treatment discontinuation in any patient.
Conclusion: Experience with single-capsule bismuth quadruple therapy (Pylera®) is still limited. Wide confidence intervals do not allow drawing conclusions for rescue regimens; however, our preliminary data suggests that given its safety profile, compliance rates and efficacy, it may be an acceptable option as first-line treatment in Europe.
Disclosure of Interest: A.G. McNicholl: Speaker for Allergan
A. Perez Aisa: Speaker for Allergan
J.P. Gisbert: Has acted as speaker and advisor for Almirall, Allergan, AstraZeneca, Casen Recordati, Nycomed.
All other authors have declared no conflicts of interest.

OP283 PAN-EUROPEAN REGISTRY ON H. PYLORI MANAGEMENT (HP-EUREG): INTERIM ANALYSIS OF FIRST-LINE TREATMENT WITH BISMUTH, AMOXICILLIN AND CLARITHROMYCIN

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Introduction: Addition of bismuth to triple therapy has been proposed as a strategy to improve its efficacy.
Aims & Methods: To evaluate the use and outcomes of a quadruple therapy containing a proton pump inhibitor, bismuth, clarithromycin and amoxicillin (BCA) in the European Registry on *H. pylori* Management (Hp-EuReg). Methods: A systematic prospective registry of the clinical practice of European gastroenterologists regarding *H. pylori* infection and treatment (31 countries and 280 recruiting investigators). A local coordinator was selected from each country. Each coordinator selected a representative group of recruiting investigators from its country. An electronic clinical research file (e-CRF) was created on AEG-REDCap to systematically register all adult patients infected with *H. pylori*. Variables included: Patient's demographics, previous eradication attempts, prescribed eradication treatments, adverse events, and outcomes (cure rates, compliance, follow up, etc.). Patients with both eradication confirmatory test and with less than one year follow up have been considered ongoing and were excluded from the analysis.
Result: Up to now, 16,025 patients have been included, and 12,921 have finished follow up (59% females, 87% Caucasian). Mean age was 55 years. BCA was used in 248 patients (1.7% of all treatments registered): 92% in first-line. Overall efficacy was 94% (95%C.I. = 91–97%) by ITT and 95% (92–98%) by PP. First line efficacy was 95% (91–99%) both by ITT and PP. Esomeprazole coadjuvation (36%) achieved higher eradication rates than other PPIs (98% vs. 94%). Treatment was prescribed in 10 or 14 days regimens (50% in each). 14-day regimen achieved higher eradication rates than 10 day both by ITT (97% vs. 92%; N.S.) and PP (97% vs. 93%; N.S.) Compliance with treatment was 95%. Adverse events were reported in 28% of cases and caused treatment discontinuation in 1 patient.
Conclusion: A 14-day regimen combining bismuth salts with standard triple therapy (PPI + amoxicillin + clarithromycin) as first-line treatment for *H. pylori* eradication offers near 95% eradication rates.
Disclosure of Interest: A.G. McNicholl: Speaker for Allergan
A. Perez Aisa: Speaker for Allergan
J.P. Gisbert: Scientific and teaching speaker and advisor for: Almirall, Allergan, AstraZeneca, Casen Recordati, Nycomed.
All other authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 15:45–17:15
VISUALISING SMALL BOWEL DISEASES – ROOM E1

OP284 NOVEL MOTORIZED SPIRAL ENDOSCOPY: FIRST RESULTS OF A EUROPEAN PROSPECTIVE TRIAL

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Introduction: Currently available methods for small bowel endoscopy are complex to use and time consuming. Novel Motorized Spiral Endoscopy (NMSE) represents a new technology which offers all advantages of spiral enteroscopy with a faster and less invasive approach.
Aims & Methods: To prospectively study the efficacy and safety of peroral NMSE. Primary objective: diagnostic yield of NMSE in patients with suspected small bowel diseases. Secondary objectives: procedural success, - time, depth of maximal insertion, therapeutic yield, adverse events. Patients with occult gastrointestinal bleeding (OGB) or indeterminate iron-deficiency anemia (IDA) or positive findings of small bowel imaging examinations were included in a two-center prospective clinical trial. In total 132 cases will be enrolled to determine the diagnostic yield. A rate of ≥28% would be considered as clinically efficacious under consideration of a two sided non-inferiority margin of 20% in comparison to conventional enteroscopy. A novel reusable endoscope (Olympus Corp.) with an integral motor was used for rotating a disposable short spiral overtube mounted on the insertion tube portion. Rotation of the spiral allows to "pleat" or "unpleat" the bowel either on or off the insertion tube as the spiral thread rotates in a clockwise or counter-clockwise direction. All procedures were performed under general anesthesia.
Result: Thirty patients (12 f, 18 m; mean age [range]: 62 [20–92] years) with positive findings of video capsule endoscopy or other small bowel imaging modality (angiectasias n = 18, jejunal/ileal polyps n = 3, thickening of wall/stricture n = 3, other n = 1) have so far been included in the trial. 27 of 30 patients had IDA. NMSE could be performed in 29 of the 30 patients with advancement of the endoscope beyond the ligament of Treitz. In one case further insertion was not be performed because of a bradycardia which caused discontinuation of the procedure. Mean insertion time to the jejunum was 6.4 [2–19] min. and to the deepest point of insertion distal from ligament of Treitz 22.6 [7–52] min. The mean insertion depth from ligament of Treitz was 393 [0–600] cm. Panenteroscopy to cecum could be achieved in one patient from the oral route. The diagnostic yield of NMSE was 83.4% corresponding to no findings in 5 cases, at least one angiectasia in 18 cases, one or more benign polyps in 6 and other findings in 12 patients. Thirty-two interventions were performed in 22 patients (biopsies n = 8, APC n = 17, tattooing n = 3, clipping n = 3, EMR n = 1). Mean withdrawel time without interventions was 14.7 [5–45] min. Mild mucosal trauma in the esophagus or duodenum was registered in 6 cases. There were no serious adverse events.
Conclusion: First clinical data of an ongoing large prospective trial demonstrate that NMSE can be effectively and safely performed for diagnostic and therapeutic enteroscopy. The procedure offers advantages over traditional methods in terms of procedural duration and ease of use.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP285 CROSS-SECTIONAL EVALUATION OF TRANSMURAL HEALING IN PATIENTS WITH CROHN'S DISEASE ON MAINTENANCE TREATMENT WITH BIOLOGICS

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Introduction: Transmural healing (TH) of Crohn's disease (CD is a new under-explored and interesting outcome of the concept of deep remission.
Aims & Methods: The aim of this study was to assess the rate of TH evaluated by bowel sonography (BS) and magnetic resonance enterography (MRE) in CD patients treated with biologics, directly comparing the two cross-sectional procedures. We performed a 2-year observational longitudinal prospective study evaluating steroid-free clinical remission (CR), mucosal healing (MH), and TH in all patients with CD who would complete a 2-year period of maintenance treatment with biologics. All patients underwent endoscopy, BS and MRE before starting biologics and 2 years later. Furthermore, the Crohn's Disease Activity Index (CDAI) score was calculated before treatment and 2 years later.
Result: The study included 40 CD patients biologics (38% infliximab and 62% adalimumab). TH was evident in 10 patients (25%) at BS and in 9 patients (23%) at MRE ($k = 0.84$; $P < 0.01$). No significant differences were noted about TH in relation to the type of biologic used (P = NS). MH was obtained in 14 subjects (35%). A good agreement was observed between MH and TH at BS ($k = 0.63$; $P < 0.001$) and TH at MRE ($k = 0.64$; $P < 0.001$). CR was achieved in 24 patients (60%). A poor agreement was found between CR and TH, both at BS and MRE ($k = 0.27$ and 0.29, respectively; $P < 0.01$).
Conclusion: TH can be reached in about 25% of CD patients treated with biologic with high agreement between BS and MRE on defining this outcome. After considering the advantages of BS (high diagnostic accuracy, low costs, high patient compliance, high availability) and the limitations or MRE (high costs, low availability), we suggest the use of BS as first cross-sectional procedure in defining TH in patients with CD.
Disclosure of Interest: All authors have declared no conflicts of interest.

Table 1 (OP288): Association between number of pathophysiological alterations and Patient Reported Outcomes (data shown as mean ± SD)

	No abnormality (n = 76)	1 abnormality (n = 128)	2 abnormalities (n = 121)	≥3 abnormalities (n = 82)	ANOVA
IBS symptom severity (z score)	−0.55 ± 0.94	−0.22 ± 1.06	0.11 ± 0.96	0.37 ± 0.86	F = 14.0; p < 0.0001
Somatic symptom severity (z score)	−0.47 ± 0.80	−0.30 ± 0.93	0.17 ± 9.91	0.68 ± 0.98	F = 26.7; p < 0.0001
IBSQOL Emotional	60 ± 19	55 ± 24	44 ± 19	37 ± 17	F = 20.3; < 0.0001
IBSQOL Mental Health	82 ± 16	76 ± 22	65 ± 20	51 ± 20	F = 35.4; p < 0.0001
IBSQOL Sleep	82 ± 16	76 ± 23	69 ± 24	58 ± 24	F = 15.3; p < 0.0001
IBSQOL Energy	69 ± 24	58 ± 27	48 ± 24	35 ± 23	F = 25.0: p < 0.0001
IBSQOL Physical Functioning	75 ± 20	74 ± 21	68 ± 20	57 ± 26	F = 11.8; p < 0.0001
IBSQOL Food	67 ± 20	64 ± 21	59 ± 18	55 ± 20	F = 6.3; p < 0.0001
IBSQOL Social Role	71 ± 20	65 ± 23	56 ± 20	51 ± 24	F = 13.5; p < 0.0001
IBSQOL Physical Role	64 ± 28	56 ± 31	47 ± 29	40 ± 28	F = 10.3; p < 0.0001
IBSQOL Sexual	71 ± 23	70 ± 25	63 ± 25	50 ± 25	F = 8.2; p < 0.0001

TUESDAY, OCTOBER 18, 2016 15:45–17:15

COELIAC DISEASE FOR THE CLINICIAN – ROOM F1

OP286 THE ENZYME ACTIVITY OF SMALL INTESTINAL MUCOSA IN ADULT PATIENTS WITH CELIAC DISEASE

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Introduction: Some patients with celiac disease (CD), who have followed gluten-free diet (GFD) and have a normal histological structure of small intestine mucosa, may still have symptoms of bloating, rumbling and diarrhea. These symptoms may be associated with changes of the activity of the small intestine enzymes. Objective: To determine the activity of enzymes (glucoamylase, maltase, sucrase and lactase) in CD patients.

Aims & Methods: Thirteen patients with newly diagnosed CD: 9 women and 4 men, (mean age 38.68 ± 15,75 years) and 30 patients with previously diagnosed CD: 22 women and 8 men (mean age 41.96 ± 18,46 years) were observed. The diagnosis of CD was based on clinical presentation, serology, including anti-gliadin antibodies (AGA) IgA and anti-tissue transglutaminase (anti-tTG) IgA antibodies and duodenal biopsy. Histological changes of intestinal biopsy were classified according to the revised Marsh criteria 1999. In 1 group Marsh IIIb lesions were seen in 23%, Marsh IIIc – in 77%. In 2 group - Marsh IIIa and Marsh IIIb lesions were seen in 30% respectively, Marsh II - in 13.3%, the normal structure of small intestine were observed in 26.6%. The enzyme activity was measured in small intestine mucosa by Dahlquist modified method.

Result: In patients with newly diagnosed CD, the activity of all enzymes was decreased in 92.3% in the group of patients followed GFD - in 36.5% ($p < 0.05$). It was found that the total atrophy (Marsh IIIc) was associated with a reduced activity of all enzymes in all patients; whereas all patients with Marsh IIIb atrophy had a decreased activity of lactase, 90% had a decreased activity of glucoamylase and maltase, and in 81.8% of cases we observed a decreased activity of sucrase. The recovery of the intestine mucosa showed improvement of activity of all enzymes. However, even in normal small intestine mucosa the reduction of glucoamylase activity was observed in 37.5% reduction of maltase activity - in 62.5%, the activity of sucrase was reduced in 50% and activity of lactase was decreased in 37.5%. The reduced activity of all enzymes was found in 37.5% of patients with normal structure of small intestine mucosa. A weak correlation between the degree of atrophy and the activity of sucrase and maltase ($rs = -0.513$, $p = 0.005$ and $rs = -0.406$, $p = 0.029$, respectively) was established. Activity of other enzymes had no significant correlation with the degree of atrophy.

Conclusion: In 37.5% of adult patients with CD who follow GFD and have a normal structure of mucosa, a decreased activity of intestinal enzymes may occur, which may be one of the reasons for the persistence of intestinal symptoms.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP287 FODMAP RESTRICTION OF A GLUTEN-FREE DIET IN PATIENTS WITH COELIAC DISEASE: A RANDOMIZED, CONTROLLED CLINICAL STUDY

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Introduction: 20–30% of coeliac patients on a gluten free diet still have irritable bowel syndrome (IBS) symptoms. A low FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet is effective to reduce symptoms in IBS patients.

Aims & Methods: We wanted to investigate the benefit from restricting the FODMAP content of the diet in patients with coeliac disease, who are still symptomatic on a gluten-free diet. 40 patients with coeliac disease and IBS symptoms confirmed by the Rome III-criteria and IBS-SSS (Symptom Severity Scale) were randomized and instructed by dieticians: Group A excluded all wheat starch and "traces of gluten" from their diet, Group B excluded FODMAPs as well as gluten. Symptoms on IBS-SSS were recorded at baseline, 3 and 6 weeks, as well as quality of life (SF-36). Four days prospective dietary intake records at baseline and 6 weeks, compliance and satisfaction after 6 weeks, and 1 month later. Dietist Net Free was used for FODMAP calculations. Statistics: paired T-tests and Wilcoxon's.

Result: 20 patients were included in each group; A (18F/2M, age 39 ± 15) and B (15F/5M, age 43 ± 12). 42.5% had constipation, 27.5% diarrhoea and 30% both. The mean total IBS-SSS score was significantly reduced: Group A from 260 to 204 ($p = 0.0022$), group B from 263 to 145 ($p < 0.0001$), $p = 0.0247$, group B vs. A. In group A 10% reached remission, in Group B 25% ($p = 0.408$). All subscales improved significantly in group B, but only abdominal pain severity in group A. SF-36 physical health score improved in group B ($p = 0.0081$), but not in group A. Patients in group B were significantly more satisfied with pain relief ($p = 0.0132$), but it was also more challenging to follow their diet ($p = 0.0008$).

Conclusion: Patients with coeliac disease and IBS-symptoms had significant improvement in abdominal symptoms and physical health from a low FODMAP diet for 6 weeks. A gluten-free diet with reduced FODMAP content was more effective than a more strict gluten-free diet, and should be offered to coeliac patients with refractory IBS-symptoms on a gluten-free diet.

Disclosure of Interest: All authors have declared no conflicts of interest.

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PATHOPHYSIOLOGY OF IBS – ROOM N2

OP288 ADDITIVE EFFECT OF PATHOPHYSIOLOGICAL FACTORS ON PATIENT REPORTED OUTCOMES IN IBS

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Introduction: Both central and peripheral pathophysiological factors are thought to contribute to the symptoms of IBS. Psychological symptoms reflect CNS dysfunction, while abnormal GI sensorimotor function reflects mainly peripheral dysfunction; both have been associated with symptoms in IBS. These factors may have additive effects on patient reported outcome (PRO) measures in IBS.

Aims & Methods: Our aim was to study whether these pathophysiological alterations have additive effect on PROs in patients with IBS. To achieve this, we included 407 patients fulfilling the Rome II or Rome III IBS criteria (74% females; mean age 36 ± 12 years). The following pathophysiological factors were measured in all subjects: colonic transit time (radiopaque markers); compliance, allodynia (low pain thresholds) and hyperalgesia (increased pain intensity) (rectal barostat); and anxiety and depression (HAD scale). Abnormal findings on the physiology assessments were defined based on the 5th and 95th percentiles in healthy controls, and on the HAD scale by a score >7. The patients also completed questionnaires to assess IBS symptom severity (IBS-SSS or GSRS-IBS), and bowel habit (stool diary). To be included in the analysis, a pathophysiological factor had to be associated with severity of ≥one IBS-related symptom. As PRO measures we used z-scores of IBS symptom severity (IBS-SSS or GSRS-IBS total score) and somatic symptom severity (SCL-90 somatization subscale or PHQ-15), and quality of life (IBSQOL).

Result: Allodynia was seen in 40% of patients, hyperalgesia in 17%, accelerated colonic transit in 18%, delayed transit in 7%, anxiety in 52% and depression in 24% - these factors were associated with severity of at least one IBS symptom. Rectal compliance (increased in 10% and reduced in 14%) was not associated with more severe IBS symptoms. At least 3 pathophysiological abnormalities relevant for symptoms were present in 20% of patients, 2 in 30%, 1 in 31%, and 18% of patients had none. The number of pathophysiological abnormalities was not associated with age ($p = 0.15$), gender ($p = 0.12$) or IBS subgroup ($p = 0.21$). With increasing number of pathophysiological abnormalities, there was a gradual increase in the severity of IBS symptoms ($p < 0.0001$) and somatic

symptoms ($p < 0.0001$), and a gradual reduction of QOL ($p < 0.0001$) (table 1). When assessing central (anxiety and depression) and "peripheral"/GI pathophysiological factors (allodynia, hyperalgesia, accelerated and delayed transit) separately, cumulative effects on symptom severity and QOL were also observed.
Conclusion: Visceral hypersensitivity, i.e. allodynia and hyperalgesia, abnormal colonic transit and psychological factors are all pathophysiological factors that are associated with GI symptom severity in IBS. These factors have an additive effect on GI and non-GI symptoms, as well as on quality of life in IBS, and are therefore relevant treatment targets.
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All other authors have declared no conflicts of interest.

OP289 INCREASED INHIBITORY NEUROTRANSMISSION WITHIN ANTERIOR CINGULATE CORTEX IS RELATED TO COMORBID ANXIETY IN IRRITABLE BOWEL SYNDROME

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Introduction: Inspired by the concept of Irritable Bowel Syndrome (IBS) as a disorder of brain-gut-communication, alterations in central mechanisms are increasingly acknowledged in IBS pathophysiology. Given high comorbidity with affective disorders, emotional factors likely play a role in disturbed central processes in IBS. Dysfunctions particularly in brain regions involved in emotion processing, including the rostral anterior cingulate cortex (rACC) as a unique hub of both, affect regulation and anti-nociception, may constitute a central link between abdominal pain and psychiatric comorbidities. While a growing number of neuroimaging studies support a crucial role of rACC in altered pain processing and emotional disturbances in IBS, the biochemical basis of these alterations remains unknown.
Aims & Methods: We compared IBS patients and healthy controls (HC) regarding concentrations of glutamate (Glu) and γ-Aminobutyric acid (GABA+) in rACC using quantitative magnetic resonance spectroscopy (qMRS). We further addressed associations with anxiety and depression as the most common psychiatric comorbidities in IBS. In a combined MRI and MRS study, GABA+ and Glu concentrations in 38 female IBS and 19 age-matched female HC were measured using a Philips Ingenia 3T scanner and a MEGA-PRESS sequence with a $3x3x3cm^3$ voxel placed in the rACC, localized based on individual T1-weighted images. Symptoms of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS) and correlated with metabolite concentrations. Patients were subdivided into a group with (IBS^+) and without (IBS^-) comorbid anxiety based on published HADS cut-offs.
Result: Compared to HC, IBS as a group exhibited significantly increased GABA+ concentrations within rACC ($p < 0.05$), while no differences were observed in concentrations of Glu. Both anxiety ($r = 0.407$; $p < 0.01$) and depression ($r = 0.276$; $p < 0.05$) correlated with GABA+ concentrations. Inclusion of HADS scores as covariates diminished group differences in GABA+ concentrations in ANCOVA with anxiety, but not with depression. Analyses on IBS subgroups revealed a group effect ($p < 0.05$) with higher GABA+ levels in IBS^+ compared to HC ($p < 0.01$) and compared to IBS^- ($p = 0.056$), whereas differences between IBS^- and HC did not yield significance.
Conclusion: Our findings provide first evidence of dysregulated rACC neurotransmission in IBS. This imbalance appears to be driven by increased GABA+ concentrations in rACC as a crucial structure for anti-nociception and affect regulation. Abnormal GABA+ levels were most pronounced in patients with comorbid anxiety, supporting a key role of psychiatric comorbidities in altered brain processes in IBS. Altered inhibitory GABAergic neurotransmission may be fundamental for dysregulations of affective and nociceptive processing, contributing to functional as well as long-lasting neuroplastic changes in IBS.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP290 BACTERIAL PASSAGE IS INCREASED IN THE COLON OF WOMEN WITH IRRITABLE BOWEL SYNDROME INDEPENDENTLY OF STOOL CONSISTENCY SUBGROUP

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Introduction: Irritable bowel syndrome (IBS) is a chronic functional intestinal disorder with a strong female predominance. The pathophysiology is incompletely understood, but an increasing body of evidence demonstrates a role of the brain-gut-microbiota axis[1]. Alterations in microbiota have been associated with onset as well as changes in symptoms of IBS. Prior data suggest that intestinal barrier function is disturbed in IBS, but to our knowledge the passage of living bacteria through the colonic mucosa has never been investigated.
Aims & Methods: Aims: To study the paracellular permeability and the passage of living bacteria, both commensal and pathogenic, through the colonic mucosa of women with IBS and female healthy controls (HCs). The second aim was to investigate whether IBS stool consistency subgroups differ in terms of intestinal barrier function. Methods: Colonic biopsies from 32 women with IBS (mean age 32.6y; 17 with mixed stool pattern IBS-M, 7 with diarrhea IBS-D and 8 with constipation predominance IBS-C, according to Rome III criteria) and 15 HCs (mean age 29.7y) were mounted in Ussing chambers[2]. Mucosal passage of living *Escherichia coli* (*E.coli*) HS and *Salmonella typhimurium* was investigated. The paracellular passage was measured by using ^{51}Cr-EDTA.
Result:

Table: Mucosal passage of bacteria (bacteria/chamberx10^3) and^{51}CrEDTA (cm/sx10^{-6}) are shown in median (25%–75% percentile)

	IBS	HC	p
E.coli	627 (563–688)	333 (291–387)	0.0001
Salmonella	880 (689–1104)	315 (194–437)	0.0001
51Cr-EDTA	1.1 (0.7–1.5)	0.9 (0.5–1.1)	<0.05

The colonic mucosa of IBS patients had a significantly greater passage both for living *Salmonella typhimurium* and *E. coli* HS compared with HCs ($p < 0.0001$ and $p < 0.0001$ respectively). The ^{51}Cr-EDTA passage was also significantly increased in IBS ($p < 0.05$). IBS-M, IBS-D and IBS-C did not differ significantly in terms of mucosal barrier function measures, neither for bacterial nor for paracellular passage.
Conclusion: The present study demonstrated that passage through the colonic mucosa of both pathogenic and commensal living bacteria is altered in female IBS patients. These findings elucidate new aspects of peripheral abnormalities and support the importance of microbiota as a major factor in the pathophysiology of IBS.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP291 LUBIPROSTONE IMPROVES THE INTESTINAL PERMEABILITY, A NEW APPROACH FOR "LEAKY GUT"; A PROSPECTIVE RANDOMIZED PILOT CLINICAL STUDY IN HEALTHY VOLUNTEERS

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Introduction: Several diseases and disorders are associated with "leaky gut" (or increased intestinal permeability), such as inflammatory bowel diseases, celiac disease, food allergy, irritable bowel syndrome, and obesity-metabolic disorders. Therefore, this topic is an area of growing interest, and a well-established therapy for preventing or reverting increased intestinal permeability would be valuable. Since there are no effective medications for "leaky gut" to date, it would be important to establish a new therapy which aiming at improvement of intestinal permeability. Previous studies have reported that non-steroidal anti-inflammatory drugs (NSAIDs) induce small intestinal damage and increased permeability [1]. Other basic studies have reported that lubiprostone, a chloride channel activator used for chronic constipation, repairs intestinal mucosal barrier function and also prevents NSAID-induced small intestinal damage in rodent models [2].
Aims & Methods: Our aim was to verify the effect of lubiprostone on intestinal permeability in healthy volunteers administrated with diclofenac. We conducted a prospective, randomized parallel-group trial. Healthy male volunteers, with documented abstinence from certain drugs (NSAIDs, proton-pump inhibitors, antibiotics, and probiotics) for at least 3 months prior to the study were enrolled. The subjects were randomly assigned to either the lubiprostone or control groups. All participants performed sugar permeability tests on baseline, after 14 days of treatment (day14), and after 28 days of treatment (day28). The

subjects ingested 400 ml of water containing 10 g lactulose and 5 g mannitol, after an overnight fast. Total urine for the following 4 hours was collected and rapidly frozen for analysis. Both groups started with oral intake of 75 mg diclofenac daily for 7 days. Thereafter, the lubiprostone group was treated by oral intake of 24 mg lubiprostone daily for 28 days, while the control group did not receive any medicine after diclofenac. Permeability was expressed as lactulose/mannitol ratio (LMR), calculated from urinary excretion of the initial administrated dose of each sugar.

Result: Fourteen subjects for each group with a median age of 23.5 (range, 21–32) completed the study. The background characteristics including baseline LMR between the two groups showed no significant difference. Treatment after 28 days of lubiprostone showed significant improvement of LMR ($p = 0.0497$), while 14 days treatment did not reach statistical significance compared to control group ($p = 0.403$).

LMR results (analyzed by analysis of covariance: ANCOVA)

LMR	control group (n = 14)	lubiprostone group (n = 14)	p value
baseline	0.019 (0.016–0.022)	0.021 (0.017–0.025)	
day14	0.035 (0.023–0.047)	0.024 (0.019–0.029)	0.403
day28	0.028 (0.023–0.033)	0.017 (0.015–0.019)	0.0497

Conclusion: In our study, 28 days treatment with lubiprostone demonstrated an improvement of increased intestinal permeability after 1-week administration of diclofenac in healthy volunteers. This is the first study to demonstrate a significant effect of a medication for treatment of increased intestinal permeability, and suggests a new approach towards several diseases associated to ''leaky gut''.

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All other authors have declared no conflicts of interest.

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OP292 VISCERAL HYPERSENSITIVITY IS ASSOCIATED WITH GI SYMPTOM SEVERITY IN FUNCTIONAL GI DISORDERS: CONSISTENT FINDINGS FROM FIVE DIFFERENT PATIENT COHORTS

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Introduction: Divergent results have been reported regarding the association between visceral hypersensitivity and GI symptoms in patients with functional GI disorders (FGIDs). Moreover, it has been proposed that the association between hypersensitivity and GI symptoms is secondary to psychological factors and tendency to report symptoms.

Aims & Methods: Our aim was to evaluate the association between visceral hypersensitivity and GI symptom severity in large cohorts of FGID patients. To do this, we included 5 cohorts of patients with FGIDs, who had undergone GI balloon distensions and completed questionnaires to assess GI symptom severity, somatization, anxiety and depression: 1. Belgian functional dyspepsia cohort (n = 242; 180 females (f); age 39 ± 13 years (mean ± SD); gastric barostat (ramp inflation, 2 mmHg steps, 2 min/step). 2. US IBS cohort (n = 243; 203 f; age 34 ± 12 years); colonic barostat (phasic distensions, 30 s duration, 30 s rest; 2 mmHg increments); 3. US IBS cohort (n = 159; 126 f; age 37 ± 14 years); rectal barostat (phasic distensions, 30 s duration, 30 s rest; 2 mmHg increments); 4. Swedish IBS cohort (n = 353; 267 f; age 38 ± 13 years); rectal barostat (phasic distensions, 30 s duration, 30 s rest; 5 mmHg increments); 5. Swedish IBS cohort (n = 147; 102 f; age 34 ± 11 years); rectal barostat (ramp inflation, 4 mmHg steps, 1 min/step). Subjects were divided into sensitivity tertiles based on pain/discomfort thresholds. GI symptom severity (z scores of IBS-SSS, GSRS-IBS or dyspepsia symptom severity (DSS)) was compared between sensitivity tertiles in each cohort and corrected for somatization (RPSQ, PHQ-12 or SCL-90), and anxiety and depression (HAD or BSI).

Result: The results are summarized in table 1. In all five cohorts GI symptom severity increased gradually with increasing GI sensitivity, with significant differences in GI symptom severity between the sensitivity tertiles, and small, but significant correlations between pain/discomfort thresholds and GI symptom severity, across all five patient groups ($r = -0.20$ – -0.29). The differences between sensitivity tertiles remained significant in all cohorts after correction for anxiety and depression, and also after correction for somatization (without GI symptoms) in all of the cohorts ($p < 0.05$).

Conclusion: A gradual increase in GI symptom severity with increasing GI sensitivity was demonstrated in IBS and functional dyspepsia, which was consistent across several large patient groups from different countries, different methods to assess sensitivity, and assessments in different parts of the GI tract. This association, although modest, was independent of tendency to report symptoms or anxiety/depression comorbidity. These findings confirm that visceral hypersensitivity is a contributor to symptom generation in FGIDs.

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O. Palsson: Salary support from research grants from Salix Pharmaceuticals, Takeda Pharmaceuticals and Ironwood pharmaceuticals, as well as honoraria for participation in educational programs supported by these companies
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OP293 CHRONIC ORAL ADMINISTRATION OF THE GUANYLATE CYCLASE-C AGONIST LINACLOTIDE ATTENUATES COLITIS INDUCED LONG-TERM BLADDER AFFERENT HYPERACTIVITY

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Introduction: There is significant comorbidity between the symptoms of IBS and the urological symptoms of urgency and frequency experienced in overactive bladder and interstitial cystitis/painful bladder syndromes. Viscero-visceral cross-talk has also been described in pre-clinical studies, whereby acute colitis in rodents is associated with altered bladder cystometry and bladder afferent sensitisation [1,2]. However, it remains to be determined if bladder overactivity persists following the resolution of colitis, in a model of chronic colonic hypersensitivity (CCH) [3], or if reducing colonic nociception is able to alter bladder overactivity. Linaclotide, an FDA approved guanylate cyclase-C (GC-C) agonist, reduces abdominal pain in IBS patients with constipation [3], reverses colonic mechanical hyper-sensitivity in CCH mice, and reduces noxious signalling to the spinal cord in mice in vivo. We hypothesized that oral linaclotide administration may also reduce bladder hypersensitivity.

Aims & Methods: We investigated healthy C57BL/6 J mice and mice with CCH, 28 days after intra-colonic TNBS administration. CCH mice were randomly assigned to either chronic linaclotide (3 μg/kg/day) or placebo (water)

Table 1 (OP292): Association between visceral hypersensitivity and GI symptom severity in five FGID cohorts

z score GI sx severity (mean ± SD)	Belgian FD cohort (n = 242) DSS	US IBS cohort (colon; n = 243) IBS-SSS	US IBS cohort (rectum; n = 159) IBS-SSS	Swedish IBS cohort 1 (n = 353) IBS-SSS/GSRS-IBS	Swedish IBS cohort 2 (n = 147) IBS-SSS
Low sensitivity tertile	−0.48 ± 0.99	−0.29 ± 0.99	−0.34 ± 0.90	−0.40 ± 0.98	−0.46 ± 0.89
Mid sensitivity tertile	−0.07 ± 0.88	−0.04 ± 1.00	−0.00 ± 1.04	0.11 ± 0.99	0.31 ± 0.83
High sensitivity tertile	0.32 ± 0.99	0.25 ± 0.95	0.28 ± 0.97	0.25 ± 0.95	0.06 ± 1.14
ANOVA	$F = 13.2$; $p < 0.0001$	$F = 5.9$; $p = 0.003$	$F = 5.1$; $p = 0.007$	$F = 14.0$; $p < 0.0001$	$F = 8.5$; $p < 0.0001$
ANCOVA (adjusted for somatization)	$F = 9.2$; $p < 0.001$	$F = 4.9$; $p = 0.008$	$F = 3.1$; $p = 0.046$	$F = 6.3$; $p = 0.002$	$F = 3.9$; $p = 0.02$
ANCOVA (adjusted for anx & depr)	$F = 13.3$; $p < 0.0001$	$F = 5.0$; $p = 0.006$	$F = 4.1$; $p = 0.018$	$F = 10.8$; $p < 0.0001$	$F = 8.3$; $p < 0.0001$
Correlation sensitivity - GI sx	$r = -0.27$; $p < 0.0001$	$r = -0.20$; $p < 0.0001$	$r = -0.27$; $p = 0.001$	$r = -0.29$; $p < 0.0001$	$r = -0.20$; $p < 0.02$

administration, consisting of a once daily oral gavage for 2 weeks prior to experimentation. In all four groups, whole cell patch clamp recordings from retrogradely traced thoracolumbar and lumbosacral bladder dorsal root ganglion (DRG) neurons determined neuronal excitability, whilst ex-vivo electrophysiological recordings determined bladder afferent and contractile sensitivity to ramp distension as well as muscarinic, purinergic and TRPV1 channel agonists. Micturition pattern analysis was performed by analysing in-vivo natural voiding behaviour.

Result: Bladder traced DRG neurons from mice with CCH displayed hyperexcitability with a significant decrease in rheobase ($P < 0.01$) as well as enhanced bladder afferent responses to distension ($P < 0.001$), and exogenous agonists ($P < 0.01$), with no changes in muscle compliance or contraction responses. As a reflection of altered physiological signalling, CCH mice also displayed significant changes in voiding frequency ($P < 0.01$). CCH mice treated with linaclotide displayed attenuated bladder DRG neuron excitability compared with placebo treated mice ($P \leq 0.001$), and attenuated bladder afferent hypersensitivity to distension ($P < 0.001$). Linaclotide treatment in the CCH mice also resulted in a restoration of natural voiding behaviour ($P \leq 0.05$).

Conclusion: Mice with CCH also display increased bladder afferent excitability accompanied by abnormal bladder voiding behaviour, an example of viscero-visceral cross-talk. Chronic oral administration of linaclotide, a gut-restricted GC-C agonist that inhibits colonic nociceptors, reverses these colitis-induced changes in bladder function and sensitivity. Agents that improve abdominal pain may be able to improve urological symptoms through common sensory innervation pathways.

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G. Hannig: Employee, stock holder, and stock options from Ironwood pharmaceuticals Inc.
C.B. Kurtz: Employee, stock holder, and stock options from Ironwood pharmaceuticals Inc.
A. Silos-Santiago: Employee, stock holder, and stock options from Ironwood pharmaceuticals Inc and Decibel Therapeutics.
S.M. Brierley: Research support: Ironwood Pharmaceuticals Inc., Takeda Pharmaceuticals Inc., Key Pharmaceuticals Inc.
All other authors have declared no conflicts of interest.

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TUESDAY, OCTOBER 18, 2016 15:45–17:15

(EPI)GENETICS IN IBD – ROOM L7

OP294 DIAGNOSING RARE INHERITED DISORDERS USING TARGETED NEXT GENERATION SEQUENCING IN PATIENTS WITH EARLY-ONSET INFLAMMATORY BOWEL DISEASE: A POPULATION-BASED STUDY

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Introduction: Several recent referral center studies showed that a significant proportion (3–10%) of children with an early-onset (EO, defined by an age at diagnosis less than 12 years) inflammatory bowel disease (IBD) present with an underlying monogenic disorder. Currently, more than sixty disorders of this type have been identified and their pathophysiological mechanisms are very heterogeneous. Most of them affecting the intestinal epithelial barrier, are associated with defects in phagocytosis or immune deficiency, or are hyper- and auto-inflammatory diseases. However, they all share the ability to present in the form of an array of intestinal inflammation with EO.

Aims & Methods: Using a next-generation sequencing (NGS) of the 63 genes whose abnormalities are responsible for these disorders, and a targeted CGH array analysis of their chromosomal loci, 91 patients with an initial diagnosis of EO-IBD between 1988 and 2004 (54% of the whole EO-IBD cohort) issued from EPIMAD population-based registry were screened; 71 had a Crohn's disease and 20 an ulcerative colitis.

Result: Analysis isolated 24 patients (26.4%) with very rare or not yet reported potential pathogenic variants in 17 genes. Seven of them (7/91; 7.6%) had a genotype compatible with one of the tested disorders: Burton agammaglobulinemia, familial diarrhea, familial Cγ2 defect, hyper-IgM syndrome or Omenn syndrome. The remaining 17 patients (17/91; 18.7%) were heterozygous carriers of genes variants involved in autosomal recessive trait. The genotype identified in these patients was thus probably not likely to be the underlying cause of one of these disorders. However, one cannot exclude that it may contribute to IBD as suggested by the unusually high prevalence of these genotypes.

Conclusion: Our study issued from a population-based registry, provides further evidence to recommend screening for inherited disorders using targeted NGS in children with an EO-IBD with the potential to enhance optimal selection of treatment options and adequate counseling of families. This study also indicates that targeted NGS used in this study may be an adequate and efficient tool for the reappraisal of the diagnosis in these patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP295 HYPOXIA INHIBITS INTESTINAL INFLAMMATION THROUGH THE INHIBITION OF NLRP3 INFLAMMASOME AND THE ACTIVATION OF AUTOPHAGY

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Introduction: The impact of environmental hypoxia on the development of inflammatory bowel disease (IBD) is controversial, with studies supporting both a proinflammatory and a protective effect. Hypoxia is known to activate the autophagy and inflammasome pathways, which are ancient innate immune mechanisms linked by mutual regulation. In recent years, polymorphisms in gene loci containing autophagy- and inflammasome proteins have been associated with an increased risk of IBD. Evidential data suggest that the imbalance in the mutual regulation of autophagy and NLRP3 inflammasome activation under hypoxia plays a role in the development of IBD.

Aims & Methods: To study the effects of hypoxia in IBD, healthy volunteers ($n = 10$), patients with Crohn's disease (CD, $n = 11$) and patients with ulcerative colitis (UC, $n = 9$) were subjected to hypoxic conditions resembling an altitude of 4,000 m above sea level for 3 h using a hypobaric chamber. Distal colon biopsies were collected the day before hypoxia, immediately after hypoxia, and one week after collection of the first biopsy. To further study the effects of hypoxia in colitis and the role of the NLRP3 inflammasome, wild-type (WT), interleukin (IL)-10$^{-/-}$, Nlrp3$^{-/-}$ and IL-10$^{-/-}$ Nlrp3$^{-/-}$ double knockout mice were subjected to hypoxia (8% O_2) for 18 h prior to colon biopsy collection. Mice under normoxic conditions were used as controls. For the in vitro studies, the human monocytic cell line THP1 and the intestinal epithelial cell line HT-29 were subjected to hypoxia (0.2% O_2) in the presence and absence of lipopolysaccharide.

Result: Colon biopsies of patients with CD, but not UC showed increased levels of tumor necrosis factor (TNF)α and NLRP3 mRNA expression prior to hypoxia. Interestingly, hypoxia inhibited the expression of both genes immediately and one week after hypoxia concomitantly with the induction of the autophagy-associated gene p62. IL-10$^{-/-}$, but not IL-10$^{-/-}$ Nlrp3$^{-/-}$ mice presented an increased expression of TNFα, IL-6, and inflammasome-associated IL-1β as well as increased levels of phospho-p65/RelA concomitantly with an accumulation of the autophagy proteins p62 and LC3, suggesting an autophagy blockage orchestrated by NLRP3. Interestingly, hypoxic conditions significantly inhibited the expression of TNFα, IL-6 and IL-1β, and restored autophagy in IL-10$^{-/-}$ mice. THP1 and HT-29 cells subjected to hypoxia showed a decrease in NF-κB activation concomitantly with an increase in autophagy, evidenced by a reduction in p62 and LC3, and the phosphorylation of mTOR, a major regulator of autophagy. siRNA-mediated silencing of NLRP3 further activated autophagy under hypoxia.

Conclusion: Our results suggest a protective effect of hypoxia in CD patients and the IL-10$^{-/-}$ mouse model of colitis. IL-10$^{-/-}$, but not IL-10$^{-/-}$ NLRP3$^{-/-}$ mice under presented inhibition of autophagy indicating that NLRP3 is involved in the blockage of autophagy. Interestingly, hypoxia restored autophagy in IL-10$^{-/-}$ mice, as well as in THP1 and HT-29 cells concomitantly with a reduction of inflammatory gene expression and signaling. Hypoxia-induced autophagy was enhanced in the absence of NLRP3 further supporting a role for NLRP3 in the regulation of autophagy. Our results confirm a reciprocal regulation between hypoxia, inflammation, and autophagy, and suggest that hypoxia ameliorates inflammation through the induction of autophagy via the regulation of NLRP3.

Disclosure of Interest: All authors have declared no conflicts of interest.

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Table 1. (OP297)

Feature	CCD n = 19	UC n = 32	P value
Age at testing (mean ± SD, y)	32.0 ± 14.9	36.0 ± 10.6	0.3
Age at diagnosis (mean ± SD,y)	25.7 ± 15.5	25.3 ± 10.2	0.9
Disease Duration at testing (mean ± SD,y)	6.2 ± 4.8	10.5 ± 8.4	0.047
Gender (%,n), male	42 (8)	50 (16)	0.44
Clinically active (%,n)	58 (11)	66 (21)	0.77
Endoscopically active (%,n)	89 (17)	71 (25)	0.45
Histologically active (%,n)	79 (15)	63 (20)	0.35
Treatment (%,n) Biologic Azathioprine ASA Steroid Antibiotic	15.8 (3) 15.8 (3) 15.8 (3) 0 0	7.2 (3) 0 69 (22) 2.3 (1) 0	0.67 0.047 0.0004 1 1
CRP (mean ± SD, mg/mL)	16.1 ± 21.1	8.7 ± 16.3	0.2
WCC (mean ± SD,X 10^9/ L)	6.5 ± 2.0	6.3 ± 1.3	0.7

OP296 EPIGENETIC ALTERATIONS IN INFLAMMATORY BOWEL DISEASE - THE INFLUENCE OF GERMLINE VARIATION (MEQTLS) ON GENOME-WIDE METHYLATION ALTERATIONS

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Introduction: Exploring DNA methylation in Inflammatory Bowel Disease (IBD) may provide an insight into complex gene-environment interactions, identify novel targets involved in pathogenesis, and allow development of powerful new biomarkers. Our study aims to characterize disease-associated methylation changes in newly diagnosed IBD and to define the contribution of genetic variation, by discovery of associated quantitative trait loci (meQTL).

Aims & Methods: Genome-wide methylation was measured in 641 DNA samples from peripheral blood (298 controls, 150 Crohn's disease (CD), 167 ulcerative colitis (UC), 26 IBD unclassified (IBDU)) using the Illumina 450k platform with covariates of age, sex, and differential cell counts, deconvoluted by the Houseman method; genotyping was performed using Illumina HumanOmniExpressExome-8 BeadChips. Samples were obtained from new onset IBD cases in six European centres as part of the European Comission funded IBD-Character project.

Result: 195 probes exhibited Bonferroni significant IBD-associated methylation differences, including VMP1/MIR21 ($p = 3.7 \times 10^{-20}$), RPS6KA2 (1.1×10^{-19}), SBNO2 (2.7×10^{-19}), and TNFSF10 (1.1×10^{-15}); data which provide important replication and confirmation of methylation differences previously reported in paediatric CD and adult IBD. Novel findings include PHOSPHO1 (1.3×10^{-15}), MUC4 (5.5×10^{-15}), and CDH24 (1.7×10^{-14}). 1709 differentially methylated regions of consecutive FDR significant probes were defined in genes including VMP1/MIR21, ITGB2, TNF, and at multiple sites throughout the HLA region. Results were highly similar in CD and UC, with only one probe showing a significant methylation difference between diagnoses (NAV2, 6.82×10^{-8}). Paired genetic and methylation data showed 2327 FDR significant MeQTLs indicating a genetic influence on key methylation loci such as RPS6KA2 (8.6×10^{-34}), and ITGB2 (3.3×10^{-38}), and a replication of two SNPs previously described as correlated to VMP1/MIR21 methylation (rs8078424, $p = 4.4 \times 10^{-25}$, rs10853015, $p = 7.4 \times 10^{-21}$). There was an enrichment of highly significant IBD-associated methylation changes in proximity to IBD GWAS loci. Previously published two-probe methylation biomarkers derived from a new onset paediatric CD cohort accurately distinguished IBD from controls in this new onset adult cohort (AUC $\leq$ 0.82).

Conclusion: These data allow methylome profiling in a large multinational cohort of new onset IBD, identifying novel disease-associated methylation changes and important unequivocal replication of recent discoveries, together with insight into the genetic contribution to epigenetic alterations in complex disease, and the utility of peripheral blood DNA metylation as a biomarker.

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J. Jahnsen: Served as a speaker, a consultant and a advisory board member for MSD, Tillot, Ferring, AbbVie, Celltrion, Orion Pharma, Takeda, Napp Pharm, Meda, AstroPharma, Hikma and Pfizer.
F. Gomollon: Advisor: Grifols, Abbvie, MSD. Travel Grants: Abbvie,MSD. Research funding (Department) MSD
J. Satsangi: JS has served as a speaker, a consultant and an advisory board member for MSD, Ferring Abbvie and Shire, consultant with Takeda, speaking fees from MSD and has received research funding from Abbvie
All other authors have declared no conflicts of interest.

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OP297 AN AUTOPHAGY-RELATED PERIPHERAL BLOOD MICRORNA SIGNATURE DIFFERENTIATES COLONIC CROHN'S DISEASE FROM ULCERATIVE COLITIS

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Introduction: Phenotypic expression of colonic inflammation in inflammatory bowel disease (IBD) in patients with colonic Crohn's disease (CCD) and ulcerative colitis (UC) can sometimes have a similar appearance and be difficult to differentiate. MicroRNAs (miRNAs) may offer a method of distinction as differential expression of peripheral blood miRNAs has been shown in small studies of IBD patients and healthy controls.

Aims & Methods: This study aimed to assess peripheral blood mononuclear cell (PBMC)-derived miRNA signatures in a well-phenotyped cohort of colonic IBD and to identify differentially expressed miRNAs in patients with CCD and UC. An IBD cohort with UC and CCD was prospectively accrued. Ileocolonoscopy was performed and patients with CCD (Montreal Classification L2/L3) or left-sided UC (Montreal Classification E2/E3) were enrolled. Colonoscopies were reviewed by IBD endoscopists and scored for presence/absence, severity and site of inflammation. Pathology reports were reviewed for presence/absence and severity of inflammation. On the day of endoscopy, C-reactive protein (CRP) was measured and blood was collected in PAXgene tubes (Qiagen). Total RNA was extracted from blood using the PAXgene Blood miRNA kit (Qiagen) and miRNA counts from 798 probes were measured using the Human v3 miRNA nCounter Platform (NanoString Technologies). Raw counts were normalized, log2 transformed and batch corrected. Non-parametric Kruskal-Wallis tests assessed differential miRNA expression across phenotypes. Raw p-values were corrected for multiple testing by the Benjamini-Hochberg false discovery rate method. Target prediction and gene ontology biological process (GO BP) enrichment analyses were performed with miRWalk 2.0. Receiver operating characteristic (ROC) curves were generated following logistic regression through 5-fold cross validation repeated 10 times. Area under the curve (AUC) values for the ROCs were derived in order to evaluate the discriminating capacity of the differentially expressed miRNAs in CCD versus UC.

Result: 51 subjects, 32 UC (50% male, 36 yrs mean age), 19 CCD (42% male, 32 yrs mean age) were included in the analysis (see Table 1). There were no significant differences in mean CRP or among clinical, endoscopic or histologic disease activity between the CCD and UC groups suggesting that the degree of inflammation was similar in both groups. Comparing CCD and UC, 5 miRNAs were differentially expressed: miR-129-5p, miR-603, miR-619-3p, miR-874-3p, miR-933 (FDRp = 0.0214 all probes), all of which were upregulated in CCD vs UC. In the ROC analysis, the AUC for CCD vs UC for the combined expression of the 5 miRNAs was 0.89 (95% CI: 0.88–0.90). 2 out of 5 miRNAs putatively target the Autophagy Related 16-Like 1 (ATG16L1) gene, and 4 out of 5 miRNAs had significant GO BPs on putative target genes in the regulation of autophagy pathway (FDRp < 0.05).

Conclusion: A PBMC-derived miRNA panel of markers identified here differentiates CCD from UC with similar degrees of inflammation. All of these differentially expressed miRNAs are upregulated in CCD compared to UC, and

several appear to be associated with the autophagy pathway. These findings may aid individualization of patient care through identification of novel diagnostic and therapeutic targets.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP298 ASSESSMENT OF INFLAMMATORY BURDEN IDENTIFIES CROHN'S DISEASE AND ULCERATIVE COLITIS PATIENT GROUPS WITH DIFFERENT DISEASE-DRIVING PATHWAYS AND THERAPEUTIC RESPONSE TO ANTI-TNF TREATMENT

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Introduction: Crohn's disease (CD) and ulcerative colitis (UC) are considered to be driven by both common and distinct underlying mechanisms of pathobiology. In both diseases there is heterogeneity underscored by the variable clinical responses obtained to therapeutic interventions. We aimed to identify disease-driving pathways as well as classify individuals into subpopulations that differ in their disease pathobiology and response to a specific treatment.
Aims & Methods: Hierarchical clustering on enrichment scores (ES) from gene set variation analysis (GSVA) was used probing a normal healthy volunteer (NHV), CD and UC data set of colonic biopsies (GSE16879) with a library of gene set signatures representative of various immunological and inflammatory processes as well as specific activated cell types. Patient stratification at baseline (BL) or after anti-TNF treatment (PT) in either clinical responders (R) or non-responders (NR) was queried.
Result: Gene set signatures whose ES differed significantly (ES change ≥ 0.2, $p \leq 0.05$) between comparisons were identified from general linear model analyses. Comparisons were made at BL in all participants irrespective of clinical response, in clinical R and in clinical NR respectively compared to NHV. 59% of the tested signatures were commonly enriched in both CD and UC at BL underlining the commonality of both diseases. These signatures included e.g. activated T cells, monocytes, macrophages or neutrophil signatures as well as poly:IC and bleomycin signatures, representing acute inflammation and a complex mix of potential disease-driving biology. Comparing R and NR separately at BL to NHV, 43% and 70% of signatures were enriched, respectively, indicative of a higher inflammatory burden in NR. Indeed, specific macrophage, innate lymphoid and dexamethasone signatures were uniquely enriched in NR. Hierarchical clustering of the ES that significantly differed in the comparisons clearly separated diseased BL from NHV samples. It also clustered R PT samples with the NHV while the NR PT samples clustered with the BL diseased samples, with a better separation observed in CD when compared to UC. Also, clear UC and CD patient clusters could be observed with increasing ES at BL correlated with NR to anti-TNF treatment recapitulating the observation of a higher inflammatory burden in NR.
Conclusion: Our analysis has identified common disease-driving pathways for CD and UC supporting the notion of a disease continuum rather than two distinct diseases. However, within that disease continuum, distinct patient groups could be defined by their overall inflammatory burden correlating with their response to an anti-TNF therapy. This methodological approach could facilitate better targeted design of clinical studies to test therapeutics under development, concentrating on subsets of patients sharing similar underlying molecular pathology and therefore increasing the likelihood of clinical response.
Disclosure of Interest: S. Pavlidis: Employee of Janssen Research & Development Ltd, High Wycombe, UK
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OP299 CROHN'S DISEASE-ASSOCIATED CIRCULATING MICRORNAS ARE SECRETED IN EXOSOMES FROM AIEC-INFECTED HUMAN MACROPHAGES AND INVOLVED IN REGULATION OF HOST INNATE IMMUNE RESPONSES IN RECIPIENT CELLS

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Introduction: A high prevalence of invasive *Escherichia coli* strains, named AIEC (adherent-invasive *E. coli*), has been reported in the intestinal mucosa of Crohn's disease (CD) patients. A deregulated microRNA (miRNA) expression profile has been reported in CD patients' peripheral blood. Exosomes are small endosomal-derived vesicles involved in cell-to-cell communication. Exosomes have been shown to carry miRNAs that can be efficiently transferred to recipient cells. We recently showed that AIEC-infected human macrophages released exosomes that trigger a pro-inflammatory response and an increased bacterial intracellular replication in recipient cells.
Aims & Methods: Here, we investigated whether exosomal miRNAs are involved in such processes. Exosomes were purified using ExoQuick Exosome Precipitation kit. miRNA expression levels were analyzed by qRT-PCR. In vivo infection with AIEC bacteria was performed using ileal loop assays and exosomes were purified. Purified exosomes were then intravenously injected in naïve mice (10 µg/mouse).
Result: We analyzed the levels of the CD-associated circulating miRNAs reported in literature in exosomes released from AIEC LF82-infected (Exo-AIEC) THP-1 macrophages. A significant upregulation of several miRNAs in Exo-AIEC compared with exosomes released from uninfected (Exo-UI) cells or cells infected with a non-pathogenic commensal *E. coli* HS strain was observed (Exo-HS). To analyze their transfer to recipient cells, naïve THP-1 macrophages were stimulated with the exosomes, and the levels of miRNAs in recipient cells were analyzed. The levels of several exosomal miRNAs were increased in THP-1 cells stimulated with Exo-AIEC compared with cells stimulated by Exo-UI or Exo-HS, suggesting an efficient transfer. In silico analysis showed that the upregulated and transferred miRNAs are involved in inflammatory responses and autophagy, which is necessary to control AIEC intracellular replication, among other biological processes. Transfection of antisenses of these miRNAs in THP-1 cells inhibited the Exo-AIEC-triggered increases in pro-inflammatory response and AIEC intracellular replication in recipient cells, suggesting that these exosomal miRNAs are functional and are involved in the effects of Exo-AIEC in recipient cells. To confirm the in vitro data, we developed an in vivo model to analyze the impact of Exo-AIEC on gut colonization by AIEC and AIEC-induced inflammation. In this model, exosomes were isolated from ileal loops of genetically susceptible mice infected with AIEC. Purified exosomes were then intravenously injected in naïve genetically susceptible mice (10 µg/mouse), and AIEC colonization in the gut and AIEC-induced intestinal inflammation were analyzed.
Conclusion: Our study shows that infection with CD-associated AIEC induces secretion of exosomes carrying several CD-associated circulating miRNAs by human THP-1 macrophages. These exosomal miRNAs, when being transferred into recipient naïve THP-1 macrophages, may be involved in the regulation of inflammatory and autophagic responses, contributing to host innate defense to AIEC infection.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 15:45–17:15
NOVEL TECHNIQUES IN LOWER GI MALIGNANCIES – ROOM L8

OP300 THE IMPLANTABLE MEDICATED MICRORESERVOIRS IN THE TREATMENT OF COLORECTAL CANCER. THE GOOD EFFECTS OF A SIMPLE PROCEDURE. EARLY RESULTS

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Introduction: Colorectal cancer (CRC) is the third most common in the world of men, and the second - in women. In Europe remains steady increase in incidence and mortality according to Globocan 2012 and source EuropaColon. The main problem after surgery is local recurrences that often develop even after resection R0. Five-year survival is less than 60% in developed countries [2,3]. Due to this more and more often there are ideas about intraoperative prevention of local recurrence. There are a number of studies on intraoperative radiation therapy, which gives good results for the prevention of CRC recurrence and increase the five-year survival [4,5]. In fact, we have proposed a method of supporting intraoperative chemotherapy with prolonged effect, because most of the local recurrence accounts for the second half of the first year after surgery. [2]
Aims & Methods: We aimed to investigate the possibility of using implanting microreservoirs to improve the results of surgical treatment CRC. To study the safety and efficacy of this modification surgery. Materials and methods: We have investigated the number of CRC recurrence for patients without distant metastases, lymph node involvement and no germination of the tumor to other organs after surgery in a volume R0 for a year after surgery. The study involved 87 patients (54 women and 33 men, mean age 62.4 years +/− 8.4 years) who were operated in the Dnipropetrovsk regional proctology centre from February 2014 to February 2015. The control group (42 patients, 17 men and 25 women) performed surgery in standart volume according to giudeline. In the test group (45 patients, 16 males and 29 females) before the anastomosis were formed medicated microreservoirs with 5-fluorouracil (5FU) supported on polyvinylpyrrolidone (PVP). In fact, it was a mixture of 30% PVP solution 5 ml and 5 ml 5FU (250 mg). This mixture was introduced into the muscle layer from the side of mucosa the 1 ml syringe with needle 0,40 × 10 mm 27G × 1/2 at a distance of 1–1.5 cm from the edge of the intestine. In one procedure was introduced approximately 10 ml of the drug. The volume of the reservoir was 0.5 ml. Next, the operation was completed in a standard way. As the drug delivery system has been selected PVP in the concentration of 30% as its safety is confirmed by the FDA. [8] PVP as a delivery system allows for the gradual release of the drug, due to 5FU linked ionic bonds with PVP [9], and drug release depends on the rate of destruction of the carrier polymer. An important advantage is the fact that the PVP is practically not destroyed at a pH of less than 7 [7], which allows to delay the release of 5FU, since pH in the stage of inflammation in the tissues is reduced and consequently the release of the bulk of 5FU will begin after completion of the inflammation. The 5FU was selected as a drug for the treatment because it does not require pre-transformation to acting form and is quite effective on condition achieving sufficient concentration in the tissues.

Result: In the control group, local recurrence was detected in 12 cases (28.6%). The following postoperative complications were found: early adhesive intestinal obstruction in 2 (4.8%) cases of postoperative pneumonia in 1 (2.4%) case. Within 8 months after surgery 1 patient died of acute coronary syndrome. In the studied group of local recurrence was detected in 8 cases (17.8%). The following postoperative complications were found: early adhesive intestinal obstruction in 1 (2.2%) case, even one patient has been adhesive intestinal obstruction in 3 months after the operation, which resulted in the death of the patient on 2 day after the re-operation due to acute of cardiovascular failure.
Conclusion: 1. Intraoperative implantation of medicated microreservoirs is a safe and effective procedure for the prevention of early recurrent CRC. 2. Notwithstanding the low total dose, good effect can be achieved due to the high concentration of the drug in the tissues. 3. This procedure avoids many resorptive effects of the chemotherapeutic drug, associated with systemic administration and high doses required to achieve therapeutic concentrations in tissues. 4. Obviously, it is necessary to continue the monitoring of these patients. 5. It is possible to consider a combination of other drugs and carrier polymers.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP301 ENDOSCOPIC SUBMUCOSAL DISSECTION IN LATERALLY SPREADING TUMORS: EXPERIENCE OF 282 CASES FROM A TERTIARY REFERENCE CENTER IN TURKEY

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Introduction: Endoscopic submucosal dissection (ESD) is a minimally invasive technique, providing en-bloc resection of premalignant and malignant lesions in early stage gastrointestinal (GI) cancers. Lateral Spreading Tumors (LSTs), which are endoscopically seen as granular (LST-G) or non granular (LST-NG) types, are technically difficult to remove as en-bloc with ESD method because of anatomical features of the colon. In the present study, we present our results of colorectal ESD procedures in LSTs.
Aims & Methods: Between April 2012- April 2016, a total of 655 colorectal lesions were referred to our unite for the purpose of removal with advanced endoscopic techniques (EMR or ESD). Colorectal ESD was performed to 290 lesions. Data was recorded prospectively before and after the procedure. 8 ESD cases were excluded because the lack of control endoscopy. The results of 282 ESD procedures performed in colon and rectum with diagnosed LST were analyzed retrospectively.
Result:

Table: Demographic data and colorectal endoscopic submucosal dissection results [Case (n) = 273 Lesion (N) = 282]

	N = 282
Lesion size, mm, mean (SD) (median; range)	40.44 (26.2)
(33; 14–176)	
Tissue size, mm, mean (SD) (median; range)	49.81 (28.9)
(42; 20–198)	
Duration of procedure, min, mean (SD) (median; range)	79.5 (71.1)
(61.5; 6–540)	
Dissection speed, mm^2/min, mean (SD) (median; range)	24.46 (15.41)
(21; 1.74–79.55)	
En-Bloc resection rate, N (%)	257 (91.1)
Complete Resection, N (%)	255 (90.4)
Paris Classification, N (%) 1s 1s + 2a 2a 2a + 2c	4 (1.4) 142 (50.4) 101 (35.8) 35 (12.4)
Adverse Events, N Delayed bleeding Perforation	2 9
Localization, N Rectum Sigmoid colon Descending colon Splenic flexura Transverse colon Hepatic flexura Ascending colon Cecum Ileocecal valve	133 42 16 6 15 25 25 14 6
Pathology, N (%) Carcinoma Intramucosal Sm1 invasion Sm2 invasion Tubular Adenoma Tubulovillous Adenoma Villous Adenoma Serrated Adenoma	124 (44) 99 (35.2) 4 (1.4) 21 (7.4) 28 (9.9) 102 (36.2) 17 (6.0) 11(3.9)
LST LST-G LST-NG	236 46

The 282 colorectal ESD procedures were performed in 273 patients, the demographic data and results of which are shown in the table. The overall en-bloc and complete resection rates were 91.1% and 90.4%, respectively. The lesions were LST-G type in 236 and LST-NG in 46 patients. Histopathology revealed carcinoma in 124, tubulovillous adenoma in 102, tubular adenoma in 28, villous adenoma in 17, serrated adenoma in 11 lesions. The rate of carcinoma was more frequent in LST-NG types than in LST-G type (55,5% vs 37.7%). Complete resection was not achieved in 9.6% of the patients with positive vertical border. Perforation occurred in 9 patients which were treated successfully with endoscopic clip without the need for surgery except for one patient with delayed perforation. Surgical treatment was performed in all patients with deep submucosal (sm2) invasion, however neoplasia was observed in none of these patients.
Conclusion: Colorectal ESD is a safe and effective method to provide en-bloc and curative resection of LSTs.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP302 EVALUATION OF RECTAL CANCER ANGIOGENESIS USING IMMUNOHISTOCHEMICAL AND COMPUTER-ASSISTED ENDOSONOGRAPHIC METHODS

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Introduction: The conventional way for evaluation of rectal cancer angiogenesis requires a biopsy or a tissue specimen applying specific immunohistochemical or molecular biological tests. The evaluation of microvessel density is a gold standard in the assessment of tumour angiogenesis. Doppler ultrasound is an attractive modality for imaging angiogenesis in vivo which can be repeated without exposing the patient to any risk.
Aims & Methods: The aim of the current study is to evaluate the preoperative rectal cancer angiogenic status with Endorectal Power Doppler Ultrasound by using Doppler Vascularity Index calculated by imaging analysis software and to compare results with microvessel density in surgical specimens A total of 110 patients (59 males; 51 females, mean age 61.5 years) with rectal cancer were enrolled in this study. The patients were operated and staged as follows: in stage I – 20pts (18%), stage II – 29 (26%); stage III – 47 pts (43%); stage IV – 14 pts (13%). Microvessel density was evaluated by using immunohistochemical staining of surgical specimens with anti-CD-31 antibody. The PDVI of each tumor was determined using endorectal power Doppler ultrasound with computer-assisted quantification of colour pixels. The PDVI was defined as the ratio of the number of the colored pixels within a tumor section to the number of total pixels in that specific tumor section, and was calculated by using a software.
Result: The mean microvessel density (MVD) was 163 ± 69 microvessels/mm^2(50–328). Median MVD used as the cutoff point divided two groups of tumours with high (≤160 vessels/mm2) and low angiogenic activity (>160 vessels/mm2). Mean PDVI was 8.9 ± 6.0% (range: from 0 to 27,3). Median PDVI (8%) was used as the cutoff divided two groups of tumours with high (≤8%) and low PDVI (>8%). The MVD and PDVI showed a good positive linear correlation (r = 0.438, p = 0.002).
Conclusion: Endorectal Power Doppler ultrasonography is a useful noninvasive method of evaluating the extent of angiogenesis. Tumor angiogenesis assessed by power Doppler vascular index correlated with histological microvessel density determination The presented endoultrasound Power Doppler examination is a reliable and reproducible mean for in vivo preoperative quantitative assessment of the tumour vascularisation.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP303 COMPARISON OF CLINICAL OUTCOMES AMONG DIFFERENT ENDOSCOPIC MODALITIES FOR RECTAL NEUROENDOCRINE TUMOR

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Introduction: Rectal neuroendocrine tumor (NET) less than 10 mm in diameter can be removed by various endoscopic techniques, such as endoscopic mucosal resection (EMR), modified EMR, and endoscopic submucosal dissection (ESD). This study aimed to compare efficacy and safety of endocrine submucosal resection with a ligation device (ESMR-L) or circumferential submucosal incision prior to EMR (CSI-EMR) versus ESD
Aims & Methods: Fifty-six patients, who underwent endoscopic resection of a rectal NET less than 10 mm in diameter, were enrolled consecutively from March 2013 to June 2015. The patients were classified into three groups according to the type of endoscopic procedure: ESMR-L group (n = 17), CSI-ESD group (n = 18), and ESD group (n = 21). We compared treatment outcomes and complications associated with these methods.
Result: There was no different in tumor diameter between different endoscopic procedures (ESMR-L, 4.5 ± 1.6 mm; CSI-EMR, 5.6 ± 2.0 mm; ESD, 5.0 ± 2.2 mm, p = 0.236). En bloc rsection was achieved in all patients. There was no lateral margin involvement in all patients. Basal margin involvement occurred in one patients in the ESD group and two in the CSI-EMR group. The rates of pathological complete resection were 100% (17 of 17) in the ESMR-L group, 88.9% (16 of 18) in the CSI-EMR group, and 95.2% (20 of

21) in the ESD group, respectively ($p = 0.354$). Perforation or delayed bleeding did not occur. Procedure time of ESMR-L was significantly shorter than those of the other groups and procedure time increased in order of ESMR-L, CSI-EMR, and ESD group (4.3 ± 2.0 min, 11.2 ± 12.5 min, 18.6 ± 3.9 min, respectively, $p = 0.000$)

Conclusion: All endoscopic resection method, including ESMR-L, CSI-EMR, and ESD were effective and safe for the treatment of rectal NET. compared with CSI-EMR or ESD, ESMR-L procedure has the advantages of easier and shorter procedure time. ESMR-L may be considered the treatment of choice for rectal NET less than 10 mm in diameter

Disclosure of Interest: All authors have declared no conflicts of interest.

OP304 ANAL CYTOLOGY, HISTOPATHOLOGY, AND ANOSCOPIC VISUAL IMPRESSION IN AN ANAL DYSPLASIA SCREENING PROGRAM: IS ANAL CYTOLOGY ENOUGH?

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Introduction: The human papilloma virus (HPV) is the leading cause of anal squamous cell carcinoma. The cytological screening can reduce morbidity and mortality associated with this cancer, although current recommendations are based on expert opinion.

Aims & Methods: The authors intend to estimate agreement between anal cytologic examination, histopathology, and anoscopic visual impression. This is a prospective study of patients receiving anal dysplasia screening between 2010 and 2015, in a proctology consultation of a tertiary referral center. Descriptive statistics was performed using IBM SPSS Statistics 22 with $p < 0.05$ deemed to be statistically significant. Agreement between measures was estimated by weighted kappa-statistics.

Result: During the period of the study, 141 patients (91% men, mean age 37 ± 14 years, 87% with HIV infection) underwent 175 anal cytology tests: 33% negative for intraepithelial lesion or malignancy (NILM), 22% atypical squamous cells of uncertain significance (ASCUS), 33% low-grade squamous intraepithelial lesion (LSIL), 10% high-grade squamous intraepithelial lesion (HSIL) and 1% carcinoma in situ (CIS). Concerning anoscopic visual impression, 40% patients had no lesions (53% NILM, 22% ASCUS, 25% LSIL). In the remaining patients, excision/biopsy of the identified lesions was performed detecting 40 (23%) high-grade dysplasia (HGD), 33 (19%) low-grade dysplasia (LGD) and 4 (2%) CIS. Weighted kappa-agreement between abnormal cytological results and anoscopic visual impression was moderate ($k = 0.48$). Weighted kappa-agreement between the presence and degree of dysplasia in anal cytologic tests and concurrent histopathology was low ($k = 0.23$ and $k = 0.20$, respectively). Of the 57 NILM cytologic tests, 26% had suspicious lesions in anoscopic visual impression and of these, 9 (60%) had dysplasia on histopathological exam (4 HGD and 5 LGD). By other hand, concerning the patients with HGD/CIS on histologic exam, 28 (64%) patients had lower dysplasia grade on cytological exam (6 ASCUS, 18 LSIL and 4 NILM).

Conclusion: The low correlation between anal cytology, histopathology and anoscopic visual impression associated with the high number of histological exams with HGD/CIS with lower dysplastic degree on cytological exam (including NILM anal cytologies) suggest that anal cytology screening should not be used as the unique method of anal dysplasia screening. The authors suggest that anoscopic screening should be offered to all patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP305 NEW PLATFORM FOR TRANS-ANAL SUBMUCOSAL ENDOSCOPIC RESECTION- (TASER): UPDATED CLINICAL RESULTS FROM TERTIARY CENTRE

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Introduction: Current trans-anal surgical (TEMS/TEO) and advanced endoscopic resection procedures (P-EMR/ESD) have the potential to resect complex rectal polyps (CRPs). However both approaches have limitations in terms of practicality and safety.

Aims & Methods: Consecutive patients (Jan13/Dec15), referred for the excision of CRPs, were being considered for proctectomy and/or had failed conventional endoscopic or trans-anal therapy. The GelPoint Path trans-anal access port comprises a soft plastic extension, (with a diameter of 3.6 cm) allowing simultaneous passage/triangulation of an endoscope and two laparoscopic retractors and permitting dynamic tissue manipulation to facilitate endoscopic submucosal dissection/ESD. Supplementary techniques were also used to complete the resection such as piecemeal endoscopic mucosal resection or ablation/P-EMR or EMA and trans-anal excision/TAE. The aim of this study was to evaluate the feasibility, technical success and safety profile of this new hybrid, endo-surgical Trans-Anal Submucosal Endoscopic Resection- (TASER) approach for CRPs.

Result: Thirty-two TASER procedures were employed in 31 patients (mean age 65years/17 males–14 females) with 31 CRPs (mean size 8 cm/range 5 cm–18 cm). Complete endoscopic excision in a single session was achieved in 28/31 patients (93%); in one patient a second TASER session was required for completion polypectomy, in another deep submucosal invasion was suspected during TASER-ESD/P-EMR/EMA – patient had an elective laparoscopic anterior resection (T1,sm3,N0,M0 confirmed) and in a third patient intraperitoneal perforation necessitated a de-functioning ileostomy before complete polypectomy could be undertaken. Mean procedure time was 185 min, range 65–480 min. Thirty two TASER sessions were employed using ESD in 12/32, ESD + P-EMR in 6/32, ESD + P-EMR + EMA in 4/32, ESD + TAE in 3/32, ESD/P-EMR/TAE in 3/32 and ESD + P-EMR + EMA + TAE in 4/32. Intra-procedural bleeding was controlled with haemostatic endoscopic devices (coagrasper/clips); surgical clipping and suturing on 2 occasions. Prophylactic endoscopic clipping was also applied in 8 cases and suturing on 4 occasions. In 6/10 TASER -TAE cases there was a need for a full-thickness rectal dissection due to severe submucosal fibrosis: 4/6 cases were closed with surgical sutures plus endoscopic clips and in the remaining 2/6 cases only endoscopic clips were deployed. Two episodes of delayed bleeding were reported among the TASER-ESD/P-EMR and TASER-ESD sub-cohorts with no transfusion or re-intervention requirement. All patients were discharged the day after the TASER PROCEDURE apart from one patient who developed bacteremia post TASER-ESD requiring intravenous antibiotics and a 4-night hospital stay and the patient who required a defunctioning ileostomy, discharged on day 4 post operation. First follow-up performed at 4–6 months interval in 25/31 patients showed: 21/25 with no recurrence (84%) and 4/25 (16%) with a minimal (< 15 mm) polyp recurrence, amenable to endoscopic therapy. No rectal stricturing was identified and only one episode of transient faecal incontinence were reported.

Conclusion: TASER appears to be a safe and efficient endo-surgical approach providing an optimal platform for the minimally-invasive management of high-risk, complex rectal polyps.

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B.P. Saunders: Consultancy Agreement Creo Medical Ltd Paid Lecturers Olympus Keymed
All other authors have declared no conflicts of interest.

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THE INTESTINAL EPITHELIUM – STEM CELLS, INFLAMATION AND CANCER – ROOM 1.86

OP306 THE PROREGENERATIVE ROLE OF INTERLEUKIN-22 SIGNALS IN THE INTESTINAL EPITHELIUM DEPENDS ON AUTOPHAGY AND ER STRESS

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Introduction: Endoplasmic reticulum (ER) function and autophagy are necessary to maintain cellular homeostasis. Genetic variants of inflammatory bowel disease (IBD) risk genes *ATG16L1* or *XBP1* are associated with epithelial endoplasmic reticulum (ER) stress which promotes cell death. While *XBP1* plays a beneficial role in resolving ER stress, *ATG16L1* represents an essential component of the autophagic machinery, a conserved mechanism for protein degradation. Both processes are strongly connected since impaired autophagy subsequently results in deregulation of ER function. Interleukin-22 (IL-22) is known to be a protective cytokine in mucosal regeneration by promoting epithelial proliferation via STAT3 activation. Therefore, conjugates of IL-22 are in trials as potential drugs in IBD treatment.

Aims & Methods: Here, we investigate the impact of the IBD risk genes *ATG16L1* and *XBP1* on regenerative function of IL-22 in intestinal epithelium in mice and human. Human colon carcinoma HT-29 and Caco2 cells were treated with recombinant IL-22 and ER stress inductors like Tunicamycin or autophagy inducers like Rapamycin before they were subjected to wound healing assays, gene expression analysis and immunoblot analysis. Intestinal organoids derived from *Xbp1* ΔIEC (intestinal epithelial cell-specific deletion) and *Atg16l1* ΔIEC mice were treated with recombinant IL-22 and gene expression analysis using qRT-PCR, RNA sequencing and transcriptome analysis were performed. Secreted cytokines in supernatants from cells and organoids were detected with

ELISA. *Atg16l1* ΔIEC and *Atg16l1* ΔIEC/*Xbp1* ΔIEC mice were treated with recombinant IL-22 for 6 or 12 days before sacrificing.
Result: IL-22 induces transient self-limiting ER stress in the intestinal epithelium. While IL-22 improves wound healing in the absence of ER stress, IL-22 leads to impaired wound closure and increased cell death under ER stress conditions. This effect is dependent on STAT3 and autophagy as pharmacological STAT3 inhibition or autophagy induction with Rapamycin completely restores IL-22 dependent ER stress induction. On the contrary, impairment of the autophagic flux by Bafilomycin A provokes inflammatory features as well, which are aggravated by IL-22. Regulation of transient ER stress is dependent on *Xbp1* and *Atg16l1* as IL-22 treatment of intestinal organoids derived from *Atg16l1* ΔIEC und *Xbp1* ΔIEC mice induces a dramatic increase of inducible ER stress and pro-inflammatory gene expression. In addition, mRNA transcriptome analysis reveals differential expression of several IBD related risk genes in *Xbp1* ΔIEC and *Atg16l1* ΔIEC organoids in response to IL-22 stimulation. *Atg16l1* ΔIEC mice display defective autophagy in the intestinal epithelium and spontaneous cell death in intestinal crypts which exacerbates after IL-22 treatment. Finally, IL-22 aggravates preexisting spontaneous transmural intestinal inflammation in *Atg16l1* ΔIEC/*Xbp1* ΔIEC mice. On the flipside, same treatment of wild type control mice does not affect cell death and inflammation, underlining a genotype dependency of beneficial and adverse effects of IL-22 application.
Conclusion: These data suggest an unexpected role of the IBD risk genes *ATG16L1* and *XBP1* in coordinating regenerative IL-22 function in intestinal epithelium and may contribute to the development of genotype-based personalized medicine. However, further studies are necessary to decipher the molecular link between IL-22 signaling and the ER stress/autophagy axis.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP307 HOXA9 IS OVEREXPRESSED IN COLONIC ADENOMAS AND CAUSES AN INCREASE IN CELL GROWTH

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Introduction: Colonic adenomas are premalignant epithelial tumors with glandular origin. Identifying the molecular aberrations in this tissue may help to understand its malignant potential and could lead to better understanding of colorectal cancer development. The mammalian HOX clusters encode regulators of embryonic anterior to posterior specification and are important for the formation of tissues, structures, and organs. Besides having a function in embryology, HOX genes have pro-oncogenic activity in various malignant diseases. For example, HOXA13 overexpression predicts poor outcome for patients with cancer of the esophagus, stomach, and liver. In a portion of acute myeloid leukemias (AML), a translocation encoding the NUP98-HOXA9 oncogene gives overexpression of HOXA9. HOXA9 overexpression is the molecular factor most strongly correlated with poor prognosis in AML and is also correlated with poor prognosis in ovarian epithelial cancer. HOX gene aberrations are reported in colorectal cancer, however, it is unclear whether HOX gene aberrations are present at a premalignant stage and could, thus, contribute to cancer formation.
Aims & Methods: This study firstly aimed to assess the expression of HOXA9 in colonic adenoma tissue and location matched control tissue. Secondly, it aimed to evaluate potential effects of increased HOXA9 expression, both in terms of its influence in anterior to posterior specification and its oncogenic properties. We collected biopsies from colonic polyps and location matched normal colonic tissue in patients undergoing colonoscopy. A pathologist classified the colonic polyp after its resection and we only included tubular adenomas. We used RT-qPCR to quantify the expression of HOXA9 in relation to UBC, TPT1 and GAPDH using the efficiency$^{\wedge\Delta\Delta Ct}$ method. In addition, we transduced Caco2 cells with a lentiviral vector containing HOXA9 and a lentiviral vector without an insert, enabling inducible expression. Subsequently, we analyzed expression of genes important in anterior to posterior specification. We determined cell number and total cell pool with an automatic cell counter and a MTT assay. Finally, we assessed the expression of genes implicated in oncological transformation and epithelial to mesenchymal transition.
Result: HOXA9 expression in tubular adenomas of the colon is increased compared to location matched control tissue ($p = 0.04$). HOXA9 overexpression in Caco2 cells led to a decrease in FGF2 mRNA level ($p < 0.001$) and an increase in BMP4 mRNA level ($p = 0.02$). HOXA9 overexpression led to increased cell numbers when assessed with an automatic cell counter ($p = 0.004$). Additionally, when assessed with a MTT assay ($p < 0.001$), HOXA9 overexpression led to increased total cell pool. The growth factor IGF1 increased significantly ($p = 0.02$) as a result of HOXA9 overexpression. Genes important for epithelial to mesenchymal transition were not found to have significantly changed.
Conclusion: HOXA9 expression is increased in colonic adenomas. Overexpression of HOXA9 leads to a decrease in FGF2 and an increase in BMP4, which emphasizes that HOXA9 alters anterior to posterior specification. HOXA9 overexpression leads to growth of the cell pool. A mechanism through which HOXA9 exerts this effect is the upregulation of IGF1. In conclusion, HOXA9 appears to have pro-oncogenic activity in the premalignant stage of colorectal cancer.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP308 TOLL-INTERACTING PROTEIN DEFICIENCY PROTECTS MICE FROM COLITIS-ASSOCIATED CANCER BY MODULATING ANTI-TUMORAL IMMUNITY

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Introduction: Genetic deletion of the Toll-interacting protein (Tollip) -an IL-1R and TLR2/4 regulator- leads to increased acute and chronic colitis in mice (1). We sought to investigate whether increased susceptibility to inflammation had an impact on inflammation-driven colorectal carcinogenesis.
Aims & Methods: Colitis-associated cancer (CAC) was induced in 18–20-week old littermates C57BL/6 mice by azoxymethane (AOM) i.p. injection and 3 cycles of 2.5% oral dextran sodium sulfate (DSS) treatment. Tumor development was assessed endoscopically, microscopically and histologically. Apoptotic and proliferative index in the colon were determined by Tunel assay and Ki67 immunohistochemistry and quantified using the Image J software. Cytokine and gene expressions were measured by RT-qPCR. SMAD2 phosphorylation was assessed by Western blot.
Result: Tollip KO mice had significantly lower endoscopic tumor scores than WT littermates upon AOM-DSS exposure (8.4 ± 7.8 vs 13.4 ± 6.4, $p > 0.05$). Likewise, tumor numbers (4.9 ± 3.5 vs 7.1 ± 3.0, $p > 0.05$) and size were reduced. Immunohistological studies demonstrated reduced apoptotic index (79.3 ± 75.0 vs 246.8 ± 152.9, $p > 0.05$) and lower proliferation (21.0 ± 8.5 vs 27.9 ± 7.3, ns) in Tollip KO tumors when compared to wt controls. RNA analyses showed that Tollip ablation favors an anti-tumorigenic environment with reduced Bcl-xl (85.8 ± 50.9 vs 36.2 ± 39.5) and c-myc expression (6.2 ± 4.9 vs 2.1 ± 2.6). Importantly, Tollip deficiency led to reduced Foxp3 abudance (3.7 ± 2.6 vs 2.1 ± 1.7) in unchallenged colonic as well as in tumoral tissues. In addition, Tollip deficient tumors harbored reduced TGFbeta expression as well as reduced SMAD2 phosphorylation suggesting that TGFbeta signaling is dysfunctional in the absence of Tollip.
Conclusion: Our data show that Tollip partially favors colonic oncogenesis despite being protective against colitis. Putative mechanisms include reduced tumor-associated regulatory T cells and aberrant TGFb-induced signals in Tollip deficient mice.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP309 CONSTRUCTION OF IN VITRO MODEL OF ULCERATIVE COLITIS USING MOUSE PRIMARY COLONIC ORGANOID

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Introduction: The patients with ulcerative colitis (UC) are at increased risk of developing colitis-associated cancer, because long-term inflammation leads to the development of carcinogenesis. However, the transformation of colonic epithelial cells during long-term inflammation has not been elucidated. Recently, 3-dimentional (3D) primary organoid culture of colonic epithelial cells in mice has been established in our group (TMDU method)[1].
Aims & Methods: We therefore aimed to assess the effect of long-term inflammation on the epithelial cells by in vitro model, which might mimic natural history of UC. Colonic crypts were isolated from 8 week old female mouse and were cultured by TMDU method. To mimic chronic inflammation, the inflammatory reagents, the mixture of cytokines and the ligands of toll like receptors, were added into the medium every other day for 40 weeks. Thereafter, glycogen synthase kinase 3 (GSK3) inhibitor, CHIR99021 was added into the medium for 8 weeks with stimulation of inflammatory reagents. To evaluate transformation into tumor, the organoids were cultured without R-spondin1 and Wnt3a. The assessment of cell signaling pathways in organoids during long-term inflammation was performed by 3D immunohistochemistry of whole organoid and

western blot analysis. The gene expression of transformed organoids was assessed by microarray analysis and quantitative RT-PCR.
Result: The treatment with the inflammatory reagents in mouse colonic organoids showed the time-dependent induction of NF-κB target genes. Particularly, the expression of DUOXA2 gene was gradually increased by the continuous stimulation with the inflammatory reagents for 40 weeks. 3D immunostaining analysis showed NF-κB p65 was accumulated in nuclei by longer time of the stimulation, indicating that long-term stimulation might lead to a stronger activation of NF-κB signaling. Interestingly, accumulated NF-κB signaling by long-term stimulation remained active after the removal of all inflammatory reagents, whereas NF-κB signaling induced by short-term stimulation was completely shut down by the removal of all inflammatory reagents, suggesting that NF-κB might be irreversibly activated by long-term stimulation. Moreover, the organoids required neither R-spondin1 nor Wnt3a after the treatment with GSK3 inhibitor for 8 weeks, indicating that the organoids might be transformed like colitis-associated cancer. Microarray analysis and Gene Set Enrichment Analysis of transformed organoids showed irreversible Akt signal activation and reduced expression of Tgfb2, indicating that this transformation might involve the inflammatory-rerated carcinogenesis.
Conclusion: Long-term inflammation and nuclear accumulation of β-catenin leads to irreversible cell transformation, which is wnt independent survival capacity of colonic organoids. This in vitro model might mimic the natural history of epithelial cell transformation during inflammation-related carcinogenesis in UC.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP310 THE RIBONUCLEASE RNASEH2B CONTROLS INTESTINAL STEM CELL INTEGRITY

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Introduction: The stability of genomic DNA is under a tightly controlled surveillance. Especially in highly proliferating cells, as e.g. intestinal stem cells, RNA/DNA hybrids display a menace to DNA integritiy. The ribonuclease RNAseH2b removes RNA/DNA hybrids and thereby ensures cellular proliferation. Hypomorphic mutations of the RNAseH2b gene are associated with Aicardi-Goutières syndrome that results in a spontaneous inflammatory phenotype. We tested the role of RNAseH2b in maintaining proliferation and regeneration in the intestinal epithelium.
Aims & Methods: We generated RNAseH2b$^{fl/fl}$ and RNAseH2b$^{\Delta IEC}$ to study the role of RNAseH2b in the intestinal epithelium. WB, RT-PCR and IHC were performed to study the basal phenotype of unchallenged WT and KO mice. Acute DSS colitis was induced to investigate the impact of RNAseH2b on intestinal regeneration. AOM-DSS colitis was induced to study the role of RNAseH2b on intestinal carcinogenesis. Organoids of RNAseH2b$^{fl/fl}$ and RNAseH2b$^{\Delta IEC}$ were subjected to RNA sequencing.
Result: No macromorphological difference was seen between RNAseH2b$^{fl/fl}$ and RNAseH2b$^{\Delta IEC}$, with respect to age dependent body weight gain. Histological characterization reveals spontaneous DNA double strand breaks (DSB) in epithelial crypts of RNAseH2b$^{\Delta IEC}$, which leads to a restriction of epithelial stemness, as measured by expression of stem cell markers (Olfm4, Lgr5) and reduced KI67 staining of intestinal stem cells. When mice were challenged to acute DSS colitis, RNAseH2b$^{\Delta IEC}$ mice reveal a strong phenotype with dramatic weight loss, increased histological disease activity and impaired intestinal regeneration. Interestingly, when mice were challenged to AOM-DSS colitis, mice again showed increased intestinal inflammation but developed significantly less tumors. Decreased tumor development was due to DNA induced cellular senescence, as shown by acid ß- galactosidase staining in intestinal crypts in RNAseH2b$^{\Delta IEC}$ but not RNAseH2b$^{fl/fl}$mice.
Conclusion: We show for the first time, that the RNAseH2b plays an essential role in maintaining intestinal regeneration by protecting genomic DNA of high proliferating cells from DNA/RNA hybrids induced DNA damage. Knockout of RNAseH2b leads to loss of epithelial stemness and induction of cellular senescence.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP311 COMMENSAL FUNGI AND THEIR CELL-WALL GLYCANS INDUCE AUTOPHAGY IN INTESTINAL EPITHELIAL CELLS

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Introduction: Intestinal epithelial cells (IECs) are the first to encounter luminal antigens and play an active role in intestinal immune responses. We recently reported that the β-glucan receptor Dectin-1 and its major signaling mediator spleen tyrosin kinase (Syk) are expressed by normal ileal and colonic IECs. Furthermore, β-glucans, major fungal cell wall glycans, induced chemokine secretion by IEC lines in a Dectin-1 and Syk dependent manner. Autophagy is a homeostatic process in the gut and defects in autophagy were associated with Crohn's disease (CD) susceptibility. Vague data exist regarding the role of fungi and their glycans in inducing autophagy.
Aims & Methods: To investigate whether fungi and fungal glycans induce autophagy in IECs. Human IEC lines (HT-29 and SW480) were activated by *C. albicans* and *S. cerevisiae* and the β-glucan-rich cell-wall component zymosan. Autophagy was detected by Western blot (WB) and immunofluorescence (IF) of microtubule-associated protein 1A/1B-light chain 3 (LC3) or directly visualized in cells stably expressing GFP-LC3. Syk phosphorylation was assessed by WB and IF. Mucosal samples were obtained from patients undergoing colonoscopy and active autophagy was assessed by the punctal stain of endogenous LC3 in paraffin embedded sections or in frozen sections by IF.
Result: *C. albicans* (live, heat-killed [HK] - or UV-inactivated, *S. cerevisiae* (HK) and zymosan particles induced autophagy of IEC lines. This was indicated by 1) Increase in the active (cleaved) form of LC3 (LC3 II) e.g. up to 3.5 fold increase in LC3 II/actin ratio in response to HKCA vs. no treatment in HT-29 cells; 2) Appearance of LC3 puncta, indicating autophagosome binding, of endogenous LC3 as well as GFP-LC3. Comparable levels of autophagy were obtained upon amino- acid starvation of IECs -e.g. up to 3.7 fold increase in LC3 II/GAPDH ratio in starved SW480 cells vs. no treatment. Fungal–induced autophagy was accompanied by Syk phosphorylation and prevented upon Syk inhibition. In ileal and colonic mucosal samples, active autophagy in IECs was observed as LC3 puncta. Autophagy was further induced ex-vivo by UV-inactivated *C. albicans*, zymosan or rapamycin (mTOR inhibitor, autophagy inducer).
Conclusion: Commensal fungi and their cell-wall glycans induce autophagy in IECs. Syk-dependent autophagy suggests the involvement of antifungal receptors such as Dectin-1. Fungal-induced autophagy may play a role in mucosal sensing of luminal microorganisms, and contribute to fungal tolerance. Thus, imbalanced response to commensal fungi (recognition, autophagy or downstream processes), may impair homeostasis and contribute to the pathogenesis of CD.
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 15:45–17:15

ABSTRACTS ON FIRE: ACUTE PANCREATITIS: FROM MECHANISMS TO DISEASE – HOTSPOT

OP312 HEPARANASE IN ACUTE PANCREATITIS: NEW INSIGHTS INTO PATHOGENESIS AND THERAPY

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Introduction: Despite advances in understanding the pathogenesis of acute pancreatitis (AP), the mechanisms underlying this disease have not been fully determined. In the majority of cases, AP is a self-limited process, yet 20% of patients develop a severe form of AP with pancreatic necrosis, multi-organ involvement, and high mortality. Heparanase (HPSE), an endoglycosidase which cleaves heparan sulfate, degrades and remodels the extracellular matrix. HPSE is preferentially expressed in human tumors, including pancreatic adenocarcinoma. While the role of HPSE in cancer has been extensively studied, the involvement of this enzyme in inflammation and in AP in particular remains obscure. Therefore, this current study examines if HPSE is involved in the pathogenesis of Cerulein-induced AP in mice.
Aims & Methods: HPSE over-expressing transgenic mice (hpa-TG) and wild-type (WT) BALB/c mice were intraperitoneally injected with either Cerulein (50 mg/kg, 5 times, at 1 hour apart) or vehicle, with or without low and high doses of Roneparstat (SST0001, HPSE inhibitor) pretreatment. The animals were sacrificed 24 hours following the development of pancreatitis. The pancreatic response and the severity of AP were evaluated by pancreatic HPSE activity (determined by Na2^{35}SO4-labeled ECM), pancreatic edema index (determined by organ to animal weight ratio), tissue inflammatory response (determined by histopathological analysis), autophagy response (determined by electron microscopy and immunohistochemistry staining) and serum pancreatic enzymes (amylase and lipase) levels.
Result: Cerulein-induced AP in wild type mice was associated with significant rises in the serum levels of amylase and lipase. These increases were characterized by an enhancement of HPSE activity, a higher pancreatic edema index, tissue inflammation and autophagy response. All types of responses to administration of Cerulein were profoundly exaggerated in hpa-TG mice. In contrast, when Cerulein was injected to hpa-KO mice, the severity of pancreatic injury was

attenuated as compared with their wild type controls. Importantly, pretreatment with Roneparstat significantly reduced, in a dose-related manner, the HSPE activity, the tissue inflammatory response, autophagy and serum amylase and lipase levels.
Conclusion: HSPE appears to play an important role in the pathogenesis of AP. The HSPE inhibitor (Roneparstat) significantly reduced the severity of the AP in an animal model. This new concept may provide a basis for prophylaxis and treatment of AP.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP313 CIGARETTE SMOKE EXTRACT INHIBITS FLUID AND HCO3-SECRETION AND CFTR ACTIVITY IN GUINEA PIG PANCREATIC DUCTAL CELLS

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Introduction: Smoking represents an independent risk factor for the development of chronic pancreatitis (CP). It is well documented that secretion of pancreatic ductal alkaline fluid (which is regulated mostly by anion exchangers and CFTR) is diminished in CP.
Aims & Methods: In this study, we would like to understand whether smoking has any effects on pancreatic ductal fluid and HCO_3^- secretion. Guinea pigs were exposed to cigarette smoke four times a day for 30 min for 6 weeks. The expression of CFTR was analysed by immunohistochemistry. Intra/interlobular pancreatic ducts were isolated from guinea pig pancreas. Cigarette smoke extract (CSE) was prepared by smoking of 15 cigarettes into 10 ml distilled water by a smoking machine. Three different concentraion (20, 40 and 80 µg/ml) were diluted using the stock solution. Intracellular pH was evaluated by microfluorometry. Basal and forskolin-stimulated fluid secretion was measured by video microscopy. CFTR currents were detected by whole cell configuration of patch clamp technique.
Result: Cigarette smoking significantly diminished the expression of CFTR and the fluid and HCO_3^- secretion in guinea pig pancreas. 40 µg/ml CSE decreased HCO_3^- secretion via inhibition of Cl^-/HCO_3^- exchanger activity. CSE dose-dependently decreased forskolin-stimulated fluid secretion in guinea pig pancreatic ducts and forskolin-stimulated Cl^- current of CFTR Cl^- channel (20 µg/ml by 44.5%, 40 µg/ml by 69.3% and 80 µg/ml by 81.3%).
Conclusion: Cigarette smoking and CSE inhibits pancreatic ductal fluid and HCO_3^- secretion and the activity of CFTR which may play role in the smoke-induced pancreatic damage. This study was supported by OTKA, MTA and TÁMOP.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP314 GHRELIN INHIBITS TNF-ALPHA PRODUCTION IN ACUTE PANCREATITIS

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Introduction: Ghrelin (GHRL), a 28-amino acid polypeptide, that was originally isolated from the stomach, was shown to protect the pancreas from caerulein-induced pancreatitis (AP) [1–3].
Aims & Methods: To determine the effects of GHRL on tumor necrosis factor-alpha (TNF-α) concentration in the rats with AP and on the signals for growth hormone secretagogues receptor type 1a (GHS-R1a) and TNF-α in the pancreatic acini. AP was induced by caerulein infusion (25 µg/kg s.c.). GHRL (12.5; 25; 50 µg/kg i.p.) was given to the control rats and prior to the start of inflammation in vivo. Plasma TNF-α concentration was measured by ELISA. Pancreatic acini were isolated from control, GHRL rats and then hyperstimulated by caerulein (10^{-8} M) in vitro. The gene expressions were determined by RT-PCR and the protein contents by Western-blot
Result: Administration of GHRL to the control rats failed to affect TNF-α concentration in plasma. AP significantly increased its, but application of GHRL prior to the inflammation significantly dose-dependently reduced this pro-inflammatory cytokine. Protein expressions and mRNA signals for GHS-R1a and TNF-α have been detected in the pancreatic acini under basal conditions and GHRL resulted in a statistically increase of GHS-R1a without changing signals of TNF-α. Caerulein significantly changed the test signals: downregulated receptor and upregulated cytokine. These adverse effects were reversed by GHRL.
Conclusion: Caerulein upregulated molecular signals for TNF-α and downregulated that for GHS-R1a in the pancreatic acini. This effect could be prevented by pretreatment of the AP rats with GHRL. Above mechanism could be implicated in the protective action of this polypeptide in AP.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP315 IDENTIFICATION AND CHARACTERISATION OF A NOVEL EARLY ONSET DIABETES GENE USING HUMAN PLURIPOTENT STEM CELLS

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Introduction: Diabetes represents one of the major burdens in the 21st century with approx. 350 million people affected worldwide. Monogenic diabetes such as juvenile onset insulin-dependent diabetes (JOD) or maturity onset diabetes of the young (MODY) accounts for approximately 1–2% of diabetes cases and results from mutations that primarily reduce β-cell function. The identification of the genetic basis of these diabetes forms has translated into novel avenues of personalized medicine in the diabetes field, but only few of these genes have been identified to date.
Aims & Methods: Based on published data, we hypothesize that a proportion of the genetic contribution to common diabetes (T1D and T2D) may be caused by rare monogenic variants/mutations missed by the current GWAS strategies targeting common variants. The current project reports on such a novel gene relevant as regulator of human pancreatic islet formation but also as a novel early onset diabetes gene.
Result: Using stage-specific genome-wide profiling complemented with Chip-Seq data in differentiating human embryonic stem cells, we show that our gene binds and activates Nkx2.2, Nkx6.1 and Pdx1, all belonging to the core suite of isletogenesis transcription factors. Interestingly, this gene co-occupies the enhancer and promoter regions of the latter genes together with Foxa2, Pdx1 and Gata6. Finally, we engineered human embryonic stem cells with previously identified mutations in JOD patients. Directed differentiation studies of these cells shows an altered binding pattern of Nkx2.2, Nkx6.1 and Pdx1 finally leading to reduced amounts of monohormonal β-cells. This reduced target gene binding results from a limited zinc affinity, due to the mutation, that would be necessary as co-factor for gene binding.
Conclusion: This platform not only allows personalised drug-testing but also sheds light on the mechanism how our JOD gene regulates pancreatic development and leads to diabetes in case of certain mutations in humans.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP316 LACK OF CFTR RESULTS IN THE IMPAIRED FUNCTION OF THE PLASMA MEMBRANE CA2+ PUMP THAT CAUSES INTRACELLULAR CA2+ OVERLOAD AND MITOCHONDRIAL DAMAGE IN THE PANCREATIC DUCTAL EPITHELIAL CELLS OF CFTR KNOCK OUT MICE

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Introduction: The cystic fibrosis transmembrane conductance regulator (CFTR) has a significant role in pancreatic ductal epithelial secretion and it's genetic defects damage the pancreas. The exact mechanism of this pancreatic damage is only partially known. The toxic cellular Ca^{2+} overload is a hallmark of acute pancreatitis and in CFTR-deficient airway epithelial cells the intracellular Ca^{2+}homeostasis was disturbed. However the Ca^{2+} homeostasis of CFTR-deficient pancreatic ductalepithelial cells (PDEC) has never been investigated
Aims & Methods: Our aim was to characterize the Ca^{2+} homeostasis of CFTR-deficient PDEC. Pancreatic ducts and acinar cells were isolated from wild type (WT) and CFTR knockout (KO) mice. Intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) and changes of the mitochondrial membrane potential was measured.
Result: Maximal $[Ca^{2+}]i$ release upon carbachol stimulation showed no difference in WT and CFTR KO PDEC. Notably, the plateau phase of the Ca^{2+} signal was significantly higher in CFTR-deficient PDEC, but completely normal in pancreatic acinar cells. Interestingly, the functional inhibition of CFTR with 10µM CFTR(inh)-172 had no effect on the Ca^{2+} signals. Next we investigated the Ca^{2+}-efflux in PDEC and found that the Ca^{2+} extrusion was significantly lower

in CFTR KO PDEC compared to WT due to the impaired function of the plasma membrane Ca^{2+} pump (PMCA). In addition, the sustained elevation of $[Ca^{2+}]i$ caused a drop in mitochondrial membrane potential in CFTR KO PDEC.
Conclusion: Dysfunction of PMCA leads to disturbed Ca^{2+} homeostasis in CFTR-deficient PDEC and the consequent cellular Ca^{2+} overload impairs mitochondrial function. These changes might contribute to the pancreatic damage seen in cystic fibrosis.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP317 ENDOSCOPIC DILATION OF PANCREATIC DUCT STRICTURES IN CHRONIC PANCREATITIS WITH MULTIPLE PLASTIC STENTS: RESULTS IN 48 PATIENTS

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Introduction: Main pancreatic duct (MPD) strictures located in the head of the pancreas often occur in the course of chronic pancreatitis (CP). Common management of these strictures is endoscopic placement of a single plastic stent. Refractory strictures require repeated stent replacement or surgical pancreaticojejunostomy. Insertion of multiple plastic stents (MPS) obtained, in a series of 19 patients, symptomatic MPD stricture resolution in 84% of the cases, after 3-year follow-up (1) The aim of this study was to evaluate the results of the MPS strategy in a larger series of CP patients.
Aims & Methods: Forty-eight patients (34 men; mean age 44 years, range 5–86) with severe CP and a symptomatic dominant MPD stricture located in the head of the pancreas, were evaluated. All the patients experienced pain resolution following MPD drainage with a single plastic stents. The MPD stricture was refractory to single plastic stent placement in all cases and patients underwent insertion of MPS according to the following protocol: balloon dilation of the stricture if necessary, insertion of the maximum number of plastic stents allowed by the stricture tightness and pancreatic duct diameter, stents removal after 6 months.
Result: The median number of stents placed through the major or minor papilla was 3 (range 2–5), 8.5 to 11.5 Fr in diameter and 3 to 7 cm in length. MPS were removed after a mean time of 6.7 months (range 2–18). Eight patients (16.6%) had persistence of the MPD stricture after MPS removal and underwent replacement of an increased number of stents; 3/8 patients had a dilation of the stricture after further multistent placement (overall success 89.5%). Following a mean follow−up of 9.5 years (range 0.3–15.5) after MPS removal, 77.1% of patients were asymptomatic. Symptomatic MPD stricture recurrence was reported in 11 patients (22.9%), after a mean time of 26.4 months (range 5–108) from MPS removal. No major complications were recorded.
Conclusion: Endoscopic dilation of CP-related dominant MPD strictures seems possible with the MPS technique. According to this experience on 48 patients, MPS is highly effective even at long-term follow-up in the majority of patients.
Disclosure of Interest: A. Tringali: Boston Scientific Corporation No current consulting agreements in place One day animal lab in 2012 and 2013. Speaking and teaching in 2014
I. Boskoski: Cook Inc. Consultant
G. Costamagna: Olympus Japan Grant/Research Support Cook, Inc Advisory Committees or Review Panels. Grant/Research Support Boston Scientific Corporation Advisory Committees or Review Panels. Taewoong Medical Inc Advisory Committees or Review Panels.
All other authors have declared no conflicts of interest.

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OP318 CARDIOVASCULAR RISK IN PATIENTS WITH CHRONIC PANCREATITIS AND PANCREATIC EXOCRINE INSUFFICIENCY

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Introduction: Mortality in patients with chronic pancreatitis (CP) is increased. Some previous studies suggest that chronic pancreatitis (CP) is an independent risk factor of cardiovascular disease (CVD). It is well known that malnutrition secondary to different diseases and conditions increases the risk of CVD too. Pancreatic exocrine insufficiency (PEI) causes malnutrition in patients with CP, but if PEI secondary to CP is associated with the risk of CVD and cardiovascular (CV) events is unknown.
Aims & Methods: Aim of the present study was to assess the risk of CV events in patients with CP and the impact of PEI and other factors in these patients. A retrospective analysis of a prospectively collected database of patients with CP, who were under follow-up in our Pancreas Unit was carried out. Diagnosis of CP was based on endoscopic ultrasound (EUS), magnetic resonance cholangio-pancreatoscopy (MRCP) and pancreatic MRI. PEI was defined as the need of pancreatic enzyme replacement therapy due to the presence of maldigestion-related symptoms and/or abnormal nutritional markers together with an abnormal 13C-MTG breath test result. Major CV events (stroke, heart attack) and peripheral arterial disease (claudication, thrombosis) during follow-up were analysed. Patients with a past history of CV events previous to the diagnosis of CP were excluded. Data about sex, age at diagnosis of CP, aetiology, alcohol consumption, smoking, PEI and other comorbidities (including diabetes mellitus) were evaluated. Statistical analysis was done by logistic regression adjusted for confounding factors.
Result: 455 patients were finally included (77,8% men), with a median age of 46 years (range 15–88 years). Mean follow-up was 7.8 years. CP was secondary to alcohol and/or smoking in 301 patients (66.1%). 149 patients (32.7%) had PEI and 131 (28.8%) had diabetes mellitus. A total of 46 CV events were recorded in 43 patients (9.5%). 22 patients (4.8%) suffered from a mayor CV event and the remaining 24 patients (5.3%) presented a peripheral arterial disease. CV events occurred more frequently in patients with PEI ($n = 28$, 18.8%) than in patients without PEI ($n = 15$, 4.9%) ($p < 0.001$). In the logistic regression analysis, PEI (OR 3.76; 95%CI 1.65–8.58), diabetes mellitus (OR 2.55; 95%CI 1.11–5.83) and smoking (OR 3.90; 95%IC 1.19–12.7) were significantly and independently associated with CV events.
Conclusion: Patients with CP are at high risk of CV events. PEI, diabetes mellitus and smoking are independent risk factors associated with the risk of CV events in patients with CP.
Disclosure of Interest: J.E. Domínguez-Muñoz: Has actued as speaker and advisor international of Mylan and Abbot
All other authors have declared no conflicts of interest.

OP319 USE OF THE URINARY TRYPSINOGEN-2 DIPSTICK TEST IN EARLY DIAGNOSIS OF PANCREATITIS AFTER ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

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Introduction: One of the most serious complications of (ERCP) is acute pancreatitis. The reported incidence varies from 1.3% to 24.4% [1]. Measurement of serum amylase and lipase levels after the procedure may have a possible role for early recognition of post-ERCP pancreatitis [3]. Asymptomatic elevation in serum amylase and lipase activities after ERCP is common, occurring in approximately 25% to 75% of all patients. A rapid test strip has been developed for the detection of trypsinogen-2 in urine (The urinary trypsinogen-2 dipstick test—UT2DSTactim pancreatitis) which is based on the immunochromatography principle and shows a good sensitivity and specificity in diagnosing acute pancreatitis [6]. The aim of this study was to evaluate the diagnostic value of urinary trypsinogen-2 dipstick test for early diagnosis of post-ERCP pancreatitis.
Aims & Methods: After an informed consent by the patients the selected patients were subjected to: Full clinical assessment (history taking and clinical examination), laboratory investigations including (complete blood count (CBC), Bilirubin (total and direct), (ALT), (AST), alkaline phosphatase (ALP), Prothrombin time and concentration (PT & PC), urea, creatinine, serum amylase, serum lipase, urinary trypsinogen-2 dipstick test (UT2DST).
Result: Post ERCP UT2DST was negative in 30 patients of the non pancreatitis group (96.8%) and positive in one of them (3.2%) The test was positive in all patients with Pancreatitis (100%). The sensitivity of the post ERCP UT2DST was 100% the Specificity was 97% with PPV 86%, NPV 100% and the P value was <0.01. Comparison between serum lipase and amylase levels post ERCP in relation to UT2DST test shows that positive UT2DST test was significantly associated with higher amylase and lipase serum levels after ERCP (post amylase and post lipase) ($P < 0.01$).
Conclusion: The urinary trypsinogen-2 dipstick test can be used as an easy and rapid test for early diagnosis of post-ERCP pancreatitis with high sensitivity and specificity and can help clinicians to provide intensive care and possible medical treatment as early as possible.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP320 WHAT KIND OF INTRAVENOUS HYDRATION SHOULD BE USED FOR THE PREVENTION OF POST-ERCP PANCREATITIS: A PROSPECTIVE RANDOMIZED MULTICENTER CLINICAL TRIAL

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Introduction: A pilot study suggests that aggressive intravenous hydration with lactated Ringer's solution may reduce the development of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. The present larger multicenter study aimed to determine what kind of intravenous hydration could reduce the incidence of post-ERCP pancreatitis.

Aims & Methods: In a prospective randomized multicenter clinical trial, patients who underwent first-time ERCP were randomly assigned to 3 groups (1:1:1) that received aggressive hydration with lactated Ringer's solution (3 mL/kg/h during the procedure, a 20 mL/kg bolus after the procedure, and 3 mL/kg/h for 8 hours after the procedure), standard hydration with the same solution (1.5 mL/kg/h during and for 8 hours after the procedure), or aggressive hydration with physiologic saline (3 mL/kg/h during the procedure, a 20 mL/kg bolus after the procedure, and 3 mL/kg/h for 8 hours after the procedure). The primary end point, post-ERCP pancreatitis, was defined as hyperamylasemia (level of amylase > 3 times the upper limit of normal) and increased epigastric pain (≥3 points on visual analogue scale) persisting for ≥24 hours after the procedure.

Result: A total of 406 patients were enrolled, and 395 of them completed the protocols. The three groups had no significant difference in demographic characteristics or other risk factors before ERCP ($P > 0.05$). The intention-to-treat post-ERCP pancreatitis rates were 3.0% (4/132) in the aggressive hydration with lactated Ringer's solution group and 11.6% (15/129) in the standard hydration group ($P = 0.008$), whereas the per protocol (PP) post-ERCP pancreatitis rates were 1.6% (2/128) in the aggressive hydration with lactated Ringer's solution group and 11.6% (15/129) in the standard hydration group ($P = 0.001$). No significant differences in the intention-to-treat and PP post-ERCP pancreatitis were found between the aggressive hydration with physiologic saline group (6.7%, 9/134; 7.0%. 9/128) and standard hydration group (11.6%, 15/129, $P = 0.167$, $P = 0.205$).

Conclusion: Aggressive hydration with lactated Ringer's solution is more effective than standard hydration for prevention of post-ERCP pancreatitis.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP321 GASTROINTESTINAL SAFETY OF LEVODOPA-CARBIDOPA INTESTINAL GEL IN ADVANCED PARKINSON'S DISEASE PATIENTS: FINAL RESULTS FROM THE GLORIA LONG-TERM REGISTRY

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Introduction: Levodopa-carbidopa intestinal gel (LCIG, designated in the US as carbidopa-levodopa enteral suspension [CLES]) is a long-term treatment option for advanced Parkinson's disease (PD) patients and administered via percutaneous gastrojejunostomy (PEG-J) from an external pump.

Aims & Methods: The gastrointestinal (GI)-related safety of the LCIG treatment system (drug/device) has been assessed in advanced PD patients with final safety data from the GLORIA[1] registry. This observational registry of 375 advanced PD patients treated with LCIG was conducted at 75 centers in 18 countries. Patients were initially titrated to an optimal dose of LCIG via nasojejunal (NJ) tube for up to 2 weeks, followed by infusion via PEG-J for 24 months. Final safety data from patients with advanced PD who had ≥1 infusion of LCIG (n = 356) were included in this analysis. Adverse drug reactions (ADR), which are adverse events with a reasonable possibility of causal relationship to the treatment according to investigators' judgment, were recorded throughout the registry. The authors categorized ADRs post hoc as either PEG-J procedure-related, device-related, or "other" type of GI event.

Result: Of the 375 enrolled patients, 332 (89%) were treated with LCIG via PEG-J, and 258 (69%) completed the 24 month follow-up. The median [range] duration of exposure via NJ was 6.0 [1, 53] days (n = 307) and via PEG-J was 722 [1, 957] days (n = 351). During titration via NJ, there were 3 patients (0.8%) who had ≥1 GI related ADR. Within the 24 months of treatment post-PEG-J placement (n = 356) ≥ 1 GI related ADR was reported in 139 patients (39%), of which procedure-related ADRs were reported in 35 patients (9.8%), device-related in 93 (26%), other GI events in 63 (18%); the ADRs in all GI categories reported for ≥4% patients were weight decreased (6.7%), device related infection (5.9%), device dislocation (4.8%), device issue (4.8%); and the serious ADRs reported for ≥2% patients were device dislocation (2.2%) and device issue (2.0%). During the 28-day follow up period, there were 4 patients (1.1%) who had ≥1 GI related ADR. ADRs led to the discontinuation of 10 patients (2.8%) overall, 2 of whom discontinued due to a procedure-related ADR, 5 due to a device-related ADR, and 3 due to another type of GI ADR. Of the 29 deaths reported, 23 were deemed unrelated to treatment, 5 possibly related (to drug/device) and 1 probably related (to tubing). Of the possibly/probably related deaths, 2 had GI related events; 1 had a small bowel obstruction and died approximately 3 weeks later of unknown causes, and 1 had a small bowel perforation and peritonitis.

Conclusion: Most GI-related ADRs were related to the device in this registry. The incidence of GI-related ADRs and discontinuations due to GI-related ADRs were relatively low, which is supportive of the overall tolerability of LCIG and consistent with previous studies.[2]

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A. Antonini: Angelo Antonini has received research support from Mundipharma and compensation from UCB, Boston Scientific, Boheringer-Ingelheim, AbbVie Inc., and Zambon for serving as a consultant and lecturer.
L. Bergmann: Lars Bergmann is an employee of AbbVie Inc. and hold stock or stock options.
A. Yegin: Ashley Yegin is an employee of AbbVie Inc. and holds stock or stock options.
W. Poewe: Dr. Poewe: royalities from Thieme, Wiley Blackwell, Oxford University Press; compensation from AbbVie, Astra Zeneca, Teva, Novartis, GSK, Boehringer-Ingelheim, UCB, Orion Pharma, Zambon, Merz Pharmceuticals for consulting and lecturing.
All other authors have declared no conflicts of interest.

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OP322 ENDOSCOPICALLY ASSISTED PERCUTANEOUS TRANSESOPHAGEAL GASTROTUBING (PTEG) AND THE PROGRESS

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Introduction: Endoscopically assisted percutaneous transesophageal gastrotubing (PTEG) was developed as an alternative route to access the gastrointestinal tract

for the patients that Percutaneous Endoscopic Gastrostomy was contraindicated. PTEG by endoscopic assistance may enhance the safety of the procedure and the new item that may enhance the reliability was developed.
Aims & Methods: The aim of this study is to evaluate the clinical usefulness of PTEG supported by endoscopy. A rupture-free balloon (RFB) catheter is inserted into the upper esophagus. Percutaneous balloon puncture with a specialized needle is then performed from the left side of patient's neck under ultrasonographic control. A guide wire is inserted through the needle into the RFB, followed by a dilator and sheath. A placement tube is then inserted through the sheath, and the sheath is removed. We started to perform PTEG under endoscopy in a total of 119 patients (74 men and 45 women, mean age 71.5 years) in whom PEG was not feasible. Double Balloons equipped Overtube type RFB were used instead of primary RFB in seven cases that the puncture needle is punctured into the overtube trough the balloon. PTEG was performed for nutrition in 65 patients and for decompression in 54.
Result: Satisfactory results were achieved in all 119 patients. Median follow-up was 64.0 days in patients who received decompression because of the obstruction due to malignancies and 270.0 days in those who received nutrition. Four of 65 patients for nutrition were able to be free from tube feeding due to PTEG tube feeding support. There was one patient had tracheal penetration, which was managed conservatively. Other complications were minor oozing bleeding in seven patients that did not require blood transfusion, subcutaneous emphysema in two patients, which were managed conservatively. The complication rate was 13.4%. A stable procedure could performed in all seven cases using the new overtube, and also there was no complications. No patient required surgical treatment or died after PTEG.
Conclusion: PTEG is feasible, safe, and useful. PTEG could be an optimal procedure for long-term nutrition and/or decompression even for the patients who failed PEG insertion. The use of endoscopy enhances the safety of the procedure and allows better confirmation of each step involved. New overtube type RFB will be useful but need more experiences.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 08:30–10:00
EOSINOHILIC OESOPHAGITIS AND GORD – ROOM M

OP323 STEP-UP EMPIRIC ELIMINATION DIET FOR PEDIATRIC AND ADULT EOSINOPHILIC ESOPHAGITIS: THE 2–4-6 STUDY

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Introduction: A six-food elimination diet (SFED) for eosinophilic esophagitis (EoE) requires almost a year on a high level of dietary restriction and multiple endoscopies. A four-food elimination diet (FFED), eliminating the four most common culprit foods in EoE (animal milk, gluten-containing cereals, egg, legumes) has been a first step to simplify empiric elimination strategies.
Aims & Methods: To assess the effectiveness of a step-up empiric elimination diet strategy for EoE. Prospective multicenter study conducted in 12 Spanish hospitals in both children and adults. All patients included fulfilled clinic and histologic criteria for EoE and lack of response to PPI therapy was documented before inclusion. Initial two-food elimination diet (animal milks and gluten-containing cereals) was evaluated in all patients, stepping up to a FFED and eventually to a SFED in non-responders. Response to dietary therapy was defined by symptom improvement and <15 eos/HPF. In responders to empiric diet, each food group was individually reintroduced for 6 weeks with further histologic reevaluation. Food triggers were defined as those leading to esophageal inflammation >15 eos/HPF after individual reintroduction.
Result: Presently, 93 patients (25 pediatric) have been included. A two-food elimination diet achieved EoE remission in 38 patients (40%) unresponsive to PPI therapy. Remission rates increased to 52% and 65% with a FFED and SFED, respectively. Individual food reintroduction has been completed in 26/38 of responders to a two-food elimination diet, of whom 85% had a single food trigger. The most common food triggers were animal milk (60%), gluten-containing cereals (25%) and both (15%). Compared to starting with a SFED, this step-up strategy (2–4–6) allows reducing endoscopic procedures and the diagnostic process time by 35%.
Conclusion: A two-food elimination diet (animal milk, gluten-containing cereals) achieves EoE remission in up to 40% of patients unresponsive to PPI therapy. This diet allows prompt identification of two thirds of responders to empiric elimination diets, with few food triggers (one food trigger in 85% of responders) and consequently, good candidates for dietary maintenance therapy. A step-up empiric diet strategy (2–4–6) might be a cost-effective dietary strategy for pediatric and adult EoE.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP324 INCREASED MUCOSAL EXPRESSION OF TOLL-LIKE RECEPTORS IN ADULT PATIENTS WITH EOSINOPHILIC ESOPHAGITIS

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Introduction: An adaptive Th2-type immune response to food antigens is involved in eosinophilic esophagitis (EoE). Evidences of a potential role for the innate immunity in EoE has also arisen in parallel to the recognition of changes in esophageal microbiome in adult and pediatric EoE patients compared to non-EoE controls. The likely role that microbial pattern recognition receptors (PRRs) might play in EoE arises as a potential source of research in understanding the relationship of diet, the esophageal microbiome, and the immune system activation in EoE, that has not been assessed yet.
Aims & Methods: To gather data about the potential implication of Toll like receptors (TLRs), the most investigated group of transmembrane PRR in EoE, we characterized TLR mRNA expression and protein staining in esophageal mucosal biopsy samples from adults before and after dietary treatment, and compared with control patients. Esophageal mucosal samples were fixed in formalin, embedded in paraffin, and routinely processed for hematoxylin and eosin staining. Specific antigen retrieval and permeabilization processes were performed before samples were incubated with the primary antibodies anti-TLR1, TLR2, TLR3, TLR4, TLR6, or TLR9. Incubation with the secondary antibodies Alexa Fluor 594 goat anti-rabbit IgG or Alexa Fluor 488 goat anti-mouse IgG Nuclei were counterstained with DAPI. Gene expression for the different TLR assessed was evaluated in all samples after RNA was isolated with MirVanaTM Kit. Simultaneous real-time PCRs were performed with TaqMan Low-Density Arrays. Thermal cycling conditions were 2 min at 50°C, 10 min at 95°C, followed by 40 cycles of denaturation at 95°C for 15 s, and annealing and extension at 60°C for 1 min in an ABI PRISM 7900 HT Sequence Detection System. Relative changes in mRNA expression were calculated with the cycle threshold (Ct) method.
Result: A total of 10 EoE patients (8 men) and 10 gender-matched control subjects were included in the analysis. The groups had a mean age of 33.1 (10.1) and 53 (19.9) years, respectively. In the EoE group, peak intraepithelial eosinophil density was 56.8 (29.9) cells/hpf, which decreased to 3 (4.2) cells/hpf after SFED-based treatment ($p < 0.001$). No intraepithelial eosinophils were detected in any of the esophageal samples from controls. No differences in eosinophil counts were detected for atopic and non-atopic EoE patients, being 55 (30.4) vs. 61 (34.8) cells/hpf, respectively. Active EoE characterized by significant upregulation of TLR1 (2.7-fold increase), TLR2 (3.7-fold increase) TLR4 (4.6-fold increase) and TLR9 (3.4-fold-increase) in comparison with the controls ($p < 0.05$ for all comparisons). Dietary treatment significantly decreased all the four TLRs to control group values ($p < 0.05$) Immunofluorescence staining demonstrated epithelial-predominant staining in TLR2 and TLR4, and scattered cell staining for TLR1 and TLR9. TLR expression patters showed differences in lamina propria and epithelial layers.
Conclusion: EoE is associated with changes in expression levels of several TLRs, that reverse after effective dietary therapy. Our results points towards an interplay of diet, microbiome and innate immune responses in the pathophysiology of EoE.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP325 A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF A NOVEL RECOMBINANT, HUMANISED, ANTI-INTERLEUKIN-13 MONOCLONAL ANTIBODY (RPC4046) IN PATIENTS WITH ACTIVE EOSINOPHILIC OESOPHAGITIS: RESULTS OF THE HEROES STUDY

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Introduction: Interleukin-13 (IL-13) has been implicated in the pathogenesis of eosinophilic oesophagitis (EOE). RPC4046 prevents the binding of IL-13 to both the IL-13Rα1 and IL-13Rα2 receptors. This study evaluated the efficacy and safety of 2 dose levels of RPC4046 compared to placebo (PBO).

Aims & Methods: Subjects were randomized 1:1:1 to receive either RPC4046 180 mg [LD] (n = 31), RPC4046 360 mg [HD] (n = 34), or PBO (n = 34). An IV dose on Day 1 was followed by weekly subcutaneous doses. Oesophageal biopsies, read by a central blinded pathologist, were obtained at baseline (BL) and Wk16 to assess change in mean eosinophil count, the primary endpoint. Secondary endpoints included symptom improvement measured by a Daily Symptom Diary (DSD), improvement in endoscopic features as measured by the EOE Endoscopic Reference Score (EREF), and Subject's Global Assessment of Disease Severity. Safety was also assessed.

Result: 90 subjects completed the 16Wk double-blind period. Demographic/disease characteristics were generally comparable between treatment arms. At BL, mean oesophageal eosinophil counts (cells/hpf) were 92.4 (PBO), 116.6 (LD), and 122.6 (HD). At Wk16, the mean count was significantly reduced from BL for both RPC4046 dose levels compared to PBO (mean change: PBO –4.4, LD –94.8, and HD –99.9 [both $p < 0.0001$ vs PBO]). There was a greater improvement in dysphagia symptoms as measured by the DSD with HD compared to PBO, but this did not achieve statistical significance (PBO –6.4, LD –5.3 [$p = 0.996$ vs PBO], and HD –13.3 [$p = 0.073$ vs PBO]). There were significant improvements in endoscopic features as determined by the reduction in the total mean EREF score with both RPC4046 dose levels (mean change: PBO –0.9, LD –4.2, and HD –4.8 [both $p < 0.0004$ vs PBO]). There was a significant improvement in Subject's Global Assessment of Disease Severity at the HD (PBO −1.5, LD −2.0, HD −2.8 [HD $p = 0.0107$ vs PBO]). The rates of overall adverse events (AEs) were 64.7% (PBO), 64.5% (LD), and 85.3% (HD). The most frequent AEs were headache (PBO 14.7%, LD 16.1%, HD 20.6%), upper respiratory infection (PBO 8.8%, LD 16.1%, HD 14.7%), and arthralgia (PBO 0%, LD 12.9%, HD 5.9%).

Conclusion: RPC4046 demonstrated significant reductions in oesophageal eosinophilic inflammation and improvements in endoscopic features at both dose levels. Subjects receiving the HD had greater symptom improvement than those on LD. These phase 2 data support the further study of RPC4046 as a novel treatment for EOE. (clinicaltrials.gov ID: NCT02098473)

Disclosure of Interest: I. Hirano: I am a consultant for Receptos, Regeneron, Shire pharma
M. Collins: I have received research funds (through contracts) from Receptos (now Celgene), Meritage (now Shire), Shire, and Regeneron, and I am a consultant for Banner Life Sciences and Adare.
S. Gupta: Sandeep K. Gupta received consulting fees and/or speaker fees from Abbott Laboratories, Nestlé S. A., QOL, Receptos, Inc., and Meritage Pharma, Inc.
A. Schoepfer: I received consultant fees from: Receptos, Regeneron and grant support from: Receptos, Regeneron, Falk.
A. Straumann: Dr. Staumann is a consultant to Dr Falk Pharma GmbH and has received consulting fees and/or speaker fees and/or research grants from Actelion, AG; AstraZeneca, AG;, Aptalis Pharma; GSK, AG; Nestlé S. A.; Novartis, AG; Pfizer, AG, and Regeneron.
M. Grimm: I am an employee of Celgene.
H. Smith: I am an employee of Celgene.
C. Tompkins: I am an employee of Celgene.
A. Woo: I am an employee of Celgene.
R. Peach: I am a former employee of Celgene.
P. Frohna: I am an employee of Celgene.
S. Gujrathi: I am a former employee of Celgene.
R. Aranda: I am an employee of Celgene.
E. Dellon: I have received research funding from Receptos/Celgene; and am a Consultant for Receptos/Celgene.
All other authors have declared no conflicts of interest.

OP326 IMPAIRMENT OF CHEMICAL CLEARANCE AND MUCOSAL INTEGRITY DISTINGUISH HYPERSENSITIVE ESOPHAGUS FROM FUNCTIONAL HEARTBURN

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Introduction: Hypersensitive esophagus (HE) is defined by endoscopy-negative heartburn with normal esophageal acid exposure time (EAET) but positive symptom association probability (SAP) and symptom index (SI) at reflux monitoring, and/or heartburn suppression with proton pump inhibitor (PPI) therapy. Functional heartburn (FH) is distinguished by PPI-refractoriness and negative SAP/SI. However, diagnostic accuracy of SAP and SI has been recently questioned leading to consider with caution the diagnosis of FH/HE based on symptom-reflux association analysis only.

Aims & Methods: We aimed to investigate whether impairment of chemical clearance, expressed by post-reflux swallow-induced peristaltic wave (PSPW) index, and of mucosal integrity, expressed by mean nocturnal baseline impedance (MNBI), distinguish HE from FH independently from SAP and SI. Impedance-pH tracings from 303 patients with PPI-dependent (i.e. heartburn repeatedly abolished by 4-week PPI-therapy and repeatedly recurring after PPI withdrawal) or PPI-refractory (i.e. <50% of symptom relief after 8-week high-dosage PPI therapy) heartburn were blindly reviewed, 125 with non-erosive reflux disease (NERD) defined by abnormal EAET, 108 with HE (normal EAET, but positive symptom-reflux correlation) and 70 with FH (normal EAET and negative symptom-reflux correlation). Impedance-pH tracings were manually analyzed to detect: EAET (abnormal if ≥3.2% over 24 hours), characteristics of reflux episodes (acid/weakly acidic) and symptom-reflux association using both SAP (positive if ≥95%) and SI (positive if ≥50%). MNBI values were calculated at 3 cm above the LES, during the overnight rest, for at least 30 minutes after excluding swallows and reflux induced changes. The PSPW index was calculated by dividing the number of refluxes followed within 30 seconds by swallow-induced peristaltic waves with the number of total refluxes.

Result: In PPI-dependent patients with HE, PSPW index and MNBI were the most sensitive impedance parameters; at multivariate analysis, they were independent predictors of HE. At receiver operating characteristic analysis, PSPW index with MNBI efficiently separated HE from FH: the area under the curve was 0.957. Only 50/108 (46%) patients with HE had concordant SAP/SI positivity, 48 (96%) of them with abnormal PSPW index and/or MNBI. Abnormal values for PSPW index and/or MNBI were found in 34/39 (87%) of SAP/SI negative and in 15/17 (88%) of SAP/SI discordant cases.

Conclusion: HE is characterized by impairment of chemical clearance and of mucosal integrity. When EAET is normal and SAP/SI afford inconclusive results, PSPW index and MNBI should be analyzed to objectively distinguish HE from FH

Disclosure of Interest: All authors have declared no conflicts of interest.

OP327 THE ADDED VALUE OF POST-REFLUX SWALLOW-INDUCED PERISTALTIC WAVE INDEX AND NOCTURNAL BASELINE IMPEDANCE IN REFRACTORY GERD STUDIED WITH ON-THERAPY IMPEDANCE-PH MONITORING

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Introduction: On-therapy impedance-pH monitoring in proton pump inhibitor (PPI)-refractory gastroesophageal reflux disease (GERD) yielded conflicting results. Recently, novel impedance parameters assessing esophageal chemical clearance and mucosal integrity, namely the post-reflux swallow-induced peristaltic wave (PSPW) index and the mean nocturnal baseline impedance (MNBI), have been shown to increase the diagnostic yield of impedance-pH monitoring in

investigating PPI-refractory patients studied off-therapy, further improving the management of these patients.
Aims & Methods: We aimed to investigate whether the impairment of chemical clearance, expressed by PSPW index, and of mucosal integrity, expressed by MNBI, are helpful in segregating NERD from FH studied with impedance-pH monitoring on-PPI therapy. Further, we assessed the value of these novel parameters as predictors of PPI-refractory GERD confirmed by 3-year positive surgical outcome. On-therapy impedance-pH tracings from consecutive patients referred for PPI-refractory heartburn with/without regurgitation (i.e. <50% of symptom relief or mucosal healing after 8-week high-dosage PPI therapy) were blindly reviewed. All tracings were manually analyzed to detect: acid exposure time (AET; abnormal if ≥3.2% over 24 hours), characteristics of reflux episodes (acid/weakly acidic) and symptom-reflux association using both symptom association probability (SAP; positive if ≥95%) and symptom index (SI; positive if ≥50%). MNBI values were calculated at 3 cm above the LES, during the overnight rest, for at least 30 minutes after excluding swallows and reflux induced changes. The PSPW index was calculated by dividing the number of refluxes followed within 30 seconds by swallow-induced peristaltic waves with the number of total refluxes. Patients were subdivided into refractory reflux esophagitis (RRE), healed reflux esophagitis (HRE), non-erosive reflux disease (NERD; defined by abnormal acid exposure time or normal AET but positive symptom-reflux correlation) and functional heartburn (FH; defined by normal AET and negative symptom-reflux correlation) according to endoscopy and conventional impedance-pH variables.
Result: Median PSPW index and MNBI were significantly lower in 39 RRE (16%; 1145 Ohms) than in 41 HRE (25%; 1741 Ohms) and in 68 NERD (29%; 2374 Ohms) patients, and in all three GERD subgroups compared to 41 FH cases (67%; 3488 Ohms) (P = 0.0001). Comparing NERD to FH, PSPW index showed an area under curve greater than MNBI at receiver-operating-characteristic analysis (0.886 vs. 0.677, P = 0.005). PSPW index was abnormal preoperatively in 53/53 patients with positive surgical outcome and resulted independent predictor of PPI-refractory GERD at multivariate analysis, (odds ratio 0.6983, P = 0.012).
Conclusion: At on-therapy impedance-pH monitoring, impaired chemical clearance and mucosal integrity characterize PPI-refractory typical GERD. PSPW index and MNBI efficiently distinguish PPI-refractory NERD from FH and PSPW index appears useful for selecting surgical candidates.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP328 PRELIMINARY RESULTS OF A PROSPECTIVE MULTI-CENTER REGISTRY OF LOWER ESOPHAGEAL SPHINCTER STIMULATION FOR GERD: THE LESS-GERD REGISTRY

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Introduction: Safety and effectiveness of electrical stimulation of the lower esophageal sphincter (LES-ES) using the EndoStim® LES Stimulation System (The Hague, The Netherlands) was demonstrated in clinical trials. Limited data available on outcomes in clinical practice.
Aims & Methods: An ongoing, prospective international multicenter web-based registry is collecting data in patients with disruptive GERD symptoms treated with LES-ES in clinical practice at baseline and at routine follow-ups for 5-year. Demographics, adverse events, GERD symptoms recorded in daily diaries, GERD health related quality of life scores (GERD-HRQL), structured GI symptom questionnaires for extra-esophageal symptoms, use of proton pump inhibitors (PPIs) and physiological data (esophageal pH / manometry) are collected when available.
Result: Data was available in 50 patients enrolled in eleven sites with 6 months post-op follow upand from 28 patients with 12 months follow-up. Ninety% (43/48) patients showed an improvement in their GERD-HRQL score on LES-ES at 6 months and 93% (25/27) showed an improvement at 12 months compared to baseline. The median (IQR) composite GERD-HRQL score improved from 22 (17–27) preoperatively to 8.0 (4.0–13.3) at 6-month (p < 0.001) and from 20.0 (17–23.5) to 5.0 (2.0–7.0) at 12-months (p < 0.001). At baseline, 44% of patients (22/50) complained on daily bothersome heartburn symptoms affecting sleep which decreased to 8% (4/50) at 6 months (p < 0.001) and 0% (0/28) at 12 months (p < 0.001). At baseline, 52% and 15% of subjects reported moderate or severe regurgitation, respectively which decreased to 22% and 7% at 6 months (n = 27) and 14% and 0% at 12 months (n = 14). Data on prior hospitalization due to GERD was available from 40 patients who with hospitalization data available for their 6 m visit (±1 m). Annualized hospitalization rates due to GERD at baseline pre EndoStim was 1.1 days/year (n = 40) and 45% (18/40) reported at least one hospitalization due to GERD which at last follow up decreased to 0.3 days/year with 83% of patients who were required hospitalization pre-op reporting no hospitalization post-op. All patients were on long-term PPI at baseline. Seventy-one% (45/63) patients at 6 month and 75% (27/36) patients at 12 months were completely off PPI. Data on 24 h esophageal pH at 6 m showed a non-statistically significant improvement. Safety data was adjudicated by an independent DSMB. Four serious adverse events in three patients were reported. One myocardial infarction related sudden death at 11 month post-op, not related to device or procedure was reported. One event of lead erosion into the esophagus was detected during routine endoscopy. The device was removed during laparoscopic fundoplication procedure. Two events of gastroparesis, possibly related to the device requiring hospitalization were reported in one patient.
Conclusion: Electrical stimulation of the LES is safe and effective in clinical practice in treating GERD patients with disruptive GERD symptoms despite PPI. LES stimulation results in significant improvement in GERD outcomes and reduced healthcare resource utilization. LES-ES should be considered a viable treatment option for treating GERD patients with disruptive GERD symptoms despite maximal medical management.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 08:30–10:00
DIAGNOSIS AND TREATMENT OF PANCREATIC CANCER AND ITS PRECURSORS – ROOM N1

OP329 SURVEILLANCE OF HIGH-RISK INDIVIDUALS DETECTS RESECTABLE PANCREATIC MALIGNANCIES AND HIGH-GRADE PRECURSORS: RESULTS OF A 16-YEAR EARLY DETECTION PROGRAM FOR FAMILIAL PANCREATIC NEOPLASIA

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Introduction: Endoscopic ultrasonography (EUS) and/or magnetic resonance imaging (MRI) screening of asymptomatic individuals (HRI) at high risk for PDA to detect for early pancreatic neoplasia can lead to the detection of small pancreatic cysts in almost 40%[1]. However, there is limited understanding risk for neoplastic progression and the natural history of low risk detected lesions after baseline screening. The long-term clinical outcomes of radiologic surveillance aiming to detect early PDA and high-grade precursor lesions (IPMN HGD or PanIN3 = HPCLs) are also not well understood.
Aims & Methods: To determine the incidence of surveillance-detected pancreatic lesions following baseline screening and calculate the incidence rates of invasive malignancy and high-grade neoplasia in HRI undergoing long-term surveillance. We prospectively enrolled HRI in the Cancer of the Pancreas Screening (CAPS) studies from 1998 to 2014 (n = 578) at a tertiary referral academic medical center with a comprehensive multidisciplinary pancreas screening program. HRI consisted of familial PDA relatives or PDA-associated gene mutation carriers (BRCA 1/2, PALB2, p16, PRSS1, STK11) who had a >6 months of follow-up imaging after baseline EUS and MRI. HRI with baseline solid masses or prevalent PDA were excluded from the surveillance cohort analyses. Radiological features of progression (new solid mass, and worrisome features defined by Sendai International Consensus Guidelines (ICG) for pancreatic mucinous cysts) were compared to pathologic diagnoses or repeat abdominal imaging according to clinical surveillance protocol.
Result: 343 HRI were screened and underwent follow-up imaging with EUS and/or MRI every 6–12 months (depending on baseline findings). 293 (85%) familial PC relatives and 50 (15%) mutation carriers were studied, mean age 56.4 (range 22–81), 47% male. Mean follow-up time was 5.1 years (range 0.5–15.1). 132/341 HRI (38%) had no pancreatic lesions at baseline and follow-up, 155 (45%) had a low risk cyst at baseline, and 12 (3.5%) had a solid mass or nodule at baseline. 74 HRI (22%) developed new low risk cysts on follow-up. 54/343 HRI (16%) developed radiological progression, with detection of a new solid mass (n = 24,7%%), cyst growth >2 mm in 6 months (n = 11, 3.2%), or >1 ICG worrisome features (mural nodule n = 7, 2%), dilated main pancreatic duct (MPD) >5 mm(n = 15,4.4%), abrupt change in MPD caliber (n = 1), cyst size >3 cm (n = 2). Of these 54 HRI with progression, 38 had surgery and 21 of these (58%) had PDA, malignant pancreatic neuroendocrine tumor (PanNET), or HPCLs. The median time to radiological progression from baseline screening was 3.2 years (IQ range 1.2–6 years), with some HRI progressing at 10.9 years. In contrast, none of HRI without detected lesions at baseline or follow-up developed PDA (p = .002). During surveillance, 13/343 (3.8%) incident PDA and 8/343 (2.3%) incident malignant neuroendocrine tumors were detected (all with radiologic progression). An additional 8/343 (2.3%) HRI had HPCLs. The incidence of PDA was 1/50 (2%) in mutation carriers and 12/293 (4%) in familial PC relatives. Of the 50 patients with pathological diagnoses (45 surgical resection, 5 biopsy), 27 of 29 (93%) with radiological features of progression had a malignancy (PDA = 13 or PanNET tumor = 6), or at least one HPCL (n = 8). 10 of 13 (77%) of incident PDA were resectable (3 unresectable PDAs were late for surveillance or lost to follow-up). 16/45 (36%) HRI who had surgery had lower-grade neoplasms (BD-IPMN LGD/IGD, PanIN2, combined IPMN, SCA, benign neuroendocrine microadenomas). In surgically-treated HRI, the prevalence of IPMN HGD in cysts with mural nodules was 5/7 (71%).

Conclusion: In our 16-year cohort with long-term surveillance, the incidence of PDA was modestly elevated but majority of detected cancers were asymptomatic and resectable. Surveillance also detects early stage PanNETs and HPCLs. The majority of detected proven malignancies had radiologic progression but more research is needed to improve the selection of patients for surveillance and surgery.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

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OP330 CLINICAL IMPACT OF ENDOSCOPIC ULTRASONOGRAPHY IMAGING OF CHRONIC PANCREATITIS IN THE PANCREATIC PARENCHYMA IN PATIENTS WITH INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

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Introduction: The recent guideline for intraductal papillary mucinous neoplasms (IPMNs) focuses on morphological features of the lesion as signs of malignant transformation, but ignores the background pancreatic parenchyma, including features of chronic pancreatitis, a risk factor for pancreatic malignancies. Endoscopic ultrasonography frequently reveals evidence of chronic pancreatitis (EUS-CP findings) in the background pancreatic parenchyma of patients with IPMNs. Therefore, we investigated whether background EUS-CP findings were associated with malignant IPMN.

Aims & Methods: Clinical data for 69 consecutive patients with IPMNs who underwent preoperative EUS and surgical resection between April 2010 and October 2014 were collected prospectively. The association of EUS-CP findings (total number of EUS-CP findings; 0 vs. $\geq$1) with invasive IPMN was examined. The association of EUS-CP findings with pathological changes of the background pancreatic parenchyma (atrophy/inflammation/fibrosis) was also examined.

Result: Among patients with EUS-CP findings, invasive intraductal papillary mucinous carcinoma (IPMC) was significantly more frequent than among patients without EUS-CP findings (42.5% (17/40) vs. 3.4% (1/29), $p = 0.0002$). In addition, patients with EUS-CP findings had higher grades of pancreatic atrophy and inflammation than patients without EUS-CP findings (atrophy: 72.5% (29/40) vs. 34.5% (10/29), $p = 0.003$, inflammation: 45.0% (18/40) vs. 20.7% (6/29), $p = 0.04$).

Conclusion: In IPMN patients, detection of EUS-CP findings in the background pancreatic parenchyma was associated with a higher prevalence of invasive IPMC. Accordingly, EUS examination should not only assess the morphological features of the lesion itself, but also EUS-CP findings in the background parenchyma.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP331 NEEDLE-BASED CONFOCAL LASER ENDOMICROSCOPY (NCLE) FOR THE DIAGNOSIS OF SOLITARY PANCREATIC CYSTS: A PROSPECTIVE MULTICENTER STUDY

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Introduction: Diagnosis of solitary pancreatic cyst is clinically challenging due to the malignant potential of several cyst subtypes. nCLE is emerging as a powerful technique which enables the observation of the inner wall of pancreatic cysts, in vivo and in real-time, during an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Three clinical trials evaluated the feasibility, the safety and highlighted specific criteria for the characterization of pancreatic cystic lesions. This study aims to prospectively evaluate the diagnostic performance of nCLE procedure on a larger cohort of patients.

Aims & Methods: 217 patients carrying a single large (>2 cm) pancreatic cystic lesion (PCL) without evidence of communication with the main pancreatic duct and scheduled for EUS-FNA procedure were included in five centers. nCLE diagnosis was based on published criteria: "superficial vascular network" for Serous CystAdenoma (SCA), "papillae" for Intraductal Papillary Mucinous Neoplasms (IPMN), "epithelial border" for Mucinous Cystic Neoplasms (MCN), "dark spots of cell aggregates surrounded by gray areas of fibrosis and vessels" for NeuroEndocrine Neoplasms (NEN) and "field of bright gray or black particles" for PseudoCyst (PC). In case of doubt between IPMN and MCN, Undetermined Mucinous Lesion (UML) was proposed. The absence of criteria led to inconclusive nCLE diagnosis considered as false-negative. Nine patients were withdrawn for screen failure (n = 6) or procedure failure (n = 3). Among the 208 analyzable patients, final diagnosis was proven in 90 cases by cytopathological analysis of cystic fluid obtained by FNA (n = 59) or by surgical histopathology (n = 31). Statistical analysis of nCLE performance was done for cysts sufficiently represented.

Result: Among the 217 nCLE procedures, 98.6% were successfully performed. The pancreatitis rate was 2.3% and no other significant complication occurred. nCLE was inconclusive in 27 cases. The 90 proven final diagnosis were 32 SCA, 46 Mucinous Lesions (ML) (23 IPMN, 14 MCN and 9 UML), 6 NEN, 2 PC, 1 cystic solid pseudopapillary neoplasm, 1 cystic lymphoma, 1 cystic lymphangioma and 1 congenital pancreatic cyst. These last 6 cysts were underrepresented and therefore withdrawn from statistical analysis. In the remaining 84 patients, nCLE was inconclusive in 5 cases. The performances of nCLE were as follows:

	SCA	ML	IPMN	MCN	NEN
n	32	46	23	14	6
Se (%)	88	87	87	57	100
Sp (%)	98	97	96	97	100

Conclusion: This large prospective study validates the very high sensitivity and specificity of nCLE for the diagnosis of solitary non communicating PCL which represents the main diagnostic issue. Being able to precisely discriminate between benign (SCA) or premalignant lesions (ML, NEN), the nCLE procedure would significantly improves patient management by avoiding either repeated follow-up procedures or unnecessary resections due to diagnosis uncertainties. nCLE procedures should now be included in the guidelines.

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OP332 RISK OF PROGRESSION AMONG LOW RISK IPMNS IN A LARGE MULTICENTER SURVEILLANCE COHORT STUDY

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Introduction: Intraductal papillary mucinous neoplasms (IPMNs) are pancreatic cysts that carry a risk of malignant transformation to pancreatic ductal adenocarcinoma (PDAC). Guidelines have been evolving to best identify which criteria should qualify a patient for resection and which cysts can safely remain under

surveillance. Our aim was to understand which baseline cyst and patient features predict disease progression and malignant transformation.
Aims & Methods: Patients with clinically suspected IPMN who did not meet consensus criteria for resection at diagnosis and were surveyed for at least 12 months or underwent surgery after a minimum surveillance of 3 months were included. All patients evaluated by radiologic studies or endoscopic ultrasound between 1998 and 2015 were included. We defined progression as either an increase in size of the dominant cyst ≥20% or ≥2 mm or the development of worrisome features (mural nodule or mass, thick septations, main duct involvement or high grade dysplasia or cancer on cytology or surgical pathology). Statistical analysis was performed with the Chi square and Fisher exact tests for categorical variables and Mann-Whitney U test for continuous variables. All covariates of interest with $p < 0.05$ in the univariate analysis were included in the logistic regression model.
Result:

	Non-progressors (n = 248)	Progression by cyst size increase (n = 205)	Progression by development of worrisome features (n = 46)
Age at 1st study, mean (SD)	65.3 (11.3)	66.6 (10.7)	68.5 (10.6)
Male gender, n (%)	95 (38.3%)	80 (39%)	24 (52.2%)
Race			
White, n (%)	174 (86.6%)	152 (85.4%)	33 (82.5%)
Black, n (%)	11 (5.5%)	11 (6.2%)	5 (12.5%)
Asian, n (%)	9 (4.5%)	8 (4.5%)	0
Smoker ever, n (%)	100 (43.1%)	86 (44.1%)	22 (51.2%)
EtOH use ever, n (%)	108 (47%)	85 (44.7%)	22 (50%)
CP, n (%)	9 (3.7%)	5 (2.5%)	3 (6.8%)
AP, n (%)	18 (7.5%)	10 (5.1%)	2 (4.5%)
Cancer, n (%)	75 (30.5%)	78 (38.4%)	21 (46.7%) *
Colon, n (%)	3 (1.2%)	4 (2%)	3 (6.7%) *
Breast, n (%)	7 (2.8%)	12 (5.9%)	0
Prostate, n (%)	6 (2.4%)	12 (5.9%)	8 (17.8%) *
Diabetes, n (%)	56 (23%)	45 (22.4%)	20 (44.4%) *
Family hx of PDAC, n (%)	22 (9.5%)	21 (11%)	2 (4.8%)
Baseline symptoms, n (%)	71 (28.6%)	60 (29.3%)	14 (30.4%)
Abd pain, n (%)	65 (26.2%)	49 (23.9%)	11 (23.9%)
Weight loss, n (%)	11 (4.4%)	18 (8.8%)	6 (13%) *
Jaundice, n (%)	1 (0.4%)	1 (0.5%)	0
Serum CEA, median (IQR)	1.6 (1, 3)	1.6 (1, 2.2)	1.1 (.8, 2.3)
Serum CA 19–9, median (IQR)	13.5 (4.8, 37.3)	17 (8, 46)	14 (10.3, 27.5)
Cyst size, mean (SD), mm	11.8 (6.0)	11.1 (6.4)	16.9 (6.7) *
Cyst size 0–1 cm, n (%)	100 (40.3%)	94 (45.9%)	7 (15.2%) *
Cyst size 1–2 cm, n (%)	120 (48.4%)	87 (42.4%)	22 (47.8%)
Cyst size 2–3 cm, n (%)	28 (11.3%)	24 (11.7%)	17 (37%) *
Multifocality, n (%)	95 (38.3%)	72 (35.1%)	24 (52.2%)
Location			
Head, Uncinate, Neck, n (%)	93 (37.7%)	79 (38.7%)	17 (37%)
Body, n (%)	93 (37.7%)	72 (35.3%)	15 (32.6%)
Tail, n (%)	61 (24.7%)	53 (26%)	14 (30.4%)
Cytopathology			
Benign, n (%)	35 (52.2%)	27 45%)	4 (26.7%)
Non-malignant n (%)	3 (4.5%)	5 (8.3%)	1 (6.7%)
Atypical, n (%)	3 (4.5%)	4 (6.7%)	3 (20%)
Nondiagnostic, n (%)	26 (38.8%)	24 (40%)	7 (46.7%)
Cyst CEA, median (IQR)	24 (4.1, 104.5)	101 (14, 333)	2555 (13, 5775) *
Cyst CEA ≧192 ng/mL, n(%)	8 (19.5%)	13 (37.1%)	11 (68.8%) *
Cyst amylase, median (IQR)	2749 (261, 124527)	8660 (634, 32905)	1028 (40.5, 4684)

*Statistically significant difference as compared to non-progressors. We identified 499 patients who met inclusion criteria. Average surveillance time was 47 (+/− 28.7) months. 251 (50%) patients showed progression: 205 (41%) progressed by size alone and 46 (9.2%) developed worrisome features. 55 (11%) met resection criteria and 21 of these went on to surgery; pathology demonstrated 4 invasive carcinoma, 5 IPMN with high-grade dysplasia, 8 IPMN with low-grade dysplasia, 2 mucinous cystadenoma, 1 serous cystadenoma and 1 neuroendocrine tumor. We then compared predictors of progression. In a univariate analysis, progression to cancer or high-grade dysplasia was associated with male gender, a history of prostate cancer and diabetes, weight loss and initial cyst size >2 cm. A history of prostate cancer, diabetes, weight loss, elevated cyst fluid CEA and cyst size >2 cm were associated with development of worrisome features. In logistic regression analysis, a history of prostate cancer (OR 2.9; 95% CI 1.7–7.7) and weight loss (OR 2.47; 95% CI 1.18–6.1) were associated with development of worrisome features ($p < 0.05$). There were no baseline predictors of cyst size increase alone. Baseline characteristics such as race, smoking or alcohol use, a strong family history of PDAC, multifocality and location of cysts were not associated with increased disease progression.
Conclusion: In the largest multicenter surveillance study of low risk IPMNs to date, we showed that 41% of suspected IPMNs increased in size only, 9% developed worrisome features and 2% developed high-grade dysplasia or cancer. Among baseline characteristics, none were predictive of size increase. A personal history of prostate cancer and weight loss were the strongest predictors of the development of worrisome features.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP333 MULTIMODALITY TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER, INCLUDING FOLFIRINOX CHEMOTHERAPY, SURGICAL EXPLORATION AND IRREVERSIBLE ELECTROPORATION: PROSPECTIVE SERIES OF 132 CONSECUTIVE PATIENTS

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Introduction: Novel treatment options in locally advanced pancreatic cancer (LAPC), including FOLFIRINOX and irreversible electroporation (IRE) have shown promising survival-rates. However, outcomes are heavily influenced by selection bias as most studies were retrospective and excluded patients who did not receive FOLFIRIONX or had progressive disease.
Aims & Methods: We aimed to describe outcomes of multimodality treatment with chemotherapy, surgical exploration and IRE in a prospective consecutive LAPC-cohort. Patients with histologically proven LAPC (Dutch guideline: >90° arterial and/or >270° venous involvement) were prospectively registered (September 2013–March 2015). After 3 months of chemotherapy (FOLFIRINOX for WHO physical status 0–1 patients, otherwise gemcitabine), restaging was performed by assessing RECIST 1.1-response, resectability, and IRE-eligibility (tumor ≤5 cm, sufficient vascular patency). All patients with non-progressive disease, eligible for IRE proceeded to laparotomy, regardless of resectability. The study was registered with the Dutch trial registry NTR4230.
Result: Of 132 consecutive LAPC-patients, 93 (70%) received chemotherapy (59 (45%) FOLFIRINOX). After 3 months, 59 (45%) had non-progressive disease and 36 (27%) were IRE-eligible and underwent laparotomy, resulting in 14 (11%) pancreatic resections and 15 (11%) IREs. In 36 patients who underwent laparotomy, 14 (39%) suffered from Clavien-Dindo grade ≥3 complications (6/14 resection, 7/15 IRE, 1/7 palliative exploration). Four patients (11%) died within 90 days (1/14 resection, 2/15 IRE, 1/7 palliative exploration). Median overall survival after resection, IRE, in non-progressive disease without resection/IRE and in all 132 patients was 34, 19, 17 and 11 months respectively.
Conclusion: This is the first prospective study on multimodality treatment, including FOLFIRINOX and IRE, in a consecutive LAPC-cohort. An 11% resection-rate with a median overall survival of 34 months seems highly promising where no clear survival benefit was seen after IRE. This study highlights the importance of reporting on unselected LAPC-cohorts.
Disclosure of Interest: R.C. Martin: Prof. Dr. Marin is a paid consultant for AngioDynamics
K.P. van Lienden: Dr. Krijn van Lienden is a paid consultant for AngioDynamics
All other authors have declared no conflicts of interest.

OP334 NATIONWIDE MULTIDISCIPLINARY ONLINE EXPERTPANEL FOR PANCREATIC CANCER: INITIAL RESULTS

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Introduction: Due to the centralization of pancreatic cancer treatment, both post-operative mortality and overall survival are improving. However, a downside of centralization is the decreasing knowledge on new treatment strategies and clinical trials in non-pancreatic centers.
Aims & Methods: The Dutch Pancreatic Cancer Group (DPCG) aimed to develop an online expertpanel to facilitate and tailor rapid expert advice for patients with (locally advanced) pancreatic cancer. In collaboration with Aexist (The Hague, the Netherlands) we developed the ImageHub® system which allows for secure, online review of CT scans. Next, a nationwide multidisciplinary expertpanel for pancreatic cancer consisting of surgeons, (interventional) radiologists and medical oncologists was installed. This study prospectively analyses the first patients who were referred to the online expertpanel between June 2015 and February 2016.
Result: A total of 59 patients from 7 centers were referred to the expertpanel. All had locally advanced pancreatic cancer and in 46% (27/59) of the patients this led to an additional treatment or a change in treatment strategy. A resection with curative intention was performed in 5 patients (8%) and 21 patients (42%) were included in a clinical trial, investigating local ablative therapies. In all cases the expertpanel advice was provided within one week.
Conclusion: The results show that an online expertpanel is feasible and changed the treatment strategy in almost half of the patients with locally advanced pancreatic cancer. Future studies have to determine the impact of an online expertpanel on the accessibility of new treatment strategies, survival and quality of life.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 08:30–10:00

CONSTIPATION AND FECAL INCONTINENCE: FROM BENCH TO BEDSIDE – ROOM N2

OP335 ORAL ADMINISTRATION OF THE GUT-RESTRICTED GUANYLATE CYCLASE-C AGONIST, LINACLOTIDE, REDUCES ENDOMETRIOSIS-INDUCED VAGINAL HYPERALGESIA

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Introduction: Linaclotide, a locally acting GC-C agonist, is an FDA-approved guanylate cyclase-C (GC-C) agonist, for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) and Chronic Idiopathic Constipation (CIC). Linaclotide reverses colonic mechanical hypersensitivity in chronic colonic hypersensitive mice, and reduces noxious signaling in vivo to the spinal cord. Painful Bladder Syndrome/Interstitial Cystitis and Overactive Bladder are common comorbidities of IBS-C. Chronic oral administration of linaclotide in a mouse model of bladder overactivity reverses colitis-induced changes in bladder function and sensitivity via a proposed mechanism involving viscero-visceral organ cross-talk. We hypothesized that linaclotide may be able to similarly reduce visceral pain in other chronic pelvic pain conditions, and tested this hypothesis in a rat model of endometriosis-induced vaginal hyperalgesia.
Aims & Methods: One centimeter segments of the uterine horns of female Sprague-Dawley rats were surgically removed and 4 pieces of uterine horn tissue/rat were implanted around the mesenteric arteries adjacent to the cecum (endometrium side down). Pelvic organ/tissue permeability was measured by Evans Blue dye plasma extravasation (vascular permeability). The severity of vaginal hyperalgesia was accessed by viscero-motor responses (VMR) to vaginal balloon distension. VMR was recorded by electromyography (EMG) using a wireless telemetry system (telemetric probe was surgically implanted 6 weeks past the uterine horn tissue implantation). Linaclotide (3 ug/kg/day) was dosed chronically for 14 days to measure its effects on plasma extravasation, and the effects of linaclotide (3 ug/kg/day) on vaginal hyperalgesia were measured after acute (day 1, 2 hours after dosing) and chronic (day 5) dosing, compared to vehicle. Plasma extravasation and EMG measurements were done 10 weeks after the first surgical procedure, when rats were in the proestrus stage of their reproductive cycle. GC-C mRNA expression was determined by qRT-PCR.
Result: Chronic oral dosing of linaclotide ($n = 12$) significantly ($P < 0.01$) reduced Evans Blue plasma extravasation in the small intestine compared to vehicle ($n = 12$). In contrast, linaclotide did not have an effect on plasma extravasation of endometrial cysts and other pelvic organs. Consistent with these findings, expression of GC-C was restricted to the small intestine, and not detected in endometrial cysts and other pelvic organs. Both, acute and chronic oral administration of linaclotide significantly ($P < 0.05$ ($n = 14$) and $P < 0.01$ ($n = 14$), respectively) reduced endometriosis-induced vaginal hyperalgesia, compared to vehicle treated animals ($n = 9$).
Conclusion: Oral administration of linaclotide significantly reduced visceral pain in a rat model of endometriosis-induced vaginal hyperalgesia. These data suggest that GC-C agonism, beyond its established effect of improving abdominal pain in IBS-C patients may also be able to alleviate pain in a spectrum of chronic pelvic pain conditions possibly through common sensory peripheral and central innervation pathways.
Disclosure of Interest: P. Ge: Employee, stock holder and stock options from Ironwood pharmaceuticals Inc.
J. Ren: Contractor at Ironwood Pharmaceuticals, Inc
N. Dmitrieva: Contractor at Ironwood Pharmaceuticals, Inc
A. Silos-Santiago: Employee, stock holder and stock options from Ironwood pharmaceuticals Inc and Decibel Therapeutics.
C.B. Kurtz: Employee, stock holder and stock options from Ironwood pharmaceuticals Inc.
G. Hannig: Employee, stock holder and stock options from Ironwood pharmaceuticals Inc

OP336 GUANYLATE CYCLASE-C EXPRESSION IS DOWN-REGULATED IN COLONIC BIOPSIES FROM FEMALE IRRITABLE BOWEL SYNDROME PATIENTS WITH CONSTIPATION

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Introduction: Linaclotide, a guanylate cyclase-C (GC-C) agonist, reduces abdominal pain and improves constipation in patients with Irritable Bowel Syndrome with Constipation (IBS-C). We have shown that linaclotide activates GC-C expressed on intestinal epithelial cells, resulting in the production and release of cyclic GMP (cGMP), which accelerates gastrointestinal transit and inhibits colonic nociceptors. Furthermore distinct alterations in key components of the GC-C/cGMP signalling pathway across different subtypes of IBS patients from the Australian population, have been shown. However, it remains to be determined if these changes extend to 1) other components of this pathway, 2) a separate U.S. cohort of IBS patients, and 3) patients with chronic idiopathic constipation (CIC).
Aims & Methods: Female Rome III IBS and CIC patients and healthy controls ages 18–55 yrs were recruited mainly by community advertisement in the U.S. Recto-sigmoid mucosal biopsies were taken at 30 cm from the anal verge during sigmoidoscopy. RNA was extracted from all biopsies and Taqman qRT-PCR used to assess mRNA expression of 18 different known components of the GC-C/cGMP signalling pathway. These targets included GC-C (GUCY2C), its endogenous ligands (GUCA2A, GUCA2B), PDZ proteins regulating GC-C activity (PDZD3), cGMP-dependent protein kinases (PRKG2), phosphodiesterases (PDE3A, PDE3B), components involved in ionic secretion (PDZK1, SLC9A2, SLC9A3, SLC26A3, CFTR) and transporters of cGMP (ABCC4, ABCC5).
Result: We compared female healthy controls ($N = 12$, mean age 36.4 yrs) with IBS patients with constipation ($N = 12$, mean age 32.8 yrs), diarrhea (IBS-D; $N = 11$, mean age 30.2 yrs), mixed bowel habits (IBS-M; $N = 10$, mean age 40.8 yrs), and patients with CIC ($N = 12$, mean age 30.7 yrs). In IBS-C biopsies, GC-C expression was significantly reduced (2-fold reduction) compared with biopsies from healthy controls ($P < 0.05$). However, in these IBS-C biopsies none of the other GC-C/cGMP pathway components were significantly altered compared with healthy controls ($P > 0.05$). In contrast, biopsies from CIC patients did not display significant alterations in GC-C or the other GC-C/cGMP pathway components compared with healthy controls ($P > 0.05$). Similarly, biopsies from IBS-D and IBS-M patients did not display any significant alterations in the GC-C/cGMP pathway components tested ($P > 0.05$).
Conclusion: In this cohort of female IBS-C patients, GC-C, but not other evaluated components of the GC-C cGMP pathway, was significantly reduced. A lack of GC-C expression in these patients may result in a lack of cGMP production, which may reduce intestinal secretion and the anti-nociceptive actions of cGMP compared with healthy controls. Given these changes were apparent in IBS-C but not in CIC, IBS-D or IBS-M patients, these changes may help to explain some aspects of the pathophysiology associated with IBS-C.
Disclosure of Interest: G. Hannig: Employee, stock holder, and stock options from Ironwood pharmaceuticals Inc.
C.B. Kurtz: Employee, stock holder and stock options from Ironwood pharmaceuticals Inc.

A. Silos-Santiago: Employee, stock holder, and stock options from Ironwood pharmaceuticals Inc and Decibel Therapeutics.
L. Chang: Scientific advisory boards or consultation for AstraZeneca, Synergy, Ardelyx, Irownwood, Bioamerica, Takeda, Allergan, Commonwealth Labs, QOL Medical, Salix, and Drais.
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All other authors have declared no conflicts of interest.

OP337 PATIENTS' PERCEPTIONS OF CONSTIPATION DIFFER STRIKINGLY FROM THOSE OF GASTROENTEROLOGY SPECIALISTS AND GENERAL PRACTITIONERS, AND THERE IS NO CONSISTENT AGREEMENT WITH THE ROME III CRITERIA

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Introduction: Constipation is a prevalent condition with a huge socioeconomic burden. It is unclear whether patients' and doctors' perceptions of the definition of constipation agree with each other or with formal diagnostic criteria proposed by expert committees (e.g. Rome III).
Aims & Methods: A cross-sectional survey was undertaken to compare the symptoms perceived to be important for the diagnosis of constipation within the adult general population (with and without constipation), gastrointestinal (GI) specialists (gastroenterologists, colorectal surgeons) and general practitioners (GPs) in the UK. Symptoms considered important in diagnosing constipation and their perceived burden, together with 10 case studies based on the Rome III criteria were investigated. Responses were compared between groups using chi squared tests.
Result: 2,257 members of the general population (1,623 self-reported constipation, 934 without), 365 GI specialists and 411 GPs completed the survey. Only a minority of the general population considered the Rome III symptoms important for diagnosing constipation (Table 1). Infrequent bowel movements were most frequently reported as important by GI specialists (65%), compared with less than half of GPs (41%) and less than a third of the constipated (26%) and non-constipated (28%) general population ($P < 0.001$). The symptom most frequently reported as important for diagnosing constipation by the general population was straining (40–43%), whereas for GPs it was hard stools (66%).

Table 1: Frequency of symptoms perceived to be important for a diagnosis of constipation

	General Population				
	Without constipation	With constipation	GI specialists	GPs	P value
Rome III symptoms					
Infrequent bowel movements	28%	26%	65%	41%	<0.001
Hard stool	26%	32%	57%	66%	<0.001
Straining	43%	40%	53%	61%	<0.001
Sense of incomplete evacuation	15%	24%	21%	13%	<0.001
Manual disimpaction	14%	15%	32%	34%	<0.001
Non-Rome III symptoms					
Long time on toilet without stool	42%	29%	33%	23%	<0.001
Laxative use	37%	33%	56%	40%	<0.001

The symptoms most frequently considered to be bothersome were different for each of the groups: manual disimpaction for the constipated general population, bloating for GI specialists and straining for GPs. In the 10 case studies, correct diagnoses were made by doctors (GPs and GI specialists) on 79–80% of occasions. However, on average, the absence of constipation was correctly identified by doctors in 85–92% of the six cases without constipation, whereas the presence of constipation was correctly identified in only 60–70% of the four cases with constipation.
Conclusion: There are striking differences in the perceived definition and burden of symptoms of constipation between the general population, GI specialists and GPs, and variable agreement with the Rome III criteria. These differences have major implications for patient care, management and satisfaction with treatment. The findings reinforce the need to re-evaluate current diagnostic criteria for constipation in clinical practice and to ensure these are communicated widely.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP338 EFFICACY AND SAFETY OF NALDEMEDINE FOR THE TREATMENT OF OPIOID-INDUCED CONSTIPATION IN SUBJECTS WITH CHRONIC NON-CANCER PAIN RECEIVING OPIOID THERAPY: RESULTS FROM TWO PHASE 3 CLINICAL TRIALS

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Introduction: Opioids effectively treat pain but their use is limited by side effects including opioid-induced constipation (OIC). Naldemedine is an oral, peripherally-acting μ-opioid receptor antagonist that is being evaluated for the treatment of OIC.
Aims & Methods: Two identical Phase-3, double-blind, randomized, placebo-controlled 12-week studies were conducted. In both studies, subjects 18 to 80 years old, with chronic non-cancer pain and OIC, taking opioids for ≥3 months and on a stable regimen for ≥1 month, not on laxatives, and meeting all other eligibility criteria were randomized (1:1) to naldemedine 0.2 mg taken orally QD or placebo. The primary objective was to evaluate the efficacy of naldemedine vs. placebo as assessed by the proportion of responders. A responder was defined as someone who had ≥9 positive- response weeks (PRW) out of 12 weeks and 3 PRW out of the last 4 weeks. A PRW was defined as ≥3 spontaneous bowel movements (SBMs)/week and ≥1 SBM/week increase from baseline. The safety and tolerability of naldemedine was also assessed. Studies were approved by an IRB prior to randomization of subjects and conducted in accordance with GCP Guideline (ClinicalTrials.gov identifier NCT01965158 and NCT01993940).
Result: In study 1, 547 subjects were randomized (naldemedine 274; placebo 273) and in Study 2, 553 subjects were randomized (naldemedine 277; placebo 276). In both studies, there were a significantly greater proportion of responders with naldemedine relative to placebo (Study 1: naldemedine 47.6%; placebo 34.6%, $P = 0.0020$, Study 2: naldemedine 52.5%; placebo 33.6%, $P < 0.0001$). A significantly greater increase in the frequency of SBMs per week from baseline to Week 1 was observed with naldemedine relative to placebo and this difference remained generally stable between the two groups throughout the 12-week study period. The naldemedine group also showed a greater increase, relative to the placebo group, from baseline to the last 2 weeks of the study period in the frequency of complete SBMs and the frequency of SBMs without straining. Summary measures of treatment-emergent adverse events (TEAEs) were generally similar between naldemedine and placebo groups in both studies. The TEAEs reported for >5% of subjects and at a higher frequency in naldemedine relative to placebo were abdominal pain and diarrhea. In both studies, treatment with naldemedine was not associated with signs or symptoms of opioid withdrawal, and the analgesic effect of opioids was not affected.
Conclusion: Results from two identically designed Phase 3 studies demonstrated a consistent efficacy and safety profile of naldemedine as a treatment for OIC in subjects with chronic non-cancer pain. Naldemedine treatment resulted in a significantly greater proportion of responders than placebo, with improvement early on and throughout the 12-week study period. Naldemedine was generally well tolerated in these two studies.
Disclosure of Interest: M.E. Hale: I was a Principle Investigator for the Clinical Trials, and a consultant for Shionogi
J. Wild: 1) I was a Principal Investigator on Compose1 trial and 2) I did receive a stipend from Shionogi for clinical study review. Otherwise I have no relationship with the company.
J. Reddy: Employee of Shionogi
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OP339 PILOT STUDY COMPARING THREE METHODS OF SCREENING FOR FECAL INCONTINENCE

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Introduction: Fecal incontinence (FI) affects 8% of US adults overall including 15% over age 70. However, less than 1/3 of people with FI have discussed this problem with their physicians, and most of these report that they were not screened but volunteered this symptom. This suggests many physicians are not screening for FI.
Aims & Methods: The goal of this study was to provide preliminary information on the effectiveness of 3 simple screening interventions for increasing screening rates in a Geriatric Medicine Clinic (GMC) at the University of North Carolina: a gastrointestinal (GI) symptom checklist distributed in the clinic waiting room, screening by the clinic nurse, and screening by the medical provider. The GI symptom checklist included fecal incontinence [accidental bowel leakage] and 7 other common GI symptoms. Patients checked all they had experienced in the last month, and gave the checklist to the clinic nurse. To facilitate screening by nurses and providers, we suggested three screening questions. We also gave

providers and nurses a modified Fecal Incontinence Severity Inventory (FISI) to help them decide whether FI was severe enough to warrant referral to a specialist, and instructions on how to refer to the GI Medicine Clinic.
All patients attending the GMC during 4 two-week periods were considered subjects. After an initial two-week baseline, all patients were exposed to the screening methods in the same sequence for two weeks each: GI symptom checklist, provider screening, and nurse screening. Three types of outcome data were collected: (1) A limited review of electronic medical records of all patients seen during these 4 two-week periods was used to identify the number of new FI diagnoses during these 4 periods. (2) Following the last screening intervention, all 11 clinic providers rated the effort required by each intervention and indicated whether they believed the benefit outweighed the burden. (3) Telephone interviews were conducted 2–4 weeks after the index clinic visit to determine what proportion of patients had been screened during their clinic visit. A p-value of $<.10$ accepted as significant in this small pilot study.
Result: 1034 unique patients were seen during the 4 two-week periods: 60 had a diagnosis of FI somewhere in their medical record, and 24 had a diagnosis of FI at their index visit for this study, including 6 new FI diagnoses. Three of the 6 new diagnoses occurred during the GI checklist intervention and 3 during provider screening ($p < .10$). None occurred during nurse screening. The GI symptom checklist was rated the least burdensome by the 11 providers ($p = .09$). Five of 11 providers said the benefits of screening outweighed the burden, 4 were undecided, and 2 rated screening as too burdensome ($p = .001$). Phone interviews were completed by 88 patients: 33/88 (37.5%) confirmed they were screened by their doctor or nurse, 55.7% said no, and 6.8% said they did not know or declined to answer.
Conclusion: Systematically encouraging geriatric medicine providers to screen for FI significantly increased the number of patients receiving a new diagnosis of FI compared to baseline, and most geriatricians thought the benefits outweighed the burden. Distributing a GI symptom checklist in the clinic was rated least burdensome and was as effective as direct screening by the geriatrician. However, these interventions to improve screening were only partially effective: 37.5% of patients remembered being asked about FI at their clinic visit.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP340 COPING WITH FAECAL INCONTINENCE: A POPULATION STUDY

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Introduction: Faecal incontinence (FI) is a common and devastating condition that significantly impacts quality of life. Many individuals suffer in silence and population surveys report that fewer than 30% of those affected consult a physician. Little is known about how people prevent or cope with symptoms in the community.
Aims & Methods: This study aimed to describe the most common coping strategies, the impact of FI severity on ways of coping, whether those under a physician's care cope differently and the perceived overall effectiveness of individuals' coping efforts. A 54-question survey was designed and distributed online (Qualtrics, UT, USA) to individuals in the US general population in March 2016 who reported symptoms of FI occurring at least twice per month. Respondents were asked to report coping behaviors using both a pre-defined list of 15 coping strategies and free-text fields. Symptom severity was defined by the Fecal Incontinence and Constipation Assessment (FICA) scale as mild if ≤ 6, moderate if 7–10 or severe if ≥ 11.
Result: A total of 254 complete datasets were received, of which 182 (122 F, median age 41, range 18–86) were retained for analysis after eliminating inconsistent responders. The median FICA score was 9 (4–13) with 149 (82%) respondents reporting either moderate or severe symptoms. 103 (57%) had consulted a physician for FI. The median number of coping strategies used was 3 (range: 1–13). The most commonly reported strategies were the use of pads (111/182, 61%), scheduling of bowel movements (88/182, 49%), the use of anti-diarrheal medication (86/182, 43%) and food avoidance (77/182, 42%). The number of strategies used was significantly related to FI symptom severity (2.69 for those with mild, 4.17 moderate, and 4.89 severe symptom categories, $p < .001$), and consulting status (3.32 for non-consulters vs. 4.28 for consulters, $p = .013$). Number of coping strategies was unrelated to sex, age, race/ethnicity, or education. The coping strategies reported to be most effective were antidiarrheal medications (48/182, 26% of sample), food avoidance / dietary manipulation (27/182, 14%) and incontinence pads (21/182, 13%). Individuals who had consulted a physician, compared to those who had not consulted, were more likely to use antidiarrheal medication (55% vs. 37%; $\chi^2 = 6.23$, $p = 0.016$) and schedule bowel movements (56% vs. 38%; $\chi^2 = 6.02$, $p = .017$). Only 43/182 (24%) reported that their coping strategies were "very" or "completely effective" at reducing the impact of symptoms.
Conclusion: Individuals in the community employ multiple coping strategies to reduce the impact of FI, but most report poor satisfaction with their effectiveness. The most commonly used strategy is wearing pads, but the strategy reported to be the most effective by the largest proportion of subject is taking anti-diarrheal medication. Consultation with a physician may reinforce the use of more positive preventative strategies such as the use of medication and scheduling bowel movements.

Table 1: Prevalence of Coping Strategies and Impact of Faecal Incontinence Severity on Coping

Coping Strategy	% who use	Effect of FI Severity
Wear pads	61	
Schedule BM	49	
Antidiarrheal drug	43	.029
Avoid food that cause diarrhea	47	
Locate all toilets in area	31	
Fiber or drugs for constipation	30	
Take spare clothes when going out	24	
Avoid leaving home if possible	19	.018
Avoid physical activity	19	
Avoid eating in restaurants	19	.002
Avoid sex	14	.026
Restrict eating before going out	12	.047
Enema before going out	10	
Shop online or have food delivered	06	
Discourage visits from friends	04	
Average number of coping strategies	3.86 (2.61)	<.001

Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 08:30–10:00
NEW INSIGHTS IN UPPER GI ENDOSCOPY TECHNIQUES – ROOM L7

OP341 NOVEL ENDOLOOP VS. OVER-THE-SCOPE-CLIP (OTSC) IN ENDOSCOPIC CLOSURE OF GASTRIC FULL-THICKNESS DEFECT: A MULTI-CENTER STUDY

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Introduction: Endoscopic full-thickness resection (EFTR) of the gastric lesion using a snaring technique has been applied for gastric subepithelial tumors. We identified criteria for the use of a novel type of nylon loop device vs. traditional 'Over the scope'-clip (OTSC) for containing artificial submucosal lesions.
Aims & Methods: One hundred and twenty- eight patients with submucosal tumors in gastric fundus were randomly divided into two groups, study group with 56 patients and control group with 72 patients, all patients were treated with endoscopic full-thickness resection. After the resection, novel LeCampTM endoloop device and OTSC were used respectively to close the gastric defects in the study group and control group. The closure success rate, closure time, complications and the wound-healing rate were compared.
Result: All lesions were removed by using EFTR technique. The closure success rates of the two groups were both 100%. Of the total of 128 patients, a comparison between the novel endoloop ($n = 56$) and OTSC ($n = 72$) groups demonstrated no differences in closure time(14.86 ± 4.93 min vs. 8.04 ± 5.63 min, $p > 0.05$) and readmission rate (17.03% vs. 18.2%, $p > 0.05$). The average time of removing the stomach tube in the study group was slightly longer (4. vs. 1 day, $p < 0.05$), and there was a significant differences in the length of hospital stay for the study group (4.32 ± 2.45 days vs. 2.1 ± 0.63 days). 24 hours after the operation, X-ray examination showed minor subdiaphragmatic free air. Due to its low quantities and lack of symptoms, abdominal puncture was deemed unnecessary. No subcutaneous emphysema, pneumothorax, pneumomediastinum were found in 24 hours after the operations. There were no significant differences in the incidence and severity of complications rate, even though all patients experienced no postoperative complications such as bleeding, perforation and abdominal infection in control group. However one case receiving treatment of endoloop that induced localized peritonitis resulted in serosal inflammation. The patient was managed conservatively with medical therapy, such as the administration of intravenous fluids and broad-spectrum parenteral antibiotics to cover the colonic bacterial flora until the symptoms subsided. All wounds healed in two month after the operations.
Conclusion: Closure of gastric full-thickness defects with the novel type of endoloop device is technically feasible and effective. Both techniques should be regarded as equally acceptable reconstructive options following endoscopic full-thickness resection for gastric lesion.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP342 ENDOSCOPIC SUBMUCOSAL DISSECTION FOR DUODENAL ADENOMA: COMPLICATION RATE AND FOLLOW UP OF 38 CASES

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Introduction: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are used for endoscopic treatment of superficial duodenal adenoma. They can be combine for the resection of a same lesion (Hybrid Endoscopic Resection, HER). ESD has higher rates of complications than EMR, and is technically challenging. We present results on the adverse events and clinical outcome of ESD/HER compared to EMR in our cohort of patients.
Aims & Methods: In a single tertiary center, we cross-examined our database of endoscopic procedures to identify patients with duodenal adenoma treated by ESD, HER and EMR between 2006 and 2016. We included patients with non-ampullary lesions and familial adenomatous polyposis. Procedure was qualified as ESD when an endoscopic knife was used. When resection was achieved with endoscopic knife and resection loop, the procedure was considered as HER. We divided complications in 3 groups (ASGE and ESGE recommendations): intra-procedural, early complications (occurring within 15 days) and late complications (occurring after 15 days). Results were expressed as medians, and compared with Student's t-test, Pearson's chi-squared test.
Results: Thirty-eight patients underwent ESD/HER procedure out of a total of 111 patients. The resection was complete in 38/39 lesions in ESD/HER group, and 141/149 lesions in EMR group ($p = 0.182$). Histological finding showed 4% adenocarcinomas, 34% HGD, and 60% LGD. No significant differences were observed in terms of age, sex, location of lesions or length of hospitalization. There were significant differences in the procedure time (108 min ESD/HER, 79 min EMR), intraprocedural complications (46% ESD/HER, 23% EMR) and early complications (23% ESD/HER, 9% EMR). Intra-procedural complications occurred in 46% of ESD/HER vs 23% in EMR ($p = 0.015$), including haemorrhage (ESD/HER 25.6%, EMR 20.1%) and perforation (ESD/HER 20.5%, EMR 3.4%, $p = 0.07$). In ESD/HER, perforations occurred between 2006 and 2010. Early complications (Haemorrhage, perforation, pancreatitis) occurred in 23% ESD/HER vs 9% in EMR ($p = 0.001$), managed either by medical or endoscopic treatment. Five cases of perforation occured (4 ESD/HER, $p = 0.001$) and 2 cases needed surgery. Three cases of late complications (stenosis) occured in the EMR group. No mortality reported during the study.
Conclusion: There is a higher rate of intraprocedural and early complications in the ESD/HER group, especially in case of perforation. Those events can be well managed in a tertiary center, experienced in ESD and HER. Perforation rate tends to decrease over time, reflecting the experience acquired in our team. This highlight the importance of a learning process in ESD/HER procedure, which results in better management of intraprocedural and early complications.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP343 ENDOSCOPIC TREATMENT OF GASTRIC ANTRAL VASCULAR ECTASIA: A RETROSPECTIVE MULTICENTRE CLINICAL STUDY

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Introduction: Gastric antral vascular ectasia (GAVE) represents a burden both to the healthcare system and the patients' quality of life as the rate of transfusion dependence due to occult bleeding might be up to 60–70%. Currently, argon plasma coagulation (APC) is the gold standard treatment, however its efficacy impairs on the long term. Besides, its efficiency depends on the settings, the size of the area treated, as well as the individual variations in performance. Endoscopic band ligation (EBL) has been proven to be a good and a potentially superior alternative with less variability in the treatment of mucosal and submucosal lesions. Nevertheless, there is still no consensus regarding the end-point of the treatment (cessation of the endoscopic lesions or resolution of transfusion need), the optimal treatment choice, and the preferable treatment settings.
Aims & Methods: Our retrospective multicentre study aimed to evaluate and compare the efficacy of APC and EBL in patients with GAVE both in terms of required treatment sessions and hospitalization rates, and changes in haemoglobin levels and transfusion need. Four tertiary endoscopic centres were involved. Data were collected retrospectively between January 2009 and December 2014. APC was performed with 30–70 W power and 2.4 L/min argon gas flow settings. In case of EBL, 5–6 ligation bands were applied per treatment session. The average follow-up period was 18.3 months.
Results: A total of 34 patients with GAVE were treated with either APC or EBL at one of the four centres involved throughout the study period. 26 patients presented with diffuse and 8 with linear type of GAVE. Occult gastrointestinal bleeding occurred in 25, acute bleeding in 15 patients. Both acute and occult gastrointestinal bleeding was present in 6 cases. 22 patients were treated with APC and 12 with EBL. Both treatment methods increased haemoglobin levels and decreased transfusion need significantly (3.01 g/dl and −10.41 blood units in case of APC, and 2.14 g/dl and −7.78 blood units in case of EBL). The need for blood transfusions ceased totally in 18 patients after the endoscopic resolution of the lesions. Significantly less treatment sessions were required in case of EBL compared to APC (1.50 vs. 5.23, $p = 0.011$), with a longer interval between each session (4.50 vs. 2.69 months, $p = 0.480$). On the other hand, APC resulted in a higher increase in haemoglobin levels (3.37 g/dl vs. 2.36 g/dl, $p = 0.213$) and a higher decrease in the need for blood transfusion (10.41 vs. 7.78 units, $p = 0.566$), although the differences were not significant. In case of APC, fewer treatments (4.25) and hospitalizations (2.33) were needed, and higher increase in haemoglobin level per treatment session (0.76 g/dl) could be observed with the 50 W power setting compared to the 30 W and 70 W setting (number of treatments: 12.5 and 6.13; hospitalizations: 2.5 and 4.63; and increase in haemoglobin level/treatment session: 0.38 g/dl and 0.46 g/dl), although the small case number was a severe limiting factor. Generally, more treatment sessions were required for the endoscopic resolution of GAVE lesions compared to the one needed for the cessation of the transfusion need (3.45 vs. 3; $p = 0.037$), but the difference was not significant in case of APC and EBL separately.
Conclusion: Both APC and EBL are effective in the treatment of GAVE. Although EBL may seem to be superior to APC in terms of the number of treatment sessions and hospitalizations, no significant difference was found in the extent to which the two methods influence the haemoglobin level and transfusion need. Optimizing APC setups may also improve the performance and efficacy. There is a pressing need for further prospective studies with homogenized large case number to establish recommendations about the endoscopic treatment of GAVE.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP344 WATERJET SUBMUCOSAL DISSECTION OF PORCINE ESOPHAGUS WITH THE HYBRIDKNIFE® AND ERBEJET® 2 SYSTEM

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Introduction: Esophageal endoscopic submucosal dissection (ESD) is technically difficult because of narrow working spaces and ease of perforation due to the lack of serosa. HybridKnife® is a recently developed ESD device that is combined with the high-pressure waterjet ERBEJET® 2 system to lift mucosa. We hypothesized that this waterjet could make submucosal dissection safer and studied this in porcine esophagus.

Aims & Methods: Water pressures of 30–70 bar were tested to determine the appropriate waterjet ESD with HybridKnife® (WJ-ESD) pressure in one pig. WJ-ESD safety and completion were compared with those of conventional ESD using DualKnife® (C-ESD). Each of 3 virtual esophageal lesions in 2 pigs were resected alternatively using both methods from the lower to upper esophagus. For WJ-ESD, the submucosa, except for hard fibrous tissues, was dissected using water pressure alone.

Results: Using 50 bar of water pressure resulted in the best balance between dissection speed and view-disturbing water backflow. The dissection speeds for the lower, middle, and upper esophagus were 0.2, 0.9, and 0.2 cm^2/min in 50 bar WJ-ESD and 1.1, 0.5, and 1.0 cm^2/min in C-ESD, respectively. Minor bleeding was frequent in WJ-ESD, but was easily stopped by electrocoagulation with the same needle. No perforation was observed in either group. Thermal damage of dissected tissues appeared mild, and the extent of muscle injury was smaller for WJ-ESD (4, 6, and 8%) compared with C-ESD (14, 16, and 7%).

Conclusion: WJ-ESD spent longer dissection time, but damaged less muscle layer. It can be combined with electrocautery ESD.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP345 ORAL ADMINISTRATION OF CONDITIONED MEDIUM OBTAINED FROM AMNION-DERIVED MESENCHYMAL STEM CELL CULTURE PREVENTS ESOPHAGEAL STRICTURE AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION IN PIGS

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Introduction: Endoscopic submucosal dissection (ESD) for esophageal cancer has been widely accepted in last decade; however, it often causes postoperative stricture when over three-quarters of the circumference of the esophagus is dissected, and lowers quality of life for patients. Although steroid is generally used to prevent the stricture by expecting anti-inflammatory actions, complications and side effects are of concern. Mesenchymal stem cells (MSCs) have been reported to be a valuable cell source in regenerative medicine, and large amounts of MSCs can be noninvasively isolated from human amnion, which is discarded after delivery. Moreover, conditioned medium (CM) obtained from MSCs has been reported to have anti-inflammatory and anti-fibrotic effects in several animal models. In this study, we evaluated whether CM obtained from amnion MSC culture could prevent the stricture after large esophageal ESD in pigs.

Aims & Methods: We resected semicircumference of pig's esophagus by ESD under general anesthesia. We prepared CM gel by mixing CM with carboxymethyl cellulose, and endoscopically applied 20 mL of MSC-CM gel onto the wound bed immediately after ESD, and on day 7 and on day 14 (CM weekly (CM-W) group, n = 3). Standard medium gel was used as a control group (n = 3). We also injected triamcinolone acetonide (80 mg) into the remained submucosa immediately after ESD (steroid group, n = 3). In addition, we administered 40 mL of CM gel orally from day 1 through day 4 after ESD (CM daily (CM-D) group, n = 3). Finally, we humanely euthanized the pigs on day 21 to measure the stricture rate and for histological analysis evaluating fiber thickness and muscle fiber atrophy (masson-trichrome staining), re-epithelialization (p63 and Ki-67), the number of activated myofibroblasts (a-SMA), capillary density (CD31), infiltration of macrophages (CD107a) and neutrophils (myeloperoxidase). The experimental protocol was approved by the Animal Care and Use Committees of Hokkaido University.

Results: Stricture rate in CM-W, CM-D and steroid groups was significantly lower than control group (56.3 ± 7.1%, 52.3 ± 4.7% and 49.3 ± 4.2% vs 80.0 ± 2.0%, respectively). Histological examination demonstrated that the number of activated myofibroblasts and fiber thickness were significantly suppressed in CM-W, CM-D and steroid groups as compared with control group (26.8 ± 8.6, 21.5 ± 4.9 and 20.6 ± 2.3 vs 68.3 ± 5.7 cells/HPF; 832.9 ± 26.1, 987.1 ± 145.1 and 944.3 ± 250.8 vs 1,609 ± 418.2 μm, respectively). There were no differences in re-epithelialization, capillary density, infiltration of macrophages and neutrophils among four groups; however, muscle fiber atrophy was significantly suppressed in CM-W group compared with the control group.

Conclusion: Myofibroblast activation causes fibrosis and contributes to the stricture after ESD, and CM gel prevented the esophageal stricture by suppressing the myofibroblast activation and fibrosis. Oral administration of CM would be a promising treatment to prevent post-ESD esophageal stricture, and it is as effective as steroid treatment.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP346 ENDOSCOPIC ULTRASOUND VS PET-CT IN GASTRIC CANCER STAGING BEFORE AND AFTER NEOADJUVANT CHEMOTHERAPY

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Introduction: Gastric cancer is one of the most common malignant tumors in the gastrointestinal tract. Treatment is based in an accurate staging. Emerging methods, as EUS or PET-CT, are increasingly being used for this purpose. With the increasing evolution of those techniques and the expanded clinical experience, studies comparing the most accurate and efficient methods in this setting are needed.

Aims & Methods: Our aim was to analyze the results of EUS and PET-CT in stating and restaging our patients with gastric cancer, comparing both of them with the histological results. Patients with a confirmed gastric cancer were prospectively enrolled. Only patients who finally received a surgical resection were included. All patients underwent preoperative TNM staging by means of EUS and PET-CT within 21 days prior to the surgical treatment. All endoscopic ultrasounds were performed by two experienced ultrasonographers (E.R-C, J. M-C). For most of the procedures radial echoendoscope (GF-UM160; Olympus Europe) reserving curvilinear echoedoscope for FNA, in the rare cases in which we perform it (UCT-180-OL5; Olympus). Every patient received propofol sedation guided by the endoscopist and by a trained nurse. A systematic complete US evaluation was performed in each patient. Statistical analysis was carried out using the software PAWS Statistics 17.0 (SPSS Inc, Chicago, ILL). The chi-square and the Kappa tests were used to evaluate the consistency between the EUS and histopathological staging of gastric cancer. Chi-square and Fisher exact tests were used to compare EUS and PET-CT as appropriate. A p-value less than 0.05 was considered statistically significant.

Results: 256 patients (178 men; aged 67.6 ± 12.1 years) with an endoscopic and pathologic diagnosis of gastric adenocarcinoma were included between January 2011 and December 2014. The overall accuracy of T staging using EUS was 78% in our series. Regarding restaging, the overall accuracy for of T staging was 80.2%. Considering lymph node involvement, the accuracy of EUS was 76.2%, very similar to what it was observed for PET-CT (72.5%), but with statistical differences (p = 0.02). The accuracy of EUS for preoperative N0, N1, N2 and N3 staging was 76.2%, 78.6%, 76.2% and 90% respectively. When studying the performance of both techniques in restaging we found that EUS had a better performance when considering the main staging differences which can change patients' management. In this regard, the accuracy in distinguishing T1-T2 tumors vs. T3-T4 tumors was 91.3%, better than in the first staging. Indeed, similar results were found in N staging with an accuracy of 88.3% for N-positive vs. N-negative distinction. By contrast, PET-CT showed an accuracy

of 69% for lymph node involvement when restaging, inferior to what was found for EUS and for the initial staging ($p < 0.0001$).

TABLE 1.: Accuracy of EUS and PET vs Histology

	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa
T1	50%	98.5%	75%	95.7%	94.5%	0.57
T2	41.7%	88.5%	41.7%	88.5%	80.8%	0.30
T3	38.5%	86.5%	50%	80%	74%	0.27
T4	77.3%	61%	61%	77.3%	68%	0.37
T4a	76.2%	65.5%	61.5%	75%	70%	0.40
T1-T2/T3-T4	87.3%	50%	84.2%	56.3%	78.1%	0.39
N0	73.9%	78.9%	81%	71.4%	76.2%	0.52
N1	50%	83.3%	33.3%	90.9%	78.6%	0.28
N2	55.6%	81.8%	45.5%	87.1%	76.2%	0.35
N3		97.4%		90.2%		
N+/N−	78.9%	73.9%	71.4%	81%	76.2%	0.52
PET N+/N−	50%	90.9%	81.8%	69%	72.5%	0.42
RESTAGING						
T1–T2/T3–T4	95%	66.7%	95%	66.7%	91.3%	0.62
T2	66.7%	95%	66.7%	95%	91.3%	0.62
T3	50%	76.9%	62.5%	66.7	65.2%	0.28
T4	70%	61.5%	58.3%	72.7%	65.2%	0.31
N0	56.3%	83.3%	82%	58.8%	67.9%	0.38
N1	75%	87%	50%	95.5%	85.7%	0.52
N2	33.3%	76%	14.3%	90.5%	71.4%	0.06
N3	20%	87%	25%	84%	75%	0.08
N+/N−	83.3%	92.9%	90.9%	86.7%	88.5%	0.77
PET N+/N−	41.7%	88.2%	71.4%	68.2%	69%	0.32

Conclusion: Our results, obtained from a real clinical practice, showed that the overall accuracies of EUS and PET-CT for preoperative N staging were 76.2% and 72.5%, with significant differences between both techniques. The overall accuracy of EUS for T staging was 78% and 80.2% for restaging. More importantly, our results show a significant advantage of EUS over PET-CT in restaging, even in our series, in which the vast majority of suspicious lymph nodes were not sampled. In conclusion, EUS performance in gastric cancer N staging and restaging is better than PET-CT. Both procedures showed suboptimal accuracies when considered alone, and more than one single staging method should be used.

Disclosure of Interest: All authors have declared no conflicts of interest.

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WEDNESDAY, OCTOBER 19, 2016 08:30–10:00

LIVER CELL BIOLOGY AND FIBROSIS – ROOM L8

OP347 CHARACTERISATION OF DIFFERENTLY ISOLATED HEPATIC PROGENITOR CELL POPULATIONS IN HUMAN ALCOHOLIC LIVER

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Introduction: Hepatic progenitor cells (HPCs) are small cells with a relative large oval nucleus and a scanty cytoplasm situated in the canals of Hering. Phenotypically, HPCs express both markers of (immature) hepatocytes (e.g. α-fetoprotein) and markers of cholangiocytes (e.g. cytokeratin K7 and K19). The mechanisms facilitating proliferation and differentiation of human HPCs are still poorly understood.

Aims & Methods: In this study, we aimed to characterize human HPCs in order to use them as a potential incessant source of cells for cellular transplantation or to control their activation and differentiation in vivo in chronic liver diseases. Therefore we isolated and compared, on both protein and RNA level, HPC-enriched cell populations from adult human liver tissue using different isolation methods: side population (SP), TROP-2 and EpCAM-based cell sorting. Fresh human liver tissue was collected from alcoholic steatohepatitis explant livers, and HPC-enriched cells were obtained via three different isolation methods. A first method is the SP which is based on the efflux capacities of the progenitor cells of the fluorescent DNA binding dye Hoechst-33342. The other methods are based on the expression of membrane markers EpCAM and TROP-2 in HPCs. Human livers were dissociated and the cell suspension was analysed and separated by FACS. The sorted cells and the whole liver extracts were evaluated on both protein level (immunohistochemical staining) and RNA level (RNA sequencing). Pathway analysis was performed using KEGG pathways, Ingenuity Pathway Analysis and Gene Set Enrichment Analysis.

Results: Immunohistochemical evaluation of the isolated fractions indicated the enrichment of HPCs in the SP, EpCAM-positive and TROP-2-positive cell fractions. Pathway analysis of the RNA sequencing data from the different isolated HPC fractions shows an enrichment and activation of known HPC pathways like Wnt/β-catenin and Notch pathways, known for their role in proliferation and differentiation of HPCs. In addition we identified several novel pathways activated in human HPC-enriched cells such as the TNF and IL17A pathways. Mutual comparison of the different isolation methods indicates some slight differences between the different HPC populations, e.g. the ErbB signalling pathway is activated in the TROP-2 positive cells while this is not the case in the EpCAM-positive or SP cell populations.

Conclusion: Our results indicate that gene signatures of human HPCs are enriched in pathways already known to be involved in HPC activation in human and in animal models, but we also identify previously unknown pathways like TNF, IL17A and ErbB signalling pathways. Comparison of the 3 isolation methods sheds light on the possible existence of different HPC populations residing in the human liver. The isolated HPC populations will be used to further characterize human HPCs and to understand the molecular mechanisms underlying their activation and differentiation, with the ultimate goal of using HPCs for the treatment of liver diseases.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP348 SORTILIN DEFICIENCY REDUCES DUCTULAR REACTION, HEPATOCYTE APOPTOSIS AND LIVER FIBROSIS IN CHOLESTATIC-INDUCED LIVER INJURY

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Introduction: Sortilin, a member of the Vps10 domain receptor family, traffics newly synthesized proteins from the trans-Golgi network to secretory pathways, endosomes or to the cell surface. Sortilin trafficked molecules, including acid sphingomyelinase (aSMase), cathepsins and IL-6, mediate activation of hepatic stellate cells (HSC), hepatocyte apoptosis, cholangiocyte proliferation and liver inflammation and fibrosis.

Aims & Methods: We investigated sortilin role in the development of biliary damage leading to hepatocellular injury and fibrosis, based on its regulation of aSMase trafficking and on its involvement in IL-6 secretion.Cholestatic injury was induced in wild type (WT) and Sortilin-/- mice by bile duct ligation (BDL). Fibrosis was induced both by BDL and by administration of CCl_4.Liver inflammation and cholangiocyte activation and proliferation were assessed by qRT-PCR for inflammatory cytokines and by immunohistochemistry with Ki67 (marker of proliferation) and with Ly6G (neutrophil marker). Liver damage and hepatocyte apoptosis were determined by serum liver enzymes and by TUNEL assay. Liver fibrosis was assessed by Sirius Red staining quantitation and by qRT-PCR for fibrotic markers. ASMase activity was inhibited in vivo by amitriptyline administration.IL-6 effect was neutralized by administration of an anti-IL-6 antibody to WT mice after BDL.

Results: Sortilin$^{-/-}$ mice displayed strongly attenuated liver fibrosis following BDL and CCl_4 treatment, accompanied by an attenuated in vitro activation phenotype of Sortilin$^{-/-}$ HSCs. Reduced Sortilin$^{-/-}$hepatic aSMase activity was in line with reduced hepatocyte apoptosis following BDL and CCl_4 injury and reduced susceptibility of hepatocytes from Sortilin$^{-/-}$mice to bile acid-induced apoptosis in vitro. The role of aSMase in hepatocyte apoptosis was further demonstrated using in vivo pharmacological inhibition of aSMase activity after BDL. Strikingly, Sortilin$^{-/-}$ mice displayed impaired inflammation and ductular reaction three days after BDL, demonstrated by reduced reactive cholangiocytes, reduced cholangiocyte proliferation and accompanied by reduced serum IL-6. Short-term treatment of bile duct-ligated WT mice with a neutralizing antibody to IL-6 attenuated hepatic inflammation and expression of reactive cholangiocyte-derived cytokines and chemokines.

Conclusion: Sortilin mediates cholestatic liver damage and fibrosis via its effects on aSMase activity and serum IL-6.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP349 ACTIVATION OF NECROPTOSIS IN HUMAN AND EXPERIMENTAL CHOLESTASIS

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Introduction: Targeting necroptosis, a programmed necrotic cell death pathway regulated by receptor-interacting protein 3 (RIP3), is being considered as a promising therapeutic approach for inflammation-driven liver diseases. Still, the role

of necroptosis in the pathogenesis of cholestatic liver injury has been poorly explored.
Aims & Methods: We aimed to evaluate the role of necroptosis in patients with primary biliary cirrhosis (PBC), a cholestatic chronic liver disease, and in mice after common bile duct ligation (BDL), a classic experimental model of acute cholestasis and secondary biliary fibrosis. Thioflavin T staining and immunohistochemistry of RIP3 and its target phosphorylated-mixed lineage kinase domain-like protein (p-MLKL) were performed in liver biopsies of patients with PBC and healthy controls. C57BL/6N wild-type (WT) or RIP3-deficient ($RIP3^{-/-}$) mice were subjected to BDL or sham surgeries for 3 and 14 days, with subsequent histological and biochemical analysis of hepatic damage. Necroptotic markers and the functional crosstalk between RIP3, antioxidant response and iron homeostasis were investigated in vivo and in vitro.
Results: In PBC patients, expression of RIP3 and p-MLKL was found increased in hepatocytes surrounded by lymphocytic infiltrates and also in cells morphologically resembling bile duct cells. Moreover, p-MLKL fluorescence co-localized in cells with increased thioflavin T staining, suggesting necrosome assembly and necroptosis activation. BDL in mice resulted in progressive bile duct hyperplasia, multifocal necrosis, fibrosis and inflammation. Concomitantly, necroptosis was activated as evidenced by increased RIP3 expression and activity and sequestration of RIP3 and MLKL in the insoluble protein fraction of the liver. Remarkably, RIP3 deficiency blocked BDL-induced necroinflammation at 3 and 14 days post-BDL. Serum hepatic enzymes, fibrogenic liver gene expression and oxidative stress decreased in $RIP3^{-/-}$ mice at 3 days after BDL. However, at 14 days, cholestasis aggravated and fibrosis was not ameliorated. RIP3 deficiency further associated with increased hepatic expression of heme oxygenease-1 (HO-1) and accumulation of iron in BDL mice. The functional link between HO-1 activity and bile acid toxicity was established in RIP3-deficient primary hepatocytes. Finally, TUNEL-positive cells and caspase-3/-7 activity increased 14 days after BDL in both WT and $RIP3^{-/-}$ mice, while remaining at basal levels at day 3, indicating that apoptosis is activated at late time-points in the BDL murine model, reflecting the peak of liver fibrosis.
Conclusion: In conclusion, necroptosis is triggered in PBC patients and mediates hepatic necroinflammation in BDL-induced cholestasis. Targeting necroptosis may provide an opportunity to develop novel therapeutic strategies to attenuate acute cholestatic liver injury. However, therapeutic strategies to inhibit RIP3-dependent signalling during chronic cholestasis should be undertaken with a complete understanding of the potential duality of this pathway. (Supported by HMSP-ICT/0018/2011, SFRH/BD/91119/2012, SFRH/BD/88212/2012 and SFRH/BD/104160/2014, FCT, Portugal).
Disclosure of Interest: All authors have declared no conflicts of interest.

OP350 HEPATOMA-INTRINSIC CCRK SIGNALING PROMOTES IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT BY REGULATING MYELOID-DERIVED SUPPRESSOR CELL ACCUMULATION

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Introduction: Myeloid-derived suppressor cells (MDSCs) comprise a heterogeneous population of immature myeloid cells that induces the exhaustion of anti-tumor immune responses. The accumulation of $CD33^{+}HLA\text{-}DR^{-}$ MDSCs correlates with tumor stage and metastatic burden in various cancers including hepatocellular carcinoma (HCC) [1]. Cancer cells can secrete a variety of cytokines and chemokines to facilitate the peripheral expansion and tumor infiltration of MDSCs to maintain tumor microenvironment. However, the cancer cell-specific signaling cascades that promote MDSC expansion and infiltration remain poorly understood. We have recently demonstrated that cell cycle-related kinase (CCRK) acts as a new oncogenic signaling hub in hepatocellular proliferation and transformation [2–4].
Aims & Methods: To investigate whether CCRK regulates tumor microenvironment in hepatocarcinogenesis, we determined the role of CCRK signaling in the crosstalk between HCC cells and MDSCs. We have used a liver-specific CCRK transgenic mouse model and HCC orthotopic model in C57/BL6 immunocompetent mice. Molecular techniques including co-immunoprecipitation and ChIP assay were used to investigate the underlying mechanisms.
Results: Transgenic over-expression of CCRK in murine liver led to expansion of polymorphonuclear MDSCs in circulation. Moreover, co-culture of human peripheral blood mononuclear cells (PBMCs) with CCRK-over-expressing immortalized hepatocytes and HCC cells induced the accumulation of $CD33^{+}CD11b^{+}HLA\text{-}DR^{-}$MDSCs. The CCRK-induced MDSCs possessed immune suppressive functions by inhibiting T cell proliferation and interferon gamma expression (IFN-γ). In contrast, knockdown of CCRK in hepatic cells reduced the expansion and immune suppression of MDSCs. Using a Hepa1–6 orthotopic HCC model in immune-competent C57BL/6 J mice, we demonstrated that knockdown of Ccrk significantly decreased hepatic tumorigenicity and the levels of circulating and tumor-infiltrating MDSCs as well as their T cell suppressive functions. Notably, adoptive transfer of MDSCs rescued the effects of Ccrk knockdown. In a complementary experiment, we found that MDSC depletion by specific IA8 antibody significantly reduced CCRK-induced tumorigenicity. Cytokine profiling analysis revealed that CCRK significantly induced hepatocellular interferon-6 (IL-6) expression and production, which mediated MDSC expansion as shown by IL-6 rescue and antibody neutralization experiments. Mechanistic studies demonstrated that CCRK triggered nuclear factor-kappa B (NF-κB) signaling in an enhancer of zeste homolog 2 (EZH2)-dependent manner. Simultaneously, the phosphorylation of NF-κB by CCRK facilitated the co-occupancy of IL-6 promoter by NF-κB-EZH2 complex for transcriptional activation.
Conclusion: As we also showed elevation of $CD33^{+}CD11b^{+}HLA\text{-}DR^{-}$MDSCs and concordant over-expression of CCRK/EZH2/NF-κB/IL-6 signaling in human HCCs, our results uncover CCRK to be a critical immune regulator to promote MDSC functions, thereby providing a new mechanistic link between aberrant oncogenic signaling and tumor evasion for therapeutic exploitation.
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OP351 PROTECTIVE ROLE OF SPECIFIC PATHOGEN FREE MICROBIOTA IN BILE DUCT LIGATED AND CCL4 MICE

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Introduction: In chronic liver disease the presence of gut-derived bacterial products and the resultant increase in inflammatory cytokines in the splanchnic and systemic circulation may contribute to the progression of fibrosis. However, the composition of the intestinal microbiota and the host-microbe interaction in the development of liver fibrosis remain largely unknown. We hypothesized that fibrosis would be attenuated in a gnotobiotic model of limited intestinal colonization (altered Schaedler flora, ASF) compared to a more complex colonization with specific pathogen free flora (SPF).
Aims & Methods: We aimed to investigate the development of fibrosis and portal hypertension in ASF and SPF mice. Liver fibrosis was induced by common bile duct ligation (BDL) for 14 days or intraperitoneal injection of 20% (dilution in olive oil) carbon tetrachloride (CCL_4) for 10 weeks in ASF or SPF male, C57BL/6 mice. Hemodynamic measurements were performed after 14 days in BDL or 10 weeks in CCL_4 treated mice. Liver histology and collagen deposition were evaluated using Sirius red staining for determination of fibrosis degree. To assess bacterial translocation, mesenteric lymph nodes, spleen and liver were dissected aseptically and then cultured on Luria Bertani agar and blood agar plates for aerobic and anaerobic culture respectively.
Result: There were no differences in portal pressure between sham-operated (controls) ASF or SPF mice. After BDL or CCL_4 treatment portal pressure (PP), portosystemic shunts (PSS) and collagen deposition within the liver showed a significant increase in both groups. However, the increase in portal pressure and degree of fibrosis was significantly higher in ASF than SPF mice:

	ASF-sham	ASF-BDL	SPF-sham	SPF-BDL	ASF-control	ASF-CCL_4	SPF-control	SPF-CCL_4
PP cmH_2O	8.4	11.8**	7.2	9.7*	8.5	12.2**	7.4	10.4*
PSS %	0.29	2.91**	0.38	2.42*	0.6	3.5*	0.5	1.8*
Collagen %	0.1	9.6***	0.3	5.2***	1.1	7.6***	0.8	4.3***

*($p < 0.05$ ** $p < 0.005$ *** $p < 0.005$) Bacterial translocation was significantly higher in ASF-BDL than SPF-BDL mice suggesting that bacterial translocation occurred more frequently in ASF-BDL mice. The increase in the bile infarcts area was significantly higher in ASF mice (ASF-BDL 13.5% vs. SPF-BDL 4.8% $P = 0.026$). No significant bacterial translocation was observed in CCL_4 treated mice.
Conclusion: SPF mice presented attenuated fibrosis and portal hypertension compared to ASF mice. Contrary to our hypothesis, these findings suggest that a more complex intestinal bacterial flora may play a hepato-protective role. Our results are in line with studies showing that germ free mice are more susceptible

to liver injury and fibrosis suggesting the beneficial role of intestinal microbiota in preventing liver injury[1, 2].

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP352 IMPROVING METABOLIC PARAMETERS IN NAFLD BY TARGETING NUCLEAR RECEPTORS

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Introduction: Non-alcoholic fatty liver disease (NAFLD) pathogenesis and treatment remain unsolved. microRNAs and bile acids were recently suggested to participate in disease pathogenesis and, as such, constitute potential therapeutic tools and targets. Moreover, nuclear receptors, namely peroxisome proliferator-activated receptors (PPARs) and the farnesoid X receptor (FXR) are currently under scrutiny as modulators of lipid and glucose metabolism in non-alcoholic steatohepatitis (NASH).

Aims & Methods: We aimed to elucidate the role of the miR-21/PPARα pathway in liver and muscle tissues of murine NASH models and ascertain the therapeutic potential of miR-21 abrogation alone or in combination with obeticholic acid (OCA). Wild-type (WT) and miR-21 KO mice were fed with chow (n = 10) or methionine and choline-deficient (MCD; n = 10) diets for 2 and 8 weeks. Alternatively, mice were fed either chow (n = 12) or fast food diet (FF; n = 12) for 25 weeks. Six animals from each group had their diet supplemented with OCA 10 mg/kg/day (Intercept Pharmaceuticals, Inc.). Human liver biopsies were obtained from morbid obese NAFLD patients (n = 28). Liver/muscle samples were processed for histological analysis and assessment of miR-21, pro-inflammatory/pro-fibrogenic cytokines, PPARα and metabolic relevant genes, by qRT-PCR and immunoblotting. A Taqman® Array was performed to evaluate modulation of lipid regulated genes. ROS levels were analysed through the use of 2',7'- dichlorodihydrofluorescein diacetate.

Results: WT mice fed with the MCD diet developed steatohepatitis and fibrosis, displaying increased levels of apoptosis, necroptosis and serum ALT and AST. In contrast, miR-21 KO mice displayed a significant decrease in steatosis severity, liver damage, inflammation and did not develop fibrosis. WT FF-fed mice developed hepatomegaly, macrovesicular steatosis, inflammatory infiltrates and increased oxidative stress. miR-21 levels were increased in WT FF-fed mice, in both liver and muscle, concomitantly with decreased expression of PPARα, a key miR-21 target. Similar findings were observed in NAFLD patients. Further, WT FF+OCA-fed mice exhibited decreased steatosis and miR-21 expression, compared with WT FF-fed mice. Importantly, KO FF+OCA-fed mice exhibited significantly reduced liver inflammation, oxidative stress and steatosis, in parallel with increased expression of PPARα and its metabolic targets, including CPT-1 and ACOX2. Finally, lipid regulated genes such as ACAT1, ALOX5 and FABP5 were found to be severely deregulated in WT FF-fed mice and reverted to control levels in KO FF+OCA-fed mice.

Conclusion: In conclusion, activation of PPARα, as a result of miR-21 abrogation, together with FXR activation by OCA, significantly improves metabolic parameters in NASH, highlighting the therapeutic potential of multi-targeting therapies for NAFLD. (Supported by PTDC/BIM-MEC/0873/2012, SFRH/BD/88212/2012, FCT, Portugal).

Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 08:30–10:00

MURINE MODELS OF INTESTINAL INFLAMMATION – ROOM 1.86

OP353 AN AUTOIMMUNITY-ASSOCIATED VARIANT IN PTPN22 PROTECTS FROM DISEASE ONSET IN MOUSE MODELS OF COLITIS

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Introduction: Presence of the single nucleotide polymorphism (SNP) rs2476601 in the gene encoding protein tyrosine phosphatase non-receptor type 22 (PTPN22) results in an altered-function PTPN22 protein product and is associated with increased risk to develop autoimmune disorders, including type 1 diabetes, rheumatoid arthritis, systemic lupus erythematous. However, the same variant reduces the risk for Crohn's disease (CD) onset. We have previously shown that protein and mRNA levels of PTPN22 are reduced in intestinal biopsies from CD patients, and that loss of PTPN22 results in enhanced inflammatory cytokine secretion from mononuclear cells treated with interferon-gamma or the bacterial product muramyl dipeptide.

Aims & Methods: In this study, we addressed how presence of the altered-function variant in PTPN22 influences the susceptibility to intestinal inflammation in mouse models of colitis. For this aim, colitis was induced in 10–12 week old female mice by administration of 2% DSS for 7 days (acute DSS colitis), administration of four cycles of DSS (1.5% DSS for 7 days, followed by 10 days normal drinking water each; chronic DSS colitis), or by transferring naïve T cells into RAG2-/- recipients. PTPN22 deficient (PTPN22-/-) mice, or mice expressing the IBD-associated variant in PTPN22 (PTPN22-619 W mice), and their respective wild-type (WT) littermates were used for the study.

Result: PTPN22-/- mice suffered from aggravated acute DSS colitis as characterized by pronounced weight loss, increased endoscopic and histologic colitis scores ($p < 0.05$ each), while PTPN22-619 W mice reacted only weak to the DSS treatment when compared to WT littermates ($p < 0.05$ for weigh development, $p < 0.01$ for other parameters). In chronic DSS colitis however, PTPN22-/- mice suffered from a milder disease course (reduced weight loss [$p < 0.05$], decreased histological severity [$p < 0.05$]) from the third cycle onwards. PTPN22-619 W on the other hand mice tended to show a more pronounced disease course in the later phase. In the T cell transfer model, PTPN22-/- T cells induced an enhanced histological pathology ($p < 0.05$), while weight loss was not affected when compared to mice receiving WT T cells. In contrast, mice transfected with PTPN22-619 W T cells were protected from disease development in the first weeks, and later on developed only a mild disease (moderate weight loss [$p < 0.01$], reduced shortening of the colon [$p < 0.05$], low histological disease scores [$p < 0.05$]) when compared to mice receiving WT T cells.

Conclusion: Taken together, we here describe for the first time how the IBD-associated variant in PTPN22 affects colitis development. This helps to explain why this variant is associated with a reduced risk for CD onset, although it increases the risk to develop classical autoimmune disorders.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP354 TOLL LIKE RECEPTOR 2 MODULATES THE INHIBITORY MOTOR RESPONSE INDUCED BY HYDROGEN SULPHIDE IN MOUSE COLON

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Introduction: The recognition of intestinal microbiota is in part carried out by toll-like receptors (TLR), which are responsible for initiating the innate immune response. Alterations in the intestinal microbiota and its recognition may contribute to the development of intestinal inflammatory pathologies. Otherwise, hydrogen sulphide (H_2S) is an endogenous gaseous signalling molecule and it potentially plays a relevant role in the intestinal motility. In mammals, two pyridoxalphosphate-dependent enzymes are responsible for H_2S synthesis: cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE).

Aims & Methods: The aim of this study was to investigate the influence of TLR2 on the motor response induced by H_2S and the enzymes responsible for H_2S synthesis (CBS and CSE) in mouse colon. Colon strips from male C57/BL10 wild-type (WT) and TLR2$^{-/-}$ mice of 8–12 weeks old were suspended in an organ bath in the direction of circular smooth muscle. We studied the effect of NaHS (10 μM–1 mM), D,L-propargylglycine (PAG, 10 μm–10 mM), an inhibitor of CSE, and amino-oxyacetic acid (AOAA, 10 μm–10 mM), an inhibitor of CBS, on WT and TLR2$^{-/-}$ mice colonic motility. Gene expression (mRNA) of CSE and CBS were determined by real time-PCR and protein expression of CSE and CBS were quantified by Western blotting in colon from WT and TLR2$^{-/-}$ mice.

Results: The NaHS, as a source of exogenous H_2S, reduced the frequency but not the amplitude of the spontaneous contractions in colon from WT mice. The inhibition of CSE or CBS with PAG or AOAA, respectively, increased the frequency but not the amplitude of the spontaneous contractions in colon from WT mice. The NaHS induced a higher reduction of the frequency of the spontaneous contractions in TLR2$^{-/-}$ respect to WT mice. The PAG and AOAA did not modify the spontaneous contractions in colon from TLR2$^{-/-}$ mice. The mRNA and protein expression of CBS resulted decreased in colon of TLR2$^{-/-}$ compared with WT mice. The mRNA but not the protein expression of CSE resulted decreased in TLR2$^{-/-}$ compared with WT mice.

Conclusion: These results suggest that exogenous and endogenous H_2S may regulate the colonic spontaneous contractions in WT mouse, reinforcing the hypothesis that H_2S is a gaseous inhibitory mediator of intestinal motility. TLR2

regulates the expression of CBS and modulates the inhibitory motor response induced by H_2S in mouse colon.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP355 DIRECT INHIBITION OF HMGB1 BY NEUTRALIZING ANTIBODY AMELIORATES EXPERIMENTAL COLITIS IN MICE VIA TLR4-MYD88 PATHWAY

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Introduction: Biologics targeting inflammatory cytokines has reveal a new era in inflammatory bowel disease treatment. High mobility group protein B1 (HMGB1) acts as an alarmin in early stage and inflammatory cytokine in late stage during inflammation. Direct blockade of HMGB1 can be protective against intestinal inflammation.

Aims & Methods: Potential role of anti-HMGB1 neutralizing antibody (HnAb) in inhibiting intestinal inflammation and the underlying mechanism is investigated in DSS-induced mice colitis (DSS-C) models. 200μg HnAb was administrated intraperitoneally to DSS-C at d0, d3 and d6 in HnAb group, whereas 200μg anti-IgY was used as control in DSS-C (DSS-C group) or normal control (ctrl group). Colon shortening, disease activity index (DAI), histological score of colitis (HS), MPO activity and inflammatory cytokines were evaluated to determine the colonic inflammation severity. Mucosa barrier function was assessed by immunofluorescent staining of mucus layer (mucin2) and tight-junction (T-J) protein detection. mRNA was detected by qPCR. T-J protein, HMGB1, TLR4, MyD88 was detected by Western blotting and measured by Grey-scale value. Statistical analysis was performed using one-way ANOVA analysis and the Post Hoc LSD test or Tamhane's T2 test.

Results: Treatment with HnAb significantly suppressed colonic inflammation in DSS-C mice by improving colon shortening (6.2 ± 0.4 cm vs. 5.3 ± 0.5 cm, $p < 0.05$), DAI (2.7 ± 0.5 vs. 3.7 ± 0.3, $p < 0.05$) and HS (6.0 ± 0.1 vs. 9.6 ± 0.7, $p < 0.05$). Besides, MPO activity (2.6 ± 0.8 vs. 4.8 ± 1.0, $p < 0.05$) and TNF-α (1.61 ± 0.05 vs. 3.04 ± 0.11, $p < 0.05$), IFN-γ (2.14 ± 0.06 vs. 7.87 ± 0.21, $p < 0.05$) and IL-1β (1.53 ± 0.10 vs. 2.48 ± 0.04, $p < 0.05$) mRNA expression was decreased when treated with HnAb as compared to DSS-C group (mRNA in ctrl group was set to 1). Relatively intact mucus layer was seen in mice colon of HnAb group as compare to DSS-C group. Significantly higher expression of tight-junction protein ZO-1 (0.38 ± 0.01 vs. 0.15 ± 0.05, $p < 0.0001$), claudin-5 (0.50 ± 0.09 vs. 0.17 ± 0.07, $p < 0.0001$) and occludin (0.85 ± 0.09 vs. 0.39 ± 0.01, $p < 0.0001$) was detected in HnAb mice as compared to mice in DSS-C group. Interestingly, colonic HMGB1 protein in both nucleus (0.58 ± 0.02 vs. 0.79 ± 0.03, $p < 0.0001$) and cytoplasm (0.23 ± 0.01 vs. 0.40 ± 0.03, $p < 0.0001$) were all decreased when treated with HnAb as compare to DSS-C, suggesting that primary inhibition of HMGB1 by HnAb blocked sequential HMGB1 formation and release. Lastly, TLR4 (0.31 ± 0.03 vs. 0.77 ± 0.08, $p < 0.0001$) and MyD88 (0.30 ± 0.03 vs. 0.78 ± 0.01, $p < 0.0001$) protein was significantly reduced in HnAb group than mice in DSS-C group though MyD88 mRNA was relatively higher in HnAb group than DSS-C group (0.69 ± 0.04 vs. 0.38 ± 0.01, $p < 0.05$).

Conclusion: Administration of HnAb ameliorated DSS-C by suppressing inflammation and strengthening mucosa barrier function possibly through inhibition of HMGB1-TLR4-MyD88 pathway, suggesting a potential interventional target of HMGB1 in ulcerative colitis treatment.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP356 NEW, PEPTIDE INHIBITOR OF DIPEPTIDYL PEPTIDASE IV, EMDB-1 ATTENUATES COLITIS IN MICE AFTER TOPICAL ADMINISTRATION

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Introduction: PETIR (PEptidase-Targeted ImunoRegulation) is a novel therapeutic strategy which takes for the purpose restoration of the immune balance by limiting the activation of immune cells and induction of endogenous protective mechanisms, such as TGFβ and glucagon-like peptide-2 (GLP-2) through inhibition of DPP IV-dependent pathways. Experimental data indicate that PETIR results in suppression of cell proliferation and reduced synthesis of pro-inflammatory cytokines without affecting cellular vitality.

Aims & Methods: The objective of this study was to test the anti-inflammatory activity of a novel DPP IV inhibitor EMDB-1 in the mouse models of colitis. The inhibitory effect of EMDB-1 on DPP IV was characterized in vitro using the HPLC system measuring the degradation rate of endomorphin-2 (EM2, natural DPP IV substrate) in the presence of the test compound. Anti-inflammatory activity of EMDB-1 was investigated in the model of acute and semi-chronic colitis induced by trinitrobenzenesulfonic acid (TNBS). Body weight, macroscopic score, ulcer score, colon length and thickness, as well as myeloperoxidase (MPO) activity were recorded. Mesalazine was used as a reference drug.

Results: EMDB-1 is a potent and specific DPP IV inhibitor as shown by significantly decreased degradation rate of EM2 by DPP IV ($t_{0.5} = 1.73$ vs. 3.60 min in the absence and the presence of EMDB-1, respectively). The intracolonic (i.c.) administration of EMDB-1 (0.1, 1 and 3 mg/kg, twice daily) attenuated both acute and semi-chronic TNBS-induced colitis in mice in a dose-dependent manner, as indicated by significantly reduced macroscopic parameters and MPO activity. Anti-inflammatory effect of EMDB-1 was not blocked by naloxone, thus the opioid receptors are not involved in its mechanism of action.

Conclusion: EMDB-1 is a potent inhibitor of DPP IV in vitro and exhibits substantial anti-inflammatory activity in the GI tract in vivo. Results of this study validate the EMDB-1 backbone for further development of peptide DPP IV inhibitors and suggest their potential use in the treatment of colitis.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP357 CHROMOFUNGIN (CHR) AMELIORATES EXPERIMENTAL COLITIS IN MICE VIA MODULATION OF MACROPHAGES' PLASTICITY

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Introduction: Macrophages play a major role in inflammatory bowel disease (IBD) pathogenesis through an inappropriate response to migration, and an impaired transition from a pro-inflammatory (classical activated macrophages (CAMs)) to an anti-inflammatory (alternative activated macrophages (AAMs)) phenotype. While there is growing awareness of a relationship between Chromogranin (Cg)-A and a susceptibility to inflammatory conditions, the specific interaction between CgA-derived peptides and macrophage plasticity in IBD is unknown. Recently, we have shown a linear correlation between CgA and inflammatory markers in patients with active ulcerative colitis, and colitic CgA-deficient mice demonstrated a significant decrease of colitis associated to a modulation of macrophage activation. As Cg-A is a prohormone, herein, we assessed the functional role of a specific CgA-derived peptides (Chromofungin (CHR): hCg-A47-66) in the regulation of acute colitis and the functional plasticity of murine macrophages.

Aims & Methods: Colitis was induced in C57BL/6 mice (7–8 weeks old) by administrating dextran sulfate sodium (DSS 5%) in drinking water for 5 days. Preventive CHR (2.5 mg/kg/day) or vehicle treatments started 1 day before induction of colitis and lasted for a total of 6 days. Disease activity index (DAI) was evaluated daily and mice were sacrificed on day 5 post-DSS induction to assess the extent of colitis. At sacrifice macroscopic scores were evaluated, serum level of C-reactive protein (CRP) was quantified using ELISA, and colonic interleukin (IL)-1β, IL-6, TNF-α, MIP-1α, MIP-1β, and ARG-1 were assessed using ELISA and RT-qPCR. Naïve peritoneal macrophages were isolated from non-colitic C57BL/6 mice and treated by CHR (200 ng/ml) then exposed for 6 h to LPS (100 ng/ml) to promote CAMs, or to IL-4/IL-13 (20 ng/ml) to promote AAMs. CAMs markers (IL-6, IL-1β, TNF-α, MIP-1α & MIP-β) and AAMs markers (ARG-1) were quantified by using ELISA and RT-qPCR.

Results: Preventive treatment with CHR significantly reduced the DAI onset and severity of colitis associated to rectal bleeding, stool consistency and weight loss. Macroscopic scores, serum-CRP, colonic IL-1β, IL-6, TNF-α, MIP-1α, MIP-1β were significantly decreased, while ARG-1 was significantly increased. In vitro, CHR-conditioned CAMS expressed significantly less IL-1β, IL-6, TNF-α, MIP-1α, MIP-β, but, surprisingly, more ARG-1 when compared to LPS control condition. Moreover, CHR-conditioned AMS expressed significantly more ARG-1 when compared to IL-4/IL-13 control condition.

Conclusion: These findings suggest that CHR can modulate the severity of experimental colitis. CHR treatment can attenuate the severity of experimental colitis and the inflammatory process via the modulation of the functional plasticity of murine macrophages and their functions. Targeting CgA-derived peptides may lead to novel therapeutic strategies in ulcerative colitis.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP358 DEFICIENCY OF PH-SENSING RECEPTOR TDAG8 AMELIORATES T-CELL TRANSFER COLITIS

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Introduction: The adaptive immune system plays a crucial role in the pathogenesis of inflammatory bowel diseases (IBD). Inflammation in IBD is typically associated with a decrease in local pH. The proton-sensing receptor T-cell death associated gene 8 (TDAG8), also known as G-protein-coupled receptor 65 (GPR65), has been identified as a risk gene for IBD in recent genome wide association studies.
Aims & Methods: We investigated the role of TDAG8 in T cell-mediated pathogenesis in intestinal inflammation using a murine adoptive transfer colitis model. Naïve T-cells ($CD4^+CD62L^+$), from WT and $TDAG8^{-/-}$ donor mice, were injected into Rag-/- male mice. Injection of PBS was used in a control group. The results of colitis were evaluated by weight change, colonoscopy score, spleen weight, H&E staining, IHC and mRNA expression.
Results: Induction of colitis was observed after 3 weeks by weight loss, diarrhea and bloody stool. The WT group showed severe weight loss ($p = 0.013$), whereas the $TDAG8^{-/-}$ group displayed only a minor delay in weight gain. No significant differences were observed in colon length, spleen weight and colonoscopy score between PBS and the $TDAG8^{-/-}$ groups. H&E staining of distal and proximal parts of the colon showed severe infiltration and crypt damage in the WT group. The $TDAG8^{-/-}$ group displayed significantly less histopathological signs of colitis in comparison to PBS and WT groups. CD3+ and IL-17A immunoreactive cells were rarely detected in colonic tissue of $TDAG8^{-/-}$ in comparison to the WT group. Downregulation of mRNA expression of pro-inflammatory cytokines (IFNγ, TNF, IL17A) was observed in the $TDAG8^{-/-}$ group in comparison with the WT group. No significant differences were observed in mRNA expression levels of Foxp3, $RORg^+$and IL18.
Conclusion: Our data demonstrate that TDAG8-deficiency in T-cells ameliorates the development of colitis suggesting an important physiological role of this pH receptor.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30–12:00
SURGERY MEETS ENDOSCOPY IN THE COLON – ROOM F1

OP359 TRANSANAL ENDOSCOPIC MICROSURGERY VERSUS ENDOSCOPIC MUCOSAL RESECTION FOR LARGE RECTAL ADENOMAS (TREND-STUDY)

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Introduction: Non-randomized studies suggest that endoscopic mucosal resection (EMR) is equally effective in removing large rectal adenomas as transanal endoscopic microsurgery (TEM). EMR might be more cost-effective and safer. This trial compares the cost-effectiveness and cost-utility of TEM and EMR for large rectal adenomas.
Aims & Methods: For this randomised controlled non-inferiority trial, patients with rectal adenomas ≥3 cm, without malignant features, from 20 hospitals were included and randomised (1:1) to EMR or TEM, allowing endoscopic removal of residual adenoma at 3 months. Unexpected malignancies were excluded post randomisation. Primary outcomes were recurrence within 24 months and the number of recurrence-free days alive and out of hospital, analysed by intention to treat. The trial was designed to demonstrate non-inferiority of EMR with regards to recurrence rate with an upper limit of 10%. Secondary outcomes were complications, quality of life, anorectal function and costs. This trial is registered in the Dutch Trial Registry (NTR1422).
Results: Between Feb 2009 and Sept 2013, 209 patients were randomised to EMR ($n = 106$) or TEM ($n = 103$). 4 patients withdrew consent. 1 patient had prostate carcinoma instead of rectal adenoma. The remaining 204 patients (103 EMR, 101 TEM) were treated; 27 (13%) had unexpected cancer and were excluded. One additional patient withdrew consent. Of the remaining 176 (87 EMR, 89 TEM) patients, overall recurrence rates were 15% after EMR and 11% after TEM (relative risk 1.33, 95% confidence interval (CI) 0.77–2.46). However, EMR was statistically not non-inferior to TEM. The number of recurrence-free days alive and out of hospital was similar (EMR 609 ± 209, TEM 652 ± 188, $p = 0.15$). Complications (mostly hemorrhage) occurred in 18% (EMR) vs. 26% (TEM) (odds ratio (OR) 0.65 (95% CI 0.32–1.33)). Major complications occurred in 1% (EMR) vs. 8% (TEM) (OR 0.14 (95% CI 0.02–1.13), $p = 0.064$). Quality adjusted life years were equal in both groups. Although EMR patients scored more favourable on disease specific quality of life questionnaires, manometries were similar and continence improved after adenoma resection regardless of treatment. EMR was approximately €3000 cheaper and therefore more cost-effective.
Conclusion: Due to unexpected high recurrence rates after both TEM and EMR, non-inferiority of EMR could not be demonstrated. Taking into account the high rate of unexpected malignancies, a trend towards more severe complications after TEM and the cost-effectiveness of EMR, EMR is the recommended technique in case of similar expertise of TEM and EMR.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP360 EFFICACY OF NON-EXPOSED ENDOSCOPIC WALL-INVERSION SURGERY (NEWS) AS AN ADVANCED METHOD OF FULL-THICKNESS RESECTION FOR GASTRIC TUMOR

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Introduction: Endoscopic submucosal dissection (ESD) has been widely accepted as an effective treatment for gastrointestinal tumors. However, ESD for early gastric cancer (EGC) with ulcer scarring is still technically difficult. Non-exposed endoscopic wall-inversion surgery (NEWS) is an advanced method of endoscopic full-thickness resection (EFTR) without transluminal communication, applying ESD technique.
Aims & Methods: The aim of this study is to clarify the short-term outcomes of NEWS for gastric tumors. Between July 2011 and March 2016, 26 patients (9 females, 17 males; mean age 65.9 years, range 49–85 years) underwent NEWS for gastric tumors. After marking around a tumor on both the mucosal and serosal surfaces and submucosal injection of sodium hyaluronate, circumferential seromyotomy and sero-muscular suturing were made laparoscopically, followed by circumferential muco-submucosal incision endoscopically. The resected specimen was perorally retrieved.
Results: The mean tumor size and resected specimen were 23.3 mm (range, 7–45 mm) and 36.1 mm (range, 20–66 mm), respectively. All lesions were curatively resected in an en-bloc fashion. The mean operation time was 219.0 minutes (range, 98–397 minutes), and the median estimated blood loss was 0 g (range, 0–250 g). Patients started oral intake on mean postoperative day 3.1 (range, 2–4), and the mean length of postoperative hospital stay was 8.2 days (range, 6–14 days). There were no severe postoperative complications. Histopathological examination of the tumors showed 21 GISTs, 1 schwannoma and 4 early gastric cancer. No tumor residual or recurrences was confirmed by performing gastroscopy and the mean body weight loss was 2.5 kg (range, −3.2–10.9 kg) during a median follow-up of 11 months (range, 0–37 months).
Conclusion: NEWS is an effective full-thickness resection with minimum possible margin without contamination and tumor dissemination into the peritoneal cavity, considering the quality of life of patients. NEWS could be utilized as a novel treatment option especially for node-negative EGC difficult to resect by ESD, or EGC with possible lymph node metastasis with a combination of sentinel node navigation surgery.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30–12:00
UPPER GI BLEEDING – ROOM M

OP361 MEDIUM- AND LONG-TERM RESULTS OF TREATMENT WITH LANREOTIDE IN CASES OF CHRONIC OR RECURRENT OBSCURE GASTROINTESTINAL BLEEDING OR DUE TO GASTROINTESTINAL ANGIODYSPLASIAS

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Introduction: Somatostatin analogues have been proposed as a rescue therapy in cases of chronic or recurrent obscure gastrointestinal bleeding (GIB) or attributable to gastrointestinal angiodysplasias (GIADs). The long-term results with lanreotide are still very scarce.
Aims & Methods: Our aim is to determine the medium and long-term benefit of lanreotide in cases of chronic or recurrent refractory obscure gastrointestinal bleeding or from gastrointestinal angiodysplasias, in terms of savings of health resources. This was a retrospective single-center study conducted under conventional clinical practice, following a defined management protocol, between 2003 to 2012. Patients with chronic or recurrent obscure GIB or due to GIADs, refractory to or not candidates for iron therapy, endoscopic, surgical or angiographic treatments, were included. Cirrhotic patients and those ones with very severe comorbidity (IV-V of the American Society of Anesthesiologists Classification-ASA-) were excluded. The diagnostic protocol included upper and lower endoscopy, abdominal computed tomography, video capsule endoscopy and/or single balloon enteroscopy. Lanreotide 60 or 90 mg was administered monthly, for at least 6 months. During the previous year and 36 months after starting the drug it was recorded demographics data, comorbidities, chronic use of antiplatelets and anticoagulants, hemostatic treatments, side effects, hospital admissions related to GIB, number of transfused red cells units, intravenous

Table (OP361)

Comparison in health resources consumption before and after Lanreotide.

Variable	Mean	SD	p value	Variable	Mean	SD	p value
Admission days - Prior yr - 1 yr–2 yr–3 yr	33.4 9.9 10.0 8.5	24.3 11.6 15.7 14.3	<0.01 <0.01 <0.01	Iron iv doses - Prior yr–1 yr–2 yr–3 yr	4.0 2.0 2.5 2.6	6.1 5.9 4.5 5.5	<0.01 0.08 0.02
Red cell units - Prior yr–1 yr–2 yr–3 yr	11.4 4.5 5.9 6.4	11.6 7.1 10.2 12.6	<0.01 0.01 0.04	N.Endoscopies - Prior yr–1 yr–2 yr–3 yr	1.6 0.1 0.6 0.7	1.7 0.3 1.1 1.6	<0.01 0.01 0.03

SD: Standard deviation. Yr: year

iron doses, and non-diagnostic endoscopies. Differences between data from one year before and each one of the three years after starting lanreotide were evaluated using Wilcoxon test, with significance level of $p < 0.05$.
Results: Twenty-two patients (median age 76.1 years, range 56–90; 50% male sex) were included. Before starting treatment 19 were ASA III, 22.7% consumed antiplatelet and 31.8% anticoagulants drugs. At the end of follow-up only one patient had stopped the anticoagulant. The bleeding was attributed to GIAD in 77.3% and 22.7% was obscure. The bleeding was overt in 68.2% and occult in 31.8%. Before starting lanreotide 4 patients had received endoscopic treatment using argon plasma coagulation (APC), 2 hormonal therapy and 1 thalidomide. Two patients received APC concomitant to lanreotide, and 1 hormonal therapy after stopping this one without reaching bleeding cessation. The average duration of treatment with lanreotide was 28.4 months (range 6–36). Mean follow-up was 32.4 months (range 9–36), with the results shown in the table. Five patients did not complete the follow-up for not related to GIB deaths. No side effects forced to suspend lanreotide.
Conclusion: The use of lanreotide for al least 6 months in patients with chronic or recurrent obscure gastrointestinal bleeding or from gastrointestinal angiodysplasias, refractory to or not candidates for other therapies, is safe and is associated with a decrease in consumption of medical resources within the three years following its indication.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP362 SOMATOSTATIN ANALOGUES ARE LESS EFFECTIVE IN PATIENTS WITH ANGIODYSPLASIAS AT MULTIPLE SITES OR LOCATED IN THE COLON: A POOLED ANALYSIS OF INDIVIDUAL PATIENT DATA

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Introduction: Cohort studies have shown a beneficial effect of octreotide in decreasing the rebleeding rates in patients with gastrointestinal angiodysplasias, however with large variation among individuals. Most studies have a small sample size and different primary outcomes, such as haemoglobin and rebleed, which makes it difficult to estimate the true effect on clinical relevant outcomes such as transfusion dependency and to investigate predictors for good clinical response.
Aims & Methods: The aim of this individual patient data meta-analysis is to investigate efficacy of SST on transfusion dependency and identify subgroups of patients that benefit most from SST. A systematic review was performed to identify articles reporting the effect of SST in gastrointestinal angiodyplasias. We collected individual patient data of included articles. Patients with only oral iron dependency were excluded. The primary outcome was response to SST, defined as good: ≥50% reduction of parenteral iron and/or red blood cell (RBC) transfusions; or poor: <50% reduction of parenteral iron and/or RBC transfusions. We used univariate logistic regression to determine the effects of patient and disease characteristics on SST. The variable "study" was included in the univariate analysis to correct for study-effect.
Results: We identified 7 studies and obtained individual data from 6 (n = 180) studies. We analyzed data of 159 patients (mean age 70 years, 56% men) with transfusion dependency due to gastrointestinal angiodysplasia bleeding that were treated with SST. Fifty percent of patients had angiodysplasias at multiple sites (small bowel (75%), stomach (45%), and colon (45%)). Endoscopic treatment prior to SST was started in 48%. Octreotide LAR 20 mg was the most frequent prescribed (81%). Side-effects occurred in 31% (41/131) of the patients, with gastrointestinal symptoms (19.8%) and erythema / pain at the injection site (8.4%) the most frequent. In 8 patients (6%) SST was discontinued due to side-effects. There was a high SST response with 89% of the patients having >50% reduction of their parenteral iron and/or RBC transfusion dependency. Sex, age, small bowel and stomach localization, the use of anticoagulants, dose, only parenteral iron dependent and prior endoscopic treatment were not associated with treatment response. Angiodysplasia localization in the colon (OR 0.28, 95% CI 0.09–0.88, p = 0.03) and at multiple sites (OR 0.37, 95% CI 0.17–0.77, p = 0.008) were negatively associated with a good response.
Conclusion: Based on this pooled analysis of data from individual patients with transfusion dependent angiodysplasia bleeding, SST is effective and safe in the majority of patients. A decreased SST response is found in patients with angiodysplasias located at multiple sites or in the colon.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP363 ESOPHAGEAL VARICES POST BANDING ULCER BLEEDING - DETERMINANTS AND IMPACT IN MORTALITY

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Introduction: Endoscopic band ligation (EBL) is the choice for both prophylaxis and treatment of esophageal varices hemorrhage. Post-EBL ulcer bleeding is a deemed complication for which risk factors and impact in mortality are not clearly understood.
Aims & Methods: We aimed at identifying risk factors for variceal post-EBL ulcer bleeding and determine its impact in short and long-term mortality. We conducted a case control study. Cases: all admissions for post-EBL ulcer bleeding, in a tertiary gastrointestinal service, from January 2003 to December 2015. Controls: EBL treated patients without post-therapeutic ulcer bleeding. Matching was made for Child-Pugh-Turcotte (CPT) score and indication (bleeding vs elective) in a 1 case for 2 controls ratio. Patient's demographics, comorbidities and endoscopic findings were reviewed from medical records. Endpoints were re-bleeding from post therapeutic ulcer and mortality assessed at 28, 90, 180 and 360 days post-therapeutic.
Results: A total of 50 post-EBL ulcer bleeding cases and 100 controls were included. Mean age (57.1 ± 12.0); male:female ratio (4.1:1). Cirrhosis etiologies: alcoholic (70.7%), HCV (29.3%) and HBV (15.7%). CPT distribution: A (17,3%) B (46%) and C (36.7%); mean MELD was 14.5 ± 6.1. All patients underwent EBL and 7.3% also received a sclerosing agent. Mean time to rebleed: 12.6 ± 5.4 days. A higher number of rubber bands (5.8 ± 1.7 vs 5.0 ± 2.1 p = 0.003), lower baseline hemoglobin (10.7 ± 1.5 vs 11.5 ± 2.1 g/dL p = 0.007), hemodynamic instability (OR:2.0 p = 0.048) portal vein thrombosis (OR:2.8, p = 0.022), HBV cirrhosis (OR:6.2, p = 0.007), and endoscopic stigmata of active or recent bleeding (OR:5.0 $p < 0.001$) correlated with rebleeding. In multivariate logistic regression analysis HBV cirrhosis, multiple concomitant aetiologies of cirrhosis and endoscopic stigmata of recent bleeding were independently associated with rebleeding. Post-EBL ulcer bleeding did not significantly impacted overall short and long term mortality. However CPT class B patients with post-EBL ulcer bleeding showed a trend for lower survival which was significant at 180 days (16% vs 6% log rank p = 0.04).
Conclusion: We identified both patient's and endoscopic features correlating with post-EBL ulcer bleeding, namely HBV infection related cirrhosis, higher number of concomitant aetiologies/aggressors, and endoscopic stigmata of recent/active bleeding. Though overall patient's short and long-term mortality was not affected by post-EBL ulcer bleeding, CPT class B patients showed a trend for

lower survival. Thus, we hypothesize that CPT class B patients may be a cluster of patients with low hepatic reserve, to whom post-EBL bleeding may impose an additional risk for disease progression, that can significantly impact on survival.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP364 INTERNATIONAL PROSPECTIVE STUDY OF UPPER GI HAEMORRHAGE: DOES WEEKEND ADMISSION AFFECT OUTCOME?

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Introduction: Weekend admissions have been associated with higher mortality. For upper gastrointestinal haemorrhage (UGIH) some studies show significantly increased mortality[1] and delayed endoscopy while the UK UGIH audit reported no difference[2]. We studied whether out of hours (OOH) admissions had more co-morbidity, were less stable and/or had higher mortality.
Aims & Methods: Prospective study over 12 months (from March 2014) from 2 UK and 2 international centres. Admission time, demographics, pulse, BP, lab results, endoscopy findings, further procedures and 30d mortality were recorded. 3 pre-endoscopy scores (Glasgow Blatchford (GBS), AIMS65 and admission Rockall scores) and 2 post-endoscopy scores (PNED and full Rockall scores) were determined. Chi-squared, Fisher's exact and Kruskal-Wallis tests were used as appropriate. A two-tailed significance level of 5% was used.
Results: 2118 consecutive patients, 60% male, median age 66 years were seen. There were no significant differences in mortality, need for endoscopic therapy, surgery/embolisation or rebleeding in both UK and non-UK centres. There were no differences in comorbidity, mean ASA 2.3, pulse or BP although weekday admissions had a lower Hb (110 g/l vs 118 g/l (weeknight) vs 117 g/l (weekend) $p < 0.001$ and higher GBS ($p < 0.05$). No difference in peptic ulcer disease or varices incidence between periods although more weekday admissions had normal endoscopy($p = 0.002$). OOH admissions were less likely to have an endoscopy (30% not endoscoped vs 23% for weekday admission $p < 0.005$). Time to endoscopy was less for weeknight admissions (13 h vs 17 h for weekend and 20 h for weekday admissions $p = 0.0001$). 67% weekday, 75% weeknight and 60% weekend admissions had their endoscopy within 24 hours

Outcome of patients with UGIH and time of presentation

	Weekdays: working time	Weekdays: overnight	Weekends	Total
Number	858	603	642	2118
Units blood transfused	1.4 [0–6]	1.3 [0–6]	1.4 [0–6]	1.4 [0–6]
Endoscopic therapy	185 (22)	116 (19)	126 (20)	430 (20)
Surgery/embolisation	4 (0.5)	6 (1.0)	6 (0.9)	16 (0.8)
Rebleeding	49 (5.8)	33 (5.7)	43 (6.9)	126 (6.1)
30 d mortality	61 (7.1)	43 (7.1)	48 (7.5)	153 (7.2)

2118 consecutive patients admitted March 2014-March 2015 from Glasgow (600), Truro (544), Odense (541) and Singapore (433). Data shown are mean [95% CI] or number (%).
Conclusion: There is no difference in mortality in patients admitted with UGIH OOH compared to weekday admissions although weekday admissions had a lower haemoglobin and higher GBS. There was no evidence of delay in time to endoscopy with OOH admissions. The severity of UGIH was not related to time of admission. Similar findings were noted in all four centres.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP365 PROGNOSTIC FACTORS FOR SECOND ENDOSCOPIC THERAPY FAILURE IN PEPTIC ULCER BLEEDING

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Introduction: According to current guidelines a second endoscopic therapy is generally encouraged for patients with rebleeding secondary to peptic ulcer disease (PUD). Although risk factors for endoscopic hemostasis failure are well defined in the setting of the first endoscopic therapy, literature lacks studies that focused on the risk factors for rebleeding after the second endoscopic therapy.[1]
Aims & Methods: To assess risk factors related to the failure of the second endoscopic therapy in patients with upper gastrointestinal bleeding (UGIB) secondary to PUD, in order to define high-risk patients that could benefit from alternative methods like angiography or surgery. Retrospective analysis of all cases of UGIB secondary to PUD that were submitted to two endoscopic therapies between 2010 and 2014 in a tertiary center. We recorded demographic, clinical, analytical and endoscopic data. Comorbidities were evaluated according to the age adjusted charlson comorbidity index (ACCI). The main endpoint was rebleeding, defined as: objective evidence of UGIB, with hemodynamic instability and Hb decrease $\geq$2g/dL, or need for more than 3 units of blood in the 72-hour period after the endoscopic treatment.
Results: We identified 56 patients who underwent a second endoscopic therapy. The mean age was 76 years (males: 63%) and the mean ACCI was 7 ($\pm$3.1). The most common location of PUD was duodenal (80.4%) and 26.8% were classified as having a high-risk location (small gastric curvature / posterior wall of the bulb); the estimated mean size of PUD was 13.3 mm ($\pm$6.8). The mean number of blood units transfused was 3 ($\pm$2.4). Rebleeding occurred in 23% and in-hospital mortality was 20%. In univariate analysis the female gender ($p = 0.041$), presence of active non gastrointestinal neoplasia ($p = 0.021$), high-risk location ($p = 0.001$), large-ulcers ($p = 0.045$), Idiopathic-PUD ($p = 0.006$) were associated with hemostatic failure. The number of red blood cells (RBC) units that were transfused was correlated to hemostatic failure ($Rs = 0.548$; $p = 0.000$). Drug-induced peptic ulcers (presence of anticoagulation or antiaggregation agents, non-steroidal anti-inflammatory drugs and no evidence of *Helicobacter pylori* infection) were associated with a successful hemostatic treatment ($p = 0.027$). The variables ACCI, presence of hemodynamic instability, Forrest classification of the PUD in the second endoscopic therapy, gastric or duodenal location, were not statistically significant different between groups when evaluated the hemostatic success. In the multivariate analysis, large ulcers ($p = 0.014$; $OR = 7.08$) and transfusion of $\geq$4 blood units ($p = 0.030$; $OR = 1.71$) were independent risk factors for rebleeding.
Conclusion: In patients with UGIB secondary to PUD that require a second endoscopic therapy for rebleeding, the need for higher blood transfusion ($\geq$4) and large ulcers (>20 mm) were independent risk factors for hemostasis failure. Early surgery or angiography should be considered in this group of patients.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP366 A HISTORY OF ISCHEMIC HEART DISEASE, HIGH BLOOD UREA NITROGEN AND C-REACTIVE PROTEIN LEVELS, AND LOW HEMOGLOBIN LEVELS: AS PREDICTIVE CLINICAL FACTORS FOR EARLY DEATH AFTER PERCUTANEOUS ENDOSCOPIC GASTROSTOMY

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Introduction: Percutaneous endoscopic gastrostomy (PEG) is accepted as the method that enables enteral feeding in patients with swallowing difficulties. However, complications and early death are considerably prevalent after PEG. To decrease the incidence of early mortality after PEG, it is very important to identify risk factors of this procedure.
Aims & Methods: The aim of our study was to determine factors that could predict early death within 30 days following PEG. A retrospective analysis of the records of all patients who underwent PEG at Kure Medical Center and Chugoku Cancer Center from April 2008 to March 2016 were performed. We examined clinical and preoperative laboratory data and extracted predictive factors of early death after PEG by using univariate and multivariate analyses.
Results: A total of 1077 patients [502 female (46.7%) and 575 male (53.3%); mean age 78 y.o.] were assessed. Predictors of poor survival after PEG included history of ischemic heart disease (odds ratio [OR] 2.32, 95% confidence interval [CI] 1.2–4.3, $P < 0.01$), blood urea nitrogen level $\geq$30 mg/dl (OR 3.14, 95% CI 1.8–5.5, $P < 0.0001$), C-reactive protein level $\geq$2.6 mg/dl (OR 4.04, 95% CI 2.2–7.3, $P < 0.0001$), albumin level $\leq$2.7 mg/dl (OR 4.2, 95% CI 2.1–8.2, $P < 0.0001$), and hemoglobin level $\leq$11.2 g/dl (OR 4.0, 95% CI 2.0–8.0, $P < 0.0001$). Multivariate analysis on predictive factors of early death revealed a significant correlation between early death and each of the following: history of ischemic

heart disease ($P < 0.01$), high blood urea nitrogen ($P = 0.02$) and C-reactive protein levels ($P < 0.01$), and anemia ($P < 0.0001$).

	odds ratio (95% CI)	p-Value
History of ischemic heart disease	2.32 (1.2–4.3)	<0.01
Blood urea nitrogen level ≥ 30 mg/dl	3.14 (1.8–5.5)	<0.0001
C-reactive protein level ≥ 2.6 mg/dl	4.04 (2.2–7.3)	<0.0001
Albumin level ≤ 2.7 mg/dl	4.2 (2.1–8.2)	<0.0001
Hemoglobin level ≤ 11.2 g/dl	4.0 (2.0–8.0)	<0.0001

Conclusion: A history of ischemic heart disease and laboratory data, such as high blood urea nitrogen and C-reactive protein levels and low hemoglobin levels may be useful predictive clinical factors for early death after PEG. If patients have a history of ischemic heart disease, high blood urea nitrogen, high C-reactive protein, or anemia, PEG should be considered carefully.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30–12:00
IMMUNOTHERAPY IN CANCER – ROOM 1.61/1.62

OP367 GLUTAMINOLYSIS INHIBITION AS A THERAPEUTIC STRATEGY IN GLUTAMINE-ADDICTED KRAS MUTANT COLORECTAL CANCER

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Introduction: Colorectal cancer (CRC) with KRAS mutations represents an unmet clinical need due to the lack of effective therapies. A defining characteristic of oncogenic KRAS-driven cancers is an altered cellular metabolism, in which glucose and glutamine metabolism are extensively rewired satisfy their anabolic needs. In this study, we investigated the metabolic dependencies of KRAS-mutant CRC, established the role of glutaminolysis in KRAS-mutant CRC growth and evaluated the synergism between glutaminolysis inhibition and chemotherapy in this subset of CRC.
Aims & Methods: Metabolic dependencies of KRAS mutant CRC cell lines were assessed by colony formation and apoptosis assays. Glutamine metabolism in KRAS mutant CRC cells were traced using stable $U^{-13}C_5$-glutamine labeling and Ultra-high Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS). Role of glutaminase (GLS1) and the mitochondrial glutamate transporter (SLC25A22) in mediating glutaminolysis was evaluated. Finally, the functional effect of glutaminolysis inhibition (via GLS1 or SLC25A22 blockade) and its synergy with chemotherapeutic agents were tested.
Results: Deprivation of glucose, glutamine or their combination in six KRAS mutant CRC (DLD1, HCT116, LOVO, SW480, SW620 and SW1116) and four KRAS wild type CRC cell lines (CACO-2, COLO205, HT29 and SW48) revealed that KRAS mutant CRC cells were profoundly sensitive to glutamine depletion as compared with KRAS wild type CRC cells; whilst exhibiting resistance to glucose depletion. This indicates that supply of glutamine is obligatory for KRAS mutant CRC survival. $U^{-13}C_5$-glutamine labeling in DLD1 cells and UPLC-MS revealed that a majority of glutamine was metabolized into glutamate, aspartate and the intermediates of the tricarboxylic acid (TCA) cycle, indicating that glutamine-derived carbons were channeled to the mitochondria for the replenishment of TCA cycle (a process known as glutaminolysis). We further revealed that glutamine was first converted to glutamate by GLS1 at the outer side of inner mitochondrial membrane, which is coupled to SLC25A22 for the import of glutamate into the mitochondrial matrix. Consistent with this model, the silencing of GLS1 or SLC25A22 significantly suppressed cell proliferation in KRAS mutant CRC cells, indicating that their coupled action is indispensable for cell growth. $U^{-13}C_5$-glutamine tracing in DLD1 cells with SLC25A22 knockdown showed an attenuated entry of glutamine-derived carbons into the TCA cycle, confirming its involvement in glutaminolysis. Inhibition of SLC25A22-dependent glutaminolysis triggered metabolic stress, suppressed ATP production and promoted oxidative stress. Moreover, a combinatorial approach utilizing SLC25A22- shRNA plus 5-Fluorouracil synergistically suppressed KRAS mutant CRC growth in vitro and in subcutaneous xenograft models.
Conclusion: KRAS mutant CRC cells are addicted to glutamine and the blockade of glutaminolysis enzymes GLS1 and SLC25A22 suppressed cell survival. SLC25A22 represents a novel therapeutic target in KRAS mutant CRC and its synergistic effect with chemotherapy warrants further investigation.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP368 MOLECULAR DISSECTION OF TUMOR ANGIOGENESIS IN COLORECTAL CANCER

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Introduction: Angiogenesis is a hallmark of cancer development and is considered as an attractive therapeutic target.
Aims & Methods: In this study, we aimed to unravel the molecular mechanism underlying tumor angiogenesis in colorectal cancer (CRC). We isolated endothelial and epithelial cells from surgically resected 14 CRC tissues and corresponding normal colonic tissues using antibodies against endothelial (CD146) and epithelial markers (EpCAM). RNA sequencing (RNA-seq) was carried out in 3 pairs of normal and tumor endothelial cells. Gene expression was validated by quantitative RT-PCR (RT-qPCR) and immunohistochemistry. Functions of a selected gene were analyzed by tumor conditioned medium (TCM) experiments, in vitro tube formation assay, cell cycle analysis, gene expression microarray and xenograft experiments.
Results: Through RNA-seq analysis, we identified a series of 18 genes which were upregulated in the endothelial cells isolated from CRC tissues. We further validated the results by qRT-PCR and immunohistochemistry in a larger number of clinical samples, and identified gene A as a novel candidate of the tumor endothelium-related gene. Expression of gene A was also upregulated in human umbilical vein endothelial cells (HUVECs) treated with TCM obtained from CRC cell lines. Knockdown of gene A suppressed in vitro tube formation and induced G1 cell cycle arrest in HUVECs. Microarray analysis revealed that knockdown of gene A induced expression changes of approximately 300 genes in HUVECs, and gene ontology analysis showed that cell cycle-related genes were significantly enriched in the affected genes. To confirm our findings in vivo, we co-transplanted CRC cells with HUVECs into nude mice. We found that knockdown of gene A in HUVECs resulted in reduced micro vessel formations in the xenograft tissues. Finally, we evaluated the clinical implication of gene A in colorectal cancer. The Cancer Genome Atlas (TCGA) datasets of primary CRCs ($n = 411$) revealed that higher expression of gene A is associated with worse overall survival, suggesting that upregulation of gene A in tumor endothelial cells may promote aggressiveness of CRC.
Conclusion: Our results suggest that gene A may play an important role in the angiogenesis in colorectal cancer, and that it could be a potential therapeutic target.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30–12:00
COMPLICATIONS OF LIVER CIRRHOSIS: BEYOND BLEEDING AND ASCITES – ROOM N1

OP369 RANDOMIZED CONTROLLED TRIAL OF BACLOFEN IN TREATMENT OF MUSCLE CRAMPS IN PATIENTS WITH LIVER CIRRHOSIS

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Introduction: Muscle cramps adversely influence the quality of life of patients with liver cirrhosis. However, despite the obvious association of muscle cramps with liver disease, there is a paucity of information regarding pathogenesis and treatment in these patients.
Aims & Methods: This is the first randomized placebo controlled trial of baclofen in the treatment of muscle cramps in patients with liver cirrhosis. One hundred patients with liver cirrhosis and suffering from muscle cramps signed informed consent to participate in this study. They were recruited from Department of Tropical Medicine-Tanta University hospital. They were randomized to receive either baclofen or placebo for 3 months. Patients were followed monthly and one month after withdrawal. Each visit, the clinico-epidemiological data were recorded, muscle cramp questionnaire was filled, and any drug related side effects were reported.
Results: In the baclofen group, the frequency of muscle cramps was significantly decreased after one and three months of treatment ($p < 0.005$), with a significant rebound after withdrawal ($P < 0.001$). Patients receiving baclofen had a significant decrease in the severity and duration of muscle cramps ($P < 0.001$). After three months of baclofen therapy at dose of 30 mg/day, muscle cramps disappeared completely in 72%, reduced in 20%, and no change in 8% of patients. No significant changes in the frequency, severity and duration of muscle cramps were noted in the placebo group. There were few but non-significant side effects in the baclofen group when compared to placebo group.
Conclusion: Baclofen was well tolerated, safe, and effective in the treatment of muscle cramps in Egyptian patients with post-hepatitis C liver cirrhosis.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP370 SPONTANEOUS BACTERIAL PERITONITIS – DOES THE INFECTION ACQUISITION SITE MATTER?

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Introduction: Spontaneous bacterial peritonitis (SBP) develops in up to 25% of patients with cirrhosis and its associated with significant short and long-term morbidity and mortality. With the ambulatorization of medical care, the use of antibiotics for primary and secondary prophylaxis of SBP, there is some controversial concerning whether the acquisition site of the infection has an effect on the prognosis of SBP and if the international guidelines for antibiotic therapy (mainly based on the acquisition site) are still considered to be the best practice.
Aims & Methods: 1) To compare clinical, analytical and microbiological features between nosocomial and community-acquired SBP; 2) to assess the influence of the infection acquisition site when evaluated in-hospital mortality and 1 year-mortality. Retrospective cohort study, conducted in 3 tertiaries centers that evaluated all cases of SBP between 2010 and 2014. Medical records and laboratory data were reviewed. For defining the acquisition site of the infection, we followed the criteria described by European Center for Disease Prevention and Control (ECDC). Healthcare-Associated infections and Nosocomial infections were analyzed as the same variable. Multiresistant bacteria (MDR) was defined according to the ECDC criteria (resistant to 3 antibiotic families, including beta-lactam antibiotics).
Results: We identified 222 episodes of SBP, from which 110 were considered as community-acquired; in-hospital mortality was 28,8% and 1 year-mortality was 56,9%. In 85 episodes we obtained microbiological isolation (MDR = 28), with a predominance of gram negative (53,6%). Community-acquired SBPs were more frequently caused by gram negative bacteria and Nosocomial-acquired SBPs were more frequently by gram positive bacteria ($p = 0{,}033$); SBPs secondary to MDR-bacteria were more frequent in Nosocomial-acquired group (19,64 vs 6,36%; $p = 0{,}003$). No statistically significant differences were noticed between centers when analysed microbiological isolation rate, gram staining of MDR isolations. There were no statistically significant differences between Community-acquired SBP and Nosocomial-acquired SBPs for the variables age, gender, Child-Pugh, MELD, Hb, leukocytes, platelets, CRP, Na, INR, bilirubin, albumin, ascites fluid characteristics, gastrointestinal bleeding, acute kidney injury and hemodynamic instability at diagnosis. Nosocomial-acquired SBPs were associated with longer hospitalizations (17,8 vs 11,7 days; $p = 0{,}007$). No statistically significant difference was detected when analyzed in-hospital mortality (Nosocomial-acquired = 29,5 vs Community-acquired = 28,2%; $p = 0{,}833$). When assessed 1 year-mortality, Nosocomial-acquired SBPs were associated with a worse prognosis (63,0 vs 51,7%; $p = 0{,}025$).
Conclusion: Nosocomial-acquired SBPs were associated with higher rates of MDR-bacteria, longer hospitalization lengths and higher 1 year-mortality. Clinical and laboratorial features were not significantly different between SBP according to the infection acquisition site; 6,36% of community-acquired SBPs were secondary to MDR-bacteria and so in a relevant percentage of our sample, empiric antibiotic therapy according to the current guidelines would eventually fail.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30–12:00
IMPROVING QUALITY OF SCREENING COLONOSCOPY – ROOM N2

OP371 SEVEN YEARS OF QUALITY ASSURANCE IN SCREENING COLONOSCOPY IN AUSTRIA

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Introduction: Screening colonoscopy only effectively prevents from colorectal cancer if performed with high quality.
Aims & Methods: Austria implemented a quality assurance program in screening colonoscopy in 2007. This study provides a report on 8 years of quality assured screening colonoscopy.
Results: In the investigated time period, 301 endoscopic units provided data of 159,246 screening colonoscopies. 49.1% were female patients. Mean age was 61.1 years. Significant increases over time were found for ADRs, which rose from a mean of 22.2% (SD 10.7%) in 2007–2008 to 24.2% (11.6%) in 2013–2014, corresponding to an average increase of +1.5% per two-year-period (95% confidence interval [95%CI] +0.9%, +2.2%, $p < 0.001$). Likewise, proximal lesion detection rates rose from 15.8% (SD 9.8%) to 21.7% (SD 13.3%, +2.5% per two-year-period, 95%CI +1.9%, 3.1%, $p < 0.001$). Adverse events occurred in 0.3%, 63% thereof were associated with polypectomy. There was a decline in complication rates of −7.3 per 10,000 endoscopies per two-year-period (95%CI −13.1, −1.5 per 10,000 endoscopies per two-year-period, $p = 0.013$). Sedation increased the probability of adverse events (0.24% in sedated and 0.16% in unsedated patients, $p = 0.025$). Notably, all perforations occurred under sedation.
Conclusion: This study showed a strong improvement in quality of screening colonoscopies performed within a quality assurance program in Austria between 2007 and 2014. Both overall adenoma detection rate and detection rate of proximal lesions increased strongly in the investigated study period. Interestigly, the detection rate of advanced adenomas decreased.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP372 ENDORINGS™ INCREASES ADR EVEN IN HIGH-RISK SCREENING COLONOSCOPY: RESULTS OF A SINGLE CENTRE PILOT STUDY

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Introduction: Colonoscopy remains the gold standard procedure for screening and polyp detection, with adenoma detection rate (ADR) being a widely accepted key performance indicator (KPI). It has long been recognised that even experienced endoscopists incur an appreciable 'miss-rate' and a number of novel devices have been marketed to assist this aspect of practice. The Endorings™ device is a simple soft silicone, single-use device consisting of a series of rings arranged around a central tubular core. As the colonoscope is inserted the rings fold backward to allow intubation and flare on withdrawal to flatten colonic folds and aid inspection.
Aims & Methods: This was a single-centre pilot study to determine the effect of Endorings used in a high-risk cancer screening population (national), when used by experienced operators with an established ADR already >45%. Prospective data was collected during screening colonoscopy (performed by two accredited colonoscopists) when the Endorings™ device was used and compared the results to outcomes from the previous few months, for the same two colonoscopists) when the device was not in use (ie. historical controls).
Results: The ADR without Endorings™ (n = 85) was 49.4% with a per-procedure detection rate (ppr) of 0.97. With the device (n = 66), ADR was 66.7% ($p = 0.0006$) with ppr of 1.625. This represents a 35% increase in ADR and a 68% increase in the number of polyps detected at any given procedure. There were no significant differences in completion rates, withdrawal time, use of sedation or comfort scores. The device was removed in 5/66 procedures due to interference with intubation (in the presence of either an angulated sigmoid or diverticulosis). No complications were recorded.
Conclusion: Use of the Endorings™ device was associated with a significant increase in ADR. Qualitatively, the three-ring design was felt to interfere with normal intubation such that insertion technique had to be modified. An updated design iteration with two rings in slightly different positions along the central tube, has been produced and appears to offer a significant advantage in this regard. Furthermore, the central tube can be pushed further along the distal end of the colonoscope to allow the terminal ileum to be intubated with the device in place. The Endorings™ may offer an advantage in screening colonoscopy and, in this cohort, further prospective investigation is warranted.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP373 THE FIRST RANDOMISED CONTROLLED TRIAL OF ENDOCUFF VISION® ASSISTED COLONOSCOPY VERSUS STANDARD COLONOSCOPY FOR POLYP DETECTION IN BOWEL CANCER SCREENING PATIENTS (E-CAP STUDY)

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Introduction: Up to 25% of colonic polyps are missed during colonoscopy. The Endocuff Vision® is a cap with soft flexible arms which attaches to the end of a colonoscope and improves views during withdrawal. We have performed the first randomised controlled trial to identify the role of Endocuff Vision® in improving polyp detection.
Aims & Methods: Our aim was to investigate the impact of Endocuff Vision®-assisted colonoscopy on polyp detection, as compared to standard colonoscopy, in the UK Bowel Cancer Screening Programme (BCSP). This was a single-centre, parallel group, randomised controlled trial. Ethics approval was obtained (ref:

14/SC/0207). Patients attending for BCSP colonoscopy were stratified based on whether they were attending for index screening colonoscopy or for polyp surveillance. Within each stratum participants were randomised to either Standard or Endocuff assisted colonoscopy. All procedures were performed by experienced, nationally accredited BSCP endoscopists, who had carried out >5000 colonoscopies and had cecal intubation rates of >90%.
Result: 534 patients were recruited from Sep 2014 to Sep 2015. 3 were excluded due to new diagnosis of polyposis syndrome, to avoid skewing of results. 531 were included and randomised to the 2 study arms. No significant difference was seen between the 2 groups for the primary endpoint of number of polyps per patient. Secondary endpoints: No significant difference was observed between the 2 groups for adenoma detection rate (ADR) or number of adenomas per patient (Table 1). Endpoints were also evaluated separately for: screening group, surveillance group, and the individual 4 endoscopists. In all these analyses, no significant difference was found between the 2 study arms for any of the study endpoints. No significant adverse events were encountered during the study in either arm. The cecal intubation time was not prolonged and patients did not experience any additional discomfort due to the Endocuff Vision.

Table 1: E-CAP results

	Standard	Endocuff	
Patients	265	266	
Polyps	470	436	
Polyps/patient	1.77	1.64	p = 0.441
Adenomas	359	336	
Adenomas/patient	1.35	1.26	p = 0.536
PDR	185/265 = 69.8%	187/266 = 70.3%	p = 0.925
ADR	167/265 = 63%	162/266 = 60.9%	p = 0.851
Cancer detection rate	15/265 = 5.7%	14/266 = 5.3%	p = 0.851

Conclusion: In the UK, bowel cancer screening is performed by highly experienced endoscopists with special accreditation. Our results suggest that in expert hands, ADR exceeds 60% even without Endocuff. In such settings, Endocuff Vision did not improve polyp detection rates (PDR) or ADR. However, Endocuff did not cause any adverse events, prolong procedure duration or cause additional discomfort. These data demonstrate the safety and feasibility of Endocuff. However, no additional gain was demonstrated in expert hands.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP374 INCREASED ADENOMA DETECTION RATE BY G-EYE HIGH DEFINITION COLONOSCOPY IN COMPARISON TO STANDARD HIGH DEFINITION COLONOSCOPY- A PROSPECTIVE RANDOMIZED MULTICENTRE STUDY

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Introduction: Colorectal cancer (CRC) detection is attributed to the early detection and removal of polyps and adenomas during colonoscopy procedures. Although colonoscopy is considered to be the ''gold standard'' for CRC prevention, a significant number of polyps and adenomas go undetected during standard procedures. This is largely due to polyps that are hidden behind colonic folds that obscure endoscopic optics and result in interval cancers. The G-EYE endoscope (Smart Medical Systems Ltd., Ra'anana, Israel) comprises a standard forward-viewing endoscope with a permanently integrated balloon at the distal end. Upon withdrawal of the endoscope, the G-EYE balloon is inflated to a partial pressure allowing for the flattening of haustral folds, centralization of the endoscope optics, and reduction in bowel slippage, thus providing improved visualization of the colon anatomy and increased detection of polyps and adenomas.
Aims & Methods: This prospective, randomized, multicentre study compares the adenoma detection rate (ADR) of the G-EYE HD colonoscopy with that of standard HD colonoscopy (SC). Patients (age > 50) referred to colonoscopy for screening, surveillance, following positive FOBT, or due to change in bowel habits were randomized to either G-EYE colonoscopy or SC. Detected polyps were removed and sent for pathology. Polyp and adenoma detection rates were calculated.
Result: 480 patients were enrolled in the study, of which 238 subjects were randomized to SC and 242 subjects were randomized to G-EYE™ colonoscopy. Baseline parameters and indication for colonoscopy were similar in both groups. The ADR, adenoma per patient, number of adenomas by size and advanced adenomas for each group are presented in Table 1. G-EYE colonoscopy improved ADR by 45.6% when compared to SC. More specifically, the G-EYE endoscope increased the number of advanced adenomas and large-size adenomas by 96.9% and 96.2%, respectively. Procedural times were similar in both groups.

Table 1: Results Summary

	SC	G-EYE	% Increase
ADR	33.8%	49.2%	45.6%
Adenoma per patient	0.57	0.93	63.2%
Diminutive adenomas (2–5 mm)	67	105	56.7%
Small adenomas (6–9 mm)	19	26	36.8%
Large adenomas (≥10 mm)	26	51	96.2%
Advanced adenomas	32	63	96.9%

Conclusion: Our study shows that the G-EYE endoscope can substantially improve ADR when compared to SC. In addition to diminutive and small adenomas, the G-EYE endoscope detects a larger number of advanced and large-size adenomas. Consequently, we conclude that the G-EYE endoscope can significantly enhance the quality of CRC screening and thus reduce colonoscopic miss rates and interval cancer incidents.
Disclosure of Interest: H. Jacob: Board of directors
All other authors have declared no conflicts of interest.

OP375 EFFICACY AND SAFETY OF THE NOVEL 1L PEG AND ASCORBATE BOWEL PREPARATION NER1006 VERSUS TRISULFATE SOLUTION IN OVERNIGHT SPLIT-DOSING ADMINISTRATION: RESULTS FROM THE PHASE 3 STUDY NOCT

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Introduction: Successful colon cleansing enables effective colonoscopy. PEG based split dosing preparations are traditionally seen as the gold standard in cleansing, but many still require a high preparation volume intake. NER1006 is the first 1L PEG3350 and ascorbate bowel preparation in phase 3 clinical development. The low volume of NER1006 is achieved through the use of ascorbate in the second dose only.
Aims & Methods: This phase 3, randomised, multicentre, colonoscopist-blinded, non-inferiority study assessed the efficacy, safety and tolerability of a 2-day overnight split-dosing regimen of either NER1006 (N2D) or trisulfate solution (TS) in patients undergoing colonoscopy. Two alternative primary endpoints were evaluated: overall bowel cleansing success and 'Excellent plus Good' cleansing rate in the colon ascendens using the Harefield Cleansing Scale (HCS). Secondary endpoints included hierarchical evaluation of lesion detection rates (key), and cleansing assessment using the Boston Bowel Preparation Scale (BBPS; supportive). Patient tolerability, acceptability and compliance were assessed using questionnaires. Safety was monitored through adverse events and clinical laboratory evaluation. The threshold for statistical significance in this study was $P < 0.025$. The confidence interval (CI) for the difference between the groups used a 10% margin to demonstrate non-inferiority vs. TS.
Result: Patients were randomised to receive either N2D (n = 310) or TS (n = 311). For N2D and TS, respectively, the mean age (SD) was 57.7 (10.36) and 57.3 (10.56) years. The distribution of males vs. females was 158 (51.0%) vs. 152 (49.0%) for N2D and 169 (54.3%) vs. 142 (45.7%) for TS. High successful overall bowel cleansing efficacy was achieved in both treatment groups (Table 1). N2D demonstrated non-inferiority (lower CI limit ≥ −10%) to TS for both alternative primary endpoints. Numerically, more patients on N2D achieved an 'Excellent plus Good' cleansing rate in the colon ascendens compared with TS. Non-inferiority for N2D in adenoma detection rate in the colon ascendens was not demonstrated; other key secondary endpoints were not formally tested. Tolerability and acceptability as assessed by the Bowel Cleansing Impact Review (BOCLIR) Questionnaire were comparable for N2D and TS (Table 1). Compliance rates were high in both treatment groups. There were no deaths. NER1006 was not associated with any serious treatment-emergent adverse events (TEAEs). The most frequently reported related TEAEs in both treatment groups were nausea and vomiting.
Conclusion: When administered as a 2-day split dosing regimen, and compared to trisulfate solution, NER1006 was non-inferior in overall bowel cleansing success and in achieving an 'Excellent plus Good' cleansing rate in the colon ascendens. Both treatments were well tolerated; most TEAEs were mild or moderate in severity and reflected the expected safety profile of respective treatments. The

Table 1 (OP375): Efficacy and safety endpoints

Abstract legend	NER1006 2-day split-dosing N2D	Comparator: trisulfate solution TS	CI for the difference [P value] N2D vs. TS
EFFICACY	Primary analysis set, n = 276	Primary analysis set, n = 280	
Primary endpoint: Patients with successful overall bowel cleansing efficacy (HCS) [n]	235 (85.1%)	238 (85.0%)	−8.15%* [0.528]
Supportive secondary endpoint: Patients with successful overall bowel cleansing efficacy (BBPS) [n]	228 (82.6%)	227 (81.1%)	n.a.
Primary endpoint: Excellent plus Good cleansing rate in colon ascendens [n]	99 (35.9%)	82 (29.3%)	−1.69%* [0.059]
Key secondary endpoint: Adenoma detection rate, colon ascendens	14.1%	17.1%	−11.36%, 5.28%** [0.863]
Key secondary endpoint: Adenoma detection rate, overall colon	33.7%	35.0%	n.a.
Key secondary endpoint: Polyp detection rate, colon ascendens	18.5%	23.9%	n.a.
Key secondary endpoint: Polyp detection rate, overall colon	45.7%	48.6%	n.a.
Compliance rate (min 75% of both doses taken) [n]	255 (92.4%)	255 (91.1%)	n.a.
BOCLIR score [mean (SD)]	39.9 (17.70)	39.6 (17.51)	n.a.
SAFETY	Safety set, n = 262	Safety set, n = 265	
All treatment-emergent adverse events [n]	118	67	n.a.
Patients with any related treatment-emergent adverse event [n]	39 (14.9%)	25 (9.4%)	n.a.

* = 97.5% 1-sided CI; ** = 95% 2-sided CI; n.a. = not applicable

1L NER1006 showed high efficacy and safety in overnight split-dosing administration.

Disclosure of Interest: M. DeMicco: Contractor for Norgine through Anaheim Clinical Trials LLC; Principal Investigator for the NOCT study.
L.B. Clayton: Employee of Norgine
R. Ng Kwet Shing: Employee of Norgine
M.S. Epstein: Contractor for Norgine through Investigative Clinical Research. Investigator for the NOCT study.

OP376 THE USE OF A SELF-EXPLANATORY BOOKLET FOR BOWEL PREPARATION WITHOUT ORAL INSTRUCTIONS OVERCOMES BARRIERS AGAINST SPLIT-DOSE ADOPTION FOR EARLY MORNING COLONOSCOPY: A RANDOMIZED CONTROLLED TRIAL

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Introduction: Split-dose cleansing regimen for colonoscopy is recommended over day-before preparation by practice guidelines and it has been shown to increase the adenoma detection rate. Nevertheless, the compliance with split-dose prescription for early-morning colonoscopy (8–10 am) is poor [1].

Aims & Methods: Present randomized study was aimed at evaluating weather the addition of oral instructions to a self-explanatory booklet for bowel preparation increases compliance with split-dose. We prospectively enrolled consecutive 50–70 yr-old outpatients undergoing screening colonoscopy from 8:00 to 10:00 am. Exclusion criteria were inability to provide consent and contraindications to the preparation adopted in the study. All patients received a low-volume preparation. We designed a dedicated booklet underlying the advantages of split-dose regimen including: 1. reduction of the risk of missing neoplastic lesions; 2. improvement of colon cleansing and lower risk of rescheduling the procedure; 3. increase of bowel prep tolerability; 4. reduction in procedure duration. Day-before preparation was left as an alternative and discouraged, secondary option. In order to evaluate whether additional oral explanation, aimed at reinforcing the benefits of split-dose, may further improve compliance, patients were randomized in two groups: group A-only booklet delivered; group B-oral explanation along with booklet. Patients' data (demography, education, socioeconomic status), along with prep-related and procedural data, were collected by a structured questionnaire on colonoscopy day. Colon cleansing was evaluated by Boston Bowel Preparation Scale (BBPS). Proportions were compared by chi-squared test or chi-squared for trend, as appropriate. A logistic regression analysis was performed to disclose factors associated with compliance to split-dose prescription. A p-value <0.05 was considered significant for all comparisons.

Results: During the study period (January–April 2016), 286 patients were enrolled (mean age 59.8 ± 7, males 53.7%), 143 in group A and 143 in group B; of them 266 have undergone colonoscopy (group A: 130, group B: 136). The two groups were well balanced as concerns age, gender, education, employment and marriage status. Split-dose was adopted by 106/130 and by 118/136 patients in group A and B, respectively (81.5% vs 86.8%, p = 0.317). Among patients who complied with split-dose the quality of bowel cleansing was adequate (BBPS > 2 in each segment of the colon) in 215/224 (96.0%). No significant differences between group A and B were observed with regards to adherence to preparation scheme, which were both optimal, (98.1% vs 97.5%, p = 0.693) and to the adequacy of bowel prep (BBPS > 2 in each segment) (97.2% vs 94.9%, p = 0.785). No variable was significantly associated with split-dose uptake at logistic regression analysis.

Conclusion: Present data show an excellent compliance with split-dose prescription for early morning colonoscopy in both written only and oral and written instruction groups, leading to very satisfactory levels of colon cleansing. This finding underlines that the adoption of a self-explanatory booklet clearly describing the benefits of split-dose marginalizes the need of additional oral instructions. This result is relevant in an open-access system, where routine oral education is unfeasible, and does not support ESGE indications, which recommend both oral and written explanation by healthcare professionals.

Disclosure of Interest: All authors have declared no conflicts of interest.

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WEDNESDAY, OCTOBER 19, 2016 10:30–12:00

BURDEN OF LIVER DISEASE – ROOM L7

OP377 THE BURDEN OF OVERT AND OCCULT LIVER CIRRHOSIS IN PATIENTS WITH METABOLIC SYNDROME: ANALYSIS FROM A LARGE GENERAL PRACTITIONERS DATABASE

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Introduction: Liver cirrhosis represents the end stage of chronic liver disease, characterized by high mortality and morbidity (1,2) with relevant health and social costs (3). Metabolic syndrome represents one of the major risk factors of liver disease in western countries (4). The real prevalence of this condition is difficult to assess, since liver disease is silent until clinical decompensation of cirrhosis occurs.

Aims & Methods: The aim of this study was to estimate the prevalence of occult liver disease in the Veneto region and to compare the results with the burden of patient with overt diagnosis in the same geographic area. For the epidemiological analysis the MilleinRete dataset was used, where medical records of 139,104 subjects were stored by 99 general practitioners in the Veneto region. As indicators, transaminases elevation (>2 nv in at least two occasions) for liver disease and thrombocytopenia (<120,000 μ/L) for liver cirrhosis were used. Patients with thrombocytopenia due to hematologic disorders were excluded. Prevalence of patients with already diagnosed chronic hepatitis, cirrhosis and comorbidities was assessed using ICD9-CM-1997 codes.

Result: Among 11.540 patients with elevated transaminases, 35% were already diagnosed as patients with liver disease of known etiology (viral hepatitis, alcohol abuse or hepatic steatosis), while in the remaining 65% no liver disease diagnosis

was recorded. Sex distribution of these patients was similar to that of the patients without liver enzymes alteration (M/F:0.91 vs 0.9, respectively), while age was higher in patients with elevated transaminases [mean age (yrs) = 55.5 vs 48.9, $p < 0.0001$]. Patients with overt diagnosis of cirrhosis were 0.3% of the overall population, while thrombocytopenia, as indicator of occult cirrhosis, was detected in 1.3% of the remaining patients. The epidemiological profile of these two groups was similar [M/F:1.59; mean age (yrs) = 65.6 vs M/F:1.67; mean age (yrs) = 65, p = ns], but significantly different ($p < 0.0001$) compared to the normal population and to subjects with only liver enzyme alterations. Patients with occult and overt cirrhosis presented a similar prevalence of metabolic syndrome profile (49% and 56% respectively), while these figures were lower in patients without signs of liver disease (33%, $p < 0.0001$).
Conclusion: In conclusion, a large proportion of patients with biochemical signs of chronic hepatitis and cirrhosis are still undiagnosed. Metabolic syndrome seems to be the major risk factor that characterizes patients with more severe liver disease.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP378 THE NATIONAL BURDEN IN FRANCE OF HOSPITAL CARE FOR PATIENTS WITH HEPATIC ENCEPHALOPATHY: DATA FROM THE FRENCH NATIONAL HOSPITAL DATABASE (PMSI)

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Introduction: Hepatic encephalopathy (HE) is a complication of cirrhosis characterized by a broad spectrum of neuropsychiatric manifestations. According to the clinical symptoms there are two types of HE: covert HE and overt HE (OHE). In general, the prevalence of OHE is estimated at 10%–14% in cirrhotic patients and at 10%–50% in patients with transjugular intrahepatic portosystemic shunt (TIPS). In France, the prevalence of OHE was estimated at 25,000 patients (21,000 to 30,000 patients). Yet little is published on the national burden of hospitalisation of patients with hepatic encephalopathy. The first objective of this study was to use the retrospective national PMSI data (Programme Médicalisé des Systèmes d'Information) to assess the public health burden of hospitalisations for OHE, documenting its incidence rate but also to analyse the characteristics of hospitalisations. The second objective was to study the factors independently associated with length of stay in patients with HE.
Aims & Methods: A retrospective cohort was performed from the national PMSI database from 2012 and 2013. Given the absence of coding specificity of hepatic encephalopathy via ICD 10 code "K72 *" Hepatic failure, not elsewhere classified", an algorithm of patients hospitalised for HE was implemented according to a medical expertise from the expression of the main symptoms of the disease. A negative binomial regression model was used to estimate the link between lengths of stay and HE patient's characteristics like age, sex, comorbidities (malnutrition, renal failure, bacterial infection and respiratory diseases), stays in reanimation, intensive care units and death.
Result: The study collected respectively 13,484 patients on 2012 corresponding to 17,001 hospitalisations and 13,672 patients in 2013 corresponding to 17,491 hospitalisations. The mean age was 63.1 ± 13.8 years in 2013 and 62.7 ± 13.9 years in 2012. Thirty percent of patients were admitted to the intensive care units. In nearly all hospital stays, the illness was medically managed (87% of stays in 2013 and 89% in 2012). Nevertheless, there are 12% of surgical stays (1,664 stays in 2013 and 1,514 stays in 2012). The mean length of HE stay was 15 days (SD 19 days) and the median was 10 days. The length of stay was 48% longer for patients with malnutrition, and 52% longer in case of a bacterial infection. The length of stay was 12% and 14% longer for patients with renal failure and respiratory diseases, respectively. More 40 million euros per year are spent by Social Security in France for HE hospitalisations with a mean cost per hospital admission estimated at €5,535 (± SD €6,411).
Conclusion: The mean length of stay in patients with HE was high (15 ± 19 days). The binomial model confirmed the significant longer length of stay induced by patients with comorbidity such as malnutrition, renal insufficiency, bacterial infection and respiratory disease. The annual economic burden of HE hospitalisations in France amounted to €40 million.
Disclosure of Interest: H. Hagege: Herve Hagege has acted as a medical expert for Norgine and Alfa Wassermann
R. Benamouzig: Robert Benamouzig has acted as a medical expert for Norgine and Alfa Wassermann
C. Bureau: Cristophe Bureau has acted as a medical expert for Norgine and Alfa Wassermann
C. Blein: Cécile Blein is an employee of HEVA, who were contracted by Norgine and Alfa Wassermann to participate in this study.
C. Amaz: CAMILLE Amaz is an employee of HEVA, who were contracted by Norgine and Alfa Wassermann to participate in this study.
E. Ribot-Mariotte: Emmanuelle Ribot-Mariotte was an employee of Alfa Wassermann at the time the study was undertaken.
I. Leurs: Irina Leurs was an employee of Norgine at the time the study was undertaken.
All other authors have declared no conflicts of interest.

OP379 THE IMPACT OF RIFAXIMIN-ALPHA ON NHS HOSPITAL RESOURCE USE IN UK PATIENTS WITH HEPATIC ENCEPHALOPATHY: A RETROSPECTIVE OBSERVATIONAL STUDY (IMPRESS)

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Introduction: In clinical trials rifaximin-α (RFX) has been shown to reduce the risk of an overt episode of hepatic encephalopathy (HE) and the number of HE-related hospitalisations, but there are limited data describing its impact on healthcare resource use in real-world UK practice. This study compared hospital resource use pre- and post-RFX initiation in UK patients.
Aims & Methods: A retrospective observational study in 11 specialist National Health Service (NHS) centres of 145 patients prescribed RFX for HE between July 2008 and May 2014. Local clinical staff reviewed patients' medical records for demographics, RFX prescribing and adverse drug reactions (ADRs) to RFX. Details of inpatient hospitalisations and hospital visits in the 12 months pre- and post-RFX initiation were extracted from NHS Trust electronic databases. Ethics reference 14/WS/1017.
Results: Of the 145 patients evaluated, 89 (61%) were male. At RFX initiation, mean age was 61 years (standard deviation [SD] = 11), 119 patients (82%) were on lactulose. Child-Pugh score was recorded for 67 (46%) patients (10% Class A, 54% B, 36% C). Resource use in the 6/12 months pre- and post-RFX initiation is shown in Table 1; to avoid nonsurvivor confounding this analysis includes the 114 patients (78%) who were alive at 6 months and 102 (70%) alive at 12 months post-RFX initiation. 3 patients (2%) had ADRs and 4 (3%) developed C.difficile infection (none of whom discontinued treatment).
Conclusion: In UK clinical practice, treatment with RFX for HE is well-tolerated and associated with significant reductions in hospitalisation frequency, bed occupancy (including critical care) and emergency room visits; reductions are observed within 6 months of treatment initiation and sustained at 12 months. This is the first study to demonstrate a reduction in critical care bed occupancy with RFX.
Disclosure of Interest: R. Aspinall: Consultant and UK advisory board member for Norgine
A. Radwan: Employee of Norgine
G. Shaya: Employee of Norgine
H. Sodatonou: Employee of Norgine
R. Cipelli: Consultant for Norgine. Employee of pH Associates which was commissioned by Norgine Pharmaceuticals to provide support with study design and management, data analysis and scientific editorial services.
M. Hudson: Consultant for Norgine. Attended advisory board and has given sponsored lectures (national or international) on behalf of Norgine.

Table 1 (OP379): All-cause resource use pre- and post-RFX initiation

	6 months (n = 114)				12 months (n = 102)			
	Mean (SD)	n*	Pre-RFX	Post-RFX	P	n*	Pre-RFX	Post-RFX	P
	Hospitalisations with overnight stay per patient	101	2.2 (1.9)	1.0 (1.3)	<0.001	99	2.7 (2.8)	1.7 (2.0)	0.002
	Total bed days	101	2890	1206	-	99	3138	1621	-
Total bed days per inpatient	101	28.6 (31.4)	11.9 (23.2)	<0.001	99	31.7 (35.9)	16.4 (29.1)	<0.001	
Critical care bed days per inpatient	19	7.9 (10.1)	2.0 (5.1)	0.046	18	11.3 (11.8)	2.4 (6.0)	0.017	
Emergency room visits per patient	63	1.9 (2.3)	1.0 (1.0)	<0.001	65	2.4 (3.4)	1.8 (2.6)	0.099	

OP382 PREGNANCY OUTCOME IN MORE THAN 5000 BIRTHS TO WOMEN WITH VIRAL HEPATITIS IN A POPULATION-BASED COHORT STUDY IN SWEDEN

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Introduction: Previous studies have shown inconsistent results with respect to hepatitis B (HBV), Hepatitis C (HCV) and pregnancy outcome.
Aims & Methods: The aim of this study was to investigate pregnancy outcome in women with HBV or HCV. In a nationwide cohort of pregnancies between 1997 and 2011 we investigated the risks of adverse pregnancy outcomes in 3 077 births to women with HBV and 2 150 births to women with HCV using data from Swedish healthcare registries. Births to women without HBV (n = 1 428 238), and births without HCV (n = 1 429 165) served as population controls. Crude and adjusted relative risks (RR) were calculated using Poisson regression analysis.
Results: Women with HCV were more likely to smoke (47.62% vs. 8.65%) and to have alcohol dependence (18.79 vs. 1.07) compared with population controls. Most women with HBV were born in non-Nordic countries. HCV was associated with a decreased risk of preeclampsia (aRR: 0.42, 95% CI: 0.25–0.65), an increased risk of late neonatal death (7–27 days: aRR: 4.47, 95% CI: 1.01–12.44) and an increased risk of preterm birth (aRR: 1.31, 95% CI: 1.08–1.59). HBV was associated with an increased risk for preterm birth (aRR: 1.21, 95% CI: 1.01–1.44).
Conclusion: Both HBV and HCV are risk factors for preterm births, while HCV seems to be associated with a protective effect against preeclampsia. Future studies should corroborate these findings.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30–12:00
TRANSLATIONAL ASPECTS OF IBD – ROOM L8

OP383 ALTERATION OF THE RENIN-ANGIOTENSIN SYSTEM IN THE CIRCULATION, TERMINAL ILEUM AND COLON IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A POTENTIAL NOVEL THERAPEUTIC TARGET

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Introduction: The renin-angiotensin system (RAS) has well-recognised roles in cardiovascular and renal homeostasis, but may also regulate inflammation, fibrosis and angiogenesis in multiple other organs, including the gastrointestinal tract. The recently recognised alternative RAS axis comprising angiotensin converting enzyme 2 (ACE2), the effector peptide angiotensin (Ang) (1–7) and the Mas receptor, mediate anti-inflammatory and anti-fibrotic effects as opposed to the classical axis comprising ACE, Ang II and the AT1 receptor. This study aimed to prospectively characterise the RAS in the circulating and intestinal compartments in patients with inflammatory bowel disease (IBD) and non-IBD controls.
Aims & Methods: Circulating components of the RAS were measured in patients with Crohn's disease (CD), ulcerative colitis (UC) and non-IBD controls, and associations with markers of disease activity evaluated. Terminal ileum, ascending and sigmoid colon from patients undergoing intestinal resection and colonoscopy were surveyed for these components by mRNA expression by qRT-PCR, and immunohistochemical localisation and semi-quantification of particle density using microscope image processing software. ACE2 activity was measured in biopsy samples.
Results: 56 patients with CD (mean age 41 [range 21–76] y, 27 females), 45 with UC (44 [22–82] y, 19 females) and 39 non-IBD controls (46 [22–83] y, 21 females) were studied. No significant differences in demographic features were noted across the three groups. Circulating renin (mean 25.4 (95% CI 21.6–29.1) vs 18.6 (13.9–23.3) mIU/L, p = 0.026), ACE2:ACE ratio (mean 0.61 (95% CI 0.48–0.75) vs 0.40 (0.32–0.47), p = 0.028) and Ang (1–7) (mean 22.8 (20.1–25.4) vs 14.1 (10.8–17.4) pg/ml, $p < 0.001$) were higher, and ACE and Ang II similar in participants with IBD compared with controls. No significant correlations between circulating RAS components and markers of disease activity (faecal calprotectin, C-reactive protein, platelet or white cell counts, or albumin) were noted. Amongst patients undergoing colonoscopy (20 CD, 15 UC, 14 non-IBD controls) and intestinal resection (5 each with CD, UC and non-IBD), angiotensinogen, renin, ACE, ACE2, Ang II, Ang (1–7), AT1R, AT2R and Mas receptor were identified by qRT-PCR and/or immunohistochemistry in healthy and diseased bowel, with significantly higher gene expression of angiotensinogen (3–4 fold), ACE (30–40 fold) and ACE2 (10 fold) expressed in the terminal ileum than colon ($p < 0.0001$ for all). RAS components were consistently localised to the epithelium; variably in the lamina propria and submucosa, especially microvascular endothelium; and circular muscle myocytes. Expression of mRNA of angiotensinogen was two-fold higher in inflamed IBD and non-inflamed IBD or non-IBD control colonic segments ($p < 0.001$, Kruskall-Wallis); immunohistochemical staining intensity for ACE2 was higher in the colon in patients with CD (p = 0.002), and that for Ang (1–7) lower (p = 0.001) in the colon in patients with IBD than non-IBD controls. Staining intensity of Mas receptor was higher in non-inflamed colon in patients with IBD than in inflamed colon or healthy control tissue (p = 0.045, Kruskall-Wallis).
Conclusion: All of the components of the classical and alternative RAS pathways are present in healthy intestinal tissue suggesting a role in normal physiology, especially in epithelial cells. Circulating and mucosal components of the alternative RAS axis are upregulated in patients with IBD, but mucosal Ang (1–7) is reduced, suggesting dysregulation and a potential role of the RAS in pathogenesis or perpetuation of inflammation in IBD. Novel therapies that increase mucosal Ang (1–7) may have a role in IBD.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP384 BLOCKADE OF AEB7 INTEGRIN CONTROLS TRAFFICKING OF CD8+ AND TH9 LYMPHOCYTES FROM IBD PATIENTS TO THE INFLAMED GUT IN VIVO

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Introduction: The anti-α4β7 antibody vedolizumab (VDZ), which inhibits gut homing of lymphocytes via interaction of α4β7 with MAdCAM-1, has greatly increased therapeutic options in patients with IBD. However, lymphocyte homing may also occur via other homing molecules like the α4β1 integrin[1] and a considerable portion of patients does not respond to VDZ therapy[2]. The anti-β7 antibody etrolizumab[3] (ETZ) is currently tested in phase III trials and additionally blocks the binding of αEβ7 to E-Cadherin, which is believed to mediate epithelial retention of homed lymphocytes[4].
Aims & Methods: We aimed to compare lymphocyte trafficking upon blockade of β7 vs. α4β7 integrin. Hence, α4β7 and αEβ7 expression was determined on peripheral blood and lamina propria lymphocyte subsets of UC and CD patients and healthy donors by flow cytometry or immunofluorescence staining, respectively. The regulation of αEβ7 expression upon lymphocyte stimulation and incubation with cytokines was studied. In in vitro adhesion assays the adhesive capacities of lymphocytes to MAdCAM-1 and E-Cadherin and the inhibitory potential of VDZ and the ETZ surrogate antibody FIB504 (ETZs) were tested. Finally, lymphocytes from UC patients were treated with either of the compounds, fluorescence labelled and injected into the ileocolic artery of immunosuppressed mice. Gut homing was assessed by in vivo confocal microscopy and flow cytometry of lamina propria cells.
Results: AEβ7 expression was significantly higher on $CD8^+$ lymphocytes than on $CD4^+$ lymphocytes both in the peripheral blood and the gut. Among both subsets αEβ7 expression was correlated with IL-9 secretion, while $CD4^+IL9^+$ cells expressed less α4β7 than other $CD4^+$ subsets. At the same time, $CD8^+$ cells exhibited a notably greater potential to increase αEβ7 expression upon T cell receptor stimulation and TGF-β treatment, while butyric and retinoic acid decreased αEβ7 expression on $CD8^+$ cells. ETZs markedly inhibited binding of $CD4^+$ and $CD8^+$ lymphocytes to rhE-Cadherin and blocked the adhesion of $CD4^+$ and $CD8^+$lymphocytes to rhMAdCAM-1 to a degree comparable with VDZ. Fewer lymphocytes bound to a mix of both ligands upon treatment with ETZs compared with VDZ. In our humanized mouse model the portion of human $CD8^+$ cells in the murine gut was significantly reduced three hours after injection when cells were treated with ETZs vs. VDZ. Among $CD4^+$ cells, the fraction of $PU.1^+$ cells was decreased. The expression of αEβ7 on $CD8^+$ cells from IBD patients treated with VDZ was higher in the maintenance than in the induction phase of treatment.
Conclusion: VDZ may not equally cover all pathogenetically relevant lymphocyte subsets leading to insufficient therapeutic response in predisposed patients. ETZ seems to offer superior reduction of intestinal lymphocyte infiltration especially concerning $CD8^+$ and Th9 cells.
Disclosure of Interest: S. Zundler: The etrolizumab Surrogate antibody was provided by Genentech, San Francisco, CA, USA. The company was neither involved in conception and design of the study nor in analysis and interpretation of the results. SZ received funding from Takeda.

M.F. Neurath: M.F.N. has served as an advisor for Abbvie, MSD, Boehringer, Takeda, Pentax and Giuliani.
All other authors have declared no conflicts of interest.

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OP385 VITAMIN D REGULATES DENDRITIC CELL ACTIVITY AND TRAFFICKING IN CROHN'S DISEASE

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Introduction: Dendritic cells (DC) can determine whether the mucosal immune system mounts an inflammatory or regulatory response to antigen and likely contributes to the pathogenesis of Crohn's disease. Vitamin D down-regulates DC inflammatory responses and could prove beneficial as a treatment adjunct in Crohn's. Vitamin D also modulates DC homing marker expression. This study assessed the effect of high dose parenteral vitamin D treatment on circulating DC phenotype and function in patients with active luminal Crohn's disease receiving anti-TNFα therapy.
Aims & Methods: Peripheral blood mononuclear cells were isolated from 14 patients with active luminal Crohn's disease and suboptimal vitamin D levels (< 75 nmol/L) prior to and 6 weeks after starting anti-TNFα (infliximab) therapy. Patients with low vitamin D (< 50 nmol/L) were also given a single high dose of parenteral vitamin D (300,000 international units $1,25(OH)_2$vitamin D3). Flow cytometry was used to identify total DC, ($HLA\text{-}DR^+$ cells negative for markers of other cell lineages (CD3, CD14, CD16, CD19 & CD34)). DC were further subtyped as myeloid (mDC, $CD11c^+CD123^-$) and plasmacytoid (pDC, $CD123^+CD11c^-$). Expression of phenotypic markers (including maturation and homing markers and pattern recognition receptors) and on-going intracellular DC cytokine production during 4 hours' culture were assessed.
Results: Production of TNFα by myeloid DC was significantly reduced ($p = 0.016$) in those patients who received vitamin D alongside anti-TNFα therapy, beyond that of those who received anti-TNFα therapy alone (mean post-treatment expression of TNFα 24.9% v 39.1% respectively). There was a significant correlation between increase in vitamin D level and decrease in TNFα production by myeloid DC ($p = 0.025$; $R^2 = -0.76$). An increase of serum 25(OH)vitamin D greater than 20 nmol/L was associated with a decrease in myeloid DC TNFα production. Anti-TNFα therapy alone induced a significant upregulation of the skin homing marker cutaneous lymphocyte antigen (CLA) on myeloid DC ($p = 0.0055$), an effect which was not seen in patients receiving adjunctive vitamin D.
Conclusion: High dose parenteral vitamin D, given as an adjunct to anti-TNFα therapy in Crohn's, promotes down-regulation of circulating myeloid DC production of TNFα. This may influence the subsequent interaction of DC and T cells. TNFα promotes a TH-17 response characteristic of Crohn's inflammation; thus the ability of vitamin D to further block TNFα production may promote a more regulatory T cell response and improve outcomes when used as an adjunct to anti-TNFα therapy. The upregulation of the skin homing marker CLA following anti-TNFα therapy may explain the high rates of cutaneous side effects to this drug class. The down-regulation of CLA by vitamin D in this setting may be clinically useful in those patients suffering cutaneous sequelae of anti-TNFα therapy.
Disclosure of Interest: P. Hendy: Advisory board: DrFalk; AbbVie
All other authors have declared no conflicts of interest.

OP386 CIRCULATING DENDRITIC CELL SUBSETS IN CROHN'S DISEASE SHOW ALTERATIONS IN TISSUE HOMING AND CYTOKINE PRODUCTION

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Introduction: Crohn's disease is characterised by an exaggerated immune response to mucosal antigen. Dendritic cells (DC) are the primary antigen presenting cells and may promote either tolerogenic or inflammatory T cell responses to mucosal antigens. DC are also capable of imprinting tissue specific homing markers on T cells which direct T cell migration to sites including the skin, gut and lymphoid tissue. We characterised homing marker profile and ongoing cytokine production of circulating DC subsets from patients with Crohn's disease and from healthy controls.
Aims & Methods: DC within peripheral blood mononuclear cells from adults with active luminal Crohn's disease or from healthy controls were characterised using flow cytometry. DC were identified as $HLA\text{-}DR^+$ and negative for markers of other cell lineages (CD3, CD14, CD16, CD19, CD34). Myeloid DC (mDC, $CD11c^+CD123^-$) and plasmacytoid DC (pDC, $CD11c^-CD123^+$) were assessed for phenotype (maturation status, homing markers and pattern recognition receptors) and on-going cytokine production by surface and intracellular staining, respectively.
Results: In patients with Crohn's disease ($n = 20$), a greater proportion of myeloid DC expressed a gut-homing profile ($CLA^-\beta7^+$, $p = 0.0011$) compared to healthy controls ($n = 13$) where most myeloid DC were not tissue-specific ($CLA^+\beta7^+$, $p = 0.0016$). In both Crohn's and controls, myeloid DC were largely gut-homing ($CLA^-\beta7^+$, $p = 0.001$) whilst plasmacytoid DC were strongly skin ($CLA^+\beta7^-$) and lymph node ($CCR7^+$) homing ($p < 0.0001$). Production of pro-inflammatory cytokines was up-regulated in Crohn's, with myeloid DC producing higher levels of TNFα and plasmacytoid DC producing higher levels of IL-6 than controls ($p = 0.0042$ and $p = 0.013$ respectively). Expression of maturation marker CD86 was increased on myeloid DC in Crohn's but not on plasmacytoid DC ($p = 0.027$ and $p = 0.13$ respectively). Expression of IFN-α, Il-1β, Il-12, CD40, CD80, TLR2 and TLR4 on DC did not differ between Crohn's and controls for either DC subset.
Conclusion: The increased myeloid DC expression of gut homing phenotype markers and production of TNFα in Crohn's disease compared with controls highlights the central role that this dendritic cell subset plays in the pathogenesis of Crohn's disease. Differences between homing markers on myeloid DC (gut homing) and plasmacytoid DC (skin homing) suggest that they may have different roles in different manifestations of Crohn's, with myeloid DC being central to gut inflammation whilst plasmacytoid DC might be involved in cutaneous Crohn's disease and the skin sequelae of anti-TNFα therapy.
Disclosure of Interest: P. Hendy: Advisory board for: Falk, AbbVie
All other authors have declared no conflicts of interest.

OP387 A PROTEOMIC APPROACH TO EXPLORE THE PROTECTIVE ROLE OF INULIN IN PREVENTING LPS-INDUCED HUMAN COLONIC SMOOTH MUSCLE IMPAIRMENT

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Introduction: Fructans, such as inulin, are dietary fibers which stimulate gastrointestinal function acting as prebiotics. We recently demonstrated the protective effect of inulin on LPS-induced damage of colonic smooth muscle in an ex vivo experimental model, which seems to be related to presence of oxidative stress.
Aims & Methods: In the present study, the protective role of inulin against LPS-induced oxidative stress was evaluated on colonic mucosa using a proteomic approach. Human colonic mucosa and submucosa, obtained from disease-free margins of resected segments for cancer, were sealed between two chambers containing Krebs solution, with the luminal side of the mucosa overlayed with 5 ml of Krebs, or 100 μg/mL LPS solution, or 100 μg/mL LPS +100 mg/mL inulin Fructafit IQ (LPS + INU). The biological system was kept oxygenated for 30 min at 37°C. The solutions on the submucosal side were collected following mucosal exposure to Krebs in the absence (N-undernatant) or presence of LPS (LPS-undernatant) or LPS + inulin (LPS + INU-undernatant). Undernatants were tested for the effects on human colonic smooth muscle strips contractility using an organ bath system. Proteomic analysis (iTRAQ based analysis) was used to separate and compare the total soluble proteomes from human colonic mucosa and submucosa treated. Each sample was labelled by one of four reagents of the iTRAQ 4-plex and then combined into one aliquote. Triplicate labelling was performed, which showed a high level of reproducibility.
Results: Inulin exposure was able to restore, in human colonic mucosa, the LPS-dependent alteration of some proteins involved in the host response and in the intestinal smooth muscle contraction (ZG16, CALM1/MLCK/MYL signaling pathway) and to reduce the upregulation of two proteins involved in the radical-mediated oxidative stress induced by LPS (APEX1, CCT7). Moreover the administration of inulin entails a higher level of some detoxification enzymes (MT2A, GSTK1, and UGT2B4) with respect to LPS treatment. Following exposure to the LPS-undernatant, a significant decrease in maximal Ach-induced contraction was observed when compared to the contraction induced in control muscle strips incubated with the N-undernatant ($49 \pm 5\%$ vs $10 \pm 1\%$ respectively, $P < 0.05$.) and this was completely prevented by pre-incubation of the LPS with Inulin ($12 \pm 2\%$, P = ns versus N-undernatant)
Conclusion: Our data suggest that the exposure of colonic mucosa to inulin is able to prevent LPS-dependent altered expression of some key proteins which promote intestinal motility and the host response, reducing the radical-mediated oxidative stress.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP388 TLR4 IS STILL ACTIVE IN GP96-DEFICIENT MACROPHAGES

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Introduction: Gp96 is an endoplasmic reticulum chaperone for multiple protein substrates which plays an important role in innate and adaptive immunity. Lack of this protein in intestinal macrophages (iMACs) of Crohn's Disease (CD) patients is correlated with a loss of tolerance against the host gut flora, triggering a chronic and persistent inflammation. iMACS are crucial for pathogen recognition at the mucosal surface of the gastrointestinal tract and Toll-like receptors (TLR), one of the best investigated family of pattern recognition receptors, lead to the phosphorylation of NFκB after their activation. Previous studies of our group revealed a strong expression of TLR2 and 4 on inflammatory iMACS leading to a higher susceptibility of CD patients to LPS, in parallel with a specific loss of gp96.

Aims & Methods: We aim to study the impact of the gp96-knockdown on TLR-function in the human monocytic cell line MM6 and in a conditional gp96-LysMcre knock-out mice. MM6 cells were stably transduced with lentiviral gp96-knockdown vector. The lentiviral vector particles were produced by co-transfection of HEK293T cells with transfer, packaging and envelope plasmids using Fugene HD Transfection Kit. After transduction, cells were treated with LPS (100 ng/ml) for 2 hours. Furthermore, in order to analyze the relevance in vivo, conditional LysMcre-gp96 knock-out (KO) mice were also generated after crossing gp96flox-mice with LysMCre mice. Peritoneal macrophages were isolated from both, wild-type (WT) and KO mice, and treated with LPS (100 ng/ml) for 2 hours. In transduced MM6 cells and peritoneal macrophages, TLR2 and TLR4 expression was analyzed by flow cytometry and the expression of NFκB, IκB-α, IL-8, IL-6 and TNF-α were analyzed by Western blot, qPCR and ELISA. Results are expressed as percentage or fold induction $\pm$ SEM. All experiments were performed with an $n \geq 3$.

Results: After checking that the efficiency of lentiviral knockdown was more than 90% by Western blot, flow cytometry experiments revealed that the number of TLR4+ and TLR2+ gp96 shRNA transduced cells were slightly decreased, 81% and 77% respectively, compared with mock-transduced MM6 cells, 92% and 97% respectively. In line with this, the analysis of the expression of TLR4 and TLR2 receptors in peritoneal macrophages showed a similar slight decrease in KO mice (74.4% and 77.0% respectively) compared with WT mice (78.2% and 90.5% respectively). The functionality of TLR4 receptor was also analyzed and treatment with LPS induced a significant increase in the ratio pIκB-α/IκB-α in gp96 shRNA cells (1.6 fold induction) and in KO peritoneal macrophages (5 ± 1.5); and in protein expression of pNFκB in both gp96 shRNA (1.7) and in KO peritoneal macrophages (1.5 ± 0.6) compared with non-treated mock-transduced cells and WT peritoneal macrophages. Furthermore, LPS induced a significant increase in the mRNA and protein expression of IL-8 (9 fold induction and 800 pg/ml respectively) in gp96 shRNA compared with mock-transduced cells. These results were strongly reinforced since LPS also induced a significant increase in the mRNA expression of IL-8 (11.7 ± 2.6), IL-6 (12.3 ± 3.9) and TNF-α (7.9 ± 1.9) in KO peritoneal macrophages compared with non-treated macrophages.

Conclusion: TLR4 receptor is still active and functional even in the absence of gp96 in macrophages.

Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30–12:00
GASTRIC AND JUNCTIONAL CANCERS – ROOM 1.86

OP389 A NEW, BIOLOGICALLY RELEVANT CLASSIFICATION FOR ADENOCARCINOMA AT THE GASTRO-OESOPHAGEAL JUNCTION

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Introduction: Adenocarcinomas at the gastro-oesophageal junction (GOJ) are currently stratified according to the Siewert classification by location of the main tumour mass (GOJ1: 1–5 cm proximal to the junction, GOJ2: 1 cm proximal to 2 cm distal to the junction, GOJ3: 2–5 cm distal to the junction). It is unclear whether this also reflects the molecular phenotype and hence how this stratification might influence therapy and prognosis in an era of personalised medicine.

Aims & Methods: The aim of this study was to determine the molecular phenotypes of GOJ tumours and to relate this to the Siewert classification. The gene expression profile of 107 treatment naïve gastro-oesophageal adenocarcinomas was assessed by the Illumina HTv4.0 beadchip array (GOJ1: 35, GOJ2: 31, GOJ3: 18, true gastric comparators: gastric fundus/proximal body: 6, distal body: 9, antrum: 8). Only tumours of intestinal Lauren type were included. Differential gene expression analysis was done using limma in R, unbiased subgroup assignment was performed applying a model-based algorithm using MCLUST in R. Gene-set enrichment based pathway analysis was done using GAGE in R based on KEGG and Gene Ontology terms. Whole genome sequencing data was analysed for a subset of 45 GOJ tumours (50x for tumours and 30x for matched germline) to assess mutational burden, recurrently mutated genes, copy number aberrations, and mutational signatures in the identified subgroups.

Results: The Siewert classification did not reveal differential gene expression apart from the gene REC8, a member of the meiotic recombination proteins, which was upregulated in GOJ3 compared with GOJ1 ($p = 0.003$). Unbiased assignment of the gene expression profiles instead revealed three distinct groups which were not correlated with Siewert type, tumour stage or grade ($p > 0.05$). Group 1 showed strong expression of MUC5AC, CTSE, and CLDN18, and was enriched for pathways involved in cell metabolism and cell turnover. Group 2 was positive for CDX1, CDX2 and CDH17, and was enriched for digestive and absorptive processes. Group 3 showed high expression of genes involved in immune-cell function including CXCL10, IDO1 and HLA-genes, and was enriched for pathways involved in immune response and cell-cell-communication. Immunohistochemistry for a subset of the above mentioned genes confirmed expression of these genes within the respective subgroups. Comparison of whole-genome sequencing data showed comparable features across all groups with the expected recurrent mutations and trinucleotide mutational context. Survival was significantly different between groups: Group 1 had the worst overall survival (group 1: 25.9 m, group 2: 45.2 m, group 3: 83.5 m; $p = 0.019$) and shorter recurrence-free survival in patients undergoing curative treatment pathways (group 1: 24.3 m, group 2: 73.5 m, group 3: 86.2 m; $p = 0.051$).

Conclusion: Adenocarcinomas at the GOJ comprise three distinct molecular phenotypes, which are not reflected by the anatomical location. These subgroups have differences in biological pathways and survival and may thus have implications for prognosis and targeted therapy.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP391 SRGAP1, A CO-TARGET OF MIR-340 AND MIR-124, FUNCTIONS AS A POTENTIAL ONCOGENE WITH AMPLIFICATION AND RECURRENT MUTATION IN GASTRIC TUMORIGENESIS

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Introduction: SRGAP1 (Slit-Robo GTPase-activating protein 1) functions as a GAP for Rho-family GTPases and downstream of Slit-Robo signaling. However, the involvement of SRGAP1 activation and functional role in gastric carcinogenesis has not been investigated.

Aims & Methods: We aim to investigate the biological functions of SRGAP1 and comprehensively reveal its regulation by deregulated miRNAs in gastric carcinogenesis. The mRNA and protein expression of SRGAP1 were examined by qRT-PCR and Western blot. The biological role of SRGAP1 in GC was demonstrated by MTT proliferation, monolayer colony formation, cell invasion and migration assays through siRNA-mediated knockdown. The prediction of miRNAs which potentially target SRGAP1 was performed by TargetScan (http://www.targetscan.org/) and miRDB (http://mirdb.org). miR-340 and miR-124 were screened out for further validation. The regulation of SRGAP1 by miRNAs was confirmed by qRT-PCR, Western blot and dual luciferase activity assays by ectopic expression of miR-340 and miR-124.

Results: SRGAP1 is over-expressed in 9 out of 12 (75.0%) GC cell lines both from the mRNA and protein level. In clinical samples form TCGA cohort, SRGAP1 shows gene amplification in 5/258 (1.9%) cases and its mRNA upregulation shows positive correlation with the copy number change. The mutation rate of SRGAP1 in primary GC is 8/258 (3.1%) Knockdown of SRGAP1 in MKN28, MGC-803 and SGC-7901 cells exhibited significant anti-oncogenic effect in vitro. SRGAP1 downregulation suppressed cell proliferation, reduced monolayer colony formation, and inhibited at least 50% of the cell invasion and migration ability. Moreover, luciferase activity experiments revealed SRGAP1 knockdown significantly inhibited Wnt/β-catenin pathway, which was further confirmed by the inactivation of β-catenin and downregulation of CCND1 and c-Myc. In addition, SRGAP1 was confirmed to be a direct target of miR-340 and miR-124 in GC. These two miRNAs showed decreased expression compared with adjacent normal epithelium cells and the downregulation of miR-340 and miR-124 were associated with poor survival. Enforced overexpression of miR-340 and miR-124 in GC cells also exerted tumor-suppressive function by inhibiting cell proliferation and inducing G1 phase cell cycle arrest. In 28 paired GC samples, the expression of SRGAP1 protein showed negative correlation with the expression of miR-340 and miR-124.

Conclusion: SRGAP1 is over-expressed and plays an oncogenic role in GC through activating Wnt/β-catenin pathway. Apart from gene amplification and mutation, the activation of SRGAP1 in GC is partly due to the downregulation of tumor suppressor miRNAs, miR-340 and miR-124. These findings provided

clinical implications that targeting SRGAP1 might have therapeutic potential for GC.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP392 HOXB7 PROMOTES EPITHELIAL-MESENCHYMAL TRANSITION AND METASTASIS IN GASTRIC CANCER

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Introduction: In the previous study we observed that HOXB7 is highly expressed in gastric cancer and promote migration or invasion, and inhibit apoptosis in gastric cancer cells.
Aims & Methods: We aimed in this study to demonstrate the roles of HOXB7 in development of epithelial-mesenchymal transition (EMT) and metastasis in gastric cancer using in vitro and in vivo model. We established HOXB7-expression stable cell lines (MKN45-B7) and mock cells (MKN45-mock). Western blot was performed to validate EMT markers and phospho-Akt/PTEN activity. By injection of stable cell lines, xenograft tumors were produced on the 8-week old male Balb/C nude mice (nu/nu). 4 weeks after injection, we extracted xenograft tumors, and implanted fragment of tumors on the stomach of another 8-week old nude mice. 6 weeks after implantation, mice were sacrificed and their peritoneal metastasis, perigastric lymph node and volume of gastric tumor were compared between both groups.
Results: MKN45-B7 cells frequently showed fibroblast-like mesenchymal phenotype, whereas most of MKN45-mock cells showed epithelial phenotype. Mesenchymal markers (snail, vimentin) were up-regulated and epithelial marker (E-cardherin) was down-regulated in MKN45-B7 cells, as well as phospho-Akt level was increased and PTEN expression was decreased compared by MKN45-mock cells. The volume of xenograft tumor was significantly increased in MKN45-B7 cell-injected mice than MKN-mock cell injected mice. Mean number of peritoneal metastasis/perigastric lymph node and volume of gastric tumor were also significantly increased in MKN45-B7 tumor-implanted mice. When we transiently transfected siAkt on MKN45-B7 cells, snail and vimentin expression were down-regulated, whereas E-cadherin expression was up-regulated, compared by siControl-transfected MKN45-B7 cells.
Conclusion: Our findings suggest that HOXB7 may play crucial role in inducing EMT and promoting metastasis in gastric cancer via modulating Akt/PTEN axis.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP393 SIGNIFICANCE OF COLONOSCOPY IN PATIENTS WITH GASTRIC HIGH GRADE DYSPLAIS OR EARLY GASTRIC CANCER

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Introduction: Relationship of gastric cancer and colon cancer, it is not yet clearly identified. But usually there is high risk of colorectal cancer known as gastric cancer patients.
Aims & Methods: The purpose of this study was to discuss the development risk of colorectal neoplasmand colon cancer in patients with gastric category 4 lesion (high-grade dysplasia, HGD and early gastric cancer, EGC) who underwent endoscopic submucosal dissection (ESD) compared to healthy controls. We also investigated the associated risk factors for colorectal neoplasm and colon cancer. The study group included a total of 209 patients with gastric category 4 lesion (95 HGD and 114 EGC) that underwent ESD. And 610 healthy controls were included. All of the patients underwent concurrent screening colonoscopy between January 2009 and May 2014. High risk colorectal neoplasm was defined as >1 cm, adenoma with villous component, adenoma with HGD, three or more polyps or adenocarcinoma.
Results: High-risk colorectal neoplasm was found in 50/209 patients (23.9%) in patient group and 47/610 (7.7%) in controls ($p < 0.05$). Colon cancer was diagnosed in 16/209 patients (7.6%) in patient group and 18/610 (2.9%) in controls ($p < 0.05$). The risk factors of high-risk colorectal neoplasm were associated with age, DM, colon cancer family history, and presence of gastric category 4 lesion. The risk factors of colon cancer were associated age, and colon cancer family history, and presence of gastric category 4 lesion.
Conclusion: The incidence of high-risk colorectal neoplasm and colon cancer in patient group who underwent gastric ESD was higher than that in the control group. Therefore, patients undergoing ESD with category 4 lesions may need screening colonoscopy.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP394 PALLIATIVE CHEMOTHERAPY AND TARGETED THERAPIES FOR ESOPHAGEAL AND GASTRO-ESOPHAGEAL JUNCTION CANCER

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Introduction: More than 50% of patients with esophageal (EC) or gastro-esophageal junction cancer (GEJC) have metastatic disease at the time of diagnosis. Chemotherapy and targeted therapies are increasingly used for palliative treatment with the intent to control tumor growth, improve quality of life, and prolong survival. To date, scientific proof is lacking.
Aims & Methods: Therefore, the aim of this study was to systematically review and compare the effectiveness of chemotherapy and targeted therapy to best supportive care (BSC) and, to compare the addition of a cytostatic or targeted therapeutic to a control arm in patients with EC/GEJC. This abstract is based on a pre-peer review of a formal Cochrane Review. Upon completion and approval, the final version is expected to be published in the Cochrane Database of Systematic Reviews. We searched the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE, and searched reference lists of studies. The search was not restricted to English language publications only. Randomized controlled trials on palliative chemotherapy and/or targeted therapy, versus BSC or versus a control arm, in patients with esophageal or gastro-esophageal junction cancer were included. Two authors independently extracted data.
Results: For the comparison of palliative chemotherapy or targeted therapy versus BSC, five trials with a total of 751 patients were included in the meta-analysis for overall survival (OS). This analysis demonstrated a significant benefit in OS in favor of the group receiving palliative chemotherapy and/or targeted therapy compared to BSC (hazard ratio (HR) 0.81 (0.71 to 0.92)). A similar trend was observed for progression free survival (PFS), including two trials and 541 participants, with a HR of 0.58 (95%CI 0.28 to 1.18). For the comparison of adding a cytostatic and/or targeted agent to a control arm, ten trials, with 1288 patients in total were included for the meta-analysis of OS. This analysis demonstrated a significant benefit in OS in favor of the arm with an additional cytostatic or targeted therapeutic with a HR of 0.77 (95% CI 0.70 to 0.85). The median increased survival time was limited, one month for adding an additional cytostatic or targeted therapeutic to the control arm. Subanalysis with second line therapies showed a similar benefit as first line therapies. Ramucirumab was the only agent, investigated more than once, that significantly improved both OS and PFS. Palliative chemotherapy and/or targeted therapy increased the frequency of treatment related toxicity of at least grade 3. However, treatment related deaths did not occur more frequently. Quality of life, for the studies that reported this outcome, often improved in the arm with an additional agent.
Conclusion: Palliative chemotherapy and/or targeted therapy significantly increase OS compared to BSC in patients with esophageal or gastroesophageal-junction carcinoma. Additionally, patients who receive multiple chemotherapeutic or targeted therapeutic agents have an increased OS, PFS and improvement of quality of life, on the expense of treatment-associated toxicity of at least grade 3. Based on this meta-analysis, palliative chemotherapy and/or targeted therapy should be considered standard care for esophageal and gastro-esophageal junction carcinoma.
Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30–12:00

ABSTRACTS ON FIRE: NEW APPROACHES TO COLORECTAL DISEASE – HOTSPOT

OP395 ECONOMIC EVALUATION OF ANTIBIOTIC THERAPY VS APPENDECTOMY FOR TREATMENT OF UNCOMPLICATED ACUTE APPENDICITIS: RESULTS OF THE APPAC RANDOMIZED CLINICAL TRIAL

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Introduction: Appendectomy has been the standard treatment for acute appendicitis for over a century and more than 300 000 appendectomies are performed annually in the United States[1]. Although appendectomy is generally well tolerated, it is a major surgical intervention and can be associated with postoperative morbidity. Our APPAC trial[2] comparing antibiotic therapy with appendectomy for treatment of uncomplicated acute appendicitis showed that the majority of CT-proven uncomplicated acute appendicitis patients were successfully treated with antibiotics. Most patients randomized to antibiotic treatment did not require appendectomy during the 1-year follow-up period, and those who required appendectomy did not experience significant or increased complications.
Aims & Methods: The objective of this study was to compare the treatment costs of antibiotic therapy and appendectomy for treatment of uncomplicated acute appendicitis in our Appendicitis Acuta (APPAC) randomized clinical trial. The APPAC multicenter, open-label, non-inferiority randomized clinical trial was conducted in Finland from November 2009 until June 2012. A total of 530 adult patients aged 18 to 60 years with CT-scan confirmed uncomplicated acute appendicitis were enrolled in six Finnish hospitals. Patients were randomly assigned to early appendectomy (n = 273) or antibiotic treatment (n = 257). The cost estimates were based on the cost levels of the final quarter of year 2012. All costs were recorded, whether generated by the initial visit and subsequent treatment or possible recurrent appendicitis during the one-year follow-up period.
Results: In the operative group, the overall societal costs were 16 times higher than in the antibiotic group. In both groups productivity losses represented a slightly higher proportion of overall societal costs than all treatment costs together, with diagnostics and medicines having a minor role. Patients in the operative group were prescribed significantly more sick leave days (16.96, SD 8.30) compared with the antibiotic group (9.17, SD 6.89) ($p < 0.001$). When the age and sex of the patient as well as the hospital of care were controlled simultaneously, the operative treatment option generated significantly more costs in all models.
Conclusion: To our knowledge, this is the first randomized study comparing antibiotic therapy and appendectomy in uncomplicated acute appendicitis to report thorough cost analysis. Avoiding unnecessary appendectomies in our study resulted in major cost savings. Although 27% of the antibiotic group patients underwent surgery, the differences in costs both to the service providers and to the society overall strongly support evaluating antibiotic therapy as the first alternative for uncomplicated acute appendicitis. Further studies evaluating the optimal treatment of acute uncomplicated appendicitis are strongly encouraged also from an economic standpoint.
Disclosure of Interest: P. Salminen: Research grant / a government research grant (EVO) awarded to Turku University hospital
All other authors have declared no conflicts of interest.

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OP396 SURGERY VERSUS CONSERVATIVE TREATMENT FOR RECURRENT AND ONGOING DIVERTICULITIS; RESULTS OF A MULTICENTER RANDOMIZED CONTROLLED TRIAL (DIRECT-TRIAL)

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Introduction: Patients with recurrent or persisting complaints following an episode of diverticulitis are managed with either conservative measures or elective sigmoidectomy. To date no studies have been done comparing these two treatment modalities. We aimed to determine which treatment is superior in terms of improving quality of life. (DIRECT trial,NTR1478 (www.trialregister.nl)).
Aims & Methods: An open-label, multicenter, randomized clinical trial was performed in 24 teaching and 2 academic hospitals in the Netherlands (DIRECT trial). Patients presenting with either recurrent or persistent abdominal complaints after an objectified episode of diverticulitis were included. Patients were randomly assigned to either conservative treatment, according to current day practice, or elective (laparoscopic) sigmoidectomy using a stratified digital en-block randomization system. Primary endpoint was quality of life measured by the Gastro-intestinal Quality of life Index (GIQLI) after six months.
Results: Between July 1, 2010 and April 1, 2014, 109 patients were randomized when the data safety and monitoring board prematurely terminated the trial because off increasing difficulties in recruitment. Fifty-three patients were randomized to resection and 56 to conservative treatment. The GIQLI score was significantly higher among patients randomized to resection (114.4 (SD 22.3) vs 100.4 (SD 22.7) $p = 0.0001$). Seven (13.2%) patients developed anastomotic leakage. Among patients treated conservatively, 13 (23.2%) ultimately underwent elective resection due to ongoing abdominal complaints. There was no mortality.
Conclusion: Elective sigmoidectomy is superior to conservative managements in terms of quality of life in patients with recurrent and persisting abdominal complaints after an episode of diverticulitis.
Disclosure of Interest: All authors have declared no conflicts of interest.

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OP397 PREVALENCE OF SESSILE SERRATED ADENOMAS/POLYPS IN DISTAL COLON DURING SCREENING COLONOSCOPY/ FLEXIBLE SIGMOIDOSCOPY: A SINGLE BOWEL CANCER SCREENING CENTRE EXPERIENCE FROM UK

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Introduction: Sessile Serrated Adenomas/Polyps (SSA/P) are responsible for nearly 20% of colorectal cancer (CRC). Despite the utility of novel image enhancing techniques including narrow band imaging it is difficult to differentiate hyperplastic (HP) polyps from SSA/Ps. Vast proportion of endoscopists leave the diminutive and possibly small HP polyps in situ in the recto sigmoid area (diagnose and disregard approach). Hence there is a possibility of leaving SSA/P in the recto sigmoid region which could potentially lead to CRC later in life.
Aims & Methods: We aim to estimate the prevalence of SSA/P in recto sigmoid colon at screening colonoscopy and flexible sigmoidoscopy (FS). Patients aged > 55 years underwent a screening colonoscopy (n = 500) or a flexible sigmoidoscopy (n = 500) at our institution between August 2014 and April 2015 were included. Data collected from 500 consecutive patients who underwent a colonoscopy or a FS. Demographic, procedural and polyp data were retrieved from our endoscopy database.
Results: 99.6% of (498/500) colonoscopy and 97.6% of flexible sigmoidoscopy procedures were completed. Screening colonoscopy detected 1006 polyps and FS detected 249 polyps. Polyp size ranged between 1–80 mm (colonoscopy mean size 6 mm, SD 7.2 mm; FS mean 3.4 mm, SD 3.9 mm). While colonoscopy detected 43 SSA/Ps (4.3%), FS detected only 6 SSA/Ps (2.4%) which equates to an overall prevalence of 3.9% (49/1255). Table 1 summarises the SSA/Ps prevalence data from our cohort. In rectum there were 8 SSA/Ps detected and resected which equals to a 3.6% of all rectal polyps. All SSA/Ps detected in rectum were less than 10 mm in size (range 2–9 mm). Prevalence of SSA/Ps in proximal colon was 4.5%.

Site	Total number of polyps	Number of SSA/Ps	Prevalence of SSA/Ps
Rectum	222	08	3.6%
Sigmoid colon	320	13	4%
Descending colon	133	02	1.5%
Splenic flexure	37	00	0%
Transverse colon	217	07	3.2%
Hepatic flexure	37	01	2.7%
Ascending colon	168	09	5.4%
Caecum	114	09	7.9%
Site not specified	07	00	0%

Conclusion: Our cohort showed a slightly higher prevalence of SSA/Ps in rectum and sigmoid colon. Therefore, it becomes clinically relevant to differentiate SSA/Ps from HP polyps in recto sigmoid before adapting a diagnose and disregard approach for small (6–9 mm) hyperplastic looking polyps in this location.
Disclosure of Interest: All authors have declared no conflicts of interest.

OP398 SERRATED POLYPOSIS SYNDROME: A SURGICAL PERSPECTIVE

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Introduction: Serrated Polyposis Syndrome (SPS) is associated with an increased risk of colorectal cancer (CRC). Some patients may require colonic surgery but the literature regarding indication, procedure performed, outcomes and surgical decision making is sparse. We aimed to address these issues.

Aims & Methods: 434 patients with SPS, were retrospectively enrolled from 7 centers in the Netherlands and 2 in the UK. Data were retrieved from medical charts, pathology and endoscopy reports and collected in a centralized database. Data relating to surgical resection and surveillance outcomes were assessed.

Results: A total of 164 (38%) patients underwent colorectal surgery; 114 (70%) for CRC, 31 (19%) for high polyp burden and 14 (9%) for unresectable polyps. **Surgery for SPS Cancer** Twenty seven (25%) SPS cancers were managed with total colectomy and ileorectal anastomosis (IRA), with the remaining 87 (75%) patients having a more limited resection. 90% of those undergoing IRA had a formal diagnosis of SPS at the time of their surgery compared with only 39% of those undergoing more conservative resections. Fifty eight (50%) patients had a resection for cancer before a diagnosis of SPS was made. Total polyp burden (median 40 v 22.5, $p < 0.01$) and proximal polyp numbers (median 20 v 12, $p < 0.019$) were significantly higher in those having more extensive surgery. In the limited resection group eight (9%) patients developed metachronous tumours; of these only three have recorded formal post-operative endoscopic surveillance. None of these patients met SPS criteria at the time of index surgery. Three had total IRA as management of their second tumour. The median interval to development of second CRC was 24 months. In the limited resection group seven (8%) patients required further surgical intervention for endoscopically unmanageable polyp load. All had IRA as their second procedure. Total polyp burden (median 40 v 25, $p < 0.01$), proximal polyp burden (median 25 v 15, $p = 0.002$) and number of proximal polyps >10 mm (median 10 v 2, $p = 0.005$) were higher in this group compared with those having surgery for CRC alone. **Surgery for High Polyp Burden** All 31 patients had a diagnosis of SPS and underwent IRA. The median total polyp count was 43 (IQR 34–56.5) and median proximal polyp burden was 31 (IQR 26.8–47.5). **Surgery for Unresectable Polyp** Fourteen patients had unresectable polyps and had segmental resections. None have developed CRC to date. Polyp burden in this group was equivalent to those having CRC surgery.

Conclusion: 1. Over one-third of SPS patients required colorectal resection. The vast majority for CRC, of whom only half were known to fulfil criteria for SPS at the time of their cancer resection. 2. Developing metachronous cancer is uncommon. Segmental resection and close endoscopic surveillance may be appropriate for at least some of this patient cohort and more extensive surgery reserved for those whose SPS cancers present concurrently with higher polyp counts. Surgical decision making should be guided by the endoscopic assessment of the SPS.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP399 IMPROVED RISK CLASSIFICATION FOLLOWING COLORECTAL ADENOMA REMOVAL

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Introduction: Current colonoscopy surveillance recommendations after polyp removal are arbitrary and resource demanding. We developed a novel risk classification system for colorectal cancer following adenoma removal.

Aims & Methods: We included all individuals who underwent screening colonoscopy with adequate bowel cleansing and caecum intubation in the Polish National Colorectal Cancer Screening Program between January 2000 and December 2008. They were followed for colorectal cancer incidence and death through national registries until December 2013. We estimated adjusted hazard ratios (HR) for individuals with different adenoma characteristics compared to individuals without adenomas and derived a novel risk classification system.

Results: Among 159,928 individuals (median age 56 years; 37.6% males) with a median follow-up of 7.1 years we identified 82 colorectal cancers after adenoma removal (0.31%) and 194 in individuals without adenomas (0.15%). The strongest predictors for colorectal cancer risk were adenoma size $\geq$20 mm in diameter (HR 8.70; 95% CI 5.43–13.95, $P < 0.001$), high-grade dysplasia (HR 4.15; 95% CI 2.05–8.43, $P < 0.001$) and $\geq$3 adenomas (HR 3.13; 95% CI 1.60–6.12, $P = 0.001$). In a novel risk classification system using only these three predictors the number of individuals in the high-risk group was reduced by 56% with no increased risk of overlooked cancer (absolute risk difference per 10,000 individuals: 2.2; 95% CI −11.9–16.3).

Conclusion: Limiting surveillance recommendations to patients with adenomas $\geq$20 mm in diameter or high-grade dysplasia or $\geq$3 adenomas significantly reduces the need of surveillance colonoscopies without increasing the risk for cancer.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP400 COST-EFFECTIVENESS ANALYSIS OF POST-POLYPECTOMY COLONOSCOPY SURVEILLANCE USING JAPANESE DATA: RISK-STRATIFIED SURVEILLANCE BASED ON POLYP RESULTS IS MORE COST-EFFECTIVE

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Introduction: To maximize the usefulness of total colonoscopy (CS) in reducing deaths from colorectal cancer (CRC), it is essential that cost-effective post-polypectomy CS surveillance programs are implemented. However, this has not been well examined. European Union and United States guidelines for post-polypectomy surveillance recommend risk-stratified programs based on initial CS results.[1,2] Japanese guidelines, however, recommend that post-polypectomy surveillance CS should be performed within 3 years of polypectomy, regardless of the results of resected polyps.[3] Given that different surveillance programs are recommended in different settings, it is important to determine the most cost-effective surveillance program.

Aims & Methods: The aim of this study was to determine the most cost-effective post-polypectomy CS surveillance program by performing a Markov model analysis using Japanese data. The model was developed by simulating the clinical course of CRC as a transition from normal epithelium, low-risk adenomatous polyps sized 1–4 mm and 5–9 mm, high-risk adenomatous polyps, CRC, and finally to death from CRC.[4] High-risk polyps included intramucosal cancers and adenomas with a diameter $\geq$ 10 mm, with high-grade dysplasia, or with villous histology ($\geq$25%). The initial population comprised 100,000 average-risk individuals aged 40 years. Parameters of transition probabilities, costs, and test characteristics were determined based on Japanese data.[4] Four surveillance

strategies were evaluated for costs, gained quality-adjusted life-years (QALYs), and the required number of CS procedures. In strategy 1, post-polypectomy surveillance CSs were performed 1 year after polypectomy regardless of the polyp results. In strategy 2, the interval between surveillance CSs and polypectomy was 3 years regardless of the polyp results. Strategy 3 was a risk-stratified one; surveillance CSs were performed 3 years after the resection of high-risk polyps and 5 years after that of low-risk polyps. In strategies 1, 2 and 3, surveillance CSs were performed 10 years after normal CSs. Strategy 4 was also a risk-stratified one with more intense use of CS than strategy 3; the interval between surveillance CSs and the resection of high-risk polyps, low-risk polyps, and no polyps were 1, 3 and 5 years, respectively. In all strategies, a fecal immunochemical test-based CRC screening program was provided before surveillance, and uptake rates were set at 60% in the base-case analysis. A probabilistic sensitivity analysis (PSA) was also performed for all model parameters.

Results: QALYs and costs per person in strategy 1–4 were as follows: strategy 1, 23.004 QALYs and US$1,024.88; strategy 2, 23.000 QALYs and $1,009.02; strategy 3, 23.013 QALYs and $977.40; strategy 4, 23.046 QALYs and $970.31. The required numbers of CS procedures per person in strategy 1, 2, 3 and 4 were 2.143, 1.664, 1.617 and 2.548, respectively. Risk-stratified strategies (strategies 3 and 4) yielded higher QALYs with lower costs than strategies 1 and 2. Comparing strategy 3 with strategy 4, yielded QALYs were higher and required cost was lower in strategy 4. Strategy 4 was most-cost-effective, showing simple dominance over the other strategies, followed by strategy 3; however, strategy 4 required the most CS procedures. The PSA showed that the probability of strategy 4 being chosen as the most cost-effective at the willingness-to-pay value of $50,000 was 67.8%.

Conclusion: After polypectomy, risk-stratified CS surveillance programs based on the polyp results should be recommended owing to higher expected effectiveness and cost-effectiveness. Furthermore, more intense use of CS procedures in risk-stratified surveillance can heighten the effectiveness and cost-effectiveness in the Japanese setting. However, it does require a larger number of CS procedures; thus, it would be preferable to determine the most appropriate use of CS procedures in risk-stratified surveillance programs depending on the nationwide availability of CS resources.

Disclosure of Interest: All authors have declared no conflicts of interest.

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OP401 NEW NBI MAGNIFYING ENDOSCOPIC CLASSIFICATION FOR COLORECTAL TUMORS PROPOSED BY THE JAPAN NBI EXPERT TEAM (JNET)

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Introduction: There have been many narrow-band imaging (NBI) magnifying endoscopic classifications advocated (Sano, Hiroshima, Showa, and Jikei classifications) so far in Japan. NBI magnifying endoscopy for qualitative and quantitative diagnosis for colorectal lesions is useful, however, some discussion in Japan has raised issues such as i) the presence of multiple terms for the same or similar findings, ii) the necessity of including surface patterns in magnifying endoscopic classifications, and iii) differences in the NBI findings between polypoid and superficial lesions. To resolve these issues and unify the classifications, the Japan NBI Expert Team (JNET) was set up in 2011. The aim of this study is to scientifically evaluate the NBI scale and determine the NBI findings and diagnostic criteria used in the unified classification (The JNET classification).

Aims & Methods: The JNET classification, which is a modification of NICE classification, consists of 4 categories (Types 1, 2A, 2B, and 3) based on vessel and surface patterns without color. We made a hypothesis that each of them are correlated with the histopathological findings of hyperplastic polyp/sessile serrated polyp (SSP), low grade intramucosal neoplasia, high grade intramucosal neoplasia/shallow submucosal invasive cancer, and deep submucosal invasive cancer, respectively. A web image interpretation study using the modified Delphi (UMIN000010292: Multicenter study for developing universal NBI magnifying endoscopic classification of colorectal tumors in Japan) was conducted. 25 specialists in magnification evaluated NBI magnifying findings and histology with 100 NBI still images on the web.

Results: Univariate and multivariate analyses and analysis on diagnosability from 5 candidate NBI magnifying findings such as 1) loose vessel areas, 2) interruption of thick vessels, 3) scattered vessels, 4) thick, linearized/meandering atypical vessels in the tumor, and 5) amorphous areas of surface patterns for Type 3, and i) variable caliber of vessels, ii) thick vessels iii) irregular distribution of vessels, iv) vessel meandering, and v) irregular or obscure surface pattern for type 2B. Among the five candidate NBI findings, three findings such as 1) loose vessel areas, 2) interruption of thick vessels, and 5) amorphous areas of surface patterns were identified as the diagnosis of type 3. In addition, three findings such as I) variable caliber of vessels, III) irregular distribution of vessels, and V) irregular or obscure surface pattern were selected for the diagnosis of type 2B.

Conclusion: Subclassification of NICE Type 2 (2A & 2B) could be performed scientifically with NBI magnifying findings without color using web image interpretation study, which could conduct differentiatial diagnosis between low grade intramucosal neoplasia and high grade intramucosal neoplasia/shallow submucosal invasive cancer.

Disclosure of Interest: All authors have declared no conflicts of interest.

Table (OP401)

JNET	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	Invisible	Regular caliber Regular distribution (meshed/spiral pattern)	Variable caliber Irregular distribution	Loose vessel areas Interruption of thick vessels
Surface pattern	Regular dark or white spots Similar to surrounding normal mucosa	Regular (tubular/branched / papillary	Irregular or obscure	Amorphous areas
Most likely histology	Hyperplastic polyp/ Sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia/ Shallow submucosal invasive cancer	Deep submucosal invasive cancer

OP402 SUBCLASSES OF TYPE-II PIT PATTERN REVEAL ALTERNATIVE TUMORIGENIC PATHWAYS OF COLORECTAL SERRATED LESIONS

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Introduction: Colorectal serrated lesions (SLs) include hyperplastic polyp (HP), traditional serrated adenoma (TSA) and sessile serrated adenoma/polyp (SSA/P). Emerging evidences suggest that SSA/Ps are precursor lesions of colorectal cancers (CRCs) with BRAF mutation and the CpG island methylator phenotype (CIMP). We have previously reported that Type II-Open (Type II-O) pit patterns, which is highly specific to SSA/P. However, clinicopathological and molecular features of SLs without Type II-O pits remain unclear.

Aims & Methods: We aimed to identify clinicopathological and molecular features of SLs without Type II-O pits. We analyzed the methylation of CIMP markers (MINT1, −2, −12, −31, p16 and MLH1) and BRAF and KRAS mutation in 448 premalignant and malignant colorectal tumors. By using magnifying endoscopy, surface microstructures of colorectal lesions were classified into Type II pit or tumor pit (Type III, IV or V pit) according to the Kudo's pit pattern classification system. Type II pit was subcategorized into classical Type-II pit, Type II-O pit and Type II-Long (Type II-L) pit. CIMP status (CIMP-high, -low and -negative) was determined by using the five methylation markers.

Results: Endoscopic findings were classified as 41 Type II pit, 8 Type II-L pit, 92 Type II-O pit, 21 Type II plus tumor pit, 22 Type II-L plus tumor pit, 50 Type II-O plus tumor pit and 214 tumor pit. We identified Type II-L plus tumor pit, which was specific to TSA with KRAS mutation and CIMP-low (sensitivity, 60%; specificity, 96%). As compared to lesions with only Type II-L pit, KRAS mutation and CIMP-low were more frequent in lesions with Type II-L plus tumor pits. Progression of Type II-L pit lesions to TSA was associated with KRAS mutation and accumulation of moderate DNA methylation. In contrast, BRAF mutation was frequently observed in colonic tumors with Type II plus tumor pit. These results suggest that lesions with Type II-L pit and those with Type II pit appear to develop through distinct tumorigenic pathways, though the majority of lesions with Type II or Type II-L pit were the same HP.

Conclusion: Our data suggest that Type II-L plus tumor pit is a useful hallmark of the premalignant stage of CRCs with KRAS mutation and CIMP-low.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP403 ARTIFICIAL INTELLIGENCE (AI) IN ENDOSCOPY–DEEP LEARNING FOR OPTICAL BIOPSY OF COLORECTAL POLYPS IN REAL-TIME ON UNALTERED ENDOSCOPIC VIDEOS

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Introduction: ASGE-PIVI guidelines support a "resect and discard" strategy for diminutive colon polyps, provided that the predictive value of technology allowing for "optical biopsy" depicts at least 90% agreement in assignment of post-polypectomy surveillance intervals using pathology as standard. In addition, in order for a technology to be used to guide the decision to leave suspected diminutive rectosigmoid hyperplastic polyps in place (without resection), the technology should provide 90% negative predictive value for adenomatous histology. Such standards with optical biopsy might be achievable with experts (although even that is unclear) but do not cross over into general clinical practice. Several groups have looked at supporting the process of optical biopsy decision making on endoscopic assessment of the histology of diminutive colorectal polyps using traditional machine learning, but to date there are significant limitations in terms of (1) using still images only, and non-realtime computer support, both of which are not clinically efficient or effective, and (2) often involving magnification endoscopy that is not yet a widespread clinical practice. Deep learning is a branch of artificial intelligence which is a siginificant advance on traditional machine learning, and with huge computational power, machines can now recognize objects in real time. We sought to apply novel deep learning techniques to optical biopsy for colon polyps.

Aims & Methods: We aimed to evaluate deep learning applied to the classification of colorectal polyps into NICE types 1 and 2, in real-time on unaltered endoscopic videos, for the support of clinically efficient optical biopsy. We used 92 videos of small colorectal polyps (<10 mm) under white light (WL) and narrow-band imaging (NBI) (38 NICE type 1, 52 NICE type 2), using Olympus 190 series colonoscopes. "Optical biopsy" was done on all polyps by an expert with >95% accuracy (using pathology as the reference standard) prior to removal and histological confirmation.

We investigated a Deep Learning Artificial Intelligence model with a proprietary deep convolutional neural network (DCNN) for the computer-assisted NICE type 1&2 differentiation. We designed a 3-class model representing Types 1, 2, and unsuitable (frames without statistically representative information–blur, bubbles, liquid). The model operated at the individual frame level, without prior segmentation.

For model training purposes, each frame was manually tagged. The final dataset was split into training and validation sets, without overlap. Finally, the analysis was performed separately for NBI and WL frames, allowing for reporting of frame processing time and classification performance.

Results: A total of 33,954 training frames were used, split equally across NBI & WL, and type 1, type 2, & unsuitable classes. We performed a 5-fold cross-validation on the tagged frames for quality control. The trained DCNN model was then used to evaluate the unaltered videos in real-time, with an accuracy for polyp classification of 90% for NBI, and 83% for WL. The confusion matrix on whole-video classification of colorectal polyps gives a sensitivity of 93% and specificity of 85% for NBI. Finally, the processing time of our DCNN model ran at between 25 and 30 frames per second (fps) using a decent gamer-grade GPU (NVIDIA Titan-X) on an unaltered video feed of 60 fps, delivering near-realtime computer support.

Conclusion: To our knowledge, this is the first application of deep learning to the optical biopsy challenge for polyp differentiation into NICE types 1&2 using non-magnification colonoscopy and NBI, specifically in a clinically representative workflow where computer support is provided in realtime on unaltered endoscopic video streams. Although the present investigation was carried on a limited datasets of 92 videos, our deep learning model has shown clinically efficient and relevant performance for optical biopsy, well aligned with PIVI guidelines and the performance of experts. Ongoing work will determine if such a computer support solution could aid in the widespread adoption of a ''resect and discard'' strategy, and reduce the economic burden of pathological evaluation of benign diminutive colon polyps.

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D.K. Rex: Olympus consulting and research support
N. Chapados: Imagia has commercial interests in artificial intelligence
F. Soudan: Imagia has commercial interests in artificial intelligence
C. Oertel: Imagia has commercial interests in artificial intelligence
M. Linares Perez: research support from Satis Operations Inc
R. Kelly: research support from Satis Operations Inc
F. Chandelier: Shareholder in Cadens Medical Imaging
All other authors have declared no conflicts of interest.

Age, mean (SD), y	48 (7)	48 (7)	50 (17)	52 (14)
Women, n (%)	5 (63)	5 (46)	19 (54)	17 (53)
Body mass index, mean (SD), kg/m^2	22.6 (3.6)	23.3 (4.1)	22.2 (3.1)	22.2 (2.8)*
Stoma present, n (%)	7 (88)	11 (100)	10 (29)	10 (32)*
Colon-in-continuity, n (%)	1 (13)	1 (9)	22 (63)	24 (77)*
Estimated small bowel length, mean (SD), cm	128 (98)	129 (77)†	54 (43)‡	73 (56)§
Baseline PS, mean (SD), L/wk	21.6 (8.1)	15.9 (10.4)	11.5 (5.9)	11.2 (6.4)*
Baseline PS duration, mean (SD), y	7.2 (7.4)	8.1 (8.0)	5.6 (5.3)	6.1 (5.7)*

*n = 31, †n = 9, ‡n = 32, §n = 30.

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