Oral Presentations
Monday, October 21, 2019

Opening Session: Part I
08:00 – 10:00 / Hall 6

OP001 TOP-DOWN INFLIXIMAB SUPERIOR TO STEP-UP IN CHILDREN WITH MODERATE-TO-SEVERE CROHN'S DISEASE - A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Introduction: In newly diagnosed paediatric Crohn's Disease (CD) patients current guidelines instruct to start exclusive enteral nutrition (EEN) or oral prednisolone in combination with immunomodulators to achieve remission. Infliximab (IFX) is proven to be highly effective in paediatric CD patients, but only used once patients are refractory, the so called step-up (SU) treatment strategy.

However, evidence is emerging IFX is more effective the sooner it is initiated. We hypothesize that initiation of IFX directly, i.e. top-down (TD) after diagnosis of moderate-to-severe CD, results in higher long term remission rate.

Aims & Methods: Aim: To compare efficacy of TD and SU treatment in newly diagnosed moderate-to-severe paediatric CD

Methods: For this international randomized controlled trial (RCT) 100 patients aged 3-17 years, with new-onset, untreated CD with weighted paediatric CD activity index (wPCDAI) > 40 were included in 12 centres. All patients were randomly assigned to TD or SU treatment. TD treatment consisted of 5 IFX (CT-P13) infusions of 5 mg/kg (0, 2, 6, 14, 22 weeks) combined with azathioprine (AZA). After 5 infusions, IFX was stopped while continuing AZA. SU treatment consisted of induction therapy with EEN or oral prednisolone (at physician and patient/parents discretion) combined with AZA as maintenance treatment. In both groups, IFX could be (re)started on predefined conditions. Primary endpoint of this study was sustained clinical remission (wPCDAI < 12.5) at week 52 without need for additional therapy or surgery. Secondary endpoints included patient rate using IFX at week 52, as well as clinical remission, endoscopic detection of mucosal healing (SES-CD < 3) and low fecal calprotectin levels (< 250 ug/g) at week 10.

Results: Three out of 100 patients didn't start with the study after randomization (n=97; TD:50 vs SU:47). There were no significant differences within the two groups at baseline. Median age was 15.0 years [IQR 11.7-16.6] in TD, and 14.2 years [IQR 12.0-16.3] in the SU group. 54% and 57% were males, and median wPCDAI was 55 [IQR 45-65] and 57.5 [IQR 47.5-67.5]) in the TD vs SU group, respectively.

For preliminary analysis of the primary endpoint data of 75/97 patients were available. At week 52, TD treatment resulted in sustained clinical remission for 18/37 [49%] of the patients compared to 5/38 [13%] of SU patients (p=0.001). After induction therapy IFX was (re)started in 13/37 [35%] TD patients compared to 27/38 [70%] SU patients within 52 weeks (p=0.001). Two patients underwent surgical resection (ileocecal resection), one in each treatment group.

At week 10, TD resulted in significant more patients in clinical remission (TD: 24/41 [59%] vs SU: 15/42 [36%], p=0.037) as well as endoscopic remission (47/97 consented to repeated endoscopy; TD: 17/28 [61%]; median SES-CD 0 [IQR 0-5] vs SU: 5/29 [17%]; median SES-CD 6 [IQR 3-15.5], p=0.001). Lastly, significantly more TD patients had a low fecal calprotectin level (n=44; TD: 9/23 [39%] vs SU: 4/21 [19%], p=0.005).

Conclusion: We are the first to compare TD IFX to SU treatment in an RCT of paediatric CD patients. Although this analysis is preliminary, TD treatment was superior to SU in achieving sustained clinical remission (wPCDAI < 12.5) without the need for additional therapy or surgery at week 52. Moreover, at week 10, significantly more TD patients were in clinical and endoscopic remission and had low calprotectin levels compared to SU patients.
Disclosure: Nothing to disclose

OP002 DEFINING THE CLONAL ORIGIN, EXPANSION RATE AND CLONAL DIVERSITY OF INTESTINAL METAPLASIA IN THE HELICOBACTER-INFECTED HUMAN STOMACH

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Introduction: Over half the world's population is chronically infected with Helicobacter pylori, the main risk factor for gastric cancer (GC). Chronic infection provokes a mutagenic cascade involving extensive metaplastic remodelling of the gastric mucosa. Although gastric intestinal metaplasia (GIM) is an accepted pre-cursor lesion to GC, its origins, evolution and neoplastic potential remain unclear. An understanding of the stem cell dynamics and clonal diversity of GIM may allow targeted endoscopic surveillance to patients at greatest risk of progression to GC.

Aims & Methods: Our objective was to develop a quantitative understanding of the initiation, expansion, and clonal diversity of GIM in the chronically inflamed stomach. We developed a unique workflow to visualise and trace the clonal initiation and expansion of GIM in patients' tissues. Analysis of *en face* embedded gastric mucosa from cancer patients (n=12) who underwent gastrectomy reveals a mosaic patchwork of islands of GIM. Using patch size dynamics, 3D modelling, and whole exome sequencing (WES) we quantified the clonal expansion and genetic diversity of GIM. Comparison was made with normal gastric mucosa from patients undergoing sleeve gastrectomy for weight loss (n=12).

Results: Tracing the cellular origin of GIM in 3D, we demonstrate for the first time that GIM originates from a single stem cell within a single gastric gland. These metaplastic lineages expand within the gastric gland, display all cellular lines of intestinal epithelial differentiation (enterocyte, goblet cells, etc) and rapidly colonise singular glandular units. Direct quantification of the competitive advantage of these metaplastic lineages at single cell resolution shows that metaplastic stem cell lineages display biased drift. Patch size dynamics of neutral clonal markers in chronically inflamed gastric mucosa reveals a tenfold increased clonal expansion rate when compared to non-inflamed mucosa. Analysis of the patch size dynamics of GIM reveal that its clonal expansion rate is increased further by another order of magnitude. Finally, we have carried out whole exome sequencing (WES) to reconstruct the clonal phylogeny of patches of GIM and assess the mutation burden within metaplastic patches. Our analysis shows that the mutation burden of GIM is comparable to mature gastric cancer with some patches showing arm level copy number variation. Together, these data show that *H. pylori* provokes a massive adaptive radiation of metaplastic cellular clones, greatly accelerating the selection and expansion of mutant lineages.

Conclusion: This work reveals that the metaplastic phenotype confers a fitness advantage at the level of the individual stem cell. The markedly exaggerated expansion rate of GIM explains the time-dependent transfor-

mation of the gastric mucosa into a competitive field of cancer precursor lineages. Clonal genetic diversity may be a potential marker for GC progression risk in chronic gastritis patients.
Disclosure: Nothing to disclose

Opening Session: Part II
10:30-12:00 / Hall 6

OP003 THE NEUROPEPTIDE RECEPTOR ACTIVITY MODIFYING PROTEIN (RAMP)1 PROMOTES LIVER REGENERATION BY REGULATING YES-ASSOCIATED PROTEIN (YAP) ACTIVITY DURING ACUTE OR CHRONIC LIVER INJURY

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Introduction: The adult liver has a high capacity to regenerate after acute injury. In addition, chronic liver damage in patients with liver fibrosis triggers proliferation of residual hepatocytes and, thus, prevents liver failure. The liver is innervated by sensory nerves containing the neuropeptide calcitonin gene-related peptide (CGRP) that binds to the receptor activity-modifying protein (RAMP)1.

Aims & Methods: We aim to investigate whether the neuropeptide CGRP is able to modulate liver regeneration upon partial hepatectomy and during hepatic fibrosis. Wild type and RAMP1 deficient mice were subjected either to 70% partial hepatectomy (PH) or were injected with carbon tetrachloride (CCl4) for four weeks to induce chronic liver fibrosis. The de novo synthesis of CGRP receptor components in liver tissues of both models was determined by quantitative RT-PCR. Hepatocyte proliferation was quantified using Ki67- and BrdU-specific immunohistochemistry, and cell cycle regulatory components were analyzed by western blot and quantitative RT-PCR. Sirius Red staining was performed in order to assess collagen fibers deposition within hepatic parenchyma. Protein expression of fibrotic markers, such as α-SMA and collagen, was evaluated by western blot. Involvement of CGRP/RAMP1 in the Hippo pathway was tested by the presence of global or active YAP, as well as global and active YAP-regulators LATS1/2 and MOB1 using western blot analysis. To investigate the direct effect of CGRP signaling on hepatocytes or intact liver tissue in vitro, we stimulated primary hepatocytes or precision-cut liver slices with CGRP and analyzed YAP signaling components by detecting global and phosphorylated YAP protein by western Blot analysis.

Results: Liver injury induced through partial hepatectomy or CCl4-injection caused a sustained upregulation of hepatic CGRP mRNA and a late increase of RAMP1 expression. During liver fibrosis absence of RAMP1 impairs collagen fibers deposition as well as expression of α-SMA and Collagen Type 1 proteins. RAMP1 deficiency severely delayed recovery of organ mass upon PH, and inhibited hepatocyte proliferation and cell cycle progression in both liver injury models. Mechanistically, expression of the Hippo pathway-regulated transcriptional coactivator YAP was decreased in livers of RAMP1-deficient mice following either partial hepatectomy or 4-weeks' CCl4 injection. RAMP1 deficiency impaired nuclear localization of YAP protein in hepatocytes and upregulation of YAP target genes in regenerating livers. Phosphorylation of YAP on Ser127 and Ser397, which promote YAP cytoplastic retention and extranuclear degradation, was found to be elevated in RAMP1-deficient livers in both models. Consistently, phosphorylation of the YAP kinases LATS1/2 as well as MOB1 was upregulated. Stimulation of primary hepatocytes or precision-cut liver slices with the neuropeptide CGRP corroborated our in vivo results in an in vitro setting and demonstrates that CGRP/RAMP1 signaling positively regulates YAP activity.

Conclusion: Our study identifies the neuropeptide CGRP signaling via its receptor RAMP1 as a previously unrecognized inducer of YAP activity in liver regeneration upon acute and chronic injury.

Disclosure: Nothing to disclose

OP004 EFFECTS OF FAECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS): A RANDOMISED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

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Introduction: The intestinal bacterial profile in IBS patients differs from that of the healthy subjects with a low diversity (dysbiosis) (1,2,3). Microbiota dysbiosis in IBS patients is believed to play an important role in the pathophysiology of this disorder (3). Faecal microbiota transplantation (FMT) has been tried in two double-blind placebo-controlled studies (4,5). While the first study showed improvement of the IBS symptoms, the other study did not show any effect at all. The present study was conducted to study the effect of FMT using a single donor with a favourable microbiota profile.

Aims & Methods: A randomised, double-blind placebo-controlled study was conducted, where 164 IBS patients were randomised to either placebo, 30 g transplant or 60 g transplant in ratio 1:1:1. The primary outcome was a reduction in the IBS-symptoms defined as a decrease in the IBS-SSS total score with ≥50 points 3 months after FMT. The secondary outcome was a reduction in the Dysbiosis index (DI) and a change in the intestinal bacterial profile 3 months following FMT. Abdominal symptoms, fatigue and quality of life were assessed by the IBS-SSS and Birmingham IBS symptom, fatigue Assessment Scale, IBS-Quality of Life and the Short-Form Dyspepsia index Questionnaires. Gut bacterial analysis was done using a commercially available test, GA-map Dysbiosis Test® (Genetic Analysis AS, Oslo, Norway).

Results: The response to FMT occurred in 23.6, 75.9 and 87.3% of patients received placebo, 30 g and 60 g transplant, respectively. This was accompanied by a significant improvement in fatigue and quality of life in these patients. Symptom remission (SSS≥175 points) occurred in 5.5, 35.2 and 47.3% in placebo, FMT 30 g and FMT 60 g groups, respectively. Similarly, a significant clinical improvement in fatigue (FAS≥4 points) was found in 21.8, 53.7 and 52.7% of patients received placebo, FMT30 g and FMT 60 g, respectively. The corresponding figures for the quality of life (IBS-QoL≥14 points) were 7.3, 61.1 and 58.2%. DI did not decrease significantly in patients received FMT or placebo. The intestinal bacterial profiles changed in both groups received 30 and 60 g transplant, but not in the placebo group.

Conclusion: FMT is an effective treatment for patients with IBS. A well-defined donor with normal DI and favourable specific microbial signature is essential for the success of FMT. Response to FMT increases with increased dose. There was a significant difference in the intestinal bacterial profile between responders and non-responders, which might be used to identify candidates for FMT.

References:
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Disclosure: Nothing to disclose

IBD: New drugs, new risks
10:30-12:00 / A2

OP005 REAL-WORLD SAFETY OF VEDOLIZUMAB AND ANTI-TNF THERAPIES IN BIOLOGIC-NAÏVE ULCERATIVE COLITIS AND CROHN'S DISEASE PATIENTS: RESULTS FROM THE EVOLVE STUDY

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Introduction: The GEMINI phase III clinical trials showed a favourable safety profile for vedolizumab (VDZ) in treating patients (pts) with moderate-to-severely active ulcerative colitis (UC) and Crohn's disease (CD), however real-world studies are needed comparing the safety of VDZ to anti-tumour necrosis factors (anti-TNF) agents.

Aims & Methods: The objective was to compare the safety of VDZ and anti-TNF agents in a real-world cohort of biologic (bio)-naïve pts with UC or CD. This was a multi-country (Canada, Greece and the United States), retrospective chart review study of bio-naïve pts (≥18 years old) with ≥ 6 months follow-up, initiating treatment (Tx) with VDZ or an anti-TNF [adalimumab, infliximab, golimumab, certolizumab pegol] between May 2014 and March 2018. Data were collected from Tx initiation to earliest of death, chart abstraction date or 6 months post-Tx discontinuation (Canada only). Serious adverse events (SAEs) and serious infections (SIs) (defined as either life threatening, requiring hospital admission, resulting in significant disability/incapacity, or recorded in the chart as an important medical event) occurring from Tx initiation up to five half-lives post-Tx discontinuation were assessed. Incidence rates (per 100 person-years [PYs]) of SAEs and SIs were estimated. A Cox proportional hazards model adjusted for baseline characteristics was used to compare incidence rates between Tx cohorts. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) are reported.

Results: This study included 1,095 pts (VDZ: 598 [UC: 380; CD: 218]; anti-TNF: 497 [UC: 224; CD: 273]) from 42 sites. Compared to anti-TNF pts, the VDZ cohort were older (mean [SD] age [years]: VDZ, 47.9 [17.4]; anti-TNF, 39.6 [15.2] [p< 0.01]), were proportionately more male (male: VDZ, 56.9%; anti-TNF, 49.9% [p=0.02]) and had a longer disease duration (median [range: min-max] disease duration [years]: VDZ, 5.0 [0.04- 54.0]; anti-TNF, 2.0 [< 0.1 - 49.0] [p< 0.01]). Median (range: min-max) follow-up (months) was: VDZ, 15.3 (3.0-47.0); anti-TNF, 16.3 (3.5-51.0). Incidence rates of first occurrence (per 100 PY [95% CI]) of SAEs (VDZ: 4.6 [3.5-6.8]; anti-TNF: 10.3 [9.5-14.9]) and SIs (VDZ: 2.6 [1.9-4.4]; anti-TNF: 7.0 [5.9-10.2]) were significantly lower in VDZ versus anti-TNF pts (adjusted HR: SAE, 0.42 [0.27-0.66]; SI, 0.33 [0.18-0.58]). Similar trends were shown when data were stratified by UC and CD, separately (Table 1).

	Ulcerative Colitis			Crohn's Disease		
Outcome	Vedolizumab IR (95% CI) N=380	Anti-TNF IR (95% CI) N=224	Adjusted Hazard Ratio (95% CI)	Vedolizumab IR (95% CI) N=218	Anti-TNF IR (95% CI) N=273	Adjusted Hazard Ratio (95% CI)
Serious Adverse Events	3.8 (2.6-6.2)	11.3 (8.9-17.5)	0.34 (0.19-0.63)*	3.0 (1.8-5.0)	5.7 (3.5-9.4)	0.47 (0.22-1.02)
Serious infections	6.1 (4.1-10.5)	9.5 (7.7-14.5)	0.45 (0.23-0.89)*	1.9 (0.8-4.5)	7.9 (5.5-11.3)	0.18 (0.06-0.50)*

Data are incidence rates (95% CI) and hazard ratios (95% CI). Incidence rates are unadjusted and are per 100 person-years; hazard ratios are from adjusted Cox proportional hazards models (adjusted for baseline confounders: age, sex, disease duration, albumin, C-reactive protein, UC/CD-related hospitalisations [prior 12 months] and disease severity). Indication (UC/CD) was a covariate for the overall analysis and was not included for disease specific models. CD: Crohn's Disease; UC: Ulcerative colitis, IR: Incidence rate.

Half-lives for treatments: VDZ: 125days (18 weeks), Infliximab: 47.5 days (6.8 weeks), Infliximab-dyyb: 47.5 days (6.8 weeks), Infliximab-abda: 47.5 days (6.8 weeks), Adalimumab: 70 days (10 weeks), Adalimumab-atto: 70 days (10 weeks), Golimumab: 70 days (10 weeks), Certolizumab pegol: 70 days (10 weeks). *Significant difference between VDZ and Anti-TNF cohorts based on adjusted HRs.

[Table 1. Safety Profile of Vedolizumab and Anti-TNF Therapies in Real-World Biologic-Naïve Ulcerative Colitis and Crohn's Disease Patients]

Lastly, the proportion of pts who experienced gastrointestinal (GI) infections was significantly higher among anti-TNF versus VDZ pts (4.4% versus 1.5%, respectively, p< 0.01).

Conclusion: Bio-naïve pts treated with VDZ had a significantly lower likelihood of experiencing SAEs and SIs, including GI infections, than those treated with anti-TNF therapies. These data support a favourable safety profile of VDZ versus anti-TNF in bio-naïve inflammatory bowel disease pts in real-world clinical practice.

OP006 AN UPDATE ON THE ANALYSIS OF NON-MELANOMA SKIN CANCER IN THE TOFACITINIB ULCERATIVE COLITIS PROGRAMME

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Introduction: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). We present an update on the integrated analysis of non-melanoma skin cancer (NMSC) events in the tofacitinib UC clinical programme, as of Sep 2018.

Aims & Methods: The safety of tofacitinib for the treatment of moderate to severe UC was evaluated in a randomised, placebo (PBO)-controlled induction Phase (P) 2 study (NCT00787202),[1] two induction P3 studies (NCT01465763; NCT01458951), one maintenance P3 study (NCT01458574),[2] and an ongoing open-label, long-term extension (OLE) study (NCT01470612).[3] Patients (pts) were analysed as three cohorts: Induction (P2/P3 induction studies); Maintenance (P3 maintenance study); Overall (pts receiving ≥1 dose of tofacitinib 5 or 10 mg twice daily [BID] in P2, P3 or ongoing OLE studies). For P3 studies, a blinded independent adjudication committee reviewed potential NMSC. Proportions and incidence rates (IRs; unique pts with events per 100 pt-years [PY] of exposure) for NMSC were evaluated. A Cox proportional hazards model was used for risk factor analysis. Overall Cohort data are as of Sep 2018.

Results: 1124 pts were evaluated for NMSC (P3 studies only), with 2399 PY of tofacitinib exposure and up to 6.1 years of treatment. NMSC occurred in two Induction pts receiving tofacitinib 10 mg BID. In the Maintenance Cohort, the NMSC IR for pts receiving PBO was 0.97 (one pt) and was 1.91 for tofacitinib 10 mg BID (three pts) (Table). In the Overall Cohort, the NMSC IR for tofacitinib-treated pts was 0.78 (19 pts): 0.82 for pts receiving a predominant dose (PD) of 10 mg BID (defined as an average daily dose ≥15 mg; 15 pts) and 0.67 for pts receiving a PD of 5 mg BID (an average daily dose < 15 mg; four pts). Ten pts had squamous cell carcinoma (SCC) and 12 pts had basal cell carcinoma (BCC); three pts had both SCC and BCC. No NMSC was metastatic or led to study discontinuation. Of all tofacitinib-treated pts with NMSC, seven had prior NMSC history, 18 had prior use of thiopurines and 15 had prior tumour necrosis factor inhibitor (TNFi) exposure. The Overall Cohort showed higher IRs for subgroups of pts aged ≥50 years (1.93 [95% confidence interval (CI) 1.08, 3.19]) vs 40 to < 50 years (0.74 [95% CI 0.20, 1.89]), 30 to < 40 years (0.00 [95% CI 0.00, 0.58]) and < 30 years (0.00 [95% CI 0.00, 0.77]), and for pts with prior TNFi treatment (1.23 [95% CI 0.69, 2.04]) vs those without (0.33 [95% CI 0.09, 0.84]), or prior immunosuppressant use (0.99 [95% CI 0.59, 1.57]) vs those without (0.16 [95% CI 0.00, 0.90]). Cox regression selected prior NMSC (hazard ratio [HR] 10.95; 95% CI 3.72, 32.24; p< 0.0001) and age (HR per 10-year increase 2.10; 95% CI 1.41, 3.13; p=0.0003) as significant risk factors for NMSC.

Conclusion: NMSC events were infrequent in the tofacitinib UC programme, and were more likely to occur in pts with prior NMSC and with increasing age, known risk factors for the development of NMSC.[4] NMSC IRs were similar to those reported for tofacitinib in other indications, including for tofacitinib in rheumatoid arthritis,[5] and for biologic UC treatments.[6]

All NMSC	Induction Cohort (8 weeks)		Maintenance Cohort (52 weeks)			Overall Cohort (≤6.1 years)
	Placebo (N=282)	Tofacitinib 10 mg BID (N=938)	Placebo (N=198)	Tofacitinib 5 mg BID (N=198)	Tofacitinib 10 mg BID (N=196)	Tofacitinib All (N=1157)
Age (years), mean (SD)	41.4 (14.4)	41.3 (13.8)	43.4 (14.0)	41.9 (13.7)	43.0 (14.4)	41.3 (13.9)
Exposure, PY[a]	40.39	158.37	103.20	148.77	156.80	2398.6
Pts with events, n (%)[a]	0 (0.0)	2 (0.2)	1 (0.5)	0 (0.0)	3 (1.5)	19 (1.7)[b]
IR (95% CI)[a]	0.00 (0.00, 9.13)	1.26 (0.15, 4.56)	0.97 (0.02, 5.40)	0.00 (0.00, 2.48)	1.91 (0.39, 5.59)	0.78 (0.47, 1.22)

Data are as of Sep 2018 for the Overall Cohort (OLE study database not locked)
[a]Adjudicated data do not include data from the P2 Study (A3921063; NCT00787202);
[b]Including five pts from the P3 Induction and Maintenance Cohorts
BID, twice daily; CI, confidence interval; IR, incidence rate (unique patients with events per 100 PY of exposure); N, number of patients randomised and treated; N/A, not applicable; NMSC, non-melanoma skin cancer; OLE, open-label, long-term extension; P, Phase; pts, patients; PY, patient-years

[Table. Demographics, and proportions and IRs for all NMSC events, for the Induction, Maintenance and Overall Cohorts]

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6. FDA Advisory Committee Meeting sNDA 203214. FDA 2018: Supplement 018 (available at www.fda.gov).

OP007 TOFACITINIB FOR THE TREATMENT OF ULCERATIVE COLITIS: ANALYSIS OF INFECTION RATES IN THE TOFACITINIB ULCERATIVE COLITIS CLINICAL PROGRAMME

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Introduction: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). The safety of tofacitinib for the treatment of moderate to severe UC was evaluated in an 8-week induction Phase 2 study (NCT00787202),[1] two 8-week induction Phase 3 studies (OCTAVE Induction 1 & 2; NCT01465763 & NCT01458951) and a 52-week maintenance Phase 3 study (NCT01458574),[2] plus an ongoing, open-label, long-term extension (OLE) study (OCTAVE Open, NCT01470612).[3] Here, we present an update on infections observed in the tofacitinib UC clinical programme as of Sep 2018.[4,5]

	Induction Cohort		Maintenance Cohort			Overall Cohort		
	Placebo (N=282; 44.8 PY)	Tofacitinib 10 mg BID (N=938; 156.2 PY)	Placebo (N=198; 100.4 PY)	Tofacitinib 5 mg BID (N=198; 146.2 PY)	Tofacitinib 10 mg BID (N=196; 154.3 PY)	PD Tofacitinib 5 mg BID (N=197; 595.5 PY)	PD Tofacitinib 10 mg BID (N=960; 1808.1 PY)	Tofacitinib All (N=1157; 2403.6 PY)
AEs (all), n (%)	155 (55.0)	515 (54.9)	149 (75.3)	143 (72.2)	156 (79.6)	183 (92.9)	793 (82.6)	976 (84.4)
Infections (all), n (%), IR [95% CI][b]	43 (15.2)	196 (20.9)	48 (24.2), 58.16 [42.88, 77.12]	71 (35.9), 62.54 [48.85, 78.89]	78 (39.8), 72.82 [57.56, 90.88]	131 (66.5), 46.76 [39.10, 55.49]	498 (51.9), 53.45 [48.86, 58.35]	629 (54.4), 51.90 [47.92, 56.12]
Serious infections, n (%), IR [95% CI][b]	0 (0.0)	8 (0.9)	2 (1.0), 1.94 [0.23, 7.00]	2 (1.0), 1.35 [0.16, 4.87]	1 (0.5), 0.64 [0.02, 3.54]	8 (4.1), 1.32 [0.57, 2.61]	35 (3.6), 1.89 [1.32, 2.63]	43 (3.7), 1.75 [1.27, 2.36]
OIs, n (%), IR [95% CI][b,c,d]	0 (0.0)	3 (0.3)	1 (0.5), 0.97 [0.02, 5.42]	2 (1.0), 1.36 [0.16, 4.92]	4 (2.0), 2.60 [0.71, 6.65]	8 (4.1), 1.37 [0.59, 2.71]	20 (2.2), 1.09 [0.66, 1.68]	28 (2.5),[e] 1.16 [0.77, 1.67]
Non-herpes-zoster OIs, n (%), IR [95% CI][b,c,d]	0 (0.0)	1 (0.1)	0 (0.0), 0.00 [0.00, 3.57]	0 (0.0), 0.00 [0.00, 2.48]	0 (0.0), 0.0 [0.00, 2.35]	1 (0.5), 0.16 [0.00, 0.92]	3 (0.3), 0.16 [0.03, 0.47]	4 (0.4), 0.16 [0.04, 0.42]
Herpes zoster (all), n (%), IR [95% CI][b]	1 (0.4)	6 (0.6)	1 (0.5), 0.97 [0.02, 5.42]	3 (1.5), 2.05 [0.42, 6.00]	10 (5.1), 6.64 [3.19, 12.22]	19 (9.6), 3.62 [2.06, 5.35]	64 (6.7), 3.42 [2.78, 4.62]	83 (7.2), 3.57 [2.84, 4.43]

Data are as of Sep 2018 for the Overall Cohort (OLE study database not locked)
[a]Only patients with events occurring within 28 days after the last dose are included in this table for calculation of proportion and IR; [b]Data for the Induction Cohort are shown as n (%) due to the short duration (8 weeks) of the induction studies; [c]Infection endpoints are based on adjudicated data; adjudicated events are calculated as percentage (%), based on the number of patients in the studies in which adjudication was performed; [d]Excludes Phase 2 patients; [e]Of the 28 patients with OIs in the Overall Cohort, 24 had herpes zoster (herpes zoster OIs were either multidermatomal [2 non-adjacent or 3-6 adjacent dermatomes] or disseminated [any of: diffuse rash >6 dermatomes, encephalitis, pneumonia, other non-skin organ involvement]), 1 had cytomegalovirus infection, 1 had histoplasmosis, 1 had cytomegalovirus hepatitis and 1 had pulmonary mycosis
AE, adverse event; BID, twice daily; CI, confidence interval; IR, incidence rate (patients with events per 100 PY of exposure); N, number of patients treated in the treatment group; n, number of patients with a particular AE; OI, opportunistic infection; OLE, open-label, long-term extension; PD, predominant dose; PY, patient-years

[OP007 Table. Summary of incidence of treatment-emergent infections (all causality)[a] in the Induction, Maintenance and Overall Cohorts]

Aims & Methods: Patients who received placebo, tofacitinib 5 or 10 mg twice daily (BID) were analysed as three cohorts: Induction (Phase 2 & Phase 3 studies, N=1220), Maintenance (Phase 3, N=592) and Overall (patients in Phase 2, Phase 3 & ongoing OLE studies receiving tofacitinib 5 or 10 mg BID, N=1157). Proportions and incidence rates (IRs; patients with events per 100 patient-years [PY] of exposure, 95% CI) were evaluated for infections of special interest (including serious infections, opportunistic infections [OIs], herpes zoster and tuberculosis). OIs were based on review by an independent adjudication committee. Overall Cohort data are as of Sep 2018.

Results: In total, 1157 patients received $\geq$1 dose of tofacitinib 5 or 10 mg BID (83% of patients received a predominant tofacitinib dose of 10 mg BID [average daily dose $\geq$15 mg]), with 2403.6 PY of tofacitinib exposure (median 623 days) and up to 6.1 years of treatment. In the Overall Cohort, the infections IR (95% CI) was 51.90 (47.92, 56.12), with nasopharyngitis being the most frequently occurring infection. For serious infection events, the IR (95% CI) for all tofacitinib-treated patients in the Overall Cohort (1.75 [1.27, 2.36]) was similar to those of the Maintenance Cohort (1.35 [0.16, 4.87] for tofacitinib 5 mg BID and 0.64 [0.02, 3.54] for 10 mg BID). No serious infection events resulted in death. OIs occurred infrequently in the UC programme, with an Overall Cohort IR (95% CI) of 1.16 (0.77, 1.67). Of 28 patients with OIs, the majority were patients with herpes zoster (n=24; IR 0.99 [95% CI 0.63, 1.47]) mostly limited to skin involvement. Not all herpes zoster events were reported as OIs, with 83 patients overall with herpes zoster events (IR 3.57 [95% CI 2.84, 4.43]), of which six were classed as serious herpes zoster (IR 0.24 [95% CI 0.09, 0.53]).

Conclusion: Serious infections were infrequent in the UC clinical programme and IRs in the Overall Cohort did not suggest an increasing risk of serious infections with longer duration of tofacitinib treatment when compared with IRs of the Maintenance Cohort. OIs were rare, with the exception of herpes zoster. The incidence of serious infections was similar in the Overall Cohorts of the UC and rheumatoid arthritis programmes (including increased risk of herpes zoster)[6] and that of other UC therapies including biologics.[7]

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OP008 HIGH SEROCONVERSION RATE TO TRIVALENT INFLUENZA VACCINE DURING USTEKINUMAB TREATMENT IN CROHN'S DISEASE: RESULTS FROM A PROSPECTIVE COHORT STUDY

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Introduction: Influenza vaccination may be less effective in patients with inflammatory bowel disease treated with immunosuppressive therapy, especially with combined use of anti-TNFα agents and immunomodulators. However, little is known regarding the effects of anti-IL-12/23 therapy on the efficacy of vaccination. Therefore, the aim of this study was to investigate the immune response to the 2018-2019 inactivated trivalent influenza vaccine (TIV) in Crohn's disease (CD) patients treated with ustekinumab (UST) as compared to CD patients treated with adalimumab (ADA) and healthy controls (HC).

Aims & Methods: A prospective open-label study was conducted to examine the immunogenicity of the 2018/2019 inactivated TIV in adult CD patients treated with UST. Patient details, disease characteristics and vaccination history were recorded. Age and gender matched CD patients treated with ADA and healthy controls were included as control populations. Blood samples were drawn at 3 time points, T0: before vaccination, T1: 4 to 6 weeks after vaccination and T3: 3 months after vaccination. Hemagglutinin inhibition (HI) assays for all 3 influenza vaccine strains (A/Michigan/2015/H1N1; A/Singapore/2016/H3N2, B/Victoria) were performed simultaneously on all study samples.

Results: A total of 15 CD patients treated with UST, 14 CD patients treated with ADA and 20 healthy controls (HC) were included and received TIV between October and December 2018. In UST group, 4 patients received co-medication (2 MTX, 1 high-dose prednisone and 1 low-dose prednisone). In ADA group, 5 patients received co-medication (2 thiopurine and 3 low-dose prednisone). Post-vaccination seroprotection rates (HI titer $\geq$1:40) were high in all 3 study groups, no significant differences between study groups were observed (Table 1).

			HC	ADA	UST	P-value overall	P-value ADA vs HC	P-value UST vs HC	P-value ADA vs UST
A/H3N2	Seroprotection rate (%)	T1	100	100	100	1*	1**	1**	1**
	Seroconversion rate (%)	T1/T0	30.0	18.2	69.2	**0.023***	0.676**	**0.038****	**0.019****
	Beyer corrected MFI	T1/T0	2.15	1.86	2.31	0.121°	0.070^	0.624^	0.087^
	Beyer corrected MFI	T3/T0	1.93	1.55	2.12	**0.030°**	**0.026^**	0.396^	**0.017^**
A/H1N1	Seroprotection rate (%)	T1	100	90.9	91.7	0.280*	0.355**	0.375**	1**
	Seroconversion rate (%)	T1/T0	47.4	33.3	70.0	0.335*	0.687**	0.433**	0.179**
	Beyer corrected MFI	T1/T0	1.96	1.79	2.03	0.280°	0.451^	0.431^	0.091^
B/Victoria	Seroprotection rate (%)	T1	85.0	66.7	92.3	0.281*	0.379**	1**	0.160**
	Seroconversion rate (%)	T1	35.0	33.3	61.5	0.278*	1**	0.169**	0.238**
	Beyer corrected MFI	T1/T0	1.49	1.15	1.73	**0.022°**	0.307^	**0.043^**	**0.008^**
	Beyer corrected MFI	T3/T0	1.319	1.055	1.627	**0.021°**	0.346^	**0.036^**	**0.009^**

*[Table 1 Immune response to seasonal trivalent influenza vaccine in 3 study groups. *Fisher-F.-H. exact, **Fisher's exact, ° Kruskal-Wallis, ^Mann-Wh.U]*

Seroconversion rates ($\geq$4-fold increase in HI titer compared to pre-vaccination) for strain A/H3N2 were significantly higher at both time points in UST group as compared to ADA group (T1; p = 0.019, T3; p = 0.015) and HC (T1; p = 0.038, T3; p = 0.029). Geometric mean titres (GMT) at T1 and T3 were lower for all strains in ADA group, as compared to UST group and HC, and

significantly lower for the A/H3N2 strain in ADA group as compared to HC (T1; p= 0.032, T3 p = 0.015). After correcting for high GMTs at baseline using Beyer's method, mean fold increase (MFI) in titers at T3 for A/H3N2 strain was significantly lower in ADA group as compared to HC (p = 0.026) and UST group (p = 0.017). MFI for the B/Victoria strain was high in UST group and significantly higher than in ADA group (T1; p = 0.008, T3; p = 0.009). Sub-analysis after exclusion of patients on combination therapy showed similar seroconversion rates.

Conclusion: Seroconversion rate to the seasonal trivalent influenza vaccination during ustekinumab treatment in CD patients is high, in contrast to the reduced rate observed for adalimumab. Patients treated with ustekinumab can be effectively vaccinated with the trivalent influenza vaccine.

Disclosure: Nothing to disclose

OP009 RISK OF IMMUNOMEDIATED ADVERSE EVENTS OR SECONDARY LOSS OF RESPONSE TO INFLIXIMAB IN ELDERLY PATIENTS WITH INFLAMMATORY BOWEL DISEASE. A COHORT STUDY OF THE ENEIDA REGISTRY

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Introduction: Infliximab is one of the most used biological drugs in inflammatory bowel disease (IBD). Immunomediated adverse events (IAE) are of the most frequent reported infliximab-related adverse events. Elderly patients have differential pharmacodynamic and pharmacokinetic characteristics.

We recently reported an increased risk of thiopurine-related AEs in this population; hence, it would be relevant to ascertain if combined treatment is adequate in this population.

Aims & Methods: Our aim was to evaluate the rate of infliximab-related IAE in elderly IBD patients. Methods: All adult patients in the ENEIDA registry (a large, prospectively maintained database of the Spanish Working Group in IBD -GETECCU) who received a first course of infliximab treatment were identified. Patients were selected in two cohorts regarding the age at the beginning of infliximab treatment: over 60 years, and between 18 and 50 years of age. The rates of IAE recorded in the ENEIDA database (infusion

reactions, delayed hypersensitivity, edema, allergy, anaphylaxis, psoriasis, lupus-like syndrome) were compared, as well as the rate of secondary loss of response (SLR).

Results: We included 939 (12%) patients who started infliximab over 60 years and 6,844 (88%) patients below 50 years. The rate of IAE (15% vs. 15%, ns) and treatment withdrawal due to IAE (13% vs. 12%, ns) was similar in both groups. Neither differences were observed according to IAE: infusion reactions (8.3% vs. 8.2%), late hypersensitivity (1.4% vs. 1.2%), paradoxical psoriasis (0.9% vs. 1.4%) and drug-induced lupus erythematosus (0.7% vs. 0.6%). Patients below 50 years were significantly more often treated with concomitant immunosuppressants (57% vs. 48.1%> 60 years, p< 0.05). In the multivariate analysis, combination with immunomosuppressants (OR 0.741; 95%CI 0.64-8.5, p< 0.05) and female sex (OR 1.8; 95%CI 1.6-2.1 p< 0.05) were the only independent predictors to develop IAE. The rate of SLR was also similar in both study groups (20% vs. 21%). Combination therapy with immunomosuppressants was the unique risk factor to develop SLR (OR 0.85; CI95% 0.73 to 0.98, p=0.021).

Conclusion: Elderly IBD patients who start treatment with infliximab have a similar risk of developing IAE and SLR than younger patients. From this point of view, elderly would benefit from combination therapy.

Disclosure: Nothing to disclose

OP010 NO SEVERE NEONATAL AND MATERNAL COMPLICATIONS IN FEMALE PATIENTS WITH INFLAMMATORY BOWEL DISEASES TREATED WITH USTEKINUMAB OR VEDOLIZUMAB DURING PREGNANCY

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Introduction: Inflammatory bowel disease (IBD) has a high incidence in population of childbearing age. Ustekinumab, a fully human monoclonal antibody targeting the p40 subunit of interleukins 12 and 23, and vedolizumab, an anti α4β7 integrin, are biologics currently used in IBD with immunosuppressant or anti TNF failure. Data concerning use and safety of these new biologics during pregnancy are scarce.

Aims & Methods: We conducted a retrospective multicenter study in the GETAID group and collected cases of women with IBD who received at least one injection of ustekinumab or vedolizumab during pregnancy or in the last 2 months before conception. The aims of the study were (1) to evaluate pregnancy and neonatal outcomes in IBD female patients exposed to ustekinumab or vedolizumab during pregnancy, and (2) to observe the impact of ustekinumab or vedolizumab withdrawal on disease activity during pregnancy and postpartum.

Results: Sixty-seven pregnancies in 62 IBD females (43 for Crohn's disease and 19 for ulcerative colitis) were reported among 19 centers of the GETAID group. Median age at conception was 29 years. Median time between introduction of ustekinumab or vedolizumab treatment and pregnancy was 12 months. Twenty-five pregnancies occurred on ustekinumab: 7 received

ustekinumab in the last 2 months before conception, 11 received 1 injection after conception, and 7 stopped ustekinumab in the 2nd trimester. Among the 25 pregnancies occurred on ustekinumab, there were 22 (88%) live births, 1 elective termination and 2 spontaneous abortions. Maternal complications were reported in 2 women (one gestational diabetes and one threat of premature labor). Fetal complications were reported in 3 pregnancies (intra uterine growth restriction). Four newborns presented a non severe neonatal complication (3 preterm deliveries, one low birth weight) and one a Tetralogy of Fallot . Forty-two pregnancies occurred on vedolizumab: 15 received vedolizumab in the last 2 months before conception, 16 received 1 injection after conception, and 11 stopped vedolizumab (6 during the 2nd trimester and 5 during the 3rd trimester). Among the 42 pregnancies occurred on vedolizumab, there were 36 (86%) live births, 1 elective termination (for Down Syndrom) and 5 (12%) spontaneous abortions. Maternal complications were reported in 5 women (one cholestasis and 4 pre-eclampsia). Fetal complications were reported in one pregnancy (intra uterine growth restriction) and 13 newborns developed a neonatal complication (6 preterm deliveries, 6 low birth weight and one congenital corpus callosum hypoplasia). Concerning IBD activity, 65% of women were in remission at conception. Among them, only 2 patients flared during pregnancy.

Conclusion: We reported in 67 pregnancies under vedolizumab or ustekinumab exposition, no severe neonatal (except a cardiac malformation) and maternal complications. However, additional prospective evaluations regarding safety concerns pregnancy outcomes in patients directly exposed to ustekinumab or vedolizumab are needed.

Disclosure: Travelling: Janssen, Biogaran Board: Ferring Speaker: Takeda

Therapeutic nutrition in IBD
10:30-12:00 / A3

OP011 HIGH PHENOLIC ACID INTAKE IS A PROTECTIVE FACTOR FROM COLORECTAL ADENOMAS AMONG EVER-SMOKERS

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Introduction: Polyphenols are a family of phytochemicals, demonstrating anti-inflammatory and antioxidant properties. High intake of phenolic acid have been linked with reduced risk of colorectal cancer (CRC) and adenoma, while smoking has been linked with a higher risk. However, the association of phenolic acids with different types of colorectal adenomas and the interaction with smoking has yet been tested.

Aims & Methods: The aims of this study were to explore the independent association between phenolic acid intake and colorectal adenomas, and to evaluate the potential interaction with smoking. This was a case-control study, among consecutive subjects aged 40-70 years, undergoing colonoscopy during 2010-2015. Cases with colorectal adenomas were compared to controls with no past or present polyps. Detailed information was gathered regarding adenoma size, histology and anatomic location, to enable the definition of non-advanced and advanced adenomas, and their location in the distal and proximal colon. Demographics, medical history, anthropometrics, smoking status, lifestyle and dietary intake was assessed. Data on the phenolic acid content in foods was obtained from the Phenol-Explorer database[1]. High phenolic acid intake was defined according to the study sample median (214.8 mg/day). Based on the questionnaires, smoking status was defined as: never-smokers and ever-smokers (past/current smokers). Smoking intensity was calculated in pack-years as: daily cigarettesXyears smoking/20. Pack years were categorized by the group median (≥19.55 pack-years).

Results: The analysis included 711 patients (cases of colorectal adenomas n=326; non-advanced adenomas n=160; advanced adenomas n=166; controls n=385). High phenolic acid intake was negatively associated with colorectal adenomas (OR=0.60, 95%CI 0.43-0.83, P=0.003), both non-advanced and advanced adenomas (OR=0.63, 0.42-0.95 vs. OR=0.56, 0.37-0.86 respectively), independently of demographic, medical and lifestyle confounders. Associations were significant with distal adenomas but not with proximal adenomas (OR=0.56, 0.37-0.84 vs. OR=0.71, 0.47-1.09 respectively). The association was modified by smoking, as high phenolic acid intake had a strong negative association with colorectal adenomas among ever-smokers but not among never-smokers (P for interaction=0.013) (Table 1). Furthermore, the association was also modified by smoking intensity, as strong inverse associations were observed between high phenolic acid intake and all types of colorectal adenomas among participants who reported high smoking intensity (≥19.55 pack years, Table 1).

Conclusion: Intake of phenolic-acids is negatively associated with colorectal adenomas, both distal and proximal, among ever-smokers. A high phenolic-acid diet should be further studied as a potential mean to reduce smoking induced oxidative stress, and prevent adenoma-carcinoma pathway.

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Disclosure: Nothing to disclose

Type of adenoma	Polyphenol intake mg/day	Never smokers		Ever smokers		Smokers of 1.1-19.54 pack years among smokers		Smokers of ≥19.55 pack years among smokers	
		n (cases/controls)	OR (95%CI), P	n (cases/controls)	OR (95%CI), P	n (cases/controls)	OR (95%CI), P	n (cases/controls)	OR (95%CI), P
Total adenomas	< 214.8 mg/day	65/87	1.00 (ref.)	122/78	1.00 (ref.)	46/38	1.00 (ref.)	76/39	1.00 (ref.)
	≥ 214.8 mg/day	70/114	0.88 (0.54-1.44) 0.625	70/105	0.42 (0.26-0.67) <0.001	41/62	0.63 (0.31-1.27) 0.202	29/41	0.33 (0.16-0.68) 0.003
Advanced adenomas	< 214.8 mg/day	35/87	1.00 (ref.)	59/78	1.00 (ref.)	17/38	1.00 (ref.)	42/39	1.00 (ref.)
	≥ 214.8 mg/day	34/114	0.95 (0.51-1.76) 0.888	38/105	0.54 (0.31-0.94) 0.029	23/62	1.26 (0.50-0.31) 0.614	15/41	0.39 (0.17-0.90) 0.028
Non-advanced adenomas	< 214.8 mg/day	30/87	1.00 (ref.)	63/78	1.00 (ref.)	28/38	1.00 (ref.)	35/39	1.00 (ref.)
	≥ 214.8 mg/day	36/114	0.88 (0.47-1.66) 0.710	31/105	0.33 (0.18-0.60) <0.001	17/62	0.40 (0.16-1.05) 0.058	14/41	0.32 (0.12-0.84) 0.021
Distal adenomas	< 214.8 mg/day	32/87	1.00 (ref.)	65/78	1.00 (ref.)	24/38	1.00 (ref.)	41/39	1.00 (ref.)
	≥ 214.8 mg/day	32/114	0.95 (0.50-1.78) 0.873	35/105	0.41 (0.23-0.72) 0.002	19/62	0.52 (0.20-1.32) 0.170	16/41	0.36 (0.15-0.85) 0.021
Proximal adenomas	< 214.8 mg/day	33/87	1.00 (ref.)	57/78	1.00 (ref.)	22/38	1.00 (ref.)	35/39	1.00 (ref.)
	≥ 214.8 mg/day	39/114	0.90 (0.48-1.66) 0.742	35/105	0.46 (0.26-0.82) 0.009	22/62	0.81 (0.34-1.93) 0.816	13/41	0.28 (0.10-0.75) 0.011

[OP011 Table. Multivariate association between high polyphenol intake and colorectal adenoma groups, according to smoking status and intensity.]

OP012 SHIFTS IN BACTERIAL COMMUNITY FUNCTION ARE ASSOCIATED WITH SHORT CHAIN FATTY ACID PATHWAYS DURING NUTRITIONAL THERAPY IN PEDIATRIC CROHN'S DISEASE PATIENTS

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Introduction: Changes in gut bacterial community structure are associated with Crohn's Disease (CD) and response to therapy. A recently completed randomized controlled trial (RCT) showed improved sustained remission with the Crohn's Disease Exclusion Diet + Partial Enteral Nutrition (CDED+PEN) as compared with Exclusive Enteral Nutrition (EEN)[1].

Aims & Methods: We examined changes in the microbiome functional network in patients reaching remission with nutritional therapy. Stool samples from 53 CD patients reaching remission after 6 weeks of dietary treatment were collected at weeks 0, 6 and 12 and whole shotgun sequence data were obtained. In total, 146 CD patient samples were combined with 26 healthy controls (previously published by Lewis et al.[2]), and characterized using HUMAnN2. Reactions, substrates and products for genes with an enzymatic commission were input into an unsupervised Bayesian analysis of community metabolism (BiomeNet). Statistical analysis of community metabolism were performed using R. Non-negative matrix factorization (NMF) and Structural topic models (STM) were used to identify patient-associated microbial metabotypes.

Results: Unsupervised analyses revealed two metabotypes. All healthy controls possessed one metabotype (M1). CD patients possessed a mixture of two metabotypes (M1 & M2), with mixtures related to time in treatment, with 48% belonging to M1 at baseline before dietary therapy. At week 6, the number of M1 samples had increased to 63% and further increased to 74% M1 at week 12 which was closer to healthy controls. Among the pathways identified within metabotypes, one differed substantially between the two metabotypes; the key reactions involve the metabolism of various sugars.

Using NMF and STM, we identified five communities; two were predominant in M1, and the other three were predominant in M2. The communities identified in M1 samples had high levels of Bacteroidetes, including *Odoribacter*, *Alistipes*, *Prevotella*, *Barnesiella* and *Bacteroides* as well as increases in Firmicute taxa *Eubacterium*, *Ruminococcus*, *Oscillibacter*, *Clostridium*, *Faecalibacterium* and *Roseburia*. The Proteobacteria were decreased in M1. M2 samples were characterized by Enterobacteriaceae.

Genes involved in butyrate formation were also associated with M1 and M2. Genes involved in the 4-aminobutyrate pathway, and crotonoyl-CoA to butyrate pathway, (p=0.03 to 0.0001) were associated with M1. M2 was associated with genes involved in the acetyl-CoA pathway as well as ato genes (p< 0.001), involved in the degradation of SCFA.

Conclusion: Diet-induced remission samples were more similar to healthy controls, having shifted away from the baseline. The functional network, associated with active disease, changes as patients progress to remission at week 6 and sustain the remission through week12. The butyrate-related change in community function is attributable to distinct shifts in bacterial species abundance. Genes significant for the M1 butyrate pathway appeared to be driven by *Bacteroides* and *Clostridium*, while genes significant for M2 butyrate pathways were driven by taxa in Enterobacteriaceae notably *Citrobacter*, *Escherichia* and *Enterobacter*.

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Disclosure: Nothing to disclose

Modern management of oesophageal dysmotility: Can we do better?
10:30-12:00 / B2

OP013 FUNCTIONAL LUMEN IMAGING PROBE TOPOGRAPHY (FLIP) AS A SCREENING TOOL FOR ESOPHAGEAL DYSMOTILITY: COMPARISON TO HIGH-RESOLUTION MANOMETRY (HRM) IN PATIENTS WITH ESOPHAGEAL SYMPTOMS

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Introduction: High resolution manometry (HRM) is the current gold standard for the evaluation of esophageal motility. Functional lumen imaging probe topography (FLIP) is a novel approach that enables assessment of esophago-gastric junction (EGJ) distensibility and esophageal peristalsis.

Aims & Methods: Our aim was to evaluate the agreement between FLIP and HRM for esophageal motility assessment, and to assess the role of FLIP as a screening tool for dysmotility in patients undergoing endoscopy. Methods:FLIP and HRM were compared in patients who underwent both procedures. FLIP was performed with a 16 cm balloon; peristaltic response was assessed at 30-40-50-60 ml and classified as repetitive antegrade contractions (RACs), repetitive retrograde contractions (RRCs), diminished/disordered contractile response (DDCR) or absent contractility; median EGJ distensibility index (DI) was calculated at 60 ml and classified as abnormal (< 2 mm²/mmHg), indeterminate 2-3 mm²/mmHg), normal (> 3 mm²/mmHg). FLIP was considered normal if EGJ DI was normal and RACs were present without concomitant RRCs. For HRM, ten 5-ml liquid swallows were administered; Chicago classification version 3.0 was applied for manometric diagnosis. HRM diagnoses were dichotomized as normal/minor disorder (normal, ineffective esophageal motility (IEM), or fragmented peristalsis) or abnormal (achalasia, jackhammer esophagus, distal esophageal spasm (DES), EGJ outflow obstruction (EJGOO), absent contractility). Sensitivity, specificity, and positive/negative predictive values for FLIP were calculated.

Results: 75 patients were included, age 17-92, 65% women. HRM was performed a median 18 days from FLIP. HRM diagnoses: normal/minor disorder 45% (28% normal, 16% IEM, 1% fragmented) and abnormal 55% (17% absent contractility, 16% achalasia, 15 % EGJOO, 4% Jackhammer, 3% DES). FLIP diagnoses: 33% normal, 77% abnormal. In patients with normal FLIP topography, HRM diagnoses were normal/minor disorder in 58% (52% normal and 5% IEM), absent contractility 26%, jackhammer 11%, EGJOO 5%. In patients with normal FLIP, HRM never showed achalasia or DES. Normal FLIP had 80% specificity for HRM being normal or showing only minor motility disorder. When FLIP was abnormal, HRM diagnoses were achalasia 21.4%, normal 19.6%, IEM 19.6%, EGOO 17.9%, absent contractility 14.2%, distal spasm 3.6%, jackhammer 1.8%, fragmented 1.8%); FLIP had sensitivity of 80% for a major motility disorder on HRM. A normal EGJ DI by itself had a negative predictive value of 90% for normal HRM or minor motility disorder. FLIP was abnormal in 100% patients with achalasia or DES diagnosed by HRM.

Conclusion: FLIP topography performed during sedated endoscopy appears to be a good screening tool for esophageal dysmotility, with 80% specificity for normal or minor disorder on HRM, and 80% sensitivity for major disorder on HRM. With subsequent evolution and refinement of FLIP analysis, and data confirmation, a normal FLIP topography during endoscopy for evaluation of esophageal symptoms may obviate the need for manometry. Likewise, HRM is clearly indicated in patients with abnormal FLIP topography, as the likelihood of a major motility disorder on HRM is high in these patients.

Disclosure: Nothing to disclose

OP014 INEFFECTIVE ESOPHAGEAL MOTILITY WITH CONTRACTION RESERVE ON ESOPHAGEAL HIGH RESOLUTION MANOMETRY (HRM) IS ASSOCIATED WITH LOWER ACID EXPOSURE TIMES COMPARED TO ABSENT CONTRACTION RESERVE

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Introduction: Ineffective esophageal motility (IEM) is a minor motor disorder that may have reflux implications. Augmentation of esophageal body contraction on multiple rapid swallows (MRS) indicates presence of contraction reserve, which is associated with lower likelihood of late postoperative dysphagia following antireflux surgery. We hypothesized that presence of contraction reserve in IEM will be associated with reduced esophageal acid burden.

Aims & Methods: Our aim was to evaluate the interrelationship between contraction reserve on HRM and esophageal acid burden on ambulatory reflux monitoring performed off antisecretory therapy. Esophageal HRM and ambulatory reflux monitoring studies were reviewed on all patients undergoing both tests between 01/2016 and 12/2017 at a tertiary care referral center. Patients fulfilling the following three HRM motor diagnoses (using Chicago Classification 3.0 criteria) were identified: normal, ineffective esophageal motility (IEM, ≥50% ineffective swallows), and absent contractility (100% failed swallows). Single swallows (SS) and multiple rapid swallows (MRS) were analyzed using HRM software tools assessing integrated relaxation pressure (IRP, normal< 15 mmHg), distal latency (DL, normal >4.5 s), distal contractile integral (DCI, normal 450-8000 mmHg. cm.s), esophagogastric junction contractile integral (EGJ-CI, normal>39.3 mmHg.cm) and EGJ morphology. Contraction reserve required mean MRS DCI to mean SS DCI ratio >1. Total acid exposure time (AET) was abnormal if >6%; thresholds utilized for upright and supine AET were 6% and 2% respectively. Univariate analysis was performed to determine the role of contraction reserve on esophageal acid burden, and multivariate regression analyses were performed to determine predictors of abnormal total, supine and upright acid burden in the context of contraction reserve.

Results: Study criteria were fulfilled by 191 patients, 109 (57.1%) with normal HRM (53.6 ± 1.4, 70.7% F), 71 (37.2%) with IEM (52.2 ± 1.7, 72.7% F), and 11 (5.76%) with absent contractility (51.4 ± 2.5, 58.3% F). Within IEM, a higher proportion of patients without contraction reserve demonstrated upright AET >6% compared to those with contraction reserve (59.1% vs 32.7%, p=0.04); this difference was not seen with supine AET, and did not affect total AET. Contraction reserve had no impact on AET in normal HRM and absent contractility. When the IEM group was further subdivided into severe IEM (8-10 ineffective swallows, n=40) and non-severe IEM (5-7 ineffective swallows, n=31), the non-severe IEM category demonstrated significantly lower proportions with abnormal AET in the presence of contraction reserve (30.4% vs. 75.0%, p=0.03). Abnormal AET proportions in non-severe IEM with contraction reserve resembled normal HRM (p=0.96), while that in severe IEM with or without contraction reserve resembled absent contractility (p=0.39). Multivariate analysis demonstrated EGJ morphology to be an independent contributor to total AET in IEM (p=0.03). Additionally, absence of contraction reserve associated with increased total AET (p=0.01) in non-severe IEM, while EGJ morphology associated with upright AET in non-severe IEM (p=0.04), and with supine AET in severe IEM (p=0.02).

Conclusion: The presence of contraction reserve is associated with lower upright acid burden in IEM, particularly in non-severe IEM, where acid burden resembles that seen with normal HRM. In contrast, the acid burden profile of severe IEM resembles that seen with absent contractility, regardless of contraction reserve. EGJ morphology is also a contributor to acid burden in IEM.

Disclosure: Nothing to disclose

OP015 CODEINE INDUCES INCREASED RESISTANCE AT THE OESOPHAGO-GASTRIC JUNCTION IN HEALTHY VOLUNTEERS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER TRIAL

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Introduction: The adverse effects of short- and long-term use of opioids, such as codeine and morphine, on gastrointestinal transit are well known. More recently, studies showed that chronic opioid use may induce oesophageal dysfunction with symptoms similar to achalasia (eg. dysphagia) and a manometric pattern of functional oesophago-gastric junction outflow obstruction (OGJ-OO). However, little is known whether this is generalized or occurs only in susceptible subjects, and whether acute opioid administration has similar effects.

Aims & Methods: After positioning a High-Resolution impedance Manometry catheter (HRiM, Unisensor, Attikon, Switzerland), codeine (30mL codeine phosphate 10mg/5mL) or placebo (30mL glucose syrup) was infused in the proximal stomach. Forty-five minutes post-infusion, participants received different volumes (5mL and 20mL) of liquid and semi-solid boluses, classified as 0/1/2/3/4 according to the International Dysphagia Diet Standardization Initiative (IDDSI) classification and bread (2x2cm and 4x4cm). Blood samples were collected to detect slow morphine metabolizers. HRiM analysis was performed adhering to the Chicago classification v3.0 (CC v3.0) using dedicated software (Solar GI, Laborie, Canada). Additionally, pressure-flow analysis (PFA) was performed, using the online software platform swallowgateway.com for calculating the following metrics: pressure flow index (PFI), distension pressure emptying (DPE) as a measure of OGJ resistance to bolus flow, impedance ratio (IR) as measure of bolus clearance failure, distal ramp pressure (DRP) which reflects bolus pressurization and distension-contraction latency (DCL), time from nadir impedance to peak pressure.

Results: Twenty-three HV (6 men, 38±3y) completed the study. Eight participants were excluded from analysis: one due to biliary type pain, a rare side effect of codeine, one due to the presence of an OGJ-OO during placebo and six were slow metabolizers. Integrated relaxation pressure 4 seconds (IRP4) values were significantly higher after codeine (except for 4x4cm bread) and distal latency (DL) values were significant lower (except for 5mL IDDSI3). Distal contractile integral (DCI) values were similar in both conditions, except for IDDSI0 (5mL and 20mL). Based on the CC v3.0, acute infusion of codeine induced an OGJ-OO in five HV (*p*-value=0.042). PFI values were significantly higher after codeine infusion, for all given boluses except for 5mL IDDSI3 and bread 4x4cm. DPE was significantly increased for all boluses except for 5mL IDDSI2. The DRP was significantly increased for 5mL IDDSI0/2 and bread 4x4cm and DCL values were significantly lower for 5mL IDDSI0/3/4 and 20mL IDDSI0 in the codeine condition. No significant differences were noted for IR between placebo and codeine infusion, except for bread 2x2cm. Results are presented in Table 1.

	5mL IDDSI0 IRP4	5mL IDDSI1 DL	5mL IDDSI3 DCI	20 mL IDDSI0 PFI	5 mL IDDSI4 DPE	5mL IDDSI2 DRP	20 mL IDDSI0 DCL	5 mL IDDSI3 IR
Placebo	10 (8 -14)	6.8 (6.4 -7.4)	923 (621 -1281)	8.1 (6.9 -10.4)	21.9 (17.9 -27.4)	4.7 (3 -7.1)	4.2 (3.7 - 4.8)	0.3 (0.3 -0.5)
Codeine	18 (15 -21)	5.9 (5.5 -6.8)	1075 (523 -1568)	15.8 (10.1 -42)	37.7 (31.4 -47.6)	7.6 (6.5 -10.6)	2.7 (2.5 - 3.8)	0.3 (0.3 -0.5)
p-value	<0.0001*	<0.0001*	0.2339	0.009*	0.013*	0.025*	<0.0001*	0.821

[Table 1: Median (interquartile range) values of IRP4, DCI, DL, PFI, DPE, DRP, DCL and IR for codeine and placebo administration]

Conclusion: Acute administration of codeine increases bolus resistance at the OGJ in HV and is able to induce major motility disorders in a subset of subjects. These are mainly localized in the distal oesophagus as the IR data indicate no bolus clearance failure in the oesophageal body.

Disclosure: Nothing to disclose

OP016 EVALUATION OF THE HEIGHT OF THE WATER COLUMN RETAINED AFTER A RAPID DRINK CHALLENGE TEST (RDC) USING HIGH RESOLUTION IMPEDANCE MANOMETRY (HRIM) IN PATIENTS WITH ACHALASIA TREATED WITH PERORAL ENDOSCOPIC MYOTOMY (POEM)

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Introduction: High resolution impedance manometry (HRIM) allows simultaneous assessment of esophageal motility and bolus transport. Previous studies have shown that the height of the retained column after a rapid drink challenge test (RDC) correlates with the height of the barium column measured 5-min after timed barium esophagogram, with the increment of the pressurization of the esophageal body and with the intensity of dysphagia. However, evaluation of the height of the water column after treatment with POEM, which means a larger myotomy that is often associated with reflux, has not been reported.

Aims & Methods: To evaluate the effect of treatment with POEM on the height of the retained water column after a RDC, and its correlation with pressurization of the esophageal body and esophageal symptoms, in patients with achalasia.

We prospective studied 16 consecutive patients (8M, 8F, mean age 56 yr) diagnosed with achalasia and treated with POEM. In each patient, a 200-ml RDC was performed before and 2-12 months after treatment. Pressure responses, height of the retained column, number and length of reflux episodes were measured using HRIM. Symptoms were scored by the Eckardt Scale. An upper endoscopy has been performed before treatment and after treatment.

Results: Before treatment, all patients showed an obstructive pattern of pressure responses characterized by pressurization of the esophageal body (37±7 % of time with pressure >20 mmHg, pressure gradient across the EGJ 20±4 mmHg) that reverted to a non-obstructive pressure pattern after POEM in all (3±1% of time with pressure >20 mmHg, pressure gradient across the EGJ 2±2 mmHg; p< 0.05 vs before treatment for both) and that was associated to clinical improvement (Eckardt score 8.0±0,6 before vs 0.9±0,2 after POEM, p< 0.05). Treatment with POEM was associated to a reduction in the height of the water column retained immediately after the RDC, from 12±2 cm to 5±1 at 1 min after the RDC (before and after treatment respectively; p< 0.05), and this reduction correlated with the reduction of the Eckardt score (r=0.703; p=0.005). After this immediate clearance of the bolus, 6 patients had 2.5±0.5 reflux episodes of 29±18 sec duration (range 4-120sec), occurring at 81.3±13.2 sec after the end of the RDC, leading to an increment in the height of the water column measured at 5 min after the RDC (1.4±0.6 cm vs 8,5±1.3 cm after treatment; NS). The endoscopic follow up showed mild esophagitis in 7 patients that did not correlate with the presence of reflux after the RDC (p=0.622).

Conclusion: Measurement of the height of the column retained after a RDC using HRIM may objectively confirm treatment success after POEM in patients with achalasia. However, reflux of the ingested bolus occurs frequently after the RDC, and needs to be carefully considered to determine the right timing for evaluation of bolus clearance in patients treated with POEM.

References: Cho et al. Am J Gastroenterol 2014;109:829, Marin et al. Neurogastroenterol Mot 2018: e13438. DOI:10.1111/nmo.13438).

Disclosure: Nothing to disclose

OP017 A RANDOMIZED CLINICAL TRIAL ON THE THERAPEUTIC EFFECT OF TRPA1 AND TRPM8 AGONISTS ON THE SWALLOWING FUNCTION OF PATIENTS WITH OROPHARYNGEAL DYSPHAGIA

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Introduction: Oropharyngeal dysphagia (OD) is a major complain among older people, patients with neurological diseases or stroke patients. Classical treatment of OD is based on compensatory strategies that do not promote the recovery of the swallowing function. Pharyngeal sensory stimulation through transient receptor potential channel (TRP) agonists is a promising active treatment.

Aims & Methods: The main aim of this study was to assess the therapeutic effect of TRPA1 and TRPM8 agonists in improving swallowing function in OD patients. For this purpose, we designed a prospective, double-blind, randomized, interventional study (NCT02193438), in which we included 58 patients with OD caused by ageing, stroke or neurodegenerative disease. Swallowing safety and efficacy and the kinematics of the swallow response were assessed by videofluoroscopy (VFS) during the swallow of nectar boluses of a xanthan gum based thickener supplemented with a) 756.6mM cinnamaldehyde and 70mM zinc (CIN-Zn) (TRPA1 agonists), b) 1.6mM citral (CIT) (TRPA1 agonist) or c) 1.6mM citral and 1.3mM isopulegol (CIT-ISO) (TRPA1 and TRPM8 agonists). The effects on pharyngeal event-related potentials (ERP) were assessed by electroencephalography during the deglutition of two supplemented boluses with the same agonist the patients received during the VFS. The brain activation was determined with sLORETA software.

Results: Compared to control series, TRPA1 stimulation with either CIN-Zn or CIT reduced time to laryngeal vestibule closure (CIN-Zn p=0.002, CIT p=0.023) and upper esophageal sphincter opening (CIN-Zn p=0.007, CIT p=0.035). In addition, CIN-Zn reduced the penetration-aspiration scale score (p=0.009), the prevalence of penetrations (p=0.039), the latency of the P2 peak of the ERP and enhanced the brain activation of the frontal gyri and the transverse temporal gyrus. The combination of CIT-ISO had not shown any beneficial effects on swallow biomechanics or neurophysiological measures. No significant adverse events were observed.

Conclusion: TRPA1 stimulation with CIN-Zn or CIT improves swallow response which, in the case of CIN-Zn, is associated with an enhanced cortical activation, and leads to a significant improvement in swallow safety in patients with OD. These results set the basis to develop new active treatments for OD using TRPA1 agonists, moving away from compensation to the recovery of the swallowing function.

Disclosure: This study was supported by a grant from Nestlé Health Science and presented in the 8th ESSD Congress as an oral presentation.

OP018 WITHDRAWN

IBD: Basic science
10:30-12:00 / B3

OP019 TLR4-INDUCED DYSBIOSIS PROMOTES AN EXPANSION OF PROTEOBACTERIA THAT INCREASES SUSCEPTIBILITY TO TUMORIGENESIS

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Introduction: Dysbiosis in inflammatory bowel diseases (IBD) and colitis-associated cancer (CAC) is characterized by an increase in the relative abundance of facultative anaerobes (Proteobacteria). These bacteria

bloom by performing anaerobic respiration using certain substrates that are generated in the presence of reactive oxygen species (ROS). However, the interplay between the host and the microbiota that leads to dysbiosis is not fully understood. Our laboratory has shown that IBD dysplasia and colorectal adenomas overexpress toll-like receptor 4 (TLR4) in intestinal epithelial cells (IECs). Moreover, we have described that epithelial TLR4 activation increases susceptibility to CAC.

Aims & Methods: In this study, we tested the hypothesis that IECs, via TLR4 activation, provide the microbiota with ROS that can be used by Proteobacteria to outgrow obligate anaerobes. Furthermore, we aimed to determine whether TLR4-mediated susceptibility to CAC is induced by the dysbiotic microbiota.

IECs isolated from villin-TLR4 mice (which express a constitutively active form of TLR4 in IECs) and their WT littermates were analyzed for H_2O_2 production (Amplex Red) and expression of NADPH oxidase 1 (Nox1) and dual oxidase 2 (Duox2; qPCR). Colonoids from wild-type (WT), TLR4-KO, Nox1-KO, and DuoxA2-KO mice were stimulated with lipopolysaccharide (LPS) and tested for H_2O_2 production in the presence of the NADPH oxidase inhibitor, diphenyleneiodonium. Mucosa-associated microbiota (MAM) of villin-TLR4 and C57Bl/6 mice was used to colonize WT germ-free mice. After 3 weeks of engraftment, half of the MAM-engrafted mice were euthanized to verify engraftment via 16S sequencing, whereas the other half of mice underwent a chemical model of CAC by administration of azoxymethane followed by 3 cycles of 3% dextran sulfate sodium. Tumor burden and size as well as H_2O_2 production in IECs were measured at the end of the experiment.

Results: Constitutive activation of epithelial TLR4 in vilin-TLR4 mice significantly increased the production of H_2O_2, which was accompanied by a marked upregulation of Nox1, Duox2, and DuoxA2 transcripts. Similarly, LPS stimulation in WT colonoids induced the upregulation of Nox1, Duox2, and DuoxA2 and the release of H_2O_2 in a TLR4- and NADPH oxidase-dependent manner, as demonstrated by total abrogation of responses in TLR4-KO colonoids and in diphenyleneiodonium-treated WT colonoids. DuoxA2-KO colonoids showed a marked attenuation in the production of H_2O_2 upon LPS challenge, demonstrating that this NADPH oxidase drives TLR4-mediated production of H_2O_2. Villin-TLR4 MAM was characterized by an expansion in Proteobacteria that could be transmitted to WT GF recipient mice. In addition, this TLR4-induced microbiota caused an upregulation in Duox2 and DuoxA2 expression in IECs of WT germ-free recipient mice. After the chemical model of CAC, recipient mice of villin-TLR4 MAM developed more tumors of bigger size when compared to C57 MAM. Consistently, IECs isolated from non-involved areas demonstrated higher release of H_2O_2 in villin-TLR4 MAM-recipient mice, indicating that dysbiosis increases susceptibility to CAC by promoting an oxidative milieu.

Conclusion: Our findings demonstrate that TLR4 activation in IECs promotes a Duox2-mediated oxidative phenotype that facilitates the blooming of Proteobacteria in the absence of overt inflammation. Furthermore, we show that such TLR4-induced dysbiosis increased the susceptibility to CAC. These findings suggest that the intestinal epithelium plays pivotal roles in promoting dysbiosis.

Disclosure: Nothing to disclose

OP020 MYELOID CALCINEURIN IN THE CONTROL OF IMMUNE CHECKPOINT INHIBITION IN INTESTINAL TUMOR DEVELOPMENT

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Introduction: Colorectal cancer (CRC) development is based on somatic mutations in tumor suppressor genes and oncogenes. Intestinal inflammation is a risk factor for CRC but recent work has demonstrated that immunological pathways also play critical roles in the development of sporadic CRC, in the absence of clinically overt intestinal inflammation. We have previously shown that the phosphatase calcineurin and its downstream mediators of the NFAT transcription factor family are active in the intestinal epithelium and support tumor development through promotion of epithelial proliferation.

Aims & Methods: Here, we asked whether calcineurin and NFAT play similar tumor-promoting roles in myeloid cells and analyzed potential synergistic effects of epithelial and myeloid calcineurin in intestinal tumor development. We studied mice with myeloid-specific deletion (LysM-Cre) of calcineurin or NFAT in the $Apc^{Min/+}$ model of genetically-induced intestinal tumor development as well as in an orthotopic colonic CRC model associated with liver metastasis. In addition, we analyzed 1500 human CRCs.

Results: We observed barrier dysfunction at sites of intestinal adenomas, which was associated with tumor infiltration by the commensal microbiota and microbiota-dependent activation of calcineurin and NFAT in myeloid tumor-infiltrating cells. Calcineurin-NFAT signaling in myeloid cells promoted the expression of IL-6, which was associated with activation of epithelial STAT3. STAT3 in turn supported tumor cell proliferation and survival in a cell-intrinsic manner and was also associated with dramatic induction of epithelial expression of the two co-inhibitory proteins B7H3 and B7H4. Antibody-mediated blockade or epithelial deletion of these co-inhibitory proteins led to an increased CD8^{+} cytotoxic T cell response against tumor cells in mice, which was associated with protection from intestinal tumor growth as well as the development of liver metastasis, suggesting a central role of myeloid calcineurin in licensing T cell responses against intestinal tumors. Moreover, increased expression of these immune checkpoint proteins correlated with reduced CD8^{+} T cell infiltration in human CRCs and reduced CRC-associated survival.

Conclusion: Our studies reveal a novel pathway of calcineurin-dependent cross-talk between epithelial, myeloid, and T cells, which promotes tumor development through inhibition of cytotoxic T cell responses and which is potentially amenable to therapeutic targeting.

Disclosure: Nothing to disclose

OP021 SUPPLEMENTATION WITH BUTYRATE PRODUCING BACTERIA REDUCES TUMOR LOAD IN A MOUSE MODEL OF COLORECTAL CANCER

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Introduction: Colorectal cancer (CRC) is one of the most prominent cancers with increasing incidence rates, and originates at the crossroad of the microbiome and its host. Besides genetically predisposing factors, CRC is strongly influenced by the inflammatory status of the tissue, the presence of carcinogenic substances (such as microbiome metabolites), and the regulation of the host's immune response. Although the link of the intestinal microbiota to these functions is well established, the biological understanding of the modes of action is not well understood. Here, we studied how certain intestinal microbiota contributes to the prevention of CRC.

Aims & Methods: In a first approach, colitis associated tumourus were induced in wild-type (WT) and RAG2^{-/-}C57BL/6 mice via administration of three cycles of 1% dextran sodium sulfate (DSS) + azoxymethane (AOM). PBS, *Peptostreptococcus stomatis* or a mix of 4 butyrate-producing strains was supplemented via daily oral gavage on days 8-10 of each AOM/DSS cycle.

Next, we used an inflammation-independent model of CRC, where MC-38 tumour cells were injected into the cecum wall after WT mice received PBS or the mix of butyrate-producing bacteria for three consecutive days. Intestinal microbiome was analyzed in stool samples before, during and after administration of the bacteria to the mice. Colon tumour and non-tumour tissue were analyzed using RNAseq, flow cytometry and histology techniques.

Results: We found that tumour burden in the DSS/AOM model was associated with increased levels of fecal *P. stomatis*, but overall reduced levels of butyrate-producing bacteria. In DSS/AOM-treated WT mice, supplementation with *P. stomatis* significantly enhanced tumour load when compared to PBS-treated controls. In contrast, only a small fraction of WT mice treated with butyrate producers developed tumours. Supplementation with *P. stomatis* was associated with increased intestinal inflammation as assessed in endoscopy and histology after each AOM/DSS cycle compared to WT mice supplemented with butyrate producers. However, the beneficial effect of

butyrate-producing bacteria was lost in RAG2^{-/-} mice, indicating that T-cells are crucially involved in mediating the anti-tumour effect. As causative mechanisms, we found an increased number of IFNγ+ CD8+ cytotoxic T- cells and IFNγ+ NK cells inthe tumour tissue of WT mice supplemented with butyrate producers compared to control and *P. stomatis* groups, indicating that supplementation with butyrate producers promoted increased anti-tumour immune responses. Further, the increase in PD-L1+/PD-L2+ tumour-associated macrophages was absent in those mice.

In the cecum injection model, we found a reduction in tumour development in mice treated with butyrate producers. Interestingly, tumours from mice receiving butyrate producers had a higher amount of activated CD8+ T cells compared to controls, while in the surrounding tumour tissue there were more naïve CD8+ T cells in mice supplemented with butyrate-producing bacteria, suggesting that butyrate producers induce the infiltration and differentiation of naïve CD8+ T cells into the tumours.

Conclusion: Our results indicate that oral supplementation with selected butyrate producers protects from CRC tumour development via promoting anti-tumour T cell responses *in vivo* in inflammation-dependent and independent CRC mouse models. Our findings suggest that manipulation of the intestinal microbiota might be a promising novel approach to promote anti-cancer immune responses.

Disclosure: Nothing to disclose

OP022 HIGH-THROUGHPUT PHENOTYPIC SCREENING OF COLON CANCER STEM CELL INHIBITORS USING TUMOURSPHERES

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Introduction: Cancer stem cells (CSCs) are a subpopulation of cancer cells implied in tumour formation, metastasis and recurrence due to their long-lasting properties and chemotherapy resistance.
Aims & Methods: Here, we aimed to optimize, validate and apply a high-throughput screening (HTS) platform to identify novel molecules from large compound libraries that specifically impact on colorectal CSC phenotype.
Results: For validation of the HTS platform, HT29 human colorectal adenocarcinoma cells were plated in undifferentiated medium in ultra-low attachment conditions for sphere formation and treated with previously reported CSC-targeting agents (e.g. salinomycin; 1 µM) or traditional chemotherapeutic agents (e.g. 5-fluorouracil (5-FU), irinotecan and oxaliplatin; 1 µM) or vehicle controls. Following 7 days of incubation, the number and size of spheres were assessed, while cell viability was determined based on measurement of ATP. This screening system was tested in both 96- and 24-well plates. Classical chemotherapeutics such as 5-FU and irinotecan were not able to impact on HT29-derived spheres, while the anti-CSC agent salinomycin markedly reduced cell viability, sphere formation potential, as well as sphere size in both plate formats.
Next, we proceeded with the evaluation of the effectiveness of ~1,420 chemical compounds as potential anti-CSC agents from selected in-house and external libraries. For hit selection, a cut-off threshold > 70% of ATP depletion led to 150 hits, corresponding to ~11% hit rate for the full library, with some series particularly rich in actives. Additional compounds decreased ATP activity under 1% and have been excluded due to eventual excess of toxicity and impossibility to build a dose-response curve. To quantitatively assess hit inhibitory potency, dose-response curves were built using a 10-point concentration range of 0.03 - 16.00 µM. From those, 69 compounds showed a sigmoidal dose-response curve-fit and a half-maximal inhibitory concentration (IC$_{50}$) ≤ 2 µM. Twenty-four compounds were further selected for testing on other colorectal cancer cell lines (SW-620, HCT116), based on their structural diversity and predicted drug-like properties. Seventeen compounds displayed an IC$_{50}$ ≤ 2 µM in both cell

lines, whereby anti-CSC effect was further validated by assessing impact on tumoursphere formation. Five compounds at the IC$_{50}$ dose robustly decreased the number of HT29-, SW-620- and HCT116-derived spheres. Those hits were tested on colorectal cancer cell lines plated in adherent conditions (5,000 cells/well) and primary mouse hepatocytes (10,000 cells/well) for 72h using a 10-point concentration range of 0.01 - 243.00 µM and 1 compound was excluded for potential severe hepatotoxicity. Future work comprises *in vivo* proof-of-principle experiments, hit-to-lead medicinal chemistry and identification of precise mechanisms of action.
Conclusion: In conclusion, a novel HTS platform to test a wide range of candidate compounds to target CSCs was developed and validated, allowing the identification of potent colon cancer stem cell inhibitors.
Supported by COMPETE (LISBOA-01-0145-FEDER-016405) and FCT (SAICTPAC/0019/2015).
Disclosure: Nothing to disclose

OP023 XBP1 COORDINATES DNA DAMAGE INDUCED STEM CELL REPRESSION IN THE INTESTINAL EPITHELIUM VIA DDIT4L-DEPENDENT MTOR INHIBITION

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Introduction: Intestinal stem cells are particularly prone to the accumulation of hazardous mutations leading to malignant transformation. We have shown that RNase H2-mediated ribonucleotide excision repair (RER) preserves genomic integrity of intestinal stem cells. In the absence of RNase H2, intestinal epithelial cells generate DNA damage and induce a p53-driven suppression of the intestinal stem cell (Aden, Bartsch et al. 2019). XBP1 encodes for a transcription factor critically involved in resolving endoplasmic reticulum (ER) stress (Kaser, Lee et al. 2008). Whether Xbp1-mediated signalling is directly involved in DNA damage response mechanisms is not known.
Aims & Methods: The aim of the study is to investigate the role of XBP1 in coordinating epithelial DNA damage response and p53-driven intestinal stem cell suppression.
For this purpose, murine intestinal epithelial ModeK cells (iCtrl and i*Xbp1*) were stimulated with the DNA-damaging agent Cytarabin A (AraC) and subjected to gene expression analyses, FACS cell death assays and immunoblot analyses. We generated conditional intestinal epithelial knockout of *Xbp1*, *Rnaseh2b* and the combined DKO. Intestinal organoids of derived from *Rnaseh2b/Xbp1*^{fl/fl}, *Xbp1*[ΔIEC], *Rnaseh2b*[ΔIEC] and *Rnaseh2b/Xbp1*[ΔIEC] mice were derived used for immunoblot analyses, colony formation assays and RNA sequencing. We employed *Rnaseh2b/Xbp1*^{fl/fl}, *Xbp1*[ΔIEC], *Rnaseh2b*[ΔIEC] and *Rnaseh2b/Xbp1*[ΔIEC] mice were used for *in-vivo* basal phenotyping of young (8 week) and aged (52 week) mice as well as, acute and chronic DSS-colitis models. *Post mortem* analyses included fluorescence or IHC stainings, western blot analyses and gene expression analyses.
Results: *Xbp1*-deficiency elevates AraC-induced DNA-damage and epithelial cell death *in-vitro*. Untreated and DSS-treated *Rnaseh2b/Xbp1*[ΔIEC] mice exhibit display heightened amounts of DNA damage, cell death and intestinal inflammation. Compared to *H2b*[ΔIEC] mice, which were previously shown to exhibit a *p53*-dependent stem cell arrest that protects them from intestinal carcinogenesis, *Xbp1*-deficiency impairs stem cell arrest in *Rnaseh2b/Xbp1*[ΔIEC] mice, leading to epithelial hyperproliferation and spontaneous intestinal carcinogenesis. Mechanistically, RNA sequencing of intestinal organoids (*Rnaseh2b/Xbp1*^{fl/fl}, *Rnaseh2b*[ΔIEC], *Rnaseh2b/Xbp1*[ΔIEC] and *Rnaseh2b/p53*[ΔIEC]) reveals that XBP1 coordinates a *p53*-dependent induction of the DNA damage inducible transcript 4l (*Ddit4l*). *Mechanistically*, Xbp1 directs a Ddit4l- mediated mTOR-inhibition and dephosphorylation of the translation initiator 4E-BP1, leading tothereby determining suppression of epithelial proliferation. In *in-vitro* intestinal organoid growth assays we demonstrate, that pharmaceutical inhibition of the mTOR pathway by Rapamycin restores epithelial stem cell suppression in *Rnaseh2b/Xbp1*[ΔIEC] organoids.

Conclusion: Our data suggest a crucial role for XBP1 in directly coordinating epithelial DNA damage responses and intestinal stem cell suppression via a novel Ddit4l-mTOR dependent feedback mechanism.

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Disclosure: Nothing to disclose

OP024 STEM CELL DERIVED INTESTINAL ORGANOIDS AS AN ADVANCED SCREENING PLATFORM FOR POTENTIAL CLOSTRIDIUM DIFFICILE TOXIN INHIBITORS

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Introduction: The establishment of organoid culture systems represents a milestone on the route towards successful personalized medicine. Intestinal organoids dervied from human pluripotent stem cells display essential attributes of adult intestinum even composed of different tissue types. Moreover, complex organoid structures represent a highly realistic testing platform for advanced toxicity assays and subsequent evaluation of potential toxin inhibitors. Organoids can be defined as 3D structures derived either from pluripotent or organ restricted stem cells harboring the ability to mimic in vivo architecture and multi lineage differentiation of terminally differentiated tissues. The pathogeinicity of Clostridium difficile is mainly attributable to the production of the large protein toxins (C difficile toxins [Tcd]) A (TcdA) and B (TcdB) and -in few bacterial strains- the binary enterotoxin CDT.
Aims & Methods: The toxin-inhibiting effect of different potential proteins and small molecules like albumin or VER-155008 was evaluated in stem cell derived induced human intestinal organoids (iHIOs). iHIOs are derived from hair sheet keratinocyte cultures from a healthy donor. After cellular reprogramming towards induced pluripotent stem cells, intestine organoids were generated in a stepwise differentiation protocol. These organoids display basic characteristics, such as crypt-like structures and architecture of a polarized intestinal epithelium, of human intestine tissue, containing both epithelial and non-epithelial cell types. Direct effects of clostridial toxins and potential protective effects of various substances were evaluated in a standardized approach.
Results: Toxin inhibitors like VER-155008 or Albumin decreased toxin-mediated F-actin destruction, while cortical F-actin was clearly more preserved and resembled more to the structure in untreated control organoids. Moreover, a clear distribution/organization of the adhesion protein E-cadherin mainly at the cortex of cells was observed in control miniguts whereas in toxin-treated organoids E-cadherin was more diffusely distributed and clustering of E-cadherin became obvious. Toxin-inhibiting treatment led to reduced clustering while E-cadherin maintained its cortical localization comparable to control organoids.
Conclusion: iHIOs may serve as a highly advanced toxicity-screening platform with essential advantages compared to pervious single cell toxicity assays.
Disclosure: Nothing to disclose

Basic science: Neurogastroenterology
10:30-12:00 / B5

OP025 RECTAL COMPLIANCE IS AFFECTED BY ENTERIC NERVOUS SYSTEM AND INTERSTITIAL CELLS OF CAJAL IN MURINE SMOOTH MUSCLE

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Introduction: Rectal compliance, contributing to fecal storage, is different from the colonic propulsive movement. Abnormal rectal compliance is presented in many functional gastrointestinal motility disorders, such as irritable bowel syndrome, constipation and fecal incontinence.
Aims & Methods: This study aimed to explore the electromechanical characterisics of rectal compliance in the murine rectum and investigate the contribution of intrinsic inhibitory neurotransmission and interstitial cells to rectal compliance.
Male C57BL/6 mice, aged 8 weeks or more were used. For in vivo experiments, the mice were anesthetized with isoflurane, and anorectal manometry was applied to measure rectal compliance through rectum. In ex vivo experiments with using murine rectum, intra-rectal pressure was measured in organ bath. The colonic migrating motor complex (CMMC) measurements and electrophysiological microelectrode recordings for membrane potential were performed using smooth muscle strips and segments. Calcium imaging was used to measure the calcium transients in the interstitial cells and smooth muscle cells within the rectum of the mice expressing a genetically encoded calcium indicator (GCaMP). Drugs affecting inhibitory neurotransmission including L-NNA and apamin were applied.
Results: The rectal compliance was significantly decreased after in vitro intraperitoneal injection and ex vivo infusion into organ bath of L-NNA and apamin, respectively ($p=0.002$ vs 0.005; $p=0.016$ vs 0.015) (Fig 1). In ex vivo experiments, rectum did not have CMMC, and after treatment of the L-NNA or apamin in the organ bath, the rectal contractions were increased, not CMMC (6.19±3.98 vs 20.35 ±15.78 mN·min, $p=0.031$), and propagation of contractions from the distal colon increased (7.20±3.32 vs 29.12±20.75 mN·min, $p=0.046$). In membrane potential with electric field stimulation, inhibitory junction potential significantly increased after L-NNA and apamin, respectively (17±2.9 vs 16±1.6 mV, $p=0.04$; 24±2.5 vs 13±3.6 mV, $p=0.02$). In calcium transient of smooth muscle, AUC (area under the curve) in rectum was smaller than that of colon (9.36±4.57 vs 3.49±2.58 IU·min, $p=0.03$), and AUC in rectum increased after L-NNA and apamin, respectively (3.79±1.93 vs 9.71±4.52 IU·min, $p=0.001$; 3.26±1.92 vs 8.31±4.12 IU·min, $p=0.021$). In calcium transient of ICC of rectal circular muscle, AUC significantly increased after L-NNA (7.39±2.52 vs 10.98±3.71 IU·min, $p=0.012$).
Conclusion: Murine rectal compliance were identified in the study. Enteric inhibitory neurotransmissions was related to the rectal compliance. ICC could control the rectal smooth muscle activities.
Disclosure: Nothing to disclose

OP026 EVALUATION OF PLASMA M2-PYRUVATE KINASE IN DIFFERENTIATION BETWEEN FUNCTIONAL AND ORGANIC COLONIC DISORDERS

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Introduction: M2-pyruvate kinase (M2-PK) is a key regulator of tumor growth and important for tumor metabolism and can dynamically regulate aerobic glycolsis. Differentiating between functional bowel disorders, such as irritable bowel syndrome (IBS), and organic colonic disorders such as inflammatory bowel disease (IBD), colorectal polyps, and colorectal cancer (CRC) can often be difficult as they present with similar and/or overlapping clinical presentations. The investigation and procedures to differentiate between organic and functional bowel disorders often incurs consider-

able health-care costs both for patients and community health service. The selection of patients who should undergo colonoscopy and/or imaging procedures is one of the key points of the diagnostic process, which should avoid the abuse of invasive and costly tests as well as the underestimation of potentially harmful diseases.

Aims & Methods: The aim of this study is to evaluate the diagnostic value of plasma M2-pyruvate kinase level in differentiating functional colonic disorders (e.g: IBS) from organic colonic disorders(e.g: IBD, colorectal polyps and CRC).This case control study included 150 patients with different colonic disorders, 75 patients with IBS, 25 patients with ulcerative colitis (UC), 25 patients with colorectal polyp and 25 patients with CRC. We measured the plasma M2-PK using Enzyme-linked immunosorbent assay (ELIZA) in IBS patients and comparing these levels with those obtained from patients with UC, colorectal polyp and CRC.

Results: Our study revealed a highly significant increase in plasma M2-PK in patients with organic colonic disorders compared to functional group (IBS). Using Receiver operating characteristic (ROC) curve at area under curve (AUC) 0.872 and cut-off value of >3 U/ml, our overall sensitivity and specificity for organic group over the functional group were 81.94% and 83.3% respectively with 35.3% positive predictive value and 97.6% negative predictive value.

Conclusion: M2-PK is a good marker for discrimination of functional from organic colonic disorders (IBD and colorectal polyp, and CRC). Future researches including a large studies population and long-term follow-up studies is recommended.

Disclosure: Nothing to disclose

OP027 A NEW ACCURATE TEST BASED ON FAECAL MICROBIOTA TO POSITIVELY DIAGNOSE IRRITABLE BOWEL SYNDROME

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Introduction: The Irritable Bowel Syndrome (IBS) is a functional disorder affecting up to 15% of world population. Despite its high prevalence, there is not a specific diagnostic test for this syndrome. Currently, diagnosis is based on the characteristic symptoms systematized in the Rome IV criteria. Although Rome IV criteria are mandatory, they are not enough to stablish the diagnosis and the patients are not exempt from going through relevant explorations to discard some organic pathologies which share symptomatology to IBS. RAID-Dx is a non-invasive test developed to positively diagnose IBS patients based on specific faecal bacterial signature.

Aims & Methods: The aim of this work was to develop a non-invasive test to positively diagnose IBS and demonstrate its capacity. A cohort consisting on 52 IBS patients and 61 healthy subjects was used to develop a specific bacterial signature. IBS patients met Rome IV criteria and H subjects were asymptomatic, all of them went through a colonoscopy and presented no valuable macroscopic lesions in the colon. Different bacterial markers were analysed from a stool sample obtained from each subject prior to the diet-preparation for the colonoscopy. RAID-Dx was defined in a proof-of-concept with 70% of the cohort (36 IBS patients and 43 H subjects) and the obtained results were validated with the remaining 30% (16 IBS patients and 18 H subjects).

Results: In the proof-of-concept, RAID-Dx showed high sensitivity and specificity values of 91.67% and 86.05%, respectively. In addition, a Positive Predictive Value (PPV) of 84.62% and a Negative Predictive Value (NPV) of 92.50% for the diagnosis of IBS patients were also found.
In the validation of the defined bacteria signature for RAID-Dx, sensitivity increased up to 93.75% and specificity decreased until 72.22%. The PPV were also decreased (75.00%) whereas NPV was kept similar (92.86%).

Conclusion: RAID-Dx is an accurate marker to diagnose IBS with high sensitivity and specificity, which makes it a candidate to become a standard, widely accepted diagnostic method of IBS.

OP028 DELETION OF DELTA OPIOID RECEPTORS ON NOCICEPTIVE SENSORY NEURONS ABOLISHES T CELL-MEDIATED ANALGESIA WITHOUT ALTERING INTESTINAL INFLAMMATION IN MICE

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Introduction: T lymphocytes play a pivotal role in the endogenous regulation of inflammatory visceral pain. Thus, we have previously shown that the local release of enkephalins by effector CD4^{+} T lymphocytes relieves from inflammatory pain in the later phase of the Dextran Sulfate Sodium (DSS)-induced colitis model. In this model, intestinal epithelium integrity disruption leads to the translocation into the mucosa of bacteria which activate innate immune cells. This early phase of the disease results in visceral hypersensitivity. In the later phase of the disease, when the adaptive immune response against bacterial antigens took place, the migration of effector T lymphocytes within the colon normalizes the visceral sensitivity. This T-cell analgesic effect is dependent on the activation of opioid receptors expressed on nociceptor terminal endings by enkephalins locally released by mucosal effector T lymphocytes accumulating into the intestinal mucosa.

Aims & Methods: The aim of the study was to identify the receptor(s) for enkephalins (*i.e.* μ and δ opioid receptor subclasses) responsible for T cell-mediated analgesia. For this purpose, we compared colitis severity, mucosal T cell density and visceral sensitivity in both early and late phases of DSS-induced colitis in floxed (littermates) and conditional knockout mice in which each opioid receptor has been specifically deleted in $Na_v1.8^+$ sensory neurons.

Results: We show that analgesia induced by T cell-derived opioids is elicited via activation of δ but not μ opioid receptors expressed on peripheral sensory nerves. The absence of each receptor on sensory nerves did not change neither the inflammatory status nor the time-course of the adaptive immune response.

Conclusion: Endogenous regulation of inflammatory visceral pain by T cell-derived enkephalins is mediated by δ opioid receptors expressed on enteric $Na_v1.8^+$ sensory neurons

Disclosure: Nothing to disclose

OP029 INTESTINAL MICROBIOTA AS A MEDIATOR OF LUMINAL PROTEOLYTIC ACTIVITY AND ALTERED INTESTINAL PERMEABILITY IN CAMPYLOBACTER JEJUNI POST INFECTION IRRITABLE BOWEL SYNDROME

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Introduction: Up to 15% of *Campylobacter jejuni* enteritis patients may develop post-infection irritable bowel syndrome (PI-IBS). The mechanisms for PI-IBS development remain unclear. A subset of PI-IBS patients (~40%) have elevated proteolytic activity (PA) in their stool correlating with looser and more frequent bowel movements[1].

Aims & Methods: Our aim was to determine microbiota associations with PA in PI-IBS patients and microbial mediation of PA and intestinal permeability using microbiota-specific humanized mouse model. 29 PI-IBS patients (Rome III) {20 females, mean (SD) age 46.8 (16.7) yrs}, 14 PI-no-IBS controls {5 females, 50.1 (15.6) yrs} and 21 healthy volunteers (HV) {16 females, 40.6 (13.7) yrs} were recruited. Fecal PA was assessed using FITC-casein assay. Shotgun metagenomics was performed for microbiota assess-

ment. β-diversity was summarized using Unifrac and Bray-Curtis distance with significance assessed using nonparametric PERMANOVA method. Differentially abundant taxa were identified using a multivariable linear model with permutation to assess statistical significance, accounting for non-normality of abundance data. To investigate microbiome regulation of luminal PA, stool from a subset of these patients (n=6 stool/PA classification) were used to humanize 4-week old germ-free (GF) mice (ex-GF). Six weeks post humanization, fecal PA and stool frequency was measured and serum was collected after administration of creatinine, 4kDa FITC-Dextran and 70kDa Rhodamine B-Dextran to assess *in vivo* permeability.

Results: 12/29 PI-IBS {8 females}, were classified as High PA (>85th percentile of HV, >891 BAEE/mg of protein). Compared to Low PA patient stool, High PA patients had significantly decreased microbial diversity (Bray-Curtis, PERMANOVA p< 0.001). Low PA patients had an increased abundance of genus *Prevotella* and *Firmicutes* and decreased abundance of *Bacteroides*. Humanization of mice with microbiota from Low PA stool suppressed baseline PA of GF mice while microbiota from High PA patients resulted in unchanged PA from baseline (% of baseline, Low PA 17.2 ± 30.0; High PA 100.4 ± 122.0, p< 0.05). High PA mice had increased PA at six weeks post humanization (BAEE units/mg protein, High PA 1570.9 ± 1834.3, Low PA 240.5.2 ± 374.8; p< 0.05). No difference was observed in stool frequency (pellets/hr, High PA 9.4 ± 3.0; Low PA 9.0 ± 3.6); however High PA mice had looser pellets when scored for fecal consistency (Scored 0=normal to 4=diarrhea, High PA 0.82 ± 0.49; Low PA 0.18 ± 0.33 p< 0.001. Permeability of creatinine increased only in mice humanized with High PA microbiota (mg/dL, High PA 0.81 ± 0.28); Low PA 0.58 ± 0.24; HV 0.51 ± 0.36 p< 0.05), while permeability of 4kDa FITC-Dextran increased in both Low and High PA humanized mice compared to HV humanized mice (mg/dL, High PA, 19.1 ± 14.6; Low PA 23.9 ± 23.9; HV 13.7 ± 30.3 p< 0.05). Creatinine and 4kDa FITC-Dextran permeability positively correlated with terminal PA (Spearman r=0.31 and 0.27 respectively, p< 0.05).

Conclusion: High PA PI-IBS patients have significantly decreased fecal microbial diversity. Low PA microbiota suppresses host luminal PA while High PA microbiota did not change host PA. Compared to Low PA microbiota, High PA microbiota causes increased intestinal permeability through the pore pathway. Therefore, microbiota may influence intestinal permeability in PI-IBS through modulation of proteases. *Supported by NIH K23 DK 103911.*

References: Edogawa S, Edwinson AL, Peters SA, et al. Serine proteases as luminal mediators of intestinal barrier dysfunction and symptom severity in IBS. Gut 2019:gutjnl-2018-317416.

Disclosure: Nothing to disclose

OP030 CIPROFLOXACIN TREATMENT AFFECTS THE STRUCTURE AND ACTIVITY OF ENTERIC NERVOUS SYSTEM IN MOUSE SMALL INTESTINE

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Introduction: Commensal gut microbiota ensures the functional and structural integrity of enteric nervous system (ENS) circuitries. Any change of its composition elicited by environmental factors or drugs could disrupt ENS homeostasis and determine the onset of functional bowel disorders. Ciprofloxacin is a synthetic broad-spectrum antimicrobial agent, belonging to the fluoroquinolone family, used for treating respiratory, urinary tract, gastrointestinal and abdominal infections. Ciprofloxacin usage has been associated with many adverse reactions, including neurotoxicity.

Aims & Methods: The aim of the present study was to evaluate the effect of ciprofloxacin on ENS integrity and gastrointestinal motility in young mice. Male C57Bl/6 mice (age=9±1 weeks; N=44) were orally gavaged with ciprofloxacin (50 mg/kg, suspended in 1% methylcellulose; CPX group) or vehicle (CNTR group) for 14 days. In CPX and CNTR animals we assessed:
i) gastrointestinal transit 30 minutes after intragastric administration of nonabsorbable-FITC-labeled dextran;
ii) pellet frequency, measured as changes in stool output during a 60-minute collection period;
iii) stool water content;
iv) contractile activity of isolated ileum segments, measured as changes

in isometric muscle tension following carbachol (0.001- 100 μM), KCl (60 mM), electric field stimulation (EFS, 1-40 Hz) or inhibition in non-adrenergic, non-cholinergic (NANC) conditions (EFS=10 Hz, 1 μM atropine, 1 μM guanethidine, with or without 0.1 mM L-NAME);
v) distribution of the neuronal HuC/D and glial S100β markers by confocal immunofluorescence in ileal frozen cryosections;
vi) neurochemical coding integrity, evaluated by acetylcholinesterase and NADPH-diaphorase biochemical staining in longitudinal-muscle myenteric plexus preparations (LMMPs).

Results: Ciprofloxacin treatment determined a significant reduction in the number/hour output of fecal pellets (-36±8%, N=5/group, P< 0.01) and increased stool water content (+32±9%, N=5/group, P< 0.01). Gastrointestinal transit was delayed in CPX mice compared to CNTR mice (geometric center: 8.3±0.2 vs 7.3±0.2, N=6/group, P< 0.01), respectively). In vitro contractility studies showed a significant downward shift of the concentration-response curve to carbachol in CPX group (Emax=-36±5%, N=5/group, p< 0.01) compared with CNTR group, together with a reduced KCl-induced excitatory responses (-32±8%, N=5/group, p< 0.05). Altered excitatory and inhibitory neurotransmission in CPX mice was shown by decreased EFS-elicited contractions with a significantly reduction of 10 Hz-neuronal cholinergic response (CPX=-67±11%, N=5/group, p< 0.01) and by an impaired NANC-mediated relaxation of ileal segments from CPX mice. In the ENS of CPX mice, increased HuC/D immunoreactivity and NADPH-d-positive cells (+38±2%, N=5/group, P< 0.01) in the ileum of CPX mice together with reactive gliosis, evidenced by S100β immunofluorescence distribution.

Conclusion: Ciprofloxacin-induced gut dysbiosis determines complex anomalies in ENS architecture, neurochemical coding and function leading to neuromuscular dysfunction. Such neuroglial plastic changes are highly indicative of the negative effects mediated by ciprofloxacin on the integrity of gut microbiota-ENS axis, possibly contributing to promote functional bowel disorders later in life.

Disclosure: FC, CR, GCV are employees of Alfasigma SpA. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Hot topics from Latin America
10:30-12:00 / C2

OP031 A COMPARATIVE ANALYSIS OF DIGITAL CHOLANGIOSCOPY AND PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY FOR THE MALIGNANCY DETECTION IN BILE DUCT LESIONS

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Introduction: The differentiation of malignant from the benign biliary lesion is challenging in clinical practice. Peroral digital cholangioscopy (POCS) predicts malignancy through the visual impression of biliary lesions; whereas, Probe-based confocal laser endomicroscopy (pCLE) via in vivo, real-time tissue examination. Currently, both pCLE and cholangioscopy classification systems are available; however, a comparison between these classification systems remains unknown.

Aims & Methods: To compare the Paris classification criteria (pCLE) and the visual impression classification system (POCS) for the detection of malignancy in biliary lesions.

The following is a cross-sectional study. Data from patients referred for cholangioscopy and pCLE due to indeterminate biliary stricture was consecutively recorded and analyzed. The visual impression of biliary lesions during POCS were recorded following the classification system proposed by Robles-Medranda et-al. pCLE was performed using the Cellvizio CholangioFlex probe (Mauna Kea Technologies, Paris, France) during the ERCP procedure, and the pCLE findings for the diagnosis malignancy were recorded according to the Paris classification. pCLE videos were reviewed by one endoscopist, blinded to any clinical or ERCP information, and indicated which descriptive criteria (Paris classification) were observed in the videos displayed. Malignancy detection was defined following histopathology results. A video-set of 20 patients with pCLE were evaluated for interobserver agreement by two endoscopists (J.O and J.A).

Results: Forty-three patients were included; the median age was 62.2± 15.6 years; the 65.1% were female. The main reason for the evaluation was indeterminate biliary stenosis (44.18%) and suspected biliary tumor (55.8%). 67.44% of lesions were located in the proximal common bile duct. POCS visual impression detected malignancy in 76.7 % of patients, with a sensitivity, specificity, PPV, and NPV of 94%, 92%, 92%, and 94%, respectively. pCLE detected malignancy in the 79.0% of patients, with a sensitivity, specificity, PPV, and NPV of 64%, 100%, 100%, and 83%, respectively. Table 1 summarizes the overall accuracy of each pCLE criteria for malignancy prediction. A moderate interobserver agreement for pCLE criteria was obtained (K< 60).

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Tick blank band (>40 um)	85	24	37	75
Thick white band	87	40	42	83
Dark clumps	69	96	90	86
Epithelium	54	50	37	67

[Table 1. Overall accuracy for each pCLE features of malignancy.]

Conclusion: The visual impression of POCS using a classification system showed to be more sensitive than in vivo, real-time tissue examination of pCLE for the detection of malignancy in indeterminate biliary obstruction.
Disclosure: Nothing to disclose

OP032 WHOLE TRANSCRIPTIONAL ANALYSIS IDENTIFIES THE MESENTERIC ADIPOSE TISSUE OF CROHN'S DISEASE PATIENTS AS SITES OF T- AND B-CELL ACTIVATION

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Introduction: Crohn´s disease (CD) is a multifactorial disease characterized by chronic intestinal inflammation. The increased visceral adiposity near the affected intestinal area, of which mesenteric adipose tissue (MAT) is the main component, is a feature of CD. Both protective, as well as pathological, roles have been attributed to this disease-associated tissue in CD.
Aims & Methods: Our aim was to understand the contribution of MAT to CD pathophysiology by providing a molecular and cellular signature of disease-associated adipose tissue in CD patients. To do that we performed whole transcriptional analysis by RNA sequencing (RNA-seq) of MAT and ileum from CD patients with active disease (CD group, n=8) and non-IBD controls (CTR group, n=4). The biological validation of a panel of differentially expressed genes was conducted by qPCR in 26 CD patients and 17 non-IBD controls. Immunohistochemistry was also performed for validation analysis.
Results: RNA-seq identified 17 significantly regulated genes (|FC|>1.5; FDR< 0.05) in CD-MAT compared to non-IBD controls, with a marked upregulation of plasma cell genes (i.e., IGLL5, MZB1, CD79A, POU2AF1, FCRL5, JCHAIN, DERL3, SDC1, PIM2). A less strict statistical cutoff value (|FC|>1.5, nominal p£0.05) revealed a larger list of 651 genes in CD-MAT compared to controls. Ingenuity Pathway Analysis of this signature revealed a significant regulation of pathways related to T- and B-cell functionality. In contrast to MAT, transcriptional analysis of the ileum revealed a set of 849 genes significantly regulated in CD compared to non-IBD controls (|FC|>1.5; FDR< 0.05), and 2,654 genes when applying the lower cutoff (nominal p value< 0.05). Despite the differences between the MAT and ileal signatures of CD patients, we identified a subset of 204 genes significantly modulated in both tissues. This common signature included genes related to the plasma cell signature (MZB1, POU2AF1, IGLL5, JCHAIN, DERL3 and PIM2) that were significantly up-regulated both in CD-MAT and ileum. In contrast, other genes that are highly increased in CD ileum such as S100A8 and S100A9 (calprotectin), IL1B, CD14, CXCL1, CXCL8, MMP1, OSMR, all of which are related to an acute inflammatory response, were exclusively regulated in the ileal mucosa of CD disease, but not in the adjacent MAT. In

contrast, some genes encoding for lymphocyte receptors were exclusively regulated in CD-MAT, (i.e., MS4A1, CD6, CTLA4, CD3D, CD3E, IL2RG, LAG3-2, CD24, CD79A, CD5 and CD69), showing a different pattern of immune cell activation in this tissue compared to the ileum. Real-time RT-PCR in an independent patient and control cohort confirmed the significant upregulation of CD79A, SM4A1 (CD20), CTLA4 and CD3D in CD-MAT compared to controls, with no significant differences in IL1B and S100A8. Finally, immunohistochemistry and immunofluorescence analysis confirmed the large infiltrates and localized follicular structures containing both CD3+ and CD20+ lymphocytes in CD-MAT.
Conclusion: Our study reveals the marked accumulation of lymphocytes that form disseminated aggregates, as well as well-structured lymphoid follicles, in the MAT associated with CD inflamed ileum, but not in controls. Remarkably, acute inflammatory genes highly expressed in the ileum were not markedly upregulated in the adipose tissue. Our data strongly supports the role of CD-associated MAT as a site for T- and B-cell activation and suggests that it could also act as a reservoir of memory immune responses. Whether these antigen-specific responses would be detrimental or protective will require further study.
Disclosure: Nothing to disclose

Gastric intestinal metaplasia: The premalignant stomach
10:30-12:00 / C3

OP033 RISK FACTORS FOR THE PROGRESSION OF GASTRIC INTESTINAL METAPLASIA IN A LOW RISK POPULATION: A MULTICENTER, PROSPECTIVE, COHORT STUDY

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Introduction: Gastric cancer (GC) is mostly preceded by gastric precursor lesions (GPL). The recently updated MAPS guideline for surveillance of GPL now includes the recommendation for surveillance in case of a positive family history for GC. However, the evidence for this recommendation and our tools to identify patients at risk for progression are still scarce. This study therefore aimed to investigate if risk factors such as family history, lifestyle, genetic polymorphisms, and serology at baseline are possible predictors for progression of GPL in low risk areas.
Aims & Methods: Patients with GPL were included in the PROREGAL study; a multicenter, prospective cohort study. At upper endoscopy biopsies were obtained from 12 standardised sites in the stomach and from visible lesions. These were histologically assessed according to the operative link on gastric intestinal metaplasia (OLGIM) system. At baseline, patients completed a questionnaire on family history and lifestyle factors, and fastening blood samples were taken for pepsinogen and gastrin-17. All patients underwent at least two upper endoscopies. Progression of intestinal metaplasia (IM) was defined as progression of OLGIM classification between follow-up (FU) endoscopies. Previously associated single nucleotide polymorphisms (SNPs) with *H. pylori* infection or GC were determined using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP): *NCF4* (rs4821544), *TLR1* (rs28393318), *TLR4* (rs11536889) and *ATG16L1* (rs2241880). Cox-regression was performed for analysis on risk factors. Differences in proportions for the presence of SNPs were calculated using z-test. For all tests a significance level of 0.05 was used.
Results: 308 patients (median age 61 years, IQR 17;male 48.4%) were included. Median FU was 48 months (IQR 24). During FU 116 (37.7%) patients showed progression of their OLGIM status and six patients (1.9%) developed high grade dysplasia or GC. Family history (HR 1.4; p=0.154),

smoking (HR 1.3; p=0.260), and history of Hp-infection (HR 1.1; p=0.684) were associated with non-significant risks for progression. Alcohol use (HR 0.8; p=0.428), serum levels of PG I/II (HR1.0; p=0.446) and gastrin-17 (HR 1.0; p=0.908) were not associated with an increased progression risk. The minor allele (C) on the *TLR4* (rs11536889) was negatively associated with progression (OR 0.4; p< 0.001), while the minor allele (G) in the *ATG16L1* (rs2241880) was positively associated with progression (OR 1.5; p=0.001).
Conclusion: This is the first study to assess potential risk factors for the progression of IM in a low risk area. Over one third of patients showed progression of IM during surveillance. We did not find any significant risk factors for progression. However, SNPs in *TLR4* and *ATG16L1* showed significant associations with progression of IM, suggesting that genetic risk stratification may contribute to the identification of patients eligible for surveillance.
Disclosure: Nothing to disclose

OP034 EVOLUTION OF GASTRIC PRECANCEROUS LESIONS: A LONG TERM FOLLOW-UP SINGLE CENTER STUDY IN FRANCE

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Introduction: International guidelines recommend surveillance of gastric precancerous lesions (GPL), but there are limited data on the evolution of these lesions, especially in countries of low gastric cancer incidence. Our objective was to study the evolution of GPL in France.
Aims & Methods: From the cohort of 507 patients diagnosed with GPL [atrophic gastritis (AG), or intestinal metaplasia (IM), or low grade dysplasia (LGD), or high grade dysplasia (HGD)]in our center between 2000 and 2015, the patients fulfilling the following criteria were identified:
1) at least one follow-up endoscopy performed after a minimal period of 6 months,
2) at each endoscopy, random gastric biopsies obtained, at least 3 from antrum and 2 from corpus,
3) all biopsy material available for histological review.
The biopsy specimens were retrieved from the hospital tissue bank and analysed prospectively by an expert pathologist for the presence of GPL and their extent (according to OLGA and OLGIM score). The type of IM (complete or incomplete) was also evaluated. The evolution of the lesions was assessed by comparing the initial and the final histology. Additionally, for the patients with multiples endoscopies during the follow-up, a precise evaluation of the evolution on individual level was performed.
Results: Seventy nine patients (35 men, median age 61 years), were included. At initial endoscopy, the GPL found were, by order of severity: AG in 5 patients (OLGA 1, n=4; OLGA 2, n=1), IM in 73 patients (OLGIM 1, n=39; OLGIM 2, n=28; OLGIM 3, n=6) and LGD in 1 patient. Thirty-seven patients (47%), were *H. pylori*positive by histology. Among the 73 patients with IM, 59 had IM in the antrum, 8 in the corpus, and 6 in the antrum and in the corpus. Sixty patients had complete IM and 13 incomplete IM. The mean (±SD) follow-up period was 66 ±48 months (Min=7, Max=208), the mean (±SD) number of endoscopies per patient was 4±2 (Min= 2, Max = 14), and the total number of endoscopies performed in all patients was 341.
At final endoscopy, the GPL found were AG in 2 patients, LGD in 4 patients, HGD in 1 patient, adenocarcinoma (ADK) in 2 patients, IM in 58 patients and normal gastric mucosa (+/- superficial gastritis) in 12 patients. Six patients (7%) were *H. pylori*positive by histology.
The comparison between the initial and final endoscopy, showed stability of GPL in 56 patients (71%), progression to more severe lesion in 10 patients (13%) (from AG to IM in 4 patients, from IM to LGD in 3 patients, from IM to HGD in 1 patient, and from IM to ADK in 2 patients), and the regression in 13 patients (16%). Both patients who progressed to ADK had incomplete type of antrum IM, one OLGIM 2 and one OLGIM 3. Altogether, among 10 patients who progressed to more severe lesions, 6 (60%) had incomplete type of IM.

Among the 13 patients in whom the regression to the normal (+/-gastritis) gastric mucosa was observed, 9 had initially antrum limited OLGIM 1 complete IM and 4 had antrum limited complete OLGIM 2 IM.
Conclusion: This study shows that:
1) Most of the GPL remain stable over time,
2) Antrum-limited IM, especially of incomplete type, has the highest risk of progression to dysplasia and cancer,
3) Regression of IM is possible, especially for low grade (OLGIM 1) and for complete type.
Disclosure: Nothing to disclose

Clinical update on H.pylori management
10:30-12:00 / F3

OP035 EUROPEAN SURVEY OF *HELICOBACTER PYLORI* PRIMARY RESISTANCE TO ANTIBIOTICS - EVOLUTION OVER THE LAST 20 YEARS

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Introduction: Antibiotic resistance of *Helicobacter pylori* is the main cause of failure of most current eradication regimens. As antimicrobial susceptibility testing (AST) is not performed in all cases, it is important to have regular surveys to infer the treatments which can be used. For this purpose, European surveys were performed in 1998, 2008 and we report here the results of 2018.
Aims & Methods: Centres were recruited on a voluntary basis, one for each small country (in the range of 10 million inhabitants) and several for larger countries. The request was to include 50 adult patients who had not received previous eradication treatment.
Information collected included demographic, clinical, and endoscopic results as well as AST results (clarithromycin, levofloxacin, metronidazole, amoxicillin, tetracycline and rifampicin) performed by Etest or disk diffusion according to a standardized procedure. Control strains were also made available and a 10% random sample was sent to the coordinating centre at the end.
Results: The crude data show 1,246 *H. pylori* positive patients included in 24 centres from 19 countries (minimum: 20 cases per centre) The distribution with regard to age, gender, reason for consultation and endoscopic examination is in the range of what is usually observed for this type of patients. *H. pylori* resistance was present in 21.9% for clarithromycin, 16.6% for levofloxacin, and 38.5% for metronidazole; 30 strains were reported as resistant to amoxicillin (2.4%), 4 to tetracycline (0.3%) and 48 to rifampicin compounds (3.8%). These unusual resistance strains are now being controlled as well as a random sample of the other strains. The kit Amplidiag *H.pylori* (MobiDiag) will be used for clarithromycin and AST for the other antibiotics.
Conclusion: These results indicate a global and continuous rise in *H. pylori* primary resistance to clarithromycin but lower than in the previous decade (9.9% in 1998, 17.5% in 2008, and 21.9% in 2018), a slight increase to levofloxacin and a more important increase for metronidazole (from 33.1 to 38.5% since 2008).
Disclosure: The authors acknowledge the support of bioMérieux for providing Etests and Mobidiag for providing with PCR kits.

OP036 PAN-EUROPEAN REGISTRY ON *H. PYLORI* MANAGEMENT (HP-EUREG): EXPERIENCE WITH SINGLE CAPSULE BISMUTH QUADRUPLE THERAPY IN 2,326 PATIENTS

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Introduction: Bismuth-quadruple therapy with a PPI, bismuth salts, tetracycline and metronidazole has resurfaced in Europe thanks to a new single-capsule formulation (Pylera®).
Aims & Methods: Our aim was to evaluate the efficacy and safety of the single-capsule bismuth-quadruple therapy (Pylera®) in the European Registry on *Helicobacter pylori* management. Patients were systematically registered at an e-CRF by AEG-REDCap. *Variables included*: Patient's demographics, previous eradication attempts, prescribed treatment, adverse events, and outcomes. Intention-to-treat and per-protocol analyses were performed. Data monitoring was performed to ensure the quality of the data
Results: So far, 30,394 patients have been included. Of these, 2,326 valid patients treated with single-capsule bismuth-quadruple therapy have been evaluated. 1,900 (81.7%) were prescribed following the technical-sheet (10 days, 3 capsules q.i.d.), the remaining where excluded. Average age was 52 years, 64% women, and 13% had peptic ulcer. Table summarizes results. The majority of cases (63%) were naïve. PPI type or dose did not influence eradication rate. 33% of cases suffered from adverse events (severe in 3%, and only 1% withdrew treatment due to adverse events). Only two serious adverse events were reported: hospitalization for diarrhea, and an allergic reaction treated with anti-histamine drugs, both solved without complications.
Conclusion: Treatment with single-capsule bismuth-quadruple therapy (Pylera®) achieves *H. pylori* eradication in approximately 90% of patients by intention-to-treat in clinical practice, both in first- and second-line, with a favorable safety profile.

	Frequency	Percent	mITT	PP
Naive (no previous treatment)	1,195	63%	92%	95%
2nd	412	22%	87%	90%
3rd	220	12%	84%	85%
mITT: Modified intention-to-treat; PP: per-protocol.				

[Prescription and eradication rates of single-capsule bismuth quadruple therapy]

Disclosure: Prof. Gisbert has served as a speaker, consultant and advisor to, or has received research funding from, Almirall, Nycomed, Astra-Zeneca, Casen Recordati, Mayoly, and Allergan. Dr McNicholl has received retributions from Allergan and MSD for training activities, and he is an advisor for Mayoly.

Pancreatic neoplasms: Improving diagnosis and outcomes
10:30-12:00 / Barcelona

OP037 ROBOTIC PANCREATODUODENECTOMY IN THE NETHERLANDS: A MULTICENTER ANALYSIS OF THE FIRST 100 PROCEDURES

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Introduction: Minimally invasive surgery is currently the gold standard for many surgical procedures. Most pancreatoduodenectomies, however, are still being performed through laparotomy. As conventional laparoscopy is limited by the rigid visual- and working axis, it might be less suited for complex procedures such as pancreatoduodenectomy. Potentially, the use of robotic technology offers a solution. The technically enhanced articulating instruments and 3D vision allow for optimal surgical dexterity, as needed during meticulous dissection and construction of the anastomoses in pancreatoduodenectomy. The aim of this study was to determine safety and feasibility of a robotic approach to pancreatoduodenectomy in the Netherlands and compare our results to recent studies reporting on the outcomes of open pancreatoduodenectomies.
Aims & Methods: This is a multicenter post hoc analysis of prospective databases from three high volume Hepato-Pancreato-Biliary (HPB) centers in the Netherlands. The first 100 patients undergoing robot-assisted pancreatoduodenectomy were included. Primary endpoint was severe complication, defined as the occurrence of one or more of the following complications: ISGPS gr. B/C postpancreatectomy hemorrhage, ISGPS gr. B/C pancreatic fistula, multiple or single organ failure, or death. Outcomes were scored during index admission. In addition, we performed a systematic review of observational, monocenter studies reporting on outcomes of > 500 open pancreatoduodenectomies, published in the past 5 years.
Results: In total, 100 consecutive patients underwent robot-assisted pancreatoduodenectomy. A total of 22 (22%) patients suffered from a severe complication. Pancreatic fistula (ISGPS gr. B/C) occurred in 19 (19%) patients and 9 (9%) patients suffered from post-pancreatectomy hemorrhage (ISGPS gr. B/C). Delayed gastric emptying (ISGPS gr. B/C) occurred in 26 (26%) patients. In 8 (8%) patients the procedure was converted to an open pancreatoduodenectomy. Seven patients (7%) underwent a relaparotomy. There was no postoperative in-hospital or 30-day mortality. The systematic review of 14 studies (n=12.708 patients) on open pancreatoduodenectomy demonstrated that complications occurred in 38% of all patients and reoperations in 7%. The weighted mean mortality was 3%.
Conclusion: These outcomes of the first 100 robot-assisted pancreatoduodenectomies demonstrate that this procedure was introduced safely in three hospitals in the Netherlands without postoperative mortality and acceptable morbidity. Clinical outcomes in this study were in line with outcomes reported in 14 recent, large, international studies on open pancreatoduodenectomies.
Disclosure: Nothing to disclose

OP038 NATIONWIDE PRACTICE AND OUTCOME OF PREOPERATIVE BILIARY DRAINAGE USING METAL OR PLASTIC STENTS IN PATIENTS WITH PANCREATIC DUCTAL ADENOCARCINOMA

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Introduction: In patients with resectable pancreatic ductal adenocarcinoma and biliary obstruction, early surgery is the preferred treatment. In patients with severe jaundice, neoadjuvant therapy, delayed surgical treatment, and acute cholangitis endoscopic biliary drainage (EBD) is often indicated. In the updated European Society of Gastrointestinal Endoscopy guidelines, self-expanding metal stents (SEMS) are strongly recommended for EBD, because of lower rates of stent dysfunction, cholangitis and endoscopic re-interventions as compared to plastic stents. We aimed to assess the implementation of SEMS use in daily clinical practice in patients with resectable pancreatic head cancer undergoing EBD and the relation between SEMS,drainage related complications and postoperative complications.
Aims & Methods: We performed a nationwide, retrospective cohort study including all patients with pancreatic ductal adenocarcinoma who underwent EBD prior to pancreatoduodenectomy in the mandatory Dutch Pancreatic Cancer Audit (January 2017 - December 2018). Patients undergoing percutaneous biliary drainage were excluded. Missing data (range 0.-10.4%) were imputed by multiple imputation techniques in which 15 dummy sets were created. Multivariable logistic regression models with adjustment for patient characteristics (sex, age, BMI, and ASA score) were performed to assess the association between type of stent and drainage-related or post-operative complications. Drainage-related complications were pancreatitis, cholangitis, perforation, bleeding, occlusion. Postoperative complications were postoperative pancreatic fistula, delayed gastric emptying, postpancreatectomy hemorrhage, bile leakage, chyle leakage, pneumonia and wound infection.
Results: In total, 585 patient, with a mean age of 68 (standard error 0.41) years, were included and 321 (55%) were male. EBD was mostly performed with plastic stents (331, 57%) compared to SEMS (254, 43%). Overall, drainage-related complications were comparable between patients with SEMS (18%) and plastic stents (19%). Cholangitis occurred less often in patients with SEMS compared to plastic stents (5% vs. 11%, p=0.029). Post-ERCP pancreatitis occurred in 9% and 8% in patients with SEMS and plastic stents, respectively. In multivariable logistic regression, adjusted for patient characteristics, SEMS was associated with lower odds of cholangitis (OR 0.394, 95% CI 0.176-0.881). Postoperative pancreatic fistula occurred less often in patients with SEMS compared to plastic stents (10% vs. 19%, p=0.011) and this effect remained after adjustment for patient characteristics in multivariable logistic regression (OR 0.568 95% CI 0.324-0.995).
Conclusion: This nationwide study shows that biliary drainage with SEMS placement is insufficiently implemented in the Netherlands despite explicit European guideline recommendations. Importantly, this nationwide study confirmed that those patients, drained with a SEMS, had a reduced rate of cholangitis and clinically relevant postoperative pancreatic fistula. Therefore, preoperative biliary drainage using SEMS should be strongly promoted and this may be facilitated and accelerated by a nationwide implementation programme.
Disclosure: Nothing to disclose

OP039 MULTICENTER RANDOMIZED CONTROLED TRIAL (RCT) COMPARING THE HISTOLOGICAL MATERIAL QUANTITY OBTAINED BY ENDOSCOPIC ULTRASOUND FINE NEEDLE BIOPSY (EUS-FNB) OF PANCREATIC MASSES WITH TWO „BIOPSY" NEEDLES: THE 20-GAUGE PROCORE® (COOK) AND THE 22-GAUGE ACQUIRE® (BOSTON SCIENTIFIC)

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Introduction: Endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) has been proposed to obtain high-quality tissue samples for pancreatic tumors. We performed a multicenter randomized control trial comparing EUS-FNB with a 20-gauge Procore® needle versus a 22-gauge Acquire® needle. Our primary endpoint was the quantity of the obtained tissue, as defined by the mean cumulative length of tissue core biopsies per needle pass. The secondary aim was the tumor characterization.
Aims & Methods: Patients admitted for EUS-FNB of a pancreatic mass in 3 endoscopy units were included. One pass was performed consecutively with both needles. The order of use of the 2 needles was randomized. Histological material was studied in a blinded manner with respect to the needle, and the cumulative length of tissue core biopsies per needle pass was determined (sum of all the target tissue core lengths as measured manually with a graduated ruler under microscopy assistance, on the best cell block section). The gold standard was based on histological diagnosis, surgical resection, or more than 6 months follow-up. Assuming a 4mm difference in length of tissue core biopsies (based on a previous comparative study) [1], with a type-I error of 0.05 (2-sided) and a power of 0.9, the study required a total 60 patients.
Results: 38 men and 22 women, with a mean age of 67±9 years were included. No adverse effect was noted. Final diagnosis (based in all cases on histology for malignant tumor, and on histology and follow-up in benign pathology) was adenocarcinoma in 45 cases (75%), neuroendocrine neoplasm in 11 cases (18%), auto-immune pancreatitis in 2 cases, and others in 2 cases. Histological diagnosis was achieved in 41 out of 60 patients (68%) with the 20-gauge Procore® pass and in 53 out of 60 patients (88%) with the 22-gauge Acquire® pass (P< 0.02). The mean cumulative length of tissue core biopsies per needle pass was significantly higher with the 22-gauge Acquire® needle with 11.78±9.2mm versus 5.86±6.7mm for the 20-gauge Procore® needle (P< 0,0001).
Conclusion: Our results suggest significant differences, with a tumor characterization rate and a mean cumulative length of tissue core biopsies per needle pass significantly higher with the 22-gauge Acquire® needle than with the 20-gauge Procore®.
ClinicalTrials.gov ID: NCT03567863
References: 1- Karsenti D, Tharsis G, Zeitoun JD, et al. Comparison of 20-gauge Procore® and 22-gauge Acquire® needles for EUS-FNB of solid pancreatic masses: an observational study. Scand J Gastroenterol 2019
Disclosure: Nothing to disclose

OP040 INMEDIATE ON-SITE DIAGNOSIS OF MUCINOUS PANCREATIC LESIONS BY GLUCOMETRIC ANALYSIS OF CYSTIC FLUID OBTAINED BY ENDOSCOPIC ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION (EUS-FNA)

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Introduction: Differential diagnosis of pancreatic cystic lesions is required for an appropriate therapeutic approach. Several markers have been evaluated in cystic fluid obtained by EUS-FNA, but they have shown limited accuracy.

Aims & Methods: Our aim was to assess the accuracy of intracystic glucose for the differential diagnosis between non-mucinous and mucinous cystic neoplasia (MCN).

Prospective, observational and analytic study of patients undergoing EUS-FNA of cystic pancreatic lesions from January to December 2018. Intracystic glucose concentration was evaluated on-site by glucometry. Additionally, fluid samples were sent to the lab for glucose and CEA quantification, and for cytological analysis. Diagnostic accuracy of glucose and CEA was evaluated by using cytology and imaging features (EUS and MRI), evaluated by two expert pancreatologists blinded to glucose and CEA levels, as gold standard.

Results: Thirty-three patients with cystic pancreatic lesions were included (mean age 73 years, range 35-88 years, 17 male). Mean size of the lesions was 37 mms (range 11-120 mms). Final diagnosis was MCN in 21 cases (18 branch duct IPMN, 1 main duct IPMN, 1 mucinous cystadenoma and 1 mucinous cystoadenocarcinoma) and non-mucinous lesions in 12 cases (4 serous cystadenomas, 2 cystic endocrine tumours, 4 walled-off necrosis, 1 pseudocyst and 1 post-surgical collection). Intracystic glucose concentration in MCN was 27.3 mg/dl (5.4-49.3) and 123.1 mg/dl (93.7-152.5) in non-mucinous lesions (p< 0.001). Intracystic glucose quantification in the lab showed an area under the ROC curve for the diagnosis of non-mucinous lesions of 0.93 (0.84-1.00). Using a cut-off point of >66 mg/dl, intracystic glucose allows diagnosing non-mucinous lesions with a sensitivity of 100% (72.0-100) and specificity of 80.0% (58.4-91.9). Intracystic glucose could be evaluated by on-site glucometry in 22 cases, showing a sensitivity of 100% and specificity of 75.0% for a cut-off of 74 mg/dl, with and area under the ROC curve of 0.85 (0.63-0.96). Compared to glucose, intracystic CEA showed an area under the ROC curve of 0.71 (0.52-0.87), sensitivity 72.2% (49.1-87.5) and specificity 81.8% (52.3-94.9) for the diagnosis of non-mucinous lesions.

Conclusion: Intracystic glucose, which can be measured on-site by glucometry, is an accurate tool for the differential diagnosis of mucinous and non-mucinous cystic pancreatic lesions.

Disclosure: Nothing to disclose

OP041 A RANDOMIZED CONTROLLED TRIAL ON THE CONTRAST ENHANCED GUIDED EUS-FNA AGAINST STANDARD EUS-FNA IN DIAGNOSING THE SOLID PANCREATIC LESIONS

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Introduction: The contrast enhanced endosonography (CH-EUS) may visualize the necrotic areas and the vessels inside the lesions. Its results combined with endosonography- fine-needle aspiration (EUS-FNA) improves the diagnosis in pancreatic solid masses. Also, CH-EUS can target EUS-FNA (CH-EUS-FNA) which might improve the diagnostic rate of EUS-FNA, but their superiority was not proved in prospective studies.

Aims & Methods: to assess if the efficiency of the targeted contrast- enhanced-EUS-FNA (CH-EUS-FNA) is superior to standard EUS-FNA in obtaining diagnosis or diagnosing malignancy in solid pancreatic masses and to evaluate whether the hypovascular aspect of the mass influences the accuracy of the diagnosis of FNA.

This randomized controlled study in one tertiar medical academic center included patients with the suspicion of pancreatic solid masses on transabdominal ultrasound or CT scan. Two passes with 22G standard FNA needle were done in random order by using EUS-FNA or CH-EUS-FNA and the visible core obtained was sent for pathology analysis. The final diagnosis was based on EUS-FNA or surgical specimen results and on following up data every three month by imaging methods.

Results: The study included 150 patients and two of them were lost from follow-up. There were 99 adenocarcinoma, 13 neuroendocrine tumors, 3 schwanomma, 1 GIST, 3 cholangiocarcinoma, 11 metastases, 19 benign lesions.

The EUS-FNA pass and CH-EUS FNA had the accuracy of diagnosis of 86.48% and 89.18% respectively (p=NS) and the global accuracy of the two passes was 93.2%. The rate of false negative cases did not differ between hypoenhanced or hyperenhanced lesions. No difference were seen for the results related to the location , size or tumor stage.

Conclusion: The diagnostic rate of core obtained by using 22G FNA needles with standard EUS-FNA and guided CH-EUS-FNA did not differ statistically.

Disclosure: Nothing to disclose

OP042 LIVING ON THE EDGE: LONG-TERM COMPLICATIONS, AND IMPLICATIONS FOLLOWING EUS-DIRECTED TRANSGASTRIC ERCP (EDGE): A MULTICENTER STUDY

Runge T.[1], Kowalski T.E.[2], Baron T.H.[3], Chiang A.[2,4], James T.[5], Nieto J.[6], Khara H.[7], Kumar V.[7], Irani S.[8], Nasr J.[9], Krafft M.[9], Law R.[10], Chahal P.[11], Stevens T.[11], Khashab M.A.[12]

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Introduction: Endoscopic ultrasound-directed transgastric ERCP (EDGE) is an alternative to enteroscopy- and laparoscopy-assisted ERCP in patients with RYGB anatomy. It allows for direct access via lumen-apposing metal stents (LAMS) to the excluded stomach, followed by ERCP across the gastro-gastric (GG) stent.

Although short-term results are promising with technical success in the majority of cases, the long-term outcomes are not known. Specifically, the rate of persistent GG fistula (GGF) is unknown.

Aims & Methods: To

1) determine rates of long-term adverse events (AEs) after EDGE, with a focus on rates of persistent GGF;

2) identify predictors of persistent GGF;

3) assess outcomes of endoscopic closure when persistent GGF is encountered.

This is a multicenter, retrospective study involving 12 centers between 1/2014 and 10/2018. AEs were defined according to ASGE lexicon. Persistent GGF was defined as UGI series or EGD showing evidence of fistula. Presumptive GGF was defined as weight gain of 5% of total body weight without having objective documentation of GGF. Multivariable analysis was used to determine predictors of AEs.

Results: A total of 166 patients (58yr, F 80%) underwent EDGE and had a mean follow-up of 5.7 months. EDGE was performed in a single session in 51% (n=85) of cases, and two sessions in 49% (81 patients). The excluded stomach was accessed from a transgastric location in 52% of cases and a transjejunal location in 48%. Technical success was achieved in 98% of cases (163/166) with a mean procedure time of 87 min. The LAMS was anchored in 21% of EDGE procedures (35/166; suturing 25, plastic double pigtail stents 7, hemoclips 2, and over-the-scope clip 1) with the majority (57%) done in a single session. Periprocedural AEs occurred in 28 patients (17%). Mild, moderate and severe AEs occurred in 3.1%, 11.5% and 2.4% of patients respectively. The 4 severe adverse events were managed laparoscopically.

Overall, mean LAMS dwell time was 47d. Initial fistual tract closure was performed with suturing in 31%, OTSC in 9%, and TTS clips in 4%. In 28% of patients the fistula edges were treated with APC alone without attempted closure. In 27% of patients the fistula was left entirely undisturbed following LAMS removal. GGF was identified following EDGE in 12% of those sent for objective testing (10/85). In addition, 61 (37%) patients had presumptive GGF after LAMS removal.

Following identification of GGF, 70% of patients underwent a mean of 1.2±0.8 closure attempts which at last follow-up had been successful in 71% of cases (5/7). Univariate and multivariate analyses suggested diabetes was associated with persistent GGF (OR 7.2; 1.5, 34).

Conclusion: The EDGE procedure is safe with a low risk of short-term and long-term AEs. Persistent GGF is uncommon and is independently associated with diabetes.

Disclosure: Nothing to disclose

Endoscopy: The heat in diagnosis and therapy
10:30-12:00 / Hotspot

OP043 LONG-TERM OUTCOMES AFTER ENDOSCOPIC TREATMENT FOR BARRETT'S NEOPLASIA IN 641 PATIENTS IN A CENTRALIZED CARE SETTING IN THE NETHERLANDS: RECURRENT NEOPLASIA IS RARE AND NEOSQUAMOUS BIOPSIES DO NOT CONTRIBUTE TO ITS DETECTION

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Introduction: Radiofrequency ablation (RFA), with or without endoscopic resection (ER) is the standard of care for treatment of early neoplasia in Barrett´s esophagus (BE). We aimed to report durability outcomes based on a large cohort of patients with uniform treatment and follow-up (FU) in a centralized care setting.

Aims & Methods: Endoscopic therapy for BE neoplasia in the Netherlands is centralized in 8 expert centers, where care is provided by specifically and jointly trained endoscopists and pathologists. Uniformity of treatment/FU is ensured by a joint protocol and quarterly group meetings. In an ongoing registry, prospectively collected treatment/FU data from all Dutch BE patients treated since 2008 is being registered in a uniform database. In the current study, we report on the completed data of 3 centers. Treatment indications were BE with low/high grade dysplasia (LGD/HGD) or early adenocarcinoma (EAC). Visible lesions were removed by ER, followed by RFA until complete endoscopic remission of BE and absence of intestinal metaplasia (CR-IM). FU consisted of high-resolution endoscopy and optical chromoendoscopy. From 2008 to 2015, FU endoscopy was done every 3mo in year 1, followed by yearly endoscopies in year 1-5, then every 2-3 yrs. Since 2015, FU endoscopies within the first year were abandoned. Initially, 4Q-random biopsies (Bx) were obtained from NSE and cardia (i.e. < 5mm distal from the neo-squamocolumnar junction) at every FU endoscopy. These were abandoned in 2013 and 2016 respectively.

Outcomes: Sustained CR-neoplasia (SCR-N) after CR-IM, diagnostic yield for NSE and cardia Bx.

Results: 641 patients with median BE length C2M4 and LGD (19%), HGD (32%) or EAC (49%) achieved CR-IM. Over a total FU of 2,747 person years (median 4 (IQR 2-6) yrs and 4 endoscopies per patient), 625 (98%) patients had SCR-N. The overall annual recurrence risk was 0.6%/year, with a relatively low risk in year 1 (0.1%). Based on 205 pts with FU >5yrs, there was no decrease in the recurrence risk after 5 years (0.7%/year). In total, 16 pts developed recurrent neoplasia after median 30mo (23-42). A more severe baseline histology significantly increased the recurrence risk (HR 3.1, 95%-CI 1.1-8.2). In 81% (13/16), CR-N was re-achieved after endoscopic treatment for LGD (3) HGD (4) or EAC (6), but 3 (0.5% of all pts) eventually progressed to advanced cancer (2 metastatic disease without BE, 1 submucosal cancer identified after an 18 months interval). The 3 cases were at baseline identified as highly complicated due to multifocal HGD/EAC and/or severe reflux stenosis. All recurrences were detected as visible non-flat lesions (10) or by biopsies from recurrent BE (1) or cardia (3). None of the 5,992 NSE Bx which were obtained, contributed to detection of recurrence. Abandoning NSE sampling in 2013 saved approximately 10,000 Bx in our cohort. Cardia Bx were obtained in 1,687 endoscopies with LGD (0.2%), IM

(7%) or no abnormalities (93%). In total, 69 pts (11%) had IM in a normal appearing cardia at some time point; this was reproduced in a minority and none progressed to dysplasia.

Conclusion: In a setting of centralized BE care, the 2-step approach of ER and RFA has remarkably low rates of neoplastic recurrence after CR-IM, with an annual recurrence risk comparable to the NDBE surveillance population. The vast majority of recurrences are detected at early stages that are amendable for curative endoscopic treatment. In conclusion, our data support more lenient FU intervals, especially in the first year after CR-IM, with emphasis on careful endoscopic inspection whilst NSE biopsies can be abandoned.

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OP044 CONVENTIONAL VERSUS TRACTION-ASSISTED ENDOSCOPIC SUBMUCOSAL DISSECTION FOR LARGE-SIZE ESOPHAGEAL CANCERS: A MULTICENTER, RANDOMIZED CONTROLLED TRIAL

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Introduction: Endoscopic submucosal dissection (ESD) is considered as minimum invasive treatment for large-size esophageal cancers. However, prolonged procedure time and life-threatening adverse events are a crucial matter of esophageal ESD.[1] Stable view during ESD is essential for less adverse events and more technical success. Traction-assisted ESD (TA-ESD) has the potential to maintain an adequate view during the procedures.[2]

Aims & Methods: The present study was a randomized, open-label, multicenter trial done in 7 hospitals in Japan and designed to evaluate the impact of traction assist on the efficacy and safety of ESD for esophageal neoplasms. Eligible patients were aged at least 20 years old and had endoscopically diagnosed squamous cell carcinoma or basal cell carcinoma meeting the following all conditions:

i) tumor size ≥20 mm and

ii) clinically-diagnosed intramucosal cancer (cT1a) or slightly infiltrating submucosal cancer (cT1b-SM1) according to the Japanese diagnosis and treatment guidelines for the esophagus.[3]

Enrolled patients were randomized in a 1:1 allocation ratio to receive either conventional ESD or TA-ESD via dynamic balancing using the minimization method. The primary endpoint was to ascertain if there was a difference in ESD procedure time between the two groups. The pre-defined secondary endpoints were as follows: handover to another operator; frequency of conversion from conventional ESD to TA-ESD; en bloc resection; histological assessment; and incidence of adverse events.

Results: From October 2016 to March 2019, 241 patients with large-size esophageal cancers were included in this trial and randomized. After excluding patients who did not undergo treatment (conventional ESD, three; TA-ESD, five), 233 patients were included in the analysis. ESD procedure time was significantly shorter in the TA-ESD group (60.5 vs. 44.5 minutes, P< 0.001). Six (5.2%) patients in conventional ESD were converted to TA-ESD technique to overcome technical difficulties during the procedure. Moreover, handover to another operator tended to be more frequently observed in the conventional ESD group (6.0% vs. 0.9%, P=0.066) Importantly, perforation occurred only in conventional ESD (5 cases, 4.3%), resulting in discontinuation of the procedure in one patient. Conversely, no adverse event in the TA-ESD group. En bloc resection rate and horizontal margin involvement of tumor were similar (99.1% vs. 100%, P=1.000; 10.3% vs. 6.9%, P=0.484, respectively).

Conclusion: TA-ESD significantly reduced ESD procedure time without any adverse event compared with conventional ESD and should be applied for esophageal ESD as the standard method.

	Conventional ESD	TA-ESD	P value
Total procedure time, min (range)	60.5 (18-245)	44.5 (13-156)	0.000
Conversion to TA method, n (%)	6 (5.2)	N/A	N/A
Handover to another operator, n (%)	7 (6.0)	1 (0.9)	0.066
En bloc resection, n (%)	116 (99.1)	116 (100)	1.000
Horizontal margin involvement, n (%)	12 (10.3)	8 (6.9)	0.484
Adverse events, n (%)			
Perforation	5 (4.3)	0 (0)	0.060
Delayed bleeding	0 (0)	0 (0)	1.000
Pneumonia	0 (0)	0 (0)	1.000
Mediastinitis	1 (0.9)	0 (0)	1.000

En bloc resection and adverse events were calucurated for 117 patients in the conventional ESD group including one discontinuation case after perforation. ESD, endoscopic submucosal dissection; TA, traction assisted; N/A, not available

[Clinical outcomes of conventional ESD and TA-ESD]

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Disclosure: Nothing to disclose

OP045 LINKED COLOR IMAGING FOR THE DETECTION OF GASTRIC NEOPLASM IN HIGH RISK PATIENTS: A PROSPECTIVE MULTICENTER RANDOMIZED CONTROLLED TRIAL (LCI-FIND TRIAL)

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Introduction: Gastric cancer remains one of the most common causes of cancer-related death worldwide, particularly in East Asian countries. Although the prevention and eradication of *Helicobacter pylori* infection decreased the incidence of gastric cancers, it is still high. Recently, image-enhanced endoscopy (IEE) technologies including narrow-band imaging (NBI) and blue laser imaging (BLI) have been developed. A more recently developed IEE technology, linked color imaging (LCI), enhances slight color differences in hue in the red region of the spectrum, and has been reported to be useful for the diagnosis of gastrointestinal (GI) diseases.

Aims & Methods: The aim of this study is to compare the detection rate of neoplasms in upper GI endoscopy between conventional white-light imaging (WLI) and LCI observation for high-risk patients. In this prospective multicenter randomized controlled trial (RCT), patients with a history or presence of esophageal or gastric neoplasms were enrolled in 19 Japanese institutions between November 2016 and July 2018. Patients were assigned to 2 groups; primary observation with WLI followed by LCI (WLI-LCI group) or primary LCI observation followed by WLI (LCI-WLI group). Additional detection rates of gastric neoplasms were compared between WLI-LCI and LCI-WLI groups. The characteristics of the neoplastic lesions additionally detected by each mode were also evaluated. The number of lesions detected, and endoscopic diagnosis (neoplastic or non-neoplastic) were recorded for each procedure during examination, and all lesions detected were biopsied for histopathological diagnosis. Neoplastic lesions

were defined as adenoma and adenocarcinoma. This study was approved by the institutional review board of all participating institutions and was registered with UMIN Clinical Trial Registry (UMIN000023863).

Results: A total of 1508 patients were enrolled and 1504 patients were randomly allocated to each group; 752 for WLI-LCI and 750 for LCI-WLI group. There was no significant difference in demographics including age, sex, presence/absence of surgical history, and the ratio of current and previous cancer between the two groups. In the WLI-LCI group, a total of 63 gastric neoplastic lesions were detected, which included 37 lesions detected by primary WLI and 26 lesions by secondary LCI. In the LCI-WLI group, a total of 71 gastric lesions were detected, which included 66 lesions detected by primary LCI and 5 lesions by secondary WLI. Additional detection rates of gastric neoplasm in WLI-LCI group was significantly higher than in LCI-WLI group; 41.3% vs 7.0%, p< 0.001. Additional detection rate of the patients with gastric neoplasm in WLI-LCI was also significantly higher than in LCI-WLI group; 8.0% (60/750) vs 4.8% (36/752), p< 0.05. When images of 85 gastric cancer lesions were compared between LCI and WLI, LCI showed more reddish color in 56 cancer lesions and more whitish color in 17 lesions than WLI. All 17 lesions, which were overlooked by WLI, showed enhanced color contrast in LCI image. All 10 isochromatic lesions with WLI exhibited enhanced reddish color in LCI images.

Conclusion: Our large-scale RCT strongly suggest that LCI is superior to conventional WLI for detection of gastric neoplasm during upper GI endoscopy. It is supposedly due to the characteristic color enhancement function of LCI. LCI may be a standard examination tool for the detection of gastric neoplasm for high-risk patients.

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OP046 EFFICACY OF POLYGLYCOLIC ACID SHEETING WITH FIBRIN GLUE FOR THE TREATMENT OF PERFORATIONS RELATED TO GASTROINTESTINAL ENDOSCOPIC PROCEDURES: A MULTICENTER RETROSPECTIVE STUDY AMONG THE PGA STUDY GROUP

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Introduction: Polyglycolic acid (PGA) sheets with fibrin glue have been reported to be useful for preventing perforation and delayed bleeding after endoscopic treatment [1,2]. Although they can be useful for the closure of perforations related to gastrointestinal (GI) endoscopic procedures, no large-scale multicenter treatment outcomes have been reported yet.

Aims & Methods: This is a retrospective multicenter study conducted by the PGA study group, which is the affiliated study group of the Japanese Gastroenterological Endoscopy Society and consists of 18 institutions.

From April 2013 to March 2018, patients with perforations related to GI endoscopic procedures and endoscopically closed using PGA sheeting with fibrin glue were extracted, and were retrospectively examined. "Intraoperative perforation" was defined as a perforation through which the outside of the GI tract was visible during the endoscopic procedure, or as the case where free gas was detected outside the lumen on radiography or computed tomography (CT) just after the endoscopic procedure. Delayed perforation was defined as a perforation or symptoms appearing after the completion of the endoscopic procedure and the case where free gas was detected on radiography or CT, even though no perforation or symptoms occurred immediately after the completion of the endoscopic procedure. Perforations were filled with one or several pieces of PGA sheets followed by spraying fibrin glue using an endoscopic catheter. This procedure was sometimes repeated at 1- or 2-week intervals before closure.

Results:

Intraoperative perforation: Sixty-six cases (esophagus 6, stomach 22, duodenum 12, and colon 26) during endoscopic procedures, including 58 endoscopic submucosal dissections (ESDs), 2 endoscopic mucosal resections, 1 endoscopic submucosal resection with a ligation device, 2 endoscopic papillectomies, and 3 endoscopic balloon dilations, were detected. The median lesion and perforation diameters were 27 mm (range, 3-163 mm) and 5 mm (range, 1-30 mm), respectively. PGA sheets were filled at a median of once after perforation (range, 1-3). Nasal drainage and endoscopic clipping were performed adjunctly in 23 (35%) and 49 cases (74%) with PGA sheeting, respectively. Complete closure was attained in 60 cases (91%). The median period from the first sheeting to the diet resuming was 6 days (range, 0-23).

Delayed perforation: Twenty-four cases (esophagus 5, stomach 10, duodenum 7, and colon 2) occurred after 20 ESDs, 3 dilations, and 1 Per-Oral Endoscopic Myotomy (POEM). The median lesion and perforation sizes were 24 mm (range, 4-58) and 5 mm (range, 1-30), respectively. PGA sheets were filled at a median of once (1-4) after perforation. Nasal drainage accompanied the procedure in 12 cases (50%) and endoscopic clipping in 7 cases (29%). Complete closure was attained in all 24 cases (100%). The median period from the first sheeting to the diet resuming was 10 days (range, 1-124 days). No adverse events related to PGA sheeting occurred in all the cases.

Conclusion: PGA sheeting with fibrin glue was effective for the treatment of intraoperative or delayed perforation related to GI endoscopic treatment.

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OP047 ENDOSCOPIC SUBMUCOSAL DISSECTION VS ENDOSCOPIC MUCOSAL RESECTION FOR TREATMENT OF BARRETT'S RELATED SUPERFICIAL ESOPHAGEAL NEOPLASIA: MULTICENTER RETROSPECTIVE STUDY IN THE WEST

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Introduction: The difference in long-term outcomes of endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) for Barrett's related superficial neoplasia remain unclear.

Aims & Methods: We aimed to compare the rates of local and metachronous recurrence of ESD and EMR in patients with clinically staged BE-associated high-grade dysplasia (HGD) and T1a esophageal adenocarcinoma (EAC). A retrospective multicenter study was performed at six academic

hospitals in the U.S. Patients who underwent ESD with a pre-procedural diagnosis of BE-HGD or T1a EAC were included in the study. Data was collected on demographics, tumor and procedure characteristics, procedure pathology, and follow-up. The main outcome was a composite of rate of local and metachronous recurrence. Local recurrence was defined as that appearing at a similar location as previous resection and confirmed by histopathology. Flat dysplasia requiring radiofrequency ablation (RFA) was not included in the definition. Follow-up time was defined as months from initial procedure to recurrence or last follow-up visit if recurrence-free. A time-to-event analysis was performed to evaluate recurrence. A Kaplan-Meier plot was constructed, and a log-rank test was used to compare the groups. A Cox proportional hazard ratio regression analysis was performed to identify predictors of recurrence.

Results: A total of 219 patients were included. 154 underwent EMR, while 65 underwent ESD. ESD had higher en bloc (92% vs 33%, p< .0001), R0 (55% vs 31%, $p=0.023$) and curative resection rates (66% vs 32% , p< .0001) when compared to EMR. The 24-month local recurrence rate for EMR and ESD was 43.3% and 15%, respectively ($p=.0007$). Significantly more endoscopic resection procedures were required to treat recurrence after EMR compared to after ESD. EMR, piecemeal resection, positive margins, and non-curative resection were identified as predictors of recurrence on univariate analysis. EMR remained significant after multivariate analysis (Table 2).

Conclusion: This multicenter study showed that ESD results in more definitive treatment of BE-associated early neoplasia than EMR, with significant lower recurrence rates and less need for repeat endoscopic therapeutic procedures than EMR.

Disclosure: Nothing to disclose

Factor	Univariable HR 95% CI	Univariable P-value	Multivariable HR 95% CI	Multivariable P value
Technique: EMR vs ESD	3.7 [1.7-9.6]	0.0003	4.1 [1.3-18.4]	0.01
En bloc resection: Piecemeal vs en bloc	7.6 [3.9-16.5]	< .0001	1.6 [0.5-5.6]	0.42
Margins: R1 vs R0	2.6 [1.5-4.6]	0.0038	1.9 [0.9-4.4]	0.07
Lymphovascular invasion: Yes vs No	1.52 [0.4-9.3]	0.52	--	--
Differentiation: Well + moderate vs Poor	2.0 [0.8-5.4]	0.23	--	--
Curative resection: No vs Yes	6.1 [3.2-13.3]	< .0001	2.6 [0.11-8.8]	0.08

[Table. Cox proportional hazard ratio regression analysis for recurrence]

OP048 CLINICAL CHARACTERISTICS AND RISK FACTORS OF UPPER GASTROINTESTINAL CANCERS MISSED DURING ENDOSCOPY: A NATION-WIDE REGISTRY-BASED STUDY

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Introduction: Upper gastrointestinal (UGI) cancers, including esophageal, gastric and duodenal cancers, usually present at an advanced stage in the Western world, when the treatment options are limited and the prognosis is dismal. Endoscopy remains the gold standard for UGI cancer diagnosis, however, a significant proportion of these neoplasms are missed during this examination. The clinical characteristics of missed UGI cancers remain poorly understood.

Aims & Methods: This was a retrospective registry-based study done in collaboration between clinicians and data analysts from Ministry of Health in Poland aimed to characterize patients with missed UGI cancers during

endoscopy. We used National Health Fund Registry (NFZ) to identify adult patients who underwent UGI endoscopy between 2009-2015 and had a subsequent diagnosis of UGI cancer. Cancers diagnosed within 1 year after endoscopy were defined as "prevalent" cancers, those diagnosed after 1 year and within 3 years after UGI endoscopy were considered as "missed" cancers, and those diagnosed after 3 years were classified as "latent" cancers. To reduce the number of miscoding errors we included only cases of cancer confirmed at least twice in the registry on two subsequent occasions. We used Polish National Cancer Registry (KRN) for data validation. Clinical characteristics of prevalent and missed cancers where compared using t-test and chi-square test, where appropriate, with Holm-Bonferroni correction. Survival data were compared by Kaplan-Meier analysis and log-rank test.

Results: In total, we analyzed 8,040,178 UGI endoscopies [46.3% ambulatory and 53.7% secondary care] performed in 3,856,210 patients [2,178,859 females (57.7%), mean age 58.7 (±3.8) years]. After excluding cancers with a single record in the NFZ (n=11,180) and those diagnosed before the first registered endoscopy (n=10,171) we included 51,123 UGI cancers in the analysis, of which 43,388 were classified as prevalent (84.9%), 3,964 as missed (7.8%), and 3,771 as latent cancers (7.4%). NFZ data was cross-linked with KRN registry showing a 84.2% agreement. We observed a steady decline of UGI cancer incidence within the study time-frame (from 8,881 cases in 2009 to 6,231 cases in 2015), however, the proportion of missed cancers remained relatively stable oscillating between 7.3% to 8.5% in 2009-2014. Median time of missed cancer diagnosis after UGI endoscopy was 1.8 years (IQR 1.4-2.4). Gastric cancers constituted majority of missed cancers (81.4%), however, the miss-rate was highest for duodenal cancers, followed by gastric and oesophageal cancers (16.9%, 7.4% and 5.2%, respectively). When compared to prevalent cancers, patients with missed UGI cancers were more commonly female (40.9% vs 33.1%, *P*< .001), less commonly resided in rural areas (30.0% vs 35.1%, *P*=.003) and were statistically younger, however, this difference wasn't clinically significant (mean age 67.5 vs 68.1, *P*< .001). Missed cancers had a higher survival rate as compared to prevalent cancers cases (5-year survival: 12.6% vs 9.0%, *P*< .001). Within missed UGI cancers, oesophageal had the worst survival as compared to gastric and duodenal cancers [5-year survival rate: 6.9%, 13.6% and 13.0%, respectively (*P*< .001)].

Conclusion: Despite declining UGI cancer incidence, proportion of missed UGI cancers remain stable over time. Patients with missed UGI cancers are more commonly female, reside more often in urban areas and have a higher survival rate than prevalent cancers. Oesophageal cancers are least commonly missed, however, have the poorest survival among missed UGI cancers.

Disclosure: Nothing to disclose

OP049 LONG TERM OUTCOMES OF PER-ORAL ENDOSCOPIC MYOTOMY BEYOND 6 YEARS: A MULTICENTER STUDY OF ACHALASIA PATIENTS

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Introduction: Per-oral endoscopic myotomy (POEM) is as a safe and effective treatment for achalasia with short-term clinical response reported in over 80% of patients. However, long-term data are limited.

Aims & Methods: To (1)evaluate outcomes in achalasia patients at least 6 years post-POEM and (2)identify factors associated with clinical failure. We conducted a retrospective review of achalasia patients at 8 tertiary-care centers (2 USA, 4 Europe, 2 Asia) who underwent POEM from 2010 to 2012 with a minimum follow-up of 6 years. Response was defined by an Eckardt score of ≤3. Adverse events (AEs) were also reported and categorized by the ASGE lexicon for AEs. Univariable analysis was performed to determine factors associated with clinical failure.

Results: A total of 73 patients (46 females (63.0%); mean age 49.7 years) with at least 6 years of follow-up (type I 16, type II 15, type III 4, and un-

	Patients with available data Total; total clinical response; total clinical failure	Overall (n=73)	Clinical success (ES ≤3) n=65	Clinical failure (ES>3) n=8	p-value
Age, years (mean±SD)	73;65;8	49.7±17.4	50.6±18.0	42.4±10.1	0.07
BMI, kg/m2 (mean±SD)	37;32;5	26.5±12.4	26.3±12.6	28.3±11.6	0.73
Female, no. (%)	73;65;8	46 (63.0)	41 (63.1)	5 (62.5)	0.99
Disease Classification	73;65;8				0.005
Type 1		16 (21.9)	10 (15.4)	6 (75.0)	
Type 2		15 (20.6)	14 (21.5)	1 (12.5)	
Type 3		4 (5.5)	4 (6.2)	0 (0.0)	
Unspecified		38 (52.1)	37 (56.9)	1 (12.5)	
Any prior therapy, no. (%)	73;65;8	23 (31.5)	22 (33.9)	1 (12.5)	0.42
HRM IRP, mmHg (mean±SD)	25;21;4	32.5±14.2	32.4±15.1	33.1±9.2	0.90
Pre-poem Eckhart score, mean±SD	71;65;6	7.1±2.3	7.1±2.3	7.7±2.7	0.61
Follow up time, months, median (IQR)	50;42;8	79.5 (73.9-82.6)	76.9 (73.9-82.2)	81.6 (74.7-89.1)	0.25
72 months Eckhart score (mean±SD)	73;65;8	1.1±1.1	0.9±0.8	2.5±1.8	0.04
36 months Eckhart score (mean±SD)	61;58;3	0.9±1.1	0.8±0.8	4.3±1.2	0.03
6 months Eckhart (mean±SD)	69;63;6	0.8±1.1	0.6±0.8	3.2±1.5	0.007
Patients with adverse events, no. (%)	73;65;8	16 (21.9)	16 (24.6)	0 (0.0)	0.19
Symptomatic reflux, no. (%)	72;64;8	27 (37.5)	25 (39.1)	2 (25.0)	0.43
PPI use, no. (%)	73;65;8				0.41
Daily		23 (31.5)	22 (33.9)	1 (12.5)	
Occasionally		6 (8.2)	5 (7.7)	1 (12.5)	
Esophagitis on EGD, no. (%)	60;57;3	17 (28.3)	17 (29.8)	3 (0.0)	0.55

[OP049 Table. Clinical characteristics and outcomes in patients with clinical success versus failure.]

specified 38) were identified. Median follow-up was 79.5 months (IQR 73.9-82.6). Twenty-one (28.8%) patients had prior dilatation, 4 (5.5%) botulinum injection and 2 (2.7%) Heller myotomy. A total of 17 AEs occurred in 16 (21.9%) patients and included: 1 arrhythmia, 1 delayed bleeding, 1 esophageal leak, 3 mucosotomies, 1 subcutaneous emphysema, and 10 symptomatic capnoperitoneum (13 mild, 2 moderate, and 2 severe). Clinical success was observed in 96%(66/69), 96%(67/70), 93%(65/70), 91%(64/70), and 91%(64/70) of patients within 6, 12, 24, 36, and 48 months respectively. At 72 months, success was noted in 89%(65/73) of cases. Of 66 patients with response at 6 months, only 3 (4.5%) experienced recurrence of symptoms. Overall, mean Eckardt score decreased from 7.1±2.3 to 1.1±1.1 (p< 0.001) and 4sIRP pressure improved from 32.5±14.2 to 12.2±8.8 mmHg (p< 0.001). In univariable analysis, type I achalasia (OR 10.8, p=0.04) was associated with clinical failure. Four patients with clinical failure underwent retreatment with pneumatic dilation and clinical response was noted in 3 (75%) of these patients. Of the remaining 4 patients who did not undergo retreatment, 2 were managed conservatively and 2 were lost to follow up. After POEM, symptomatic reflux was reported by 27/72 (37.5%) patients and esophagitis was reported in 17/60 (28.3%) of patients who had post-procedure EGDs.

Conclusion: This international study reports the longest follow-up of a POEM cohort to date. POEM is safe and provides long-term symptomatic relief with sustained response in almost 90% of patients.

Disclosure: Nothing to disclose

OP050 OUTCOMES OF THE FIRST 500 PERORAL ENDOSCOPIC MYOTOMY FOR ESOPHAGEAL MOTILITY DISORDERS: OUTCOMES OF THE FIRST 500 PATIENTS WITH A MID- AND LONG-TERM FOLLOW-UP. IN A SINGLE EUROPEAN CENTER

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Introduction: Peroral endoscopic myotomy (POEM), which combines the efficacy of surgical myotomy with the benefits of an endoscopic, minimally invasive, procedure, is now considered an effective treatment for esophageal motility disorders. We report on the mid- and long-term outcomes of a large series of patients treated with POEM in a single European center.

Aims & Methods: The first 500 adult patients successfully treated in our center between May 2011 and January 2018 were retrospectively identified from a prospective database, and included in this study. Patients were treated according to the original a standard technique describe by Inoue in 2010. Demographics, clinical, procedural and follow-up data were collected and analysed.

Results: Mean age of patients was 51 years (18-85); 50.5% were male. 79.4% patients were treatment naïve; 14.4% had undergone pneumatic dilatation, 2.6% botulin toxin injection,3.6% Heller-Dor myotomy. A total of 16.6% patients had a type- I achalasia, 57.2% type- II, 13.8% type- III, 1.2% Jackhammer esophagus, 0.8% distal esophageal spasm; in 10.4% the achalasia type was not adequately classified. POEM was completed in 98% of patients. Mean symptoms duration before POEM was 24±64.1 months. Mean operative time was 62.9 minutes (19-180 minutes). Severe complications occurred in 5 patients (1%), but all were managed conservatively. A mean follow-up of 23.7 months (3-60 months) was available for 96.7% of patients. Clinical success (Eckardt score ≤3) was documented in 98% of patients, and was 96.4%, 95.6%, and 93% after 6, 24 and 36 months respectively. 13 patients with failure underwent pneumodilation with success, 4 have persisting symptoms after pneumodilation, 2 underwent surgery.

Success was 97.5% (435/424) in achalasia-patients and 81.8% (11/2) in those with spastic motility disorders (p< 0.05).

An altered esophageal pH-study was documented in 31.2% patients; esophagitis rate was 27.7% (86.9% grade A/B; 13.1% grade C/D).

At the date of the last follow-up, 10% of patients receive daily PPI for GERD.

Conclusion: Our results confirm the efficacy of POEM in a large cohort of patients, with an adequate follow-up. Benefits of POEM seem durable, with and acceptable incidence and severity of iatrogenic GERD.

Disclosure: Nothing to disclose

OP051 PERORAL ENDOSCOPIC SEPTOTOMY (POES) FOR TREATMENT OF ZENKER'S DIVERTICULUM: A PILOT STUDY

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Introduction: The definitive treatment of ZD is to transect the cricopharyngeal muscle to eliminate the septum between the diverticulum and the upper esophagus thus relieving the dysfunctional condition. In the last decade, a septotomy performed utilizing a flexible endoscope has been reported as a safe and effective alternative to both open surgery and rigid endoscopic diverticulotomy. More recently, submucosal tunneling endoscopic septum division (STESD) or Z-POEM has been developed to reduce the risk of perforation and allow a safer, more complete cricopharyngeal myotomy. However, patients with short septum (≤20mm) ZD still represent a difficult-to-treat subgroup of patients because of the anatomical limitation leading to reduced operating space for both rigid and flexible endoscopic treatments or even a STESD approach.

Aims & Methods: The aim of this pilot study is to investigate the efficacy and safety of a novel alternative third space approach, called Per-Oral Endoscopic Septotomy (POES) to treat symptomatic patients with short-septum ZD. The POES technique consisted of:

1) using a hook knife, after submucosal injection, a 15mm mucosotomy performed directly on top of the diverticular septum directed along its long axis;

2) dissection of the underlying submucosa to create an endoscopic window to directly visualize the muscular septum with continued submucosal dissection along either side of the cricopharyngeal muscle, sparing the overlying mucosa, to create two short tunnels;

3) complete myotomy of the now fully exposed cricopharnyngeal muscle fibres extended a 5-10 mm into the esophageal body;

4) closure of the mucosotomy with clips.

All patients with short-septum (≤20mm) ZD who were referred to Humanitas Research Hospital (Rozzano, Italy) for flexible endoscopic septotomy from September 2017 to present were considered for POES. Exclusion criteria consisted of previous interventions for ZD, ongoing use of anticoagulants and inability to provide informed consent.

We determined pre- and post-procedural dysphagia scores using the Dakkak and Bennett (D&B) scale (0-4). Complete or near-complete resolution of symptoms (D&B 0 or 1) was the primary endpoint. Procedure-related adverse events according to ASGE lexicon and procedure time were also recorded. Follow up was carried out by patient visits or via telephone calls by a dedicated nurse at 24 hours, 4 weeks and then regularly every month. Recurrence was defined as new onset dysphagia with a D&B score > 1 or requiring re-intervention.

Results: Sixteen patients (M/F: 11/5, mean age: 64.6±14.0) underwent POES. All procedures were performed under deep sedation with C02 insufflation. Mean size of ZD was 18.4±5.4 mm and mean pre-procedure D&B dysphagia score was 2.75±0.4. Average procedural time was 14.9±5.0 min (range: 8-26 min). No intra- or post- procedural adverse events occurred. Septal myotomy was successfully completed in all patients. There was complete or near-complete resolution of symptoms in 15 out of 16 patients (93.8%) with the D&B dysphagia score dropping from 2.75±0.4 to 0.3±0.6 (p < 0.0001). No symptomatic recurrences were reported after a mean follow up time of 8.9 ± 3.1 months (range: 6-15 months).

Conclusion: According to the preliminary results of this pilot study, third-space approach with POES provided a very safe, efficient and effective treatment for this specific difficult-to-treat group of patients with short septum ZD. Larger comparative studies with longer follow-up are needed to confirm this preliminary data.

Disclosure: Nothing to disclose

Towards microbiome targeted therapies

14:00-15:30 / A1

OP052 TOWARDS ANTI-INFLAMMATORY DIETARY RECOMMENDATIONS BASED ON THE RELATION BETWEEN FOOD AND THE GUT MICROBIOME COMPOSITION IN 1423 INDIVIDUALS

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Introduction: Gut microbiota are essential for intestinal health. As microbes thrive on dietary substrates, the question arises whether we can nourish a protective gut flora. While there is increasing interest in anti-inflammatory capacities of isolated nutrients, little is known on the association between dietary patterns or individual foods and gut microbial features. In this study, we investigated the effect of 160 dietary factors on the gut microbiome across four cohorts, comprising the general population, patients with Crohn's disease, ulcerative colitis, and irritable bowel syndrome. Connecting the diet to the gut microbiome gives us more insight into the relation between diet and intestinal disease and could guide us towards more rational dietary interventions.

Aims & Methods: For every participant one stool sample was collected along with a Food Frequency Questionnaire. To reconstruct the microbiota composition of stool samples, microbial DNA was isolated and shotgun metagenomic sequencing was performed. Unsupervised cluster analyses were performed to identify dietary patterns associated with particular microbial clusters, using hierarchical clustering. Dietary clusters were computed based on squared Euclidean distances, clusters of microbial species and pathways were based on Bray-Curtis dissimilarity. Next, linear models were conducted, adding caloric intake, age, sex, and sequencing read depth as covariates. Analyses were performed separately per cohort, followed by a meta-analysis and heterogeneity estimation. Multiple testing correction was performed on the obtained p-values and a FDR < 0.05 was defined as significance cut-off.

Results: We identified 61 individual food items associated with 123 taxa and 249 pathways (FDR< 5%) as well as 49 correlations between food patterns and microbial groups. A plant-based diet was associated with increased abundances of short chain fatty acid (SCFA) producing bacteria, as well as associated pathways of fermentation. Moreover, plant protein was associated with pathways involved in the biosynthesis of vitamins and amino acids (biotin, thiamine, L-ornithine) and degradation of sugar alcohols. While plant protein was associated with an increase in *Bifidobacteria* and a decrease in *Blautia* and *Streptococci*, the opposite was found for animal protein. Expectedly, low-fat fermented dairy correlated with an increase of *Lactococcus lactis*, *Lactobacilli* and *Bifidobacterium bifidum*, as well as pathways of peptidoglycan synthesis possessed by lactic acid bacteria. A pattern comprising plant protein, vegetables, fruits, cereals, nuts, wine and fish was associated with increased abundances of *Roseburia hominis*, *Faecalibacterium prausnitzii* and *Bifidobacteria* and carbohydrate fermenting pathways. A cluster of wine correlated with an increased abundance of the Bifidobacterium shunt, a fructose fermenting pathway. Interestingly, wine was also correlated with a decrease in clusters of potentially harmful species, namely *Bacteroides fragilis*, *Escherichia coli*, *Coprobacillus* and *Clostridium bolteae*, potentially related to a high polyphenol content.

Conclusion: We show that specific foods are associated with the abundance of gut bacteria capable of the biosynthesis of essential nutrients and carbohydrate fermentation to SCFAs, inferring that certain foods could exert mucosal protection by inducing bacteria with anti-inflammatory properties. Our work provides support of the idea that the diet represents a therapeutic strategy for intestinal diseases, through the modulation of the gut microbiome.

Disclosure: Nothing to disclose

OP053 GUT MICROBIAL CO-ABUNDANCE NETWORKS IDENTIFY FUNCTIONAL HUBS FOR INFLAMMATORY BOWEL DISEASE AND OBESITY

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Introduction: Recent studies have shown the importance of unraveling the role of the gut microbiota in human health and disease. While knowledge is increasing on abundance differences in diseases like inflammatory bowel disease (IBD) and obesity on microbial compositional level, it is also important to study the gut microbiota as an entire ecosystem. One way of doing this, is to study which microbial species and functional pathways show co-abundance networks which may also be relevant for disease.

Aims & Methods: Here, we present the largest study to date in which microbial networks are constructed from an IBD, an obesity and two general population cohorts. We collected metagenomics sequencing data of stool samples from 2,379 participants. DNA isolation was performed by using the same standardized procedures for all four cohorts. MetaPhlAn2 and HUMAnN2 tools were used to characterize the composition and functional pathways of the gut microbiota. Co-abundance of species or functional pathways were identified by using pairwise Spearman correlation. The heterogeneity Cochran's- Q test was used to analyze whether results were derived from a single cohort. A false discovery rate of < 5% was used as significance threshold to also account for multiple testing.

Results: We established co-abundance networks that revealed 1,057 species-species and 8,381 pathway-pathway co-abundance edges. Notable, 113 (10.7%) of the species edges and 4,824 (57.6%) of the pathway edges showed significant differences between the cohorts. The heme anaerobic biosynthesis pathway for example showed co-abundance with biosynthesis pathways of fatty acids in the IBD cohort. Heme is a cofactor of inducing oxidative stress and the identified fatty acids are known for their lipotoxicity. This data suggests that the gut microbiota may play an important role in inducing gut inflammation through biosynthesis of toxic fatty acids in IBD patients. Another example is the sulfur amino acids biosynthesis in the obesity cohort. This pathway has been recognized as potent modulator of lipid metabolism. This pathway was positively correlated with five carbohydrate degradation pathways in the obesity cohort, indicating that these pathways may play an important role in regulating functional dysbiosis in obesity.

Conclusion: By performing a large microbial co-abundance network comparing patients with IBD, obesity and population based subjects, we show that not only microbial abundances but also microbial co-abundance relationships are shifted in disease states. We show that the pathway networks are more different than the species networks. The obesity and IBD specific networks could point to key species or functional pathways which could potentially be used as therapeutic targets.

Disclosure: Nothing to disclose

OP054 FIRST LARGE SCALE EVALUATION OF THE SMALL INTESTINAL MICROBIOME IN PATIENTS WITH OBESITY

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Introduction: Obesity has reached epidemic proportions globally, nearly a third of the world population is now classified as overweight or obese. In 2016, the prevalence of obesity was 39.8% and affected about 93.3 million adults in US. The World Health Organization (WHO) defines overweight

and obesity as abnormal or excessive fat accumulation that presents a risk to health. In the past decade, the gut microbiome has been implicated as an important factor involved in obesity, but most of the research has focused on the stool microbiome and not the metabolically and functionally important small intestine.

Aims & Methods: In this study, we examined the small bowel microbiome in obese subjects. Subjects with normal weight (Body Mass Index (BMI) 18.5 to < 25) and subjects with obesity (BMI > 30) undergoing sole upper endoscopy were recruited. Blood was collected before the procedure. Duodenal aspirates were collected using a novel sterile aspiration catheter technique and DNA was isolated using the MagAttract PowerSoil DNA Kit. Microbiota was analyzed by 16S rRNA metagenomic sequencing. Operational Taxonomic Units clustering and taxonomic analysis were performed with CLC Microbial Genomics Module v. 2.5. The blood levels of glucagon-like peptide-1 (GLP-1) and leptin were determined by Luminex. The Wald test and Mann-Whitney test were used to determine significance between groups.

Results: 92 normal weight subjects (controls) and 45 subjects with obesity had their duodenal microbiome (DM) completely sequenced. The α-diversity indexes of subjects with obesity were similar when compared to controls (Total number, P=0.3846; Simpson's index, P=0.4938; Shannon entropy, P=0.5203). The DM of subjects with obesity and controls was predominantly colonized by taxon from Firmicutes phylum (56-60%), followed by Proteobacteria and Actinobacteria (19-21% and 7-11%). The relative abundance (RA) of the Bacteroidetes phylum represented less than 6% of the total abundance in both groups and the DM Firmicutes/Bacteroidetes ratio in subjects with obesity was also similar when compared to controls (P=0.1899). However, at the family level, the RA of the families Lactobacillaceae and Clostridiaceae, both from Firmicutes phylum, were increased when compared to controls (Fold change (FC)=11.17, P=2.73E-8; FC=16.11, P=2.96E-10 respectively). Additionally, the RA of the Neisseriaceae and Pasteurellaceae families, both from Proteobacteria phylum, were also increased in the DM of subjects with obesity when compared to controls (FC=2.05, P=0.021; FC=2.28, P=0.01, respectively). Interestingly, the RA of the Neisseriaceae family had a positive correlation with the levels of GLP-1 (Spearman r=0.193, P=0.037) and leptin (Spearman r=0.214, P=0.021). The RA of the Pasteurellaceae family also correlated with the levels of leptin (Spearman r=0.247, P=0.007). Impressively, subjects with obesity had higher circulating levels of GLP-1 and leptin when compared to controls (FC=1.14, P=0.038; FC=8.85, P< 0.0001, respectively).

Conclusion: In this first study of the small bowel microbiome, marked differences in the microbiome were seen at the family level and these differences appeared related to incretins and hormones linked to metabolism.

Disclosure: Nothing to disclose

OP055 DIMETHYL FUMARATE (DMF) INHIBITS PROLIFERATION AND MIGRATION OF HEPATOCELLULAR CARCINOMA CELLS (HCC)

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Introduction: Dimethyl fumarate (DMF) is used for treatment of psoriasis (Fumaderm®). Recently, we have shown that application of DMF induces cell death in NF-$_\kappa$B-dependent tumors. This data were confirmed in a mouse model. DMF application led to a reduced tumor growth and, interestingly, to a reduction of metastases formation. The inhibition of metastasis formation was NF-$_\kappa$B-independent. Thus, identification of the molecular mechanism inhibiting metastasis formation is a challenging aim for future. Solid tumors, like pancreas, breast or colon carcinoma, show no constitutive NF-$_\kappa$B activation. Interestingly, DMF also reduced the metastasis formation in these tumors. Since metastasis is the major cause of poor prognosis of HCC DMF could be an interesting new approach for a treatment of these.

Aims & Methods: Human liver tumor cell lines HepG2, Huh7 und Hep3B were treated with DMF (25 μM up to 100 μM) for up to 72 h. A luminescence based viability assay was performed. The assay measures the concentration of ATP *via* photometric quantification. The concentration of ATP is connected to the viability but also the active metabolism of cells. To maintain effects on metastasis formation a scratch assay with the cell lines HepG2, Huh7 and Hep3B were performed. The cells were treated with DMF (25 μM up to 100 μM) and cultivated for up to 48 h. Since DMF could lead to cell death cell were co-treated with 50 μM zVAD an inhibitor of apoptosis.

Migration of the cells was analyzed by microscopy. To maintain effects on proliferation HepG2 were stained with Cytopainter Cell Proliferation Staining Reagent, which stains the cytoplasm of the cells. After each cell division the dye will be divided between mother and daughter cell resulting in a reduced staining. The proliferation of the HepG2 cells was analyzed after 24 h, 48 h, 72 h and 96 h of treatment.

Results: DMF application resulted in a time- and dose-dependent reduction of the ATP-concentration in all cell lines tested. The strongest effects were observed after 72 h treatment at a concentration of 100 μM DMF. In addition, migration of Huh7 and Hep3B were inhibited time and dose-dependently. Migration of Hep3B was more effected by DMF. Inhibition of migration of Hep3B was already observed at a concentration of 25 μM DMF. At a concentration of 100 μM DMF migration of Hep3B was blocked completely. Migration of Huh7 was inhibited at a concentration of 75 μM DMF. Hence, migration of Huh7 was less effected by DMF. Migration of HepG2 could not be detected. Since the migration of the HepG2 cells could not be analyzed we switched to the measurement of the proliferation. Effects on proliferation combined with the reduction of ATP in the cells could mean that the cells will be dormant. It could be shown that the proliferation of HepG2 was also time- and dose-dependent inhibited through DMF.

Conclusion: The formation of metastases is one of the major reasons why solid tumors like HCC display a rather high mortality rate. Here, we show that DMF is capable to inhibit migration and proliferation in HCC cell lines probably caused by energy depletion. The exact mechanism which causes the inhibition of migration and proliferation still needs to be investigated. DMF is already clinical approved used for the treatment of psoriasis and shows compared to anti-cancer drugs minor side effects. Hence, DMF could be used to develop treatments against metastasis formation.

Disclosure: Nothing to disclose

OP056 DUODENAL MICROBIOME CHARACTERIZATION IN PATIENTS WITH OR WITHOUT *HELICOBACTER PYLORI* INFECTION

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Introduction: *Helicobacter pylori* a common human pathogen is a risk factor for chronic gastritis, peptic ulcer and gastric cancer. Its prevalence is higher in developing countries mainly by inadequate hygiene on food handling and preparation. *H. pylori* creates an alkaline environment on the stomach, which leads to changes in the gastric and gut microbiomes; also, *H. pylori* elicits a local immune response that could modulate gastric and duodenal microbiota. There is little information regarding the effect of *H. pylori* gastric infection on duodenal microbiota.

Aims & Methods: To conduct a culture independent metagenomic profiling of duodenal microbiome on patients with and without *H. pylori* infection, matched by age, hospital and sex.

The V3-V4 region of the 16S rRNA gene was amplified and sequenced on MiSeq Illumina platform from a total of 74 patients in 4 different hospitals in Quito, Ecuador. Patients were assessed for the presence of H. *pylori* through a biopsy obtained during an upper digestive endoscopy. From these, 34 patients had a *H. pylori* active infection on the gastric fundus, and 40 patients were negative for the bacterium. Duodenal biopsies were obtained in all patients, and additional epidemiological information was collected. Bioinformatic analysis of sequences was performed using QIIME2.

Results: Around 28 million bacterial sequences were obtained and 3,230 operational taxonomic units (OTUs) were characterized among the 74 samples. On most of the samples positive for *H. pylori* on histological observation, there was also detected *H. pylori*16S rRNA on the culture-independent metagenomic analysis. A higher alpha diversity was encountered in the duodenum of *H. pylori* positive patients (Shannon index and observed OTUs differences between the two groups *P* < 0.01). Weighted UNIFRAC, Bray-Curtis and Jaccard beta diversity indexes also showed significant differences between groups (*P* < 0.05). Relative abundance of *Haemophilus*, *Streptococcus*, *Neisseria* and *Prevotella* spp. was higher in the *H. pylori* positive patients whilst a higher abundance of *Ralstonia* spp. was on found in negative ones.

Conclusion: Duodenal microbiomes are different between *H. pylori* positive and negative patients in terms of alpha diversity, beta diversity and relative OTUs abundance. Also, *H. pylori* infected individuals have increased abundance of *Haemophilus, Streptococcus, Neisseria* and *Prevotella* spp. in their gastric microbiome (1).

References: 1. Klymiuk, I., Bilgilier, C., Stadlmann, A., Thannesberger, J., Kastner, M. T., Högenauer, C., Steininger, C. (2017). The Human Gastric Microbiome Is Predicated upon Infection with Helicobacter pylori. Frontiers in microbiology, 8, 2508. doi:10.3389/fmicb.2017.02508
Disclosure: The current project was funded by Biocodex, USFQ and UTE, however the funders did not were involved in study design, patients recruitment, experiments, data collection and analyses, or results interpretation.

OP057 CHANGES IN DUODENAL UROGUANYLIN IMMUNOREACTIVE CELLS DENSITY CORRELATE WITH SYMPTOMS OF PATIENTS WITH DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME FOLLOWING FECAL MICROBIOTA TRANSPLANTATION

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Introduction: Altered density of uroguanylin (UGN) immunoreactive (GUCA2B-positive) cells was found in the duodenum of patients with diarrhea-predominant irritable bowel syndrome (IBS-D) (1). Uroguanylin activates guanylate cyclase to regulate electrolyte and water transport in intestinal epithelia (2).
Aims & Methods: The aim was to investigate the effect of fecal microbiota transplantation (FMT) on UGN immunoreactive (GUCA2B-positive) cells density in the duodenum of IBS-D patients.
The study included 16 IBS patients according to Rome III criteria and four patients were excluded. The remaining patients (n=12, 4 females and 8 males) were divided according to the cause into post-infectious (PI, n=6) and idiopathic (n=6) IBS. They completed IBS-Symptom Severity Scoring system (IBS-SSS) questionnaire and IBS-Symptom questionnaire (IBS-SQ) before and 3 weeks after FMT. Fecal suspension (30 g fresh feces donated from patients' healthy relatives and diluted with 60 ml normal saline) was instilled via gastroscope into the duodenum. Biopsies were taken from the descending part of the duodenum before and 3 weeks after FMT. They were immunostained for UGN cells using rabbit polyclonal antibody to GUCA2B (LS-C371347, LSBio, Seattle, WA, USA) and quantified using computerized image analysis.

Fecal microbiota transplantation			
Questionnaire	Before	After	P-value
IBS-SSS	326.6±22.3	240.2±33.6	0.0009
IBS-SQ			
Total score	30.8±3.3	11.6±2.1	<0.0001
Abdominal pain	6.3±0.9	3.3±0.8	0.0012
Bloating	7.9±0.5	3.4±0.8	<0.0001
Diarrhea	6.4±0.9	1.2±0.4	<0.0001
Uroguanylin immunoreactive cells density			
Total IBS group			
Villi (cells/100 epithelial cells)	44±5.5	41±2.3	0.5
Crypts (cells/mm²)	116±8	96±3	0.049
PI-IBS			
Villi (cells/100 epithelial cells)	45.8±7.4	40.5±3.3	0.6
Crypts (cells/mm²)	108±11.8	102.5±4	0.6
Idiopathic IBS			
Villi (cells/100 epithelial cells)	42.5±8.8	40.7±3.6	0.8
Crypts (cells/mm²)	124±11	89.5±4	0.04

Paired t test. Data are presented as the mean±SEM. IBS: irritable bowel syndrome, PI: post infectious, SSS: Symptom Severity Scoring system, SQ: symptom questionnaire.

[Table 1: Symptoms scores and duodenal uroguanylin immunoreactive cells density in IBS patients before and after fecal microbiota transplantation]

Results: The total scores for IBS-SSS and IBS-SQ were significantly improved (*P*=0.0009 and < 0.0001, respectively) 3 weeks after receiving FMT. During the same period, the densities of UGN immunoreactive cells for the total group and idiopathic subgroup decreased significantly in the duodenal crypts (*P*= 0.049 and 0.04, respectively) but not in the villi (*P*= 0.5 and 0.8, respectively), as shown in Table 1. No significant changes were shown in the PI-IBS subgroups (Table 1). Using Pearson's test, UGN immunoreactive cells density in the crypts correlated positively with diarrhea (r=0.97, *P*=0.001) and negatively with bloating (r= -0.91, *P*=0.011) in the PI-IBS subgroup before FMT and positively with abdominal pain (r=0.63, *P*=0.029) in the total group of IBS patients after FMT. No correlations were found between the cells in the villi and IBS symptoms.
Conclusion: This is the first study to show the changes in the UGN immunoreactive cell densities following FMT and their correlations to IBS symptoms (pain, bloating and diarrhea). These correlations are consistent with the effects exhibited by UGN analog that is used for the treatment of IBS patients (3).

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Disclosure: Nothing to disclose

OP058 ROLE OF INTESTINAL ALKALINE PHOSPHATASE, MYOKINES AND MICROBIOME IN AMELIORATION OF EXPERIMENTAL COLITIS IN VOLUNTARY RUNNING WHEEL ACTIVITY OBESE MICE FED FAT DIET

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Introduction: Intestinal alkaline phosphatase (IAP) is an important apical brush border enzyme expressed throughout the gastrointestinal tract and secreted into both, the intestinal lumen and the bloodstream. IAP has been implicated in intestinal protection through dephosphorylating both ATP and bacterial lipopolysaccharide (LPS) released from cells during stressful conditions. The hypertrophied mesenteric white (mWAT) adipose tissue in obesity may predispose the development of colitis.
Aims & Methods: Exercise can improve colitis but the role of IAP with or without exercise in mucosal healing of colitis has been little studied. We determined the effects of daily intragastric treatment with IAP (50 - 200 U) in sixty mice fed for 6 months with high fat diet (HFD, 70% energy from fat, series A) and standard diet (SD, 10% energy from fat, series B) (Altromin, Lage, Germany) and subjected to voluntary running wheel activity on the course of trinitrobenzene sulfonic acid (TNBS) colitis. Mice (series A & B) were housed for 8 weeks in *individual running wheel cages* to measure the running distance and muscle force by grip test. Following colitis, the colonic blood flow (CBF) by Laser Doppler flowmetry, disease activity index (DAI) were determined, the plasma levels of TNF-α, IL-1β, adiponectin, leptin, TWEAK and myokines irisin, IL-6 and FNDC5 were assessed by Luminex, the expression for TNF-α, IL-1β and IL-6 mRNA was determined by qPCR and the gut microbiome was analyzed by Next-Generation Sequencing (NGS).
Results: TNBS caused a significant increase in DAI, the significant fall in the CBF, an increase in colonic tissue weight, the plasma levels, expression of IL-1β, TNF-α and IL-6 mRNA and protein (p< 0.05). In HFD mice, the running distance, muscle strength were reduced and the area of colonic damage and colonic tissue weight, the plasma IL-1β, TNF-α, TWEAK and leptin levels were significantly increased while FND5, irisin and adiponectin levels were decreased vs. SD mice. Treatment with IAP significantly

reduced DAI in SD and HFD mice, increased the skeletal muscle strenght as assessed by muscle grip test and potentiated the beneficial ameliorating effect of exercise on colitis. IAP alone or combined with exercise increased the CBF and plasma levels of myokines IL-6, FND5 and irisin while plasma levels of IL-1β, TNF-α, TWEAK and leptin was significantly diminished (p< 0.05). In HFD mice, the reduction of *Lactobacillus, Clostridium, Faecalibacterium* and an enhanced colonization by *Bacteroides, Prevotella* and *Helicobacter spp.* was detected while IAP treatment reduced *Bacteroides* and *Helicobacter* spp. and favored colonization of *Lactobacillus and Bifidobacteria spp.* compared with sedentary mice.

Conclusion: Exercise can improve the healing of experimental colitis due to release of protective myokines irisin, IL-6 and FND5 from working skeletal muscles, reduction of proinflammatory cytokines and normalization of leptin/adiponectin ratio, especially in obese mice, and 2) exogenous IAP ameliorates gut inflammation, enhances effect of exercise and favors healing of colitis due to modification of microflora and a potent enhancement in CBF. IAP may represent a novel supplementation capable of acting synergistically with moderate exercise activity in mechanism of amelioration of human IBD (grant No. K/PBO/000440).

Disclosure: Nothing to disclose

Epidemiology and treatment of IBD

14:00-15:30 / B2

OP059 INCIDENCE AND PREVALENCE OF INFLAMMATORY BOWEL DISEASE IN THE UK BETWEEN 2000 AND 2016 AND ASSOCIATED MORTALITY AND SUBSEQUENT RISK OF COLORECTAL CANCER

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Introduction: There is only limited and old data on the epidemiology of inflammatory bowel disease (IBD), including Ulcerative Colitis (UC) and Crohn's Disease (CD), in the UK. Accurate data on the IBD burden and their impact is crucial for service planning for patients. The aim of this study was to establish accurate, updated UK incidence and prevalence of IBDs and to quantify the risk of mortality and colorectal cancer in those with IBD.

Aims & Methods: Retrospective cohort studies and cross-sectional studies were carried out between 2000 and 2016 using data from the Health Improvement Network (THIN), a primary care database of 750 general practices representative of the UK population. Annual incidence rates and point prevalence among adults aged 18 years and over were calculated for CD and UC. Mortality and colorectal cancer (CRC) incidence rates were quantified using a matched cohort study design, with four controls for each UC or CD subject, matching on age, sex and general practice between 1995 and 2017. A multivariable Cox proportional hazards model was used to quantify risk of mortality adjusting for year, age-band, sex, deprivation level, Charlson comorbidity, smoking status and hypertension and a multivariable Poisson regression model was used to quantify CRC risk.

Results: 16,765 incident cases of CD and 24,410 incident cases of UC were observed among 8,767,641 subjects, totalling more than 61 million person-years at risk (py). The incidence rate (IR) of CD was 16.3 per 100,000 py. Females had a 30% higher incidence of CD than male subjects (Incidence Rate Ration 1.30 (95% CI 1.23-1.34), p< 0.001) and all age categories greater than 18-30 had a lower rate of CD incidence. Overall, CD incidence fell by 3% (0.97 (0.96-0.97), p< 0.001) over the study period, was stable in subjects under 60 years, and fell by 4% in those over 60 years (0.96 (0.95-0.97), p< 0.001). The IR of UC was 25.9 per 100,000py. Females had a 6% lower incidence of UC than males (0.94 (0.91-0.96), p< 0.001) and compared to 18-30s all older age categories had a lower rate of UC when adjusted by sex and year. Overall, UC incidence fell by 4% (0.96 (0.95-0.96), p< 0.001) between 2000 and 2016. In those aged over 60, IR fell by 6% (0.94 (0.93-0.94), p< 0.001) over the study period, but was stable

in those under 60. Point prevalence of CD increased from 218 to 414 per 100,000 population between 2000 and 2016. In 2016, prevalence was 460 and 370 for females and males respectively. UC prevalence rose from 380 to 640 per 100,000. In 2016. prevalence was 630 and 640 in females and males respectively.

CRC incidence rate in the whole THIN population was 70.6 per 100,000py (95% CI 69.6-71.5) over the study period. IR of CRC in CD was 78.4 per 100,000py (66.8-92.0). IR of CRC in UC was 133.3 per 100,000py (121.1-146.8). The adjusted incidence rate ratio (IRR) of CRC was 26% higher in CD patients than in matched controls (1.26 (1.04-1.51), p=0,014), and was 48% higher in those with UC (1.48 (1.32-1.67), p< 0.001). Among CD subjects, mortality was 41% higher (hazard ratio 1.41 (1.35-1.47), p< 0.001) and among UC subjects, mortality was 17% higher (1.17 (1.14-1.21), p< 0.001).

Conclusion: IBD prevalence in the UK is more than double that which had been previously reported. Although incidence rates of UC and CD are stable in the under 60s, there appears to have been a fall in rates of IBD in older age groups. Mortality and CRC risk was higher in both UC and CD when compared to matched controls.

Disclosure: Nothing to disclose

OP060 INFLAMMATORY BOWEL DISEASE ASSOCIATED COLORECTAL CANCER: CHARACTERISTICS AND OUTCOMES FROM AN ENGLISH POPULATION DATASET (2010 TO 2016)

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Introduction: Colorectal cancer (CRC) is an important complication of inflammatory bowel disease (IBD). Historic cohort studies have suggested that the risk of developing CRC in those with IBD (IBD-CRC) may be increasing, but contemporary, population data are lacking. There is also a paucity of information on the clinical outcomes for these cancers, including surgical outcomes, and whether there is any difference between sporadic and IBD-CRC.

Aims & Methods: This English population-based study examined the characteristics, treatments and outcomes for CRC patients with and without IBD. The CORECT-R data repository holds national, linked data on CRC diagnosis pathways, treatments and outcomes in England. Using this resource, all CRC cases between 01/01/2010 and 31/12/2016 were identified. A diagnosis of IBD (Crohn's disease or ulcerative colitis) was defined by relevant ICD-10 codes (K50-51). Study characteristics included; sex, age at diagnosis, associated comorbidity, route of diagnosis, stage of CRC, survival in days, and details of any surgical resection. Multivariable logistic regression models assessed the relationship between IBD and post-surgical outcomes and death within a year of diagnosis.

Results: There were 192,000 CRC in the study period (2,992 IBD-CRC). There was an increase in the proportion of IBD-CRC from 1,4% in 2010 to 1.9% in 2016 (p-value for trend < 0.01). IBD-CRC cases were significantly younger (median age 68 years (IQR 56-78) and 73 years (IQR 64-81) respectively), had more associated comorbidity, and more presented as an emergency. There were significantly more right-colonic, and more early (Stage I) and late (Stage IV) cancers. After a major surgical resection significantly more people with IBD were likely to be readmitted as an emergency (OR 1.30, 95% CI 1.16-1.47), have a prolonged hospital stay (≥21 days) (OR 1.47, 95% CI 1.28-1.68), and die within a year (OR 1.52, 95% CI 1.32-1.77).

Conclusion: The proportion of IBD-CRC is increasing. This is may reflect the rising incidence of IBD, but also decreasing rates of colectomy procedures leaving more people exposed to a risk of developing CRC. Outcomes for those with IBD-CRC appear worse than for sporadic CRC, and the cancers occur in younger patients. There is an urgent need to explore the diagnosis and management pathways for these individuals to try and explain the significant differences shown here.

Disclosure: Nothing to disclose

OP061 THE RISK OF FURTHER RESECTIONAL SURGERY IN THE TEN YEARS FOLLOWING A FIRST RESECTION FOR CROHN'S DISEASE IN ENGLAND

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Introduction: Most patients with Crohn's Disease (CD) will have surgery during the course of their disease[1], many of whom develop endoscopic recurrence within a year[2] and may need further surgery. This study aims to examine the proportion, timing and factors associated with further surgery following an index surgical resection.

Aims & Methods: Hospital Episode Statistics captures all patient interaction with hospitals in England. Subjects were included in the study if they had index surgical resection between 2007 and 2016 and an International Classification of Disease-10 (ICD-10) code of K51 (CD) on admission. A sub-cohort was identified whose index resection was colonic and whose ICD-10 code was K501 - this was considered a Crohn's colitis cohort. Subjects were followed for a maximum of 12-years and the primary outcome was further bowel resection. A multivariable Cox regression model assessed factors associated with further resection.

Results: 16,609 subjects with CD had a bowel resection: 53.7% female, median age 35 (IQR 26-46) years, 87.3% were white, 85.3% of subjects had no comorbidities (Charlson score of 0) and 11% of subjects were coded as having perianal disease during the study period. 70% of subjects had at least 5 years of follow-up and 19% had at least 10-years follow-up. Index surgery was performed on an emergency admission in 41.8%. The median number of annual index resections was 1,662 (IQR 1,617-1,682). 29.7% of subjects had one or more further resections during the follow-up period and 22% of these had more than two further resections. 48.7% of first further resections took place within 1-year of index surgery and 54.7% of first further operations were performed in subjects whose index surgery occurred during an emergency admission. Of those with 5 years follow-up, 26.5% had one or more further resections and in those with 10 years follow-up, 32.4% had one or more further resections. Female subjects were at lower risk of further resection (HR 0.85 (95% CI 0.80-0.90), p< 0.001), as were the older subjects 44-60 years when compared to 18-29 year olds (0.85 (0.79-0.92), p< 0.001). Those in the least deprived quintile were also at lower risk (0.90 (0.82-0.99), p=0.029), as were those whose initial resection was done on an elective basis (0.53 (0.5-0.56), p< 0.001). Perianal disease was associated with a 69% increased the risk of future resection (1.69 (1.57-1.82, p< 0.001), and a high comorbidity score was associated with a 22% increased risk (1.22 (1.03-1.44), p=0.024). Ethnicity was not associated with further resection.

In the Crohn's colitis sub-cohort, 1,933 subjects were identified. 56% female, median age 36 (IQR 26-47) years and 87% white. 33% of subjects had further resection during follow-up, 25.6% of these subjects had 2 or more further resections. Perianal disease was coded in 14.5% of this cohort. 43% of index colonic resections were performed during an emergency admission and 39.5% of these subjects had further resection. An elective admission for index resection was associated with a decreased risk of future resection in the Crohn's colitis cohort (0.68 (0.58-0.79), p< 0.001) whereas perianal disease was associated with an 85% increased risk (1.85 (1.53-2.23), p< 0.001).

Conclusion: Future resection was associated with an index resection performed during an emergency admission, perianal disease, male sex and those with greater comorbidity. Lower deprivation and older age were associated with a reduced risk of further resection. Further resectional surgery remains common in CD following index bowel resection, despite the widespread use of biologic agents.

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Disclosure: Nothing to disclose

OP062 COURSE OF INDOLENT CROHN'S DISEASE IN A PROSPECTIVE EUROPEAN POPULATION-BASED INCEPTION COHORT WITH FIVE YEARS FOLLOW-UP - THE EPI-IBD COHORT

Burisch J.[1], Goldis A.[2], Kievit L.[3], Schwartz D.[4], Nielsen K.R.[5], Arebi N.[6], Fumery M.[7], Kupcinskas L.[8], Dahlerup J.F.[9], Belousova E.[10], Oksanen P.[11], Hernández V.[12], Langholz E.[13], Turcan S.[14], Valpiani D.[15], Giannotta M.[16], Magro Dias F.J.[17], Duricova D.[18], Salupere R.[19], Kaimakliotis I.[20], Lakatos P.L.[21], Katsanos K.H.[22], Ellul P.[23], Krznaric Z.[24], D'Incà R.[25], Pedersen N.[26], Andersen V.[27], Halfvarson J.[28], Sebastian S.[29], Epi-IBD
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Introduction: The lack of scientific evidence regarding the efficacy of 5-aminosalicylate (5-ASA) in patients with Crohn's disease (CD) is in sharp contrast to its widespread use in clinical practice. Up to one out of three of CD patients are treated with 5-ASA at any given time during their disease course, many as monotherapy, suggesting a mild phenotype. Population-based data regarding this subgroup of patients are sparse.

Aims & Methods: The Epi-IBD cohort is a prospective population-based cohort of 1,289 unselected, uniformly diagnosed patients with IBD diagnosed from 31 centres in Europe in 2010. Clinical data were captured prospectively throughout the five-year follow-up period. Diagnosis were made according to the Copenhagen Diagnostic Criteria. Patient management was left to the discretion of the treating gastroenterologists. Patients receiving 5-ASA monotherapy or in no need of medical therapy during the first year following diagnosis were combined for the sake of analysis (Indolent cohort). The aim of the study was to investigate the course and characteristics for these patients as well as the use of 5-ASA in patients diagnosed with CD.

Results: A total of 488 (38%) patients were diagnosed with CD. Patient characteristics are shown in Table 1. Overall, 303 (62%) patients received 5-ASA at any point during follow-up for a median duration of 28 months (IQR 6-60). A total of 97 (20%) patients received either 5-ASA monotherapy (n=80, 82%) or no medical treatment (n=17, 18%) during the first year following diagnosis. These patients were older (p=0.03) and had less complicated disease behaviour (p< 0.01) compared to the other patients but were otherwise similar.

During follow-up, 4 (4%) patients in the indolent group stepped up to corticosteroids as their highest treatment step, 12 (12%) patients to immunomodulators, and 1 (1%) patient to biological therapy. Furthermore, 19 (20%) patients were hospitalized and 5 (5%) patients needed surgery. Most patients in the indolent group (n=75 [80%], 15% of the total cohort) never needed more intense therapy during follow-up. A total of 4 (5%) patients diagnosed with B1 disease behaviour progressed to B2/B3 during follow-up.

	All CD patients (n=488)	Indolent CD patients (n=97)	Other (n=391)
Age, years (IQR)	33 (23-49)	37 (27-58)	32 (23-47)
Males, n (%)	244 (50%)	47 (48%)	197 (50%)
Diagnostic delay, months (IQR)	4.2 (1.7-12.0)	3.6 (1.1-9.7)	4.3 (1.8-12.0)
Extraintestinal manifestations at diagnosis, n (%)	79 (16%)	17 (18%)	62 (16%)
Smoking at diagnosis, n (%)			
Never	183 (40%)	40 (41%)	143 (37%)
Current	171 (37%)	27 (28%)	144 (37%)
Former	103 (23%)	15 (15%)	88 (23%)
Disease behaviour, n (%)			
B1: non-stricturing, non-penetrating	347 (71%)	84 (86%)	263 (67%)
B2: stricturing	100 (21%)	11 (12%)	89 (23%)
B3: penetrating	41 (8%)	2 (2%)	39 (10%)
Perianal disease	46 (9%)	5 (5%)	41 (11%)
Disease location, n (%)			
L1: terminal ileum	128 (77%))	28 (30%)	100 (26%)
L2: colon	134 (28%)	30 (32%)	104 (27%)
L3: terminal ileum + colon	111 (23%)	21 (22%)	90 (23%)
L4: Upper GI	30 (6%)	7 (7%)	23 (6%)
L1-L3 + L4	76 (16%)	8 (9%)	68 (18%)

[Patient characteristics 2010-2015]

Conclusion: In this European population-based inception cohort of unselected CD patients, a substantial group of patients needed only mild or no treatment during follow-up and experienced a quiescent disease course. Patient stratification at baseline to prevent not only under- but also overtreatment is important. Further studies are needed to identify clinical, serological or genetic markers to identify this group of patients.
Disclosure: Nothing to disclose

OP063 EARLY SYMPTOM IMPROVEMENT WITH RISANKIZUMAB TREATMENT IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE: ANALYSIS FROM A PHASE 2 STUDY

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Introduction: Risankizumab (RZB), an IL-23 p19 inhibitor, has shown safety and efficacy in inducing clinical remission in patients with Crohn's disease (CD) in a Phase 2 study.[1] Here we assessed early symptom improvement during the randomized, double-blind, placebo-controlled induction phase of the trial.
Aims & Methods: This Phase 2 study enrolled adult patients with moderate-to-severe CD with a Crohn's Disease Activity Index (CDAI) of 220-450, ulcers in the ileum and/or colon, and a Crohn's Disease Endoscopic Index of Severity (CDEIS) ≥7 (≥4 for patients with isolated ileitis) assessed by ileocolonoscopy confirmed by a blinded central reader. Patients were randomized 1:1:1 to receive intravenous RZB (200 mg or 600 mg) or placebo at Weeks 0, 4, and 8. Endpoints examined in this post hoc analysis included changes from baseline at Weeks 2, 4, 8, and 12 in CDAI, average daily stool frequency (SF) and average daily abdominal pain score (AP) for all patients with available data, and newly defined clinical remission at Week 12, based on symptom improvement, defined as SF ≤2.8 and AP ≤1, both not

worse than baseline, in patients with baseline SF ≥4 or AP ≥2. Continuous endpoints were analyzed using observed case; non-responder imputation was used for missing data of binary endpoints. Statistical comparisons of median change were based on Wilcoxon rank sum test.
Results: 121 patients were randomized in the induction phase. Baseline characteristics were similar among treatment arms.[1] Mean (SD) disease duration at baseline was 13.4 (9.4) years; 94.2% of patients received previous anti-TNF therapy. Significant improvements in CDAI and AP were observed with RZB (600 mg) versus placebo as early as Week 2 and in SF at Week 8 (Table). The proportion of patients with clinical remission based on symptom improvement was significantly higher in the 600 mg RZB group versus placebo at Week 12 (23.7% versus 6.1%; p< 0.05), supporting the previously reported superiority of RZB versus placebo for inducing CDAI remission at Week 12 (36.6% of 600 mg RZB versus 15% of placebo; p< 0.05).[1]
Conclusion: RZB induction treatment was associated with significant early improvements in clinical symptoms and disease activity in a highly refractory patient population with moderately to severely active CD.

	PBO	RZB 200 mg	RZB 600 mg
CDAI BL (median)	287.3	304.1	298.1
CDAI Median Change from BL			
Wk 2	11.0	-18.0*	-42.0***
Wk 4	7.3	-37.0*	-39.3*
Wk 8	-2.2	-38.9	-68.8**
Wk12	-33.0	-54.6	-58.8*
SF[a] BL (median)	5.9	5.9	6.3
SF[a] Median Change from BL			
Wk 2	0.0	-0.9	-0.9
Wk 4	-0.4	-1.4*	-1.3
Wk 8	-0.1	-1.2	-1.2*
Wk12	-0.4	-1.4	-1.7*
AP[a] BL (median)	5.2	5.7	5.1
AP[a] Median Change from BL			
Wk 2	0.1	-0.6	-0.8*
Wk 4	0.0	-1.3**	-0.8*
Wk 8	-0.4	-1.0	-1.2*
Wk12	-0.7	-1.5	-1.2

[a]Based on patient diaries.
*p<0.05; **p<0.01; ***p<0.001 for RZB vs PBO.
AP, abdominal pain score; CDAI, Crohn's Disease Activity Index; RZB, risankizumab; SF, stool frequency.

[Baseline values and change from baseline in median CDAI, SF, and AP over time with RZB versus placebo (as observed)]

References: 1. Feagan BG et al. Lancet 2017;389:1699-1709.
Disclosure: Brian G. Feagan: Consultant and research support from Abbott/AbbVie. William J. Sandborn: Research grants from AbbVie and others; consulting fees from AbbVie and others; and stock or stock options from BeiGene, Escalier Biosciences, Gossamer Bio, Oppilan Pharma, Precision IBD, Progenity, Ritter Pharmaceuticals, Ventyx Biosciences, and Vimalan Biosciences. Julian Panés: Consulting fees from AbbVie and others; speakers' fees from AbbVie, Janssen, MSD, Shire Pharmaceuticals, and Takeda; and research funding from AbbVie and MSD. Marc Ferrante: Advisor fees: AbbVie and others; research grants: Janssen, Pfizer, and Takeda; speakers' fees: AbbVie and others. Edouard Louis: Research grant: Takeda, Pfizer; educational grant: AbbVie, MSD, Takeda; speakers' fees: AbbVie, AstraZeneca, Ferring, MSD, Chiesi, Falk, Takeda, Hospira, Janssen, Pfizer; Advisory Board: AbbVie, Ferring, MSD, Mitsubishi Pharma, Takeda, Celltrion, Celgene, Hospira, Janssen; consultant: AbbVie. Geert R. D´Haens: Consulting and/or lecture fees from AbbVie and others; research grants from AbbVie, Janssen, Given Imaging, MSD, Dr Falk Pharma, and PhotoPill; and speaking honoraria from AbbVie, Tillotts, Tramedico, Ferring, MSD, UCB Pharma, Norgine, and Shire. Arthur Kaser: Consulting fees from Boehringer Ingelheim, Ferring, Genentech, GlaxoSmithKline, Hospira, Janssen, Pfizer, and VHsquared. Olivier Dewit: Speaker or consultancy fees from AbbVie, Ferring, Janssen, MSD, Pfizer, Takeda, Mylan, and Sandoz. Ursula Seidler: Grants from Boehringer Ingelheim, Pfizer, Janssen, Roche, Gilead, AbbVie, Takeda, Index Pharmaceuticals AB; personal fees from Janssen and Takeda. Kyung-Jo Kim: Nothing to declare. Markus F. Neurath: Reports personal fees from Boehringer Ingelheim, Index Pharmaceuticals AB, Janssen, Merck Sharp & Dohme, Pentax Europe, PPM Services, Shire, and Takeda. Wan-Ju Lee, Kristina Kligys, Xiaomei Liao, and Kori Wallace: AbbVie employees, and may own AbbVie stock and/or options. The au-

OP064 EFFICACY OF UPADACITINIB AS AN INDUCTION THERAPY IN SEVERE AND REFRACTORY ULCERATIVE COLITIS: SUB-GROUP ANALYSIS OF THE PHASE 2B STUDY U-ACHIEVE

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Introduction: An unmet need exists to find effective therapy in more severe ulcerative colitis (UC) patients, especially those who have failed multiple therapies. The efficacy and safety of upadacitinib, a selective Janus Kinase 1 inhibitor, has been assessed in an 8-week double-blind, placebo-controlled, dose-ranging, phase 2b induction study in adult patients with moderately-to-severely active UC (U-ACHIEVE).[1,2]

Aims & Methods: In U-ACHIEVE, adult patients with moderately-to-severely active UC as determined by the Adapted Mayo Score (5-9 points and centrally-read endoscopy subscore 2-3) were randomized to receive extended-release upadacitinib 7.5, 15, 30, 45 mg once daily (QD) or placebo for 8 weeks. In the current sub-analysis, the efficacy of upadacitinib in more severe and/or more refractory patient populations was assessed. Patients who at baseline had failed ≥ 2 prior biologic agents, had pancolitis, and/or an Adapted Mayo score >7, were included. Pairwise comparisons between upadacitinib doses and placebo for the primary endpoint, clinical remission per Adapted Mayo Score at Week 8 (defined as stool frequency subscore ≤1, rectal bleeding subscore =0, and endoscopic subscore ≤1) and secondary endpoints were conducted using the Fisher's Exact test and no multiplicity adjustments were applied. Non-responder imputation was utilized for missing values.

Results: At baseline, 142 (56.8% of the total study population) patients had failed ≥ 2 prior biologics, 135 (54.0%) patients had pancolitis, and 90 (36.0%) patients had an Adapted Mayo score >7. The proportions of patients achieving endoscopic improvement, clinical response per Adapted Mayo score, and clinical response per Partial Mayo score were significantly higher (nominal p-value < 0.05) with upadacitinib doses ≥30 mg QD versus the placebo group in patients who failed ≥ 2 biologics or had pancolitis at baseline (Table). Trends of higher proportions of patients achieving clinical remission per Adapted Mayo score, endoscopic improvement, clinical response per Adapted Mayo score, and clinical response per Partial Mayo score were observed with all upadacitinib groups versus placebo in all the sub-analyses.

Conclusion: In this dose-ranging induction study, upadacitinib demonstrated greater efficacy compared to placebo with dose response in the more severe and refractory population; significantly greater efficacy was demonstrated with upadacitinib at doses ≥30 mg QD for most of the endpoints evaluated.

References:
1. Sandborn, W.J., et al. Presentation #OP195. United European Gastroenterology (UEG) Week 2018.
2. Sandborn, W.J., et al. Presentation #OP14. European Crohn´s and Colitis Organisation 2019.

Endpoints, n (%)	Placebo	UPA 7.5 mg QD	UPA 15 mg QD	UPA 30 mg QD	UPA 45 mg QD
Clinical remission per Adapted Mayo Score (SFS ≤1, RBS=0, and ES ≤1) at Week 8[a]					
Biologic use ≥ 2	0/28	2/27(7.4)	2/27(7.4)	4/30(13.3)	4/30(13.3)
With pancolitis	0/27	3/25(12.0)[+]	4/24(16.7)*	3/29(10.3)	4/30(13.3)
BL Adapted Mayo score >7	0/19	1/17(5.9)	0/18	1/19(5.3)	2/17(11.8)
Endoscopic improvement (ES ≤1) at Week 8[b]					
Biologic use ≥ 2	0/28	3/27(11.1)	6/27(22.2)*	7/30(23.3)*	10/30(33.3)***
With pancolitis	0/27	5/25(20.0)*	8/24(33.3)**	7/29(24.1)*	10/30(33.3)***
BL Adapted Mayo score >7	0/19	4/17(23.5)*	3/18(16.7)	3/19(15.8)	8/17(47.1)***
Clinical response per Adapted Mayo score (decrease from baseline ≥2 points and ≥30% and in RBS ≥1 or an absolute RBS ≤1) at Week 8[b]					
Biologic use ≥ 2	2/28(7.1)	7/27(25.9)[+]	10/27(37.0)*	11/30(36.7)*	12/30(40.0)**
With pancolitis	3/27(11.1)	5/25(20.0)	9/24(37.5)*	12/29(41.4)*	13/30(43.3)**
BL Adapted Mayo score >7	4/19(21.1)	5/17(29.4)	7/18(38.9)	8/19(42.1)	10/17(58.8)*
Clinical response per Partial Mayo score (decrease from baseline ≥2 points and ≥30% and in RBS ≥1 or an absolute RBS ≤1) at Week 2[b]					
Biologic use ≥ 2	3/28(10.7)	5/27(18.5)	8/27(29.6)[+]	11/30(36.7)*	17/30(56.7)***
With pancolitis	3/27(11.1)	5/25(20.0)	9/24(37.5)*	12/29(41.4)*	18/30(60.0)***
BL Adapted Mayo score >7	3/19(15.8)	5/17(29.4)	5/18(27.8)	8/19(42.1)	11/17(64.7)**
Endoscopic remission (ES=0) at Week 8[b]					
Biologic use ≥ 2	0/28	1/27(3.7)	0/27	0/30	4/30(13.3)
With pancolitis	0/27	3/25(12.0)[+]	0/24	3/29(10.3)	2/30(6.7)
BL Adapted Mayo score >7	0/19	1/17(5.9)	0/18	2/19(10.5)	2/17(11.8)

[a]Primary Endpoint; [b]Ranked Secondary Endpoints. ***, **, *, and [+] significant at 0.001, 0.01, 0.05, and 0.1 levels, respectively.
UPA=upadacitinib; QD=once daily; SFS=stool frequency subscore; RBS=rectal bleeding subscore; ES=endoscopic subscore.
Baseline Adapted Mayo score is missing for 1 subject in upadacitinib 45 mg QD treatment group.

[OP064 Table]

Clinical perspectives on H. pylori infection
14:00-15:30 / B3

OP065 EFFICACY OF FIRST-LINE REGIMENS IN SPAIN: RESULTS FROM THE EUROPEAN REGISTRY ON *H. PYLORI* MANAGEMENT (HP-EUREG)

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Introduction: The best empirical treatment prescribed against *Helicobacter pylori (H. pylori)* infection must be chosen following local efficacies previously observed. Therefore, updated data concerning Spanish results, obtained in daily clinical practice, is needed to meet this objective.
Aims & Methods: The aim was to analyse the efficacy of the most commonly prescribed first-line therapies in a Spanish cohort. We conducted an observational, prospective, multicenter study, carried out in 48 Spanish hospitals as part of the ´Pan-European Registry on *H. pylori* management´. The database was provided by AEG-REDCap. Gastroenterologists included data obtained in their clinical medical practice from February 2013 to January 2018. A multivariate analysis was performed considering the most efficacious therapies, and considering the sex of the patient, type of PPI (first vs. second-generation), type of PPI dose (simple vs. double), treatment duration (10 vs. 14 days), compliance and penicillin allergy.
Results: 8,581 patients naive to *H. pylori* treatment have been included so far, 61% of them being women and 4% having penicillin allergy. Median age was 51 ± 15 years. The therapies most frequently prescribed as a first-line therapy (all of them including a proton pump inhibitor, PPI) were: non-bismuth quadruple concomitant therapy (Q-NBCT, 41%), standard triple therapy containing clarithromycin and amoxicillin (T-CA, 34%), the three-in-one single capsule bismuth containing metronidazole, bismuth and tetracycline (Q-SINGLE, 9%), bismuth quadruple therapy containing clarithromycin and amoxicillin (Q-BCA, 8%), and the non-bismuth quadruple sequential therapy (Q-NBST, 3%). 5% of the remaining patients received other minority therapies. The efficacy of these therapies was analysed on a modified ITT (mITT) and PP basis. The results are shown in Table 1, divided by 10 or 14 days duration of treatment prescription. Good compliance was associated with a higher efficacy for Q-NBCT and Q-SINGLE therapies ($p < 0.001$). Male sex and the use of second-generation PPIs also increased efficacy rates obtained with Q-NBCT ($p < 0.05$). None of the variables mentioned showed efficacy increase considering Q-BCA treatment.

		mITT efficacy		PP efficacy	
	Duration (days)	N included	mITT (95% C.I.)	N included	PP (95% C.I.)
Q-NBCT	10	2,142	86% (84-87%)	2,030	89% (87-90%)
	14	1,296	91% (89-92%)	1,248	92% (90-93%)
T-CA	10	1,978	82% (80-84%)	1,871	86% (84-87%)
	14	742	81% (78-83%)	675	87% (85-90%)
Q-SINGLE	10	721	86% (83-89%)	646	95% (93-97%)
Q-BCA	14	714	89% (86-91%)	669	94% (91-95%)
Q-NBST	10	231	78% (72-83%)	189	85% (79-90%)

[Table 1: Efficacy obtained by mITT and PP with the five more common treatments used as first-line regimens.]

Conclusion: In first-line treatments, the best efficacy results were obtained with non-bismuth concomitant therapy and bismuth quadruple therapy containing clarithromycin and amoxicillin, both therapies used for 14 days, and the three-in-one single capsule, prescribed for 10 days.

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OP066 H. PYLORI STATUS AND OLDER AGE IS MORE RELATED TO DECREASED PEPSINOGEN LEVEL COMPARED TO DIFFERENT DIETARY FACTORS

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Introduction: Gastric cancer development is a multifactorial process influenced by *Helicobacter pylori* (*H. pylori*), genetics and environmental factors. Although there is strong evidence about the role of *H. pylori* and genetic factors in the development of gastric atrophy leading to gastric cancer, data about the influence of dietary factors on carcinogenesis remain controversial. Minimally invasive way to evaluate possible gastric epithelial atrophy is to detect level of serum Pepsinogen (Pg) I and PgII, in particular - the ratio between PgI and PgII.

Aims & Methods: To analyze whether there is an association between decreased Pg level and different dietary factors.

The study was performed within GISTAR pilot study analyzing the data of participants (aged 40 to 64) from the general population of Latvia from 2013 until 2015. Participants completed a detailed questionnaire on personal characteristics and dietary habits and those who were allocated to the Intervention Group were tested for PgI and PgII by latex-agglutination test-system (Eiken Chemical, Tokyo, Japan), and *H. pylori* IgG group antibodies by ELISA (Biohit, Finland).

Gender, age (< 50 and ≥51 years), income (< 500 € vs. ≥500€), educational level (general secondary education and lower vs. professional technical education and higher), smoking (never vs. 100 cigarettes in the last 30 days), the consumption frequency of different products and alcohol was compared between participants with normal and decreased Pg level (PgI/PgII ≤3 and PgI ≤70 ng/mL).). Statistical analyses included χ^2 test and logistic regression analysis. Factors that showed association with decreased Pg level in univariate analysis (p< 0.09) were included in multiple logistic regression model adjusting for *H. pylori* status.

Results: In total, 1725 participants (mean age 51.62, SD± 6.741) were included in the analysis. Decreased Pg level was identified in 32.4% (559/1725) of individuals; it did not differ between men and women (p=0.57) and was associated with age above 51 year (p< 0.001). In the univariate analysis decreased Pg level was inversely associated with the consumption (less than twice per month vs. more than once a week) of sour dairy products (OR 0.78; 95% CI 0.64-0.96, p=0.02), cheese and cheese products (OR 0.72; 95% CI 0.54-0.97, p=0.03) and leek (OR 0.78; 95% CI 0.63-0.97, p=0.02).

In multivariate analysis (entering variables *H. pylori* status, *age, gender, sour dairy products, cheese products, leek, 200 g vodka at a time during the last year, educational level, income, smoking*) seropositive *H. pylori* status (OR 3.40, 95% CI 2.60-4.45, p< 0.001), age above 51 years (OR 1.59, 95% CI 1.27-1.99, p< 0.001), alcohol consumption (OR 1.30, 95% CI 1.02-1.64, p=0.03) and present smoking (OR 1.44, 95% CI 1.11-1.87, p=0.007) showed a positive association with decreased pepsinogen level while an inverse association (OR 0.72, 95% CI 0.52-0.99, p=0.05) was found with higher consumption of cheese and cheese products.

Conclusion: Although a few studied dietary factors showed a significant univariate association with decreased pepsinogen level, only *H. pylori* seropositivity, advanced age, alcohol consumption and present smoking were independently linked to decreased pepsinogen level while higher consumption of cheese and cheese products showed protective effect towards decreased pepsinogen level. Thus, suggesting that the bacterium and age play more important role in the development of atrophy than different dietary factors.

Disclosure: Nothing to disclose

OP067 "TEST AND TREAT" STRATEGY WITH UREA BREATH TEST: A COST-EFFECTIVE STRATEGY FOR THE MANAGEMENT OF *HELICOBACTER PYLORI* INFECTION IN SPAIN

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Introduction: *Helicobacter pylori* (*H. pylori*) infection is a common chronic infection that is associated with upper gastrointestinal diseases. There are limited data from clinical trials comparing management strategies for patients with dyspepsia. Cost-effectiveness simulation models might help to identify optimal strategies and their cost-effectiveness.

Aims & Methods: To assess the cost-effectiveness of the *H. pylori* "Test and Treat" strategy, including the use of Urea Breath Test (UBT), *versus* symptomatic treatment and endoscopy first-line strategy, in patients with dyspepsia from the Spanish healthcare system perspective. The models compared three strategies, namely "Test and Treat" strategy including the use of UBT, „Endoscopy and Treat strategy" and „Symptomatic treatment strategy". Data were derived from the European registry of *H. pylori* management and from the literature. Advanced simulations were conducted to assess cost, effectiveness and cost-effectiveness over (1) 4 weeks-time horizon for the effectiveness endpoint „Probability of dyspepsia symptoms relief" and over (2) 10 years for two other effectiveness endpoints „Probability of gastric cancer avoided" and „Probability of peptic ulcer avoided". Probabilistic sensitivity analyses were carried out using Monte-Carlo simulations considering data distributions. Models were developed in accordance with the routine Spanish medical practices and costs.

Results: Regarding the endpoint „Probability of dyspepsia symptoms relief", „Test and Treat" was the most cost-effective strategy (883 € per success) compared to „Endoscopy and Treat" and to „Symptomatic treatment" strategies (respectively 1,628€ and 990€ per success). Regarding the endpoint „Probability of gastric cancer „, the „Test and Treat" was the most cost-effective strategy (524 € per gastric cancer avoided) compared to „Endoscopy and Treat" and „Symptomatic treatment" strategies (respectively 716€ and 696€ per gastric cancer avoided). For the endpoint „Probability of Peptic ulcer", the „Test and Treat" was also the most cost-effective strategy (421€ per peptic ulcer avoided) compared to „Endoscopy and Treat" and „Symptomatic treatment" strategies (respectively 728€ and 632€ per peptic ulcer avoided).

Conclusion: The "Test and Treat" strategy including the use of UBT is the most cost-effective medical approach for the management of dyspepsia. The results of this study should contribute to the increase of awareness about the usefulness of the "Test and Treat" strategy and concerning its beneficial impact for patients with *H. pylori*-related diseases.

OP068 LEVOFLOXACIN SEQUENTIAL THERAPY VERSUS BISMUTH QUADRUPLE THERAPY IN THE SECOND-LINE AND THIRD-LINE TREATMENT OF *HELICOBACTER PYLORI:* A MULTICENTER RANDOMIZED TRIAL

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Introduction: A recent systematic review and meta-analysis showed that the efficacy of levofloxacin triple therapy was lower than 80% in the second-line treatment for Helicobacter pylori (H. pylori). Our previous trial showed that levofloxacin sequential therapy was superior to levofloxacin triple therapy in the second-line treatment.
Aims & Methods: Therefore, we aimed to compare the efficacy and safety of 14-day levofloxacin sequential therapy versus 10-day bismuth quadruple therapy in the second-line treatment of *H. pylori* infection. *H. pylori* infected patients who failed after one treatment were eligible in this open labeled, multicenter, randomized trial, and were randomized to receive (1) levofloxacin sequential therapy (EAML): esomeprazole 40 mg and amoxicillin 1 g for the first 7 days, followed by esomeprazole 40 mg, metronidazole 500 mg, and levofloxacin 250 mg for another 7 days (all twice daily); or (2) bismuth quadruple therapy (BQ): esomeprazole 40mg twice daily, bismuth tripotassium dicitrate 300 mg four times a day, tetracycline 500mg four times a day, and metronidazole 500mg three times a day, for 10 days. The primary end point was the eradication rate in the second-line treatment according to intention to treat (ITT) analysis. The minimum inhibitory concentrations were determined by agar dilution test.
Results: A total of 560 patients have been recruited and results were available for analysis in 533 patients up to April 2019. The demographic characteristics and antibiotic resistance rates were similar across the two treatment groups. The eradication rate in the second line treatment were 88.3% (235/266) and 88.4% (236/267) in the levofloxacin sequential therapy and bismuth quadruple therapy groups, respectively (p=1.000) in the ITT analysis. The eradication rates were 89.7% (235/262) and 92.9% (236/254) in the levofloxacin sequential therapy and bismuth quadruple therapy according to PP analyses, respectively (p=0.195). The efficacy of levofloxacin sequential therapy, but not bismuth quadruple therapy, appeared to be affected by levofloxacin resistance. The frequency of any adverse effects was higher in patients treated with bismuth quadruple therapy than levofloxacin sequential therapy (76.4% vs. 44.1%, p< 0.001).
Conclusion: Levofloxacin sequential therapy and bismuth quadruple therapy are similarly effective in the second-line treatment for *H. pylori* infection. (Trial registration number: NCT NCT03148366).
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Disclosure: Nothing to disclose

OP069 GASTRIC MICROBIOME ASSOCIATED WITH PROGRESSION OF GASTRIC INFLAMMATION, ATROPHY AND INTESTINAL METAPLASIA AFTER *HELICOBACTER PYLORI* ERADICATION

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Introduction: Infection with *Helicobacter pylori* is associated with gastric inflammation and increases the risks for precancerous gastric atrophy (GA) and intestinal metaplasia (IM). Evidences however abound that these risks persist in some patients after *H. pylori* eradication.
Aims & Methods: We aimed to identify non-*H. pylori* gastric microbes that are associated with inflammation, GA and IM post-treatment of *H. pylori* infection. Five hundred and eighty-seven H. pylori positive subjects residing in Yantai county of Shandong Province, China. A total of 295 received one-week course omeprazole, amoxicillin and clarithromycin (OAC) while 292 received placebo. Subjects underwent endoscopy with biopsy at baseline and after one year. Severity of inflammation, GA and IM was graded according to the updated Sydney classification. Progression and regression were defined as worsening or improvement, respectively, of inflammation, GA or IM scores after one year.
Analysis of 16S rRNA sequences was performed on a total of 404 gastric biopsy samples, comprising of 102 pairs before and after successful H. pylori eradication by OAC treatment estimated by negative rapid urease test and histology, and 100 pairs before and after placebo. Multiple linear regression, discriminant and microbial network analyses were used to identify microbes associated with inflammation, GA and IM.
Results: Analysis of microbial sequences confirmed the eradication of *H. pylori* in OAC treated group (0.013 ±0.0018) compared to placebo group (0.67 ±0.028) (P< 0.00001). Principal component analysis revealed distinct microbial clusters and proliferation of a wide variety of bacterial species, reflected by marked increase in bacterial diversity (P< 0.00001) after *H. pylori* eradication (Figure 1).
Much less microbial co-occurrence was observed after H. pylori eradication, while microbial interactions remained largely unchanged before and after placebo treatment. In addition, without *H. pylori* re-infection, gastric inflammation persisted in 16%, GA emerged in 33% and IM emerged in 17% of patients one year following *H. pylori* eradication.
A distinct cluster of oral bacterial genera comprising *Peptostreptococcus,* *Streptococcus*, *Parvimonas*, *Prevotella* and *Porphyromonas* were observed to be associated with persistent or progressive GA and IM (P< 0.05) after *H. pylori* eradication. *Streptococcus anginosus* (P=0.012, R=0.3) and *Ralstonia* (P=0.02, R=0.25) were positively correlated with inflammation scores and increased in patients with persistent inflammation, suggesting their involvement in gastric inflammation in the absence of *H. pylori*.
Two probiotic bacterial species namely *Roseburia inulinivorans* (P=0.027) and *Lactobacillus salivarius* (P=0.04) were enriched in subjects whose gastric inflammation regressed following *H. pylori* eradication.
Conclusion: Oral bacterial genera *Peptostreptococcus*, *Streptococcus*, *Parvimonas*, *Prevotella* and *Porphyromonas* are associated with the progression of gastric inflammation, GA and IM following anti-*H. pylori* therapy. Treatment targeting these bacteria may be prescribed to patients to reduce the risk of developing into gastric cancer.
Disclosure: Nothing to disclose

OP070 TIME LATENCIES OF RETREATMENT FOR *HELICOBACTER PYLORI* AND RISK OF UPPER GASTROINTESTINAL BLEEDING IN PATIENTS WHO FAILED INITIAL ERADICATION THERAPY

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Introduction: Delays in primary eradication of *H. pylori* (HP) in patients newly diagnosed with peptic ulcer could result in higher risk of ulcer complications.
However, it remains unknown whether delays in retreatment of patients who failed initial HP eradication therapy would affect subsequent risk of upper gastrointestinal bleeding (UGIB).

Aims & Methods: We determined the risk of UGIB in patients who required retreatment for HP after failure of initial eradication therapy according to time latencies of retreatment. All HP-infected patients who had received the first course of clarithromycin-containing triple therapy for HP between 2003 and 2012 were identified from the territory-wide electronic health database of the Hong Kong Hospital Authority.

We excluded patients with prior GI cancers, surgical resection of the GI tract, bleeding tendency and esophageal varices. The primary outcome was hospitalization for non-variceal UGIB after the first HP therapy. The follow-up period commenced from 60 days of the first HP therapy until the occurrence of UGIB, death or the end of the study (30 Jun 2016). Patients were divided into different groups according to time latencies between initial and final HP eradication (< 3, 3-12 and >12 month). Those who did not require retreatment were included as reference. Covariates included baseline demographics, concurrent medical illnesses and medication uses. Time-dependent Cox proportional hazards model was used to adjust for confounders, in which all medications were included as time-varying variables. Sensitivity analyses were performed with propensity score (PS) matching in a ratio of 1:5 and excluding patients with baseline peptic ulcer or UGIB.

Results: 70,518 patients were included in this analysis (7,761 in the retreatment group and 62,757 in the reference group). The median follow-up was 7.75 years (interquartile range 5.3-10.4 years). The crude incidence rate of UGIB was 6.62 per 1000 person-year (95% CI 6.01-7.28) in the retreatment group and 3.25 (95% CI 3.09-3.41) in the reference group. Compared to the reference group, patients who received retreatment have a higher risk of UGIB (adjusted hazards ratios [aHR] 1.90, 95% confidence intervals [CI] 1.70-2.12; PS matching analysis HR 1.91, 95% CI 1.71-2.15). There was a progressive increase in risk of UGIB with longer latency intervals of retreatment (Table; aHR for < 3m: 1.17, 95% CI 0.98-1.40; 3-12m: 1.88, 95% CI 1.48-2.39; >12m: 3.42 95% CI 2.92-3.99). Similar results were obtained with PS matching or after excluding patients with baseline peptic ulcer/GIB (HR 2.01; 95% CI 1.72-2.36).

Conclusion: Patients who failed initial HP eradication had a 1.9-fold increase in UGIB risk, which progressively increased with the time latencies of retreatment. Early retreatment within 3-month should be considered to minimize the risks of subsequent UGIB after failed HP eradication.

Disclosure: Nothing to disclose.

	Crude HR (95% CI)	Adjusted HR (95% CI)	PS matching HR (95%CI)
No retreatment		1.00 (reference)	
All retreatment groups	2.10 (1.84-2.28)	1.90 (1.70-2.12)	1.91 (1.71-2.15)
<3 month	1.67 (1.40-1.98)	1.17 (0.98-1.40)	1.57 (1.31-1.87)
3-12 month	1.86 (1.47-2.35)	1.88 (1.48-2.39)	1.74 (1.37-2.21)
>12 month	2.56 (2.21-2.97)	3.42 (2.92-3.99)	2.39 (2.05-2.78)

[Risk of UGIB with different latency intervals between the first and last HP eradication therapies]

Hepatology from bench to bedside
14:00-15:30 / B5

OP071 GENETIC STUDIES OF MRI LIVER IRON CONTENT IDENTIFIES LOCI REGULATING HEPCIDIN AND YIELD INSIGHTS INTO ITS LINK WITH HEPATIC AND EXTRAHEPATIC DISEASES

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Introduction: Background and aims: Excess liver iron content is common, however its genetic background and link to hepatic and extrahepatic disease risk is unknown. We aimed to identify genetic variants influencing liver iron content and use genetics to understand its link to other traits and diseases.

Aims & Methods: First, we performed a genome-wide association study (GWAS) in 8,289 individuals in UK Biobank with MRI quantified liver iron, and validated our findings in an independent cohort (n=1,513 from IMI DIRECT). Second, we used Mendelian randomisation to test the causal effects of 29 predominantly metabolic traits on liver iron content. Third, we tested phenome-wide associations between liver iron variants and 770 anthropometric traits and diseases.

Results: We identified three independent genetic variants (rs1800562 (C282Y) and rs1799945 (H63D) in *HFE* and rs855791 (V736A) in *TMPRSS6*) associated with liver iron content that reached the GWAS significance threshold (p< $5x10^{-8}$). The two *HFE* variants account for ~85% of all cases of hereditary haemochromatosis. Mendelian randomisation analysis provided evidence that higher central obesity plays a causal role in increased liver iron content.

Phenome-wide association analysis demonstrated shared aetiopathogenic mechanisms for elevated liver iron, high blood pressure, cirrhosis, malignancies, neuropsychiatric and rheumatological conditions, while also highlighting inverse associations with anaemias, lipidaemias and ischaemic heart disease.

Conclusion: Our study provides genetic evidence that mechanisms underlying higher liver iron content are likely systemic rather than organ specific, that higher central obesity is causally associated with higher liver iron, and that liver iron shares common aetiology with multiple metabolic and non-metabolic diseases.

Disclosure: Conflict of Interest statement: M.K and R.B. are employees and shareholders of Perspectum Diagnostics. H.W. and S.N. are shareholders in Perspectum Diagnostics. No other potential conflicts of interest relevant to this article were reported.

OP072 PORTAL ENDOTHELIAL DAMAGE IN CIRRHOSIS

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Introduction: Cirrhotic patients show a systemic heparin-like effect at thromboelastometric tracing during infection or bleeding. Endotoxemia, shear stress and inflammation may lead to endothelial damage and subsequent release of endogenous heparinoids by disruption of glycocalyx. The endothelium of portal vein could be persistently damaged by portal

hypertension, and this could correlate with the high incidence of portal vein thrombosis in cirrhosis. Data regarding heparin-like effect in the portal venous system are lacking.

Aims & Methods: We consecutively enrolled adult cirrhotic patients undergoing liver transplantation (LT) or transjugular-intrahepatic-portosystemic-shunt(TIPS). Rotational-thrombelastometry(ROTEM) along with evaluation of endothelial dysfunction by quantification of circulating endothelial-microparticles (MP), and endotoxemia (LPS) were performed on citrated peripheral and portal venous blood samples of all enrolled patients.

Results: Forty-one cirrhotics (16 LT and 25 TIPS) were enrolled. ROTEM-analysis showed similar coagulative-assets in portal blood of cirrhotic patients compared to their own peripheral blood. However, we highlighted the presence of a heparin-like effect in portal blood by heparinase addition to native test (median α angle NATEM 51° (46-57) vs HEPTEM median 57° (50-59), p=0.05; median CT NATEM 678sec (576-785) vs HEPTEM 596sec (560-651), p=0.026), which was not detected in peripheral blood (median angle α NATEM 53° (48-58) vs HEPTEM 53° (46-63), p=0.9; median CT NATEM 782sec (560-832) vs HEPTEM 623sec (536-741), p=0.2). Additionally, an increased concentration of endothelial-MP (CD62E-MP median 1607MP/µL (680-1885) vs 1391MP/µL (651-2031), p=0.09) and endotoxemia (LPS median 182.95pg/mL (149-300) vs 160.25pg/mL (103-243), p=0.005) were detected.

Conclusion: The detected heparin-like effect, supported by the increased levels of endotoxemia and the MP-asset could be indirect hematic signs of a higher local endothelial damage in cirrhotics portal vein, caused by portal hypertension. Portal site-specific endothelial damage could hamper its antithrombotic properties and may be an important local risk factor in the pathogenesis of PVT along with the already documented venous stasis.

Disclosure: Nothing to disclose

OP073 THE EFFECT OF *ESCHERICHIA COLI* NF73 ON LIVER TRIGLYCERIDE IN NON-ALCOHOLIC FATTY LIVER DISEASE MICE AND THE POTENTIAL MOLECULAR MECHANISM

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Introduction: In our previous research, we isolated *Escherichia coli* pathogens NF73 (patent application NO. 201610591293.4) from the intestinal mucosa of a non-alcoholic steatohepatitis (NASH) patient, and demonstrated that *Escherichia coli* NF73 increased hepatic damage in high fat diet (HFD) induced non-alcoholic fatty liver disease(NAFLD) mice. In this study, we aimed to investigate the effect of *Escherichia coli* NF73 upon hepatic triglyceride metabolism and the potential molecular mechanism.

Aims & Methods: All male C57BL/6J mice (6 weeks of age) were randomly divided into normal group and flora-deficient group, and were fed with HFD for 16 weeks. In the 8th week, mice in flora-deficient group were treated with a cocktail of broad-spectrum antibiotics (including ampicillin, vancomycin, neomycin and metronidazole) in drinking water for 2 weeks to diminish the intestinal bacteria, while the normal group received sterile tap water. After 10 weeks, both groups were further divided as HFD group, *Escherichia coli* NF73 group and *Escherichia coli* MG1655 group, treated intragastrically by Luria-Bertani (LB) medium, $1*10^8$cfu *Esherichia coli* NF73, $1*10^8$cfu *Esherichia coli* MG1655 (control bacteria) every day, respectively. Hepatic lipid depositions were detected by HE and oil red O staining. Lipid synthesis related protein expressions were determined by Western Blot.

Results: *Escherichia coli* NF73 administration induced more severe hepatic steatosis in normal and flora-deficient mice. Notably, *Escherichia coli* NF73-treated mice had higher triglyceride level, and more significant liver lipid deposition than mice in *Escherichia coli* MG1655 and HFD control groups. It was found that *Escherichia coli* NF73 increased liver triglyceride levels by upregulating SREBP-1c expression and transcriptional activity of genes involved in hepatic fatty acid synthesis (FASN, ACC). Meanwhile, *Escherichia coli* NF73 enhanced the expression of PI3K, p-AKT, mTOR and p-mTOR. The results indicated that *Escherichia coli* NF73 promoted hepatic triglyceride accumulation via upregulating SREBP-1c expression through the PI3K-AKT-mTOR pathway.

Conclusion: Triglyceride accumulation induced by *Escherichia coli* NF73 plays a key role in the pathological process of hepatic damage. Therefore, intestinal mucosal-adherent *Escherichia coli* NF73 might be a critical trigger in the progression of NAFLD to NASH.

Disclosure: Nothing to disclose

OP074 NOVEL CLINICAL AND GENETIC RISK FACTORS FOR EARLY POST-OPERATIVE THROMBOSIS IN LIVER TRANSPLANTATION

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Introduction: Post-operative thrombosis (PT) is one of the leading causes of graft loss and mortality after liver transplantation (LT), and is associated with a plethora of donor, recipient and transplant-related risk factors. While clinical risk factors can largely be accounted for, better knowledge of genetic risk factors for PT is essential for developing targeted strategies to improve graft survival.

Aims & Methods: A post-hoc analysis of a prospective cohort (*www.trialregister.nl - Trial NL6334*) of LT recipients between 1993-2017 was performed. Upon availability, donor and recipient DNA were genotyped with the Illumina Global Screening Array. Risk factors for early PT (< 90 days) were analyzed in univariate and multivariate logistic regression models. To study genetic risk factors for PT, we performed genome-wide association (GWA) analysis.

Results: A total of 1099 recipients underwent 1337 LT procedures. Only primary adult LT (748 [55.9%]) were included in subsequent analyses. Multivariate regression analyses demonstrated that smoking status of the donor (OR=2.505 [1.288-4.871]; P=0.007), and nonalcoholic steatohepatitis (NASH) in the recipient (OR=2.343 [1.057-5.193]; P=0.036) were independent clinical risk factors for early PT. Using GWA analysis with donor genotypes, we identified 42 genetic loci associated with increased risk of PT at a suggestive genome-wide significance threshold (P< $5x10^{-05}$). One of these variants (rs1336472 [P=$1.2x10^{-05}$ OR=1.84]), in a locus harboring the *AK4* gene, has been reported as a risk variant for venous thromboembolism, outside the context of LT.

Conclusion: We identified donor smoking status and NASH in the recipient as novel clinical risk factors for early PT. Moreover, we observed that genetic variation within the donor influences risk for early PT. These preliminary results warrant further investigation into the contribution of donor genetic risk factors for early PT.

Disclosure: Nothing to disclose

OP075 ANALYSIS OF GASTROINTESTINAL SYMPTOMS, DIAGNOSTIC PATTERNS, AND PROVIDER PERSPECTIVE OF ACUTE HEPATIC PORPHYRIA AMONG EU-5 COUNTRIES

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Introduction: Acute hepatic porphyria (AHP) is a family of rare genetic diseases, the most common being acute intermittent porphyria (AIP). AHP results from enzyme deficiencies involved in haem synthesis, leading to accumulation of neurotoxic haem intermediates, aminolaevulinic acid (ALA) and porphobilinogen (PBG), causing potentially life-threatening attacks and chronic symptoms. Patients afflicted by AHP often remain without a proper diagnosis for up to 15 years due to lack of awareness and testing. First-line diagnostic biochemical tests include measuring spot urinary ALA and PBG as both are elevated in the majority of AHP patients.

Aims & Methods: The study aimed to describe gastroenterologists' experience diagnosing AHP and characterize patients from the United Kingdom,

France, Italy, Germany, and Spain (EU-5).EU-5 physicians (n=100) who actively managed AHP patients (with and without recurrent attacks) in the preceding year were recruited from 9/2017-10/2017 to complete an online survey collecting information on demographics, familiarity with AHP and diagnostic tests, perspective on symptoms important to diagnosis, referral patterns, and treatment preferences. Physicians also completed a chart review of 304 patients and reported anonymized data on demographics, medical history, attacks and symptoms. Data was analysed using descriptive statistics.

Results: Physicians practiced a mean of 19 years, 65% worked in academic settings, and 19% were gastroenterologists. Gastrointestinal symptoms leading to AHP diagnosis included abdominal pain (88%), vomiting (63%), fatigue (55%), nausea (54%), weight loss (43%), and constipation (37%). Patients were aged 40 years (mean), female (52%), with AIP (83%). AHP diagnostic tests gastroenterologists considered informative for diagnosis included urinary PBG (59) and ALA (71%); however, several non-specific tests were also commonly considered informative of AHP. For most patients (68%), diagnoses were assessed as uncertain (41%) or incorrect (27%). Misdiagnoses included non-specific abdominal pain (49%), irritable bowel syndrome (47%), Crohn's disease (28%), diverticulitis (26%), appendicitis (21%), lead poisoning (19%), and gastroesophageal reflux disease (GERD) (19%). Patients had a mean of 1.9 attacks and 1.1 hospitalizations in the past year. Chronic symptoms included pain (60%), weakness (59%), fatigue (57%), anxiety (50%), nausea/vomiting (49%), constipation (39%), diarrhea (36%).

Conclusion: This study highlights the challenges diagnosing AHP due to non-specificity of symptoms and limited understanding of diagnostic procedures. Due to the frequent presentation of gastrointestinal symptoms, AHP should be included in gastroenterologists' differential diagnosis of patients presenting with non-specific abdominal pain. Among patients diagnosed with AHP, both acute attacks and chronic symptoms were reported, implicating both in the disease.

Disclosure: Joseph Salameh, Sarah Murray, and John Ko are full time employees and stock holders in Alnylam Pharmaceuticals. Stephen Meninger and Nicole Lyn are contractors for Alnylam Pharmaceuticals. Chitra Karki, Katherine Krautwurst, and Renata Mustafina are full time employees of Ipsos LLC.

OP076 THE MANAGEMENT OF BILIARY STRICTURE IN IGG4-RELATED SCLEROSING CHOLANGITIS

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Introduction: Although endoscopic biliary drainage (EBD) and corticosteroid (CS) therapy are important for the treatment of biliary stricture in IgG4-related sclerosing cholangitis (ISC), clinical evidences about short and long-term prognosis and the risk of biliary tract complications in ISC are still insufficient. This research aimed to elucidate the appropriate way to manage biliary stricture in ISC.

Aims & Methods: The study enrolled ISC patients diagnosed in our hospital or its affiliated institutes from January 2007 to December 2017. We reviewed medical records of ISC patients, such as clinical characteristics, and the way of treatment with EBD and/or CS. The appropriate duration of EBD for preventing detachment of a biliary stent was assessed. We verified the safety of treatment with CS alone without EBD for patients with obstructive jaundice. We also compared the rate of biliary tract complications between groups treated with and without EBD.

Results: A total of 70 ISC patients with the mean age of 66.9 years were enrolled. The median follow-up period was 64.5 months. Autoimmune pancreatitis was concurrent in 98.4% and extrapancreatic biliary stricture was seen in 21.9%. 64 patients (91.4%) were treated with CS and 24 (34.3%) underwent EBD. Scheduled EBD removal after clinical remission of ISC by CS treatment was carried out in 11 patients (45.8%). 9 (81.8%) of 11 patients underwent EBD removal within a month after CS initiation, all of which were safely carried out without early recurrence of obstructive

jaundice or biliary tract infection. EBD detachment during CS treatment was seen in 11 patients (45.8%) and was likely to occur from 2-3 weeks after CS initiation. 7 patients who had obstructive jaundice with serum total bilirubin levels more than 3.0 mg/dL were treated with CS alone without EBD and all of them achieved clinical improvement free from biliary tract infection. All the 3 patients who developed bile duct stones were treated with EBD. The development of bile duct cancer in ISC patients did not occur during follow-up.

Conclusion: EBD removal should be carried out within 2-3 weeks after CS initiation to prevent EBD detachment in ISC patients who achieved clinical remission by CS treatment. Obstructive jaundice due to biliary stricture can safely be treated with CS alone without EBD. We should be careful about the long-term management of ISC since bile duct stones are likely to occur in patients treated with EBD.

Disclosure: Nothing to disclose

Update in cholangiocarcinoma
14:00-15:30 / E1

OP077 ENDOTHERAPY IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: OVER 30 YEARS' EXPERIENCE

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Introduction: Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and periductal fibrosis of the intrahepatic and/or extrahepatic bile ducts. Endoscopic dilation of symptomatic dominant biliary strictures is a temporary therapeutic option in these patients frequently candidate to liver transplantation. Our experience over a 30-years period is reported.

Aims & Methods: Between March 1984 and April 2019, 73 patients with PSC (46 Males, mean age 46 ± 18 years) were identified from a prospectively collected database. Indications for endoscopic drainage were the presence of symptomatic "dominant" biliary strictures located at the common bile duct or main hepatic confluence. Strictures were dilated with balloon and/or temporary plastic stents insertion. Brush cytology of dominant strictures was performed in patients with new onset or worsening strictures. When MRC was not routinely available, abdominal US and/or CT-Scan were performed before ERCP.

Results: Indications for ERCP were: cholangitis (n=28, 38.3%), anicteric cholestasis and pruritus (n=18, 24.6%) and jaundice (n=27, 36.9%). Bile ducts morphology was assessed by MRC in 51 cases (69%) before ERCP.
A total of 161 ERCPs were performed in 73 pts [mean 4.3 (range 1-13)]. Results are summarized in table I.
One patient (0.6%) developed severe post-ERCP pancreatitis that resolved after surgical treatment.
Cholangitis recurrence requiring re-treatment occurred after a mean of 28.2 months after stents removal and 16.6 months after balloon dilation.
Brush cytology was performed in 42 patients (57.5%): 4 patients (5.4 %) resulted positive for high grade dysplasia, 1 patient (1.3 %) for carcinoma.
A mean follow-up of 7.4 years (range 0.2-21.7) is available in 46 patients (63%): 29 patients (63%) had no further episodes of cholangitis, 7 (15.2%) underwent OLT, 3 (6.5%) died for cholangiocarcinoma, 6 (13%) died for unrelated other disease, 1 (2.2%) had an incidental finding during laparoscopic cholecystectomy of gallbladder cancer and is still alive.

Conclusion: According to our experience endotherapy of dominant biliary strictures secondary to PSC is effective in the long term-follow-up and can delay liver transplantation. Early diagnosis of cholangiocarcinoma in PSC is still an unsolved issue.

Disclosure: Nothing to disclose

	N	%
ERCP failure	2	1.24
Site of "dominant" biliary strictures		
Common bile duct	51	31.6
Hilum / intrahepatic ducts	67	41.6
Common bile duct + hilum	31	19.2
No dominant strictures / presence of common bile duct stones	10	6.2
Therapeutic procedures		
Balloon dilation (diameter 4-10 mm)	71	44.1
Single plastic stent	15	9.3
Multiple plastic stents (range 2 - 7)	19	10.6
Naso-biliary drains	131	81.3

[Table I. Results from 161 ERCPs in 73 patients with Primary Sclerosing Cholangitis.]

OP078 THE ROLE OF "ROSE" FOR ERCP-GUIDED BRUSHING ON INDETERMINATE BILIARY STRICTURES: EXPERIENCE OF A REFERRAL CENTER

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Introduction: Endoscopic Retrograde CholangioPancreatography (ERCP), although nowadays used only for therapeutic purposes, still has a prominent diagnostic role in patients with indeterminate biliary strictures and no evidence of mass lesion at EUS or CT scan. The use of biliary stricture brushing is a safe, easy, cheap and fast way to acquire cytological specimen from the determination of the etiology, but the sensitivity can be as low as 50%. Rapid On-Site Evaluation (ROSE) of the sample has been used for years in referral centers for the determination of the adequacy of EUS-guided FNA cytological specimens, improving its sensitivity and specificity. Nevertheless, there are currently no studies evaluating its role for ERCP brushing.

Aims & Methods: The aim of this study was to assess the diagnostic yield of ERCP brushing of indeterminate biliary strictures when supported by ROSE.

We conducted a retrospective single center study enrolling consecutive patients undergoing ERCP and brush cytology supported by ROSE for indeterminate biliary strictures, including patients from January 1st 2010 to May 31st 2018. Data recorded included patient's characteristics, clinical/radiological and EUS features, ERCP features including stricture features, number of passages performed with the brush, final cytology or histology when biopsy was performed as an adjunct, use of cholangioscopy or confocal laser endomicroscopy, final diagnosis after surgery or follow-up when the patient would not undergo a resection. The diagnostic yield of ERCP-guided brushing with ROSE was then calculated.

Results: 96 patients underwent ERCP for indeterminate biliary stenosis, with 50% being males, mean age 68.1 years, 80% having an extrahepatic biliary stricture. 90 patients underwent brushing with ROSE and were included in the analysis, with 86.7% of patients having an adequate sample at ROSE. The preliminary diagnostic yield calculated showed a sensitivity of 80%, a specificity of 82%, an accuracy of 81%, a positive predictive value of 92% and a negative predictive value of 61%.

Conclusion: The availability of ROSE in patients undergoing ERCP with indeterminate biliary stricture without a mass lesion increases the diagnostic yield of brushing, decreasing the need of further procedures, such as cholangioscopy and confocal laser endomicroscopy and can, therefore, decrease costs and increase safety.
Disclosure: Nothing to disclose

Brave new world: Neurons vs. neuronal network
14:00-15:30 / Barcelona

OP079 APPLICATION OF CONVOLUTIONAL NEURAL NETWORK IN THE DIAGNOSIS OF THE INVASION DEPTH OF GASTRIC CANCER BASED ON CONVENTIONAL ENDOSCOPY

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Introduction: According to guidelines, endoscopic resection should only be performed for patients whose early gastric cancer invasion depth is within the mucosa or submucosa of the stomach regardless of lymph node involvement. The accurate prediction of invasion depth based on endoscopic images is crucial for screening patients for endoscopic resection. The recent findings suggest that the deep learning of endoscopic images by convolutional neural networks (CNN) can have clinical applications. In particular, we suspected that a CNN might be effective in determining the invasion depth of gastric cancer and thus could be used to screen patients for endoscopic resection. To evaluate the ability of a CNN to determine gastric cancer invasion depth, we constructed a convolutional neural network computer-aided detection (CNN-CAD) system based on endoscopic images to determine invasion depth and screen patients for endoscopic resection.

Aims & Methods: We constructed a convolutional neural network computer-aided detection (CNN-CAD) system based on endoscopic images to determine invasion depth and screen patients for endoscopic resection. Endoscopic images of gastric cancer tumors were obtained from the Endoscopy Center of Zhongshan Hospital. An artificial intelligence-based CNN-CAD system was developed through transfer learning leveraging a state-of-the-art pretrained CNN architecture, ResNet50. A total of 790 images served as a development dataset and another 203 images as a test dataset. We used the CNN-CAD system to determine the invasion depth of gastric cancer and evaluated the system´s classification accuracy by calculating its sensitivity, specificity, and area under the receiver operating characteristic curve.

Results: The area under the receiver operating characteristic curve for the CNN-CAD system was .94 (95% confidence interval [CI], .90-.97). At a threshold value of .5, sensitivity was 76.47%, and specificity 95.56%. Overall accuracy was 89.16%. Positive and negative predictive values were 89.66% and 88.97%, respectively. The CNN-CAD system achieved significantly higher accuracy (by 17.25%; 95% CI, 11.63-22.59) and specificity (by 32.21%; 95% CI, 26.78-37.44) than human endoscopists.

Conclusion: We constructed a CNN-CAD system to determine the invasion depth of gastric cancer with high accuracy and specificity. This system distinguished early gastric cancer from deeper submucosal invasion and minimized overestimation of invasion depth, which could reduce unnecessary gastrectomy.
Disclosure: Nothing to disclose

OP080 NEURAL NETWORK SYSTEM FOR IDENTIFYING UPPER-GASTROINTESTINAL ORGANS IN ENDOSCOPIC IMAGES

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Introduction: Neural networks(NNs) is the mathematical model which imitates principle of action of human's neuron in the brain. Recently, NNs is used for classifying images in various fields of medicine, for example, skin cancer classification, diabetic retinopathy, and gastro-intestinal endoscopies. Image recognition using NNs has been applied for the automated detection of gastric cancer during gastrointestinal endoscopies.
Aims & Methods: While developing NNs system, it is necessary to conduct data cleansing and classify several endoscopic images to form a training dataset, which is time-consuming. Therefore, this study aims to develop an automated system for classifying the upper-gastrointestinal organs in large sets of endoscopic images captured under various imaging conditions. For this purpose, we have developed a ten-layer NNs system. The NNs architecture comprises a 1530-dimensional input layer followed by nine fully connected affine layers with batch normalization to facilitate training and a rectified linear unit for activation. The color histogram (255 × 3) and the spatial gradient histogram(255 × 3) obtained by Scharr edge filtering were utilized as the input layer. The training dataset comprised 52,390 anonymized images collected from patients with gastric cancer who underwent upper-gastrointestinal endoscopies in our institution during 2017/01/01 to 2017/12/31.
A total of 35,537 cleansed upper-gastrointestinal endoscopic images (i.e., the training data) were manually classified as white-light (WL) stomach (15,075), WL esophagus (1,573), WL duodenum (1,673), WL stomach with local indigo carmine (IC) (5,823), WL esophagus with IC (379), narrow band (NB) imaging stomach (7,194), and NB imaging esophagus (2,309). These datasets were selected by the following criteria. 1)they must include a visually identifiable each organs, esophagus, stomach, and duodenum without excessive blur. 2)the area of halation(blackout) must be less than 50% of the effective pixels. 3)no treatment devices should be visible with the exception of old clips. 3)there must not be any therapeutic findings, such as markings, infusions, mucosal excisions, and massive hemorrhages. After the NNs were trained using the training dataset, the system performance was evaluated by the testing dataset, which was another set of 27,862 images, to classify the images into these eight categories. To evaluate the performance of the proposed system, we used the MNIST database 28×28-pixels images of hand-written digits from 0 to 9 as a benchmark, which is separated into a training dataset of 60,000 examples and a testing dataset of 10,000 examples.
Results: The accuracy of the classification system in the training and testing data were found to be 0.988 and 0.961, respectively. The accuracy of the system in the training and testing data when applied to the MNIST database reached 0.999 and 0.982, respectively.
Conclusion: Thus, it was concluded that the proposed system is effective for identifying the upper-gastrointestinal organs in endoscopic images. This system can be utilized as an organ identifier to aid the process of data cleansing in the development of an automated lesion-detection system.
Disclosure: Nothing to disclose

OP081 APPLICATION OF ARTIFICIAL INTELLIGENCE USING A CONVOLUTIONAL NEURAL NETWORK FOR DIAGNOSIS OF EARLY GASTRIC CANCER BY MAGNIFYING ENDOSCOPY WITH NARROW-BAND IMAGING

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Introduction: As many reports have indicated the usefulness of magnifying endoscopy with narrow-band imaging (ME-NBI) for diagnosing gastric cancer, the magnifying endoscopy simple diagnostic algorithm for early gastric cancer (MESDA-G) has been proposed as a new uniform diagnostic system for gastric cancer by means of ME-NBI in Japan. However, although ME-NBI is thought to have made a huge contribution to clinical practice, acquiring skill at ME-NBI diagnosis using MESDA-G requires substantial effort. Recently, there has been remarkable progress in artificial intelligence (AI) using deep learning and convolutional neural networks (CNNs) in various medical fields for diagnostic imaging. However, no reports have assessed the usefulness of AI using CNNs for diagnosis of early gastric cancer (EGC) by ME-NBI.
Aims & Methods: We aimed to develop an AI-assisted diagnostic system of EGC using ME-NBI images and evaluate the diagnostic accuracy of the AI system in diagnosing EGC. From the 745 lesions of EGC resected by endoscopic procedures at our hospital between April 2013 and March 2018, 5,227 ME-NBI images using the water immersion technique at the maximum magnification that had sufficient quality to permit diagnosis by MESDA-G were collected. ME-NBI images of gastric adenocarcinoma of fundic gland type and diffuse-type EGC were excluded, since the diagnostic yield was unclear in MESDA-G. Additionally, 2,592 ME-NBI images of non-cancerous mucosa or non-cancerous lesions that were obtained under the same conditions were collected. A CNN-based diagnostic system was pre-trained and fine-tuned on a dataset of 5,574 ME-NBI images (3,797 EGCs, 1,777 non-cancerous mucosa or lesions). To evaluate the diagnostic accuracy, a separate test data set of 2,245 ME-NBI images (1430 EGCs, 815 non-cancerous mucosa or lesions) was applied to the constructed CNN.
Results: The CNN required 60 s to analyze 2,245 test images. The overall accuracy, sensitivity, specificity, positive predictive value and negative predictive value of the CNN were 98.7%, 98%, 100%, 100% and 96.6%, respectively. All missed images of EGCs were superficially depressed and intestinal-type intramucosal cancers that were difficult to distinguish from gastritis even by experienced endoscopists.
Conclusion: The constructed CNN system for diagnosis of EGC could process many stored ME-NBI images in a short period of time and had clinically high diagnostic ability. A more advanced system will be developed by adding the EGC images of cases that could not be diagnosed by MESDA-G and images of a wide variety of non-cancerous mucosa and non-cancerous lesions. This AI-assisted diagnostic system of EGC using ME-NBI images may be able to reduce the burden of endoscopists.
References: Hirasawa T et al. Application of artificial intelligence using a convolutional neural network for detecting gastric cancer in endoscopic images. Gastric Cancer. 2018. Shichijo S et al. Application of convolutional neural networks for evaluating Helicobacter pylori infection status on the basis of endoscopic images. Scand J Gastroenterol. 2019
Disclosure: Nothing to disclose

OP082 ARTIFICIAL INTELLIGENCE FOR REAL-TIME POLYP LOCALISATION IN COLONOSCOPY WITHDRAWAL VIDEOS

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Introduction: There is considerable variation in polyp detection rates during colonoscopy. Missed adenomas may contribute to interval colorectal cancers. Artificial intelligence (AI) can potentially improve ADR. Previous work has focussed on still images and selected video sequences which may be subject to bias and lack clinical utility. This pilot work assesses whether a convolutional neural network (CNN) developed using still images and short video sequences from a multicentre dataset using different processors generalises effectively to locate polyps in new video dataset consisting of complete colonoscopy withdrawals (caecum to rectum).

Aims & Methods: Our group previously developed a CNN using 4664 polyp test frames from the MICCAI 2015 polyp detection challenge dataset. Here, we created a second dataset using 17 complete colonoscopy withdrawal videos, previously unseen by the CNN, containing 83 unique polyps consisting of 83,716 frames (14,634 polyp and 69,082 non-polyp) using Olympus EVIS LUCERA CV290(SL) processors and colonoscopes. White light frames were manually annotated by drawing bounding boxes around polyps. Polyp size, morphology, histopathology and location was recorded for each polyp sequence (Table 1). Low quality frames (blurred/indistinguishable image) were excluded. Half the procedures were randomly selected to create a testing set consisting of 24,596 frames (4,804 polyp and 19,792 non-polyp). A true positive was scored if the computer-generated prediction overlapped with the bounding box. A false positive indicated a non-overlapping location (more than one can occur per frame).

Results: The CNN operated at real-time video-rate achieving a sensitivity of 91.6% and positive predictive value 75.3% in the MICCAI challenge test set consisting of 196 high definition still images from 44 polyps. When the MICCAI trained CNN was tested on our previously unseen colonoscopy procedures, it achieved a sensitivity of 76.6% and specificity of 78.9%. This CNN was fine-tuned by using polyp positive frames from our training dataset. This improved sensitivity to 84.5% and specificity to 92.5%.

Conclusion: Whilst the CNN achieved excellent results on the public still image dataset, it is more challenging to generalise results to complete colonoscopy withdrawals. Fine-tuning using our dataset led to improved performance. Furthermore, our procedures were performed by expert endoscopists, including a significant proportion of right sided flat elevated and subtle sessile serrated lesions which were not evaluated in recently published test sets. AI development should include complete colonoscopy withdrawals to reflect true clinical practice and focus specifically on identifying challenging polyps that may be overlooked by colonoscopists.

Disclosure: Nothing to disclose

Lesions (n)	83
Mean size (mm)	5.4
Morphology (Paris Classification)	
Protruded (Ip/Isp/Is)	35
Flat elevated/Flat (IIa/IIb)	48
Location	
Right Colon	58
Left Colon	20
Rectum	5
Pathology	
High Grade Dysplasia Tubular Adenoma	1
Low Grade Dysplasia Tubular Adenoma	61
Sessile Serrated Lesion	14
Hyperplastic Polyp	7

[Polyp Details (Complete Colonoscopy Video Dataset)]

OP083 THE REAL-TIME DETECTION AND DIFFERENTIAL DIAGNOSIS OF COLORECTAL POLYPS IN COLONOSCOPY WITH AN ARTIFICIAL INTELLIGENCE ALGORITHM; A PROSPECTIVE OBSERVATIONAL STUDY

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Introduction: For supporting detection and diagnosis of colorectal polyps in real time by artificial intelligence (AI) technology, we have developed AI-aided endoscopic diagnosis system (AAE). This system has been developed using Convolutional Neural Network, one of deep learning approaches. We have already reported its polyp detectability and differential diagnostic accuracy in retrospective studies using stored still images. The aims of this study were to validate whether the AAE could detect colorectal polyps which were detected by endoscopists as the gold standard, and to evaluate differential diagnostic accuracy of AAE in real time under a clinical setting.

Aims & Methods: AAE analyzes all image frames during a colonoscopy on GPU workstation, and a box-shaped alert is presented on the lesion area in real-time. When the endoscopist presses the freeze button at the target polyp in white light imaging (WLI), the differential diagnosis between neoplastic and non-neoplastic is made by AAE. In order to prepare the training data of AAE, 69,285 images were collected from 4,147 colonoscopy case underwent in Jikei University hospital since April 2014 to December 2018. All training data was annotated by enclosing lesion area on each image with a bounding box. Following the development of the algorithm, a prospective observational study was conducted at Jikei university hospital in January 2019. The patients who underwent colonoscopy were enrolled. Patients with known IBD were excluded. In this study, results of detection and differential diagnosis by AAE were displayed on a monitor separated from the main monitor used by endoscopists. When an endoscopist detect a polyp, polyp information (size, morphologic type, location and the time to detect a polyp) were informed to research assistants and recorded. We evaluated the success rate of polyp detection during colonoscopy by reviewing videos at the recorded time to detect a polyp. Successful polyp detection with AAE was defined when a polyp detected by endoscopists as gold standard could be detected by AAE within 2 seconds from the initial appearance of a polyp on a video frame. Furthermore, the differential diagnostic accuracy between neoplastic and non-neoplastic by AAE was analyzed only for the polyp removed endoscopically. The differential diagnosis of AAE was made by freezing the video image when an endoscopist judged that highly-quality closeup images would be obtained without blur.

Results: Thirty patients (with 102 polyps) were analyzed. AAE succeeded to detect 95 polyps (93.1%) in 102 polyps within 2 sec from their initial appearance, of which 62 polyps (65.2%) were diminutive polyps of 5 mm or less. The median detection time was 0.4 seconds (range 0.1 - 20.2 seconds). AAE was able to predict differential diagnosis in 58 polyps (41 neoplasm and 17 non-neoplasm) of 81 polyps (63 neoplasm and 18 non-neoplasm) endoscopically resected (71.6%). When 23 polyps in which AAE could not predict differential diagnosis were treated as misdiagnosed polyps, differential diagnostic accuracy between neoplastic and non-neoplastic was sensitivity 58.7% /specificity 77.8% /positive predict value 90.2% /negative predict value 35.0% /accuracy 63.0% in overall 81 polyps. In diagnosable 58 polyps, it was sensitivity 90.2% /specificity 82.4% /positive predict value 92.5% /negative predict value 77.8% /accuracy 86.8%, respectively.

Conclusion: This preliminary study demonstrated that the polyp detectability of AAE and differential diagnostic accuracy between neoplastic and non-neoplastic polyp were comparable to endoscopists in a real-time clinical setting.

Disclosure: Nothing to disclose

OP084 ARTIFICIAL INTELLIGENCE FOR DETECTING DIMINUTIVE COLON POLYPS BASED ON AUTOMATIC COLLECTING SYSTEM FOR DAILY ANNOTATED DATASETS FROM THE COMMERCIALLY AVAILABLE ENDOSCOPY REPORTING SYSTEM

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Introduction: Recently, artificial intelligence (AI) has been shown the remarkable progress in image recognition. The application of AI system for the endoscopic images are expected to be the favorable assistance. The recent AI progressions are primarily are based on the availability of large-scale annotated datasets. In general, the dataset of high-quality annotated endoscopic images are retrospectively made by endoscopic specialist with much effort. In Japan, endoscopists make reports including selected key images with localized annotation at diagnosis in daily practice. Collecting system for daily annotated datasets from the endoscopy reporting systems enables continuous accumulation of high-quality annotated endoscopic dataset.

Aims & Methods: The aim of this study is to assess the validity of using daily annotated endoscopic images in constructed reporting system for prototype AI model for diminutive polyp detection. We constructed automatic collecting system for daily annotated datasets from the endoscopy reporting system (NEXUS, FUJIFILM medical Co.) with Japan Endoscopy Database (JED) project conducted by Japan Gastroenterological Endoscopy Society (JGES). By the keyword of diagnostic information, we automatically extracted annotated endoscopic images of diminutive colon polyps which diagnosed between March 2018 and September 2018. To verify the collecting system, we have created the AI model for detecting diminutive colon polyp from the collected dataset and additional collected normal colon dataset. The detection model was made by RetinaNet network architecture, which is one of the latest deep learning algorithm for object detection.

Results: We automatically collected 47391 endoscopic images of 745 colonoscopy and extracted 1356 key images of diminutive colon polyps with localized annotation which added at diagnosis. Additionally, we collected 700 images of normal colon. To validate the quality of dataset for making AI model, we used 1056 datasets of colon polyps and 400 images of normal colon for training and used 300 datasets of colon polyps and 300 images of normal colon for validation. The sensitivity, specificity, and accuracy of our trained colon polyp detector for 300 polyp images and 300 normal images was 95.0%, 97.7%, and 96.3%.

Conclusion: This automatic collecting system for daily annotated datasets enabled creating high-performance detector for diminutive colon polyps with reducing much efforts of endoscopic specialists. This scheme leads to continuous extensive information collection infrastructure for making endoscopic AI diagnostic system.

Disclosure: Nothing to disclose

Barrett's oesophagus
16:00-17:30 / Hall 6

OP085 DEEP LEARNING SYSTEM DETECTS BARRETT'S ESOPHAGUS NEOPLASIA WITH HIGH ACCURACY IN A MULTI-STEP TRAINING AND EXTERNAL VALIDATION STUDY

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Introduction: Early neoplasia in Barrett's esophagus (BE) is often difficult to detect endoscopically. Computer aided detection (CAD) systems might be able to assist endoscopists in real-time recognition of BE neoplasia. Recently, CAD *deep learning techniques* have shown promising results in other fields.

Aims & Methods: The aim of this study was to develop a deep learning CAD system for endoscopic recognition of BE neoplasia using multi-step training followed by internal- and external validation.

The CAD system was pre-trained via a novel approach, for which we created a unique dataset of 494,364 labelled images of broad endoscopic variety, named *GastroNet*. The system was further trained and refined by datasets 2 and 3. Dataset 2 consisted of *retrospectively* collected WLE overview images of BE neoplasia (n=690) and non-dysplastic BE (NDBE; n=557). Dataset 3 consisted of *prospectively* collected overview images of BE neoplasia (n=129) and NDBE (n=168). The CAD system was constructed using a fully residual, hybrid ResNet-UNet model using transfer- and ensemble learning. The system was first internally validated on dataset 3, using 4-fold cross validation methodology.

Finally, a fourth dataset was created for external validation. This dataset consisted of 40 *prospectively* collected WLE overview images of BE neoplasia and 40 WLE NDBE images from 80 patients not included in dataset 1-3. In dataset 2-4, all NDBE images were reviewed by experts for absence of neoplasia. All neoplastic images were delineated by multiple experts, where the area with ≥1 delineation served as ground truth for training- and validation.

Outcome parameters: 1) Correct classification of images (neoplastic/NDBE); 2) Correct delineation of neoplastic lesions (i.e. CAD's delineation within experts delineation: delineation score); 3) Correct positioning of preferred biopsy location within experts delineation (red flag indication score).

Results: Accuracy, sensitivity, and specificity for classification of all images in internal validation were 88%, 88% and 89%, respectively. In the external validation these values were 88%, 93%, and 83%, respectively. The CAD-delineation overlapped with the expert ground truth in all correctly classified neoplastic cases in the external validation set, and red-flagged this area in 97%.

Conclusion: We developed a deep learning CAD system for primary detection of BE neoplasia, using multi-level validation. The system detected neoplasia with high accuracy and near-perfect delineation- and red-flag performance. These performance parameters indicate that our CAD system is ready for real-time, image-based testing in clinical practice.

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OP086 HIGH ACCURACY AND EFFECTIVENESS WITH DEEP NEURAL NETWORKS AND ARTIFICIAL INTELLIGENCE IN DETECTION OF EARLY ESOPHAGEAL NEOPLASIA IN BARRETT'S ESOPHAGUS

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Introduction: The most widely used approach for surveillance of Barrett's esophagus (BE) is oesophagogastroduodenoscopy. However, the visual detection of early esophageal neoplasia (high grade dysplasia and T1 cancer) in BE with white light and virtual chromoendoscopy is still difficult.

Aims & Methods: The aim of this study is to assess if a convolutional neural artificial intelligence network can aid in the recognition of early esophageal neoplasia in BE.

Over 800 images from 65 patients were retrospectively collected of histology-proven early esophageal neoplasia in BE containing high grade dysplasia or T1 cancer (Dysplasia Group). Within each image, the area of neoplasia was masked using image annotation software by two experts in BE imaging. Over 800 control images were collected of either histology-proven or confocal endomicroscopy-proven BE without high grade dysplasia (Non -Dysplastic Group).

A training set with ~1200 images split 50/50 Dysplasia/Non-Dysplasia was used to train the algorithm. We used a convolutional neural network (CNN) and hybrid algorithm design including Inception blocks to deepen the neural net and maximize efficiency and accuracy. The algorithm was pre-trained on ImageNet and then fine-tuned with the goal to provide the correct binary classification: "Dysplastic" (1) or "Non-dysplastic" (0). Adam optimizer performed stochastic optimization of a binary cross-entropy loss function to produce a probability value between 0 and 1. A set 458 images unique of the training set was used for algorithm validation.

We additionally developed an object detection algorithm which drew localization boxes in real-time around regions classified as dysplasia. Testing was performed for near-focus images, non-near focus (far) images, white light and NBI images.

Results: The CNN analyzed 458 test images (225 dysplasia/233 non-dysplasia) and correctly detected early neoplasia in BE cases with sensitivity of 95.6% and specificity of 91.8% (Fig.1). The accuracy was 93.7% and the AUC was 0.94 (Fig.3). With regards to the object detection algorithm for all images in the validation set, the system was able to achieve a mean-average-precision (mAP) of 0.7533 at an intersection over union (IOU) of 0.3, Sensitivity 96.7% and Specificity 87.6% (Fig 2). For NBI images only, a mAP 0.802 was achieved and mAP 0.819 with Near-focus images only.

Conclusion: Our AI model was able to detect early esophageal neoplasia in Barrett's Esophagus images with 93.7% accuracy. In addition, the object detection algorithm was able to draw a localization box around the areas of dysplasia with high precision. This system appears promising and an algorithm of this kind may aid endoscopists detect dysplastic lesions more effectively. Real-time live video validation of the algorithm is currently underway.

Disclosure: Jason Samarasena and William Karnes (Co-founders of DocBot)

What's hot in eosinophilic oesophagitis
16:00-17:30 / B2

OP087 DIFFERENCES IN IMPLEMENTATION OF GUIDELINES ON DIAGNOSIS AND TREATMENT OF EOSINOPHILIC ESOPHAGITIS (EOE): AN OVERVIEW OF CURRENT PEDIATRIC AND ADULT GI PRACTICE IN EUROPE

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Introduction: Guidelines for diagnosis and treatment of Eosinophilic Esophagitis (EoE) have changed markedly over the last decade. An international survey, conducted by the ESPGHAN EGID Group, aimed to analyze differences in current practice of European Pediatric (PG) and Adult Gastroenterologists (AG) in their management of EoE, and to assess self-reported adherence to guidelines.

Aims & Methods: Gastroenterologists treating children and/or adults in 13 European countries and the United Arab Emirates were contacted and asked to complete a multiple-choice questionnaire to gauge physician demographics, EoE diagnosis and management strategies.

Results: Of the 1232 gastroenterologists who completed the questionnaire, 465 were PG and 697 were AG. In contrast to current guidelines on EoE diagnosis, only 41% of gastroenterologists (22% AG vs. 68% PG, p< 0.01) reported taking biopsies in patients with symptoms of esophageal dysfunction but without macroscopic endoscopic abnormalities; 92% (97% PG vs. 88% AG, p< 0.01) reported to take biopsies when dysphagia was the specific symptom; 81% (86.2% PG vs. 77% AG, p< 0.01) sampled multiple esophageal sites when suspecting EoE. High dose PPI administration (68.1% PG vs. 72.4% AG) followed by elimination diets (31.6% and 27.3% respectively) were the most common first line treatments. Following failure of initial PPI treatment, the majority of both PG and AG opted for oral topical steroids (56.4% PG vs. 86.9% AG, p< 0.01), however PG utilize food elimination diets as second line treatment significantly more often than AG (43.5% PG vs. 13.3% AG, p< 0.01). Geographic practice differences were noted, for example the highest use of high dose PPI as first line treatment was reported in Spain while, of elimination diets, in the United Arab Emirates. Although proven unreliable, 24.1% of prescribed food elimination diets were reported to be based on specific allergy testing (32.8% PG vs. 16.3% AG, p< 0.01) and up to 83% refer their patients for allergic assessment after diagnosis of EoE.

After initiating therapy, the majority reported monitoring therapeutic response endoscopically (86.3% PG vs. 69.7% AG, p< 0.01). German PG universally reported endoscopic follow-up while Dutch gastroenterologists were least likely to follow this approach. A greater proportion of PG

than AG indicated that had read at least one recent international guideline (89% PG vs. 56% AG), but both PG and AG alike recognize the potential benefit of national guidelines concerning the diagnosis and treatment of EoE (86% PG vs. 85% AG).

Conclusion: The general practice of pediatric and adult gastroenterologists differs and diverges from international guidelines on diagnosis as well as treatment of EoE. Geographic practice variations are apparent. Although the majority indicated awareness of recent practice standards, strategies to improve the implementation of current guidelines are urgently needed.

Disclosure: Nothing to disclose

OP088 ENDOSCOPIC AND HISTOLOGIC DIFFERENCES BETWEEN PPI-RESPONSIVE AND NON-RESPONSIVE EOSINOPHILIC ESOPHAGITIS IN CHILDREN POPULATION: A TERTIARY CENTER EXPERIENCE

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Introduction: Eosinophilic esophagitis (EoE) is defined as histological features of 15 or more eosinophils per high power resolution (hpf) without other causes of esophageal eosinophilia. Endoscopic and/or histological differences between PPI responders and non-responders were never clearly defined. PPI-responder eosinophilic esophagitis (PPI-REE) patients are defined those patients presenting clinical and histological features of EoE but with a resolution of eosinophilic infiltrate after a treatment of high dose PPI for eight weeks. Aim of this study is to evaluate if endoscopic, histological or constitutional feature may be specific of PPI responder and non responder patients in a pediatric population.

Aims & Methods: Non consecutive patients in children population with confirmed eosinophilic esophagitis were screened. All patients have undergone an initial upper GI endoscopy with esophageal biopsy and have had a definite diagnosis of eosinophilic esophagitis (eosinophilic infiltration ≥15 per hpf at the esophageal biopsy).

All patients received high dose (1mg/kg) of PPI therapy for eight weeks without changing the current diet. At the end of PPI treatment a second endoscopic look with bioptic sampling was performed to evaluate the response to PPI treatment and to assign each patients to PPI responder or non responder group. Endoscopic features (stenosis, longitudinal stripes, trachealized esophagus, white spots) and histologic findings (absolute number of eosinophils per hpf) at first endoscopy were evaluated and compared between PPI- responder and non responder group . History of food allergies and/or atopic diseases were also recorded.

Results: Of the 64 patients screened for the analysis, 6 patients were excluded because were lost during follow up and/or they did not show at the second look endoscopy. Therefore, 58 patients were included in the final analysis (mean age 10,5 years old; male: 35, female: 23). 37 patients were classified as PPI non-responder (male:21, female:16; average age: 11,1 years old) and 21 patients as PPI responder (male:14, female:7; average age: 9,5 years old). Differences between the 2 groups are shown in Table 1. [Table 1]

Endoscopic characteristics	Non responder (n. 37)		Responder (n. 21)		p-value
Stenosis	n 4	10.8 %	n 1	4.7 %	0.39
Longitudinal stripes	n 20	54.1 %	n 9	42.8 %	0.29
White spot	n 17	45.9 %	n 8	38.1 %	0.38
Trachealized esophagus	n 13	35.1 %	n 1	4.7 %	0.008
Normal mucosa	n 1	2.7 %	n 5	23.8 %	0.02
Histological findings					
15-50 eos/hpf	n 8	21.6 %	n 10	47.6 %	0.04
50-99 eos/hpf	n 12	32.5 %	n 5	23.8 %	0.35
>100 eos/hpf	n 17	45.9 %	n 5	23,8 %	0.007

[Table 1]

No differences were observed in terms of concomitant food allergies between non-responder and responder group: n= 18 (cow's milk protein: 8; egg: 7 ; fish: 5; cereals: 1) vs n=7 (cow's milk protein:2; egg: 3; fish: 2), respectively (p= 0,19). No differences were observed in terms of concomitant atopic diseases between non-responder and responder group: 22 patients (asthma: 3; rhinoconjunctivitis: 3; atopic dermatitis: 1) vs 15 patients (asthma: 7 ; rhinoconjunctivitis: 7; atopic dermatitis: 2), respectively (p= 0,26).

Conclusion: Trachealized esophagus,and a higher number of eosinophils on biopsy sample at the index endoscopy are more prevalent in PPI not responders and might be used to predict a lack of response to PPI and to guide the treatment. Conversely, a normal mucosa and a lower number of eosinophils on biopsy sample at the index endoscopy predict a response to PPI treatment.

Disclosure: Nothing to disclose

OP089 WITHDRAWN

OP090 COMPARISON OF FIRST- AND SECOND-LINE THERAPEUTIC OPTIONS AND THEIR EFFECTIVENESS RATES IN EUROPEAN PATIENTS WITH EOSINOPHILIC ESOPHAGITIS: RESULTS FROM THE *EOE CONNECT* REGISTRY

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Introduction: Eosinophilic oesophagitis (EoE) is a chronic immune-mediated inflammatory disorder of the oesophagus in response to a non-IgE-mediated food allergy. Although avoiding specific food triggers constitutes the only therapy that targets the cause of the disease, the limitations of dietary therapy in clinical practice promoted the use of anti-inflammatory drugs, mainly swallowed topic steroids and proton-pump inhibitors (PPIs).

Aims & Methods: This study aims to analyse criteria for selecting a second line therapy for EoE patients, by a searching within the *EoE CONNECT* database (a prospectively maintained registry of EoE patients from EUREOS) in order to improve our current knowledge about how EoE patients are managed in real world practice. Demographic and clinical variables were considered to seek on determinant factors. First and second-line therapies were analysed. Frequency tables were generated for each treatment modality while contingency tables were analysed by chi-square test using GraphPad software.

Results: First-line treatment data from 493 patients and second-line treatment data from 303 patients recruited at 9 hospitals in Spain and 1 more in Italy were analysed. PPIs overall constituted the preferred first-line option for EoE, followed by topic steroids and dietary interventions. When they failed, dietary interventions (mainly empiric elimination diets) were the most common second-line options used for non-responders to PPIs (51.9%), topic steroids (43.2%) or other previous dietary approaches (32.1%). Among PPIs, omeprazole was the most frequently prescribed drug in both first and second treatment lines (51.6% and 57.8%, respectively). As for topical steroids, fluticasone was the only drug used as a first-line therapy, while budesonide was used in 31.4% of patients as a second-line steroid treatment. As for dietary intervention, empiric elimination diets were the preferred alternative, with six-food and two-food elimination diets being the most commonly used as first-line (42.9%) and second-line (43.6%) therapies, respectively.

Topic steroids provided the highest effectiveness in terms of clinical and histological responses in both lines of treatment. Except for dietary therapies, second-line treatments were overall more effective than first-line ones. Endoscopic dilation was used in a minority of patients, most commonly as a second-line therapy.

Among the variables analysed, three of them were identified as significant determinants for the choice of a first-line treatment: age (p< 0.001), EoE phenotype (p< 0.05) and hospital of origin (p< 0.001). Regarding second-line therapies, differences in treatment were found also for EoE phenotype, recruiting hospitals and previous therapy (all p< 0.001).

Conclusion: Most EoE patients were initially treated with PPIs, with no responders having a two-food elimination diet as second-line therapy. Patients' age and EoE phenotype determined the choice of a first-line therapeutic option, while phenotype and previous treatment affected the selected of second-line therapy. Preferred treatment in both lines was also dependant on the referral hospital.

Disclosure: Nothing to disclose

Type of treatment	First-line treatment			Second-line treatment		
	Use (%)	Failure to achieve clinical response (%)	Failure to achieve histological response (%)	Use (%)	Failure to achieve clinical response (%)	Failure to achieve histological response (%)
PPIs	76.5	28.3	45.9	29.4	15.6	30.6
Topic steroids	10.5	14.6	21.7	16.8	3.2	13.8
Dietary interventions	7.5	18.2	50.0	48.2	28.3	50.9
Dilation	1.6	8.3	nd	5.3	0.0	nd
Other	3.9	nd	nd	0.3	nd	nd

[Table 1]

OP091 A NOVEL ORAL BUDESONIDE FORMULATION IS HIGHLY EFFECTIVE FOR INDUCTION OF REMISSION IN PATIENTS WITH ACTIVE EOSINOPHILIC ESOPHAGITIS: RESULTS FROM THE 6-WEEKS OPEN-LABEL TREATMENT PHASE OF EOS-2 TRIAL

Lucendo A.J.[1], Schlag C.[2], Miehlke S.[3], Biedermann L.[4], Santander Vaquero C.[5,6], Hartmann D.[7], Hayat J.[8], Hruz P.[9], Ciriza de Los Rios C.[10], Bredenoord A.[11], Vieth M.[12], Müller R.[13], Greinwald R.[14], Straumann A.[15,16], on Behalf of the International EOS-2 Study Group

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Introduction: In the recent EOS-1 trial, a 6-week therapy with a novel budesonide orodispersible tablet (BOT), with a unique mode of delivery and esophageal targeting, given twice daily (1mg BID) induced clinico-histological remission in 57% of adult patients with active eosinophilic esophagitis (EoE), with 93.2% achieving histological remission (1).

Aims & Methods: We report here the efficacy of a 6-week open-label induction (OLI) treatment with BOT 1mg BID in a large prospectively treated cohort of EoE patients, which was used as a feeding arm for the further double blind (DB) maintenance phase of the EOS-2 trial.

In total, 181 patients with clinical and histological active EoE were treated in the 6-week OLI phase. The major endpoint and basis for later randomization into the DB maintenance phase was clinico-histological remission, i.e. achieving clinical remission (≤2 points on numerical rating scales (0-10 points) each for dysphagia and odynophagia on each of the 7 days prior to end-of-treatment) and histological remission (peak eosinophil count <16 eos/mm² hpf). Further study endpoints included clinical, histological remission rates and change in peak eosinophil counts, beside other secondary efficacy endpoints.

Results: Clinico-histological remission of EoE was achieved in 69.6% (126/181) of patients after 6 weeks of therapy. Compared to baseline, BOT 1mg BID achieved all assessed clinical, endoscopic or histological endpoints (Table 1).

Number (%) patients in clinico-histological remission at wk 6 (LOCF)	126 (69.6%)
Number (%) patients in histological remission (peak <16 eos/mm2 hpf) at wk 6 (LOCF)	163 (90.1%)
Number (%) patients in deep histological remission (‚0' eos/mm2 hpf) at wk 6 (LOCF)	153 (84.5%)
Mean [95% CI] change in peak eos/mm2 hpf	-283 [-323; -243]
Number (%) patients in clinical remission (dysphagia and odynophagia each ≤2 points on 0-10 points NRS) at wk 6 (LOCF)	136 (75.1)
Mean (SD) total modified EREFS score (0-9) at wk 0 / wk 6 (LOCF)	4 (1.6) n=181 / 1 (1.3) n=176
Number (%) patients with all modified EREFS features graded as ‚0' at wk 0 / wk 6 (LOCF)	1 (0.6%) / 72 (39.8%)
Number (%) patients with endoscopist's overall assessment of ‚no signs of EoE' at wk 0 / wk 6 (LOCF)	-- (0%) / 101 (55.8%)

eos, eosinophils; EREFS; Endoscopic activity score; hpf, high power field; LOCF, last observation carried forward; NRS, numerical rating scale

[Open-label induction phase (n=181 patients)]

Conclusion: A 6-week open-label treatment with BOT 1mg BID was highly effective in bringing clinico-histological active EoE into remission. These findings were similar and confirm in a larger number of active EoE patients the results obtained under DB treatment with BOT 1mg BID in the EOS-1 study (n=88, amongst these 59 having received verum) (1).

References: (1) Lucendo AJ, et al. Gastroenterology 2019, DOI:https://doi.org/10.1053/j. gastro.2019.03.025

Disclosure: Mueller R and Greinwald R are empoyees of Dr. Falk Pharma GmbH

OP092 A NOVEL BUDESONIDE ORODISPERSIBLE TABLET FORMULATION IS HIGHLY EFFECTIVE TO MAINTAIN ENDOSCOPIC INFLAMMATORY REMISSION AND EVEN COMPLETE ENDOSCOPIC REMISSION IN ADULT PATIENTS WITH EOSINOPHILIC ESOPHAGITIS: RESULTS FROM THE 48-WEEKS, DOUBLE-BLIND, PLACEBO-CONTROLLED PIVOTAL EOS-2 TRIAL

Biedermann L.[1], Lucendo A.J.[2], Miehlke S.[3], Schlag C.[4], Santander Vaquero C.[5], Ciriza de Los Rios C.[6], Hartmann D.[7], Madisch A.[8], Hruz P.[9], Hayat J.[10], von Arnim U.[11], Bredenoord A.[12], Müller R.[13], Greinwald R.[14], Schoepfer A.[15], Attwood S.E.[16], Straumann A.[17,18], on Behalf of the International EOS-2 Study Group
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Introduction: In the recent EOS-1 trial, a 6-week therapy with a novel budesonide orodispersible tablet (BOT), with a unique mode of delivery and esophageal targeting, given twice daily (1mg BID) induced endoscopic inflammatory remission in 59% of adult patients with active eosinophilic esophagitis (EoE) versus 0% under placebo (1).

Aims & Methods: This maintenance study also assessed the efficacy of two doses of BOT vs placebo for maintaining EoE in endoscopic inflammatory remission and in complete endoscopic remission over 48 weeks.
In total, 204 patients being in clinico-histological remission at baseline were randomized (1:1:1) to a 48-weeks treatment with BOT 1 mg BID, BOT 0.5 mg BID or placebo.
Endoscopic assessment by using the validated modified EREFS score (2) was performed at baseline and end of treatment (EOT). Endoscopic inflammatory remission was defined as previously suggested by Greuter et al. (3): i.e., modified EREFS subscores: fixed rings = ´Grade 0: none´ or ´Grade 1: mild´, exudates = ´Grade 0: none´, furrows = ´Grade 0: absent´, and edema = ´Grade 0: absent´. Additional EREFS subscores were also assessed. Complete endoscopic remission was defined as all modified EREFS features graded as '0'.
Results: see Table:

	BOT 1mg BID (n=68)	BOT 0.5mg BID (n=68)	Placebo BID (n=68)
Number (%) patients in endoscopic inflammatory remission at baseline	48 (70.6%)	45 (66.2%)	47 (69.1%)
Number (%) patients in endoscopic inflammatory remission at wk48/EOT	51 (75.0%) p<0.0001	49 (72.1%) p<0.0001	4 (5.9%)
Number (%) of patients maintaining endoscopic inflammatory remission from Baseline to wk48/EOT	38 (79.2%) n=48 p<0.0001	32 (71.1%) n=45 p<0.0001	4 (8.5%) n=47
Number (%) of patients in complete endoscopic remission at baseline	34 (50.0%)	34 (50.0%)	35 (51.5%)
Number (%) of patients in complete endoscopic remission at wk48/EOT	39 (57.4%) p<0.0001	36 (52.9%) p<0.0001	4 (5.9%)
Number (%) of patients with no fixed rings present at baseline	42 (61.8%)	39 (57.4%)	42 (61.8%)
Number (%) of patients with no fixed rings present at wk48/EOT	47 (69.1%) p=0.0010	43 (63.2%) p=0.0098	27 (39.7%
P-values (exploratory test for superiority vs placebo; 1-sided Fisher exact test			

[Endoscopic efficacy endpoints]

Conclusion: Both BOT dosing groups were significantly superior over placebo in maintaining EoE in endoscopic inflammatory remission and even in complete endoscopic remission. Moreover, both BOT groups were able to delay or even revert fibrotic remodeling as indicated by improvement in fibrotic signs such as fixed rings. 20% of patients on placebo developed new fixed rings, compared to none on maintenance BOT.
References: (1) Lucendo AJ, et al. Gastroenterology 2019 (accepted for presentation as poster of distinction at DDW 2019) (2) Hirano I, et al. Gut. 2013;62:489-95. (3) Greuter T, et al. Am J Gastroenterol. 2017;112:1527-35.
Disclosure: Mueller R & Greinwald R are employees of Dr. Falk Pharma GmbH

Pathogenesis of H. pylori infection
16:00-17:30 / B3

OP093 RE-DIFFERENTIATION OF GASTRIC CARCINOMA AFTER SUCCESSFUL *HELICOBACTER PYLORI* ERADICATION THERAPY

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Introduction: Gastric cancer may develop after successful eradication of *Helicobacter pylori,*although the incidence is lower than in non-eradicated individuals. We previously reported that the appearance of characteristic epithelium with low-grade atypia (ELA) on the surface of gastric cancer after *H. pylori*eradication. However, whether ELA originates from cancer after re-differentiation or from the non-cancerous surrounding mucosa is unknown.
Aims & Methods: We isolated ELA regions from 10 early gastric cancer patients and analyzed the nucleotide sequences for 90 oncogenes and 35 fusion oncogenes, comparing them with counterpart cancer tissue, normal gastric mucosa, and blood cell-derived DNA. Somatic mutations in each tissue were identified by comparing them with the sequences from whole blood-derived DNA.
Results: Gene alterations were observed in nine of the ten patients, and up to 42 and 70 somatic mutations were seen in cancer and ELA samples, respectively. Common mutations shared between cancer and ELA tissues were found in eight of these nine patients. In contrast, common mutations between non-cancer mucosa and ELA was only detected in one patient, who also had common mutation between cancer and ELA. ELA-specific nucleotide substitutions were seen in seven patients. In contrast, cancer-specific substitutions were only found in two patients. 18 out of 19 amino acid substitutions present in cancer tissue were also identified in ELA. These results suggest that ELA originated from cancer tissue and accumulated further nucleotide substitutions.
Conclusion: Differential diagnosis of ELA and normal mucosa should be carefully performed to prevent misdiagnosis of ELA as normal mucosa with atypia.
Disclosure: Nothing to disclose

OP094 RECIPROCAL EXPRESSION OF 8-OHDG AND DNA REPAIR PROTEINS IN THE PROGRESSION OF *HELICOBACTER PYLORI* ASSOCIATED GASTRIC CANCER

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Introduction: Role of *Helicobacter pylori* in the establishment and progression of gastric cancer is still not well understood. It was hypothesized in this study to determine any possible role of *H. pylori* in the enhanced expression of reactive oxygen species which may result in the accumulation of DNA damages and escape from DNA repair enzymes activity, ultimately lead to the establishment and progression of gastric cancer.
Aims & Methods: Gastric tissues from dyspeptic patients (n=300), normal individuals (n=100) and gastric cancer patients (n=100) were analyzed immunohistochemically for PMS2 and ERCC1 expression in comparison with the presence or absence of *H. pylori* infection and 8-OHdG occurrence.
Results: Regression analysis of 8-OHdG, PMS2 and ERCC1 expressions showed the reciprocal relation between 8-OHdG and PMS2 (r=-0.964) / ERCC1 (r=-0.967). Statistical analyses including mean rank determination, mean comparisons and spearman coefficient analysis, of PMS2 and ERCC1 expression in gastric tissues collected from dyspeptic and gastric cancer patients also confirmed the reciprocal relation observed between expression of these proteins and *cagA -ve/cagA +ve H. pylori* infection. Intestinal type gastric cancer were highly deficient for both proteins, which may suggest the presence of critical role of *cagA +ve H. pylori* in transforming gastritis into precancerous lesions and then into intestinal type gastric cancer by causing impairment in NER and MMR systems.
Conclusion: Findings of this study can suggest the possible involvement of *cagA +ve H. pylori* in enhanced expression of 8-OHdG and decreased expression of PMS2 and ERCC1, resulting in the progression of intestinal type gastric cancer.
Disclosure: Nothing to disclose

OP095 CD44V9-POSITIVE CANCER STEM CELL IS DEVELOPED FROM CAPZA1 OVER-EXPRESSING CELL INDUCED BY OXIDATIVE STRESS

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Introduction: It is known that CD44 variant 9 (CD44v9) is a splicing variant of cancer stem cell marker and CD44v9 expression is strongly associated with the recurrence of early gastric cancer (*Br. J. Cancer* 109:379-386, 2013). However, the mechanism of CD44v9 expression in *H. pylori*-infected gastric mucosa has not been clarified. Although translocated *Helicobacter pylori*-derived CagA is usually degraded by autophagy, it specifically accumulates in CD44v9-positive cancer stem cells (*Cell Host Microbe* 12:764-777, 2012).
We recently reported that CAPZA1 functions as a negative regulator of the autophagy, and thereby translocated CagA accumulates in CAPZA1-overexpressing cells (*Autophagy* 15:242-258, 2019). The present study was conducted to examine the generating mechanisms of CAPZA1-overexpressing cells that lead to the production of CD44v9-positive cancer stem cells.
Aims & Methods: CAPZA1 expression levels in gastric mucosa were evaluated using *H. pylori*-infected Mongolian gerbils. Lipid peroxidation and protein carbonylation in the *H. pylori*-infected mucosa were evaluated on the basis of malondialdehyde and protein carbonyl levels, respectively. Expression mechanisms of CAPZA1 were examined by western blotting and chromatin immunoprecipitation. CD44v9 expressions were evaluated by western blotting and immunohistochemistry.
Results: In CAPZA1-overexpressing cells infected with *H. pylori*, CD44v9 expression was enhanced due to accumulation of CagA oncoprotein. CD44v9-expressing cells were detected among cells strongly stained for CAPZA1 in

H. pylori-infected gastric mucosa of Mongolian gerbils and human gastric cancer tissues. Moreover, CAPZA1-overexpressing cells infected with *H. pylori* exhibited enhanced expression of Sal-like protein 4 (SALL4) and Krüppel-like factor 5 (KLF5), which encode reprogramming factors. Our findings show that CD44v9-expressing cancer stem cells arise from CAPZA1-overexpressing cells following CagA accumulation. We subsequently examined the induction mechanisms of CAPZA1 expression. The levels of CAPZA1 expression in the gastric mucosa of *H. pylori*-infected Mongolian gerbils were significantly higher than that in uninfected gastric mucosa. In *H. pylori*-infected gastric mucosa, a significant linear correlation was observed between CAPZA1 expression and lipid peroxidation (r = 0.614, p < 0,005). CAPZA1 expressions in AGS cells were increased in the dose-dependent manner by the treatment with H_2O_2 or Di-*tert*-butyl peroxide. Such increased expression of CAPZA1 was abolished by treatment with N-Acetyl-L-cysteine. These results show that CAPZA1 expression is enhanced by oxidative stress stimulus.
Conclusion: CAPZA1-overexpressing cells behave as progenitor cells for CD44v9-positive cancer stem cells. Oxidative stress in *H. pylori*-infected gastric mucosa could increase CAPZA1 expression.
Disclosure: Nothing to disclose

OP096 THE CANDIDATES OF THE AMINO-ACID POLYMORPHISM IN N-TERMINAL REGION OF EAST ASIAN CAGA RELATING TO THE PATHOGENIC FUNCTION OF CAGA

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Introduction: The cytotoxin-associated gene A (CagA) is generally accepted to be the most important virulence factor of *Helicobacter pylori* and increases the risk of developing gastric cancer. Especially, infection of *H. pylori* with East Asian CagA which includes EPIYA-D segment in C-terminal region significantly increases the risk of the incidence of gastric cancer than the other type of CagA. Though there are many studies analyzing the amino acid polymorphism of East Asian CagA in C-terminal region surrounding EPIYA motif, much less works about the amino-acid polymorphism in N-terminal region relating to the high virulence of East Asian CagA have been done.
Aims & Methods: The aim of this study is to detect the amino acid polymorphisms in N-terminal region of East Asian CagA which will result in the strong pathogenesis of East Asian CagA *in sillico*. First, our previous whole-genome sequencing (WGS) data of *H. pylori* deposited in DNA Data Bank of Japan (DDBJ) were downloaded. After sequence reads of 40 *H. pylori* strains being mapped to reference using CLC Genomics Workbench, 40 *H. pylori* strains were classified by the EPIYA segment type and divided into two groups, East Asia group including 37 strains and the other group including 3 strains. Specific single nucleotide variants (SNVs) and amino acid changes (AACs) in East Asia group were detected with the tool of Fisher Exact test.
Next, possible influence of the specific AACs existing in N-terminal region of East Asian CagA on the functions of CagA were evaluated with *in silico* simulation model. The tertiary structure of mutant CagA reflecting the specific AACs was made by SWISS-MODEL server using crystal model of CagA (Protein Data Bank (PDB)-ID:4DVY). The docking simulations of CagA with phosphatidylserine (PS) were performed by Swiss-Dock. The docking simulations of CagA with α5β1 integrin were performed by ClusPro. The energy of each docked model, ΔG (kcal/mol) and total energy (kJ/mol) respectively, was calculated and analyzed by Wilcoxon test using JMP 10.
Results: Four high frequent AACs in N-terminal region of East Asian CagA were detected in our previous 40 *H. pylori* sequence data and the two AACs (V356A, Y677F) out of four were demonstrated the reproducible specificity using validation dataset (20 strains of East Asian CagA vs 20 strains of the others) obtained from National Center for Biotechnology Information (NCBI).
After the mutant tertiary structure of CagA reflecting these two specific AACs being made by SWISS-MODEL server, the docking simulations of CagA with PS were performed. As a result, there is no significant difference of ΔG between control CagA and mutant CagA. On the other hand, in docking simulation of CagA with α5β1 integrin, the total energy of complex of mutant CagA with α5β1 integrin was significantly lower than that of control CagA (*p* < 0.01).

This result indicates that the complex of mutant CagA with α5β1 integrin is more stable than that of control. Therefore, these two AACs significantly increase the binding affinity of CagA to α5β1 integrin and may contribute to the high virulence of East Asian CagA.

Conclusion: Two novel AACs which can be the candidates relating to the pathogenicity of CagA were detected in N-terminal region of East Asian CagA.

Disclosure: Nothing to disclose

OP097 HELICOBACTER PYLORI INFECTION INHIBITS NOTCH SIGNALLING IN GASTRIC EPITHELIAL CELLS AND THE GASTRIC MUCOSA

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Introduction: *Helicobacter pylori* infects approximately 4.4 billion people worldwide and poses a major health burden due to its association with chronic gastritis, ulcers, gastric cancer and mucosa-associated lymphoid tissue lymphoma. Disease progression is correlated with host and bacterial factors. Increasing *H. pylori* antibiotic resistance has led to a decrease in eradication success using current therapies. A deeper understanding of host-pathogen interaction is vital to uncover alternative therapeutic strategies. The Notch pathway is highly conserved and central to numerous biological processes including cell differentiation, proliferation and survival. Notch signalling is essential for normal function of gastric epithelial cells (1) and dysregulation is associated with inflammatory conditions and gastric cancer (2). The role of Notch signalling in *H. pylori* pathogenesis is not fully understood.

Aims & Methods: The aim of the study was to monitor expression of Notch signalling pathway components during *H. pylori* infection and assess the role of the virulence factors CagA and VacA. AGS gastric epithelial cells were infected with *H. pylori* 60190 or isogenic CagA and VacA mutant strains. Cells were lysed at 0, 3 and 6 hours post-infection and total RNA was isolated. RNA was also isolated from antral biopsies of *H. pylori*-infected and uninfected patients. Patients were classified as infected if 2 of 3 test results (rapid urease test, histology, culture) were positive. Expression of Notch pathway genes was measured using reverse transcription quantitative PCR. Changes in expression were evaluated using the comparative CT method. Results were normalised to GAPDH levels, and expressed relative to uninfected cells. IL-8 was measured as a positive control. The Student's T-test and Mann-Whitney U-test were used to compare gene expression in cell culture samples and biopsies, respectively. A P value of < 0.05 was considered significant.

Results: *H. pylori* 60190 infection led to a significant increase in IL-8 mRNA expression in AGS cells, together with a significant decrease in the production of several Notch pathway components, including Notch receptors; 1 and 3, Notch ligands; Jagged 1, Jagged 2 and Delta-like 1, as well as Notch target genes Hes1 and Hey1. A similar level of reduction was also observed following infection with *H. pylori* 60190 lacking functional CagA or VacA. In all, biopsy samples from 25 *H. pylori*-infected and 17 uninfected patients were analysed (mean age 50.8 ± 12.9 versus 49.8 ± 17.5 years, respectively; P=0.82). Histology findings reported chronic gastritis in all of the *H. pylori*-infected patients. A significant decrease in the median expression levels of Notch 4 (46%; P=0.02), Jagged 2 (39%; P=0.01), Hes1 (38%; P=0.02) and Hey1 (45%; P=0.03) was observed in the gastric mucosa of *H. pylori*-infected patients compared to uninfected controls.

Conclusion: *H. pylori* infection inhibits Notch signalling in gastric epithelial cells, independent of the CagA and VacA virulence factors. Decreased Notch signalling was also observed in the gastric mucosa of infected patients. Further experiments will be necessary to fully elucidate the role of decreased Notch signalling in *H. pylori* pathogenesis.

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Disclosure: Nothing to disclose

OP098 HELICOBACTER PYLORI INFECTION ANTAGONIZES THE PROCESS FROM INFLAMMATION TO COLITIS ASSOCIATED COLON CANCER BY REGULATING TH17/TREG BALANCE

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Introduction: Large epidemiological studies and meta-analyses have demonstrated an inverse association between Helicobacter pylori (H.pylori) infection and the risk of developing inflammatory bowel diseases (IBD). Our previous study has demonstrated H.pylori infection can modulate Th17/Treg balance to protect against colitis. Colitis associated colon cancer (CAC) is one of the most common cause of death in IBD patients. Compared with hereditary and sporadic colon cancer, the pathogenic mechanisms of CAC involve the crosstalk among tumor cells, tumor stromal cells and immune cells. The differentiation balance between Th17 and Treg cells palys significant role in the CAC. Thus, we speculate H.pylori infection might ameoliorate the severity of CAC by regulating Th17/Treg balance.

Aims & Methods: The aim of this work was to investigate whether H.pylori infection may influence the severity of CAC in a mouse model of early colorectal carcinogenesis by modulating Th17/Treg balance. C57BL/6 mice received azoxymethane (AOM) i.p. at a dose of 10 mg/kg body weight to induce dysplasia and then received 4 cycles of 2% DSS, each separated by 14 days of regular water. All mice were sacrificed 90 days after the first AOM injection to perform histology, flow cytometry analysis and immunohistochemistry of colonic mucosa. The tumor number and tumor load were counted for each group. Immunohistochemical staining for BrdU was performed to evaluate the proliferative activity of colonic epithelial cells. Flow cytometry was used to determine the percentage of Th17, IL10+Treg, IL17+Treg and tumor associated macrophages (TAM) in colon. The m-RNA expression of Th17 and Treg associated cytokines (IL6, IL10, IL17A, IL23, TGFβ).

Results: AOM/DSS treatment resulted in the formation of colon tumors in both H.pylori infected and non-infected mice. Compared with non-infected group, H.pylori infected mice exhibited less tumor number and tumor load (7.83±2.64 vs 5.00±1.51, P< 0.05 and 18.68±4.56 vs 9.04±3.40, P< 0.05). In accordance, BrdU staining revealed significantly decreased proliferative activity in both tumor and peri-tumor tissues (44.62±4.38 vs 27.65±3.24, P< 0.05 and 10.69±1.42 vs 4.45±1.24, P< 0.05). Flow cytometry study revealed lower Th17 and IL17+Treg cells percentage in the colon of H.pylori infected group mice, showing an inhibited Th17 cell differentiation by H.pylori infection (3.52±0.32 vs 1.16±0.20, P< 0.05 and 0.30±0.02 vs 0.22±0.02, P< 0.05). In turn, H.pylori infected mice exhibited higher IL10+Treg cells percentage in colon (0.42±0.02% vs 0.58±0.03%, P< 0.05), which might involve in the protective mechanism against colon cancer. In addition, we found that H.pylori infected group also presented lower TAM percentage in colon tissues (21.81±1.06 vs 13.46±0.42, P< 0.05). Accordingly, Th17 cells associated cytokines (IL17, IL6 and IL23) decreased in infected group, whereas Treg cells associated cytokines (IL10 and TGFβ) increased significantly.

Conclusion: Our data demonstrated that H.pylori infection might antagonize the process from colitis to CAC in CAC mouse model. This effect is likely mediated via regulating Th17/Treg balance by modulating TAM in colon cancer.

Disclosure: All authors have declared no conflicts of interest.

IBD: Health care and patient-reported outcomes

16:00-17:30 / B5

OP099 THE EXPERIENCE OF INFLAMMATORY BOWEL DISEASE PATIENTS WITH HEALTHCARE: A SURVEY OF 2011 PATIENTS FROM THE GETAID

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Introduction: Patient experience with healthcare is positively associated with clinical effectiveness and patient safety in a wide range of diseases. Inflammatory bowel diseases (IBD) are chronic and disabling conditions involving the gastrointestinal tract. Besides, the quality of information given by the physician to patients and the development of shared decision processes may be helpful to improve confidence and adherence in IBD management. The aim of this study was to assess experience of patients with IBD on their disease, their treatment and the relationship with their physician.
Aims & Methods: We performed a nationwide cross-sectional survey in 42 tertiary centers in France and Belgium affiliated to the GETAID from November 26th to December 2nd 2019, on consecutive outpatients with IBD. A standardized self-administered anonymous questionnaire was completed by each patient. The recorded data included patients, IBD and treatment characteristics combined with multiple-choice questions and 10-point Likert scales regarding patient global assessment of clinical remission, daily life IBD burden, treatment adherence, information on IBD, doctor-patient relationship, overall satisfaction, patient-self management, concerns about their treatment, knowledge on biosimilars and alternative management.
Results: A total of 2011 outpatients with IBD responded to the survey (930 men; median age 40.0 (29.0-52.0) years; median IBD duration 10.5 (4.5-18.5) years; 67.8% of patients with Crohn's disease). Most of the patients were treated with biological agents (63.9%) or immunomodulator (8.5%). Patient global assessment of clinical remission was noted in 49.9% and daily life IBD burden score was 5.2 ± 2.9. Assessment of doctor-patient relationship considering IBD and IBD treatment knowledge and doctor-patient relationship was good ranging from 7.4 to 8.3 (table 1) associated with a high adherence to treatment (9.1 ± 2.2).
Alternative sources of information about ongoing treatment and IBD was mainly obtained from internet in 62.9% and 79.8%, respectively, and from general practitioner in 54.3% and 61.4%. Indeed, patients with IBD reported consulting their general practitioner 2.6 ± 3.9 times a year in addition to their gastroenterologist. Lost working days were frequent in 71.2% of patients accounting for 0.8 working day loss per years. Complementary medicine was used by 28.2% of patients including 19.4% on a regular basis. Knowledge about biosimilars was poor (20.4%) and associated with a low acceptance rate (21.4%).
Main concerns about IBD treatment were the fear of adverse events (47.4%) and lack and/or loss of efficacy (32.9%), while the absence of any concerns was observed in 24.4%. Claim for prospective access to complementary and alternative healthcare professionals were noticed in 89.2% including dietician (24.9%), sports coach (22.0%), psychotherapist (14.6%), sexologist (9.4%) and social worker (8.5%).

Knowledge about IBD	7.4 ± 1.2
Sufficient information about ongoing treatment	8.1 ± 2.1
Overall satisfaction about ongoing treatment	7.6 ± 2.5
Adherence to ongoing treatment	9.1 ± 2.2
Overall satisfaction on doctor-patient relationship	8.3 ± 2.2

[Table 1]

Conclusion: In 2011 outpatients with IBD followed-up in tertiary care centres, we observed a high level of satisfaction, adherence and knowledge about IBD and IBD treatment. However, we highlight several fields that still need improvement: knowledge and acceptance of biosimilars, access to complementary and alternative healthcare professionals, loss of work productivity and concerns about effectiveness and safety of IBD treatment.
Disclosure: This study was funded by Abbvie

OP100 WORK PRODUCTIVITY LOSS IS A MAJOR COST DRIVER IN IBD PATIENTS: THE WORK-IBD STUDY

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Introduction: Inflammatory bowel disease (IBD) negatively impacts work productivity (WP). Most studies focus on absence from work (absenteeism), while on the job productivity loss (presenteeism) is present in more than 30% of patients. Indirect costs, defined as expenses incurred from WP loss due to IBD, have not been thoroughly studied in economic evaluations.
Aims & Methods: The aim of the WORK-IBD study was to determine predictors for WP loss and estimate corresponding indirect costs. Crohn's disease (CD) and ulcerative colitis (UC) patients that attended the outpatient clinic of four hospitals between May 1st and August 31st 2017 were invited. WP loss was measured using the Work Productivity and Activity Impairment questionnaire, disease activity using the patient-reported Harvey Bradshaw Index or Simple Clinical Colitis Activity Index. Severe absenteeism, presenteeism and overall WP loss were defined as ≥ 50% work time missed, ≥ 50% on the job productivity loss, and ≥ 50% overall work impairment (absenteeism plus presenteeism) in the previous week, respectively. Annual indirect costs were calculated based on hourly wage data from Statistics Netherlands (CBS) 2017, percentages WP loss, contract hours per week and 47 weeks worked annually.
Results: In total, 1590 IBD patients were invited, 768 (48%) responded (119 not eligible, 86 declined) and 536 were included (58% female, 53% CD) with a median age and disease duration of 45 (33-53) and 11 (5-20) years (table 1). Severe absenteeism, presenteeism and overall WP loss was reported by 36 (7%), 85 (16%) and 115 (22%) of patients, respectively. Eight (7%) patients using mesalamine (5-ASA), 20 (18%) using immunomodulators, 26 (30%) on anti-TNF monotherapy, 12 (29%) on combination therapy, 9 (32%) on vedolizumab, 10 (63%) on ustekinumab and 30 (22%) without maintenance treatment reported severe overall WP loss. Risk factors for severe WP loss were disease activity (OR 6.6, 95% CI 3.6-12.1) and perianal disease (OR 3.7, 95% CI 1.5-8.7), whereas 5-ASA treatment was associated with a lower risk (OR 0.2, 95% CI 0.0-0.8). Median costs per patient for absenteeism, presenteeism and overall WP loss were €0 (0-0), €0 (0-8430) and €1905 (0-10537), respectively. Median costs due to overall WP loss were €0 (0-6734) for patients using 5-ASA, €1143 (0-8767) for immunomodulators, €3810 (0-14875) for anti-TNF monotherapy, €3049 (0-16859) for combination therapy, €5603 (0-15771) for vedolizumab, €10350 (3049-28201) for ustekinumab and €762 (0-9146) for patients without treatment. Costs were higher for patients with disease activity and perianal disease (€13,338 vs 0, p< 0.001 and €14363 vs 2382, p=0.001).

	Total (n=536)	No treatment (n=138)	5-ASA (n=113)	Immuno-modulator (n=112)	Anti-TNF (n=112)	Vedoli-zumab (n=29)	Ustekinumab (n=16)
Crohn´s disease, n(%)	286 (53)	83 (60)	12 (11)	66 (59)	91 (71)	19 (66)	15 (94)
Disease duration, median years (IQR)	11 (5-20)	12 (6-21)	10 (4-20)	11 (5-20)	12 (6-20)	14 (5-20)	11 (7-15)
Disease activity, n (%)	122 (23)	28 (20)	17 (15)	28 (25)	32 (25)	7 (24)	10 (63)
Perianal disease, n (%)	32 (11)	10 (12)	2 (2)	5 (8)	10 (11)	2 (10)	3 (20)
Prior bowel resection, n (%)	143 (27)	57 (41)	3 (3)	26 (23)	40 (31)	7 (24)	10 (63)
Severe absenteeism, n (%)	36 (7)	8 (6)	2 (2)	3 (3)	13 (10)	4 (14)	6 (38)
Severe presenteeism, n (%)	85 (16)	23 (17)	6 (5)	16 (14)	29 (23)	6 (21)	5 (31)
Severe overall WP loss, n (%)	115 (22)	30 (22)	8 (7)	20 (18)	38 (30)	9 (32)	10 (63)

[Table 1. Baseline characteristics]

Conclusion: In this large IBD cohort, 7%, 16% and 22% of patients had severe absenteeism, presenteeism and overall WP loss. Major risk factors for WP loss were perianal disease and disease activity, resulting in high indirect costs. Patients using ustekinumab had the highest yearly indirect costs, patients on 5-ASA the lowest, which is most likely related to the number of patients with disease activity and perianal disease within these groups. A substantial proportion of indirect costs are related to presenteeism.

Disclosure: This work was sponsored by dr. Falk Pharma Benelux B.V.

OP101 PATIENT AND PHYSICIAN ASSESSMENT OF DISEASE BURDEN IN PATIENTS WITH EARLY UC: 2-YEAR DATA FROM ICONIC

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Introduction: ICONIC is the largest prospective, multi-country, observational study assessing disease burden in adults with ulcerative colitis (UC) under routine care over a 2-year period. The study assessed quality of life and disease burden using standard Inflammatory Bowel Disease (IBD) patient reported outcome measures as well as a visual measure of disease-associated suffering, Pictorial Representation of Illness & Self-Measure (PRISM). The final analysis of the study is presented.

Aims & Methods: Adult patients with early UC (diagnosed ≤36 months) were enrolled irrespective of disease severity or treatment. Patient visits occurred every 6 months (+/- 3months) for 2 years. The primary objective was to evaluate PRISM as a tool to assess disease-associated suffering in patients with UC. Lower PRISM scores represent a greater suffering associated with illness. The correlation between patient and physician perception of disease was also assessed. Patient self-assessments included PRISM, Patient Health Questionnaire-9 (PHQ-9), Short IBD Questionnaire (SIBDQ), and patient-modified Simple Clinical Colitis Activity Index (P-SCCAI). Physician assessments included clinical parameters, PRISM, and SCCAI. Data are presented as-observed. Mean differences between patient and physician measures, and differences between the 2-year and first visits were calculated using Wilcoxon signed-rank test. Correlation between PRISM and SIBDQ, PHQ-9, and SCCAI were performed using Spearman correlation.

Results: A total of 1806 patients were enrolled and fulfilled the selection criteria; 53.8% female, mean (SD) age 38.5 (14.6) years; 336 (18.6%) discontinued the study. At the 2-year visit, data were available for 1265 pa-

tients. The most common reasons for discontinuation were did not attend routine visit and lost to follow-up. At baseline, 37.0% and 12.9% of patients were assessed by the physician to have moderate or severe disease, respectively. At the 2-year visit, the physician assessments were 13.4% of patients with moderate disease and 2.5% with severe disease. Mean ± SD patient-reported PRISM score and P-SCCAI were significantly different than the physician measures, with patients reporting a higher disease burden than that perceived by the physician (patient PRISM: 5.1 ± 2.5 and physician PRISM: 5.6 ± 2.4; p< 0.0001; P-SCCAI: 2.5 ± 2.8 and SCCAI: 1.3 ± 2.1; p< 0.0001; Table). A high correlation was observed between patient and physician PRISM scores and between P-SCCAI and SCCAI. Mean ± SD scores for PHQ-9 and SIBDQ were 4.2 ± 4.6 and 55.7 ± 11.6, respectively. Patient PRISM scores were moderately correlated with SIBDQ, PHQ-9, and P-SCCAI (Table).

Significant differences in mean ± SD scores between the 2-year visit and the first visit were observed for all measures (PHQ-9: -1.8 ± 5.5; P-SCCAI: -1.6 ± 4.0; SCCAI: -1.5 ± 3.2; SIBDQ: 6.8 ± 13.9; patient PRISM: 1.2 ± 3.0; physician PRISM: 1.3 ± 2.9; p< 0.0001 for all measures).

	SIBDQ	PHQ-9	PRISM (physician)	P-SCCAI (patient)
PRISM (patient), r (p-value)	0.56 (0.0001)	-0.43 (<0.0001)	0.63 (<0.0001)	-0.50 (<0.0001)
SCCAI (physician), r (p-value)	Not determined	Not determined	-0.48 (<0.0001)	0.67 (<0.0001)

PRISM=Pictorial Representation of Illness & Self- Measure, SCCAI=Simple Clinical Colitis Activity Index; SIBDQ=Short Inflammatory Bowel Disease Questionnaire, PHQ-9=Patient Health Questionnaire-9.

[Table. Spearman correlation coefficients between selected instruments at the final visit.]

Conclusion: PRISM may be a valuable tool to assess disease burden in patients recently diagnosed with UC. Although patient and physician measures of disease related suffering and disease severity were strongly correlated, the perception of UC-related burden significantly differed between physician- and patient- assessments. These discrepancies between patient and physician ratings warrant further investigation.

OP102 THERE IS MORE THAN PHARMACOLOGY: COMPREHENSIVE LIFESTYLE-MODIFICATION IN PATIENTS WITH ULCERATIVE COLITIS: A RANDOMIZED CONTROLLED TRIAL

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Introduction: The chronic impairment of health related quality of life (HrQoL) is of high relevance in patients with ulcerative colitis (UC). Many patients perceive a treatment regime solely based on drug therapy as limited. A standardised multimodal lifestyle-modification program including modules in mind-body medicine, naturopathic self-help strategies, herbal treatments and dietary counseling shows promising first evidence to lower the burden of disease and increase patients HrQoL.

Aims & Methods: Ninety-seven patients with ulcerative colitis in clinical remission and impaired HrQoL were randomly assigned to a 10 week comprehensive lifestyle-modification program or a control group that received a single workshop of intense training in naturopathic self-help strategies (Table 1).

	Lifestyle-modification (n = 47)	Control (n = 50)
Age years	50.28 ± 11.90 (18 - 74)	45.54 ± 12.49 (19-71)
Female n (%)	34 (72.3)	35 (70)
Weight	72.79 ± 14.90 (52-100)	70.24 ± 16.86 (49.6 - 150)
Anamnestic pattern n (%)		
Proctitis	14 (29.8)	15 (30)
Left-sided colitis	17 (36.2)	15 (30)
Pancolitis	13 (27.7)	17 (34)
Missing	3 (6.4)	3 (6)
Time since diagnosis years	18.04 ± 12.00 (2 - 46)	14.76 ± 10.99 (1 - 43)
Smokers n (%)	2 (4.3)	3 (6)
Married n (%)	33 (70.2)	39 (78)
Blood parameters		
Leucocytes	6.40 ± 1.70	6.73 ± 4.38
Thrombocytes	272.26 ± 81.69	269.98 ± 72.68
Blood sedimentation rate	9.17 ± 10.55	9.54 ± 11.99
C-reactive protein	.36 ± .67	.29 ± .58

[Table 1. Sociodemographic and clinical characteristics at baseline.]

Patients were randomized using stratified block randomization (Strata: sex, azathioprine and biologics). Primary outcome was disease-specific total HrQoL at week 12 (Inflammatory Bowel Disease Questionnaire; IBDQ). Secondary outcomes included IBDQ sub-scores, generic HrQoL (SF-36), disease activity (Rachmilewitz clinical activity index, fecal lactoferrin, and fecal calprotectin), microbiome, and safety. In 31 patients additional endoscopy with histology was performed pre and post intervention.

Results: In both groups, a relevant increase in HrQoL (>16 in the IBDQ) at week 12 was achieved. In the Intention-to-treat analysis, the intervention group showed significantly higher improvement on the IBDQ subscale Bowel Symptoms (*p*=.045) and the SF36 mental health index (*p*=.002). In the Per Protocol (PP) analysis (pts who attended ≤50% of the intervention and screening failures were excluded), 37 patients in the intervention group and 43 patients in the self-care group were analyzed. Within the PP analysis, the LSM group showed a significant higher response in the IBDQ global score (*p*=.034; mean IBDQ=172.8) as well as the IBDQ systemic subscore (*p*=.034) and the IBDQ emotional subscore (*p*=.004) indicating a

higher HrQoL. No significant group difference was shown regarding endoscopy (*p*=.451) and histology (*p*=.406), disease activity (CAI *p*=.239), fecal Lactoferrin (*p*=.648) or fecal Calprotectin (*p*=.751). In addition, there was no significant difference in the fecal microbiota.

Conclusion: UC patients benefit from defined non-pharmacological treatment modules. A comprehensive lifestyle-modification program improves quality of life in patients with ulcerative colitis, while no effects were shown on disease activity in this group of patients in clinical remission. The results suggest that patients have to attend more than 50% of the training sessions of the 10 week lifestyle-modification program. Trial registration: Clinicaltrials.gov (NCT02721823).

OP103 RESPONDER DEFINITIONS FOR THE CROHN'S DISEASE PATIENT-REPORTED OUTCOMES SIGNS AND SYMPTOMS (CD-PRO/SS) TOOL USING PATIENTS WITH CROHN'S DISEASE TREATED WITH ETROLIZUMAB

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Introduction: Clinically relevant patient-reported outcome (PRO) tools are important for evaluating treatment efficacy. Available PRO instruments used in Crohn's disease (CD) have limitations in evaluating the full extent of disease components, appropriately quantifying clinical symptoms, and adequately capturing the patient perspective. The Crohn's Disease Patient-Reported Outcomes Signs and Symptoms (CD-PRO/SS) is the first CD PRO tool developed with input from health authorities, patients, and clinical experts.[1] In April 2019, the EMA released a letter supporting use of the CD-PRO/SS as an end point in IBD clinical trials.[2] Here, we propose responder definitions for the CD-PRO/SS using data from patients with moderate-to-severe CD treated with etrolizumab in BERGAMOT (NCT02394028).

Aims & Methods: In BERGAMOT (Phase 3 trial), aTNF-naive and aTNF-experienced patients with CD were treated with etrolizumab 105 mg, 210 mg, or placebo SC every 4 weeks during a 14-week induction phase. Cohort 1 (blinded) and cohort 2 (open-label) were analysed independently, encompassing all treatments. Data reported are from the pooled analysis. The CD-PRO/SS consists of 2 separately scored scales: a 3-item functional domain and a 3-item bowel domain. The domain score is equal to the sum of the item scores, which were calculated as an average of ≥ 4 out of 7 days before every induction visit. Mininum clinically important differences (MCID) were calculated using distributional- and anchor-based methods on a reduction of ≥ 16 points in the Inflammatory Bowel Disease Questionnaire, ≥ 70 points in the Crohn's Disease Activity Index (CDAI), and ≥ 100 points in the CDAI at week 14.

Results: As of September 2018, the CD-PRO/SS scores from patients with non-missing data (67.4% aTNF-experienced; cohort 1 n=215; cohort 2 n=264) were pooled for analysis (**Table**). Based on a reduction of ≥ 70 CDAI and ≥ 100 CDAI, the MCID from anchor-based method were 2.5 and 2.7, respectively, for the functional domain and 3.1 for the bowel domain regardless of treatment arm. Preliminary responder definitions for the CD-PRO/SS were a reduction ≥ 2.5 for the functional domain and ≥ 3.0 for the bowel domain that were determined through triangulation. Using these cutoffs, 45% of patients were responders based on the functional domain and 41% of patients were responders based on the bowel domain.

Conclusion: The proposed responder definitions determined from 479 patients show that a clinically meaningful response on the CD-PRO/SS are a reduction of ≥ 2.5 in the functional domain or ≥ 3.0 in the bowel domain. These definitions for the CD-PRO/SS will be confirmed in the ongoing etrolizumab Phase 3 CD studies for use in both clinical trials and practice to assess a clinically meaningful improvement.

	Functional Domain (0-12)	Bowel Domain (0-16)
Baseline		
N	479	479
Mean (SD)	6.41 (2.13)	8.23 (2.56)
Median	6.43	8.43
Min, max	1.43, 11.43	1, 13
Week 14		
N	421	421
Mean (SD)	4.21 (2.35)	5.83 (3.07)
Median	4.14	5.85
Min, max	0, 11.43	0.43, 13.75
Change from Baseline at Week 14		
N	334	334
Mean (SD)	-2.28 (2.55)	-2.45 (2.89)
Median	-2.08	-2.28
Min, max	-9.86, 6.01	-10.43, 4.72

CD-PRO/SS, Crohn's Disease Patient-Reported Outcomes Signs and Symptoms; SD, standard deviation.

[Table. Baseline, Week 14, and Change from Baseline in CD-PRO/SS Scores by Domain]

References: 1. Higgins PDR et al. J Patient Rep Outcomes. 2018;2:24. 2. European Medicines Agency (EMA). Letter of Support for the development of Patient-Reported Outcomes tools for use as an endpoint in Inflammatory Bowel Disease (IBD) clinical trials. April 2019.
Disclosure: PDR Higgins has nothing to disclose. K DeBusk is employee of and shareholder in Genentech/Roche and employee of Bristol-Myers Squibb (outside submitted work). R Jacob, A Hassanali, Z Sharafali, and A Matsui are employees of Genentech. YS Oh is employee of and shareholder in Genentech/Roche.

OP104 IMPACT OF BIOLOGIC TREATMENT OF ULCERATIVE COLITIS ON HEALTHCARE RESOURCE UTILIZATION IN US PATIENTS

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Introduction: This study compared healthcare resource utilization (HCRU) among Ulcerative Colitis (UC) patients currently receiving biologics and UC patients not currently receiving biologics.
Aims & Methods: Adult (18+ years) patients with ≥1 UC diagnosis code (ICD-9: 556.x; ICD-10:K51.x) from January 1, 2017 to December 31, 2017 were included in this retrospective analysis of medical and pharmacy claims data from the IBM Marketscan Commercial, Medicaid, and Medicare-Supplemental Claims database. Patients with a Crohn's Disease diagnosis were excluded from this study. Subgroups analyses were conducted to compare UC patients prescribed biologics and UC patients not prescribed biologics during 2017. A two-sample t-test was conducted to compare continuous variables and chi-squared tests were used to compare categorical variables.
Results: A total of 62,146 UC patients were included in this analysis; 7,705 patients (12.4%) were prescribed a biologic and 54,441 (87.6%) were not prescribed a biologic. Biologic users were more likely to be male (50.6% vs. 45.6%; p<0.0001) and younger (mean age: 42.94 vs. 49.88 years; p<0.0001) when compared to patients not prescribed a biologic. Biologic users were more likely to be prescribed immunomodulators (24.2% vs. 7.9%; p<0.0001), 5-ASAs (50.7% vs. 48.5%; p=0.0004), corticosteroids (47.7% vs. 29.5%; p<0.0001), and opioids (41.5% vs. 40.0%; p=0.0132). Biologic users were also more likely to have gastroenterologist visits (76.9% vs. 62.0%; p<0.0001), however patients not prescribed biologics were more likely to have ER visits (28.4% vs. 25.6%; p<0.0001) and inpatient hospital visits (13.6% vs. 15.8%; p<0.0001).
Conclusion: Medication use was higher among UC biologic users, however UC patients not prescribed biologics had higher HCRU.
Disclosure: Nothing to disclose

Management of patients with portal hypertension
16:00-17:30 / C3

OP105 SELECTIVE ACTIVATION OF STAT1-DEPENDENT APOPTOSIS IN HEPATIC STELLATE CELLS BY RILPIVIRINE AS A NEW THERAPEUTIC OPTION FOR LIVER FIBROSIS

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Introduction: Liver fibrosis is a common clinical outcome of all chronic liver diseases. Its current incidence is achieving pandemic dimensions and the lack of effective therapeutic options represent a major health problem worldwide. Among the wide range of signaling pathways that contribute to the progression of this pathology, JAK-STAT1 and JAK-STAT3 have been recently proposed as interesting therapeutic targets since they play a key role in the regulation of cell proliferation and cell death in both parenchymal and non-parenchymal cells. Rilpivirine (RPV) is a widely used antiretroviral drug that not only is considered safe in chronic treatments but also has been associated with an improvement in the lipid profile and glycemic control of HIV-infected patients after switching from other antiretroviral regimens.
Aims & Methods: We aimed to study the role of RPV in the progression of chronic liver damage as well as the involvement of JAK-STAT1 and JAK-STAT3 signaling pathways in this process, especially focusing on its actions on hepatic stellate cells (HSC) and hepatocytes.
To do this, a nutritional model of nonalcoholic fatty liver disease (NAFLD) and a CCl_4-induced liver fibrosis model (both in C57BL/6 mice) were used; RPV was daily administered at clinical doses. Human cell lines of hepatocytes (Hep3B) and HSC (LX-2), as well as primary human HSC (hHSC) were also treated with RPV. Standard molecular biology and histology techniques were used to assess the progression of liver damage and the activation of STATs. Gene silencing and conditioned medium experiments were carried out to evaluate the implication of STAT1 and STAT3 as well as the crosstalk between different cell types in response to RPV.
Results: RPV significantly reduced hepatic inflammation and fibrosis *in vivo*, and produced an increase of STAT3 activation in hepatocytes and of STAT1 in HSC. These effects were accompanied by augmented numbers of proliferating hepatocytes and apoptotic HSC. *In vitro*, RPV did not directly alter the viability or STAT3 activation in hepatocytes, but it did induce a clear pro-apoptotic effect in LX-2 cells, together with a decrease in STAT3 and collagen 1 protein expression, and an increase in STAT1 activation. Interestingly, this selective cytotoxic effect completely disappeared when STAT1 was silenced. In addition, STAT3 was activated in hepatocytes incubated with conditioned medium from apoptotic LX-2 cells. All these results were reproduced in hHSC.
Conclusion: The hepatoprotective effect of RPV is directly mediated by the selective STAT1-dependent induction of apoptosis in HSC. Additionally, RPV activates STAT3 in hepatocytes, increasing its proliferation and favoring liver regeneration. These effects could be of great clinical relevance in the development of new effective therapies for liver diseases with a fibrotic component.
Disclosure: Nothing to disclose

OP106 EUS-GUIDED PORTAL PRESSURE GRADIENT MEASUREMENT SAFELY PERFORMED WITH EUS-GUIDED LIVER BIOPSY: ENDOHEPATOLOGY IN PRACTICE

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Introduction: The portal pressure gradient (PPG) is useful to predict the development of complications of portal hypertension (PH). Recently, we showed the feasibility and safety of a simple novel technique for Endoscopic ultrasound (EUS) guided PPG measurement (PPGM) in a pilot study. EUS-guided liver biopsy (EUS-LB) has been shown to be a safe and effective alternative to percutaneously or Interventional Radiology performed liver biopsy for the diagnosis of liver disease.
Aims & Methods: We aimed to assess feasibility and safety of concomitant EUS-guided PPGM with EUS-LB in a single session. Secondarily, we aimed to evaluate the correlation between PPG and clinical markers of PH in an expanded clinical series.
This was a retrospective study of EUS-PPGM at single tertiary endoscopy center that enrolled 51 consecutive patients suspected of liver cirrhosis between February 2014 and October 2017.
Results: Technical success rate of EUS-PPGM was 100% without any severe adverse events. PPG ranged from 0 to 27.3 mm Hg. There was excellent correlation between PPG and clinical parameters of PH including the presence of clinical features of cirrhosis (11.26 vs 3.14 mmHg, p < 0.001), varices (14.94 vs 4.09 mmHg, p < 0.001), portal hypertensive gastropathy (14.37 vs 5.23 mmHg, p < 0.001), and thrombocytopenia (10.91 vs 4.81 mmHg, p = 0.0027). Platelet count also had a moderate negative correlation with PPG (R = -0.579). EUS-guided liver biopsies were performed in 35 patients (68.6%). All biopsies were deemed adequate for achieving histologic diagnosis by our pathologists. There were no early or late major adverse events.
Conclusion: EUS-guided PPG measurement using a 25-gauge needle and compact manometer correlates well with clinical markers of portal hypertension and appears safe in this study with an expanded selection of patients. EUS-LB can be performed safely at the same session as EUS-PPGM further adding value to the endoscopic evaluation of the patient with liver disease.
Disclosure: Presented at DDW

Expanding the horizons for early colonic cancer
16:00-17:30 / F2

OP107 COVERT CANCER IN COLONIC POLYPS: SIZE DOES MAKE A DIFFERENCE!

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Introduction: Colorectal polyps with overt endoscopic features of invasive cancer are referred for surgery. However, polyps without overt features might still harbour cancer. We aim to identify incidence of such covert cancers in colorectal polyps to see if the 'resect and discard' strategy could be extended beyond diminutive polyps.
Aims & Methods: We analysed outcomes of all patients who underwent screening colonoscopy between January 2007 to December 2018 and were found to have polyps. Data was prospectively collected on an online endoscopy reporting system and pathology reporting system. A using multinomial logistic regression.
Results: A total of 15906 polyps were removed at colonoscopy over the specified period. Mean size was 7.3 mm (range: 1 to 120 mm) with 82.5% polyps being < 10mm in size. 86.6% of all polyps were non pedunculated and 56.3% polyps were located in the left colon gradient and rectum. The size, site, morphology and histology of these polyps is shown in table 1.
A histopathological diagnosis of polyp cancer was made in 104 /15906 polyps (0.65%). 94/104 polyp cancers (90.25%) were associated with non pedunculated morphology [OR 1.45, 95%CI 0.75-2.78 p=0.005].

No cancer was found in polyps < 5mm in size. However, the cancer incidence was 4/2365 (0.17%) in polyps 6-10mm [OR 1.10 95% CI 1.09-1.12, p<0.001], 58/1793 (3.25%) in polyps 10-30mm and 42/973 (4.30%) in polyps > 30mm in size. Risk of developing in cancer in polyps >10mm was significantly higher than in polyps 6-10 mm [OR 21.1 95% CI 7.9-58, p< 0.001]. 89 cancers were found in the left colon and rectum compared with 15 cancers in the right colon (85.5% vs 14.5%) [OR 1.98, 95%CI 0.9-3.1 p=0.007]. All 4 cancers found in the 6-10mm category were non-pedunculated polyps in left colon.

Size	Proportion %	Morp	hology %	Location %		Dysplasia %			
		Pedunculated	Non pedunculated	Right Colon	Left Colon	None	LGD	HGD	Cancer
< 5mm (N= 10775)	67.74	3.7	96.3	50.3	49.7	34.0	65.40	0.60	0.0
6-10mm (N= 2365)	14.87	31.75	68.25	30.8	69.2	21.33	74.44	4.06	0.17
10-30mm (N=1793)	11.27	46.9	53.1	31.0	69.0	12,20	68.89	15.67	3.25
>30mm (N= 973)	6.12	14.08	85.92	24.0	76.0	10.10	69.50	16.10	4.30

[Table 1]

Conclusion: We have demonstrated that the prevalence of covert cancer in colorectal lesions < 5mm is negligible and that of polyps 6-10 mm is very low (0.17%). All these cancers were in non-pedunculated polyps in left colon.This means that the 'resect and discard' strategy could be extended to 6-10 mm polyps in right colon and potentially to pedunculated polyps in left colon.
Cancer risk, however, increased more than 20 fold in polyps between 1-3 cm (3.25%) and 25 fold in polyps > 3 cm (4.3%). This calls for careful resection (preferably en-bloc) and retrieval of these polyps to obtain all prognostic information.
Disclosure: Nothing to disclose

OP108 APPLICATION OF ARTIFICIAL INTELLIGENCE AND DEEP LEARNING ALGORITHM IN THE PREDICTION OF ADVANCED HISTOLOGY OF COLORECTAL ADENOMAS

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Introduction: Recognition of high grade dysplasia or intramucosal malignancy in colorectal polyps is of critical importance before polypectomy to ensure that the optimal operative endoscopic method is selected for the removal. This is currently mainly based on expert opinions. Therefore, we developed an artificial intelligence-based decision support system (AI-DSS) that can differentiate between low- and high-grade dysplasia or intramucosal neoplasia in adenomatous polyps.
Aims & Methods: In the present study our aim was to analyze the effectiveness and accuracy of an AI-DSS in the prediction of advanced histology. We took still images from videos (colonoscopy containing colorectal adenomas with low- and high-grade dysplasia). We enrolled 1033 HD images of a total of 91 polyps (85 patients, 57.45% male, 56.4 average age), and we set up and trained a deep learning model with these images. The images went trough a pre-process algorithm, images of malignancies (invasive cancer), and low-quality images were excluded from both the train and test sets. Using the Gradient-weighted Class Activation Mapping (Grad-CAM) technique, the software can visually explain via a „heatmap" which areas on the image contained key information for the decision.
Results: We trained the neural network with 480 images of 55 polyps with a histological diagnosis of low-grade dysplasia and 457 images of 41 polyps with high-grade dysplasia. 119 images of 17 polyps (7 with low-grade and 5 with high-grade dysplasia + 2 with intramucosal carcinoma) were used for the test set. The test group had more images of each polyp, the

program analysed all images, and the final conclusion regarding the polyp was based on the averaged results. Then the results of the AI-DSS were compared to the final histology. Thus, we achieved 82.35% accuracy with 81.82% sensitivity, 83.33% specificity, 90% PPV, 71.43% NPV.

Conclusion: AI-DSS is able to predict the advanced histology of the polyp and differentiate between adenomas with low- and high-grade dysplasia with high accuracy. This software can support everyday clinical decisions and even the training of endoscopists. Due to the nature of deep learning neural networks, accuracy of the software could be further increased with a higher number of polyp images. The software does not require medical expertise.

Disclosure: Nothing to disclose

OP109 ENDOSCOPIC SUBMUCOSAL DISSECTION FOR COLORECTAL MALIGNANT POLYPS. RESULTS OF A PROSPECTIVE MULTICENTER WESTERN COHORT

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Introduction: Endoscopic submucosal dissection (ESD) allows *en bloc* resection of early gastrointestinal tumours regardless of size, with an *en bloc* resection rate in colon around 91.7%[1], thus allowing an adequate histological examination. This is important in the resection of malignant polyps (those who invade the submucosal layer) as they carry a risk for LNM, that can be stratified in high or low risk according to the histological features.

Aims & Methods: Our aim was to describe the feasibility, technical success, en bloc resection rate and complications of ESD for colorectal malignant polyps in a western cohort.

We analyzed all the cases of colorectal ESD performed in polyps with histology showing submucosal or deeper invasion (at least pT1), that were recruited in 19 centers between January 2016 and January 2019 in a prospective Spanish study.

Stata software was used for statistical analysis. Categorical data were expressed as frequencies and percentages. Comparative data according to location was analyzed. Categorical data was compared using Pearson´s chi-squared test, and cuantitative data was compared with T student test.

Results: From a total of 851 colorectal ESDs, 58 (6.8 %) cases with submucosal or deeper invasion were evaluated.

Mean age of patients was 68 years old, being male 72%. ASA score was I-II in 39 patients, III in 18 and IV in 1.

The lesions were located in rectum n=21 (36%), sigmoid n=10 (17%), descending colon n=8 (13.7%), splenic flexure=2 (3.4%), transverse colon n=4 (7%), hepatic flexure n=3 (5%), ascending colon n=7 (12%), and cecum n=3 (5%).

Complete resection of the lesion was achieved in 48 cases (82.7%). The *en bloc* resection rate was 70.7% (n= 41). When comparing the results of ESD for malignant polyps according to location, the *en bloc* resection rate was

higher in the rectosigmoid compared to the rest of the colon (83.9% vs 55.5% respectively, p=0.02).

There were 10 (17%) aborted procedures due to technical reasons (2/10), perforation (2/10) or muscle retracting sign (6/10).

The mean size of the resection was 38.3mm x 30.7mm (CI 95% 33.9-42.7 for major axis, and 26.1-35.2 for minor axis).

Submucosal fibrosis was absent (F0) in 18 cases, it was mild (F1, white web-like structure in the submucosa) in 17 cases and there was severe fibrosis (F2, "white submucosa") in 23 cases (39.66%).

There were 6 (10%) intraprocedural bleeding, 3 (5%) delayed bleeding, 10 (17%) intraprocedural perforations and 2 (3.4%) delayed perforations.

There were a total of 30 (51.7%) surgeries: 19 (63% of surgeries) due to high risk histologic features, 10 for aborted ESD (mainly due to muscle retracting sign as discussed before), and 1 for delayed perforation.

There were 2 pT2 and 1 pT3 cases diagnosed after surgery due to aborted ESD.

LNM were positive in 6 cases (5 pT1N1 and 1 pT2N1).

Regarding the need for surgery, it was much lower after ESD in the rectum than in the colon, with 8 surgeries (38%) in rectum vs 22 surgeries (59%) in colon, p= 0.03.

Conclusion: ESD for malignant polyps in the distal colon (sigmoid and rectum) shows better results compared to more proximal locations.

In a Western population, the *en bloc* resection rate for malignant polyps proximal to sigmoid location is lower than expected for colorectal ESD according to current literature.

LST Granular	G. Nodular Mixed =18 G. Homogeneous = 2
LST NonGranular	NG Pseudodepressed=15 NG Flat = 4
0-Is	13
0-Ip	1
0-IIc or 0-IIc component	4
0-IIb	1

[Morphology of the lesions]

References: Fujiya M, Tanaka 1, Dokoshi T, et al. Efficacy and adverse events of EMR and endoscopic submucosal dissection for the treatment of colon neoplasms: a meta-analysis of studies comparing EMR and endoscopic submucosal dissection. Gastrointest Endosc 2015;81:583-95
Disclosure: Nothing to disclose

OP110 ENDOSCOPIC FULL-THICKNESS RESECTION IS FEASIBLE FOR T1 COLORECTAL CANCERS - A DUTCH NATIONWIDE PROSPECTIVE COHORT STUDY

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Introduction: For T1 colorectal cancer (CRC), endoscopic resection is an attractive alternative for surgical resection due to substantially lower morbidity and mortality. However, conventional polypectomy for T1 CRC often leads to suboptimal histologic risk assessment and colonic ESD is challenging. Exact risk stratification with certainty about resection margin status and the presence of histologic risk factors for lymph node metastasis (LNM) is crucial for further decision making. Allowing transmural resection, endoscopic full-thickness resection (eFTR) could potentially serve as a valid diagnostic and therapeutic primary treatment option for T1 CRCs as well as completion treatment after previous incomplete resection of low-risk T1 CRCs.

Aims & Methods: The aim of this study was to determine the technical success, clinical success and safety of eFTR for T1 CRCs. In our prospective multicenter cohort of all eFTR procedures performed between September 2015 and April 2019 in 21 Dutch hospitals, we evaluated all T1 related procedures. This included primary treatment for lesions with optical diagnosis of T1 CRC and secondary treatment after previous (potentially) incomplete resection of T1 CRC. To determine technical success, we studied the number of macroscopic complete (no macroscopic evidence of residual lesion judged by the endoscopist) en bloc resections. Other outcomes were clinical success (R0 resection with tumor-free lateral and deep resection margins and possibility of discrimination between high-risk versus low-risk T1 CRCs) and adverse events. A lesion was defined as high-risk if one of the following risk factors was present: poor differentiation, lymphatic or vascular invasion, deep submucosal invasion (≥1000 μm) or incomplete resection (R1/Rx resection).

Results: We included 247 procedures. Indications for eFTR were primary resection for suspected T1 CRCs (n=81) and re-resection after previous incomplete resection of T1 CRCs (n=166). Technical success of all procedures was achieved in 85.4% (n=211/247). No histopathology was obtained in 6.1% (n=15/247), because the lesion either could not be reached or retracted into the cap. In the remaining 232 cases amenable to eFTR, R0 resection rate was 88.8% (n=206/232). Final histopathology confirmed residual adenocarcinoma in 33.2% (n=77/232). Subgroup analysis showed adenocarcinoma in 85.5% (n=65/76) after primary resection and in 7.7% (n=12/156) after previous incomplete resection. Discrimination between high-risk versus low-risk T1 CRC was achieved in 97.4% (n=75/77). Low-risk T1 CRC was identified in 22.1% (n=17/77) and high-risk T1 CRC in 75.3% (n=58/77). In 46.6% (27/58) of the high risk cases, deep submucosal invasion was identified as the only risk factor for LNM. Additional surgery was performed in 41.4% (n=24/58) of the high risk cases, of which 87.5% (n=21/24) had no residual cancer or LNM. Endoscopic surveillance strategy was initiated in 46.6% (n=27/58). The overall adverse event rate was 8.5% (n=21/247), with emergency surgery in 2.4% (n=6/247) for 2 immediate and 4 delayed perforations.

Conclusion: eFTR is a feasible and safe treatment for T1 CRCs, both as primary treatment and secondary treatment after previous incomplete resection. eFTR delivers optimal histology for risk assessment and leads to R0 resection rate in 88.8% overall, avoiding surgery in most cases. Further studies focussing on long term outcomes need to clarify the role of eFTR for scars after previous incomplete resection and as a primary treatment method for deep submucosal invasive T1 CRC.

Disclosure: Nothing to disclose

OP111 LONG-TERM OUTCOMES IN 944 T1 COLORECTAL CANCER AFTER ENDOSCOPIC AND SUGICAL RESECTION

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Introduction: Lymph node metastasis (LNM) occurs in 6-12% of patients with T1 colorectal cancer (T1-CRC). In some studies, the depth of submucosal invasion, histological type, lymphovascular invasion, and tumor budding have been reported as risk factors for nodal metastasis, and the remainders were classified into high-risk group. Recent studies reported that invasion depth only has no clinical impact to LNM of CRC. pT1b CRCs have a good prognosis if treated along guidelines. However, the high rate of recurrence has been reported in rectal pT1b CRCs when they were followed it up without additional surgical resection (SR). Therefore we aim to examine the recurrence rate and clinicopathological features associated with invasive recurrence after endoscopic resection for T1 CRC, in particular in rectum.

Aims & Methods: A total of 944 patients with T1 CRCs treated by endoscopic resection (ER) or SR from January 2000 to April 2018 at our unit were analyzed retrospectively. The exclusion criteria were as follows; 1) patients with FAP, HNPCC, or IBD, 2) patients with active malignant diseases in any other organs, 3) patients with synchronous or metachronous advanced colorectal cancer, 4) patients with T1a-CRCs treated by primary SR and 5) follow up periods. We evaluated the invasive recurrence rate and clinico-pathological features of 883 T1-CRCs.

Results: A total of 883 patients were involved according to criteria of this study (median follow-up period: 76 months). Of 883 patients, 246 patients underwent ER alone, 60 of 246 patients were followed-up without additional SR. 251 patients underwent ER+SR, and 386 patients underwent primary SR. 246 patients in ER alone were divided into 186 patients in ER-L (Low risk) and 60 patients in ER-H (High risk). 637 patients in SR (ER+SR and primary SR) were divided into 281 patients in SR-L (Low risk) and 356 patients in SR-H (High risk). In ER alone, 2 patients were cancer death. The outcomes of ER-L and ER-H were that 0% vs 8.3% (5 of 60 patients) in recurrence rate (RR). ER-H was tended to be higher in recurrence than ER-L. In 5 patients with recurrence in ER-H, tumor location were all rectum. In 637 patients in ER+SR and primary SR, Synchronous LNM occurred in 10.5%. The outcomes of SR-L and SR-H were that 3.9% (11 of 280 patients) vs 15.7% (56 of 357 patients). SR-H was tended to be higher in Synchronous LNM than SR-L, and a sub-analysis showed that primary treatment and lymph invasion and vascular invasion were equivalent to the risk factors of Synchronous LNM ($p< 0.01$). In SR, 4 patients were cancer death. The outcomes of SR-L and SR-H were that 0% vs 2.2% (8 of 357 patients) in RR. Synchronous LNM was the only factor that contributed significantly to increase recurrence in SR ($p< 0.01$).

Conclusion: pT1b CRCs have a good prognosis if treated along guidelines. The invasive recurrences for T1 CRC in our study was 1.5% overall. Our results suggested that a risk factor of recurrences in ER alone was only rectum. Therefore surgery should be considered in addition to ER regardless of the risk factors in pT1b rectal CRCs. We didn't experience recurrence in SR-L, but experienced 8 recurrences (2.2%) in SR-H. So careful follow-up is required even in high-risk group undergoing surgery that included lymph node dissection.

Disclosure: Nothing to disclose

OP112 FULL-THICKNESS RESECTION BY USING LAPAROSCOPY ENDOSCOPY COOPERATIVE SURGERY (LECS) TO OVERCOME THE LIMITATIONS OF ENDOSCOPIC RESECTION FOR COLORECTAL NEOPLASMS

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Introduction: We established a new procedure, laparoscopy endoscopy co-operative surgery (LECS) applied with endoscopic submucosal dissection (ESD) technique to overcome the limitations of endoscopic resection for colorectal tumors. In this report, we clarify the feasibility of performing a safe full-thickness resection with an adequate surgical margin by LECS procedure.

Aims & Methods: We performed full-thickness resection for 18 colorectal tumors in 18 patients (male: female 11:7; mean age, 65.8 years) by LECS. The clinicopathological outcomes of these 18 cases and the feasibility of full-thickness resection were evaluated retrospectively.

The indications for LECS were as follows: 1) intramucosal cancer and adenoma (Vienna Classification; Category 3, 4) accompanied by severe fibrosis in the submucosal layer (tumor recurrence after endoscopic or surgical resection), 2) intramucosal cancer and adenoma involving the diverticulum or appendix, and 3) intraluminal or intramural growth-type submucosal tumors.

Results: We successfully performed full-thickness resection using LECS in 18 cases (intramucosal cancer [n=6], adenoma [n=10], schwannoma [n=1], and gastro-intestinal stromal tumor [GIST] [n=1]. The mean tumor size was 22.2mm (range, 8-41mm). LECS was successfully performed in 18 all cases without conversion to open surgery; the R0 rate was 100%. The indications for LECS were as follows: involvement of the appendix (n=7), tumor accompanied by severe fibrosis (n=5), involvement of a diverticulum (n=3), submucosal tumor (n=2), and poor endoscopic operability (n=1). We experienced no adverse events (e.g., grade 3 or more of Clavien-Dindo classification), and the mean hospital stay was 6.4(range, 4 to 12) days. All patients who were followed for ≥6 months (mean, 37.3 months; range, 11-80 months) showed no residual/local recurrence. Thus, the use of the ESD technique in LECS, can achieve a safe oncological margin in cases involving colorectal tumors.

Conclusion: LECS was a safe, feasible, minimally-invasive procedure that achieved the full-thickness resection of colorectal tumors and which showed excellent clinical outcomes.

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Disclosure: Nothing to disclose

Perianal fistula in Crohn's disease
16:00-17:30 / F3

OP113 STEP-UP FECAL MICROBIOTA TRANSPLANTATION: TARGETING COMPLAINTS IN CROHN'S DISEASE

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Introduction: The benefits of fecal microbiota transplantation (FMT) in Crohn's disease (CD) is unclear.

Aims & Methods: This real-world study aims to evaluate FMT's potential therapeutic targets in CD. FMT for CD as a registered trial (NCT01793831) was performed from October 2012 to December 2017. Clinical response was assessed at 1 month and 3 months after step-up FMT. We defined seven major complaints and recorded them as 1 (yes) or 0 (no) in the long-term follow up for each patient, which include abdominal pain, diarrhea, hematochezia, fever, steroid-dependence, enterocutaneous fistula, active perianal fistula. Step-up FMT strategy includes: step 1: single FMT; step 2: ≥ 2 FMTs; step 3: FMT(s) followed by immunosuppressant or enteral nutrition. Potential predictors for non-response to FMT were analyzed.

Results: Totally 174 patients completed follow-up. Median follow-up was 28 (IQR 12-47) months. 74.7% (130/174) and 67.2% (117/174) of patients achieved clinical response at one month and three months after FMT. The total complaint score decreased significantly at 3, 6, 12, 24, 36 months after FMT. 71.9% (100/139), 68.3% (95/139), 64% (89/139), 56.5% (65/115), and 52.2% (47/90) of patients had abdominal pain improvement at 3, 6, 12, 24, 36 months after FMT, respectively. 61.4% (89/145), 57.9% (84/145), 53.8% (78/145), 44.4% (52/117), 42.2% (38/90) of patients had diarrhea improvement at 3, 6, 12, 24, 36 months after FMT, respectively. 55% (11/20) of steroid-dependent patients were able to discontinue steroids after FMT. Disease duration > 2 years (p = 0.011) was associated with poor response to FMT.

Conclusion: Step-up FMT strategy could be an effective therapeutic option for CD-related complaints.

Disclosure: Nothing to disclose

OP114 PERIANAL LESIONS IN CROHN'S DISEASE AT DIAGNOSIS: ANALYSIS OF EPIMAD REGISTRY FROM 2007 TO 2012 IN A POPULATION BASED-STUDY

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Introduction: Perianal lesions (PL) affect up to 26% of Crohn´s disease (CD) patients in the first two decades after diagnosis and are associated with poor outcomes.[1] Data concerning evaluation and clinical management of PL at diagnosis are limited.[2,3]

Aims & Methods: To perform a population based-study to characterise CD patients presenting with PL at diagnosis and describe their initial diagnosis and assoicated therapeutic management.

All CD patients diagnosed between 2007 and 2012 were extracted from a French multi-centre prospective registry (EPIMAD Registry).[4] PL were defined as the presence of fistula or abscess at CD diagnosis. For all patients with PL at diagnosis, complementary data were collected via a standardised questionnaire through examination of gastroenterologist and surgeon records by a university proctologist. The following variables were described: clinical examination, perianal resonance imaging (magnetic resonance imaging [MRI]), echo-endoscopy, examination under general anesthesia (GA) and medical and/or surgical management within the first three months after CD diagnosis. Associated factors with PL at CD diagnosis were identified using a multivariate logistic regression.

Results: Among the 2,906 patients with CD diagnosed between 2007 to 2012, 116 (4%) had PL at CD diagnosis. Forty-four percent of patients were women, the median age at diagnosis was 25 years (IQR: 19-39) and 51 (45%) patients had a previous history of PL. Ileocolonic CD (L3) was predominant in 51 patients (47%); one patient (1%) had only perianal involvement and 51% of patients presented rectal lesions. Patients could present one or more PL: 81% had fistula (including 12 rectovaginal fistulas) and 58% had abscess; one patient (1%) had anal stenosis. An examination under GA was performed in 50% of patients, MRI in 34% of patients and an echo-endoscopy in 1 case. For initial therapeutic management of CD: 63% of patients received antibiotics, 42% 5-ASA and 47% steroids. Twenty-seven percent of patients received azathioprine, 29% anti-TNF therapy (87% infliximab) and 13 (12%) patients received combination therapy. Surgery was performed in 64 patients (57%) with 41 abscess drainages, 25 seton drainages, 16 fistulotomy and 2 diverting ileostomy. Multivariate logistic regression analysis found that male sex (p = 0.006), an absence of abdominal pain (p = 0.003) and colonic location (p = 0.02) were significantly associated with the presence of PL at CD diagnosis.

Conclusion: In this large population-based study, the proportion of patients with PL at CD diagnosis was 4%. Male sex, absence of abdominal pain, and colonic location were associated with the presence of PL at CD diagnosis. Surgery was performed in over half of the cases. An immuno-

suppressant, anti-TNF or combination therapy was respectively prescribed for 27%, 29% and 12% of cases, reflecting the current approach for treating CD patients with PL. Further exploration of treatment options after CD diagnosis is warranted.

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Shifting paradigms in oesophageal cancer management

16:00-17:30 / Barcelona

OP115 THE DETECTION OF ESOPHAGEAL SQUAMOUS CELL CARCINOMA IN ENDOSCOPIC MOVIES BY THE ARTIFICIAL INTELLIGENCE USING CONVOLUTIONAL NEURAL NETWORKS

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Introduction: Esophageal cancer is the eighth most common cancer worldwide, and the sixth cause of death. When esophageal cancer is diagnosed in advanced stage, it will require highly invasive treatments and its prognosis will be poor, thus it is important to detect in early stage. In recent years, artificial intelligence (AI) using deep learning has made remarkable progress in various medical fields, and we had reported the great ability of artificial intelligence to detect esophageal cancer including squamous cell carcinoma (SCC) and adenocarcinoma in still pictures.

Aims & Methods: We demonstrated the diagnostic ability of AI to detect superficial esophageal SCC in movies.

We retrospectively collected 8428 training still images of esophageal cancer that was histologically proven to be SCC or adenocarcinoma, including 6026 white light imaging (WLI) and 2402 narrow band imaging (NBI), from Cancer Institute Hospital, Tokyo, Japan from 2014 to 2017. These images were used to develop deep learning through a convolutional neural networks (CNNs) to detect esophageal cancer.

Then we prepared 80 test movies of 40 patients both in WLI and in NBI, including 20 patients with 22 superficial esophageal SCC and 20 patients with no esophageal cancer to evaluate the accuracy of AI diagnosis. All cases of esophageal cancer were confirmed to have no other cancer using WLI, NBI, iodine staining, and follow-up endoscopy after the treatment.

In the movies, we inserted endoscopy from cervical esophagus to esophagogastric junction in the speed of 2cm /sec. AI diagnosed SCC when the lesions were detected for 0.06 sec.

Results: The AI correctly diagnosed 81.8% (18/22) of esophageal cancers both in WLI and in NBI. Of them, 45.4% (10/22) of cancers were diagnosed with WLI and 77.2% (17/22) with NBI. In contrast, the AI misdiagnosed 31 non-cancerous lesions, which caused low positive predictive value (PPV) (36.7%). However, these sensitivity and PPV in movies were not so different from in still pictures (sensitivity 98%, positive predictive value 54%).

The misdiagnosed lesions included scars of endoscopic resection (3 lesion), esophagogastric junction (7 lesions), shadows of esophageal lumen (15 lesions). Inflammation of esophageal mucosa (6 lesions). This can be corrected by deep learning about each normal structure and benign lesion, which will surely reduce false positives and improve the PPV significantly. Furthermore, because endoscopists will never think esophagogastric junction or shadows of esophageal lumen as cancer, considering the practical use of this system, this PPV is not so high but acceptable.

The missed cancers were less than 1 cm in size or in background inflammation. It was very difficult to detect these lesions with WLI or NBI even by experienced endoscopist in the movies, because of their speed and indistinguishable lesions.

Conclusion: AI could detect superficial esophageal SCC in movies with high sensitivity, same as in still pictures. This system would well support endoscopists in real time during endoscopic examinations in the near future.

Disclosure: Nothing to disclose

OP116 WITHDRAWN

OP117 CLINICAL EFFICACY OF THE ESOPHAGEAL TRIAMCINOLONE ACETONIDE-FILLING METHOD: A NOVEL STENOSIS-PREVENTIVE PROCEDURE AFTER EXTENSIVE ESOPHAGEAL ENDOSCOPIC SUBMUCOSAL DISSECTION

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Introduction: Endoscopic submucosal dissection (ESD) for extensive esophageal carcinomas causes severe esophageal stenosis requiring endoscopic balloon dilation (EBD), but a standard prophylactic treatment has not been established. As a novel procedure for the local steroid administration, we developed the esophageal Triamcinolone Acetonide (TA)-filling method. This method fills the esophagus with a saline solution containing 80 mg TA for a certain time to infiltrate the drug evenly into extensively resected surface [1].

Aims & Methods: The aim of this study is to analyze the clinical efficacy and safety of the esophageal TA-filling for stenosis-prevention after extensive esophageal ESD. We enrolled a total of 44 consecutive patients with esophageal cancer requiring subcircumferential ESD, which is three quarters of the circumference or more horizontal resection but not circumferential. They had no previous treatment for the lesions, such as endoscopic resection or radiation therapy. Esophageal TA-filling was performed the day after ESD and one week later, and follow-up endoscopy was performed every 2 weeks until complete re-epithelialization. We treated severe stenosis preventing endoscope passage with EBD and additional TA-filling, and mild stenosis allowing endoscope passage with additional TA-filling only.

Primary endpoint was the incidence of severe stenosis, which is reportedly 66% to 75% after subcircumferential ESD without any preventive procedure [2-4]. Setting the clinically meaningful preventive effect to 30% incidence reduction, we determined lower boundary of the target incidence value at 40%. Secondary endpoints were total number of EBDs, execution rate of additional TA-filling, time to initial stenosis and complete re-epithelialization without stenosis, dysphagia score, and adverse events. Dysphagia score was estimated based on 5 grades: each grade of 0, 1, 2, 3, and 4 denoted the ability to eat a normal diet, some solid foods, only semisolid foods, liquids only, and nothing, respectively [5]. The horizontal resection range of ESD was divided into three grades (grade 1; ≥9/12 and < 10/12, grade 2; ≥10/12 and < 11/12, grade 3; ≥11/12 but not circumferential), and analyzed statistically for correlation with the endpoints.

Results: All lesions in 44 enrolled patients were resected en bloc. The horizontal resection grade was grade 1 in 19 patients, grade 2 in 14, and grade 3 in 11. All patients concretely followed the study protocol. The median size of the lesions and the resected specimens was 38 (22-70) mm and 52 (32-85) mm, respectively.

The incidence of severe stenosis was 6.8% (3/44; 1.4%-18.6%), which was sufficiently lower than target incidence value, showing a statistically acceptable stenosis-preventive effect. EBD was performed median 2 (1-3) times in these 3 patients. 10 patients demonstrated mild stenosis. Time to initial stenosis was median 3 (3-5) weeks, and rate of additional TA-filling was 29.5% (13/44); 5.2% (1/19) for grade 1 resection, 28.5% (4/14) for grade 2, and 63.6% (7/11) for grade 3 (P< .05). Median time to complete

re-epithelialization was 6 weeks (range, 5-14). Dysphagia score deteriorated to 1 to 2 in 31.8% (8/44), but showed a final score of 0 after complete re-epithelialization in 93.1% (41/44). No severe adverse events occurred.

Conclusion: The esophageal TA-filling method is highly effective for preventing severe stenosis after subcircumferential esophageal ESD, and the procedure is simple, feasible, and safe. However, grade 2 or higher resection has a high risk for stenosis.

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Disclosure: Nothing to disclose

OP118 COMPARABLE LONG-TERM OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION AND ESOPHAGECTOMY FOR EARLY ESOPHAGEAL SQUAMOUS CELL NEOPLASIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Endoscopic submucosal dissection (ESD) has become treatment of choice for superficial esophageal squamous cell neoplasia (ESCN) owing to the minimal invasiveness and high rate of complete resection. However, it is not clear whether ESD has similar long-term outcome compared to esophagectomy.

Aims & Methods: This study is aimed to evaluate the long-term outcomes of ESD with comparison of that to esophagectomy in patients with superficial ESCN. Comprehensive literature search and review were conducted using PubMed, Cochrane Library, and ProQuest databases through January 2019. The inclusion criteria were studies having > 20 cases and reporting survival data longer than 3 years with ESD for superficial ESCN. The exclusion criteria were those with incomplete data, or inability to extract data from mixture results with adenocarcinoma or other treatment modality. All extracted data were present and analyzed either with the original format or following appropriate calculation. The primary outcomes were overall survival, disease free survival and disease specific survival at 3 and 5 years. Secondary outcomes included adverse events, R0 resection, locoregional recurrence and distal metastasis. Meta-analyses were performed with hazard ratio (HR) for survival analysis and odds ratio (OR) for other variables using appropriate models and expressed with 95% confidence interval (CI).

Results: Total 21 eligible retrospective studies and 3796 patients were included. Among these, 5 studies compared ESD and esophagectomy and the others only reported the outcome with endoscopic treatment. For all the cases of ESD, the distribution of tumor invasion depth was 52.0% for m1-m2, 43.2% for m3-sm1 and 4.7% sm2 or deeper; however, up to 35.6% of cases had discrepancy between clinical and pathological stage. The mean R0 resection rate was 92%, and proportion of lesions exceeding 50% and 75% of circumference were 36.5% and 8.6%. The local recurrence, metachronous recurrence and nodal/distal metastasis rate of ESD were 1.8%, 8.5%, and 3.3% respectively. Severe complication of ESD included perforation (3.4%) and stricture (9.5%), although endoscopic treatment was successful in most cases, the median sessions of balloon dilatation ranged from 2-8 and more procedures were necessary for cervical lesions.

Overall survival and cancer specific survival at 5-year were 88% and 99%. In terms of the comparison between ESD and esophagectomy, there were no difference in the 5-year overall survival (HR = 0.66, 95% CI 0.39 - 1.11) and recurrence free survival (HR = 1.52, 95% CI = 0.74 - 3.09). Despite the similar perioperative mortality rate in both groups, the adverse events were remarkably lower in ESD group (19.8% vs. 44.0%, OR = 0.29, 95% CI = 0.19 - 0.43).

Conclusion: For superficial ESCN, ESD is highly effective with less morbidity than esophagectomy. It should be considered as the first line treatment in centers with expertise.

	Yamauchi (2017)	Yuan (2018)	Min (2018)	Takeuchi (2018)	Zhang (2018)
Case Number	ESD = 54, OP = 51	ESD = 69, OP = 47	ESD = 120, OP = 120	ESD = 73, OP = 54	ESD = 322, OP = 274
Lesion size (Median, mm)	Not recorded	ESD = 45.9, OP = 52.1	ESD = 17, OP = 16.4	ESD = 20, OP = 32	ESD = 26, OP = 20
Lesions > 3/4 circumference	Not recorded	ESD = 18, OP = 23	Not recorded	ESD = 13, OP = 22	Not recorded
R0 resection (%)	Not recorded	ESD 92.7%, OP = Not recorded	Not recorded	ESD 78.1%, OP 88.9%	ESD 91.9%, OP 98.2%
Adverse events (%)	ESD 29.6%, OP = 49.1%	ESD 43.4%, OP = 72.3%	ESD 18.5%, OP = 55.5%	ESD 10.9%, OP = 38.8%	ESD 15.8%, OP = 31.3%
M1-M2 invasion	Not recorded	ESD = 52, OP = 24	ESD = 64, OP = 63	ESD = 10, OP = 7	ESD = 107, OP = 24
M3-Sm1 invasion	Not recorded	ESD = 17, OP = 23	ESD = 35, OP = 37	ESD = 41, OP = 18	ESD = 215, OP = 250
Sm2 or deeper	Not recorded	ESD = 0, OP = 0	ESD = 21, OP = 20	ESD = 22, OP = 29	ESD = 0, OP = 0
Lymphovascular invasion	Not recorded	ESD = 1, OP = 0	ESD = 16, OP = 9	ESD = 17, OP = 31	ESD = 11, OP = 36

[Baseline characteristics in studies comparing the outcomes of ESD and esophagectomy]

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Disclosure: Nothing to disclose

OP119 LASTING SYMPTOMS AFTER ESOPHAGEAL RESECTION (LASER) - EUROPEAN MULTI-CENTER CROSS-SECTIONAL STUDY

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Introduction: Long-term functional outcomes and the associations to health-related quality of life (HRQOL) after esophagectomy is largely unknown.

Aims & Methods: This multi-center European study aimed to identify the most prevalent symptoms, and those with the greatest impact upon HRQOL among patients surviving more than one-year after esophagectomy for cancer, and to develop a clinically relevant tool.

Twenty European centers participated in the study. Patients who underwent esophagectomy for esophageal cancer between 2010 and 2015, and were disease-free at least one year postoperatively were invited to complete the LASER questionnaire, EORTC-QLQ30 and OG25. LASER questionnaire items that were associated with a poor HRQOL as identified by EORTC-QLQC30 and OG25 were identified by multivariable linear and logistic regression analysis and combined to form a tool, which was tested using receiver operating characteristics curve analysis.

Results: A total of 876 of 1081 invited patients responded to the questionnaire, giving a response rate of 81%. Of these, 66.9% stated in the last 6 months they had had symptoms associated with their esophagectomy and 52.4% of patients had sought medical treatment for their symptoms. Ongoing weight loss was reported by 10.4% of patients while 32.4% was struggling to maintain their body weight, and 18.8% of patients required supplemental oral nutrition. Only 13.8% of patients returned to work with the same activities as before.

Three LASER symptoms in multivariate analysis were correlated with poor HRQOL; pain on scars on chest (Odds ratio (OR) 1.27; 95% CI 0.97-1.65), low mood (OR 1.42; 95% CI 1.15-1.77) and reduced energy or activity tolerance (OR 1.37; 95% CI 1.18-1.59). The areas under the curves for the development and validation datasets were 0.81±0.02 and 0.82±0.09 respectively.

Conclusion: The three key symptoms identified in this study should be further validated, and could be used in clinical practice to identify patients who require increased long-term term support in survivorship.

Disclosure: Nothing to disclose

OP120 ENDOSCOPIC THERAPY REPLACES SURGERY FOR CLINICAL T1 OESOPHAGEAL CANCER IN THE NETHERLANDS: A NATIONWIDE POPULATION-BASED STUDY

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Introduction: Oesophageal cancer is the eight most common cancer worldwide and the sixth leading cause of cancer related mortality. The incidence of oesophageal cancer increases worldwide. Recent studies showed comparable survival after endoscopically or surgically treated oesophageal cancer in the United States and Asia. Survival after endoscopic resection or surgery of oesophageal cancer has not been investigated in a Dutch population.

Aims & Methods: This study will provide insight into the treatment and survival for patients with clinical T1 oesophageal and cardia cancer over a fifteen-year period between 2000 and 2014 in the Netherlands. Data were obtained from the nationwide population-based Netherlands Cancer Registry (NCR). All patients diagnosed with clinical in situ and T1 oesophageal or cardia cancer without lymph node or distance metastasis during the study period were extracted from the NCR. Primary outcome parameters were the trends in treatment modalities over time and relative survival of each treatment regime.

Results: A total of 1822 patients were diagnosed with a clinical in situ or T1 oesophageal or cardia cancer in the Netherlands between January 2000 and December 2014. Patients with metastatic disease (n=285) and/or unknown lymph node metastasis (n=513) were excluded. In total of 1020 patients were included. Almost half of the patients receive endoscopic therapy (44.9%), around a third underwent surgery (35.1%) and twenty per cent underwent other treatment (12.3%) or no treatment et al (7.7%). Patients who underwent surgery were significantly younger than patients treated with endoscopic therapy (median 64 years vs. 67 years; p < 0.0001). There were significantly more oesophagus carcinoma resected with endoscopic therapy compared to cardia carcinoma (96.1% vs. 79.6%; p < 0.0001) and the group with endoscopic therapy significantly had a clinical in situ tumour more often (p< 0.0001). The proportion of patients who received endoscopic treatment increased from 2.5% in 2000 to 64.1% in 2014. During the same period the proportion of patients who received surgery decreased from 57.5 to 17.1%.

The 5-year relative survival of all patients with clinical in situ or T1 oesophageal or cardia cancer was 70%. The 5-year relative survival after endoscopic therapy was 85% and after surgery 78%. Relative excess risk analyses showed significant difference in survival between patients in the endoscopic therapy group and patients in the surgery group after adjustment for age, sex, clinical TNM classification, morphology and tumour location (RER 1.80; CI interval 1.20-2.70; p< 0.001). In subgroup analysis, the 5-year relative survival of all patients with T1 oesophageal or cardia cancer was 66%. The 5-year relative survival after endoscopic therapy was 81%, after surgery 73%. Relative excess risk analyses for the subgroup T1 oesophageal or cardia cancer showed significant difference in survival between patients in the endoscopic therapy group and patients in the surgery group after adjustment for age, sex, clinical TNM classification, morphology and tumour location (RER 1.71; CI interval 1.14-2.55; p< 0.01).

Conclusion: Our results demonstrate an increase in endoscopic resections and a decrease of surgical treatment for in situ and T1 oesophageal/cardia cancer between 2000-2014 in the Netherlands. The relative 5-years survival after endoscopic treatment is high (85%) and significantly higher when compared to surgery (78%) which is different from previous studies.

Disclosure: Nothing to disclose

Different faces of microbiota along the digestive tract

08:30-10:00 / A1

OP121 COMPOSITION AND FUNCTION OF GUT MICROBIOTA AFFECTS THE RESPONSE RATE AND SURVIVAL OF MELANOMA PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Introduction: Immune checkpoint inhibitors (ICIs) have demonstrated strong clinical benefit in patients with irresectable cutaneous melanoma, with now an increased 1-year survival of up to 70%. Approximately 40% of patients, however, do not respond to ICI therapy, while 25% of patients develop serious adverse events. Previous studies in animal models and small-scale human studies identified a link between composition of gut microbiota and response to ICI therapy, but these studies showed low concordance and did not take into account common confounders such as patient sex, age, BMI as well as medications that alter composition of gut microbiom.

Aims & Methods: The aim of this study was to assess the effect of composition and function of gut microbiota on the response rate and survival of ICI-treated melanoma patients, while taking into account known factors that influence the composition of gut microbiome.

This study employed a strictly protocolized collection procedure to obtain high-quality fresh-frozen stool samples from 25 patients with metastatic melanoma before the start of ICI therapy. Twelve of these patients went on to respond to ICI therapy. Metagenomic shotgun sequencing was used to obtain a high-resolution profile of the gut microbiome composition and biochemical pathways encoded in the microbiome. Composition (192 bacterial taxa) and function (260 pathways) of microbiota were tested for association with ICI response, overall survival, and progression-free survival using multivariate associations with linear models (implemented in MaAsLin toolkit). These models included known factors that influence gut microbiota: age, sex, BMI, tumor M-stage (AJCC version 8), LDH-level (> 250 U/L vs. < 250 U/L), previous anti-melanoma therapy, type of therapy (anti-PD1 or anti-PD-1/anti-CTLA-4 combination), antibiotic use (yes/no), proton pump inhibitor use (yes/no) and colitis during ICI therapy (yes/no, any grade).

Results: We observed no differences in alpha-diversity and bacterial prevalence between responders and non-responders (p-value > 0.05). Multivariate analysis identified 68 taxa and 17 microbial pathways that showed differential abundance between responders and non-responders (FDR < 0.05), including previously reported associations with *Veillonella parvula, Bacteroides thetaiotaomicron, Akkermansia muciniphila, Escherichia coli* and *Actinomyces odontolyticus.* In addition, multiple taxa were associated with overall or progress-free survival, including *Streptococcus parasanguinis* (Overall survival HR: 6.9), Peptostreptococcaceae Family (Overall survival HR: 0.11, Progression-free survival HR: 0.18) and *B. massiliensis* (Progression-free survival HR: 3.79).

Conclusion: This study shows that composition and function of the gut microbiom influences the response to immune checkpoint inhibitors (ICIs) in patients with cutaneous melanoma. This suggests that manipulation of gut microbiota might be viable strategy to improve the response to ICIs.

Disclosure: Nothing to disclose

OP122 THE EFFECTS OF F. PRAUSNITZII ON CANDIDA ALBICANS GROWTH AND PATHOGENICITY AND RELATED MECHANISMS

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Introduction: Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and crohn´s disease (CD). The pathogenesis of the disease is complex. It is believed that genetic, environmental, intestinal microbes and immune factors are involved in the occurrence and development of IBD, especially the intestinal flora disorder has become a research hotspot in recent years. The reduction of Faecalibacterium prausnitzii (F. prausnitzi) and the increase of the opportunistic pathogen Candida albicans are one of the important features of intestinal flora disorder in patients with IBD. Many studies have shown that Faecalibacterium prausnitzii and its supernatant can improve intestinal inflammation, regulate dysbacteriosis, maintain the homeostasis of the intestinal microenvironment, etc. Intestinal bacteria and fungi influence each other in many ways.Therefore, exploring the interactions between intestinal bacteria and fungi and its role in the development of IBD is of great significance to understand the intestinal micro-ecological environment.

Aims & Methods: F. prausnitzii and its supernatant were co-cultured with Candida albicans in vitro to observe the effects of F. prausnitzii and its supernatant on Candida albicans growth, hyphal and hydrolytic enzyme production capacities. To investigate whether F. prausnitzii and its supernatant can inhibit the growth and reproduction of Candida albicans by stimulating the expression of inflammasomes (NLRP6) and antimicrobial peptides (LL-37/BD-2/BD-3) and tight junction proteins(ZO-1, occludin) in intestinal epithelial cell.

Results:
1. It was found that the amount of C.albicans with F. prausnitzii and its supernatant co-cultured were significantly decreased compared with the control group by plate counting method.
2. It was found that the expressions of Hyphae-Specific Genes (BCR1, CDC24b, ECE1, HGC1, HWP1 and EFG1) and production of hyphal phase CA were inhibited and hydrolytic enzyme production capacities (Ep, Sap, and Ha)were dcreased when F. prausnitzii and its supernatant were co-cultured with CA.
3. Western blot analysis showed that F. prausnitzii and its supernatant may inhibit the growth of CA by stimulating IEC secretion of NLRP6, ASC, IL-1β/IL-18 and antibacterial peptides BD-2 and BD-3, but caspase-1 and LL-37 had no significant effect.
4. Western blot analysis showed that F. prausnitzii and its supernatant may enhance the intestinal mucosal barrier function by promoting the expression of IEC tight junction protein (occludin, zo-1).

Conclusion: F. prausnitzii and its supernatant have inhibitory effects on CA. The direct effects are as follows: inhibiting CA growth and reproduction, inhibiting the expression of CA Hyphae-Specific Genes (BCR1, CDC24b, ECE1, HGC1, HWP1 and EFG1), reducing production of hyphal phase CA, reducing the production of CA hydrolytic enzyme production capacities (Ep, Sap, and Ha). The indirect effect is by stimulating the expression of NLRP6, ASC, IL-1β/IL-18, BD-2, BD-3 and the tight junction proteins occludin and ZO-1 in IEC to inhibition the growth of CA.

Disclosure: Nothing to disclose

OP123 ALTERATIONS IN FUNGAL MICROBIOTA AFTER CHOLECYSTECTOMY IN PATIENTS

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Introduction: Fungal microbiota of the gastrointestinal tract is affected by many factors, such as pH, diet. After cholecystectomy, the gut physico-chemical environment changes, and the fungal microbiota may change accordingly. Notably, few reports focused on gut fungal microbiota after cholecystectomy. Therefore, we tended to investigate the differences and composition characteristics of gut fungal microbiota in patients after cholecystectomy.

Aims & Methods: We called on 104 people for this study, including 52 healthy controls (HC) and 52 post-cholecystectomy (PC) patients. 9 of the 52 PC patients accompanied with precancerous lesions and colorectal cancer (preCA_CRC). Fecal samples of all patients were collected for internal transcribed spacer (ITS) 3-4 rDNA amplicons sequencing to profile the overall structure of the fecal fungal microbiota. Based on the Operational Taxonomic Units (OTUs), fungal composition and the correlation analysis with environmental factors were analyzed, respectively.

Results: Fungal richness in PC patients was similar to the one in HC, but the composition was quite different. The abundance of exogenous pathogens *Alternaria*, *Aspergillus* and opportunistic pathogen *Candida* increased significantly; while *Malassezia*, *Vanrija* and protective genus *Ganoderma* had a remarkable reduction in PC patients. *Indicspecies* analysis showed that *Candida glabrata* and *Aspergillus unassigned* were characteristic species of PC patients, and *Candida albicans* was a characteristic species of HC. Previous studies suggested that *Candida glabrata* displayed more virulence factors, triggering host cell damage. The intraspecific competition of *Candida* may play an important role, and *Candida albicans* may suppress the growth of *Candida glabrata* in HC. About 10 kinds of indexes were collected as environmental factors for correlation analysis with fungal composition. As a result, we found that the duration after cholecystectomy was an independent factor, which mainly affected the composition of the fungal microbiota. Addtionally, according to the presence or absence of precancerous lesions and CRC, we divided PC patients into preCA_CRC and nonCA. We found that preCA_CRC patients had lower fungal richness than the nonCA patients with statistical difference. In addition, most species were reduced in abundance, such as *Pleosporales unassigned*, *Sordariales unassigned* and *Gibberella zeae*.

Conclusion: Our study showed a specific gut fungal composition in PC patients. The duration after cholecystectomy was an important environmental factor which affected fungal microbiota. It was suggested that the duration after cholecystectomy may be associated with the risk of relative diseases. The abundance of *Candida glabrata* may be associated with clinical long-term outcome in patients after cholecystectomy.

Disclosure: Nothing to disclose

OP124 NEXT-GENERATION SEQUENCING OF FAECAL MICROBIOTA IN ULCERATIVE COLITIS PATIENTS TOGETHER WITH CONSANGUINEOUS AND NON-CONSANGUINEOUS RELATIVES

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Introduction: The gut microbiota has been recognized as a relevant fingerprint to predict the development of inflammatory bowel disease (IBD) like ulcerative colitis (UC). Accordingly, inter-individual variation in the gut microbial community may reflect inter-individual variation in the risk of developing IBD or other diseases.

Further recently, the Next-Generation Sequencing (NGS) has been validated for determining bacterial species in faecal samples. Essentially, NGS is a molecular biology sequencing technique for the precise identification and assessment of bacterial species.

Aims & Methods: This study was to analyse faecal bacteria and establish a biomarker of disease activity in ulcerative colitis (UC) patients. The subjects were 82 patients with UC together with 61 healthy relatives as controls. Twenty-five patients had active UC (group I) and 57 had quiescent UC; 29 with mild inflammation in the large intestine (group II), and 28 without inflammation (group III). The patients' relatives were consanguineous (group IV, n=33), and non-consanguineous (group V, n=28). Faecal bacteria between groups I to V were compared by the t-test. The Discriminant Score (Ds) for each subject together with the quantity and the diversity of each bacterial variant which had significant difference were calculated. The Discriminant analysis in all five groups was done for Species. We calculated the Discriminant Score (Ds) in each case.

Results: We obtained 1011 varieties of bacteria as Phyla, Class, Order, Family, Genera and Species. 648 bacteria that were not considered important were excluded. The t-statistic was done on 363 bacteria between groups I to V. Significant difference was calculated in 18 Species, 10 Genera, and 4 Families. The Discriminant analysis was done on these 18 Species from all groups. The Ds value showed an increasing tendency in this order: group I < group II < group III < group IV < group V. Significant difference was calculated for group I vs group II, vs group III, vs group IV, and vs group V (P< 0.01); group V vs group I, vs group II, vs group III (P< 0.01), indicating a strong association between gut microbial species and the development of UC.

The diversity of Bacteroides Genus was higher in group V, but the quantities of Bacteroides Genus and the Bacteroides fragilis were higher in group I. Further, in group I, the amount of Bacteroides fragilis was increased, but the diversity of Bacteroides Genus was decreased, while in group V, the opposite result was observed. It's very interesting, and the balance can be key point between Bacteroides fragilis and the diversity of Bacteroides in UC activity. Considering Genus, Anaerococcus, Finegoldia and Peptoniphilus were dramatically increased in group I compared with group V. All these bacteria belong to Clostridiales Family XI. Incertae Sedis.

Conclusion: In this study, we compared 363 bacteria between active UC patient (groups I) to control (group V), significant difference was calculated in 18 Species, 10 Genera, and 4 Families. To our knowledge, this is the first report on so many bacteria being related to UC activity. Additionally, the Ds related to UC, or otherwise absence of UC in the five groups. Potentially, Ds might be a clinically relevant biomarker of disease activity in UC. This is the first application of the NGS and the Ds to the study of microbiota in UC patients, consanguineous and non-consanguineous relatives. Moreover we could obtain a lot of interesting results the quantity and the diversity of the bacteria, especially Bacteroides. Clinical trial No: UMIN000017103

Disclosure: Nothing to disclose

OP125 STRAIN LEVEL ANALYSIS OF *KLEBSIELLA PNEUMONIA* SHOWS ASSOCIATION WITH INFLAMMATORY BOWEL DISEASE AND DISEASE SEVERITY

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Introduction: *Klebsiella pneumoniae* (KP) is a bacterium mainly found in the human oral cavity, but also inhabiting human skin and gut. While it is primarily associated with bacterial inflammation of the lung recent research has identified that KP-strains can cause ulcerative colitis (UC) -like pathology in germ-free mice. The prevalence and abundance of KP in IBD patients has not been studied in detail, and it is unknown if strain composition of KP differs between healthy individuals and IBD patients. It is also unclear which specific KP strains are associated to clinical characteristics of IBD such as disease severity and location.

Aims & Methods: Aim of this study was to identify if KP is associated with inflammatory bowel disease in humans, and to identify IBD-specific strains of KP.

The study utilised whole metagenome sequencing to study the gut microbiota of 447 IBD patients (291 Crohn's disease cases and 156 cases with ulcerative colitis) and 933 population-based controls. Species-level composition of metagenomes was determined by aligning metagenomic reads to

a database of unique marker genes, while KP strains were identified and quantified using reference-based approaches utilising genomes of 276 KP strains and 10,484 other bacterial species. Prevalence, relative abundance, and diversity of KP were tested against IBD-related clinical phenotypes, while unsupervised clustering and dimensionality-reduction approaches were used to study strain composition.

Results: Prevalence and relative abundance of KP were found to be significantly increased (p-value < $1.0*10^{-4}$) in the gut of IBD patients (prevalence ≈ 10%) when compared to the general population (prevalence ≈ 2%), with a trend of increased prevalence of KP in more severe cases of UC (pancolitis, severe colitis, and patients who underwent colonic resection). Strain identification was considered if the relative abundance of a specific strain was above 10% of the total KP content in the sample. In total, 54 strains of KP were identified and quantified, of which 33 were found only in IBD patients (18 in UC, 6 in CD and 9 in both CD and UC patients). Our results also show concordance with previous in-vitro studies: Two KP strains previously described to cause UC-like pathology and strong immune response in mice (strains KP-700603 and KP-2H7) were found to be specific to gut of UC patients in our cohorts.

Conclusion: We demonstrate the increase in prevalence of KP in the gut microbiome of IBD patients, and show that certain strains of KP are specific to IBD patients. Thus, KP may be involved in IBD and has a potential to be exploited as novel target for alleviating the severity of the disease.

Disclosure: This study was partially funded by Takeda Pharmaceuticals Inc., United states.

OP126 RISK OF GASTRIC CANCER AFTER *HELICOBACTER PYLORI* ERADICATION IN DIABETES MELLITUS PATIENTS: A TERRITORY-WIDE STUDY WITH PROPENSITY SCORE ANALYSIS

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Introduction: Whether diabetes mellitus (DM) increases gastric cancer (GC) risk remains controversial in prior studies due to inadequate adjustment for important risk factors including *Helicobacter pylori*(HP) infection, glycemic control, concomitant medication usage and cancer sites.

Aims & Methods: We aimed to investigate whether type II diabetes mellitus (DM) increased GC risk in patients after HP treatment.

This was a territory-wide cohort study of patients aged ≥45 years who had received clarithromycin-based triple therapy for HP between 2003 and 2012. Data were retrieved from the public electronic health database. Observation started from HP therapy to GC diagnosis, death or end of study (December 2015). Exclusion criteria included type I DM, GC diagnosed within first year of HP therapy, prior GC or gastrectomy, and failure of HP eradication. Theadjusted hazard ratio (aHR) of GCwith DM was calculated by Cox model with propensity score regression adjustmentfor 20 covariates (age, sex, smoking, alcoholism, past history of gastric and duodenal ulcers, other comorbidities [atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, hypertension and obesity] and medications [aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and proton pump inhibitors (PPIs)]).

Results: Of 46,460 eligible patients, 6,900 (14.9%) had DM. During a median follow-up of 7.1 years (IQR:4.8-9.8) with 337,313 person-years, 153 (0.33%) developed GC at a median age of 72.4 years (IQR:63.8- 82.6). There were 31 (20.3%) cardia cancers and 88 (57.5%) non-cardia cancers, while the remaining 34 (22.2%) cases did not have site specified.DM was associated with an increased GC risk (adjusted HR:1.67; 95% CI:1.08-2.58). This association was biased towards null if concomitant medication usage was not adjusted (adjusted HR:1.30; 95% CI:0.85-1.99), with the most influential effect from statins (**Table**). On the other hand, HR increased to 1.92 (95% CI:1.28-2.90) without adjusting for comorbidities.Stratified analysis shows the risk was increased for cardia cancer only (aHR:3.40, 95% CI:1.45-7.97), in those with suboptimal DM control (time-weighted average HbA1c ≥6.0%; aHR:1.68, 95% CI: 1.07-2.63) and metformin non-users (aHR 2.59, 95% CI 1.41-4.74).

Conclusion: Type II DM was associated with an increased GC risk among HP-eradicated patients, in particular cardia GC and those with suboptimal DM control. Inadequate adjustment for concomitant medications and comorbidities could potentially bias the results in previous studies.

Disclosure: Nothing to disclose

	No. of patients without DM and GC	No. of patients with DM and GC	HR	95% CI	p-value
All variables adjusted for	39,560 (GC = 117)	6,900 (GC=36)	1.67	1.08 - 2.58	0.021
Statins not adjusted for	39,560 (GC = 117)	6,900 (GC=36)	1.43	0.93 - 2.19	0.101
Statins and aspirin not adjusted for	39,560 (GC = 117)	6,900 (GC=36)	1.32	0.86 - 2.02	0.203
All drugs not adjusted for	39,560 (GC = 117)	6,900 (GC=36)	1.30	0.85 - 1.99	0.234
Comorbidities not adjusted for	39,560 (GC = 117)	6,900 (GC=36)	1.92	1.28 - 2.90	0.002
Subgroup analysis					
Metformin use					
Yes	39,560 (GC=117)	6,379 (GC=32)	1.28	0.74 - 2.20	0.378
No	39,560 (GC=117)	521 (GC=4)	2.59	1.42 - 4.74	0.002
Time-weighted average HbA1c level					
HbA1c ≥ 6.0%	39,560 (GC=117)	6,379 (GC=32)	1.68	1.07 - 2.63	0.025
HbA1c < 6.0%	39,560 (GC=117)	521 (GC=4)	1.99	0.71 - 5.54	0.188
Cancer site*					
Cardia	39,462 (GC=19)	6,876 (GC=12)	3.40	1.45 - 7.97	0.005
Non-cardia	39,513 (GC=70)	6,882 (GC=18)	1.53	0.84 - 2.78	0.161
Non-carida + unspecified site	39,541 (GC=98)	6,888 (GC=24)	1.33	0.80 - 2.23	0.271

DM, diabetes mellitus; GC, gastric cancer; HR, hazard ratio; 95% CI, 95% confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; PPIs, proton pump inhibitors; HbA1c, hemoglobin A1c * total cancer cases = 153 (non-cardia: 88, cardia: 31, unspecified: 34)

[Association between diabetes mellitus and gastric cancer (propensity score regression adjustment)]

OP127 VALIDATION OF SCORING SYSTEMS FOR DIFFERENTIATING INTESTINAL TUBERCULOSIS FROM CROHN'S DISEASE UTILIZING CLINICAL, ENDOSCOPIC AND PATHOLOGICAL FINDINGS: A MULTICENTER STUDY FROM THAILAND AND HONG KONG

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Introduction: Differentiating between Intestinal tuberculosis (ITB) and Crohn's disease (CD) is a diagnostic challenging in TB-endemic areas. Several models have been developed to distinguish these two diseases; however, no studies have externally validate these scores using data from the same cohort.

Aims & Methods: To validate existing scoring systems which used clinical, endoscopic and pathological findings in differentiating ITB from CD based on data from the same cohort.

We retrospectively collected data from patients newly diagnosed ITB and CD in 5 referral-centers in Thailand and Hong Kong. Clinical data was reviewed from medical records. Endoscopic and pathological findings were reviewed by endoscopists and pathologist blinded to the diagnosis. The data was applied to published scoring systems including score from Lee *et al* (Endoscopy 2006;38:592-7), Makharia *et al* (Am J Gastroenterol 2010;105:642-51), Jung *et al* (Am J Gastroenterol 2016;111:1156-64) and Limsrivilai *et al* (Am J Gastroenterol 2017;112:415-27). The performance of each score was evaluated with the area under the receiver operating characteristic curve (AuROC) and were compared to each other using the DeLong test.

Authors	Country	Thai n=242 (137 CD, 105 ITB)	Hong Kong n=348 (290 CD, 58 ITB)	Thai & Hong Kong n=590 (427 CD, 163 ITB)	Scores
Lee, Endoscopy 2006;38:592-7	South Korea	For Dx of ITB (242 pt, TB prevalence 43%) Sen 96% Spec 32% Accuracy 61.3% PPV 54% NPV 89% (48 pt inconclusive)	For Dx of TB (301 pt, TB prevalence 13%) Sen 96% Spec 56% Accuracy 61% PPV 25% NPV 99% (101 pt inconclusive)	For Dx of ITB (543 pt, TB prevalence 29%) Sen 96% Spec 47% Accuracy 61.2% PPV 43% NPV 96% (149 pt inconclusive)	8 parameters of endoscopic findings +1 for 4 findings favoring CD (Longitudinal ulcer, cobblestone, aphthous, anorectal lesions) -1 for 4 finding favoring ITB (Transverse ulcer, patulous IC, pseudopolyps, < 4 segmental involvement) Sum of score: > 0 = CD, < 0 = ITB, 0 = inconclusive
			Area under area under the ROC curve		
Makharia GK*, Am J Gastroenterol 2010;105:642-51	India	0.628 (0.511 - 0.746) (44 CD and 38 ITB)	0.708 (0.630 - 0.787) (180 CD, 35 ITB)	0.671 (0.605 - 0.737) (224 CD and 73 ITB)	- 2.5 × involvement of sigmoid colon - 2.1 × blood in stool + 2.3 × weight loss - 2.1 × focally enhanced colitis + 7
Jung Y, Am J Gastroenterol 2016;111:1156-64	South Korea	0.810 (0.757 - 0.863) (135 CD, 105 ITB)	0.857 (0.793 - 0.921) (205 CD, 38 ITB)	0.850 (0.815 - 0.886) (340 CD, 143 ITB)	1/[1+e−(−4.423+0.037×age+2.226×sex−2.203×diarrhea+2.345×tran_ring−1.911×longitudinal−2.123×sigmoid+5.606×pul_tbc)]
Limsrivilai, Am J Gastroenterol 2017;112:415-27 (Score from meta-analysis of each significant finding, please go to bit.ly/ITBvsCD)					
Clinical		0.741 (0.678 - 0.804)	0.766 (0.701 - 0.831)	0.766 (0.723 - 0.809)	
Endoscopy		0.769 (0.712 - 0.826)	0.735 (0.671 - 0.800)	0.786 (0.748 - 0.824)	
Clinical and endoscopy		0.833 (0.783 - 0.883)	0.849 (0.793 - 0.904)	0.858 (0.825 - 0.892)	
Clinical, endoscopy, and pathology*		0.853 (0.806 - 0.900)	0.814 (0.752 - 0.876)	0.861 (0.828 - 0.894)	

[OP127 Table 1]

Results: Of the 590 patients assessed, 163 patients had ITB, and 427 patients had CD. The mean age was 51.8 years in ITB and 36.6 years in CD (p<0.01). Fifty-four percent in ITB and 61% in CD were male (p=0.49). Applying the data to Lee's score which used only endoscopic findings, 149 patients (27%) obtained the score of zero in which the score could not conclude the diagnosis. In the remaining 394 patients, the sensitivity, specificity, and accuracy of the score for the diagnosis of ITB was 96%, 47%, and 61.2%, respectively. The AuROC was 0.713. By including clinical presentation, Jung's score and Limsrivilai's score were validated. The AuROC was 0.850 and 0.858, respectively. The difference between these two scores was not significantly different (p=0.75), but both performed superiorly than endoscopic score (p<0.01). By including pathological findings, Makharia's score and Limsrivilai's score were validated. The AuROC based on the data of 82 patients with available pathology review was 0.628 and 0.900, respectively. The difference was significant (p<0.01). The summary of each model performance in each cohort was shown in Table 1.

Conclusion: In a multi-center study across two different TB endemic areas, scoring systems which combined more potential parameters and diagnostic modalities performed better in differentiating ITB from CD. Further prospective studies to validate the model including more diagnostic modalities such as computed tomography enterography or serological tests are warranted.

Disclosure: Nothing to disclose

Primum non nocere: Making ERCP safer
08:30-10:00 / B2

OP128 ADDING INTRAVENOUS SOMATOSTATIN TO RECTAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) IN PREVENTION OF POST - ENDOSCOPIC RETROGRADE CHOLANGIO PANCREATOGRAPHY (ERCP) PANCREATITIS IN HIGH RISK PATIENTS

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Introduction: Endoscopic Retrograde CholangioPancreatography (ERCP) is used frequently for treatment of pancreatobiliary diseases. Pancreatitis is one of most frequent complication of ERCP. Pharmacologic measures have been studied for preventing this complication. Somatostatin use has been proposed by previous studies but with inconclusive results.

Aims & Methods: Regarding the prevalence and importance of pancreatitis after Endoscopic Retrograde Cholangio Pancreatography (ERCP), present study was conducted to evaluate the effect of adding intravenous somatostatin to indomethacin on the incidence of pancreatitis after ERCPIn this clinical trial study, 240 patients with primary diagnosis of pancreatobiliary disorders with high risk features of post RCP pancreatitis (patient related, operator dependent or procedure dependent) who were referred to the main academic hospital of Golestan province, Northeast of Iran for diagnostic and therapeutic ERCP during March 2018 to February 2019 were included. They were randomly divided into 2 groups to receive either intravenous somatostatin plus rectal indomethacin (group A, N=120) or rectal indomethacin plus normal salin (group B, N=120).

Serum amylase was evaluated 2 and 18 hours after ERCP and the length of hospitalization or complications had been recorded. Independent t-test was used to compare means and Chi-2 test was used to compare qualitative variables.

Results: Amounts of dye injection, duration and time of cannulation were not significant different between two groups (p>0.05). Significant difference was noted between the two groups in amylases after 2 hours (147.66 vs 198.88 U/L) and 18 hours (124.14 vs 166.55 U/L). Results showed 4.2% pancreatitis in group A and 15% in group B (p = 0.004).

Conclusion: It can be concluded that the administration of somatostatin during and after ERCP could significantly decrease the risk of pancreatitis and hyperamylasemia between the two groups.

Disclosure: Nothing to disclose

OP129 INDIRECT TREATMENT COMPARISON OF USTEKINUMAB VERSUS OTHER ADVANCED THERAPIES IN MODERATE TO SEVERE ULCERATIVE COLITIS AFTER 1 YEAR

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Introduction: Indirect evidence on the relative efficacy of ustekinumab in moderate to severe ulcerative colitis (UC) to other therapies is needed to better inform decision-makers. An indirect treatment comparison (ITC) was performed to compare the 1-year efficacy of therapies in non-biologic failure and biologic failure UC patients.

Aims & Methods: Randomised controlled trials reporting induction and maintenance clinical efficacy of anti-tumour necrosis factors (infliximab [IFX], adalimumab [ADA], golimumab [GOL]), vedolizumab (VDZ), tofacitinib (TOF) or ustekinumab (UST) were identified by a systematic literature review through MEDLINE, MEDLINE IN PROCESS, Embase and Cochrane up to the 28th March 2019. Analyses were conducted for clinical response (decrease in baseline total Mayo score ≥30% and ≥3 points, decrease in rectal bleeding subscore ≥1, or rectal bleeding subscore 0 or 1) and clinical remis-

sion (total Mayo score ≤2 points, no individual subscore >1 [definitions with rectal bleeding subscore of 0 were also included]) in each population. Due trial design differences, comparisons of maintenance data alone would be biased. To mimic an ITT-based approach, maintenance data from trials with re-randomised response designs were re-calculated to correspond to treat-through arms including responders at induction and non-induction responders. UST efficacy was calculated for patients starting on the ~6 mg/kg IV regimen. For trials with only short-term placebo (PBO) rates or missing data for PBO non-responders, end of 1-year placebo-to-placebo rates were externally imputed. Bayesian ITCs were conducted to obtain posterior distribution probabilities for UST to perform better than its comparators by population. In the non-biologic failure population, maintenance doses were pooled as no dose-response was apparent.

Results: Six trials were included in the non-biologic failure population ITC [1,2,3,4,5,6], and four included in the biologic failure ITC [1,2,3,4]. Imputed rates for the PBO responders and non-responders in the non-biologic failure group were derived from multiple trials and were consistent. UST given as a 1-year regimen showed higher probabilities of both clinical response and remission versus all treatments in the non-biologic failure group, with Bayesian probabilities of UST being better than active therapies ranging between 91% (VDZ) to 100% (ADA) doses for response and 82% (VDZ) to 99% (ADA) for remission, respectively. In the biologic failure group, the probabilities of UST being better than each active treatment were all higher than 80% for response with the exception of TOF with 10mg in maintenance, and remission was similar between the therapies.

Conclusion: Results of the 1-year ITC indicate a higher likelihood of response and remission on UST in non-biologic failure population versus comparators, especially versus anti-TNFs. In biologic failure patients, results were more uncertain due to smaller sample sizes and data limitations, though a higher likelihood of response to UST versus most comparators was observed.

Treatments sequence (induction - maintenance)	Clinical response Median OR [95% CrI] Pr UST ~6mg/kg - UST 90mg pooled (Q8W and Q12W) vs.	Clinical remission Median OR [95% CrI] Pr UST ~6mg/kg - UST 90mg pooled (Q8W and Q12W) vs.
VDZ 300mg - VDZ 300mg pooled (Q4W and Q8W)	1.93 [0.75 ; 4.82] 91.45%	1.47 [0.65 ; 3.34] 82.34%
IFX pooled - IFX pooled (5mg/kg and 10mg/kg)	2.62 [1.22 ; 5.60] 99.31%	1.89 [0.83 ; 4.30] 93.52%
GOL 200/100mg - GOL pooled (50mg Q4W and 100mg Q4W)	3.76 [1.90 ; 7.57] 99.99%	1.99 [0.93 ; 4.26] 96.27%
ADA 160/80/40mg - ADA 40mg EOW	4.76 [2.25 ; 10.16] 100%	2.43 [1.10 ; 5.41] 98.55%
TOF 10mg - TOF pooled (5mg and 10mg)	2.27 [1.06 ; 4.86] 98.21%	1.51 [0.64 ; 3.52] 83.00%
PBO - PBO	8.70 [5.03 ; 15.40] 100%	5.11 [2.83 ; 9.51] 100%

QXW: every X weeks, EOW: every other week, Pr: probability for ustekinumab to perform better than the comparator

[Table 1 ITC results in the non-biologic failure population]

References: [1]Janssen. A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis (44-Week Clinical Study Report). Research & Development (2018). [2]Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S, James A and Smyth M. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clinical Gastroenterology and Hepatology. 201;15:229-239. [3]Sandborn WJ, Van Assche G, Reinisch W, Colombel JF, D´Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65. [4]Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine. 2017;376(18):1723-36. [5]Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine. 2005;353(23):2462-76. [6]Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):85-95.

OP130 META-ANALYSIS OF RANDOMIZED TRIALS OF POST-ERCP PANCREATITIS AFTER EARLY AND LATE NEEDLE-KNIFE SPHINCTEROTOMY IN DIFFICULT BILIARY CANNULATION

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Introduction: Needle-knife sphincterotomy (NKS) and prolonged cannulation attempts are both considered as risk factors for post-ERCP pancreatitis (PEP). Previous meta-analyses compared the effect of early precut versus persistent cannulation attempts on PEP.

Aims & Methods: Our aim was to analyze the effect of early versus late NKS on PEP in difficult biliary cannulation. MEDLINE/PubMed, EMBASE were searched. Only randomized controlled trials (RCT) containing data of early (< 10 minutes of cannulation attempts and/or < 5 inadverent pancreatic duct cannulation) and late (additional 10 minutes of attempts) NKS were selected and analyzed.

A subgroup of patients where cannulation attempts were prolonged but NKS was not needed served as the prolonged cannulation group. Pooled estimates of PEP were analyzed using odds (OR) and risk ratios (RR), and number needed to treat (NNT) was calculated.

Results: 6 RCTs were found, but only 3 RCTs were included in the meta-analysis (3 excluded: 2 used prophylactic pancreatic stenting which could alter the effect of NKS; and only moderate and severe PEP were analyzed in 1 RCT). NKS was used early in 310 and late in 220 patients. In 216 patients prolonged standard cannulation was used. PEP occurred in 14/310 (4.06%) vs. 29/220 (12.23%) vs. 14/216 (9.47%) patients.

The cannulation success rates were 272/310 (86%) in early NKS vs. 187/220 (80.7%) in late NKS groups. Regarding PEP, our meta-analysis showed a significantly increased risk, when NKS was used late compared to early (OR=3.21 (95% CI: 1.65-6.23; p=0.0006); RR=2.92 (95% CI: 1.57-5.39; p=0.0006); NNT=11.54). When NKS is applied late after prolonged cannulation attempts, it further increases the risk of PEP compared to prolonged cannulation only (OR=2.19 (95% CI: 1.12-4.27; p=0.0214); RR=2.03 (95% CI: 1.11-3.74; p=0,0225); NNT=14.9).

Conclusion: Early, but not late precut NKS is safe in difficult biliary cannulation when used by experts. The incidence of PEP of early NKS is half compared to prolonged cannulation and third compared to late NKS. We suggest using early precut sphincterotomy in difficult biliary cannulation and/or using other preventive methods (eg. prophylactic pancreatic stents or rectal indomethacin) to lower PEP rates.

Disclosure: Nothing to disclose

OP131 IS THERE A DIFFERENCE IN THE INCIDENCE AND CHARACTERISTICS OF POST-ERCP PANCREATITIS BETWEEN EMERGENCY AND ELECTIVE ERCP?: A PROSPECTIVE MULTICENTER STUDY

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Introduction: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is a potentially serious complication. Risk factors for PEP after elective ERCP have been reported. ERCP is often performed urgently, but the difference in the risk factors for PEP between elective and emergency ERCP remains unclear.
Aims & Methods: We aimed to identify the incidence of and risk factors for PEP in emergency ERCP. We performed a prospective study of 3914 patients undergoing diagnostic and therapeutic ERCP at five Japanese institutions between April 2015 and May 2017. The exclusion criteria were as follows: active pancreatitis, choledochojejunostomy, inability to approach a papilla, and inspection only of the pancreatic duct (PD). In this study, emergency ERCP was defined as unscheduled inspections performed within and beyond regular working hours. A diagnosis of PEP was made when two of the following three conditions were met: (1) serum amylase levels greater than three times the upper limit of the normal range at each institution, (2) persistent abdominal pain for more than 24 h, and (3) evidence of pancreatitis on computed tomography. In the first study, we compared the incidence and characteristics of PEP between emergency and elective ERCP. In the second study, we determined the predictive risk factors for PEP in emergency ERCP using univariate and multivariate analyses.
Results: In total, 3,410 patients were enrolled in this study. < Study 1> PEP developed in 44 of 800 (5.5%) cases and 190 of 2,418 (7.9%) cases in the emergency and elective groups, respectively. No significant difference was noted in the incidence of PEP between the two groups (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.52-1.03; P = 0.07). Endoscopic sphincterotomy, pre-cutting, stone removal, endoscopic papillary balloon dilatation (EPBD), and intraductal ultrasound were more frequently performed in the elective group than in the emergency group (P < 0.001); while biliary stent placement was significantly more common in the latter group (P < 0.001) . In addition, a considerably longer procedure time (40.2min. vs 30.8min.;P < 0.001) and higher number of endoscopists with more than 5 years of experience (P = 0.02) were noted in the elective group than in the emergency group. < Study 2> The multivariate analysis showed that the following factors increased the risk for PEP in emergency ERCP: contrast medium injection into the PD (OR, 2.56; 95% CI, 1.30-5.03; P = 0.005), more than four cannulation attempts (OR, 5.72; 95% CI, 2.61-12.50; P < 0.0001), and EPBD (OR, 9.24; 95% CI, 2.13-40.10; P < 0.0001).
Conclusion: No significant difference was noted in the incidence of PEP between emergency and elective ERCP. For noninvasive methods, a procedure time less than 30 minutes is acceptable even for a trainee with less than 5 years of experience during the emergency ERCP. The contrast medium injection into the PD necessitates close monitoring, particularly when more than four cannulation attempts are required; furthermore, surgeons should refrain from performing EPBD in emergency ERCP.
Disclosure: Nothing to disclose

OP132 A NOVEL SINGLE-USE DUODENOSCOPE HAD COMPARABLE PERFORMANCE RATINGS TO REUSABLE DUODENOSCOPES IN A RANDOMIZED BENCH STUDY

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Introduction: Multidrug-resistant (MDR) infectious outbreaks are a major global concern.[1] Duodenoscope contamination during reuse and reprocessing is one of many potential nosocomial sources of patient-to-patient transmission of pathogenic MDR organisms. Duodenoscope reprocessing guidelines are evolving and impose a significant economic burden to hospitals.
In addition, guideline adherence alone cannot prevent duodenoscope contamination because the current cleaning paradigm for duodenoscopes is ineffective.[2] In this context, single-use duodenoscopes could offer benefits. No single-use duodenoscope is currently available in gastroenterology clinical practice. Similar performance to reusable duodenoscopes is a prerequisite to considering further investigation of a single-use duodenoscope for endoscopic retrograde cholangiopancreatography (ERCP).
Aims & Methods: The aim of this study was for 6 expert ERCP endoscopists to compare performance characteristic ratings of a novel single-use duodenoscope to those of 3 marketed reusable duodenoscopes.
Beginning in March 2017, 9 laboratory animal studies were conducted to develop a single-use duodenoscope intended to bring a familiar design with a minimal learning curve. Prototype revisions based on physician feedback led to the first-generation single-use duodenoscope used in the current study. Also based on physician feedback, a handmade, fully synthetic ERCP anatomical bench model was developed for use in ERCP simulation testing.
In January 2019, a bench study with randomized block design was conducted in which the 6 endoscopists rated the performance of the single-use EXALT Model D duodenoscope (Boston Scientific, Marlborough, USA) and 3 reusable duodenoscopes (Q180V (Olympus, Japan), ED-3470TK (Pentax, Japan), ED-530XT (Fujifilm, Japan) to complete 4 simulated ERCP tasks: guidewire locking (single-use and one reusable duodenoscope only), plastic stenting, metal stenting, and basket sweeping. Each task was performed once with each duodenoscope model. Task completion rates and times, and subjective performance ratings on a scale of 1 (worst) to 10 (best) were compared among duodenoscopes using non-parametric tests with adjustment for multiple comparisons.
Results: Task completion rates were 100% for all 4 duodenoscopes. Median task completion time ranged from 1.5 to 8.0 minutes per task. Overall performance (Table) and tip control (medians 9.0-10.0, *P*=0.77 among all 4 duodenoscopes) were rated similarly among the duodenoscopes tested.

Task Number	EXALT Model D	Q180V	ED-3470TK	ED-530XT	P value
1	9.0 (8.0-10.0)	9.0 (8.0-10.0)	--	--	1.00
2	8.5 (8.0-9.0)	10.0 (8.0-10.0)	9.0 (8.0-10.0)	9.0 (8.0-10.0)	0.14
3	8.5 (8.0-9.0)	9.5 (8.0-10.0)	8.0 (8.0-9.0)	9.5 (8.0-10.0)	0.11
4	8.5 (8.0-10.0)	9.0 (8.0-10.0)	9.0 (8.0-10.0)	9.0 (8.0-10.0)	0.74

[Table: Median ratings (range) for overall performance]

The 2 duodenoscopes capable of guidewire locking both received median ratings of 10 for that function (*P*=0.14 for difference in subtask ratings). Among all 4 duodenoscopes, navigation/pushability was rated lower for the single-use duodenoscope (medians 8.0, 10.0, 9,0, 9.0 respectively,

P<0.01). Image quality was rated lower for one of the reusable duodenoscopes (ED-3470TK) (medians 8.0, 9.0, 9.0, 9.0 respectively, *P*< 0.01) compared to the other duodenoscopes tested.

Conclusion: In a comparative bench study including 4 simulated ERCP tasks, performance ratings were similar for the new single-use duodenoscope and 3 brands of reusable duodenoscopes. A multicenter clinical study of the safety, feasibility and efficacy of the new single-use duodenoscope is warranted.

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OP133 ERCP IN BABIES: LOW RISK OF POST-ERCP-PANCREATITIS – RESULTS FROM A EUROPEAN MULTICENTER SURVEY

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Introduction: ERCP is rarely performed in newborns, and the risk of post-ERCP-pancreatitis (PEP) has not been defined in this age group. We therefore performed a European multicenter analysis of PEP rates and risk factors in children ≤1-year-old.

Aims & Methods: Based on a sample size estimation, 135 consecutive ERCPs in 126 children ≤1-year-old were evaluated from five European centers. All ERCP and clinical reports were reviewed manually for PEP and associated risk factors. All ERCPs were performed by endoscopists with high ERCP expertise.

Results: No PEP was observed (0/126, 0.0%, CI 0-2.9%) despite formal presence of multiple risk factors and despite lack of PEP prophylaxis (except one patient having received a pancreatic duct stent). The PEP rate was significantly lower than the PEP rate expected in adults with similar risk factors.

Conclusion: : ERCP in ≤1-year-old children is safe in terms of PEP. The PEP risk is significantly lower in children ≤1-year-old than in adults, therefore no PEP prophylaxis seems to be needed in young children. Risk factors from adults may not apply to children under 1 year. Reluctance to perform diagnostic ERCP in suspected biliary anomalies should not be based on presumed PEP risk.

Disclosure: Nothing to disclose

New impulses in management of gastroparesis
08:30-10:00 / B3

OP134 THYMIDINE PHOSPHORYLASE ABNORMALITIES AND GASTROINTESTINAL VASCULAR CHANGES IN GENETIC AND SPORADIC FORMS OF SEVERE DYSMOTILITY

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Introduction: Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an extremely rare autosomal recessive disease caused by thymidine phosphorylase (TP) enzyme defect. Normally, TP converts the nucleosides thymidine and deoxyuridine into respective nucleotides. In MNGIE these nucleosides accumulate in most tissues and induce toxic effects leading to mitochondrial DNA (mtDNA) abnormalities. MNGIE patients show severe gastrointestinal (GI) dysmotility and neurological impairment, resulting in a poor quality of life and fatal outcome. Although permanent tissue replacement of TP (via either liver or hematopoietic cell transplantation) is the best way to stably revert the biochemical imbalance, transplanted patients do not recover the poor BMI and may dye for GI massive bleeding. The liver transplant follow-up suggests that the phenotype directly linked to the accumulation of nucleosides seems to be reversible, while other mechanisms underlying non-reversible GI damage may occur. During the conversion of nucleosides TP produces 2-deoxy-D-ribose-1-phosphate (dRP) that has been demonstrated to be the chemotactic agent inducing endothelial progenitor cells to form/repair blood vessels. In MNGIE patients the conversion does not take place. In order to exert its effect dRP has to be locally released, hence vascular changes may occur in the GI tract of MNGIE patients.

Aims & Methods: This study was designed to explore the enteric submucosal microvasculature in the jejunal of MNGIE patients in comparison with asymptomatic GI controls (CTR) and non-MNGIE patients with well characterized severe dismotility (SD) and normal TP activity.

Jejunal full thickness biopsies were collected from n=4 MNGIE (4M, 24-32 yrs); n=10 CTR (7M, 30-73 yrs) and n=21 SD (9M; 16-75). Formalin fixed-paraffin embedded tissue sections were stained with orcein to identify, measure and count blood vessels. Vessels were subdivided in 4 classes: >300 μm (large); 300-101 μm (medium); 100-51 μm (small) and < 50 μm (very small). Snap frozen tissue was used to quantify TP protein expression.

Results: MNGIE patients showed two times more submucosal vessels/mm^2 (*P*< 0.05) *vs.* CTR, while SD showed only a non significant trend to increase. In contrast the area of submucosa occupied by vascular tissue was about half in MNGIE (*P*< 0.01) and SD (*P*< 0.001) *vs.* CTR. The percentage of the small vessels (< 50 μm) in CTR was very low ~19%, whereas drastically increased in SD (43%; *P*< 0.001) and MNGIE (54%; *P*< 0.01). Conversely, the percentage of higher diameter vessels (>300 μm) in CTR was ~15 % and in SD and MNGIE patients decreased up to 7% and 5% (*P*< 0.01 and *P*< 0.05), respectively. Medium vessels (300-101 μm) represented the 40% of vessels in CTR and decreased to 25% and 17% in SD and MNGIE patients (*P*< 0.001 and *P*< 0.01). The TP amount showed a significant decrease in the jejunum of SD patients (*P*< 0.0001).

Conclusion: Our results indicate that, compared to CTR, MNGIE and SD vasculature showed quantitative abnormalities likely related to the absence/lower TP conversion. This study addressed the abnormal vascularization in the small intestine of genetic (MNGIE) and sporadic SD as a possible contributory mechanism underlying gut dysfunction in these severe conditions.

Disclosure: Nothing to disclose

OP135 DIAGNOSTIC YIELD OF SYMPTOM SEVERITY, VISCERAL SENSORY TESTING, SMALL INTESTINAL, BACTERIAL LOAD AND GASTRIC EMPTYING FOR THE DIAGNOSIS OF FUNCTIONAL GASTROINTESTINAL DISORDERS

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Introduction: Patients presenting with functional gastrointestinal disorders (FGIDs) frequently report debilitating symptoms which may be more severe than symptoms experienced by patients with organic intestinal disease. While presence or absence (i.e. symptom pattern) is generally used to categorise patients with FGIDs, the role of symptom intensity to categorise and diagnose patients has not been tested. In addition, alterations of gastrointestinal sensory function, altered motility and bacterial dysbiosis are considered to play key roles in FGID pathophysiology.

Aims & Methods: In this study we aimed to explore the diagnostic yield of severity of self-reported GI symptoms, visceral sensory testing, qPCR to quantify small intestinal mucosal bacterial load and gastric emptying in differentiating functional from organic GI disease. We recruited 284 patients (150 female, 95 patients with FGID (68 functional dyspepsia (FD)/IBS overlap, 21 FD, 3 IBS), 118 organic disease (43 Crohn's disease, 48 ulcerative colitis (UC), 16 UC/primary sclerosing cholangiopathy (PSC), 4 PSC alone, 9 other) and 71 patients with a positive stool occult blood test without structural lesions). After informed consent, type and severity of GI symptoms were recorded using a standardized valid questionnaire (SAGIS). Patients underwent a nutrient challenge test and the cumulative symptom response to a standardised test meal (Ensure, 600 cc) were recorded. In addition, gastric emptying of a solid test meal was measured utilising ^{13}C-octanoic breath testing. During endoscopy, mucosal tissue samples were collected utilising the Brisbane Aseptic Biopsy Forceps (MTW, Germany) to avoid the luminal and working channel contamination of tissue, and total DNA was extracted. Tissue bacterial density was normalised to human DNA by qPCR using Bacteria-Domain 16S rRNA gene- and beta-actin gene-specific primers, respectively. Based upon on all available clinical data, patients were categorised as FGID or non-FGID. The FGID and non-FGID groups were compared utilising non parametric testing, and Spearman correlation to determine the relationships between disease category and the respective variables. In addition, Receiver Operator Curves (ROC) for the variables that were significantly different for FGID and non-FGID provided areas under the curve for comparison.

Results: SAGIS symptom scores, the symptom response to the nutrient challenge, and the tissue bacterial load were all significantly greater (all P< 0.005) in FGID patients as compared to non FGID patients (Table 1).

	SAGIS-score	Nutrient challenge score	Bacterial load, ratio	Gastric emptying, t-lag (min)
Non-FGID	10.8 (±12.9)	204 (±190)	0.04 (±0.11)	116.0 (±37.3)
FGID	30.6 (±15.1)#	458 (±399)*	0.20 (±0.5)#	115.8 (±29.3)

#P< 0.001, *P< 0.005

[Table 1. GI symptom severity, symptom response to nutrient challenge, bacterial load (ratio of 16s RNA:β actin) and t-lag gastric emptying]

There was no difference with regard to gastric emptying. SAGIS score (r=0.62, P< 0.001), nutrient challenge score (r=0.41, p< 0.001) and bacterial load (r=0.342, p< 0.001) were linked to FGID, whereas gastric emptying was not (r=0.024, p>0.8). For the total SAGIS score the AUC was .892 (95% CI 0.83-0.954), for the nutrient challenge score 0.74 (95%CI .64-0.83), bacterial load (0.71 (95%CI 0.61-0.80).

Conclusion: In patients referred to a tertiary setting for assessment and treatment, self-reported symptom severity, response to a standardised nutrient challenge and small intestinal bacterial load but not gastric emptying rate differentiate patients with functional and non-functional symptoms. Further studies need to explore the utility of these simple tests to better tailor diagnostic and therapeutic interventions for patients presenting with chronic unexplained GI symptoms.

Disclosure: Nothing to disclose

OP136 EFFECT OF RIKKUNSHITO ON GASTROINTESTINAL MOTILITY AND UPPER GASTROINTESTINAL SYMPTOMS - THE FIRST STUDY IN A BELGIAN FUNCTIONAL DYSPEPSIA POPULATION

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Introduction: Functional dyspepsia (FD) is a common chronic gastrointestinal (GI) disorder. Rikkunshito, a traditional Japanese Kampo medicine, has shown efficacy in improving FD symptoms in controlled trials in Japan. Its putative benefit for European patients has never been investigated. Further, its exact mechanism of action is incompletely elucidated.

Aims & Methods: This study aimed to examine the effect of rikkunshito on gastric motility and GI symptom perception in FD patients with postprandial distress syndrome (PDS) subtype in a randomized, placebo-controlled, cross-over study. After a 2-week run-in period, during which adequate symptom intensity was confirmed, patients were treated with rikkunshito (2.5g t.i.d.) and matching placebo for 4 weeks, separated by a 4-week washout period. Symptom severity was assessed by the Leuven Postprandial Distress Scale (LPDS) diary throughout the study. At baseline and at the end of both treatment arms, intragastric pressure (IGP) was assessed using high-resolution manometry after an overnight fast. Thirty minutes after study medication intake, a liquid meal was infused intragastrically at a constant speed (60 mL/min) until full satiation. IGP measurement continued until 2 hours after the liquid meal. GI symptoms were scored on a 100mm visual analogue scale every 10 minutes. At baseline, before and after each treatment period, the PAGI-SYM (patient assessment GI symptoms), VSI (visceral sensitivity index) and SF-NDI (short form Nepean dyspepsia index) questionnaires were completed. Data were analyzed using mixed models.

Results: Thirty-four patients were randomized in the study, of which 11 dropped-out, resulting in 23 fully evaluable patients (33±14 y, 22.7±3.22 kg/m^{2}). The IGP was numerically, although not significantly, lower after rikkunshito compared to both baseline and placebo (mean difference: 1.51 mmHg, *p*< 0.221; 2.19mmHg, *p*=0.132, respectively). No significant differences were found in gastric accommodation, nutrient volume tolerance and symptoms assessed during IGP measurements. An exploratory subgroup analysis, comparing patients on PPI (7 patients) and off PPI (16 patients), showed that the numerical difference in IGP was driven by the patients who were not on PPI treatment. However, no significant difference was observed between both subgroups. Early satiation, bloating and epigastric pain, scored on the LPDS diary, decreased after rikkunshito compared to baseline (*p*< 0.025 for all). However, comparable symptom improvement occurred after placebo (*p*< 0.045 for all; NS between groups). Exploratory subgroup analysis on overall LPDS symptom scores revealed significant improvement after rikkunshito for the patients off PPI (*p*=0.021) and after placebo for the patients on PPI (*p*=0.006). Total PAGI-SYM scores were equally improved after rikkunshito and placebo compared to baseline (*p*< 0.001 and *p*< 0.001, respectively; NS between groups). Placebo, but not rikkunshito, significantly improved frequency, severity and bothersomeness of SF-NDI scores compared to baseline (*p*< 0.008 for all). No significant changes in VSI scores occurred. No adverse reactions occurred.

Conclusion: Rikkunshito did not alter gastric accommodation and nutrient volume tolerance. Treatment with rikkunshito improved upper GI symptoms in FD patients but a similarly high placebo effect was observed using the LPDS diary, PAGI-SYM and SF-NDI. Rikkunshito was safe and well tolerated. Exploratory analyses indicate potentially better responses in patients who are not on concomitant PPI treatment.

Disclosure: Nothing to disclose

OP137 TRADIPITANT, A NOVEL NK-1 RECEPTOR ANTAGONIST, SIGNIFICANTLY IMPROVED NAUSEA AND OTHER SYMPTOMS OF GASTROPARESIS IN A PHASE II TRIAL

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Introduction: A phase II multicenter, randomized, double-blind, placebo-controlled trial with gastroparesis subjects demonstrating delayed gastric emptying and moderate to severe nausea were randomized to receive oral 85mg tradipitant bid or placebo (1:1) for four weeks. Of the 152 patients, 60% of patients had idiopathic and 40% had diabetic gastroparesis.

Aims & Methods: The primary outcome was change in average nausea score from baseline, measured using the 5-point Gastroparesis Core Symptom Daily Diary (GCSDD). Overall gastroparesis symptoms were evaluated using the Gastroparesis Cardinal Symptom Index (GCSI), and Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM).

Results: A statistically significant and clinically meaningful improvement in nausea and overall gastroparesis symptoms was observed in patients on tradipitant. Subjects receiving tradipitant had a significant decrease in their average nausea score compared to placebo with LS mean difference (95% CI) of -0.53 (-0.92, -0.13, p=0.0099) as well as a significant increase in nausea free days (28.8% increase on tradipitant compared to 15.0% increase on placebo, p=0.0160). A clinically meaningful response of 1-point or more improvement on the GCSI total score was observed in 46.0% of patients on tradipitant compared to 24.2% of patients on placebo.

Conclusion: Tradipitant treatment resulted in statistically and clinically meaningful improvements in nausea and overall gastroparesis symptoms. Tradipitant was well tolerated with comparable rates of adverse events between tradipitant and placebo groups. These robust efficacy results suggest tradipitant has the potential to become a first line pharmacological treatment for gastroparesis.

Disclosure: All authors are employees of Vanda Pharmaceuticals, Inc.

OP138 EFFICACY OF VELUSETRAG TREATMENT IN PATIENTS WITH IDIOPATHIC GASTROPARESIS: SUBGROUP ANALYSIS OF A PHASE 2B STUDY

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Introduction: Velusetrag (VEL) is a highly selective oral 5-hydroxytryptamine receptor type 4 agonist with demonstrated prokinetic effects throughout the gastrointestinal tract. A phase 2b trial evaluated VEL efficacy and safety in patients with idiopathic or diabetic gastroparesis; this subanalysis assessed effects of VEL vs placebo on symptoms and gastric emptying in only patients with idiopathic gastroparesis.

Aims & Methods: Patients with baseline 24-hour Gastroparesis Cardinal Symptoms Index (GCSI-24H) 7-day mean composite score ≥2.5 and delayed gastric emptying based on scintigraphy (GES) or gastric emptying breath test were randomized, stratified by gastroparesis type, to receive oral VEL 5, 15, or 30 mg, or placebo, once daily in the morning, in parallel for 12 weeks and followed for another 2 weeks. Symptoms were assessed daily using the GCSI-24H, a daily version of the GCSI including nausea/vomiting, postprandial fullness/early satiety, and bloating subscales. Gastric emptying was evaluated at day 28 by the same test used for screening. The primary efficacy outcome was change from baseline to week 4 in 7-day mean GCSI-24H composite score in patients receiving each dose of VEL vs placebo. Key secondary outcomes included change from baseline to day 28 in gastric emptying assessed by GES in patients receiving VEL vs placebo, and safety and tolerability of VEL in patients with idiopathic gastroparesis.

Results: Of 228 randomized patients who received study drug and had evaluable efficacy data, 112 had idiopathic gastroparesis: 29 patients received VEL 5 mg, 24 received VEL 15 mg, 31 received VEL 30 mg, and 28 received placebo. The majority of patients were female (85%); mean age was 45.4 (range, 19-73) years, and mean baseline GCSI-24H total score was 3.1 (standard deviation, 0.51) points (n=111). GES was assessed in 58 patients.

Change from baseline GCSI-24H composite score at weeks 4 and 12 showed an inverse dose response, with larger treatment effects vs placebo for VEL 5 mg vs 15 or 30 mg. In patients receiving VEL 5 mg, GCSI-24H composite score decreased from baseline significantly at week 4 (treatment difference [95% confidence interval (CI)], -0.6 [-1.08, -0.05] points; nominal p=0.03) and numerically at week 12 (treatment difference [95% CI], -0.6 [-1.19, 0.00] points; nominal p=0.05]) relative to placebo. All GCSI-24H symptom subscale scores in patients receiving VEL 5 mg vs placebo decreased from baseline in week 1 of treatment, stabilized or decreased through week 6, and were stable through week 12. No tachyphylaxis was observed. Gastric emptying assessed by GES improved from baseline to day 28 in 9/13 patients receiving VEL 5 mg, 13/13 receiving VEL 15 mg, and 16/16 receiving VEL 30 mg vs 6/16 patients receiving placebo. Gastric emptying normalized (< 10% GES hour 4 retention) in all patients receiving VEL 15 mg and 81% receiving VEL 30 mg vs 0% receiving VEL 5 mg or placebo.

VEL was generally well tolerated. The most common adverse events (AEs) across all treatment arms were diarrhea, nausea, and headache. Numerically greater proportions of patients receiving VEL 5, 15, or 30 mg vs placebo had diarrhea (13.8%, 30.8%, and 19.4%, respectively, vs 7.4%) and nausea (6.9%, 7.7%, and 19.4%, respectively, vs 3.7%).

Conclusion: VEL treatment for 12 weeks reduced gastroparesis symptoms, with greatest effect for the 5-mg dose; demonstrated gastroprokinetic activity at all doses; and was well tolerated in patients with idiopathic gastroparesis. Future phase 3 studies will further evaluate VEL efficacy in this population.

Disclosure: TLA is a consultant to Theravance Biopharma, Inc.; an investigator for Vanda, Allergan, Anylam, Censa, and Theravance Biopharma R&D, Inc.; a reviewer for Up To Date; an Editor of MedStudy, Neuromodulation, and Wikistim; and a founder of ADEPT-GI. BK reports grant funding from AstraZeneca; Evidera; Gelesis, Inc.; Genzyme; GSK; Medtronic; Takeda; Theravance Biopharma R&D, Inc.; and Vanda; and personal fees from Actavis Pharma, Inc.; AstraZeneca; Biogen; Entrega; Forest Pharmaceuticals; Gelesis, Inc.; Genzyme; GLG; GSK; Ironwood Pharmaceuticals; Medtronic; Takeda; and Theravance Biopharma R&D, Inc. TE reports nothing to disclose. DC, KZ, and CNB are former employees of Theravance Biopharma US, Inc. RT, MG, GCV, and CR are employees of Alfasigma S.p.A. DDN is an employee of Theravance Biopharma US, Inc., and shareholder of Theravance Biopharma, Inc. RM reports grant funding from Allergan Pharma; Medtronic Corp.; Takeda Pharma; Vanda Pharma; Theravance Biopharma R&D, Inc.; and Evoke Pharma; and personal fees from Salix Pharma.

OP139 GASTRIC PERORAL ENDOSCOPIC MYOTOMY (G-POEM) FOR THE TREATMENT OF REFRACTORY GASTROPARESIS: RESULTS FROM THE FIRST INTERNATIONAL PROSPECTIVE TRIAL

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Introduction: Gastric per-oral endoscopic myotomy (GPOEM) was first reported in 2013 for the treatment of gastroparesis. Early data suggested efficacy of the procedure; however, data from prospective multicenter studies are currently lacking.

Aims & Methods: The aim of this study is to prospectively evaluate the efficacy and safety of G-POEM in patients with gastroparesis refractory to conventional medical treatment. This is a multicenter study involving 6 tertiary centers (5 US, 1 South America) between 11/2015 and 11/2018. Adult patients with refractory gastroparesis, defined as failing prior conventional medical therapy, and confirmed by gastric emptying study (GES).The primary outcome was clinical success, defined as at least one score decrease in total Gastroparesis Cardinal Symptom Index (GCSI) with more than a 25% decrease in at least 2 sub-scales. Secondary outcomes were quality of life based on Short Form 36 (SF-36) and improvement of gastric motility assessed by GES. Data were collected before the procedure and 1 month, 3 months, 6 months, and 12 months after the procedure. GES was performed before and after G-POEM.

Results: A total of 73 patients with refractory gastroparesis (51 female [70 %]; median age 44yr) underwent G-POEM during the study period. The most common etiologies were idiopathic 29 (39.7 %), post-surgical 26 (35.6 %), and diabetes 18 (24.7 %). All procedures were technically successful. Clinical success was achieved in 57.9 % and 36.8% of patients at 6 and 12 months, respectively. Repeated measures ANOVA showed that the mean GCSI score and nausea/vomiting and bloating subscores improved significantly over follow-up intervals (table 1).

GCSI subscales, mean ± SD	Preprocedural	1 month after procedure	3 months after procedure	6 months after procedure	12 months after procedure	p-value
Nausea/vomiting	2.69 ± 1.29	1.44 ± 1.32	1.22 ± 1.4	1.54 ± 1.21	1.72 ± 1.48	0.17
Early satiety	2.76 ± 1.19	1.21 ± 1.14	1.12 ± 1.25	1.47 ± 1.12	1.67 ± 1.17	**0.04**
Bloating	3.65 ± 1.44	1.98 ± 1.72	1.58 ± 1.68	2.2 ± 1.7	2.06 ± 1.57	0.06
Total	2.96 ± 1.05	1.57 ± 1.14	1.39 ± 1.23	1.62 ± 1.14	1.84 ± 1.12	**0.015**

[Improvement of GCSI and its sub-scales, after G-POEM]

Quality of life generally improved after G-POEM. Subscales with significant improvement were Physical functioning (p=0.043), social functioning (0.024), and health change (0.005); however, the improvement of bodily pain, role limitations due to physical health and emotional problems, energy/fatigue, emotional well-being, and general health were not statistically significant (p>0.05). Comparison of GES results before and after G-POEM showed that gastric emptying rate normalized in 55% of patients and the mean 4-hr gastric retention percentage decreased significantly from 39.4 ± 20.4 to 18.3 ± 24.8 (p< 0.001). A total of 4 AEs occurred: 3 capnoperitoneum and 1 mucosotomy, all rated as mild according to the ASGE lexicon. The 3 capnoperitoneum cases were treated by needle decompression, while the inadvertent mucosotomy was successfully treated by stent deployment.

Conclusion: With high technical success rate, limited adverse events, and high clinical efficacy, G-POEM appears to be a feasible and promising therapeutic intervention for management of refractory gastroparesis.

Disclosure: Nothing to disclose

Advances in endoscopy and faecal testing for IBD and cancer

08:30-10:00 / B5

OP140 LOCATION BUT NOT SEVERITY OF ENDOSCOPIC LESIONS AT BASELINE INFLUENCES ENDOSCOPIC HEALING RATES IN CROHN'S DISEASE PATIENTS TREATED WITH INFLIXIMAB: A POST-HOC ANALYSIS OF THE TAILORIX TRIAL

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Introduction: Whether severity and location of endoscopic lesions may influence the likelihood of endoscopic healing in Crohn's disease patients treated with anti-TNF is poorly known. We assessed rates of endoscopic healing in CD patients responding to infliximab (IFX) in combination with an immunomodulator at the end of the induction period and at one year according to baseline endoscopic findings (severity of lesions and their location).

Aims & Methods: We conducted a post-hoc analysis of the endoscopic data prospectively collected in the TAILORIX study, a randomized trial investigating treatment with IFX based on biomarkers and therapeutic drug monitoring in biologic-naïve patients with an active luminal CD (1). All patients had endoscopic ulcerations at inclusion. Ileo-colonoscopies were performed at week 0, 12 and week 54. Endoscopic healing was defined as absence of ulcers, complete endoscopic remission as either CDEIS< 3 or SES-CD< 3, and endoscopic response as >50% decrease in CDEIS or SES-CD scores. Individual segments (ileum, right colon, transverse colon, left colon and rectum) were centrally read and scored separately for healing and response.

Results: Of the 122 patients included in the trial, the 75 patients who received IFX until week 54 and underwent ileocolonoscopy at week 0, 12 and week 54 could be analysed (median (interquartile range) disease duration: 6 (1-67) months), corresponding to 234 diseased segments (ileum n=47, right colon n=46, transverse colon n=46, left colon n=54, rectum n=41) at baseline. Thirty-five patients with early discontinuation of IFX during the study and 12 with missing ileocolonoscopy at week 12 or 54 were excluded. Overall at weeks 12 and 54, 32 (43%) and 54 (72%) patients displayed endoscopic healing, 54 (72%) and 64 (85%) complete endoscopic remission and 63 (84%) and 69 (92%) endoscopic response, respectively. The severity of endoscopic lesions at inclusion did not affect endoscopic outcomes: endoscopic healing rates at weeks 12 and 54 were similar among patients with deep ulcerations at baseline and those with only superficial ulcerations (20/50 (40%) vs.12/25 (48%), p=0.68 and 35/50 (70%) vs.19/25 (76%), respectively, p=0.79), as well as complete endoscopic remission rates (35/50 (70%) vs.19/25 (76%), p=0.79 and 43/50 (86%) vs.21/25 (84%), respectively, p=1.00) and endoscopic response rates (44/50 (88%) vs.19/25 (76%), p=0.32 and 46/50 (92%) vs.23/25 (92%), respectively, p=1.00). The location of endoscopic lesions affected endoscopic outcomes: disappearance of deep ulcerations was lower in the ileum than in the colon both at weeks 12 (18/23 (78%) vs.57/57 (100%), p < 0.01) and 54 (20/23 (87%) vs.57/57 (100%), p=0.02). Consistently, a segmental CDEIS< 3 was less frequent in the ileum than in the colon at weeks 12 and 54 (51% vs.80%, p< 0.01 and 70% vs.94%, p< 0.01, respectively). No difference was observed between disappearance rates of colonic and rectal

deep ulcerations (p=0.17). No difference of segmental remission rates was observed between colonic and rectal lesions at weeks 12 and 54 (80% *vs.*68%, p=0.10 and 94% *vs.*90%, p=0.42, respectively).

Conclusion: In biologic-naive CD patients treated with IFX combo therapy during one year, severity of endoscopic lesions at baseline does not influence healing rates at short- and long-term. Healing rate was lower for ileal than for colonic lesions.

References: 1. D'Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. Gastroenterology. 2018 Apr;154(5):1343-1351.e1.

Disclosure: Abbvie, Amgen.

OP141 ASSESSING MUCOSAL BARRIER FUNCTION IN VIVO WITH CONFOCAL LASER ENDOMICROSCOPY CAN PREDICT MAJOR CLINICAL EVENTS IN IBD PATIENTS WITH HIGH SENSITIVITY

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Introduction: Probe-based confocal laser endomicroscopy (pCLE) enables *in vivo* microscopic imaging during ongoing endoscopy. Further, pCLE enables visualization of mucosal barrier dysfunction (MBD) in patients with inflammatory bowel diseases (IBD). With this, pCLE is the only technology allowing functional imaging within the GI tract in IBD patients.

Aims & Methods: Here we evaluated whether assessment of MBD by pCLE can accurately predict major clinical events (MCE) in IBD patients. IBD patients in clinical and endoscopic remission were prospectively enrolled. pCLE was performed initially and subsequently patients were followed-up for at least 12 months. During follow-up major clinical events (MCE= IBD-related hospitalization, need for surgery, need for initiation of systemic corticosteroids, immunosuppressants or biologics, escalation of existing biologic therapy) were recorded.

Results: 60 patients were prospectively included (37 Crohn's disease [CD], 23 ulcerative colitis [UC]) with a median age of 38 years (range 19-68). CLE-scoring showed strong correlation with histopathology (r≥0.75, p≤0.05) with an almost perfect interobserver agreement of pCLE findings among different readers (Kappa >0.8). MBD as assessed with pCLE in the terminal ileum showed 100% sensitivity (95% CI, 77-100), 75% specificity (95% CI, 47-92) and 88% accuracy in CD patients and 83.3% sensitivity (95% CI, 50.8-97.1), 81.8% specificity (95% CI, 47.8-96.8) and 82.6% accuracy in UC patients for predicting MCEs during the 12 month follow-up. In those patients with MBD in the colon, sensitivity, specificity and accuracy for predicting MCEs with pCLE were 91.7% (95% CI, 59.8-99.6), 72.8% (95% CI, 39.3-92.7) and 82.6%, respectively.

Conclusion: By assessing MBD *in vivo*, pCLE allows to predict MCE in IBD patients in clinical end endoscopic remission with very high sensitivity. Therefore, pCLE can be used to effectively time and personalize anti-inflammatory treatment in IBD patients.

Disclosure: Nothing to disclose

OP142 CROHN´S DISEASE LESIONS DETECTION BY SMALL-BOWEL CAPSULE ENDOSCOPY: AN AUTOMATIC DEEP LEARNING METHOD

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Introduction: Detection of abnormalities in small-bowel capsule endoscopy (SBCE) is challenging and time consuming. Although Crohn´s disease (CD) is one of the main indications to perform SBCE, at the era of deep learning, few efficient computer-aided detection methods have been established.

We aimed to develop an artificial intelligence system based on deep learning to automatically detect CD lesions in SBCE.

Aims & Methods: An attention based-deep convolutional neural network (ACNN) system has been trained, using two databases, CrohnIPI and a public national database, CAD-CAP. The CrohnIPI database encompassed images extracted from Pillcam® SB2 and SB3 videos of patients with a known or suspected CD, in whom a SBCE was performed between 2013 and 2018 in our department. Pathologic frames have been annotated as follow: aphtoid ulceration, ulceration between 3 and 10mm, ulceration over 10mm, stenosis, erythema and edema. Lesions were not localized or delineated into the image. Pathologic and normal images were not selected in regard of their cleanliness or lighting. The CAD-CAP public database was used for the Gastrointestinal Image ANAlysis deep-learning challenge in 2018. It contains normal, vascular and inflammatory frames.

The whole original CrohnIPI's images were randomly split into three groups: 70% for the training phase, 10% for the validation phase and 20% for the test phase. The training phase was performed 10-times with random split of data to get a robust 10 folds cross-validation. CAD-CAP's images were split into the same three groups as follow: 80%, 20% and 10%. For this database, no cross-validation was done. We assessed our ACNN performance by calculating accuracy, sensitivity and specificity for each database using an independent dataset from the one used for training.

Results: The CrohnIPI database was composed of 1628 normal frames and 1590 containing CD lesions, acquired from 63 videos of 54 patients. The pathologic dataset contained 1281 ulcerations, 419 erythema, 64 stenosis and 428 edemas. Note that one frame could contain several lesions. The CAD-CAP database contained 600 images of each type (normal, vascular and inflammatory). Our classifier reached 90.85% accuracy, 91.47% specificity and 90.22% sensitivity on our own dataset, CrohnIPI. The accuracy, specificity and sensitivity for the CAD-CAP database were respectively 99.67%, 100% and 98.97%.

Conclusion: We developed a new system based on a CNN to automatically detect CD lesions in images obtained from SBCE. The AI system showed a better performance on a selected frames national database. The promising performance of this ACNN paves the way for a complete computer-aided diagnosis system that could support physician´s clinical practice. Future work is aiming to train our ACNN on entire videos and developing an application that could permits a collaborative annotation.

Disclosure: Nothing to disclose

OP143 A PATIENT SELF-MADE ONE STEP QUICK FAECAL TEST IMPROVES DIAGNOSTIC ACCURACY FOR DETECTING ENDOSCOPIC ACTIVITY COMPARED WITH FAECAL CALPROTECTIN ALONE IN INFLAMMATORY BOWEL DISEASE PATIENTS

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Introduction: Faecal Calprotectin (FC) has a good correlation with inflammatory activity in Inflammatory Bowel disease (IBD). Faecal occult blood test (FOBT) has demonstrated effectiveness detecting colorectal cancer or precancerous lesions in screening programs, but it's value for monitoring IBD activity is less well established. Other faecal biomarkers, including faecal lactoferrin or faecal transferrin, are less used in clinical practice. Quick faecal tests, performed by patients at home or in the outpatients clinic, may be a useful strategy to monitor closely the disease activity.

Aims & Methods: To evaluate the diagnostic accuracy for detecting inflammatory colorectal mucosal activity of a one-step combo card faecal test for the simultaneous semi-qualitative detection of human haemoglobin (hHb), human transferrin (hTf), human calprotectin (hCp) and human lactoferrin (hLf) in samples of IBD patients.

Methods: Consecutive IBD patients referred for colonoscopy according to our center protocol, who complete colonic examinations and returned stool samples, were prospectively recruited. Certest FOB+Transferrin+Calprotectin+Lactoferrin® (Certest Biotec S.L, Zaragoza, Spain), a coloured chromatographic inmunoassay for the simultaneous semi-qualitative detection of hHb, hTf, hCp and hLf, was performed.

Endocoscopic activity was defined using endoscopic MAYO score in Ulcerative Colitis (UC), and SES-CD score for Crohn's Disease (CD).Clinical activity was evaluated by MAYO partial score in UC and Harvey-Bradshaw Index in CD.

Laboratory data (C reactive protein, albumin, white blood cell count) were collected.

Positive and negative predictive values (PPV, NPV), sensitivity and specificity and area under ROC curve (AUROC) for each marker and for the different combinations for the detection of endoscopic activity were calculated.

Results: 106 patients (56,6% female, median age 52 years, IQR 42-61) were finally included. 54 (50,9%) with UC and 52 (49,1%) with CD. Median time since diagnosis was 14 years (IQR 9-20). 24 (22.6%) patients report clinical activity, while endoscopic activity was detected in 42 patients (39.6%). No significant difference was observed in C reactive protein mean levels according to the presence of endoscopic activity.

Diagnostic accuracy for hHb, hCp, hTf, hLf and its combination are summarized in Table 1.

AUROC were 0.62 (95% CI: 0.5-0.73) for C reactive protein and 0.83 (95% CI: 0.75-0.91) for the combination of the 4 biomarkers.

Test	Negative test	Positive test	PPV	NPV	Sensitivity	Specificity
hCp	23	83	49.3%	95.6%	97.6%	34.3%
hHb	73	33	75.8%	76.7%	59.5%	87.5%
hTf	79	27	70.4%	70.8%	45.2%	84.9%
hLf	78	28	82.1%	75.6%	54.7%	92.1%
All negative	19	87	48.3%	100%	100%	29.7%
All positive	93	13	100%	68%	30.9%	100%

[Table 1.]

Conclusion: FC alone is a good biomarker to rule out endoscopic activity in IBD, but with a low PPV. The one step quick simultaneous determination of 4 faecal biomarkers with the same kit improves the accuracy of FC alone for detecting patients with high risk of endoscopic activity.

Disclosure: Nothing to disclosure

OP144 LONG-TERM OUTCOMES FOLLOWING ENDOSCOPIC RESECTION OF NEOPLASTIC LESIONS IN ULCERATIVE COLITIS: A LARGE SINGLE-CENTRE RETROSPECTIVE STUDY

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Introduction: Patients with ulcerative colitis (UC) are enrolled into surveillance programs for the early detection of precursor dysplasia and colorectal cancer (CRC). The SCENIC[1] consensus recommends endoscopic resection of amenable dysplastic lesions; however, long-term patient outcomes, particularly for larger and/or non-polypoid lesions, remains poorly defined.

Aims & Methods: We conducted a retrospective observational study at St. Mark's Hospital to identify all patients with Montreal classification E2 & E3 UC who underwent endoscopic resection of dysplastic & serrated lesions arising within the extent of inflammation, between 01 January 2005 and 30 June 2016. Patients with incomplete endoscopic resection at index endoscopy, no follow-up endoscopy/colectomy, and those with other CRC-predisposing conditions (e.g. polyposis) were excluded. Patients were followed up until the date of colectomy, or the last endoscopy up to 31 December 2018. Survival analyses were performed using Kaplan-Meier estimation and Cox proportional hazards models.

Results: 236 patients met the inclusion criteria, with a median patient age of 64 years (range 28-88) and median 23 year duration (range 1 - 57) of diagnosed UC, at index endoscopy. CRC was found in the endoscopy resection specimens of 7 patients; 5 underwent colectomy in the following 18 months, with the other two remaining CRC-free and on active monitoring. For the remaining 229 patients, the median patient follow-up time of post-resection was 5.2 years, with a median 4 follow-up endoscopies per patient. There was a median 12.2 months until first follow-up endoscopy for patients with their largest lesion < 10mm, and median 6.2 months until first follow-up endoscopy for those with lesion(s) >=10mm. 22% of patients underwent resection of multiple lesions at their first procedure. Of the 1,259 total endoscopies, only 2 resulted in complications requiring hospitalisation (post-polypectomy bleeding).

In these 229 patients, the risks of first dysplasia recurrence at 1 and 5 years were 27.4% and 59.2% respectively. Colectomy risks at 1 and 5 years were 3.5% and 8.3% respectively in patients with the largest index lesion is < 10mm (n=142), and 8.0% and 26.4% respectively for patients with lesion(s) >10mm (n=87, log-rank p< 0.001). In all but 1 patient who required surgery for UC severity, colectomies were performed either for neoplastic progression to CRC, or for endoscopically unresectable dysplasia. CRC was detected in 45% of colectomy specimens (17/38).

Multivariate Cox proportional hazards analysis demonstrates that lesion size >=10mm (HR = 2.16 [1.06 - 4.4, 95% CI]) and non-polypoid shape (HR = 3.2 [1.51 - 6.4, 95% CI]) were significant predictors of future colectomy (model log-rank p=0.02). Covariates for the presence of multifocal dysplasia, high grade dysplasia, pseudopolyposis, patient age, IBD duration, PSC and serration were statistically insignificant. Of note, patients with LGD resected by endoscopic submucosal dissection (n=15) and piecemeal EMR (n=40) had similar risk of future colectomy (p=0.94).

Conclusion: With over 1,272 patient-years of data, this is the largest study of endoscopic resection in IBD, and the first to correlate resection outcomes with clinical & endoscopic characteristics. While endoscopic dysplasia resection is safe and effective, over 25% of patients with lesions larger than 10mm ultimately required a colectomy within 5 years despite ostensibly complete dysplasia resection at index endoscopy, highlighting the importance of long-term surveillance and counseling these patients, who face the ongoing possibility of surgery.

References: Laine L, Kaltenbach T, Barkun A et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology. 2015 Mar; 148(3):639-651

Disclosure: Nothing to disclose

OP145 PROGRESSIVE REDUCTION OF COLORECTAL CANCER INCIDENCE AND MORTALITY IN THE CZECH REPUBLIC: EFFECT OF SUBSTANTIAL TARGET POPULATION COVERAGE BY EXAMINATIONS?

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Introduction: The organized non-population based National Colorectal Cancer (CRC) Screening Program in the Czech Republic was running since year 2000. In January 2014, the transition to population-based setting has been implemented. Currently, the annual immunochemical fecal occult blood test (FIT) is offered at the age 50 - 54, followed by FIT+ colonoscopy, if positive. In age of 55, there is a choice of either FIT biennially or screening colonoscopy in 10 years interval. Besides these preventive colonoscopies, adenomas and colorectal cancers might be found out and treated with diagnostic colonoscopy. Between years 2000 and 2015, significant reduction of the CRC incidence (18.4 %) and mortality (32.4 %) was observed.

Aims & Methods: Estimation of the overall coverage of the screening target population (aged 50+) in the Czech Republic by available tests: FIT, screening colonoscopy or diagnostic colonoscopy. The analysis was performed using the newly available database (National Registry of Reimbursed Health Services), which contains individual data on reimbursed healthcare in the Czech Republic. Overall coverage was assessed over a three-year period 2015-2017.

Results: The CRC screening target population consists of 4,056,641 individuals. The FITs were performed in 1,758,596 individuals (43.4 %), screening colonoscopies in 36,387 individuals (0.9 %) and diagnostic colonoscopies

in 268,701 individuals (6.6 %). The overall target population coverage in the Czech Republic reached 50.9 % (women 52.0 %, men 49.5 %), highest in the age group of 65 - 69 years. The coverage is heterogenous among the regions (44.6 - 58.2 %), lowest in the capital city.

Conclusion: The overall target population coverage of CRC screening and diagnostic tests (50.9 %) has reached the recommended level according to the European guidelines (45-60 %). The most common examination is FIT, but significant part of screening target population (6.6.%) has been examined with diagnostic colonoscopy. The high number of preventive and diagnostic colonoscopies might be the reason for the observed CRC incidence and mortality reduction in the Czech Republic.

Disclosure: Nothing to disclose

Randomised controlled trials in IBD I

08:30-10:00 / C2

OP146 MUCOSAL MOLECULAR SIGNATURES DIFFER BETWEEN ULCERATIVE COLITIS PATIENTS WITH OR WITHOUT RESPONSE TO VEDOLIZUMAB THERAPY

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Introduction: The anti-integrin monoclonal antibody vedolizumab has been successfully incorporated in the treatment algorithms for moderate to severe ulcerative colitis. A substantial percentage of patients, however, do not respond to this agent and fail to achieve sustained clinical remission. The identification of mucosal or systemic molecular biomarkers that could predict response to vedolizumab is urgently needed to facilitate better patient selection.

Aims & Methods: In a prospective study we aimed to identify mucosal molecular signatures with predictive value for response to vedolizumab in patients with ulcerative colitis. To accomplish our aim, mucosal biopsies were obtained at baseline, i.e. before commencement of vedolizumab, from pre-defined involved areas during lower GI endoscopy. Total RNA was extracted and the mRNA expression for several inflammatory mediators were examined with an RT² Profiler PCR Array Gene Expression array (Qiagen). Baseline transcriptomic profiles were compared between patients who were subsequently responders to scheduled vedolizumab treatment until week 54 and patients who failed to respond to vedolizumab. A significant difference was considered when there was a >2-fold increase or decrease in expression and a P value of < 0.05 for the comparison between the 2 groups.

Results: To compare baseline transcriptomic profiles, overall, we assessed 10 patients who continued vedolizumab treatment and were in clinical remission at week 54 and 10 patients who failed treatment with vedolizumab. Mucosal mRNA signatures at baseline differed between the two groups of patients. In particular, we identified eight genes that were significantly upregulated at baseline in non-responders (CD40LG, CXCL10, LTB, IL-23A, CXCL9, SELE, CEBPB, CXCL5) and 9 genes that were significantly downregulated (CXCL6, CCL4, CCL5, NR3C1, TNFSF14, CCL24, CCL2, CD14, CSF1). The top two mostly differentiated genes between the two groups were CD40LG (37-fold increase in non-responders, P= 0.000961) and CXCL6 (20-fold decrease in non-responders, P= 0.0035).

Conclusion: Using a targeted transcriptomic profiling approach we were able to identify, at baseline, several differentially expressed inflammatory mediators in the colonic mucosa of patients with ulcerative colitis who were responders or non-responders after 54 weeks of vedolizumab therapy. If these results are replicated in larger cohorts they could provide reliable predictive biomarkers for better pre-treatment stratification of patients and for optimization of their clinical response to vedolizumab.

Disclosure: This study has been funded by an IISR from Takeda to G.B.

OP147 ANTI-INFLAMMATORY GUT MICROBIAL PATHWAYS ARE DECREASED DURING CROHN'S DISEASE EXACERBATIONS

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Introduction: Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by alternating periods of exacerbation and remission. We hypothesized that changes in the gut microbiome are associated with CD exacerbations, and therefore aimed to correlate multiple gut microbiome features to CD disease activity.

Aims & Methods: Fecal microbiome data generated using whole-genome metagenomic shotgun sequencing of 196 CD patients were of obtained from the 1000IBD cohort (one sample per patient). Patient disease activity status at time of sampling was determined by re-assessing clinical records three years after fecal sample production. Fecal samples were designated as taken 'in an exacerbation' or 'in remission'. Samples taken 'in remission' were further categorized as 'before the next exacerbation' or 'after the last exacerbation', based on the exacerbation closest in time to the fecal production date. CD activity was correlated with gut microbial composition and predicted functional pathways via logistic regressions using MaAsLin software.

Results: In total, 105 bacterial pathways were decreased during CD exacerbation (FDR< 0.1) in comparison to the gut microbiome of patients both before and after an exacerbation. Most of these decreased pathways exert anti-inflammatory properties facilitating the biosynthesis and fermentation of various amino acids (tryptophan, methionine and arginine), vitamins (riboflavin and thiamine) and short-chain fatty acids (SCFAs).

Conclusion: CD exacerbations are associated with a decrease in microbial genes involved in the biosynthesis of the anti-inflammatory mediators riboflavin, thiamine and folate and SCFAs, suggesting that increasing intestinal abundances of these mediators might provide new treatment opportunities. These results were generated using bioinformatic analyses of cross-sectional data and need to be replicated using time-series and wet lab experiments.

Disclosure: Nothing to disclose

OP148 EARLY HISTOLOGIC IMPROVEMENT DEMONSTRATED WITH ORAL OZANIMOD IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE IN THE STEPSTONE TRIAL

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Introduction: Ozanimod, an oral immunomodulator that selectively targets S1P$_1$ and S1P$_5$, has demonstrated efficacy and safety in ulcerative colitis (UC) (Sandborn *NEJM* 2016) and is being evaluated in active Crohn's Disease (CD). The aim of the STEPSTONE study was to examine histologic, endoscopic, and clinical outcomes, and safety of ozanimod in adults with CD.

Aims & Methods: STEPSTONE was an open-label uncontrolled phase 2 multicenter trial of ozanimod for 12 weeks, followed by an extension period. Patients with active CD (Crohn's Disease Activity Index [CDAI] score 220-450, total simple endoscopic score for CD [SES-CD] ≥6 [or in isolated

ileum disease SES-CD ≥4]) received ozanimod 1 mg daily. Ileo-colonic endoscopic biopsies (perpendicular to the mucosal surface at the edge of the largest ulcer or in the most severely affected area in segments without ulcers) were obtained from the terminal ileum and 4 colonic segments at baseline and Weeks 12 and 52 for assessment of histologic change. A post hoc analysis of histology data through week 12 are reported here, based on a 02-Oct-2017 interim data cut. The Robarts Histopathology Index (RHI) is a validated, reproducible, and responsive index that incorporates four histological descriptors (severity of chronic inflammatory infiltrate, the number of lamina propria neutrophils, the number of neutrophils in the epithelium, and the severity of erosions or ulceration), each of which is objectively graded from 0 to 3 (Mosli *Gut* 2017).

Results: Sixty-nine patients were enrolled. At baseline, mean age was 38 years, mean SES-CD was 13, mean CDAI score was 321, and mean RHI was 16.3. Mean CD duration since diagnosis was 9 years, with 54% of patients having had prior exposure to biologic therapy (i.e., anti-TNF-α, vedolizumab). Table 1 presents the mean change in RHI for paired segments from baseline to Week 12 in the overall study population and in subgroups of patients with or without prior exposure to biologic therapy and by segment. Through 12 weeks, most non-serious and serious adverse events appeared to be related to underlying moderate to severe CD. No new safety signals were identified.

Conclusion: Results of the STEPSTONE trial demonstrated early histologic improvements among patients with moderately to severely active CD who were treated for 12 weeks with ozanimod. These improvements were seen in the patients with and without prior biologic exposure and across all segments.

Study Group	N (ITT N=69)	Mean (Standard Deviation)
Overall Population	52	-4.5 (9.48)
Biologic Exposure		
Prior Biologic Exposure	30	-4.0 (8.59)
Biologic Naïve	22	-5.1 (10.75)
Segment (analysis includes patients with baseline segment scores of >3)		
Ileum	30	-5.3 (8.58)
Rectum	26	-8.2 (10.59)
Left Colon	24	-8.1 (11.38)
Right Colon	19	-4.5 (12.63)
Transverse Colon	17	-2.3 (9.29)

[Table 1: Change from Baseline in Robarts Histopathology Index (RHI) Score at Week 12 – Observed Cases, Intent-to-Treat Population]

References: Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med. 2016;374(18):1754-1762. Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. Gut. 2017;66(1):50-58.

Disclosure: Brian G. Feagan: AbbVie, Actogenix, Albireo, Amgen, AstraZeneca, Avaxia Biologics, Baxter, Biogen Idec, Boehringer Ingelheim, BMS, Calypso, Celgene, Elan, EnGene, Ferring Pharma, Roche/Genentech, GiCare, Gilead, Given Imaging, GSK, Ironwood, Janssen, Johnson & Johnson, Lexicon, Lilly, Merck, Millennium, Nektar, Novo Nordisk, Pfizer, Prometheus, Protagonist, Celgene, Sanofi, UCB - consultant; Robarts Clinical Trials - director. Geert D'Haens: AbbVie, Ablynx, Amakem, AM Pharma, Avaxia, Biogen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmo, Covidien/Medtronic, Ferring, Dr. Falk Pharma, EnGene, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Hospira, Immunic, Johnson & Johnson, Lycera, Medimetriks, Millennium/Takeda, Mitsubishi Pharma, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, Otsuka, Pfizer, Prometheus Laboratories/Nestle, Protagonist, Receptos, Robarts Clinical Trials, Salix, Sandoz, SetPoint, Shire, Teva, Tigenix, Tillotts, TopiVert, Versant, Vifor - consultant; AbbVie, Biogen, Ferring, Johnson & Johnson, Merck Sharp & Dohme, Mundipharma, Norgine, Pfizer, Shire, Millennium/Takeda, Tillotts, Vifor - speaker; Robarts Clinical Trials - director; EnGene - shareholder. Keith Usiskin: Celgene - employment/shareholder. Jerry Liu: Celgene - employment/shareholder. Rish K. Pai: none to disclose.

OP149 HISTOLOGIC REMISSION AND MUCOSAL HEALING IN A PHASE 2 STUDY OF MIRIKIZUMAB IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

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Introduction: Interleukin (IL)-23 is a key cytokine in inflammatory bowel disease pathogenesis. Mirikizumab (miri), a p19-directed IL-23 antibody, demonstrated efficacy and was well-tolerated during 12 weeks of induction followed by an additional 40 weeks of maintenance treatment in a phase 2 randomized clinical trial (NCT02589665) in patients with ulcerative colitis (UC). The histologic results at Week 12 induction and Week 52 maintenance are presented here.

Aims & Methods: Patients were randomized 1:1:1:1 to receive intravenous placebo (PBO), miri 50mg or 200mg with possibility of exposure-based dose increases, or fixed miri 600mg every 4 weeks (Q4W), with efficacy assessment at Week 12. Patients who achieved clinical response to miri at Week 12 were re-randomized 1:1 to a double-blind maintenance treatment with miri 200mg subcutaneously (SC) Q4W or every 12 weeks (Q12W), and were treated through Week 52. Endoscopy was performed at Weeks 0, 12, and 52, with biopsy of the sigmoid colon obtained at the most affected area lying at least 30 cm from the anal verge. Glass slide sections of the biopsies, stained with hematoxylin and eosin for histologic evaluation, were digitized and centrally read by one of two gastrointestinal pathologists with scoring performed using the Geboes Score. Histologic remission was defined as Geboes histologic subscores of 0 for neutrophils in lamina propria, neutrophils in epithelium, and erosion or ulceration parameters.

	Induction Treatment Groups			
	Placebo (N=63)	Mirikizumab 50 mg EB IV Q4W (N=63)	Mirikizumab 200 mg EB IV Q4W (N=62)	Mirikizumab 600 mg IV Q4W (N=61)
Mean (SD) unless otherwise specified	Baseline Characteristics			
Age, years	42.62 (13.47)	41.83 (14.06)	43.35 (14.75)	42.44 (13.71)
Male, n (%)	36 (57.1)	38 (60.3)	37 (59.7)	38 (62.3)
Disease duration, years	9.5 (9.6)	8.2 (7.2)	9.0 (9.0)	6.0 (5.7)
Previous biologic use, n (%)	40 (63.5)	39 (61.9)	40 (64.5)	38 (62.3)
	Mayo Score, n (%)			
6-8	27 (42.9)	24 (38.7)	27 (44.3)	26 (42.6)
9-12	36 (57.1)	38 (61.3)	34 (55.7)	35 (57.4)
	Induction Period, Study Week 12			
Histologic remission, n (%)	11 (17.5)	9 (14.3)	28 (45.2)	21 (34.4)
% Difference vs PBO (95% CI)	---	-3.2 (-15.9, 9.6)	27.7 (12.2, 43.2)	17.0 (1.8, 32.1)

	Maintenance Treatment Groups	
	Mirikizumab 200 mg SC Q4W (N=47)	Mirikizumab 200 mg SC Q12W (N=46)
	Maintenance Period, Study Week 52	
Histologic remission[a], n (%)	31 (66.0)	17 (37.0)
Durable histologic remission[b], n (%)	20 (42.6)	9 (19.6)
Mucosal healing[c], n (%)	23 (48.9)	11 (23.9)

[a]Histologic remission: Geboes histologic subscores of 0 for neutrophils in lamina propria, neutrophils in epithelium, and erosion or ulceration parameters.
[b]Durable histologic remission: histologic remission at both Week 12 and 52.
[c]Mucosal healing: Histologic remission + endoscopic improvement (Mayo endoscopic subscore=0 or 1).

[Table 1.]

Results: Greater proportions of patients who received 200 or 600mg of miri achieved histologic remission at 12 Weeks compared to PBO (PBO: 17.5% [95% CI: 8.1-26.8]; miri 50mg: 14.3% [95% CI: 5.6-22.9]; 200mg:

45.2% [95% CI: 32.8-57.5]; 600mg: 34.4% [95% CI: 22.5-46.3]. Of the patients who continued onto the maintenance period, 66.0% and 37.0% of patients in miri 200mg Q4W and Q12W groups, respectively, achieved histologic remission at Week 52. Moreover, 42.6% (Q4W) and 19.6% (Q12W) of patients had durable histologic remission throughout the maintenance period, and 48.9% (Q4W) and 23.9% (Q12W) achieved mucosal healing (histologic remission plus endoscopic improvement).

Conclusion: Patients treated with miri achieved and sustained histologic remission over 52 weeks of treatment. These are the first histologic data with an IL-23 p19 targeted antibody in patients with UC.

Disclosure: Study was funded by Eli Lilly and Company.

OP150 HISTOLOGIC IMPROVEMENT WITH VEDOLIZUMAB VS ADALIMUMAB IN ULCERATIVE COLITIS: RESULTS FROM VARSITY

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Introduction: Histologic remission is associated with superior long-term clinical outcomes in ulcerative colitis (UC). VARSITY, the first head-to-head comparison of biologic agents in UC (NCT02497469; EudraCT 2015-000939-33), showed superior clinical remission and endoscopic improvement at Week 52 with vedolizumab (VDZ), a gut-selective, humanised, $\alpha_4\beta_7$ integrin monoclonal antibody, vs adalimumab (ADA), a systemic, human, anti-tumour necrosis factor (anti-TNF) monoclonal antibody.[1] Both VDZ and ADA were generally safe and well-tolerated.[1] This analysis compared histologic improvements with VDZ vs ADA in VARSITY.

Aims & Methods: Patients with moderately to severely active UC were randomised 1:1 to active VDZ intravenous (IV) infusions (300 mg)/placebo subcutaneous (SC) injections or placebo IV/active ADA SC (160/80/40 mg). Prespecified histologic exploratory endpoints included histologic remission (Geboes score < 2 or Robarts Histopathology Index [RHI] score < 3) and minimal histologic disease activity (Geboes score < 3.2 or RHI score < 5) at Week 14 and Week 52. Histologic remission was also assessed based on previous anti-TNF use.

Results: A total of 769 patients received ≥1 dose of VDZ (n=383) or ADA (n=386). Median (range) duration of exposure was 477 (127, 630) days for VDZ and 420 (71, 454) days for ADA. Mean (standard deviation) baseline histologic disease activity was similar between groups (Geboes: VDZ, 15.0 [4.92]; ADA, 15.1 [5.03]; RHI: VDZ, 19.5 [8.74]; ADA, 19.6 [8.89]). Histologic remission induced by VDZ at Week 52 was greater than with ADA in the overall (Geboes or RHI), anti-TNF naïve (Geboes or RHI), and anti-TNF failure (RHI only) groups (Table). Histologic remission at Week 14 favoured VDZ over ADA, with larger differentiation when using RHI (Table). VDZ also outperformed ADA in achieving minimal histologic disease activity at Weeks 14 and 52 (Table).

Conclusion: VARSITY showed that use of VDZ, compared with ADA, achieved higher rates of histologic remission and minimal histologic disease activity at Weeks 14 and 52 in patients with moderately to severely active UC. These data support the use of VDZ over ADA in UC.

References: 1. Schreiber S, et al. J Crohns Colitis. 2019;13(suppl 1):S612-S613. Abstract OP34.

Parameter	Adalimumab SC 160/80/40 mg (n=386) Histologic Remission (Geboes Score <2), n (%)	Vedolizumab IV 300 mg (n=383)	Difference (95% CI)	P value	Adalimumab SC 160/80/40 mg (n=386) Histologic Remission (RHI Score <3), n (%)	Vedolizumab IV 300 mg (n=383)	Difference (95% CI)	P value
Overall, Wk 14	12 (3.1)	19 (5.0)	1.8 (-0.9 to 4.6)[a]	0.1944	62 (16.1)	98 (25.6)	9.5 (3.8 to 15.2)[a]	0.0011
Anti-TNF naïve, Wk 14	12 (3.9)	16 (5.3)	1.3 (-2.0 to 4.7)[b]	0.4348	58 (19.0)	82 (27.0)	8.0 (1.3 to 14.6)[b]	0.0198
Anti-TNF failure, Wk 14	0	3 (3.8)	3.8 (-11.9 to 19.5)[b]	0.1180	4 (4.9)	16 (20.3)	15.3 (0.1 to 30.6)[b]	0.0038
Overall, Wk 52	12 (3.1)	40 (10.4)	7.3 (3.8 to 10.8)[a]	<0.0001	77 (19.9)	144 (37.6)	17.6 (11.3 to 23.8)[a]	<0.0001
Anti-TNF naïve, Wk 52	11 (3.6)	40 (13.2)	9.6 (5.2 to 13.9)[b]	<0.0001	69 (22.6)	121 (39.8)	17.2 (9.9 to 24.4)[b]	<0.0001
Anti-TNF failure, Wk 52	1 (1.2)	0	-1.2 (-16.9 to 14.5)[b]	1.0000	8 (9.9)	23 (29.1)	19.0 (7.1 to 31.0)[b]	0.0022
Parameter	Minimal Histologic Disease Activity (Geboes Score <3.2), n (%)				Minimal Histologic Disease Activity (RHI Score <5), n (%)			
Overall, Wk 14	49 (12.7)	81 (21.1)	8.4 (3.2 to 13.6)[a]	0.0017	94 (24.4)	143 (37.3)	12.9 (6.5 to 19.4)[a]	<0.0001
Overall, Wk 52	53 (13.7)	128 (33.4)	19.6 (13.8 to 25.5)[a]	<0.0001	99 (25.6)	162 (42.3)	16.6 (10.0 to 23.1)[a]	<0.0001

[OP150 Table. Histologic Remission and Minimal Histologic Disease Activity]

[a]Adjusted treatment difference and nominal P value: based on the Cochran-Mantel-Haenszel method, stratified by concomitant use of oral corticosteroids (Yes/No) and prior use of anti-TNF therapy (Yes/No); vedolizumab versus adalimumab.
[b]Adjusted treatment difference and nominal P value: based on the Cochran-Mantel-Haenszel method, stratified by concomitant use of oral corticosteroids (Yes/No) or the Fisher´s exact method if the numerator is ≤5; vedolizumab versus adalimumab.
CI, confidence interval; IV, intravenous; RHI, Robarts Histopathology Index; SC, subcutaneous; TNF, tumour necrosis factor-alpha.

OP151 LONG-TERM MUCOSAL HEALING, CLINICAL RESPONSE AND CLINICAL REMISSION IN PATIENTS WITH ULCERATIVE COLITIS TREATED WITH THE ANTI-MUCOSAL ADDRESSIN CELL ADHESION MOLECULE-1 (MADCAM-1) ANTIBODY ONTAMALIMAB (SHP647): RESULTS FROM THE OPEN-LABEL EXTENSION STUDY TURANDOT II

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Introduction: Ontamalimab (SHP647), a human monoclonal IgG_2 antibody, targets endothelium expressed mucosal addressin cell adhesion molecule-1 (MAdCAM-1), to reduce lymphocyte homing to the gastrointestinal (GI) tract. In the TURANDOT II trial, ontamalimab was well-tolerated and clinical benefit was seen up to 144 wks in patients with ulcerative colitis (UC). This abstract reports long-term mucosal healing, response and remission in a subset of patients in TURANDOT II.

Aims & Methods: TURANDOT II (NCT01771809) is a phase 2, 2-part open-label (OL) extension study of ontamalimab in patients with moderate-to-severe UC who received placebo or ontamalimab 7.5, 22.5, 75 or 225mg subcutaneously (sc) in the feeder study (TURANDOT). At TURANDOT II baseline (TURANDOT wk 12), patients were randomized to ontamalimab 75 or 225mg sc every 4 wks for 72 wks (OL1). Dose escalation from 75 to 225mg was permitted between wks 8 and 72 in cases of clinical exacerbation or no response. In OL2, patients received 75mg every 4 wks for 72 wks. Endoscopies were carried out at wk 16 for all patients, and a subset of patients undergoing routine cancer surveillance underwent at least one follow-up endoscopy between wks 40 and 72 of OL1: all endoscopies were centrally-read. Mucosal healing (Mayo endoscopy subscore ≤1), clinical remission (total Mayo score ≤2, no subscore >1) and clinical response (≥3-point decrease in total Mayo score from TURANDOT baseline, ≥30% change; ≥1-point decrease in or ≤1 rectal bleed absolute score) were measured.

Results: Of 330 patients in TURANDOT II, 101 had follow-up endoscopies (Table 1), 25.7% (n = 26) of whom had mucosal healing at TURANDOT II baseline. At week 16, 43.6% of patients (n = 44) had mucosal healing, and 75% of these patients (n = 33) maintained mucosal healing up to week 40-72. Of the 65 responders in TURANDOT, 37 (56.9%) had mucosal healing at both wk 16 and at wk 40-72. Of 36 non-responders, 19.4% (n = 7) and 25% (n = 9) achieved mucosal healing at wk 16 and wk 40-72, respectively.

	Ontamalimab overall (n = 101)
Mean (SD) Age, years	39.2 (12.5)
Sex, n (%) male	62 (61.4)
Anti-TNF naïve, n (%)	51 (50.5)
Mean time since UC diagnosis, years	7.89 (6.8)
Number (%) of patients in clinical remission	17 (16.8)
Mean (SD) total Mayo score	5.1 (2.7)
Mean (SD) partial Mayo score	3.1 (2.1)
Mean (SD) concentration of hsCRP (mg/dL) (n = 98)	0.7 (1.1)
Mean (SD) concentration of fecal calprotectin (µg/g) (n = 90)	1746 (2950)

[Table 1. Patient demographics and characteristics at TURANDOT II baseline.]

Of the responders, 89.2% (n = 58) maintained response and 41.5% (n = 27) were in remission at wk 16; at wk 40-72, 81.5% (n = 53) maintained response and 50.8% (n = 33) were in remission. Of non-responders, 61.1%

(n = 22) achieved response and 13.9% (n = 5) achieved remission by wk 16; by wk 40-72, 47.2% (n = 17) had responded and 22.2% (n = 8) were in remission. Overall, the mean Mayo endoscopic subscore of 2 (SD, 0.1) was maintained from baseline to wk 40-72.

Conclusion: Mucosal healing, response and remission persisted in a subset of patients who continued ontamalimab treatment up to 72 wks and underwent surveillance endoscopies between wks 40 and 72. These findings support study of ontamalimab in on-going phase 3 trials.

Optimising treatment strategies in pancreatitis and pancreatic cancer

08:30-10:00 / E1

OP152 DOUBLE PIGTAIL PLASTIC STENTS ARE CHEAPER AND AS EFFECTIVE AS LUMEN APPOSING METAL STENT FOR THE ENDOSCOPIC DRAINAGE OF WALLED-OFF NECROSIS: A CASE CONTROL STUDY

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Introduction: The presence of infected walled off necrosis (WON) increases morbidity and mortality in severe acute pancreatitis. In the last years, endoscopic drainage has gained increased attention as part of step-up approach, through the creation of a controlled fistula between the upper gastrointestinal tract and the pancreatic necrotic collection. The patency of fistula is allowed by endoscopic stenting and, for this purpose, double pigtail plastic stents have been traditionally used. In the last years lumen apposing metal stents (LAMS) have been proposed. By harboring a wider diameter, they are supposed to allow better necrotic tissue clearance through the execution of multiple sessions of endoscopic necrosectomy. Despite a substantial higher initial cost, a non-unequivocally demonstrated safety and a still unclear effectiveness, lumen apposing metal stents have progressively gained wide spread in clinical practice. Few and mostly heterogeneous studies have compared double pigtail plastic stents and lumen apposing metal stents in terms of short and long-term outcomes. Most of previous studies lacked methodological rigorous designs and have either considered mixed cohorts of patients (WON plus pseudocyst), or have retrospectively investigated extremely inhomogeneous cohorts of patients with WON.

Aims & Methods: To compare short and long-term outcomes of plastic double pigtail versus lumen-apposing metal stents for the endoscopic drainage of infected walled-off necrosis. Single-center, 1:1 case-control study. Patients who have undergone drainage of infected or highly suspected infected pancreatic necrosis through lumen-apposing metal stents (cases) or double pigtail plastic stents (controls) were compared. Controls date up to 2016, when our center used exclusively double pigtail stents; cases date from 2016 onwards, when endoscopic necrosectomies were performed exclusively using lumen-apposing metal stents.

Results: 15 cases and 15 matched controls were enrolled at Karolinska University Hospital, Stockholm, Sweden, between 2011 and 2017. Cases and controls were homogeneous in terms of etiology and clinical characteristics. 93.0% of cases and 86.7% of controls were clinically successful, without any signifcant differences in rates of infection, bleeding and stent migration (respectively 13.3% vs 21.4%; p=0.65; 13.3% vs 0%; p=0.48; 13.3% vs 7.1%; p=1.00), nor of the need for additional percutaneous or surgical treatments (33.3% vs 13.3%; p=0.39). Cases however display a significantly prolonged mean hospital stay (90.2 days vs 18.5 days; p< 0.01) and a higher mean number of endoscopic procedures per patient (1.5 vs 4.8; p< 0.01).

Conclusion: We find that double pigtail stents are not inferior to lumen-apposing metal stents in the treatment of pancreatic WON, and are thus to be favored as a cheaper yet equally effective strategy.

Disclosure: Urban Arnelo received an unrestricted grant from Boston Scientific. Other authors declare no conflicts of interests

OP153 PRO-ACTIVE PERCUTANEOUS CATHETER DRAINAGE OF NECROTIC PANCREATIC COLLECTIONS: A LARGE SINGLE CENTER EXPERIENCE

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Introduction: A pro-active protocol that involves frequent catheter upsizing and insertions has been shown to improve the clinical success of percutaneous catheter drainage (PCD). However, there are a limited number of studies with small sample size.

Aims & Methods: In this large cohort, we aim to compare the outcomes of pro-active protocol in patients with acute pancreatitis (AP) and necrotic collections with a published PCD data.

Consecutive patients with AP who underwent PCD with a pro-active protocol between January 2018 and January 2019 were included. The pro-active protocol was defined as PCD of all the drainable collections after an indication of drainage was identified. This was followed by frequent upsizing with the aim to drain the entire collections including both the liquid and the necrotic component. The outcomes were compared with patients from a retrospective published cohort who underwent PCD between January 2011 and December 2017. Outcome measures included need for surgery, mortality, intensive care unit (ICU) stay, hospital stay and complications.

Results: 110 patients underwent PCD with a pro-active protocol. Their outcome was compared with that of 375 patients who had undergone PCD between 2011 and 2017. There was no significant difference in the age, gender, and etiology of AP between the two groups. A fewer number of patients in the pro-active group required ICU admission (34.5 % vs. 61%, $p< 0.001$). Patients in the pro-active PCD group had a significantly reduced length of hospital stay, and ICU stay (27.45 ± 14.2 vs. 36.59 ± 22.49 days; $p=0.001$ and 4.12 ± 8.5 vs. 11.5 ± 13.6 days; $p< 0.001$ respectively). However, there was no significant difference in terms of mortality and need for surgical intervention between the two groups ($p=0.558$ and 0.153 respectively). The rate of complications was also comparable.

Conclusion: Pro-active PCD protocol results in reduced length of hospital stay, and ICU stay and can reduce hospitalization costs.

Disclosure: Nothing to disclose

OP154 SUPERIORITY OF ENDOSCOPIC INTERVENTIONS OVER MINIMALLY INVASIVE SURGERY FOR INFECTED NECROTIZING PANCREATITIS: A META-ANALYSIS OF RANDOMIZED TRIALS

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Introduction: Infected necrotizing pancreatitis is a highly morbid disease managed either by minimally invasive surgery or endoscopy-based treatment approaches. This meta-analysis was conducted to compare clinical outcomes between patients treated using either approach.

Aims & Methods: MEDLINE and EMBASE were searched to identify all randomized trials that compared minimally invasive surgery and endoscopy-based interventions for the treatment of infected necrotizing pancreatitis. The main outcome measure was to compare rates of complications or death during 6-months of follow-up.

Results: Three studies (184 patients; Bakker OJ et al. PENGUIN trial, JAMA 2012; van Brunschot S et al. TENSION trial, Lancet 2018; Bang JY et al. MISER trial, Gastroenterology 2018) met inclusion criteria (Table). While there was no significant difference in mortality (14.5 vs. 16.1%, risk ratio (RR) 1.02, p=0.96), complications of new onset multiple organ failure (5.2 vs. 19.7%, RR=0.34, p=0.045), enterocutaneous fistula/perforation (3.6 vs. 17.9%, RR=0.34, p=0.034) and pancreatic fistula (4.2 vs. 38.2%, RR=0.13, p< 0.001) were significantly lower for endoscopy compared to minimally invasive surgical treatment approaches. Also, the length of hospital stay was

significantly shorter for endoscopy as compared to surgery (standardized mean difference (SMD) -0.41, p=0.01). There was no significant difference in intrabdominal bleeding (6.2 vs. 12.3%, RR=0.60, p=0.58), new onset diabetes (22.1 vs. 27.3%, RR=0.78, p=0.38) or pancreatic exocrine insufficiency (39.5 vs. 57.8%, RR=0.99, p=0.96) between the cohorts.

Conclusion: An endoscopic treatment approach, as compared to minimally invasive surgery, significantly reduces complications in patients with infected necrotizing pancreatitis.

Outcome measure	Number of patients (n)		Pooled estimate: mean % (95% CI)		Pooled risk ratio (95% CI)	p-value
	Endoscopy	Surgery	Endoscopy	Surgery		
Major complications or death	95	89	25.8 (7.9 - 49.7)	50.8 (33.5 - 68.0)	0.46 (0.17 - 1.27)	0.136
Major complications or death (inc. pancreatic fistula in all studies)	95	89	26.4 (7.5 - 51.7)	57.0 (38.7 - 74.4)	0.44 (0.19 - 1.01)	0.053
Death	95	89	14.5 (8.3 - 22.1)	16.1 (5.0 - 31.8)	1.02 (0.42 - 2.51)	0.963
New onset Multiple organ failure	95	89	5.2 (1.7 - 10.4)	19.7 (6.1 - 38.7)	0.34 (0.12 - 0.98)	0.045
Enterocutaneous fistula/perforation	95	89	3.6 (0.2 - 11.2)	17.9 (10.8 - 26.3)	0.34 (0.13 - 0.92)	0.034
Pancreatic fistula	86	83	4.2 (0.4 - 11.8)	38.2 (19.9 - 58.5)	0.13 (0.04 - 0.37)	<0.001
Intraabdominal bleeding	95	89	6.2 (0.2 - 27.0)	12.3 (3.5 - 25.4)	0.60 (0.10 - 3.59)	0.575
Endocrine pancreatic insufficiency	85	79	22.1 (14.1 - 31.3)	27.3 (18.0 - 37.7)	0.78 (0.45 - 1.36)	0.380
Exocrine pancreatic insufficiency	85	79	39.5 (3.7 - 84.5)	57.8 (17.8 - 92.5)	0.99 (0.66 - 1.48)	0.962
Length of hospital stay (days)	85	79	-	-	SMD -0.41 (-0.71 to -0.095)	0.010

[Table. Summary of pooled outcome measures and risk ratios]

Disclosure: Ji Young Bang and Shyam Varadarajulu are Consultants for Boston Scientific Corp. and Olympus American Inc.

OP155 TIMING OF PANCREATODUODENECTOMY AFTER BILIARY DRAINAGE IN PATIENTS WITH PERIAMPULLARY CANCER IN THE NETHERLANDS

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Introduction: Obstructive jaundice is a frequent symptom in patients with periampullary cancer. Preoperative biliary drainage (PBD) is indicated in patients with cholangitis, severe jaundice (serum bilirubin > 250 μmol/L), intended neoadjuvant chemotherapy and with extended waiting time for definitive surgical treatment due to logistic reasons. Several studies suggest to delay surgery until 4-8 weeks after PBD to allow for recovery of the liver and immune function but consensus is lacking. The aim of this study is to investigate the relation between time from PBD to pancreatoduodenectomy and (major) postoperative outcomes in patients who underwent resection for periampullary cancer.

Aims & Methods: Anonymized data from patients who underwent pancreatoduodenectomy after PBD for periampullary cancer (i.e. pancreatic ductal adenocarcinoma, distal cholangiocarcinoma, ampullary cancer) between Jan 2017 and Dec 2018 were extracted from the mandatory, nationwide, Dutch Pancreatic Cancer Audit. Patients who underwent (radio) chemotherapy prior to pancreatoduodenectomy were excluded from the analysis. Patients were stratified by time from PBD to surgery into group: A; short (< 4 weeks), B; intermediate (4 - 8 weeks), and C; long (> 8 weeks). The primary outcome was the rate of major postoperative complications, defined as any complication classified as Clavien-Dindo grade ≥3 within 30 days after pancreatoduodenectomy. Secondary outcomes were the rate of PBD-related complications and overall complications. PBD-related complications were pancreatitis, cholangitis, perforation, bleeding, stent occlusion or exchange. Overall complications included PBD-related complications and major postoperative complications. A logistic regression analysis was performed, adjusted for age, gender, body mass index, ASA-score, texture of the pancreas and diameter of the pancreatic duct, to assess the association between time from PBD to pancreatectomy and major postoperative complications.

Results: In total, 539 patients were included after PBD prior to pancreatoduodenectomy, group A 221 (41%), group B 251 (47%), and group C 67 (12%) patients, respectively. The median time between PBD and surgery was 56 days (range 5 - 555 days). The rate of PBD-related complications was 15%, with similar outcomes in the three patient groups (group A 13% vs. group B 16% vs. group C 16%; $P = 0.697$). Major postoperative complication (Clavien Dindo ≥ 3) rate was 26% and did not differ between the three groups (group A 25% vs. group B 25% vs. group C 38%; $P = 0.096$). The 30-day mortality rate was 2.2%. The overall complication rate was 69% , with similar outcomes in the three patient groups (group A 67% vs. group B 71% vs. group C 70%; $P = 0.574$). In the multivariable analysis, the duration of preoperative biliary drainage was not associated with a greater risk of major postoperative complications.

Conclusion: The risk for major postoperative complications after pancreatoduodenectomy is not influenced by the interval between preoperative biliary drainage and the surgical procedure.

Disclosure: Nothing to disclose

OP156 TREATMENT AND SURVIVAL OF LOCALLY ADVANCED PANCREATIC CANCER: A PROSPECTIVE MULTICENTER COHORT

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Introduction: About 30-40% of patients with pancreatic cancer present with locally advanced pancreatic cancer (LAPC). Clinical outcomes are mostly described in highly selected patient cohorts.

Aims & Methods: This study aims to give an overview of treatment and survival within an unselected, consecutive cohort of patients with LAPC. Prospective multicenter study including consecutive patients with LAPC according to Dutch Pancreatic Cancer Group (DPCG) criteria between 04/2015-12/2017 from 14 centers. The decision to start treatment was based on the advice of the multidisciplinary team meeting followed by patient consultation of a medical oncologist. Restaging of CT-scans was performed by a nationwide expert panel after two months of systemic treatment. The panel evaluated response according to RECIST criteria, resectability and eligibility for clinical trials.

Results: In total, 422 patients were included, of whom 325 (77%) started chemotherapy, 84 (20%) received best supportive care (BSC) and 13 (3%) started other primary treatments. Most patients started FOLFIRINOX (n=252, 60%), 32 patients (8%) were treated with gemcitabine plus nab-paclitaxel and 41 (10%) with gemcitabine monotherapy. 309 patients were restaged of whom 33 (11%) had a partial response, 221 (72%) had stable disease and 55 (18%) had progressive disease. A total of 34/422 patients (8%) underwent a resection. Median overall survival (mOS) in all patients was 10 months (95%CI 9-11) In patients treated with FOLFIRINOX, nab-paclitaxel plus gemcitabine or gemcitabine monotherapy, mOS was 14 (95%CI 12-16), 9 (95%CI 7-11), and 9 months (95%CI 8-10) respectively. Resected patients had a mOS of 23 months (95%CI 12-34).

Conclusion: In a large prospective multicenter cohort of LAPC, median overall survival was 10 months, 60% received FOLFIRINOX treatment and 8% were eligible for a resection after neoadjuvant chemotherapy with promising survival. Since treatment allocation bias cannot be excluded future randomized studies are needed.

Disclosure: Nothing to disclose

OP157 PAMPAC TRIAL: OCCURRENCE OF PAIN AND QUALITY OF PAIN MANAGEMENT IN PATIENTS WITH PANCREATIC CANCER

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is associated with moderate to severe cancer-related pain in most patients, as it has a high rate of neural invasion. Despite WHO management guidelines for pain management, more than 50% of cancer patients worldwide still experience pain. One-third of these patients don't receive an adequate pain treatment. This data indicates that there is a need for more investigations in this field. Especially for patients with PDACan adequate pain therapy is essential to maintain the quality of life as they are often in a palliative situation with very limited life expectancy.

Therefore we conducted this study to investigate the occurrence of pain and the quality of pain management in patients with PDAC.

Aims & Methods: A multi-center, prospective, cross-sectional study with the aim to evaluate the quality of care in patients with PDAC. The level of pain and the impact of pain on functioning was assessed by the brief pain inventory. Additionally insufficient pain treatment (undertreatment) and possible determinants (e.g. patient characteristics, disease characteristics, tumour therapy) were registered. Undertreatment was defined as a negative PMI (pain management index), which is a score constructed upon the patients level of worst pain substracted from the most potent level of analgesic drug therapy. To investigate the impact of e.g. changes in tumor therapy or disease progression on pain and pain therapy we conducted an follow up after a minimum of 4 weeks.

Results: We recruited 128 patients with histologically proven PDAC. 44% of the patients were female and the mean age was 68 yrs. 77 patients (60%) were questioned while hospitalised and 51 patients (40%) in the outpatient department or private practice. 50 patients (39%) had resectable pancreatic cancer, whereas 22 patients (17%) had locally advanced disease (LAPC) and 56 patients (44%) metastatic disease (mPDAC). A total of 79

patients suffered from pain regularly (62%). 90% of these patients showed an impaired quality of life. Patients in an more advanced disease stage (LAPC, mPDAC) suffered more frequently from pain (77%) than patients with resectable disease (38%). Most common locations of pain were the epigastric area (72%), the lumbar region (34%) and the lower abdomen (22%). 30 patients (38%) showed an insufficient pain treatment (undertreatment). Interestingly, undertreatment was more frequent in resectable disease (58%) than in LAPC (41%) or mPDAC (21%). Furthermore patients with high performance status (ECOG 0: 55%; ECOG 1: 37%) showed a higher rate of undertreatment than patients with a low performance status (ECOG 2: 18%, ECOG 3: 25%). Until now 60 patients (47%) have completed the follow up after a median of 2,2 months. The proportion of patients with pain has not changed markedly (57%), but untertreatment was less frequent (18%) compared to the first interview.

Conclusion: The preliminary results of this ongoing study confirm that there is a high percentage of patients with PDAC suffering from pain. Despite comprehensive pain management guidelines we can show that the amount of patients affected from undertreatment is still very high. Furthermore, our data indicates that especially patients in an early disease stage and with high performance status will need a better pain management in the future.

When the study will have collected more patient data, we'll might be able to identify other determinants of undertreatment and thereby help to improve the pain management in PDAC patients.

Disclosure: Nothing to disclose

Novel therapeutic approaches in microscopic colitis and c. difficile

08:30-10:00 / Barcelona

OP158 MICROBIOTA RESTORATION THERAPEUTIC CANDIDATES FOR PREVENTING RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTIONS: SIMILAR 6-MONTH OUTCOMES FOR ENEMA-ADMINISTERED RBX2660 AND ORAL CAPSULE-ADMINISTERED RBX7455

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Introduction: Recurrent *Clostridium difficile* infections (rCDI) are a public health threat and linked to intestinal microbiome disruption. In response to the need for a standardized, FDA-approved treatment, numerous microbiota-based drugs are being evaluated to restore a healthier microbiome and reduce recurrence. Herein we compare data from clinical trials of RBX2660 and RBX7455, two dosage forms of an investigational standardized, stabilized microbiome restoration therapeutic currently under study for potential FDA approval.

Aims & Methods: This comparison includes a large multicenter, open-label Phase 2 trial of RBX2660 (administered by enema; n=149) and a single-center, open-label Phase 1 investigator-sponsored trial of RBX7455 (administered by room-temperature-stable oral capsules in 3 dosing regimens; n=30). Both trials had similar participant populations. The RBX2660 trial included multi-recurrent CDI participants while the RBX7455 trial included first- and multi-recurrent CDI participants (n=17 and 13, respectively). For both trials, primary efficacy was defined as absence of recurrent CDI at 8 weeks after the last study treatment. Safety and durability were further assessed at 6 months. Microbiome restoration was assessed by shallow-shotgun sequencing of pre- and post-treatment stool samples and product samples, followed by calculation of a previously reported prototype Microbiome Health Index (MHI) that expresses collective changes in taxonomic composition.

Results: Primary efficacy was 80% for RBX2660 and 90% for RBX7455. Among primary treatment responders in the RBX2660 trial evaluable at 6 months (n=109), 97% were CDI occurrence-free at 6 months. All primary responders in the RBX7455 trial remained CDI occurrence-free at 6 months. Reported safety was similar between the studies. In addition, mcrobiome changes were similar between the studies, characterized by a predominance of *Gammaproteobacteria/Bacilli*-class bacteria before treatment and

predominance of *Bacteroidia/Clostridia*-class bacteria after treatment. The change in compositional microbiome as expressed via the MHI from before to after treatment was statistically significant for both studies.

Conclusion: Two clinical studies confirm similar safety, durable efficacy, and microbiome restoration for RBX2660 and RBX7455 microbiota restoration therapies. These 6-month outcomes suggest that microbiome restoration for preventing rCDI can be comparably effective via enema or oral administration routes. Since the manufacture of both products is standardized and adheres to quality control specifications, these results represent an important advance towards FDA-approved microbiome therapeutics. Ongoing placebo-controlled studies will expand upon these data.

Disclosure: This analysis was funded by Rebiotix Inc., Roseville, MN, USA.

OP159 CURE OF RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION WITH A MIX OF 12 GUT BACTERIA, FAECAL MICROBIOTA TRANSPLANTATION OR ORAL VANCOMYCIN: RESULTS FROM AN OPEN-LABEL MULTICENTRE RANDOMISED CONTROLLED TRIAL

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Introduction: Faecal microbiota transplantation (FMT), i.e. transfer of stool from a healthy donor to a recipient, is an effective treatment for recurrent *Clostridium difficile* infection (rCDI)[1,2] but there are concerns on safety and long-term risks. Using a mix of specified microorganisms instead of donor stool could be a solution. Rectal bacteriotherapy (RBT) using a mix of 12 well-characterised gut bacteria has a reported efficacy for rCDI at 64-88 % in case series but has not been evaluated in a randomised controlled trial (RCT).[3-5]

Aims & Methods: An open-label multicentre RCT compared the efficacy of FMT, RBT and oral vancomycin for rCDI. We hypothesized that FMT and RBT were *superior* to vancomycin and that RBT was *non-inferior* to FMT (non-inferiority margin: 5% difference in cure rate).

All consecutive patients with a positive test for *Clostridium difficile* (CD) were screened for eligibility May 2017 – March 2019 at two centres covering eastern Denmark, including primary care. Patients with rCDI, defined as diarrhoea and a positive CD-test after at least one treatment course for CDI, were eligible. Patients with life expectancy <3 months, other GI infections or GI-disease with diarrhoea, concomitant antibiotic use or severe immune deficiency were excluded.

Patients were stratified according to number of recurrences (first vs. multiple recurrences) and randomly allocated 1:1:1 to FMT, RBT or vancomycin by computer-generated stratified block randomisation. The FMT and RBT groups were pre-treated with vancomycin for 7-14 days. Both FMT and RBT was applied rectally. FMT was applied once but, if needed, repeated twice within two weeks. RBT was applied on three consecutive days. Patients in the vancomycin-group received 14 days of vancomycin, but for patients with multiple recurrences, this was continued with tapering for additional five weeks.

The primary outcome was clinical cure, defined as absence of CDI during 90 days of follow-up. We planned an interim analysis of the primary outcome after 90 participants. Treatments were compared with Mantel-Haentzel odds ratios (95 % CI) and χ^2-tests with adjustment for stratification in the superiority analysis. Non-inferiority was evaluated with the difference in cure rates (95 % CI).

Results: Cure rates for FMT, RBT and vancomycin in the interim-analysis (n=90) are shown in Table 1.

FMT, 1-3 infusions (n = 31)	RBT (n = 29)	Vancomycin (n = 30)
22 (71 %), (52 - 86 %)	16 (55 %), (36 - 74 %)	13 (43 %), (25 - 63 %)

[Table 1 - Clinical cure at 90 days (Intention-to-treat analysis): n (%), (95% CI)]

Patients receiving 1-3 infusions of FMT had a higher cure rate than patients receiving only vancomycin (OR 3.2 (1.1; 9.2), p = 0.05) with a NNT of 3.5. The cure rate for one infusion of FMT was 48 % (30 - 67 %) and 68 % (49 - 83 %) for 1-2 infusions.

We found no difference between the efficacy of RBT and vancomycin (OR 1.6 (0.6; 4.5)) or FMT and RBT in a superiority-analysis (OR 2.1 (0.7; 6.4)), but could not show non-inferiority between FMT and RBT either (difference in cure rate: 15.8 % (-43 %; 12 %)).

Recruitment for the RCT was terminated after the interim-analysis for logistic reasons.

Conclusion: Rectally applied faecal microbiota transplantation was superior to oral vancomycin in treating recurrent *Clostridium difficile* infection, but multiple infusions were often needed. The effect of rectal bacteriotherapy with 12 gut bacteria appeared similar to both faecal microbiota transplantation and vancomycin, but the study had insufficient power for non-inferiority analysis. Rectal bacteriotherapy could be a safe alternative in treating recurrent *Clostridium difficile* infection, but further RCTs are needed.

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Disclosure: Michael Tvede owns MT MicroSearch, that manufactures the bacteria mix for RBT. All other authors have nothing to disclose.

OP160 RIDINILAZOLE REDUCES RECURRENCE OF *CLOSTRIDIUM DIFFICILE* INFECTION WITH MINIMAL IMPACT ON THE GUT MICROBIOTA

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Introduction: Recurrence of *Clostridium difficile* infection (rCDI) is a particular concern with significant impacts on patient welfare and healthcare resources. Ridinilazole (RDZ) is a novel targeted spectrum antibiotic under investigation to treat CDI and reduce rCDI. Here translation of *in vitro* data to clinical trial data is reviewed.

Aims & Methods: Susceptibility testing was performed to CLSI standards with vancomycin (VAN), metronidazole (MTZ) and fidaxomicin (FDX) as comparators. The Phase 2 clinical trial was a double-blind, randomised, study of 100 patients assigned 1:1 to 10 days RDZ 200 mg BID or VAN 125 mg QID treatment. Primary endpoint was sustained clinical response (SCR), defined as cure at end of therapy (EOT) and no rCDI for the next 30 days. Primary analysis population was the modified intent-to-treat (MITT); all randomised subjects with a diagnosis confirmed by presence of free toxin. Relative effects of RDZ and VAN on the gut microbiota was examined by sequencing 16S rDNA amplicons from stool collected at baseline, days 5, 10, 25 and end of study. Bioinformatic analyses were performed in QIIME.

Results: Across 4 studies RDZ *C. difficile* (N=439) MIC range was 0.015-0.5µg/mL with no major differences by ribotype or resistance phenotype. RDZ and FDX were less active against Gram negative anaerobes, especially *B. fragilis* group, than VAN and MTZ. RDZ had limited activity against Gram positive anaerobes. The Phase 2 clinical study exceeded its primary endpoint (MITT), with RDZ shown to be superior on SCR to VAN with rates of 66.7% and 42.4%, respectively. Superiority on SCR was driven by a reduction in rCDI for RDZ (14.3%) compared with VAN (34.8%). Microbiota analysis showed at RDZ EOT that significant relative abundancy reductions were limited to 2 Firmicute families including Peptostreptococcaceae (includes *C. difficile*). In contrast VAN at EOT resulted in significant losses

(often to below detection) in 4 Firmicutes families: Peptostreptococcaceae, Ruminococcaceae, Erysipelothrichaceae and Lachnospiraceae. A 70% drop in Actinobacteria, and greater than 3 log decrease in Bacteroidetes, abundance were also observed. These changes were associated with a 25-fold increase in Proteobacteria abundance, in particular Enterobacteriaceae.

Conclusion: These data demonstrate targeted *C. difficile* activity with RDZ both *in vitro* and in CDI patients. Preservation of the microbiome likely contributed to the low rate of recurrence, and superior efficacy on SCR, compared to vancomycin. Further clinical development is warranted.

Disclosure: E. Duperchy, R. Vickers and D. Roblin: Summit Therapeutics´ Employees; Hold stock options; M. Wilcox: Consultant Summit Therapeutics; J. Freeman: Research Contractor Summit Therapeutics.

OP161 MOLECULAR CLASSIFICATION OF COLLAGENOUS COLITIS BY WHOLE-GENOME SEQUENCING

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Introduction: Collagenous colitis (CC) is a common, inflammatory bowel disease that deteriorates the patients' quality of life due to chronic watery diarrhoea. Treatment with the locally active glucocorticoid budesonide is effective in inducing clinical remission. However, how budesonide restores water homeostasis in the gut is unknown. To address this question, we performed genome-wide RNA sequencing (RNAseq) analysis on mucosal samples from different CC patient populations.

Aims & Methods: We collected colonic biopsy samples from healthy controls and CC patients with active disease. Additionally, we obtained matched samples from budesonide-responsive patients (clinical remission) under treatment with budesonide (9mg/d for 8 weeks), as well as biopsies from budesonide-refractory patients (n=9 patients/group). Ulcerative colitis (UC) samples were included as a separate control. Total RNA was isolated for library construction and RNA sequencing (RNAseq). Whole genome expression data was processed using the R statistical software, and analysed by principal component analysis (PCA), linear models with least square regression, and empirical Bayes moderates t statistics. Results were corrected using the Benjamini-Hochberg FDR method, with an adjusted *p* value < 0.05 considered to be statistically significant. Gene ontology (GO) analysis was performed in Cytoscape, using the ClueGO and CluePedia packages.

Results: Unsupervised PCA of all samples identified three principal components which separated sample groups into distinct clusters of gene expression, explaining 31% of the transcriptional variation. One of the components (8% of the variation) clearly demarcated UC samples from healthy controls and CC. Remarkably, mucosal samples from budesonide-refractory patients exhibited a discrete RNA expression profile that was distinct from all other groups. Moreover, PCA of budesonide-responsive persons revealed two principal components (24% of the variation) that separated these sample groups.

Subsequent analysis of differentially regulated genes showed that the expression of 395 genes was altered in patients with active CC patients compared to healthy controls, and that these were evenly split into 201 up- and 194 down-regulated genes. GO analysis of these genes indicated that up-regulated genes were mainly involved in immune response, whereas metabolic pathway genes were down-regulated. In samples from budesonide-treated patients, 75 genes were differentially regulated compared to controls. These genes were found to regulate glycogen metabolism and mineral absorption. A paired comparison of the matched active CC patients and budesonide-treated patients showed a dysregulation of 337 genes. A GO analysis of these genes were dominated by categories covering carboxylic acid transmembrane transport, protein ubiquitination and immune response. Finally, genes dysregulated in refractory CC were mostly associated with the transport of secretory proteins.

Conclusion: Our analyses suggest that collagenous colitis is a transcriptionally homogeneous disease that can be characterised by means of differential gene expression. We were able to identify unique gene expression profiles that describe patient sub-populations, also with regard to their treatment response. Interestingly, transcriptome analysis indicates that budesonide-refractory CC may be a discrete disease entity, which may explain the lack of treatment response. Further study of the transcriptional landscape of CC may reveal pathogenic mechanisms and therapeutic vulnerabilities for this common, debilitating inflammatory bowel disease.

Disclosure: CEH and AM have received an unrestricted research grant from Ferring Pharmaceuticals (Switzerland). The remaining authors do not have any conflicts of interest.

OP162 CRITICAL ROLE OF AQUAPORIN 8 IN COLLAGENOUS COLITIS

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Introduction: Collagenous colitis (CC) patients experience chronic watery diarrhoea that effectively can be treated by budesonide, a locally acting glucocorticoid. The diarrhoeal mechanism in CC is unclear, as well as budesonide's mode of action. We hypothesize that aquaporin (AQP) water channels are critical in the development of watery diarrhoea in CC; hence, they are highly important proteins in CC pathogenesis that could be targeted by new drugs.

Aims & Methods: Colonic biopsy samples from controls (n=27), active CC patients (n=26), matched CC patients under treatment with budesonide (9mg for 8 weeks; n=18), and refractory CC patients (active disease despite 6mg budesonide for more than 12 weeks; n=15) were collected at the local university hospital, and either preserved in AllProtect for subsequent gene analyses or embedded in paraffin. Total RNA was isolated for analysis of the AQP genetic expression profiles (AQPs 0-12) by quantitative polymerase chain reaction (qPCR); whereas paraffin embedded samples were used for fluorescent staining of AQP8 and subsequent analysis by confocal microscopy. AQP8 protein levels in the apical membrane of colonic epithelial cells were determined by computer-assisted image analysis using ImageJ. Non-parametric Mann-Whitney (for unpaired samples) or Wilcoxon (for paired samples) statistical tests with Monte Carlo algorithm were used to analyze the results in SPSS.

Results: Gene expression of AQPs 8 and 11 was significantly downregulated in all CC patient sets when compared to control samples. In patients that achieved clinical remission under budesonide treatment, AQP 8 and 11 levels were increased compared to their corresponding pre-treatment samples. In contrast, budesonide-refractory patients had similar AQP gene expression levels as non-matched patients with active CC. The gene expression of the remaining AQPs (AQP0-7, AQP10, and AQP12) did not significantly change in any group.

Protein levels of AQP8 were further studied by confocal microscopy in the apical side of intestinal epithelia of all CC patient groups. As with gene expression, AQP8 protein levels were significantly decreased in active CC patients. Budesonide treatment increased AQP8 protein in the mucosa, albeit not to the same level as in the control group. Curiously, budesonide-refractory CC patients had similar AQP8 protein levels as controls.

Conclusion: Aquaporin 8 is significantly downregulated in active CC. Both AQP8 gene and protein expression are partially restored after treatment with budesonide, which is sufficient to achieve clinical remission. In budesonide-refractory patients, AQP8 gene expression is decreased, while its protein levels do not change when compared to controls. Therefore, we conclude that AQP8 has a critical role in active CC leading to malabsorption of water in the colon which could represent a novel diarrhoeal pathomechanism.

Disclosure: CEH and AM have received an unrestricted research grant from Ferring Pharmaceuticals (Switzerland).

OP163 EFFICACY AND SAFETY OF ANTI-TNFα THERAPY IN BUDESONIDE REFRACTORY, DEPENDENT OR INTOLERANT MICROSCOPIC COLITIS: A FRENCH REGISTRY

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Introduction: Currently, budesonide is the best documented treatment for microscopic colitis (MC); however, relapses, even after maintenance therapy, remain high, and some patients become intolerant or refractory. Tumor necrosis factor (TNF) α antagonists have revolutionized the management of inflammatory bowel diseases (IBD) and may represent an interesting option in refractory MC patients. The aim of the study was to evaluate the efficacy and safety of anti-TNFα in refractory MC in France.

Aims & Methods: Budesonide refractory, intolerant or dependent MC patients treated with anti-TNFα agents (infliximab (IFX), adalimumab (ADA)) in the French Groupe d'étude thérapeutique des affections inflammatoires du tube digestif (GETAID) centers were included in the registry. The data was collected from october 2018 to february 2019. Clinical remission was defined by strictly less three daily bowel movements, and clinical response by an improvement in stool frequency ≥ 50%.

Results: Fourteen patients were included, 7 received IFX and 7 received ADA. Maintenance therapy was prescribed in 13/14 patients with a median duration of 10 months. Clinical remission without steroids at week 12 was reached in 5/14 patients (35.7%): 5/7 (71.4%) in the IFX group and 0/7 in the ADA group. Clinical response at week 12 was reached in 6/7 patients in the IFX group and 3/7 patients in the ADA group. Clinical response at week 52 was obtained in 7/14 (50%) patients. A 36.4% and 68.1% reduction rate was observed in mean daily stools at weeks 12 and 52, respectively. Histological response, evaluated in nine patients, was complete in 11.1% and partial in 44.4%. All patients in clinical remission at week 12 achieved histological response; conversely, none of the patients in clinical failure at week 12 had histological response. The only patient who achieved clinical and histological remission was on combination therapy with IFX and azathioprine. Five patients were switched to another anti-TNFα in second-line therapy and two subsequently reached clinical remission. Two patients received vedolizumab for loss of response, it was successful in one. All treatment lines confounded, seven patients (50%) and eight patients (57.1%) were in clinical remission at week 12 and 52, respectively. Six adverse events have been reported, including a serious one (anaphylactoid reaction with anti-IFX antibodies).

Conclusion: To date, this is the biggest case series evaluating the efficacy and safety of anti-TNFα in refractory MC. Anti-TNFα therapies appear to be effective and could represent a suitable option in highly refractory MC patients.

Disclosure: Nothing to disclose

Randomised controlled trials in IBD II
10:30-12:00 / A3

OP164 EFFICACY OF UPADACITINIB AS AN INDUCTION THERAPY FOR PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS, WITH OR WITHOUT PREVIOUS TREATMENT FAILURE OF BIOLOGIC THERAPY: DATA FROM THE DOSE-RANGING PHASE 2B STUDY *U-ACHIEVE*

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Introduction: Upadacitinib (UPA), a Janus kinase 1 (JAK1) selective inhibitor, shows promise as a future treatment option for ulcerative colitis (UC). Initial data analyses from an 8-week, double-blind, placebo (PBO)-controlled, dose-ranging, Phase 2b induction study in patients with moder-

Treatment groups		Clinical Remission per Adapted Mayo Score[a]	Endoscopic Improv[b]	Endoscopic Remission[c]	Clinical Response per Adapted Mayo Score[d]	Histologic Improv[e]	Clinical Response per Partial Mayo Score[f]
				Week 8			Week 2
		Primary endpoint			Secondary endpoints		
All, n (%)	Placebo n=46	0	1 (2.2)	0	6 (13.0)	3 (6.5)	7 (15.2)
	UPA 7.5 mg QD n=47	4 (8.5)	7 (14.9)*	3 (6.4)	14 (29.8)*	15 (31.9)**	11 (23.4)
	UPA 15 mg QD n=49	7 (14.3)*	15 (30.6)***	2 (4.1)	22 (44.9)***	25 (51.0)***	18 (36.7)*
	UPA 30 mg QD n=52	7 (13.5)*	14 (26.9)***	5 (9.6)*	23 (44.2)***	23 (44.2)***	19 (36.5)*
	UPA 45 mg QD n=56	11 (19.6)**	20 (35.7)***	10 (17.9)**	28 (50.0)***	27 (48.2)***	31 (55.4)***
Bio-IR, n (%)	Placebo n=34	0	0	0	2 (5.9)	3 (8.8)	5 (14.7)
	UPA 7.5 mg QD n=34	2 (5.9)	3 (8.8)	1 (2.9)	8 (23.5)	7 (20.6)	6 (17.6)
	UPA 15 mg QD n=36	3 (8.3)	9 (25.0)**	0	13 (36.1)**	15 (41.7)**	11 (30.6)
	UPA 30 mg QD n=40	4 (10.0)	8 (20.0)**	1 (2.5)	13 (32.5)**	15 (37.5)**	15 (37.5)**
	UPA 45 mg QD n=42	5 (11.9)	11 (26.2)***	5 (11.9)	17 (40.5)***	20 (47.6)***	22 (52.4)***
Non-Bio-IR, n (%)	Placebo n=12	0	1 (8.3)	0	4 (33.3)	0	2 (16.7)
	UPA 7.5 mg QD n=13	2 (15.4)	4 (30.8)	2 (15.4)	6 (46.2)	8 (61.5)**	5 (38.5)
	UPA 15 mg QD n=13	4 (30.8)	6 (46.2)	2 (15.4)	9 (69.2)	10 (76.9)***	7 (53.8)
	UPA 30 mg QD n=12	3 (25.0)	6 (50.0)	4 (33.3)	10 (83.3)*	8 (66.7)**	5 (41.7)
	UPA 45 mg QD n=14	6 (42.9)*	9 (64.3)**	5 (35.7)*	11 (78.6)*	7 (50.0)**	9 (64.3)*

Intent-to-treat population, non-responder imputation aSFS ≤1, RBS = 0, endoscopic score ≤1. bEndoscopic subscore ≤1. cEndoscopic subscore = 0. dDecrease from BL ≥2 points and ≥30%, plus RBS decrease ≥1 or absolute RBS ≤1. eDecrease from BL in Geboes score. fMayo score excluding endoscopic subscore; defined as decrease from BL in the Partial Mayo Score ≥2 points and ≥30% from BL, plus decrease in RBS ≥1 or absolute RBS ≤1. Improv, Improvement; RBS, rectal bleeding subscore; SFS, stool frequency subscore ***, **, *statistically significant at 0.001, 0.01, and 0.05 levels, respectively, for UPA versus PBO

[OP164 Table: Clinical efficacy in the overall patient population and in Bio-IR and non-Bio-IR patients]

ately to severely active UC suggest that UPA is generally well tolerated with significantly greater efficacy compared with PBO.[1] In this subgroup analysis, efficacy was assessed in patients who either had an inadequate response, loss of response, or intolerance to biologic therapies (Bio-IR), or were non-Bio-IR.

Aims & Methods: Adult patients with moderately to severely active UC (Adapted Mayo Score [Mayo score without Physician Global Assessment] 5-9 points) and centrally read Mayo Endoscopy Subscore ([MES] 2-3) were randomized to receive extended-release UPA 7.5, 15, 30, 45 mg, or PBO once daily (QD) for 8 weeks. Patients were stratified by previous biologic use, baseline (BL) corticosteroid use, and BL Adapted Mayo Score (≤7/>7). Efficacy measures (defined in Table) were the primary endpoint of Clinical Remission per Adapted Mayo Score at Week 8, and secondary endpoints were Endoscopic Improvement, Endoscopic Remission, Clinical Response (CR) per Adapted Mayo Score, Histologic Improvement (all Week 8), and CR per Partial Mayo Score (Week 2). Pairwise comparisons between UPA doses and PBO for efficacy endpoints were conducted using the Cochran-Mantel-Haenszel test stratified by randomization factors. Non-responder imputations were utilized for missing values.

Results: A total of 250 patients were randomized with a mean (SD) age of 42.3 (14.2) years and a disease duration of 8.2 (2.5) years. At BL, 74.4% were Bio-IR, 36% had an Adapted Mayo Score >7, and 79% had a MES of 3. At Week 8, a UPA dose-response relationship was observed for all efficacy endpoints in the overall population, and in each of the two subpopulations. The highest efficacy rates were observed with UPA 45 mg QD treatment for the majority of the endpoints, which were all significant for the non-Bio-IR group analyses and in the majority of the Bio-IR group analyses. While the non-Bio-IR subpopulation was small, efficacy rates were numerically higher than in the Bio-IR subpopulation. Adverse events leading to discontinuation were similar across the overall UPA groups, and numerically higher in the PBO group.[1]

Conclusion: Upadacitinib showed a dose response in Bio-IR and non-Bio-IR patients with moderately to severely active UC, with numerically greater efficacy in the non-Bio-IR population. Patient numbers were small in both groups and the findings need to be confirmed in larger Phase 3 studies.

References: 1. Sandborn WJ, et al. UEGW 2018, #OP195

Disclosure: The authors and AbbVie scientists designed the study, and analyzed and interpreted the data. AbbVie funded the research and provided writing support.

OP165 EARLY CLINICAL RESPONSE AND REMISSION WITH VEDOLIZUMAB VERSUS ADALIMUMAB IN ULCERATIVE COLITIS: RESULTS FROM VARSITY

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Introduction: VARSITY is the first head-to-head trial comparing the efficacy and safety of 2 biologic therapies, vedolizumab (VDZ) and adalimumab (ADA), in patients with moderately to severely active ulcerative colitis (UC). We previously reported significantly higher rates of clinical remission (31.3% vs 22.5%; p=0.0061) and endoscopic improvement (39.7% vs 27.7%; p=0.0005) at Week 52 with VDZ vs ADA.[1] Here we report data on early response and remission within the first 14 weeks, as well as durable clinical remission.

Aims & Methods: VARSITY was a phase 3b, randomised, double-blind, double-dummy, active-controlled study (NCT02497469; EudraCT 2015-000939-33). As predefined, exploratory endpoints, we examined early clinical response and remission, along with the durability of remission. Clinical response was defined as reduction in complete Mayo score of ≥3 points and ≥30% (or partial Mayo score reduction of ≥2 points and ≥25% from baseline if sigmoidoscopy was not performed), with a decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. Clinical remission was defined as complete Mayo score of ≤2 (or partial Mayo score ≤2 points if sigmoidoscopy was not performed) and

no individual subscore >1 point. Patients who were in clinical remission at Week 14 and Week 52 were considered as having achieved durable clinical remission.

Results: A total of 769 patients received ≥1 dose of VDZ (n=383) or ADA (n=386). Baseline characteristics were comparable between the 2 groups. A trend for separation in clinical response started to emerge at Week 6 favouring VDZ vs ADA. Clinical response at Week 14 favoured VDZ vs ADA (257 [67.1%] vs 177 [45.9%]; treatment difference 21.2%). A greater number of patients achieved clinical remission at Week 14 on VDZ vs ADA (102 [26.6%] vs 82 [21.2%]; treatment difference 5.3%). Patients on VDZ achieved higher rates of durable clinical remission (70 [18.3%] vs 46 [11.9%]); laboratory results correlated with these findings. Post-hoc analyses showed a larger mean (standard deviation) change of C-reactive protein (CRP) from baseline to Week 14 (-32.88 [155.77] nmol/L VDZ vs -3.35 [260.82] nmol/L ADA) and to Week 52 (-50.87 [174.76] nmol/L VDZ vs -37.21 [169.17] nmol/L ADA) in favour of VDZ. Greater mean declines in faecal calprotectin (FCP) levels were seen in patients on VDZ compared to ADA (Week 14: -1,551.3 [6,236.70] mg/kg VDZ vs -1,167.6 [4,647.67] mg/kg ADA; Week 52: -2,187.3 [7,440.42] mg/kg VDZ vs -1,846.6 [4,560.55] mg/kg ADA).

Conclusion: Patients on VDZ had numerically higher rates of both clinical response and clinical remission by Week 14 compared with ADA. Those patients on VDZ also achieved higher rates of durable clinical remission compared with ADA. CRP and FCP results correlated with these findings. These data on early clinical response and clinical remission, as well as durable remission, further support the use of VDZ over ADA in patients with moderately to severely active UC.

References: 1. Schreiber S, et al. J Crohns Colitis. 2019;13(suppl 1):S612-S613. Abstract OP34.

Disclosure: Silvio Danese: Lecture fee(s): AbbVie, Ferring, Hospira, Johnson and Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, Boehringer Ingelheim; Consultancy: AbbVie, Ferring, Hospira, Johnson and Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, Boehringer Ingelheim ; Edward V. Loftus Jr.:EVL has received financial support for research from: AbbVie, Takeda, Janssen, UCB, Amgen, Pfizer, Genentech, Celgene, Receptos, Gilead, MedImmune, Seres Therapeutics, and Robarts Clinical Trials; and has served as a consultant for AbbVie, Takeda, Janssen, UCB, Amgen, Pfizer, Eli Lilly, Celltrion Healthcare, Allergan, Bristol-Myers Squibb, Celgene, Gilead, Genentech, and Boehringer Ingelheim. Jean-Frederic Colombel: Consultancy/advisory board membership: AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Janssen Pharmaceuticals, Medimmune, Merck & Co., Pfizer, Protagonist, Second Genome, Seres, Takeda, Theradiag; Speaker: AbbVie, Ferring, Takeda, Shire; Research support: AbbVie, Genentech, Takeda; Stock options: Intestinal Biotech Development, Genfit.; Laurent Peyrin-Biroulet: LPB has received consulting fees from Merck, AbbVie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boehringer Ingelheim, Lilly, Pfizer, HAC-Pharma, Index Pharmaceuticals, Amgen, and Sandoz; Lecture fees from Merck, AbbVie, Takeda, Janssen, Takeda, Ferring, Norgine, Tillots, Vifor, Therakos, Mitsubishi, and HAC-Pharma; Brihad Abhyankar :Former employee of Takeda; Jingjing Chen: Employee of Takeda; Raquel Rogers: Employee of Takeda; Richard A. Lirio: Employee of Takeda; Jeffrey D. Bornstein: Employee of Takeda; Stefan Schreiber: On-spot consultancy fees from AbbVie, Celltrion, Janssen, Merck, Pfizer, Roche, and Takeda; Bruce E. Sands: Consulting fees from 4D Pharma, Abbvie, Allergan Sales, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Capella Biosciences, Celgene, EnGene, Ferring, Gilead, Janssen, Lilly, Lyndra, MedImmune, Oppilan Pharma, Otsuka, Palatin Technologies, Pfizer, Progenity, Rheos Medicines, Seres Therapeutics, Synergy Pharmaceuticals, Takeda, Target PharmaSolutions, Theravance Biopharma R&D, TiGenix, Vivelix Pharmaceuticals, and WebMD; research funding from Celgene, Pfizer, Takeda, Janssen.

OP166 EFFICACY AND SAFETY OF MIRIKIZUMAB (LY3074828) IN A PHASE 2 STUDY OF PATIENTS WITH CROHN'S DISEASE

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Introduction: Mirikizumab (Miri; interleukin [IL]-23p19 antibody) is a humanized, immunoglobulin G4 monoclonal antibody specifically targeting the p19 subunit of the IL23 cytokine. Prior studies have shown Miri to have efficacy in psoriasis and ulcerative colitis. We assessed safety and efficacy of Miri with a Phase 2, multicenter, randomized, parallel-arm, double-blind, placebo (PBO)-controlled trial (NCT02891226) in patients with moderate-to-severely active Crohn's disease (CD).

Aims & Methods: At baseline, subjects (N=191) were randomized with a 2:1:1:2 allocation across 4 treatment arms (200, 600, 1000mg Miri, and PBO, administered intravenously (IV) at Weeks 0, 4, and 8). The primary objective was to evaluate superiority of Miri to PBO in inducing endoscopic response, defined as 50% reduction from baseline in Simple Endoscopic Score for Crohn´s disease (SES-CD), at Week 12. Secondary objectives included clinical remission by Patient-Reported Outcomes (PRO remission), endoscopic remission, and safety, with Crohn´s Disease Activity Index (CDAI) assessed as an exploratory endpoint. Treatment comparisons of the primary endpoint and other efficacy variables were conducted using a logistic regression analysis with treatment, geographic region, and prior biologic CD therapy use included in the model, with a 2-sided alpha level of 0.10 considered significant.

Results: Baseline characteristics were similar among treatment groups. At Week 12, endoscopic response rates were significantly greater for all Miri groups compared to PBO, with 25.8% (8/31[95%CI: 10.4-41.2], p=0.079), 37.5% (12/32[95% CI: 20.7-54.3], p=0.003), and 43.8% (28/64[95%CI: 31.6-55.9], p< 0.001) patients in the 200, 600, and 1000mg groups, respectively, achieving endoscopic response compared to 10.9% (7/64[95%CI: 3.3-18.6]) of PBO patients. Endoscopic remission was achieved in 15.6 and 20.3% of patients treated with 600 and 1000mg Miri (p=0.032 and p=0.009, respectively; 200mg p=0.241), versus 1.6% of PBO. Likewise, PRO remission rates were greater in 200, 600, and 1000mg Miri groups (12.9% [4/31], p=0.346; 28.1% [9/32], p=0.005 and 21.9% [14/64], p=0.025, respectively), versus 6.3% PBO. CDAI response was greater in all Miri groups (200mg: 48.4%, p=0.015; 600mg: 56.3%, p=0.001; 1000mg: 42.2%, p=0.026) versus 23.4% of PBO and CDAI remission rates greater in the 600 and 1000mg Miri groups (200mg: 16.1%, p=0.321; 600mg: 40.6%, p< 0.001; 1000mg: 26.6%, p=0.013) versus 9.4% of PBO. The frequencies of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs) across treatment groups (SAEs: 0-9.4%, TEAEs: 58.1-65.6%) were similar to PBO (SAEs: 10.9%, TEAEs: 70.3%) and consistent with the previous safety profile.

Conclusion: These data affirm the efficacy of Miri in the induction of statistically significant and clinically meaningful improvements in clinical and endoscopic outcomes. Sustained efficacy and safety are being evaluated in the maintenance phase of this study.

OP167 COMPARISON OF VEDOLIZUMAB AND INFLIXIMAB EFFICACY IN ULCERATIVE COLITIS AFTER FAILURE OF A FIRST SUBCUTANEOUS ANTI-TNF AGENT: A MULTICENTRE COHORT STUDY

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Introduction: Few data are available so far to select the best therapeutic option after failure of a first subcutaneous anti-TNF agent in ulcerative colitis (UC). The objective of the present study was to compare the efficacy of infliximab (IFX) and vedolizumab (VDZ) in UC patients who stopped a first subcutaneous anti-TNF agent.

Aims & Methods: Consecutive UC patients who started IFX or VDZ from February 2009 to November 2018 in 12 French referral centres after receiving at least one injection of adalimumab or golimumab have been included in a retrospective study. Inclusion corresponded to the first administration of IFX or VDZ. Outcomes were rate of clinical remission (defined as a partial Mayo score - PMS - ≤ 1) at week 14, survival without treatment discontinuation, and survival without any UC-related event (treatment discontinuation, colectomy, acute severe UC or hospitalization). Predictors of clinical remission at week 14 were determined by multivariate analysis logistic regression.

Results: Among the 225 patients included [133 (59%) male; median age: 41; InterQuartileRange: 27-55) years; median PMS was 6/9 (5-8)], 154 (68%) received IFX and 71 (32%) VDZ after failure of a first subcutaneous anti-TNF agent. At inclusion, patients treated with IFX were significantly more often men, having more recent UC and more primary non-response to the first anti-TNF (116 (77%) in the IFX group, 44 (62%) in the VDZ group), were more often admitted for the current flare, received more combotherapy and had a higher median PMS [6 (5-8)] as compared to those treated with VDZ [5.5 (3-7)]. At week 14, 40 (26%) patients treated with IFX were in clinical remission as compared to 35 (49%) patients treated with VDZ (p< 0.01; odds ratio (OR): 2.77; 95%-confidence interval (95%CI): 1.54; 4.99). After adjustment on baseline characteristics, the difference between both drugs was nearly significant (OR 2.12; 95%CI: 0.95-4.80; p=0.07). With a median follow-up duration of 115 (55-165) months, survival rates without treatment discontinuation at 1 year and 3 years were 86% and 69% for patients receiving IFX, and 97% and 91% for those receiving VDZ (p< 0.01). Survival rates without UC-related event at 1 year and 3 years were 85% and 67% with IFX and 93% and 87% with VDZ (p< 0.01).

Conclusion: After failure of a first subcutaneous anti-TNF agent, patients treated with VDZ achieved more clinical remission at week 14 and less UC-related events - including treatment discontinuation, colectomy, acute severe UC and hospitalization - than those treated with IFX. Such results have to be confirmed by head-to-head trials.

Disclosure: Nothing to disclose

OP168 ADALIMUMAB FOR PATIENTS WITH CROHN'S DISEASE COMPLICATED BY INTRA-ABDOMINAL ABSCESS: A MULTICENTRE PROSPECTIVE, OBSERVATIONAL COHORT STUDY

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Introduction: Management of intra-abdominal abscess complicating Crohn's disease (CD) is challenging. Surgery with delayed intestinal resection is often recommended in this situation.

Aims & Methods: The aim of this study was to estimate the success rate of adalimumab (ADA) in patients with CD complicated by intra-abdominal abscess, after complete resolution of sepsis and abscess, and to identify predictive factors of success.

We performed a multicentre, prospective, observational cohort study in patients with CD complicated by intra-abdominal abscess. Patients previously treated with an anti-TNF at the time of abscess occurrence, and patients with post-operative abscesses were not eligible. Patients with complete resolution of sepsis and abscess confirmed by MR enterography (MRE) at baseline were included and received 160 mg of ADA at W0, 80 mg at W2, and then 40 mg every 2 weeks. The primary endpoint was ADA success at W24 defined as no steroids use after the 12th week following inclusion, no intestinal resection, no abscess recurrence and no clinical relapse (CDAI > 220 or HBI > 4 and CRP > 10 mg/L at two consecutive visits). Baseline factors associated with ADA success were identified using the logistic regression model.

Results: From April 2013 to December 2017, 190 patients from 27 GETAID centers were screened. Seventy-three patients were excluded, and 117 were analysed for the primary endpoint. Median age at inclusion was 28 years (inter-quartile range [IQR]:24-36), 58 (50%) patients were male and 39 (35%) were active smokers. Median disease duration before abscess occurrence was 2.4 (0-58.7) months. Thirty-three (28%) patients had been previously exposed to thiopurines. Small bowel CD was responsible for intra-abdominal abscess in 101 (86%) patients. The median size of abscess was 25 (18-40) mm. MRE at baseline showed a visible fistula tract in 67 (58%) patients. Eleven (9%) patients had a percutaneous drainage of the abscess and 114 (97%) patients received antibiotics for a median duration of 21.5 (8-31) days. Fifty-nine (50%) patients had an exclusive enteral nutrition, 12 (10%) an exclusive parenteral nutrition and 28 (24%) oral feeding. Median CRP and albumin level at inclusion after abscess resolution

were 5 (2-9) mg/L and 39 (36-43) mg/L, respectively. At W24, 83/117 (71%) patients achieved ADA success. Ten (9%) patients underwent an intestinal resection. At least one serious adverse event was reported in 40 patients, with relapse of intra-abdominal abscess in 10 patients, other infections in 7 patients, and gastrointestinal disorders including CD worsening in 27 patients. No death was reported. In multivariate analysis, predictive factors of ADA success were a mural high signal intensity on T2-weighted MRE (Odds ratio[OR]=2.92; 95% Confidence interval [CI]:1.06-7.99; p=0.04), active smoking (OR=0.37; 95%CI: 0.14-1.00; p=0.05) and CRP level at ADA initiation (OR=0.98; 95%CI: 0.96-1.00; p=0.11).

Conclusion: In this prospective cohort of CD patients complicated by intra-abdominal abscess, ADA success was observed in 71% of cases at W24. During this period, 9% of cases had an abscess recurrence and 9% needed an intestinal resection. No death was reported. Non-smoking status, low CRP level and active signs of inflammation on MRE at ADA initiation were associated with ADA success at W24.

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OP169 IMPACT OF RESPONSE AND INFLAMMATORY BURDEN AT START OF MAINTENANCE THERAPY ON CLINICAL EFFICACY OF USTEKINUMAB DOSING REGIMEN IN UC: WEEK 44 RESULTS FROM UNIFI

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Introduction: The UNIFI maintenance study was a Phase 3, double-blind, placebo-controlled, randomized-withdrawal study in pts with moderate to severely active ulcerative colitis (UC) who failed conventional or biologic therapy and were in clinical response 8 weeks after receiving a single ustekinumab (UST) IV induction dose. In this study, patients were randomized to placebo, UST 90 mg SC q8w or q12w.

Aims & Methods: To examine the relative efficacy of the UST 90 mg SC q8w or q12w maintenance regimens, subgroup analyses were performed for clinical outcomes of clinical remission, symptomatic remission, and endoscopic improvement at Week 44 for patients who did and did not achieve these endpoints at the start of maintenance. Additionally, analyses of clinical remission and endoscopic improvement at Week 44 based on pre-specified cut-points of the concentrations of inflammatory biomarkers (CRP [≤3 mg/L, >3 mg/L] and fecal calprotectin [≤250 mg/kg, >250 mg/kg]) at maintenance baseline were conducted.

Results: For patients who had achieved clinical remission, symptomatic remission, or endoscopic improvement at maintenance baseline, efficacy of UST q8w and UST q12w regimens for the respective endpoint at Week 44 was similar (Table 1). By contrast, for patients who did not achieve clinical or symptomatic remission or endoscopic improvement at maintenance baseline, UST q8w demonstrated greater efficacy than UST q12w for that endpoint at Week 44.

Patients with low inflammatory burden marked by CRP ≤3 mg/L at maintenance baseline achieved similar efficacy at Week 44 with UST q8w and q12w dosing regimens as measured by clinical remission and endoscopic improvement (Table 1). By contrast, patients with high inflammatory burden, marked by CRP>3 mg/L at maintenance baseline, achieved greater

efficacy at Week 44 with UST q8w versus q12w dosing over the endpoints. Generally similar trends were seen in patients with fecal calprotectin measurements for low (≤ 250 mg/kg) and high (>250 mg/kg) inflammatory burden at maintenance baseline.

Conclusion: Among patients with a clinically meaningful response to a single IV induction dose of UST, maintenance treatment with UST q8w or q12w demonstrated similar efficacy at Week 44. By contrast, the efficacy of UST q8w at Week 44 was greater than the q12w regimen for patients with higher inflammatory burden or who did not achieve clinical or symptomatic remission or endoscopic improvement at week 8. These data suggest that multiple clinical measures can help inform the decision on the most appropriate maintenance dosing regimen for UST in the treatment of patients with UC.

Endpoint	Patients attaining outcome at maintenance baseline			Patients not attaining outcome at maintenance baseline		
	Placebo SC[a]	UST 90 mg q12w	UST 90 mg q8w	Placebo SC[a]	UST 90 mg q12w	UST 90 mg q8w
Clinical remission[b]	37.8% (17/45)	70.0% (28/40) *	65.8% (25/38) *	19.2% (25/130)	28.8% (38/132)	37.7% (52/138) *
Symptomatic remission[c]	51.6% (63/122)	73.0% (89/122) *	73.1% (87/119) *	30.2% (16/53)	36.0% (18/50)	56.1% (32/57) *
Endoscopic improvement[d]	35.2% (25/71)	60.3% (41/68) *	64.9% (37/57) *	24.0% (25/104)	32.7% (34/104)	44.5% (53/119) *
	Subjects with CRP ≤3 mg/L at maintenance baseline			Subjects with CRP >3 mg/L at maintenance baseline		
Endpoint	Placebo SC[a]	UST 90 mg q12w	UST 90 mg q8w	Placebo SC[a]	UST 90 mg q12w	UST 90 mg q8w
Primary efficacy analysis set	111	121	111	60	49	65
Clinical remission at Week 44[b]	29 (25.4%)	53 (43.8%)*	50 (45.0%)*	13 (21.7%)	12 (24.5%)	27 (41.5%)*
Endoscopic improvement at Week 44[d]	33 (28.9%)	57 (47.1%)*	59 (53.2%)*	17 (28.3%)	16 (32.7%)	31 (47.7%)*

a: Patients who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study
b: A Mayo score ≤2 points, with no individual subscore >1.
c: Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
d: A Mayo endoscopy subscore of 0 or 1.
* Nominal p-value < 0.05.

[Table 1. Clinical Outcomes at Week 44 by Maintenance Baseline Status for the Outcome]

Disclosure: Drs. Panaccione, Peyrin-Biroulet, Danese, Leong, Arasaradnam, Rowbotham, Abreu, and Sands are all investigators for Janssen Research & Development, LLC Drs. Marano,O'Brien, Szapary, Zhang, Johanns are all employees of Janssen Research & Development, LLC.

Make the gallbladder great again
10:30-12:00 / B3

OP170 INFLUENCE OF EARLY CHOLECYSTECTOMY TIMING FOR ACUTE CHOLECYSTITIS ON SHORT TERM SURGICAL MORBIDITY AND MORTALITY: A NSQIP DATABASE ANALYSIS

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Introduction: There is growing evidence that supports early cholecystectomy is associated with better outcomes. Nonetheless, the exact timing of early cholecystectomy is still yet to be determined.

Aims & Methods: To elucidate the optimal timing of early cholecystectomy and determine the outcomes of patient undergoing early versus delayed same admission cholecystectomy in patients with acute cholecystitis. We studied all patients undergoing open or laparoscopic cholecystectomy

from the National Surgery Quality Improvement Program (NSQIP) participant use data specific file 2014-2016. NSQIP includes prospective validated 30-day outcomes and anonymized data for patients undergoing major surgery in more than 500 hospitals. The primary outcome in this study was short term surgical morbidity and mortality. The patients were divided into 4 groups, those who underwent surgery at days 0, 1, 2, 3+ for AC. We used the chi square test or Fisher's exact (when one or more cells had an expected frequency lower than 5) to compare categorical variables between groups 0 and groups 1,2 and 3+ respectively. We used the independent t-test for continuous variables. We performed multivariate logistic regression to evaluate the association between the timing of surgery after admission and 30-days postoperative outcomes. We included confounders into the models based on both clinical and statistical significance.

Results: A total of 21,392 patients were included. Laparoscopic approach was used in 86% of cases. Patients who performed their operation at 3+ were significantly older and had worse baseline clinical status prior to operation. The overall morbidity (including wound infection, cardiac and respiratory complications, urinary infections, thromboembolism and sepsis) occurred in 1439 patients (6.82%), while 1-month rebleeding and mortality occurred in 457 (2.1%) and 185 (0.9%) patients. On univariate analysis, all morbidity events and mortality increased significantly with increased surgery timing from admission (Table 1).

	Adjusted ORs (95% CI)						
	Days from hospital admission to operation				p-value		
	0 (n=8906)	1 (n=6952)	2 (n=2605)	3+ (n=2929)	1 vs 0	2 vs 0	3+ vs 0
Mortality	Reference	0.99 (0.62 - 1.56)	1.38 (0.83 - 2.30)	1.57 (1.01 - 2.44)	0.96	0.21	0.05
Composite Morbidity	Reference	0.79 (0.68 - 0.93)	0.81 (0.66 - 0.99)	0.99 (0.82 - 1.19)	0.004	0.04	0.89
Bleeding	Reference	1.14 (0.86 - 1.49)	1.41 (1.03 - 1.94)	1.83 (1.39 - 2.43)	0.36	0.03	<0.0001
Return to OR	Reference	0.86 (0.66 - 1.13)	0.76 (0.53 - 1.09)	1.07 (0.79 - 1.45)	0.28	0.14	0.67

[Adjusted 30-day outcomes]

Compared to patients who underwent surgery at day 0, and after adjusting for confounders (table 1), patients who underwent surgery at day 1 and day 2 had a significantly slightly lower composite morbidity. No significant difference among the four groups in the need for reoperation was noted. The bleeding rate was significantly higher in patients who were operated at day 2, and was highly significant in the 3+ group. Patients who underwent surgery at day 3+ had a significantly higher mortality rate.

Conclusion: Early cholecystectomy performed after 72 hours from admission was associated with higher mortality and rebleeding. Our results support the "golden 72 hours window "for surgery in AC.

Disclosure: Nothing to disclose

OP171 A NEW ENDOSCOPIC TRANSPAPILLARY GALLBLADDER DRAINAGE COMBINED WITH INTRADUCTAL ULTRASONOGRAPHY FOR PATIENTS WITH ACUTE CHOLECYSTITIS

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Introduction: Endoscopic transpapillary gallbladder drainage (ETGBD) is a useful drainage technique for acute cholecystitis, although this method is technically difficult.

Aims & Methods: When ETGBD is combined with intraductal ultrasonography (IDUS), the orifice of the cystic duct (CD) in the common bile duct is more easily detected, and the CD is more easily cannulated. The aim of the present study is to evaluate the efficacy and feasibility of ETGBD with IDUS compared to ETGBD alone.

A hundred patients with acute cholecystitis requiring ETGBD were recruited between January 2015 and December 2017. The first consecutive 50 out of 100 patients were treated by ETGBD without IDUS, and the following consecutive 50 patients were treated by ETGBD with IDUS. The primary outcome was technical success rate.

Results: The technical success rate of ETGBD with IDUS was significantly higher than that of ETGBD without IDUS (92.0% [46/50] vs 72.0% [36/50], P= 0.014). There was no significant difference between the procedure lengths of both groups (74.0 minutes [10-140] vs 65.6 minutes [14-215], p = .219). Complication rates of ETGBD with IDUS were significantly higher than those of ETGBD without IDUS (6.0% vs 0% P< .001); however, IDUS technique-related complications such as pancreatitis were found in only one case.

Conclusion: ETGBD with IDUS may be one of the best therapeutic methods for patients with acute cholecystitis.

Disclosure: Nothing to disclose

OP172 ENDOSCOPIC ULTRASOUND VS ENDOSCOPIC TRANS-PAPILLARY VS PERCUTANEOUS GALLBLADDER DRAINAGE IN HIGH-RISK ACUTE CHOLECYSTITIS PATIENTS: A SYSTEMATIC REVIEW AND COMPARATIVE META-ANALYSIS

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Introduction: Endoscopic transpapillary gallbladder drainage (ETGBD) and endoscopic ultrasound guided gallbladder drainage (EUSGBD) are alternative to percutaneous gallbladder drainage (PCGBD) in the management of acute cholecystitis unfit for surgery. Data comparing these modalities are limited and have reported conflicting results.

Aims & Methods: We searched multiple databases from inception through December2018 to identify studies that reported on ETGBD, EUSGBD, and PCGBD in the management of acute cholecystitis high risk for surgery. Our goals were to compare the pooled rates of technical success, clinical success, adverse events, and disease recurrence.

Results: 13 studies (815 patients), 12 studies (506 patients), and 8 studies (1484 patients) were treated by ETGBD, EUSGBD, and PCGBD respectively. Baseline patient characteristics were comparable between the groups. Age ranged from 65 to 85 years with 61% males. The pooled technical and clinical successes of EUSGBD was statistically superior to ETGBD [95.9% (95% CI 91-98.1, I²=6.4) vs 80.3% (95% CI 67.4-89, I²=68), p=0.001; 96.7% (95% CI 94.1-98.1, I²=0) vs 88.6% (95% CI 84.3-91.8, I²=42.3), p=0.001; respectively]. Bleeding and perforation was statistically more with EUS-GBD [3.8% (95% CI 2.3-6.2, I²=0) vs 1.6% (95% CI 0.7-3.2, I²=0), p=0.03; 4.4% (95% CI 2.8-6.9, I²=0) vs 1.7% (95% CI 0.9-3.4, I²=0), p=0.004; respectively], whereas pancreatitis was statistically more with ETGBD [6.4% (95% CI 4.1-9.8, I²=27.3 vs 0, p=0.001]. Pooled clinical success of EUSGBD was statistically superior to PCGBD [96.7% (95% CI 94.1-98.1, I²=0) vs 90% (95% CI 85.7-93.1, I²=37.6), *p*=0.001], whereas the pooled rate of technical success was comparable (Table).Pooled rate of disease recurrence was comparable between the groups (Table).

(95% CI, I2)	Technical success	Clinical Success	Adverse events	Recurrence
ETGBD	80.3% (67.4-89, 68)	88.6% (84.3-91.8, 42.3)	9.8% (5.3-17.2, 40.7)	3.6% (1.9-6.6, 17.1)
EUSGBD	95.9% (91-98.1, 6.4)	96.7% (94.1-98.1, 0)	12.1% (6.9-20.2, 7.9)	4.5% (2.7-7.4, 0)
PCGBD	94.7% (85.7-98.1, 95.3)	90% (85.7-93.1, 37.6)	18.4% (9.9-31.5, 93.7)	7.5% (4.7-11.6, 48.6)
p-value of statistical significance				
ETGBD vs EUSGBD	0.001	0.001	0.69	0.66
ETGBD vs PCGBD	0.03	0.53	0.2	0.1
EUSGBD vs PCGBD	0.91	0.001	0.37	0.1

ETGBD: endoscopic transpapillary gallbladder drainage, EUSGBD: endoscopic ultrasound guided gallbladder drainage, PCGBD: percutaneous gallbladder drainage

[Summary of pooled results]

Conclusion: EUSGBD demonstrates superior clinical success when compared to ETGBD and/ or PCGBD in the treatment of acute cholecystitis in surgically unfit patients. Based on our analysis, EUSGBD should be considered the first line approach for treating patients with acute cholecystitis who are high risk for surgery and preferable be done in high volume centers due to significant but rare adverse events.

Disclosure: Nothing to disclose

OP173 EVALUATIONS OF SEVERITY ASSESSMENT FOR ACUTE CHOLECYSTITIS : JAPAN-TAIWAN COLLABORATIVE MULTICENTER STUDY FOR ACUTE CHOLECYSTITIS

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Introduction: Acute cholecystitis is a disease frequently encountered in daily practice presenting with right hypochondrial pain as the main symptom. Tokyo Guidelines 2013 (TG13) have already been recognized as the severity assessment criteria to be recommended in today's medical care for acute cholecystitis all over the world. Severe acute cholecystitis was defined as acute cholecystitis accompanying organ dysfunctions directly related to poor prognosis. Exactly acute cholecystitis is basically not a disease with a high mortality. However, it was thought that guidelines should make it clear that adequate management with appropriate use of severity assessment criteria for acute cholecystitis does lead to improved patients' prognosis.

Aims & Methods: The aim for this study was validation of the clinical impact of TG13 severity assessment criteria for acute cholecystitis. The study was designed as Japan-Taiwan collaborative multicenter retrospective study of acute cholecystitis from 2011 to 2013. Based on the data, we investigated the TG13 severity assessment criteria by analyzing the correlations between grade and prognosis, surgical procedures, and histopathology, in addition between the numbers of organ dysfunctions and mortality.

Results: A total of 5,459 patients in 154 Japanese and Taiwanese institutions were included in our study. Of the 5,459 patients, 4,716 were from Japan and 743 from Taiwan. With exclusion criteria of missing data, 1,099 patients were excluded and a final total of 4,360 patients were included for this study. A Study revealed that 30-day overall mortality rate was 1.1% for Grade I, 0.8% for Grade II, 5.4% for Grade III. The 90-day mortality rate was 1.0% for Grade I, 0.8% for Grade II, 5.6% for Grade III. The mortality rate for Grade III was significantly higher than lower grades (P < 0.001). The relationship between the numbers of organ dysfunctions and 30-day mortality was investigated, the greater the numbers of organ dysfunction, the higher the mortality rate (P < 0.001). However, the mortality rate varied depending on the number of organ dysfunction (3.1-25%). Especially neurological dysfunction and Respiratory dysfunction were considered as a significant poor prognostic factor on 30-day mortality (P < 0.001). With respect to the surgical procedures, laparoscopic cholecystectomy was significantly selected for Grade I patients (P < 0.001), and the higher the grade, the more likely open cholecystectomy was performed (P < 0.001). Pathological findings research revealed that Gangrenous cholecystitis and Chronic cholecystitis were significantly diagnosed with higher grade of TG13 severity assessment (P < 0.001).

Conclusion: This international multicenter investigation between Japan and Taiwan revealed that severe acute cholecystitis judged by TG13 severity assessment criteria were exactly worse conditions with organ dysfunctions and it would have possible to be poor prognosis. As a result, it would be better performance for the management of acute cholecystitis with using TG13 severity assessment criteria on emergency room and after admission. TG13 for AC would be providing great impact in actual clinical practice.

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Disclosure: Nothing to disclose

OP174 IS SELECTIVE HISTOPATHOLOGIC EXAMINATION OF THE GALLBLADDER PERMISSIBLE?

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Introduction: Necessity of routine histopathologic examination of gallbladders has been debated for the past decades. Implementation of a selective histopathologic policy is hampered by fear of missing small carcinoma in macroscopically normal gallbladders. We wanted to investigate how gallbladder cancer was detected and identified. We aimed to identify GBC in macroscopically normal gallbladders and to what extend these malignancies might have had clinical consequences.

Aims & Methods: Using the Dutch Cancer Registry all patients were reviewed with diagnosis of gallbladder cancer between 2004 and 2015 in the South region of the Netherlands, a population of 2.3 million people. We identified all patients that had unexpected malignancies operated for benign gallstone disease. Based on clinical and pathological report we determined whether malignancies were macroscopically suspected or detected by microscopy only. In patients with GBC only detected by histopathology tumour stage and clinical consequence were summarized.

Results: A total of 205 malignancies of the gallbladder were identified. In 75 patients there was no suspicion of gallbladder cancer prior to surgery. Of these 37, the surgeon described a tumour in the operation report. In 38 there was no mention of abnormalities in the operation report. 8 gallbladders would probably been send for histopathologic examination based on difficulties during surgery (e.g. conversion or excessive gallbladder emphysema) or clinical indication (e.g. Mirizi syndrome). Pathologic examination identified macroscopic abnormalities in 23 cases. In the remaining 7 specimens there were no macroscopic abnormalities and samples were taken at random. None of these patients received additional treatment. In the same time period histological gallbladder examination occurred in 31902.

Conclusion: We present one of the largest single study cohort of histopathologic gallbladder examination and relation to gallbladder cancer. The major part of the invasive gallbladder cancers showed macroscopic abnormalities peroperatively. Over a decade, in a population of 2.3 million people, histology alone resulted in a change of treatment plan in just one patient. Therefore, selective histopathology seems a feasible policy and would reduce costs and pathological workload.

Disclosure: Nothing to disclose

OP175 THE APPLICATION OF INDOCYANINE GREEN-FLUORESCENCE IMAGING DURING ROBOTIC LIVER RESECTION: A CASE-MATCHED STUDY

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Introduction: The ICG-fluorescence properties are progressively gaining momentum in the HPB surgery. However, the exact impact of ICG application on surgical outcomes is yet to be established.

Aims & Methods: Twenty-five patients who underwent ICG-fluorescence guided robotic liver resection were case matched in a 1:1 ratio to a cohort who underwent standard robotic liver resection.

Results: In the ICG group six additional lesions not diagnosed by preoperative workup and intraoperative ultrasound were identified and resected. Four of the lesions proved to be malignant. Despite the similar operative time (288 vs 272 min, p= 0.778), the risk of postoperative bile leakage (0% vs 12%, p= 0.023), R1 resection (0% vs 16%, p= 0.019) and readmission (p= 0.023) was reduced in the ICG group compared with the no-ICG group.

Conclusion: The ICG-fluorescence is a real time navigation tool which enable surgeons to enhance visualization of anatomical structures and over-

come the disadvantages of minimally invasive liver resection. The procedure is not time-consuming and its applications can reduce the postoperative complication rate in robotic liver surgery.
Disclosure: Nothing to disclose

Basic science: The intestinal epithelium and IBD
10:30-12:00 / B5

OP176 THE EFFECT OF ULCERATIVE COLITIS RELATED CIRCRNA CIRC-SOD2 ON INTESTINAL EPITHELIAL BARRIER

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Introduction: To explore the dysregulated circRNAs and mRNAs profiles in inflamed ulcerative colitis (UC) colorectal mucosa and identify the crucial circRNAs associated with UC. To clarify the roles and potential mechanisms of the key circRNA involved in intestinal epithelial barrier.
Aims & Methods:
1. CircRNAs microarray and mRNAs microarray were used to determine the differences of circRNAs and mRNAs between 5 paired inflamed UC colorectal tissues and normal colorectal tissues;
2. To predict the functions and involved pathways of dysregulated circRNAs and mRNAs with bioinformatics tools and identify the critical circRNA;
3. Quantitative real-time polymerase chain reaction (qRT-PCR) was applied to examine the expression of candidate circRNAs in extended UC colorectal tissues and colon epithelial cell models;
4. Fluorescence in Situ Hybridization(FISH) was performed to confirm the cellular location in UC tissues;
5. Construct overexpressed circ-SOD2 vector and transfected into Caco2 cells to object the influences of circ-SOD2 in intestinal epithelial barrier;
6. Detect epithelial barrier related proteins such as CLDN-8, ZO-1 and occludins with Western Blotting after circ-SOD2 vector transfected;
7. Build a network included circRNAs, microRNAs and mRNAs to predict the potential role mechanisms of circ-SOD2 in intestinal epithelial barrier.
Results:
1. The microarray assays indicated that 110 upregulated and 152 downregulated circRNAs and 1004 upregulated, 865 downregulated in mRNAs;
2. The functional analysis of differentially expressed circRNAs derived parental genes found that these parental genes were involved in HIF1-α, Rap1 signaling pathway and cellular adhesion;
3. Multiple dysregulated circRNAs were validated in UC with qRT-PCR and hsa_circ_0004662 derived from SOD2 gene was upregulated significantly (named as circ-SOD2) and related to the severity of UC;
4. circ-SOD2 mostly located in colon epithelial and increased after the treatment of inflammation factors in vitro;
5. The overexpression of circ-SOD2 in Caco2 cells led to TEER decreased, FITC-dextran permeability improved, microvillus and tight junction reduced;
6. Overexpressed circ-SOD2 in Caco2 cells caused that epithelial related protein CLDN-8 was decreased;
7. The potential mechanism of the role of circ-SOD2 in intestinal epithelial barrier was that circ-SOD2 harbored some microRNAs such as hsa-miR-424-5p, hsa-miR-497-5p, hsa-miR-935, hsa-miR-16-5p, hsa-miR-152-3p to control the downstream mRNAs.
Conclusion: The profile of circRNAs and mRNAs in inflamed UC colorectal tissues changed significantly, among them, circ-SOD2 had an obvious decrease. Additionally, the overexpression of circ-SOD2 caused the injury of intestinal epithelial barrier and its possible mechanisms were that circ-SOD2 regulated the expression of CLDN-8 directly or bound microRNAs to control target mRNAs indirectly.
Disclosure: Nothing to disclose

OP177 GPX4 RESTRICTS ENVIRONMENTALLY-INDUCED COLITIS

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Introduction: Glutathione Peroxidase 4 (GPX4) is an antioxidative enzyme, which particularly reduces lipid peroxides and is the key regulator of a novel cell death pathway called ferroptosis which is characterised by uncontrolled lipid peroxidation (LPO) [1,2]. A recent study demonstrated that deletion of GPX4 in myeloid cells of mice, leads to increased susceptibility to chemical induction of colitis [3]. However, the role of intestinal epithelial GPX4 in intestinal homeostasis remains unclear.

Aims & Methods: We aimed to study a role for epithelial GPX4 in the control of intestinal homeostasis.

We crossed *Gpx4^{fl/fl}* mice with *Villin-Cre[+]* mice to obtain *Gpx4[fl/wt] VillinCre+* (*Gpx4[+/-IEC]*) mice that lack one allele of *Gpx4* specifically in intestinal epithelial cells. In these mice colitis was induced with three percent dextran sodium sulfate (DSS) in drinking water for five consecutive days followed by three days of tap water. Mice were dissected three days after withdrawal of DSS. Disease severity was assessed by comparing the colon length and the histology score.

Results: *Gpx4[+/-IEC]* mice had significantly reduced colon lengths after DSS-colitis compared to wild type littermates, indicative for severe colitis. This finding was corroborated by histopathological evaluation, which showed that mice lacking one allele of GPX4 exhibited more severe inflammation in their colons after colitis induction with DSS.

Conclusion: Intestinal epithelial GPX4, a central antioxidative enzyme in cells, protects mice against inflammation in the large intestine. So far, the mechanisms how GPX4 interacts with inflammatory pathways remain unknown, but it presents a promising target for future anti-inflammatory therapies.

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Disclosure: Nothing to disclose

OP178 BACTERIA INDUCE THE RELEASE OF PROALGESIC LIPIDS BY EPITHELIAL CELLS

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Introduction: Irritable bowel syndrome is the most common functional intestinal disorder. It is characterized by visceral hypersensitivity and an altered gut transit that are associated with a gut microbiota dysbiosis. Among the studied pronociceptive mediators, host and bacterial lipid compounds have been described as major regulators of visceral hypersensitivity.

Aims & Methods: The aim of our study was to identify the role of the host and bacterial lipids interplay on visceral hypersensitivity. To differentiate bacterial and host lipids, *Escherichia coli* were cultivated in a minimal medium with ^{13}C- glucose as unique source of carbon, leading to the production of ^{13}C-labelled bacterial lipids. Bacterial lipid extracts were added at the apical side of polarized intestinal epithelial cells (caco2) cultured in transwell. Twenty four hours after treatment, quantification by high-resolution mass spectrometry of the ^{13}C-labelled lipids from the bacteria and the unlabeled lipids from the epithelial cells in the basolateral compartment allowed us to determine epithelial and bacterial lipids that could potentially be in contact with nerve endings. Lipid quantification by liquid chromatography coupled to tandem mass spectrometry was performed in the colon of germ free and conventional mice. We then assessed the ability of the epithelial and bacterial lipids found in the basolateral compartment to increase intracellular calcium concentration in primary culture of mouse sensory neurons.

Results: Amongst the uniformly ^{13}C-labelled bacterial lipids, we identified long chain fatty acids, from 10 to 18 carbons, hydroxylated on the 3rd carbon with or without a double bound, and aminolipids in the bacterial culture. Twenty four hours after treatment by bacterial lipids at the apical side of the transwells, we quantified an increase of the concentration of bacterial C10-3OH, C12Asn*OH* and C14Asn*OH* as well as epithelial 9,10-DiHOME and 12,13-DiHOME in the basolateral compartment. Similar results were obtained when the bacterial lipids were unlabeled, meaning that these results were not due to the labelling. We found a significantly lower concentration of 9,10- and 12,13-DiHOME in the colon of germ-free mice, strengthening the link between the microbiota and the host production of those lipids. Bacterial lipids and 12,13-DiHOME did not activate sensory neurons. In contrast, the 9,10-DiHOME induced calcium flux in sensory neurons. This effect was inhibited by a pretreatment of the neurons with a TRPV1 antagonist (AMG9810).

Conclusion: Our study show that bacterial lipids induce the release of potentially proalgesic lipids by epithelial cells. Lipid metabolism could be the link between dysbiosis and visceral pain in IBS.

Disclosure: Nothing to disclose

OP179 CONTRIBUTION OF FULL FIELD OPTICAL COHERENCE TOMOGRAPHY (FF-OCT) FOR THE STUDY OF THE DIGESTIVE EPITHELIAL BARRIER IN PATIENTS WITH SPINA BIFIDA

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Introduction: Full Field Optical Coherence Tomography (FF-OCT) is an ex vivo imaging technique, with micrometric resolution, usually reserved for imaging biological environments (1) (2). It allows rapid acquisition of ex vivo tissue images on a cellular scale, and therefore represents an attractive approach for analysis of human samples such as endoscopic biopsies. Adult patients with Spina Bifida (SB) often have digestive disorders (3) whose pathophysiology is poorly known and remains to be explored. The objective of this study was to evaluate the feasibility and relevance of FF-OCT in the study of the morphology of the intestinal epithelial barrier from colonic biopsies of patients with SB.

Aims & Methods: FF-OCT analyses were performed on fixed colonic biopsies of SB patients and healthy volunteers (HV), collected during a short colonoscopy. Biopsies were scanned using the Light-CT scanner (LLTech, Paris, France). This device allows to produce contrast images in grayscale (axial resolution 1µm, frequency 75Hz), with the possibility of making a mosaic in order to obtain a maximum examination field of 25mm. The analyse depth is adjustable, with a maximum depth of several millimeters and the possibility of performing a three-dimensional reconstruction of the specimen. 2 biopsies per patient/HV were analyzed. The different morphological criteria studied in FF-OCT were: the average density of the connective tissue, the number of crypts, the average area of the crypts, the total area of the crypts, the average roundness of the crypts, the average circularity of the crypts and the average of the major axis/small axis of the crypts. These data were compared with each other by a Student t-test. A standard histological analysis was also performed.

Results: Data from 36 adult SB and 16 HV patients were analyzed. Among SB patients: 26 (72%) had abdominal pain, 6 (17%) faecal incontinence, the average number of stools was 3/week. The appearance of the mucosa was macroscopically healthy in endoscopy and the standard anatomo-pathological study found no abnormalities. The connective tissue density in FF-OCT was significantly decreased in Spina Bifida patients: p < 0.0001.

No significant differences were found concerning, per section, the number of crypt p = 0.4210, the average crypt area p = 0.2332, the total crypt area p = 0.2391, the average crypt roundness p = 0.7906, the average crypt circularity p = 0.09 and the average major/small crypt axis measurement mean p = 0.3463.

Conclusion: Morphological abnormalities of the intestinal epithelial barrier could be detected by FF-OCT in adult Spina Bifida patients. This innovative technique allows the precise quantitative study of specific histological parameters and therefore provides additional information to the classical anatomopathological study.

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Disclosure: Nothing to disclose

OP180 MIR-124A MEDIATES THE IMPAIRMENT OF INTESTINAL EPITHELIAL INTEGRITY BY TARGETING ARYL HYDROCARBON RECEPTOR IN CROHN'S DISEASE

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Introduction: Aryl hydrocarbon receptor [AHR] is a transcription factor, which induced by various ligands. AHR palsys a important role in the immune response. Meanwhile, activation of AHR can attenuate epithelial barrier dysfunction. The expression level of AHR is downregulated and miR-124a is upregulated in Crohn's Disease [CD]. How to modulate the AHR expression during the development of CD has yet to be thoroughly expounded.

Aims & Methods: The expression levels of miRNA and AHR protein were determined in Caco-2 monolayers and inflamed colon from patients with CD by RT-PCR and western blot analysis. Combining miRNA target prediction softwares, we verified microRNAs that targeted AHR. Trans-epithelial electrical resistance [TEER] and fluorescein isothiocyanate [FITC]-dextran were used to assess the permeability of the Caco-2 cell monolayers. The wild type [WT], miR-124a-Nju and AHR knockout mice were induced colitis using TNBS enema. Colitis mice using anti-miR-124a to inhibit miR-124a expression. We evaluated the intestinal inflammation and determined miR-124a, AHR and tight junction [TJ] proteins levels in mice of different treated groups.

Results: miRNA profiles of colon samples from CD patients were different with normal controls. There was an negative correlation between miR-124a and AHR protein levels in inflamed colon tissues from active CD patients. In vitro studies [Caco2 monolayers] revealed that: the downregulated AHR and TJ proteins were induced by TNF-α or miR-124 mimic. Meanwhile, TNF-α or miR-124a mimic induced-hyperpermeability via overexpression of the miR-124a, which was abrogated by miR-124a inhibitor. In vivo studies [colitis model mice] demonstrated that: miR-124-1-Nju and AHR^{-/-} mice using TNBS enema had more severe intestinal inflammation than WT colitis mice. MiR-124-1-Nju and AHR^{-/-} mice experienced severely intestinal barrier dysfunction, which was ameliorated after administrating anti-miR-124a in miR-124a-Nju mice but not in AHR^{-/-} mice.

Conclusion: This study suggested that miR-124a can cause intestinal barrier dysfunction and induce intestinal inflammation via supressing AHR. Furthermore, we will explicate the exact molecular mechanisms for CD.

Disclosure: Nothing to disclose

OP181 ACTIVE EPITHELIAL SERINE PROTEASES ARE PRODUCED BY INTESTINAL EPITHELIUM TO CONTROL MUCOSAL BIOFILMS

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Introduction: Proteolytic homeostasis is observed at the surface of intestinal mucosa and is known to be disrupted in diseases (inflammatory bowel disease, infection or irritable bowel syndrome)(1-3). Here, we investigated how mucosal proteolytic homeostasis might control microbial biofilms present at the intestinal epithelium surface.

Aims & Methods: Our aim was to determine if epithelial proteases could control microbial biofilm composition, and structure.

We measured proteolytic activity and protease expression at mucosal surfaces in mouse and human tissues, and in monolayers of human epithelial cell lines. We studied the biophysical structure, biomass and microbial composition of biofilms at mucosal surfaces, or grown on synthetic solid surfaces. For the latest, we used cultured mucosa-associated microbiota from 4 healthy human colon biopsies. Mucosal proteolytic activity was modulated by the use of selective protease inhibitors in vivo and in vitro. Finally, N-terminomics/TAILS approaches were used to identify protease cleavages in human complex microbial biofilms.

Results: We report that healthy human and mouse colon epithelium are a major source of active serine proteases, released in the lumen. Using germ-free animals, we demonstrated that mucosal serine proteases were directly regulated by the presence of commensal microbiota. Specific inhibition of luminal serine protease activity caused macro-, microscopic damage and transcriptomic alterations of genes involved in host-microbiota interactions. Further, luminal serine protease inhibition impaired the spatial segregation of microbiota biofilms, allowing bacteria to invade the mucus layer and to translocate across the epithelium, but had no obvious effect on microbiota composition. Epithelial proteases cleaved the biofilm matrix of reconstituted mucosa-associated human microbiota, and can alter in a concentration-dependent manner the biofilm biomass.

Conclusion: We demonstrate a previously unknown physiological role for epithelial proteases that constrains biofilms at mucosal surfaces. Our discovery points to an important role for proteolytic homeostasis at the intestinal mucosal surface with regards to biofilm organization and invasive behavior.

References: 1- Motta JP et al. Sci. Trans. Med. 2012 2- Motta JP et al. Gastroenterology 2011 3- Denadai-Souza A. et al. Sci. Rep. 2018

Disclosure: Nothing to disclose

Colonic ESD: Does size matter?
10:30-12:00 / C2

OP182 BRIDGE FORMATION METHOD IN COLORECTAL ENDOSCOPIC SUBMUCOSAL DISSSECTION

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Introduction: Colorectal endoscopic submucosal dissection(ESD) is becoming an established procedure, difficult cases still exist. As effective traction for approaching to submucosal layer can reduce difficulty of ESD proce-

dure, the normal mucosa on both lateral sides of lesion is used for natural traction. it is called the Bridge Formation Method (BFM). We present the procedure of BFM and comparison of treatment results of BFM group and non-BFM group in our hospital.

Aims & Methods: From January 2009 to December 2018, colorectal ESD was performed in 1577 lesions consecutively at our hospital. There were 867 cases for the BFM group and 710 cases for the non-BFM group. Flush Knife(FUJIFILM) and Distal attachment(Olympus) were used as the main devices. The procedure is as follows:
1) Make a mucosal incision on the anal side of lesion,
2) Advance submucosal dissection without mucosal incison of both lateral sides,
3) Make a mucosal incision on oral side of lesion and finish almost submucosal dissection,
4) Open the tunnel and bridge will be completed,
5) At last make a mucosal incision on both lateral sides.
The difference from the normal tunnel method is that almost submucosal dissection under the tumor is completed before mucosal incision on both lateral sides of lesion.

Results: In comparison with BFM group and non-BFM group, Average tumor size[27.0 ± 19.5 mm vs 25.0 ± 13.5 mm, P=0.017], morphology 0-Is, 0-IIc, laterally spreading tumor-granular(LST-G), laterally spreading tumor-non granular(LST-NG) [3.6%, 1.1%, 30.9%, 64.5% vs 1.7%, 0.3%, 50.7%, 47.3%, P=0.000], localization [colon: rectum, 84.1%:15.9% vs 85.4%:14.6%, P=0.528], submucosal(SM) invasion≥1000μm [13.5%, 117/867 vs 3.9%, 28/710, P = 0.000], en block resection rate [99.6%, 864/867 vs 97.6%,693/710, P=0.000], R0 resection rate [98.2%, 851/867 vs 97.0%, 689/710, P=0.181], average dissection speed [28.5 ± 17.2mm²/ min vs 24.9 ± 18.3 mm²/ min, P < 0.001], perforation rate [1.4%, 12/867 vs 1.8%, 13/710, P=0.546], post-bleeding rate [1.4%, 12/867 vs 0.8%, 6/710, P = 0.351].
In BFM group, average tumor size was significantly larger than non-BFM group, and the ratio of LST-NG was higher.
There was no significant difference in the localization of the lesions. The rate of SM massive invasion and en block resection rate were significantly higher in BFM group. R0 resection rate was higher in the BFM group but there was no statistically significant difference. Average dissection speed was significantly faster in the BFM group, and there was no significant difference in perforation rate and post-bleeding rate.
The results in the BFM group that the ratio of LST-NG is high and the high SM massive invasion rate suggests the degree of fibrosis in submucosal layer is high, so treatment difficulty is high. Despite under these conditions, the average dissection speed in the BFM group was significantly faster, and the en block resection rate was significantly higher.

Conclusion: The results suggests the usefulness of BFM is to leave the normal mucosa on both lateral sides of lesion for using the natural traction to the last of ESD. BFM enables stable manipulation under the lesion without using dedicated traction device, and dissection at an appropriate depth will be easier. Therefore, BFM is versatile method appropriate from normal lesions to difficult lesions.

Disclosure: Nothing to disclose

OP183 ROUTINE USE OF THE POCKET-CREATION METHOD FOR ENDOSCOPIC SUBMUCOSAL DISSECTION OF COLORECTAL LESIONS: A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Introduction: Endoscopic submucosal dissection (ESD) of colorectal lesions can be difficult due to submucosal fibrosis, a thin muscularis or a poorly-controlled colonoscope. To overcome these obstacles, the pocket-creation method (PCM) was developed and may be an ideal strategy for resecting all types of colorectal lesions.

However, there are no randomized clinical trials to date assessing the efficacy of the PCM for ESD of routine colorectal lesions compared with the conventional method (CM).

Aims & Methods: This study was designed as a randomized controlled parallel clinical trial in three tertiary-care hospitals. Patients with colorectal neoplasms ≥20mm were enrolled and randomly allocated to PCM or CM. Patients were excluded if lesions were suspicious for deep (≥1mm) submucosal invasion; spread to the ileocecal valve, appendiceal orifice or diverticulum; recurrent lesions after endoscopic resection; inflammatory bowel disease or familial adenomatous polyposis; and/or a bleeding tendency. Randomization was conducted to minimize differences in lesion morphology, location (colon or rectum), and institution. The primary endpoint was ESD completion rate. "Completion" was defined as achieving an en-bloc resection within 3 hours, without changing the assigned strategy. Procedures were not complete with interruption of the ESD procedure for ≥10 minutes, severe injury to the muscularis, or perforation/penetration. Secondary endpoints were en-bloc resection rate, cutting time, dissection speed and adverse events.

Results: A total of 121 patients were enrolled and randomly allocated to CM or PCM. Seven patients were excluded after randomization, and 59 patients for PCM and 55 patients for CM finally included. Patient demographics and lesion characteristics showed no significant differences between the two groups. The completion rate was significantly higher in the PCM group compared to the CM group (93% [55/59] vs. 73% [40/55]; *P*=.01). In contrast, en-bloc resection rates, cutting time and dissection speed were not significantly different comparing the two groups. Analysis of subgroups showed the PCM was better for colon lesions (P = .003), lesions 30 mm or larger (P = .03), lateral spreading tumor granular type or protruded morphology (P = .009), treatment in institution A (P = .001) and non-expert endoscopists (P = .003).The incidence of adverse events was similar in the two groups (delayed bleeding one in each group, and perforation one in the CM group). All adverse events were treated successfully with endoscopy.

Conclusion: The resection completion rate using the PCM is significantly higher than the CM. The PCM is useful for routine ESD of colorectal lesions, not only for difficult lesions.

	PCM Group (n=59)	CM Group (n=55)
Male/female Male (%) Female (%)	34 (58%) 25 (42%)	33 (60%) 22 (40%)
Median age (range, years)	70 (41-92)	68 (42-86)
Location- Cecum, Ascending, Transverse, Descending, Sigmoid, Rectum	8 (14%), 19 (33%), 9 (15%), 2 (3%), 10 (17%), 11 (19%)	9 (16%), 16 (29%), 9 (16%), 1 (2%), 8 (15%), 12 (22%)
Morphology- LST-G, Protruded, LST-NG	31 (53%), 3 (5%), 25 (42%)	28 (51%), 6 (11%), 21(38%)
Median estimated tumor size (range, mm)	30 (18-75)	30 (20-80)
Operator- Expert, Non-expert	27 (46%), 32 (54%)	28 (51%), 27 (55%)
Institution- A, B, C	27 (46%), 19 (32%), 13 (22%)	24 (44%), 14 (25%), 17 (31%)

[Baseline data of the treatment groups]

Disclosure: Dr. Yamamoto has patents for the double-balloon endoscope produced by Fujifilm Corp. He also serves as a consultant for and has received honoraria, grants, and royalties from Fujifilm Corp. All other authors disclosed no financial relationships relevant to this publication.

OP184 COLONIC ESD WITH DOUBLE-CLIP TRACTION: A REVOLUTION COMING FROM EUROPE!

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Introduction: ESD in the colon is more challenging technically than other locations.

This difficulty explain poor results of colonic RSD (except rectal cases) outside of japan with a low R0 resection rate, a high perforation rate and a long procedure time. Due to these bad results most European experts promotes piece-meal EMR instead of ESD for the endoscopic treatment of large benign colonic lesions.

Recently we presented our new systematic strategy for colonic ESD by countertraction by clips and rubber band that considerably facilitates the procedure. Here, we report a large prospective case series of colon ESD using this strategy.

Aims & Methods: Prospective consecutive sudy of all colonic ESD performed prospectively two experts centers from April 2017 (First Colonic ESD with clips and rubber band) to April 2019. Since the first case of colonic ESD with clips and rubber band in April 2017, all cases of colonic ESD were performed using this strategy.

Primary Endpoint: Monobloc, R0 and curative resection rate.

Secondary Endpoints: Perforation rate, risk factors in multivariate analysis of Perforation, R0 resection and Optimal ESD (defined by R0 resection without perforation and faster than 20mm²/min).

Results: 618 colorectal ESD were performed in the study period. Rectal cases (180) were excluded. About the 438 remaining colonic cases, appendiceal lesions, recurrent or partial resection lesions, dysplasia on IBD lesions and lesions invading diverticula were excluded. Finally 374 cases were included in the study performed by 4 operators in to experts centers. Lesions were SMSA 4 in 82% of cases with a mean size of 55 mm. Mean duration procedure was 67 min with a min speed of resection at 38,7 mm²/min. 63% of the lesions were located above the splenic flexure.

Primary Endpoint: Monobloc, R0 and curative resection rate were respectively 96%, 83% and 81%.

Secondary Endpoint:

- Perforation rate was 4,6%.

-predictive factors of optimal ESD were one operator (OR 3,9; p< 0,0001) and no F2 fibrosis (OR 4,3 p=0,0003), and ESD performed in 2018 à 2019 (OR 7; p=0,0004) in multivariate analysis.

- predictive factors of non R0 resection were presence of perforation (OR 0,32; p=0,05) and intense fibrosis (OR 0,30; p= 0,008).

- predictive factors of perforation were intense fibrosis (OR 18,4; p=0,03) and big size of the lesion (OR 1,037; p< 0,0001) in multivariate analysis.

Conclusion: Systematic countertraction using a double clip and rubber band facilitates colon ESD. Speed of ESD is twice as reported by recent Japanese teams using Pocket creation Method whereas oncologic results are similar. This strategy should become the standard for colon ESD and help to widespread colonic ESD. Our results feeds the debate between piece-meal EMR and ESD for the treatment of large colonic superficial lesions.

Disclosure: Nothing to disclose

OP185 IS THE SMSA SCORE ACCURATE ENOUGH TO PREOPERATIVELY PREDICT SUBOPTIMAL CLINICAL OUTCOMES IN COLORECTAL ENDOSCOPIC SUBMUCOSAL DISSECTION (CR-ESD)? A MULTICENTER SPANISH PROSPECTIVE STUDY

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Introduction: The SMSA (size, morphology, site, access) polyp scoring system is a method for stratifying the difficulty of polypectomy. It was developed by an expert consensus using the Delphi method.

Aims & Methods:

1. To assess the ability of SMSA to predict CR-ESD suboptimal clinical outcomes (SCOs): excessive duration of the procedure and percentages of piecemeal resections, aborted procedures and complications.

2. To develop a new preoperative model to predict those SCOs and compare its performance with that of the SMSA.

Consecutive patients were enrolled in a prospective multicenter Spanish CR-ESD registry since January 2016 to October 2018. We analyzed 585 cases in 19 hospitals. The overall ability of the scores to discriminate between those who developed SCOs and those who did not was assessed by the area under the ROC curve.

Results: Overall, 221 cases (38%) developed any of the predefined SCOs. There were 13 aborted procedures (2.2%), 92 piecemeal resections (16.1%), 86 intraprocedural perforations (14.7%), 19 delayed perforations (3.4%) and 37 delayed bleedings (6.6%). There were 40 SMSA2 (6.8%), 189 SMSA3 (32.3%) and 356 SMSA4 (60.8%) lesions. Surprisingly, SMSA2 lesions were significantly associated with piecemeal resections (SMSA2 vs SMSA3/4: 27.5% vs. 14.8%; OR= 0.5; CI95%: 0.2-0.9; p= 0.04). Statistically significant differences were observed between intraprocedural perforations and SMSA3/4 lesions (SMSA2 vs. SMSA3/4: 2.5% vs. 15.6%; OR= 7.2; IC95%: 1.01-53.1; p= 0.02). We did not observe statistically significant association between higher SMSA scores and duration of the procedure > 240 min., aborted procedures or delayed complications. The AUROC of the SMSA score >= 3 was 0.51 (CI95%: 0.46-0.55). Thus, an alternative logistic regression model was designed. It included significant variables that were associated with the predefined outcomes in the univariate analysis: case load < 10 lesions: OR=4.5 (CI95%: 1.5-13.2; p= 0.007), poor manoeuvrability, OR=1.6 (CI95%: 1.1-2.2; p= 0.007), size > 30 mm, OR=1.5 (CI95%: 1.01-2.2; p= 0.02), LST-G mixed type with a nodule > 10 mm, OR=2.8 (CI95%: 1.1-7.1; p= 0.03) and previous endoscopic electrosurgical treatment, OR=2.2

(CI95%: 1.06-4.6; p= 0.03). The AUROC for this multivariate model was 0.61 (CI95%: 0.57-0.66). The difference between both AUROCs was statistically significant (p< 0.00001).

Conclusion: The SMSA score was useless to predict CR-ESD SCOs. A new score based on a multivariate logistic regression model showed a slightly better discrimination ability to predict these suboptimal events.

Variable	Yes (n= 221)	No (n=364)	Univariate OR (CI 95%)	p	Multivariate OR (CI 95%)	p
Size > 3 cm	151 (68.3)	219 (60.2)	1.43 (1.01-2.0)	0.04	1.55 (1.08-2.24)	0.02
LST-G mixed type nodule > 10 mm	13 (6)	8 (2.2)	2.78 (1.13-6.8)	0.02	2.83 (1.13-7.07)	0.03
Previous electrosurgery	18 (8.1)	15 (4.1)	2.06 (1.02-4.2)	0.04	2.21 (1.06-4.62)	0.03
Poor manoeuvrability	122 (55.2)	163 (4.8)	1.52 (1.08-2.1)	0.01	1.60 (1.13-2.25)	0.008
Case load < 10	12 (5.4)	5 (1.4)	4.12 (1.43-11.8)	0.005	4.48 (1.51-13.2)	0.007

[Suboptimal clinical outcomes. Univariate and multivariate analysis]

Disclosure: Nothing to disclose

OP186 ENDOSCOPIC CLIPPING CLOSURE FOR PREVENTING POST-ESD COAGULATION SYNDROME AND PERFORATION (CLIPEC STUDY): A MULTICENTER, SINGLE-BLIND, RANDOMISED CONTROLLED TRIAL

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Introduction: Endoscopic submucosal dissection (ESD) has been widely applied as an endoscopic treatment for superficial colorectal neoplasms, however some complications occasionally occur after ESD, including delayed perforation and post-ESD coagulation syndrome (PECS). The PECS reveals abdominal pain, inflammation and fever without perforation after ESD, but the exact cause and epidemiology of PECS remain unknown. We thus conducted a randomized controlled trial (CliPEC study) to assess usefulness of endoscopic clipping closure for prevention of PECS and delayed perforation.

Aims & Methods: CliPEC study is a multicenter, single-blind randomized controlled trial. Patients who will receive ESD for superficial colorectal neoplasms were prospectively enrolled, and randomly allocated to ESD followed by endoscopic clipping closure (the closure group) and non-closure (the non-closure group), stratifying by institution and tumor size. According to pre-planned protocol, this study was analyzed for full analysis set: patients who could not endoscopically resect tumor and develop to perforation during ESD were excluded from this analysis. All participants routinely received computed tomography (CT) scan and blood examination on day 1 after ESD and pain severity was assessed on day 1-3 after ESD using visual analogue scale (VAS). PECS was defined as VAS ≥30mm, a raise of VAS ≥20mm from baseline, BT ≥37.5ºC or WBC ≥10,000/µl after ESD. Delayed perforation was defined as PECS accompanied with peri-luminal air (minor) or intra-abdominal free air (major).

Primary endpoint of this study was the rate of PECS and delayed perforation. Pre-planned sample size was 320 patients by estimating that clipping closure decrease the rate of PECS and delayed perforation from 15% to

5% with overall 2-sided-α and β errors of 0.05 and 0.20, and allowing an approximate 10% dropout rate. According to O'Brien Fleming type α spending rule, 2 sided α levels of 0.0056 and 0.044 were defined for the interim and final analysis, respectively.

(University Hospital Medical Network Clinical Trials Registry, Number: UMIN000027031)

Results: At the planned interim analysis with a half of study enrollment, this trial was terminated by recommendation of the independent data and safety monitoring committee because conditional power with superiority of closure to non-closure (0.12%) was less than pre-planned futility limit of 20% in the interim analysis.

In total, 181 patients were enrolled from April 2017 to August 2018 at 10 Japanese institutions, and 155 patients after exclusion (2: protocol violation for criteria, 3: consent withdrawal, 9: perforation during ESD, 12: no-completion of ESD) were finally analyzed including 71 patients in the closure group and 84 patients in the non-closure group. Patient and tumor characteristics were well balanced between 2 groups. The rate of PECS and delayed perforation was 23.9% (PECS: 19.7%, delayed perforation: 4.2%) in the closure group and 15.5% (PECS: 11.9%, delayed perforation: 3.6%) in the non-closure group, respectively (*P*=0.184). All cases with delayed perforation were within minor criteria, and all patients with PECS and delayed perforation were conservatively improved without emergency surgery. Interestingly, 15.5% (13/84) in the non-colure group and 9.9% (7/71) in the closure group revealed simple extra-luminal air without any symptoms after ESD.

Conclusion: Endoscopic clipping closure could not reduce the incidence of PECS and delayed perforation after colorectal ESD. Colorectal ESD has been safely managed in a clinical practice.

Disclosure: Nothing to disclose

OP187 COVERT CARCINOMA AMONG RECTAL ESD SPECIMEN IS HIGH: A EUROPEAN TERTIARY CENTER PROSPECTIVELY COLLECTED EXPERIENCE

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Introduction: Endoscopic resection (ER) represents the treatment of choice for superficial rectal lesions. Careful assessment of the lesions is crucial for decision making in order to optimize outcomes for the patient. Endoscopic submucosal dissection (ESD) is becoming increasingly common in Western countries and is currently proposed by the European Society of Gastrointestinal Endoscopy (ESGE) for the resection of large lesions due to the risk of harbouring a superficial invasive cancer

The rate of covert SMIC (unpredicted submucosal invasive cancer found on the specimen) has been described among endoscopic mucosal resection (EMR) specimen but is poorly known for rectal ESD in Europe.

Aims & Methods: In the current study, we aim to evaluate the rate of covert carcinoma among ESD specimen. Furthermore, we assess the efficacy and safety of this treatment approach in one European academic tertiary center.

Clinical and technical data from Erasme Hospital (Brussels) was systematically and prospectively collected from June 2015 to March 2019. Covert carcinoma is defined as no suspicion of cancer in the rectal lesion based on pit pattern analysis and pre-ESD biopsies if available. Complete resection (R0) is defined as no carcinoma and no adenoma on the margins. Curative resection is defined as en bloc R0 resection of a superficial lesion, well-differentiated adenocarcinoma (G1/G2), sm1 (≤1mm submucosal invasion, with no lymphovascular invasion, as defined by the ESGE). Procedure-associated complications and recurrence rate were also assessed.

Results: Fifty-seven patients, mostly men (57.9%), with a mean age of 67 [30-85] years underwent ESD for a superficial rectal lesion. Most of the lesions were laterally spreading tumors (64.9%), large buldging polyps representing 28.1%, mostly located in the upper rectum (> 5 cm from the

anal margin: 61.4%), with a mean size of 49 [10-130] mm. Endoscopic characterization revealed mainly Paris 0-Is-IIa lesions (58%). Mean duration of the procedure was 136 [41-480] minutes.

En bloc resection was achieved in 98.2% of patients and R0 resection in 58.9%. Histopathological examination displayed (31.6%, 18/57) adenocarcinomas comprising 50% (9/18) pTis tumors, 39% (7/18) pT1sm2/sm3 and 11% (2/18) T2 lesions. Curative oncological resection was obtained in 44.4% (8/18) of patients with carcinoma. All the pTis and 3 of the pT1sm2/sm3 were not suspected to be carcinoma at the first evaluation giving a covert carcinoma rate of 21% (12/57) and a covert SMIC rate of 5% (3/57). Three out of 4 patients proposed for complementary surgery underwent a surgical treatment and the histopathological examination showed no residual tumor on the specimen nor on lymphadenopathies.

Altogether, 95% of the patients had no complication needing an intervention: 2 presented delayed bleeding managed endoscopically and one patient presented stenosis that was calibrated after one balloon dilation.

A 6 months endoscopy follow-up was obtained in 22 patients disclosing a free-recurrence rate of 100%, in favor of coagulation artefacts on the specimen seeing the 58% R0 (no adenoma on margins) rate.

Conclusion: ESD for superficial rectal lesions is showing favorable results in terms of efficacy and safety. A 21% rate of covert carcinoma among rectal large polyps underline the added value of using ESD compared to piece-meal resections.

Disclosure: Nothing to disclose

Lower GI diseases 4.0: Integrating modern approaches into daily practice

10:30-12:00 / C3

OP188 THE IBD-DISK PROVIDES A DETAILED DISEASE ACTIVITY AND DISABILITY ASSESSMENT IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: THE IBD-DISK VALIDATION AND PERFORMANCE STUDY

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Introduction: Various instruments have been developed to assess inflammatory bowel disease (IBD)-related disability, but these tools are often time consuming and difficult to use in an outpatient setting. The IBD Disk is a fast and self-administered 10-item visual instrument developed to overcome these limitations[1]. Data on the correlation of the IBD disk with standard activity indices are lacking.

Aims & Methods: The aim of this study was to validate the performance of the IBD Disk in clinical practice and to correlate the IBD disk with standard clinical activity indices in IBD.

We prospectively evaluated consecutive patients with IBD in an outpatient setting between April 1th 2018 and December 31th 2018. All patients completed the questionnaire of the IBD disk (10 items scored from 0 to 10). In addition, the stool frequency and abdominal pain patient reported outcome (PRO-2) of the Clinical Disease Activity Index were assessed for patients with Crohn's disease (CD), whereas the Simple Clinical Colitis Activity Index (SCCAI) was used for patients with ulcerative colitis (UC) and IBD unspecified (IBD-U). All questionnaires were recorded by an e-health preassessment digital tool before the actual clinical visit. Correlation analysis between the scores was performed using Pearson's product-moment correlation coefficient.

Results: Two hundred fifty two evaluations were performed amongst 146 patients (83 CD, 59 UC, 4 IBD-U). In patients with CD, the median PRO-2 score was 4.7 (IQR: 1.6-10). Amongst the separate IBD-disk items, the 'lack of energy'-item had the highest mean score: 4.8 (SD: 3.1), whereas the 'negative impact on interpersonal relations'-item had the lowest score: 2.1 (SD: 3).

There was a significant moderate correlation between the PRO-2 and the cumulative score of all IBD disk items (r=0.53), abdominal pain (r=0.56), regulating defecation (r=0.59), interpersonal relations (0.41) and education/work (r=0.48) (all p< 0.0001). The correlation with the other items were weak to very weak (r< 0.4). In patients with UC or IBD-U, the median

SSCAI was 4 (IQR: 2-5). Amongst the separate IBD-disk items 'the lack of energy'-item had the highest mean score: 5.3 (SD: 3), whereas the 'sexual dysfunction'-item had the lowest score: 2.4 (SD: 2.6). There was a significant strong correlation between SCCAI and the cumulative score of all IBD disk items (r=0.68), regulating defecation (r=0.60), interpersonal relations specifically (0.61) and lack of energy (r=0.62) (all p< 0.0001). The correlation with the other items were moderate to weak (r< 0.6).

Conclusion: This is the first study prospectively validating the use of the IBD-disk in a large cohort. Correlation with disease activity was strong in UC and moderate in CD. Since lack of energy was the dominant item of the IBD disk and an overall weak correlation between the standard activity indices and psychosocial items, the IBD-disk provides a more detailed and holistic evaluation of the patient with IBD.

References: 1. Ghosh S, Louis E, Beaugerie L, et al. Development of the IBD Disk: A Visual Self-administered Tool for Assessing Disability in Inflammatory Bowel Diseases. Inflamm Bowel Dis 2017;23:333-340.

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OP189 CT-SCOUT™ PLATFORM, THE DIGITAL SOLUTION TO BOOST PATIENT RECRUITMENT IN INFLAMMATORY BOWEL DISEASE CLINICAL TRIALS: A MULTICENTER PROSPECTIVE OBSERVATIONAL COMPARATIVE STUDY INVOLVING 134 SITES AND 644 PATIENTS IN 6 COUNTRIES

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Introduction: The main issue to validating new molecules in the field of IBD is insufficient patient enrollment into clinical trials, resulting in premature trials termination and cost increase. CT-SCOUT™ platform is a web-based solution built by the GETAID to help clinicians to pre-screen potential candidates at their site and facilitating the coordination of the research team. It is customized per site giving access to all academic and selected industrial trials in active recruitment period.

Aims & Methods: The aim of the current assessment was to evaluate the added value of CT-SCOUT™ platform in patient enrollment in industrial IBD clinical trials. We conducted a prospective, multicenter, open-label, observational study in equipped sites in France and in non-equipped sites in different countries participating to two phase 3 trials evaluating the efficacy and safety of etrolizumab in ulcerative colitis (UC, Hickory) and in Crohn's disease (CD, Bergamot) participants previously exposed or naïve to anti-TNF. Patients' recruitment in the 21 sites in France equipped with CT-SCOUT™ at the time of studies launch was compared to the 113 sites non-equipped with the app located in 4 European countries [Belgium (n=14), Germany (n=41), Spain (n=19), United Kingdom (n=26)] and in Israel (n=13). The primary endpoint was the mean patient randomization rate per site for both studies. Secondary endpoints included mean number of patients screened and randomized in Hickory, Bergamot and in both studies. Patients who signed study informed consent (screened) and those finally randomized were compared in sites equipped and non-equipped with CT-SCOUT™ using one-way ANOVA followed by post-hoc Tukey test and Mann-Whitney test.

Results: During the observational period of 27 months (Sept 2015 - Dec 2018), 644 and 289 patients were screened and randomized in 134 sites in Hickory and Bergamot trials, respectively. There were 307 and 149 patients in 78 sites for Hickory, and 337 and 140 patients for Bergamot in 102 sites. The mean numbers of included and randomized patients were significantly higher in equipped centers compared to non-equipped centers in both pooled and separate analysis (Table 1).

The mean number of patients randomized in Hickory in CT-SCOUT™ sites has been increased by 4.04 folds as compared to non-equipped sites (p< 0.001). The mean number of patients randomized in Bergamot in CT-SCOUT™ sites has been increased by 1.88 folds as compared to non-equipped sites (p=0.009).

Conclusion: This is the first multicentric international study to demonstrate a dramatic increase in patient recruitment in IBD clinical trials, with randomization rates twice to four times higher during Crohn's disease and ulcerative colitis in sites equipped with the app versus those non-equipped. CT-SCOUT™ appears to be a promising and easy-to-use digital solution to the global issue of patient enrollment in clinical trials in reducing clinical trial duration, and allowing new drug candidates to be available to patients earlier.

	French sites equipped with CT-SCOUTTM	Sites from other countries non-equipped with CT-SCOUTTM	p
Screened in both studies (UC + CD)	7.55	3.05	p<0.001
Randomized in both studies (UC + CD)	3.79	1.28	p<0.001
Screened in Hickory (UC)	9.17	3.14	p<0.001
Randomized in Hickory (UC)	5.17	1.28	p<0.001
Screened in Bergamot (CD)	5.94	2.95	p=0.003
Randomized in Bergamot (CD)	2.41	1.28	p=0.003

[Table 1]

References: 1 Use of digital technology to boost patient recruitment in inflammatory bowel disease clinical trials. J Crohns Colitis, 2017; 1027 (doi: 10.1093/ecco-jcc/jjx002.177)

Disclosure: Nothing to disclose

Holistic management of IBD patients

10:30-12:00 / E1

OP190 EPIGENETIC PROFILING OF BLOOD FROM PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS AND ULCERATIVE COLITIS COMPARED TO PATIENTS WITH ULCERATIVE COLITIS AND HEALTHY CONTROLS

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Introduction: The aetiology of primary sclerosing cholangitis (PSC) is unknown. The concurrence of PSC and inflammatory bowel disease (IBD) has led to various hypotheses linking these two disease entities, e.g. the aberrant gut-lymphocyte homing in IBD contributing to PSC. This mechanism may be due to genetic predisposition of the host and/or epigenetic changes in circulating lymphocytes. Epigenetic changes in blood cells have been described in the context of IBD: the DNA methylome of patients with ulcerative colitis (UC) differs from patients with Crohn's disease (CD) and healthy controls (HC) (1).

Aims & Methods: We hypothesized that the peripheral blood DNA methylome of patients with concurrent PSC and UC is distinct from that of UC patients without PSC and healthy controls.

DNA was isolated from peripheral blood samples from 18 PSC-UC and 17 UC patients, as well as 12 healthy controls. Only male patients were selected, and groups were matched for age (mean age 41, 40 and 40 years for PSC-UC, UC and HC, respectively), UC duration (15 and 11 years for PSC-UC and UC patients, respectively) and medication use (all PSC-UC and UC patients used Mesalazine, 50% used Thiopurins and none used biologicals). After bisulfite conversion, DNA methylation was determined using the Illumina HumanMethylation Infinium BeadChip (850K) EPIC microarray. Additionally, in a hypothesis driven approach, changes in genes associated with PSC from previous genome wide association studies (GWAS) as well as genes involved in lymphocyte trafficking were assessed (2, 3).

Results: In a non-biased approach, no significantly differentially methylated positions (DMPs) or regions (DMRs) were identified when comparing PSC-UC with UC or HC. Principal component analysis revealed no clear separation or clustering of the different groups, and no statistically significant differences were found when comparing PSC-UC with UC or PSC-UC with HC.

In a hypothesis driven analysis, 52 genes associated with PSC, identified from previous studies, were specifically analysed. We observed that two genes, BACH2 and ASAP2, were significantly differentially methylated in PSC-UC compared to UC patients. In addition, comparison of PSC-UC with healthy controls showed that the genes FOXP1, UBASH3A, BACH2, DDIT4, CD28, TNFAIP6, SOCS3 and ITGB1 were differentially methylated, although effect sizes were limited (< 20%).

Conclusion: We observed only limited differences in the genome-wide DNA methylomes that were associated with the presence of PSC. We conclude that the total peripheral blood methylome does not discriminate PSC-UC from UC alone. The differential methylation of BACH2, a gene that plays a role in regulating memory T-lymphocyte differentiation, is of interest in the context of mistargeted lymphocyte homing in PSC, and could be an interesting target for further studies.

References: (1) McDermott E, Ryan EJ, Tosetto M, Gibson D, Burrage J, Keegan D, et al. DNA Methylation Profiling in Inflammatory Bowel Disease Provides New Insights into Disease Pathogenesis. J Crohns Colitis. 2016;10(1):77-86. (2) Chung BK, Hirschfield GM. Immunogenetics in primary sclerosing cholangitis. Current opinion in gastroenterology. 2017;33(2):93-8. (3) Aoki CA, Dawson K, Kenny TP, Gershwin ME, Bowlus CL. Gene expression by PBMC in primary sclerosing cholangitis: evidence for dysregulation of immune mediated genes. Clin Dev Immunol. 2006;13(2-4):265-71.

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OP191 IMMUNOGENICITY OF USTEKINUMAB IN PATIENTS WITH CROHN'S DISEASE: RESULTS FROM THE IM-UNITI STUDY

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Introduction: Patients (pts) with moderately to severely active Crohn's disease (CD) who completed induction treatment with IV ustekinumab (UST) were eligible for a study of maintenance treatment with SC UST or placebo (PBO). Previous analyses of randomized pts who did not undergo dose adjustment in the maintenance study showed that rates of antibody formation were higher for those who received a single IV UST induction dose and SC PBO maintenance (4.9%) than those who received IV UST induction and SC UST maintenance (2.9% and 2.0% for q12w and q8w groups, respectively). The aim of this analysis was to further characterize pts who had antibodies to UST in the maintenance study, including randomized and nonrandomized pts.

Aims & Methods: In the induction trials (UNITI-1, n=741; UNITI-2, n=628), pts were randomly assigned to a single dose of IV PBO or UST (130 mg or ~6 mg/kg). Pts who responded to UST induction were randomly assigned to SC PBO or UST 90mg (q12w or q8w) at Wk 0 of the maintenance study (IM-UNITI) (n=397). Randomized pts who lost response between Wks 8 and 32 were eligible for dose adjustment to UST 90mg q8w. Nonrandomized pts (n=884) received SC UST q12w or UST q8w. Blood samples drawn at baseline and Wk 6 in the induction trial and Wks 12, 24, 36, and 44 in the maintenance trial were evaluated for antibodies to UST using a validated, drug-tolerant electrochemiluminescence immunoassay. Analysis set included all pts who were treated in the maintenance study, received ≥1 dose of UST induction or maintenance, and had ≥1 sample evaluable for antibodies from induction Wk 6 through maintenance Wk 44.

Results: Of the 914 pts who received UST in the induction trials, 2(0.2%) were positive for antibodies through Wk 8. Of the 1,154 pts who were treated in the maintenance study, received UST in the induction or maintenance study, and had samples that were appropriate for antibody testing, 27(2.3%) had antibodies detected through Wk 44. Among the 27 pts who were positive for antibodies, 7 had at least one sample with high titers (>1:800), 7 had positive samples at ≥3 visits including Wk 44, and 7 were receiving immunomodulators at baseline (Table). No pts had infusion or injection-site reactions at the visit they were positive for antibodies. Among pts who were receiving UST maintenance, median trough UST serum concentrations at the visits of the positive antibody results were 0.18 and 0.72 µg/mL for pts whose highest antibody titers were >1:800 and ≤1:800, respectively.

Conclusion: Antibodies to UST were uncommon in pts with CD who received induction and maintenance treatment with UST. When antibodies did occur, they were usually transient and low titer.

| | Nonresponders to IV Induction | | | |
	Responders to UST IV induction →PBO[a]	Placebo IV and UST maintenance →q12w[b]	UST IV and UST maintenance →q8w[c]	Total
Analysis set[d]	396	284	474	1,154
Patients positive for antibodies to UST, n (%)[e]	14 (3.5%)	4 (1.4%)	9 (1.9%)	27 (2.3%)
Before any UST dose	1	1	0	2
1 visit then negative	8	0	2	10
Wk 44 only	1	1	0	2
Safety follow-up visit only	0	0	1	1
2 visits then negative	3	1	0	4
Wks 36 and 44 only	0	1	0	1
≥3 visits including Wk 44	1	0	6	7
Received immunomodulators at baseline	4	1	2	7
Total number of positive antibody test results, n	23	6	29	58
Patients with highest antibody titer >1:800, n (%)	2	2	3	7

a Includes patients who were in clinical response to ustekinumab IV induction and were randomized in the maintenance study to ustekinumab or placebo.
b Includes patients who did not respond to IV placebo induction, were not randomized in the maintenance study, received ustekinumab 130 mg IV at Week 0 of the maintenance study, achieved clinical response at Week 8, and initiated ustekinumab 90 mg SC q12w.
c Includes patients who did not respond to IV ustekinumab induction, were not randomized in the maintenance study, received ustekinumab 90 mg SC at Week 0 of the maintenance study, achieved clinical response at Week 8, and initiated ustekinumab 90 mg SC q8w.
d Patients who were treated in the maintenance study, received ≥1 dose of ustekinumab in either the induction or maintenance studies, and had ≥1 samples that were evaluable for antibodies from induction Week 6 through maintenance Week 44.
e Patients who had at least 1 positive sample at any time from induction Week 6 through maintenance Week 44.

[Summary of antibody to ustekinumab status through Wk 44 of the maintenance study for pts who were treated with ustekinumab induction or maintenance]

Disclosure: William J. Sandborn, MD, Bruce E. Sands, MD, Willem J. de Villiers, MD, PhD, Subrata Ghosh, MD are all investigators for Janssen Research & Development, LLC Jeannette Nussbaum, PhD, MS is an employee of Janssen Pharmaceuticals Alessandra Oortwijn, MD, PhD is an employee of Janssen Europe Christopher Gasink, MD is an employee of Janssen Scientific Affairs, LLC Douglas Jacobstein, MD,Long-Long Gao, PhD, Omoniyi J. Adekokun, MS, RPh, are all employees of Janssen Research & Development, LLC

OP192 EFFECT OF ANTI-TNF-α TREATMENT IN PRIMARY SCLEROSING CHOLANGITIS

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Introduction: Few patients with primary sclerosing cholangitis and inflammatory bowel disease (PSC-IBD) are exposed to anti-TNF-α drugs due to the often mild nature of the IBD. This study assessed the effect of anti-TNF-α drugs on liver function and their efficacy in treating IBD in in PSC-IBD patients. The effect of anti-TNF-α drugs in liver transplant (LTx) PSC-IBD was also considered.

Aims & Methods: A retrospective analysis of 141 PSC-IBD patients receiving anti-TNF-α at 20 sites across Europe and North America was carried out via the International PSC Study Group (IPSCSG). Eighty-nine (63%) were male, 84 (60%) had UC, 52 (37%) had CD and 5 (4%) had indeterminate colitis; 110 (78%) received infliximab (IFX) and 31 (22%) adalimumab (ADA). Effects on alkaline phosphatase (ALP), IBD activity (response defined endoscopically or where endoscopic data were lacking clinical response as determined by physician assessment, or calprotectin < 250 µg/g or ≥30% drop in calprotectin; remission defined as endoscopic healing, or where endoscopic data were lacking, as clinical remission as determined by physician assessment), PSC related symptoms, and adverse events were recorded. Linear regression analyses were carried out to identify significant predictors of ALP during anti-TNF-α treatment.

Results: Lever biochemistry was available for 90 patients during the first 4 months of treatment of which 67 (74%) received IFX and 23 (26%) ADA. There was no significant difference in the proportion of patients with raised ALP at baseline between IFX (n=40, 60%) and ADA (n=13, 57%, p=0.50[CH1]). Patients treated with IFX experienced a median 4% reduction (IQR -25 to +19%, n=67) in ALP compared with median 15% (IQR -29 to -4%, n=23) reduction for ADA, (p=0.035). This difference was also apparent at 12 months, although non-significant (IFX median 2% reduction in

ALP (IQR -20 to +32%, n=56), ADA median 20% reduction (IQR -32 to +9%, p= 0.084, n=16)). In regression analysis normal ALP at baseline (p < 0.01), treatment with ADA (p=0.090) and European site (p=0.083) were found to be predictive of lower ALP, (F$_{(3,61)}$=18.86, p< 0.001) R^2= 0.47. IBD-response rate to anti-TNF-α treatment was 48% and the remission rate was 23%. There was no difference between IFX and ADA in the frequency of PSC symptoms after drug exposure. Ten additional patients who underwent LTx prior to anti-TNF-α were analysed: neither ALP nor bilirubin changed significantly during the study, however the small numbers precluded comparison of IFX and ADA. The proportion of post-LTx patients whose IBD responded to anti-TNF-α was not significantly different compared with non-LTx patients, (p=0.69). Data regarding the eventual reasons for anti-TNF-α discontinuation were available for 72 patients who were exposed to anti-TNF-α for a median of 415 days (IQR 176-1735). The most common reasons for anti-TNF-α discontinuation were primary IBD non-response (30%) and adverse event (32%). Reasons for stopping anti-TNF-α were also similar between LTx and non-LTx patients.

Conclusion: Serum ALP improved during treatment with ADA but not IFX in PSC-IBD patients, indicating possible advantages for ADA in treating PSC patients with IBD. There is no obvious explanation for this difference between the two anti-TNF-α agents. However, overall IBD-response rates to anti-TNF-α appeared to be lower than in the absence of PSC. Post-LTx patients had similar IBD-response rates to anti-TNF-α drugs and similar adverse events compared with non-LTx patients.

Disclosure: Nothing to disclose

OP193 IDENTIFICATION OF RISK FACTORS ASSOCIATED WITH LOSS OF RESPONSE TO USTEKINUMAB IN CROHN'S DISEASE

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Introduction: Ustekinumab (UST) therapy induced and maintained response and remission in patients with moderate-to-severe Crohn's disease (CD) in induction, maintenance, and 2-year extension trials in the IM-UNITI program. Secondary loss of response (LoR) was observed in some patients during follow-up. This post-hoc analysis aims to characterize and identify potential predictors of LoR through 2 years of UST (Wk 96).

Aims & Methods: The analysis included initial responders (IR) to UST IV at Wk 8 who were randomized to 90 mg SC UST q8w or q12w maintenance therapy and delayed responders (DR: responders at Wk 16 after not achieving clinical response at Wk 8; subsequently received UST q8w). LoR was defined as CDAI score ≥220 and a ≥100-point increase in CDAI score from Wk 8 or 16. Discontinuation due to lack of efficacy was also considered LoR, while patients who discontinued for other reasons were excluded from the analysis. Baseline (BL), Wk 8, and Wk 16 variables were described for LoR and no LoR patients. Univariate and multivariate logistic regression modeling was conducted on BL and Wk 8/16 variables.

Results: This analysis included 473 patients, of whom 191 (40.4%) met criteria for LoR through Wk 96: 36.6% among IR randomized to UST q8w, 37.6% among IR randomized to UST q12w, and 43.8% among DR on q8w dosing. Patients with LoR versus patients without LoR during follow-up had higher mean CDAI scores at BL and at Wk 8 (321.6 [SD 60.6]and 227.8 [SD 108.3] vs 305.7 [61.6] and 184.5 [90.75] and higher FeCal at Wk 8 (622.5 [SD 1065.5] vs 446.7 [SD 671.2]). In addition, LoR was more frequent among patients with previous anti-TNF exposure (72.2%) and no use of 5-ASA (71.2%). Univariate analysis identified higher CDAI at induction and maintenance BL, lower delta CDAI after induction, Wk 8 FeCal levels, previous

anti-TNF exposure and previous TNF failure as factors associated with increased risk for LoR (Table 1). Serum UST levels and concomitant IMM use were not identified as potential predictors of LoR. At multivariate analysis, only CDAI at maintenance baseline (OR: 1.42; 1.14-1.77), and previous TNF failure (OR: 2.05; 1.15-3.65) remained significant predictors of LOR.

Conclusion: Throughout 2 years of follow up, secondary LoR occurred in ~40% of initial or delayed responders to UST. Patients with higher CDAI at maintenance BL, and history of previous anti-TNF failure were found to be at increased risk for LoR. UST levels were not helpful as potential predictors of LoR and concomitant use of IMM did not reduce the risk of LoR during UST therapy.

Predictors of LoR (vs no LoR) by Univariate Logistic Regression Model

	OR	95% CI	p-value
Induction baseline CDAI (per 100-points)	1.52	1.13, 2.05	0.0063
Maintenance baseline CDAI (per 100-points)	1.56	1.28, 1.88	<0.0001
Delta CDAI induction/ Maintenance (per 100-points)	1.40	1.13, 1.72	0.0016
FeCal levels at Week 8 (per 100 mg/kg)	1.03	1.00, 1.05	0.040
Previous TNF exposure	2.13	1.44, 3.16	0.0002
Previous TNF failure	2.46	1.69, 3.58	<0.0001

Predictors of LoR (vs no LoR) by Multivariate Logistic Regression Model

	OR	95% CI	p-value
Maintenance baseline CDAI score (per 100-points)	1.42	1.14, 1.77	0.0021
Previous TNF exposure	1.06	0.58, 1.94	n.s.
Previous TNF failure	2.46	1.15, 3.65	0.015

[Table 1: Predictors of LoR (vs no LoR): univariate and multivariate logistic regression models]

Disclosure: Drs. Hanauer, Sands, Feagan, Targan, de Villiers, Rutgeerts, Colombel, and Ghosh are all investigators for Janssen Research & Development, LLC Dr. Laliman is a consultant to Janssen Research & Development, LLC Drs. Oortwijn and van Kruchten are employees with Janssen Biologics BV Drs. Izanec and Gasink are employees of Janssen Scientific Affairs, LLC Drs Adedokun and Gao are employees of Janssen Research & Development, LLC Dr. Sloan is an employee of Janssen Global Services, LLC

OP194 SERUM METABOLOMIC FINGERPRINT OF ULCERATIVE COLITIS (UC) PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS (PSC) CAN DISCRIMINATE THEM FROM UC PATIENTS WITHOUT PSC

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic, cholestatic, idiopathic liver disease that can progress to end-stage liver disease, cirrhosis and cholangiocarcinoma. It is strongly associated with inflammatory bowel disease, especially ulcerative colitis (UC). It is still unknown why some UC patients develop PSC or why UC patients with PSC are at higher risk of colorectal cancer development.

Aims & Methods: In the present study, we aimed to compare the serum metabolomic profiles of UC patients with PSC to UC patients without PSC in order to explore the underlying pathophysiological mechanisms and to identify PSC-related biomarkers. Fasting serum samples were collected from a group of adult UC patients with confirmed diagnosis of PSC and a group of UC patients without PSC who were matched for different demographic and clinical characteristics. Metabolomic assessment was done using nuclear magnetic resonance (NMR) spectroscopy and direct infusion/liquid chromatography tandem mass spectrometry (DI-LC MS/MS).

Results: Forty-nine UC patients were recruited (24 with PSC and 25 without PSC). Their mean age was 42.9±15.6 years and 62% of them were men. Forty-seven (94%) patients had a history of pan-colitis and 20% of them were on biologic medications. Fifty-three and 129 metabolites were identified and quantified using NMR and DI-LC MS/MS, respectively. In the multivariate analysis using partial least squares discriminant analysis,

serum metabolome of UC patients with PSC were significantly distinctive from those without PSC. Increased 2-oxoglutaric acid, ethanol, alpha-ketoglutaric acid, phosphatidylcholines and decreased alpha-aminobutyric acid, malonic acid, and glutamine were among the most important metabolic changes in UC patients with PSC that could differentiate them from patients without PSC.

Conclusion: This is the first study indicating that metabolomic profiling in UC patients can discriminate between patients with and without PSC. The discriminatory metabolites are involved in host cellular energy metabolism, as well as amino acid and fatty acid metabolism and are likely involved in PSC pathogenesis and its complications in UC.

Disclosure: Nothing to disclose

OP195 ORAL FERRIC MALTOL VERSUS INTRAVENOUS FERRIC CARBOXYMALTOSE FOR THE TREATMENT OF IRON-DEFICIENCY ANAEMIA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A MULTICENTRE PHASE 3B, OPEN-LABEL RANDOMISED CONTROLLED TRIAL

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Introduction: Iron-deficiency anaemia (IDA) is a serious complication of inflammatory bowel disease (IBD), resulting from inflammation, chronic mucosal blood loss and iron malabsorption. Treatment of IDA involves iron-replacement therapy, often with oral agents; however, use of standard oral ferrous iron (Fe^{2+}) compounds may be limited by poor iron bioavailability and adverse events, in which case patients require intravenous (IV) iron. Ferric maltol (FM), a chemically stable complex of ferric iron (Fe^{3+}) and maltol, provides another oral option formulated to improve absorption and reduce adverse events. FM is effective and well tolerated in patients with IBD (Gasche et al. *Inflamm Bowel Dis* 2015;21:579-588) but no head-to-head studies between FM and IV iron have been done.

Aims & Methods:
Objectives: To compare the efficacy and safety of oral FM and IV iron (ferric carboxymaltose [FCM]) in the treatment of IDA in patients with IBD.
Methods: This prospective, multicentre, phase 3b, open-label randomised controlled trial (EudraCT 2015-002496-26) included patients aged ≥18 years with confirmed IBD and IDA (haemoglobin [Hb] 8.0-11.0 g/dL for women, 8.0-12.0 g/dL for men AND either ferritin < 30 ng/mL or ferritin <100 ng/mL with transferrin saturation < 20%). Patients were randomised to 12 weeks of oral FM 30 mg twice daily or IV FCM administered according to standard prescribing information. Treatment could continue for up to 52 weeks. Efficacy was assessed in all randomised patients (intention-to-treat [ITT] population) and in patients without serious protocol deviations (per-protocol population; PP). The primary endpoint was Hb responder rate defined as the proportion of patients achieving either a 2 g/dL increase in Hb or normalisation of Hb (women ≥12 g/dL; men ≥13 g/dL) at Week 12, with a noninferiority limit set to 20% in either the ITT or the PP population.
Results: Mean ± SD treatment exposure was 30.2 ± 17.94 weeks for FM and 15.5 ± 15.60 weeks for FCM. The PP population included 178 patients (FM n=86; FCM n=92). At 12 weeks, the PP responder rate was 74% with FM and 84% with FCM; the difference was therefore well within the 20% noninferiority limit (p=0.023; Table). In the safety population (FM n=127; FCM n=120), 118 patients had treatment-emergent adverse events (FM n=75, 59%; FCM n=43, 36%), of which 15 were severe (FM n=11; FCM n=4). For FM, most cases were gastrointestinal (n=40, 31%). For FCM, most cases were infections/infestations (n=22, 18%). No serious adverse events related to study treatment were reported. Fourteen patients discontinued because of adverse events (FM n=13; FCM n=1).
Conclusion: This first comparative trial shows noninferiority of oral FM versus IV FCM in improving Hb after 12 weeks of treatment. Both treatments were well tolerated, with safety profiles as expected from previous studies. FM may therefore be an appropriate alternative to IV iron for treatment of IDA in IBD, even in patients in whom other oral iron therapy is not an option.

Disclosure: Nothing to disclose

	IV FCM (n=92)	Oral FM (n=86)	Difference (FM-FCM)	
			%*	Risk difference (95% CI)
Mean ± SD Hb at baseline, g/dL	10.11 ± 1.077	10.02 ± 0.997		
Mean ± SD Hb at Week 12, g/dL	13.12 ± 1.456	12.68 ± 1.544		
LSM (95% CI) difference (baseline to Week 12), g/dL	3.02 (2.71-3.32)	2.69 (2.37-3.01)		-0.32 (-0.76 to 0.11), p=0.142
Hb responder rate at Week 12, n (%)	77 (84)	64 (74)	10	-0.1 (-0.2 to 0.0), p_{noninf}=0.023
≥2 g/dL increase in Hb at Week 12, n (%)	70 (76)	59 (69)	7	-0.1 (-0.2 to 0.0), p_{noninf}=0.027
Hb normalisation at Week 12, n (%)	72 (78)	52 (60)	18	-0.2 (-0.3 to -0.0), p_{noninf}=0.338

*Noninferiority limit set at 20%. CI, confidence interval; FCM, ferric carboxymaltose; FM, ferric maltol; Hb, haemoglobin; IV, intravenous; LSM, least-squares mean; p_{noninf}, p value for noninferiority; SD, standard deviation.

[Haemoglobin endpoints at 12 weeks (per-protocol population)]

Tackling the NAFLD/NASH epidemics
10:30-12:00 / F2

OP196 POSITIVE RESULTS FROM REGENERATE: A PHASE 3 INTERNATIONAL, RANDOMIZED, PLACEBO-CONTROLLED STUDY EVALUATING OBETICHOLIC ACID TREATMENT FOR NONALCOHOLIC STEATOHEPATITIS

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Introduction: Obeticholic acid (OCA), an FXR agonist, improved both fibrosis and histologic features of nonalcoholic steatohepatitis (NASH) in the Ph2 FLINT study.

Aims & Methods: : This Month 18 pre-specified interim analysis of the on-going Ph3 REGENERATE study evaluated the effect of OCA on liver histology in patients with biopsy-confirmed NASH. Patients with NASH and fibrosis stages F2-3 (ITT), and an exploratory group of F1 patients with metabolic syndrome, were randomized to placebo, OCA 10 mg, or OCA 25 mg QD. Primary endpoints were fibrosis improvement (≥1 stage) with no worsening of NASH, or NASH resolution with no worsening of liver fibrosis per liver biopsy. The safety population included all randomized and dosed patients (F1-3, N=1968). Clinical outcomes will be evaluated at the end-of-study.
Results: The ITT population included 931 patients (placebo [n=311], OCA 10 mg [n=312] or OCA 25 mg [n=308]), comprised of 44% F2 and 56% F3. Baseline characteristics were well-balanced across groups. Results in Table. The primary fibrosis endpoint was met by 11.9% placebo, 17.6% OCA 10 mg (p=0.0446 vs placebo), and 23.1% OCA 25 mg (p=0.0002 vs placebo) patients (ITT). The primary NASH endpoint was not statistically significant (ITT). More patients on OCA 25 mg showed improvements in hepatocellular ballooning (p=0.0011 vs placebo) and lobular inflammation (p=0.0322 vs placebo). Dose-dependent reductions in ALT, AST and GGT were observed. Pruritus was the most common AE (19% placebo, 28% OCA 10 mg, 51% OCA 25 mg) and was predominantly mild to moderate in severity (severe pruritus: < 1% placebo, < 1% OCA 10 mg, 5% OCA 25 mg). More OCA 25 mg patients discontinued due to pruritus (< 1% placebo, < 1% OCA 10 mg, 9% OCA 25 mg; protocol mandated discontinuation of treatment with severe pruritus). SAEs occurred in 11% placebo, 11% OCA 10 mg and 14% OCA 25 mg patients. Increases in LDLc with OCA were observed by Week 4, but approached baseline by Month 18 (OCA 25 mg: LS mean change Wk4 +22.6 mg/dL, M18 +4.0 mg/dL). Cardiovascular SAEs were similar across groups (2% placebo, 1% OCA 10 mg, 2% OCA 25 mg). Cholelithiasis or cholecystitis were reported in 1% placebo, 1% OCA 10 mg and 3% OCA 25 mg patients. Hepatic disorder SAEs were uncommon but occurred more frequently in OCA 25 mg patients (< 1%). Three deaths occurred; none were considered treatment-related (placebo n=2; OCA 25 mg n=1).

Primary: ITT Population (F2 + F3)	Placebo (n=311)	OCA 10 mg (n=312)	OCA 25 mg (n=308)
Fibrosis improvement + no worsening of NASH	11.9%	17.6% (p=0.0446)	23.1% (p=0.0002)
NASH resolution + no worsening of fibrosis	8.0%	11.2% (p=0.1814)	11.7% (p=0.1268)
Improvement in hepatocellular ballooning	23.2%	27.2% (p=0.2423)	35.1% (p=0.0011)
Improvement in lobular inflammation	35.7%	39.1% (p=0.3380)	44.2% (p=0.0322)
Overall study discontinuations (ITT): 16% Placebo, 17% OCA 10 mg, 15% OCA 25 mg			

[REGENERATE Table]

Conclusion: Treatment with OCA 25 mg improved liver fibrosis, key histologic features of steatohepatitis and liver biochemistry, demonstrating consistent efficacy with an overall AE profile similar to previous studies.
Disclosure: Nothing to disclose

OP197 MOUSE AND HUMAN ADULT LIVER – DERIVED BIPOTENT DUCTAL ORGANOIDS FUNCTIONALLY RECAPITULATE LIVER STEATOSIS

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Introduction: Recently both mouse and human adult liver – derived bipotent ductal organoids (consisting of adult ductal stem cells) have been described and shown capable of differentiation from the biliary state to the hepatic state. Although such hepatically differentiated organoids have been shown to accumulate lipids in the presence of fatty acids, the molecular pathways regulating lipid metabolism in organoids are not known. To determine if adult liver-derived organoids can be a useful experimental model for mouse and human liver steatosis we set out to functionally characterize the metabolic pathways governing lipid accumulation in mouse and human organoids and compare them to known steatotic pathways including the Trib1 deficient genetic mouse model of steatosis. The Trib1

-/- mouse model is likely relevant for at least a subset of steatotic patients because several GWAS studies strongly correlate Trib1 down – regulating mutations with high plasma LDL levels, high plasma triglyceride levels, coronary artery disease and steatotic liver disease. Indeed, Trib1's suspected role in metabolic syndrome has been functionally proven by Trib1 liver specific ko mouse models which also show that Trib1 acts at least in part through upregulation of the liver specific transcription factor C/EBPalpha which in turn causes metabolic syndrome (Bauer et al 2015 J Clin Invest 125:3809-18). It has also been convincingly demonstrated that HepG2 liver cancer cells feature strongly reduced levels of C/EBPalpha which in turn induces over expression of the transcriptional co-activator YAP, the main effector of the Hippo pathway, through direct physical interaction of C/EBPalpha with YAP (Wang et al 2013, Mol Cell 2:221-225).
Aims & Methods: Using Trib1-/- mouse liver – derived bipotent ductal organoids, we present here evidence that Trib1 deficiency – mediated upregulation of C/EBPalpha may in turn further down regulate normal – already low – YAP activity in hepatically differentiated organoids. YAP is the main effector of the evolutionary conserved Hippo pathway that regulates liver size, regeneration and some aspects of liver pathogenesis.
Results: We show that almost complete absence of YAP leads to a deficiency of the hepatically differentiated organoids to dedifferentiate back to proliferating ductal organoids, consistent with the well documented block of liver regeneration caused by low YAP activity levels. Most importantly, experimentally induced downregulation of YAP in hepatically differentiated normal organoids phenocopies the lipid droplet accumulation and reduced uptake of LDL seen in Trib1-deficient hepatic organoids. Consistent with this, drugs that upregulate YAP activity partially rescue Trib1 deficiency – mediated lipid accumulation and low LDL uptake. To our knowledge this is the first time YAP activity has been implicated in the regulation of steatosis.
Importantly, we present evidence that YAP activating drugs, which can also alleviate liver fibrosis in mice, can partially rescue experimentally induced steatosis in human organoids. Further, we show that liver – derived organoids from NASH patients, but not normal donors, spontaneously recapitulate lipid accumulation in the absence of experimental steatotic stimulus.
Conclusion: We conclude that normal and steatotic human liver- derived organoids can be used to study important aspects of patient steatosis, and may be useful in future patient specific screens for antisteatotic drugs.
Disclosure: Nothing to disclose

IBS treatment
10:30-12:00 / Barcelona

OP198 CONSEQUENCES OF CHANGING TO THE ROME IV DIAGNOSTIC CRITERIA FOR IRRITABLE BOWEL SYNDROME AMONG PEOPLE LIVING WITH THE CONDITION

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Introduction: Irritable bowel syndrome (IBS) is a common condition with a prevalence in the community of 10%. The diagnosis is made using symptom-based diagnostic criteria. There are few studies examining implications of applying the Rome IV criteria for IBS, in preference to the previous gold standard, the Rome III criteria. We conducted a cross-sectional survey of over 1000 individuals who self-identified as having IBS in order to examine this issue.
Aims & Methods: We collected complete demographic, symptom, mood, and psychological health data from 1375 adults who self-identified as having IBS, but who were not recruited from a referral population. We applied both the Rome III and the Rome IV criteria simultaneously to examine what proportion met each of these diagnostic criteria for IBS. We measured the level of agreement between the Rome III and Rome IV criteria, and assessed for presence of an alternative functional bowel disorder in individuals who no longer met diagnostic criteria for IBS with the more restrictive Rome IV criteria. Finally, we compared characteristics of individuals who met only Rome III criteria with those who met Rome IV criteria.

Results: In total, 1080 (78.9%) of 1368 individuals with IBS met the Rome III criteria. In contrast, only 811 (59.1%) of 1373 individuals with IBS met the Rome IV criteria. Agreement between the criteria was only moderate (Kappa = 0.50). The reasons for not meeting the Rome IV criteria for IBS among those meeting the Rome III criteria are shown in Table 1.

	Reported abdominal discomfort, rather than abdominal pain (%)	Reported abdominal pain, but not at the required frequency (%)	Other reasons (%)
Met Rome III criteria, but not Rome IV criteria, for IBS (n = 286)	26 (9.1)	253 (88.5)	7 (2.4)
Rome IV functional constipation (n = 33)	3 (9.1)	29 (87.9)	1 (3.3)
Rome IV functional diarrhea (n = 118)	9 (7.6)	108 (91.5)	1 (0.8)
Rome IV functional abdominal bloating (n = 68)	6 (8.8)	61 (89.7)	1 (1.5)
Rome IV unspecified functional bowel disorder (n = 67)	8 (11.9)	55 (82.1)	4 (6.0)

[Table1: Reasons for not meeting the Rome IV criteria for IBS among those meeting the Rome III criteria]

Among those who no longer had IBS according to the Rome IV criteria, 33 (11.5%) met Rome IV criteria for functional constipation, 118 (41.3%) functional diarrhoea, 68 (23.8%) functional abdominal bloating or distension, and 67 (23.4%) an unspecified functional bowel disorder. Individuals with Rome IV-defined IBS had more severe symptoms, and higher levels of mood disorder and poor psychological health, compared with those who only met the Rome III criteria for IBS (P < 0.001).

Conclusion: Changing from the Rome III criteria to Rome IV IBS has substantial implications, both for individuals who believe they suffer from IBS, and for the spectrum of disease severity seen. Understanding the impact of these changes on clinical trials of novel agents in IBS will be important. Of those individuals with Rome III IBS who did not meet the Rome IV criteria for IBS, only 11.5% were reclassified into another functional bowel disorder where licensed and evidence-based therapies are available, namely functional constipation. In contrast, the treatment of people with functional diarrhoea, functional bloating, and unspecified functional bowel disorder relies on off-label therapies with only anecdotal evidence for their efficacy. Alternatively, these individuals could still be treated as if they have IBS. If use of the Rome IV criteria for IBS makes these conditions more prevalent, this highlights the need for rigorous randomised controlled trials (RCTs) of neuromodulators, probiotics, anti-diarrheals, and other agents in these disorders.

Disclosure: Nothing to disclose

OP199 OPTIMAL DELIVERY OF CARE FOR FUNCTIONAL GASTRO-INTESTINAL DISORDERS: RANDOMISED CONTROLLED TRIAL OF STANDARD GASTROENTEROLOGIST VERSUS MULTI-DISCIPLINARY CARE (THE MANTRA STUDY)

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Introduction: Functional gastrointestinal disorders (FGIDs) are common and costly to treat. Only a minority of patients are symptomatically improved with standard gastroenterologist care[1]. Many patients have psychological morbidity, yet despite psychological, behavioural and dietary therapies being well validated in these conditions, gastroenterology services do not provide them as part of integrated routine care.

Aims & Methods: We aimed to determine whether standard or multidisciplinary care provides the best clinical outcome for patients with a FGID. In a single hospital setting consecutive new referrals of patients with a Rome IV criteria-defined FGID were randomised 1:2 to a standard care gastroenterology specialist (SC) or multi-disciplinary (MD) clinic, the latter comprising gastroenterologists, dieticians, gut-hypnotherapists, psychiatrists and behavioural ("biofeedback") therapists situated in the same clinic simultaneously. At the MD clinic all patients initially saw a gastroenterologist and were then referred to allied clinicians as felt appropriate. Outcomes were assessed at clinic discharge or at 9 months. The primary outcome was global symptom improvement: "slightly better" (4/5) or "much better" (5/5) on a 5-point Likert scale. Secondary outcomes included gut symptoms (Gastro-Intestinal Symptom Severity Index (GISSI), condition-specific symptom scores [IBS: Irritable Bowel Severity Scoring System (IBS-SSS), functional dyspepsia: Nepean Dyspepsia Index (NDI)], psychological well-being (Hospital Anxiety and Depression Scale - HADS), and Quality of Life (Euro-QOL: EQ-5D).

Results:

Patient disposition: 188 patients (mean age 39, 63% female) were randomised, of whom 144 (46 SC and 98 MD) had sufficient outcome data and form the basis of this modified intention to treat analysis. 59% had IBS, 27% functional dyspepsia, the remainder other FGIDs. In the MD clinic, 61 patients (62%) saw at least one allied clinician. Median clinic visits were 2 in SC and 6 in MD (p< 0.01), and time to discharge 226 and 179 days, respectively (p=NS).

Outcome: The primary outcome was achieved in 57% versus 84%, respectively (p< 0.01). Patients scoring "much better" was 28% versus 51% (p=0.01).

Conditions: ≥50 point decrease in IBS-SSS in IBS patients: 38% v 66% (P=0.02), and ≥ 50% decrease in NDI in functional dyspepsia patients 27% v 46% (P=0.47).

Symptoms: Whole group ≥50% drop in GISSI sub-scores was 20% v 38% for reflux, 26% v 44% for nausea and vomiting, 17% v 42% for constipation, 22% v 43% for diarrhoea (all P< 0.04), but not significantly different for abdominal discomfort or dyspepsia. HADS score decreased from baseline to discharge in MD but not SC: SC 14.4 vs 13.7 (p=0.28) v MD 14.5 vs 11.5 (P< 0.01); HADS at discharge 13.7 v 11.5 (P=0.09), respectively. Baseline v discharge EQ-5D quality of life: SC 70 vs 70 (P=0.17) v MD (67 vs 75 (P< 0.01); EQ-5D at discharge 70 v 75 (P< 0.01).

Conclusion: In this randomised, controlled trial multi-disciplinary care was significantly superior to standard gastroenterologist-only care in patients with a functional gastro-intestinal disorder. Multi-disciplinary care based in a single clinic provided superior improvement in global symptoms, specific conditions, specific symptoms, psychological well-being, and quality of life. Superior outcomes were achieved over a shorter time, but with more clinic visits. The pragmatic study design that included all referrals supports the generalisability to gastroenterological practice. Consideration should be given to providing routine multi-disciplinary care for these conditions.

References: 1. Basnayake, C. , Kamm, M. A., Salzberg, M. , Stanley, A. , Khera, A. , Burrell, K. , Wilson O'Brien, A. , Hebbard, G. and Thompson, A. J. (2019), Outcome of hospital outpatient treatment of functional gastrointestinal disorders. Intern Med J, 49: 225-231. doi:10.1111/imj.14067

Disclosure: Nothing to disclose

OP200 PELVIC FLOOR BIOFEEDBACK IS EFFECTIVE TREATMENT FOR BLOATING IN FUNCTIONAL GASTROINTESTINAL DISORDERS WITH OUTLET DYSFUNCTION

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Introduction: It has been suggested that biofeedback may improve bloating in constipation due to dyssynergic defecation (DD) (1). However, data on different functional gastrointestinal disorders (FGID) are lacking.

Aims & Methods: Aim of our study was to evaluate the efficacy of pelvic floor biofeedback for severe bloating unresponsive to diet advise in FGID patients.

Materials and methods: Sixty-nine consecutive FGID patients consulting for bloating as main complaint were considered for the study. Four refused and were excluded. All the 65 remaining patients reported bloating as not improved by NICE diet advise augmented by lactose abstinence accord-

ing to a 5 point likert scale (range worse-major improvement/cure) and rated symptom severity VAS score >24 on a 100-mm scale. All 65 subjects underwent electromyography (EMG) testing of pelvic floor muscle function on straining by a surface EMG anal plug and rectal balloon expulsion test (BET) with a 16F Foley catheter inflated with 50 ml of tepid water. BET was considered failed if the balloon could not be evacuated within two minutes (2). A biofeedback protocol previously used for constipation due to DD was provided in all patients by a registered nurse who was unaware of the physiology results (3). Primary study aims were a) subjective report of fair-major improvement from baseline, b) >50% reduction of bloating VAS score from baseline. Secondary aim was achievement of successful BET. Dropouts (4 patients total, 2 BET failure) were included in the analysis with the last observation carried forward. Clinical and physiology follow-up visits were scheduled at 1-3-6 months post-treatment.

Results: All sixty-five patients (56 Female, mean age 41 years) completed the biofeedback protocol and attended the first follow-up visit. Most of the patients were affected by functional bloating (43.5%) or constipation predominat irritable bowel syndrome (27.5%), according to Rome III Criteria. DD was diagnosed in 32 patients (59%) (failed BET, EMG evidence of paradoxical contraction of the pelvic floor muscles on straining), 4 patients (6.3%) were discordant (failed BET, EMG evidence of pelvic floor muscle relaxation on straining), while the remaining 29 patient (43.8%) showed normal defecation pattern. As a whole, 35/65 patients (53.8%) met both primary aims at 1-3-6 month follow-up (McNemar non parametric test, p< 0.0001). According to BET results, 30/36 (83.3%) patients who failed BET at baseline evaluation met both primary aims at 1-3-6 month follow-up intervals compared with 5/29 (17.2%) patients with successful BET (chi square p< 0.001). A strong correlation between adequate relief and a >50% reduction of VAS bloating score was observed (r=1.00). In the failed BET group, 30/36 (83.3%) patients learned to evacuate the balloon within two minutes at all follow-up intervals (Friedman test for non-parametric data p>0.001), while no physiology modifications was observed in the successful BET group from baseline evaluation.

Conclusion: Pelvic floor biofeedback aimed to improve defecation effort is effective treatment for severe bloating in FGID with comorbid outlet dysfunction. Dyssynergic defecation may present without prevalent obstructed defecation and/or constipation symptoms.

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Disclosure: Chiarioni G is a Member of the Anorectal Committe of the Rome Foundation. No COI to be disclosed for all of the remaining Authors

OP201 HUMAN MILK OLIGOSACCHARIDES IMPROVE ALL THE CENTRAL SYMPTOMS OF IRRITABLE BOWEL SYNDROME: A MULTI-CENTER, OPEN LABEL TRIAL

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Introduction: Altered gut microbiota is increasingly seen as a potential factor in irritable bowel syndrome (IBS) pathophysiology. Human milk oligosaccharides (HMOs) have been shown in healthy adults to increase the abundance of bifidobacteria[1], which are reported to be depleted in IBS[2]. HMOs may also have beneficial impact on gut motility and visceral pain[3].

Aims & Methods: We aimed to assess the potential for HMOs to support normal bowel habits and improve other bowel symptoms of IBS. A multi-center, open label trial was conducted in clinical patients with IBS (Rome IV criteria plus physician diagnosis) at 17 sites across the United States. The subjects took 5 grams of the HMOs 2'fucosyllactose (2'FL) and lacto-N-

neotetraose (LNnT) in a 4:1 mix daily by mouth for 12 weeks. Bowel habits, IBS symptoms and quality of life were assessed at baseline and every 4 weeks during the intervention. Results were analyzed with Intention-to-Treat (ITT) methodology (last observation carried forward for non-completers), using repeated measures Analysis of Variance.

Results: A total of 317 subjects (70.7% females; mean age 44.0 years, range 18-93 years) received the study product; 136 with constipation predominant, 85 with diarrhea predominant, 95 with mixed, and 1 with unspecified IBS. The full twelve week intervention was completed by 245 subjects. In the ITT analyses, the subjects showed a significant reduction in total percentage of abnormal bowel movements (Bristol Stool Form Scale types 1, 2, 6, or 7) from baseline to 12 weeks (means and 95% CI: 89.8% [88.1%-91.5%] vs. 54.9% [51.4%-58.4%]) as well as substantial reductions in overall IBS Symptom Severity Score (327 [317-337] vs. 128 [117-139]), abdominal pain severity (62.5 [60.1-64.9] vs. 25.4 [22.6-28.2] and bloating severity (56.8 [53.8-59.8] vs. 23.2 [20.5-25.8]), and improvement in health-related quality of life (IBS-QOL scores: 50.4 [48.0-52.8] vs. 74.6 [72.3-76.9]): p< 0.0001 for all changes. The degree of therapeutic response was similar in all IBS subtypes, and most of the symptom improvement occurred in the first 4 weeks of intervention (see Table 1). Younger age was predictive of greater improvement in stool consistency and abdominal pain severity. The study product tested was well tolerated by most patients. The only common side effects were mild GI symptoms such as abdominal discomfort, distension and flatulence.

Conclusion: Our findings suggest that oral supplementation with 2'FL and LNnT HMOs can provide nutritional support that significantly reduces abnormal stool consistency, abdominal pain and bloating and improves health-related quality of life in IBS sufferers of all subtypes. However, the results from this open label trial need to be followed up by a randomized controlled trial.

Percentage of abnormal bowel movements in the past 4 weeks measured by Bristol Stool Form Scale			
	Overall (n=317)	IBS-C (n=136)	IBS-D (n=85)	IBS-M (n=95)
Baseline	88.0 [86.4-89.7]	84.9 [82.4-87.5]	87.5 [84.0-91.1]	93.1 [90.3-95.8]
Week 4	59.2* [56.5-62.0]	55.5* [51.3-59.8]	54.6* [49.3-59.9]	68.2* [63.7-72.8]
Week 8	56.5* [53.5-59.5]	53.5* [49.1-57.8]	56.2* [50.4-62.1]	61.3* [55.3-67.3]
Week 12	56.3* [53.2-59.4]	49.3* [44.8-53.8]	60.0* [54.4-65.6]	62.8* [56.8-68.9]
Total IBS Symptom Severity Score			
	Overall (n=317)	IBS-C (n=136)	IBS-D (n=85)	IBS-M (n=95)
Baseline	323 [314-332]	316 [302-329]	322 [305-339]	332 [314-349]
Week 4	178* [167-188]	164* [148-180]	181* [163-198]	195* [174-215]
Week 8	150* [140-161]	136* [121-151]	155* [136-174]	165* [142-188]
Week 12	144* [133-155]	118* [103-134]	155* [138-172]	170* [146-193]

*significantly different from baseline at p<0.0001.

[Table 1. Changes in abnormal bowel movement percentage and IBS Symptom Severity Score (IBS-SSS) throughout the trial (ITT analyses; means [95% CI])]

References: [1] Elison, E., et al., Oral supplementation of healthy adults with 2´-O-fucosyllactose and lacto-N-neotetraose is well tolerated and shifts the intestinal microbiota. Br J Nutr, 2016. 116(8): p. 1356-1368. [2] Rajilić-Stojanović, M., et al., Intestinal microbiota and diet in IBS: causes, consequences, or epiphenomena? The American Journal of Gastroenterology, 2015. 110(2): p. 278-287. [3] Bienenstock, J., et al., Fucosylated but not sialylated milk oligosaccharides diminish colon motor contractions. PLoS One, 2013. 8(10): p. e76236.

Disclosure: Dorthe Seitzberg, Ingvild Dybdrodt Amundsen and Bruce McConnell are employed at Glycom A/S, Denmark, which funded this trial. Olafur Palsson, Anne Peery and Magnus Simren received research support from Glycom A/S related to the trial.

OP202 THE EFFICACY OF LACTIBIANE IKI (*BIFIDOBACTERIUM LACTIS LA 304, LACTOBACILLUS SALIVARIUS LA 302, LACTOBACILLUS ACIDOPHILUS LA 201)* IN REDUCING ABDOMINAL SYMPTOMS AND INFLAMMATORY BIOMARKERS IN ACUTE UNCOMPLICATED DIVERTICULATIS

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Introduction: Diverticular Disease (DD) is the most frequent abnormality in the digestive tract mainly in developed countries.

Most of people suffering from DD are asymptomatic, while 20% experience abdominal symptoms and eventually complications, episodes of diverticulitis or bleeding.

Acute Uncomplicated Diverticulitis (AUD) is defined as the inflammation of a colon diverticulum, often involving colic wall and pericolic fat. Conventional treatment of AUD includes antibiotic therapy, usually Ciprofloxacin and Metronidazole, fasting and fluid therapy.

Although several studies have been performed aimed at evaluating the clinical efficacy of probiotics in AUD, no definitive results have been achieved yet.

Aim of our pilot study is to test the efficacy of *Bifidobacterium Lactis LA 304, Lactobacillus Salivarius LA 302, Lactobacillus Acidophilus LA 201* (Lactibiane IKI, Biocure), in association with conventional antibiotics in treating AUD compared to conventional antibiotic therapy.

Aims & Methods: We enrolled 84 (25M/59F mean age 61,5 +- 11,5 years) consecutive patients who came to the Emergency Department of Foundation Policlinico A. Gemelli Hospital with a diagnosis of AUD. All patients performed routine blood test, dosage of C-Reactive Protein value and they were then randomly divided into two groups.

Group A (42 patients, 10M/32F mean age 32,23 +- 10,3 years) was treated with ciprofloxacin 400mg twice a day and metronidazole 500mg three times a day for one week, with a supplementation of Lactibiane IKI twice a day for 10 days.

Group B (42 patients, 15M/27F mean age 59,01 +- 11,3 years) was treated with ciprofloxacin 400mg twice a day and metronidazole 500mg three times a day for one week.

All patients filled a daily Visual Analog Scale (VAS) for abdominal pain, with a range value from 0 (asymptomatic) to 10, and C-RP value was determined on admission and at discharge.

Primary outcome of the study is the reduction of abdominal pain and inflammatory markers (C-RP) in the group treated with Lactibiane IKI supplementation.

Results: All patients completed the study. No side effect were observed.

As regards the VAS values: between day 1 and 3, group A decreased 4.07 points of vas scale, group B decreased 2.79 points of vas scale (p=0,0002); between day 1 and 5 group A decreased 6.3 points of vas scale, group B decreased 4.85 points of vas scale (p< 0,0001); between day 1 and 7 group A decreased 7.26 points of vas scale, group B decreased 6.1 points of vas scale (p < 0,0001); between day 1 and 10 group A decreased 7.8 points of vas scale, group B decreased 7.2 points of vas scale (p=0,048).

Regarding C-RP value, the mean decrease between the admittance value and after 72h was 49 mg/l for group A and 21,8 mg/l for group B (p=0,006). Finally, group A has a mean of 88,8 +- 17 hours (3,7 days) of hospitalization in BOU, meanwhile group B has a mean of 101 +- 20 hours (4,2 days) (p< 0,05).

Conclusion: Our study showed that the supplementation with Lactibiane IKI in the standard AUD therapy significantly reduce abdominal pain and inflammatory markers compared to control group.

These interesting results could be due to its anti-inflammatory activity, already well documented in the IBD therapy. Larger studies are needed to validate its use in the clinical practice.

Disclosure: Nothing to disclose

OP203 THE EFFECTS OF HUMAN MILK OLIGOSACCHARIDES ON BIFIDOBACTERIA AND GASTROINTESTINAL SYMPTOMS IN IRRITABLE BOWEL SYNDROME PATIENTS: A PARALLEL, DOUBLE BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Introduction: Gut microbiota alterations seem to be a relevant factor in the pathophysiology of irritable bowel syndrome (IBS). Therefore, modulating the gut microbiota by using prebiotics, such as human milk oligosaccharides (HMO), might influence gastrointestinal (GI) symptoms through their effect on specific gut bacteria. However, the safety and tolerance of HMO have not been assessed in IBS patients. Thus, we aimed to determine the dose of a HMO mix of 2'-O-Fucosyllactose (2'FL) and Lacto-N-neotetraose (LNnT) that increased fecal bifidobacteria abundance in IBS patients without aggravating overall GI symptoms.

Aims & Methods: We performed a parallel, double-blind, randomized, placebo-controlled trial in an IBS patient cohort diagnosed according to the Rome IV criteria. We studied the effects of 5g and 10g doses of 4:1 mix of 2'FL and LNnT (2'FL/LNnT) compared to placebo (powdered glucose) after 4 weeks of oral intake, followed by a 4 weeks wash-out period. Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) and fecal samples were collected at baseline, at the end of intervention and the washout period. Fecal bifidobacteria abundance was analyzed by the GA-map™ platform technology. Non-parametric analysis were performed between and within intervention groups.

Results: We included 61 IBS patients, (41 women; median age 45 (19 - 73) years); 27 IBS with diarrhea, 14 IBS with constipation and 20 mixed IBS. During the intervention phase, two patients, one from the placebo group and one from the 10g group, discontinued prematurely (after 2 weeks of intervention) due to worsening symptoms.

As can be seen in table 1, the bifidobacteria abundance differed between the groups after the intervention period, with higher abundance in the 10g group compared with the other intervention groups (p< 0.05). Within-group comparisons demonstrated a significant increase in bifidobacteria abundance in the 10g group at the end of the intervention period compared to baseline (p=0.018).

	Placebo (n=21)		5g 2´FL/LNnT (n=20)		10g 2´FL/LNnT (n=20)		#p-value
	Baseline	Week 4	Baseline	Week 4	Baseline	Week 4	
Log bifidobacteria abundance*	3.77 (± 1.48)	3.78 (±1.62)	4.81 (± 0.89)	4.86 (± 0.99)	4.21 (± 1.34)	5.03 (± 1.00)	< 0.05
GSRS-IBS scores*							
Total score	49.76 (± 10.04)	41.71 (± 10.43)	45.15 (± 7.99)	43.06 (± 13.43)	52.55 (± 8.41)	48.42 (± 11.65)	ns
Constipation score	6.05 (± 3.47)	5.24 (± 2.84)	3.70 (± 2.45)	4.33 (± 3.43)	5.35 (± 4.17)	4.68 (± 3.33)	ns
Abdominal pain score	8.57 (± 1.99)	7.76 (± 2.17)	8.10 (± 2.71)	7.06 (± 3.39)	9.20 (± 1.64)	8.53 (± 2.61)	ns
Bloating score	14.00 (± 3.54)	11.94 (± 3.99)	12.35 (± 4.00)	11.61 (± 4.54)	15.10 (± 3.02)	14.16 (± 4.07)	ns
Diarrhea score	15.52 (± 4.39)	11.94 (±4.17)	15.35 (± 4.78)	14.83 (±4.97)	17.20 (± 5.21)	15.95 (± 6.92)	ns
Satiety score	5.62 (± 3.41)	4.82 (± 3.43)	5.65 (± 2.81)	5.22 (± 2.69)	5.70 (± 3.34)	5.11 (± 2.71)	ns

*Data shown as mean (±sd). #p-values reflecting comparisons between the three groups (placebo, 5g and 10g 2´FL/LNnT) after the intervention (week 4), relative to baseline.

[Table 1. Fecal bifidobacteria abundance and gastrointestinal symptom severity (GSRS-IBS scores) at baseline and after the intervention (week 4).]

However, after the 4 weeks washout period no difference between the groups was detected. Overall GI symptom severity (GSRS-IBS total score) or individual GI symptoms did not differ between the groups after the treatment (ns, non-significant). However, tendencies towards improvements of GI symptom severity within the groups were observed at the end of the intervention (week 4). The 10g group showed a trend towards reduction in overall GI symptom severity (GSRS-IBS total score) compared to baseline (p=0.076), whereas the placebo group showed reduction of overall GI symptom severity, bloating and diarrhea at the end of the intervention (p< 0.05 for these comparisons). No symptom deterioration was seen in any of the groups.

Conclusion: In conclusion, 10g HMO dose of 2'FL/LNnT mix is able to induce the growth of the beneficial bacteria *Bifidobacterium* in patients with IBS without aggravating gastrointestinal symptoms. This approach may be worthwhile to restore IBS gut microbiota towards a healthy profile.

Disclosure: Nothing to disclose

Lower GI on fire

10:30-12:00 / Hotspot

OP204 MARKERS OF SYSTEMIC INFLAMMATION IN PRECLINICAL ULCERATIVE COLITIS

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Introduction: Data on the preclinical stage of ulcerative colitis (UC) are sparse. At diagnosis, UC often shows a modest increase in systemic inflammatory markers like C-reactive protein (CRP). However, a subclinical inflammation with elevated levels of CRP and interleukin-6 (IL6) in serum have been observed several years before diagnosis [1]. First-degree relatives, including healthy twin siblings, also display elevated levels of some inflammatory markers as a consequence of shared genetic and environmental risk factors [2]. It is reasonable to believe that the preclinical inflammation, reflecting early pathogenic mechanisms, ultimately leads to a diagnosis of UC.

Aims & Methods: We aimed to deeper examine the systemic preclinical inflammation in UC using a comprehensive set of protein markers. Cases with UC were identified at clinical follow-up of a prospectively collected population-based cohort of healthy individuals from northern Sweden. Plasma samples from cases and controls were subjected to proximity extension assay for relative quantification of 92 protein markers of inflammation. Results were validated in an inception cohort of treatment naïve, newly diagnosed patients with UC (n=101) *vs.* healthy controls (n=50). In addition, to examine the impact of shared genetic and environmental factors, a cohort of healthy mono- and dizygotic twin siblings of twins with UC (n=41) and matched healthy controls (n=37) were explored.

Results: Pre-diagnostic plasma samples from 72 cases who later in life developed UC and 140 controls, matched for gender, age, year of health survey and area of residence, were identified (table 1). Six proteins were significantly upregulated (p< 0.05) in pre-diagnostic UC compared to matched healthy controls. A receiver-operating curve based prediction model using the six protein markers combined with sex, age, smoking status and time to diagnose was set up for validation. The model discriminated newly diagnosed, treatment naïve UC cases from healthy controls (AUC=0.96; CI 0.93-0.98). An AUC of 0.73 (CI 0.62-0.84) was observed when the model was applied to healthy twin siblings *vs.* healthy controls and four out of six proteins were upregulated similarly as in the pre-diagnostic samples. The relative levels of the six proteins showed an intermediate upregulation in pre-diagnostic samples and samples from healthy twin siblings compared to samples at diagnosis of UC. Only one protein showed a significant correlation with time to diagnosis in the pre-diagnostic samples. Using pathway analysis, the six protein upregulations pointed towards subclinical inflammation in UC being caused by dysregulation of four immune pathways.

Conclusion: This is the first comprehensive characterisation of preclinical systemic inflammation in UC. Inflammatory proteins were upregulated several years prior to diagnosis of UC and to some extent these alterations were also seen in healthy twin siblings of UC patients. Characterisation of the preclinical stage of UC could pave the way for identification of predictive biomarkers and preventive strategies.

	Ulcerative colitis n=72	Controls n=140
BMI (IQR)	25.0 (23.2-27.5)	25.5 (23.1-27.8)
Sex; male (%)	34 (47.2)	64 (45.7)
Smoking status, current (%)	22 (30.6)	22 (30.6)
Median (range) age at sample (years)	50 (30-70)	50 (30-70)
Median (range) age at diagnosis (years)	54 (31-75)	
Disease extent (%)		
Proctitis (E1)	16 (22.2)	
Left-sided colitis (E2)	28 (38.9)	
Extensive colitis (E3)	28 (38.9)	

[Table 1. Clinical and demographic characteristics (before diagnose >1 year).]

References: 1. Lochhead P, Khalili H, Ananthakrishnan AN, Richter JM, Chan AT. Association Between Circulating Levels of C-Reactive Protein and Interleukin-6 and Risk of Inflammatory Bowel Disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2016;14(6):818-24 e6. PubMed PMID: 26844874 2. Zhulina Y, Hahn-Stromberg V, Shamikh A, Peterson CG, Gustavsson A, Nyhlin N, et al. Subclinical inflammation with increased neutrophil activity in healthy twin siblings reflect environmental influence in the pathogenesis of inflammatory bowel disease. Inflammatory bowel diseases. 2013;19(8):1725-31. PubMed PMID: 23669399.
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OP205 OVERALL AND CAUSE-SPECIFIC MORTALITY IN MICROSCOPIC COLITIS: A DANISH NATIONWIDE MATCHED COHORT STUDY

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Introduction: Microscopic colitis (MC) is a chronic inflammatory disease characterized by watery diarrhea and characteristic histological findings in the setting of a normal macroscopic appearance of the colonic mucosa. The etiology is assumedly multifactorial and smoking is a known risk factor.

The disease course in MC is generally considered benign. However, the long-term natural history remains largely unknown and the risk of death in these patients has not been systematically evaluated.

Aims & Methods: Using Danish nationwide registry information, we aimed to investigate the overall and cause-specific mortality in a large consecutive and unselected cohort of patients with MC.

All patients with an incident diagnosis of MC from 2001-2017 were identified from the national pathology and patient registry. Patients were subcategorized according to subtype of MC, lymphocytic colitis (LC) and collagenous colitis (CC).

Overall and cause-specific mortality in patients with MC was compared with that of an age and sex matched cohort from the general population (controls) in a variable 1:10 ratio. The relative risk of death was analyzed with Cox regression models, estimating both crude and comorbidity-ad-

justed hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were stratified according to sex, age at diagnosis and subtype of MC.

Results: A total of 14.024 patients with MC of whom 42% had LC were identified. The mean age at diagnosis was 63.6 years for patients with LC and 67.0 years for CC and patients were predominantly female (64.4% of LC patients and 74.4% of CC patients).

During follow up, 3047 patients with MC died compared to 26.395 in the control group, unraveling a 25% significantly increased risk of death (HR 1.25; 95% CI, 1.20-1.30) in crude analyses. The mortality was attenuated in analyses adjusted for comorbidity, however, the relative risk remained significantly augmented (HR 1.08; 95% CI, 1.04-1.13). Stratifying according to MC subtype, crude analyses showed a significantly increased risk of death in both patients with LC (HR 1.30; 95% CI, 1.22-1.39) and CC (HR 1.21; 95% CI, 1.16-1.27). Again, the risk of death, although reduced, remained significant increased, in comorbidity-adjusted analyses (HR$_{LC}$ 1.13; 95% CI, 1.06-1.20 and HR$_{CC}$ 1.06; 95% CI, 1.00-1.11).

Compared to matched controls, patients with MC were more likely to die due to infections, diabetes, ischemic heart diseases and chronic lung diseases.

Conclusion: In an unselected large nationwide cohort of MC patients, the risk of death was significantly increased compared to the background population. The increased mortality was largely, but not entirely, associated to an increased burden of comorbidities and patients with MC were more likely to die from smoking-related diseases.

The increased mortality associated with a diagnosis of MC, as observed in our study, is however unexpected and needs to be confirmed in other large cohorts.

Disclosure: Nothing to disclose

OP206 NOVEL NOMOGRAMS TO PREDICT LYMPH NODE METASTASIS AND LIVER METASTASIS IN PATIENTS WITH EARLY COLON CARCINOMA

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Introduction: The poor prognosis and frequent recurrence of colon carcinoma might be related to lymph node metastasis (LNM) and distant metastasis. Advanced colon carcinoma (stage III or IV) is diagnosed when LNM or distant metastasis occurs, regardless of the pathologic T (pT) classification. Studies have indicated that 27.3% of patients diagnosed with colon carcinoma develop liver metastasis (LIM) during the course of their disease. We attempted to develop and validate nomograms to predict LNM and LIM in patients with early colon carcinoma (pT1+pT2) .

Aims & Methods: A total of 32,819 patients who underwent surgery between 2004 and 2015 for pT1 or pT2 colon carcinoma were enrolled in the study and divided into a training set (n=21880) in an earlier period and a validation set (n=10939). Univariable and multivariable analysis were used to identify independent risk factors predictive of LNM and LIM in the SEER discovery set. All variables were screened using the forward stepwise selection method in a multivariate binary logistic regression model. Calibration curves were plotted to validate the accuracy and reliability of the nomograms by the Hosmer-Lemeshow test. The predictive performance of the nomograms was measured by a receiver operating characteristic (ROC) curve.The predictive accuracy and clinical values of the nomograms were measured by decision curve analysis (DCA) by calculating the net benefits at each risk threshold probability. The predictive nomograms were further validated in the internal testing set.

Results: LNM was present in 3111 of 21880 patients (14.2%) and 30 of 10939 patients (14.5%) in the training and testing sets, respectively. LIM occurred in 1.5% of patients in the training set and 1.2% of patients in the testing set. In the correlation analysis, five variables, namely, histological grade, T classification, tumor size, serum CEA level and overall survival, were significantly correlated (P< 0.001) with LNM and LIM in both the training and testing sets. Based on the independent risk factors identified in the multivariate regression analysis, two nomograms were developed to predict the possibility of LNM (marital status, histological grade, histological type, T classification, tumor size and serum CEA level) and LIM (age, histological grade, tumor size, serum CEA level and N classification). The calibration curves showed perfect agreement between nomogram predictions and actual observations. DCAs indicated the clinical usefulness of the prediction

nomograms and threshold probabilities of 0-0.3 for LNM or 0-0.2 for LIM were the most beneficial for predicting LNM and LIM with our nomograms. Receiver operating characteristic curves indicated good discrimination in the training set (area under the curve [AUC] = 0.667, 95% CI=0.661-0.673) and the testing set (AUC=0.658, 95% CI=0.649-0.667) for the LNM nomogram and encouraging performance in the training set (AUC=0.766, 95% CI=0.760-0.771) and the testing set (AUC=0.825, 95% CI=0.818-0.832) for the LIM nomogram.

Conclusion: In conclusion, based on the clinical risk factors identified in a large population-based cohort, we established the first practical nomograms that can objectively and accurately predict individualized risk of LNM and LIM. Moreover, the internal cohort validation results demonstrate that the two nomograms perform well and have high accuracy and reliability. Our nomograms were demonstrated to be clinically useful in DCAs, and they should therefore help clinicians to improve individual treatment, make clinical decisions and guide follow-up management strategies for patients with early colon carcinoma.

Disclosure: Nothing to disclose

OP207 LPA-INDUCED GPR35 SIGNALLING IN MACROPHAGES RESULTED IN ALTERED CYTOKINE EXPRESSION AND MODULATION OF COLITIS

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Introduction: Host- or bacterial-derived metabolites orchestrate immune responses in inflammatory bowel diseases through G protein-coupled receptors. Genome-wide association studies indicated that polymorphisms in GPR35 are associated with an increased risk of ulcerative colitis (UC) and primary sclerosing cholangitis (1). The chemokine CXCL17, the tryptophan metabolite kynurenic acid (KNA) and the phospholipid derivative lysophosphatidic acid (LPA) have been suggested as potential ligands (2). GPR35 also interacts with the sodium potassium pump to ensure electrochemical gradients in epithelial cells (3). The endogenous ligand and cell type in which GPR35 signaling modulate intestinal inflammation is rather unexplored.

Aims & Methods: To investigate GPR35 in macrophages the mouse lines GPR35tdTomato, GPR35Ko and GPR35$^{\Delta CX3CR1}$, in which tamoxifen injection silences GPR35 expression in CX3CR1[+]macrophages have been created. Potential ligands were screened in *Gpr35.2*-deficient zebrafish.

Results: *In situ* hybridization of *Gpr35.2* in zebrafish 120 hours post fertilization revealed restricted *Gpr35.2*expression in the intestine. *Ex vivo* imaging of GPR35tdTomato / CX3CR1-GFP double reporter animals showed GPR35 expression by intestinal epithelial cells and CX3CR1+ macrophages. Flow cytometry confirmed that monocytes but not B cells, T cells and innate lymphoid cells express GPR35. During the development of monocytes into gut macrophages GPR35 expression is down-regulated, which can be discriminated in GPR35-positive and -negative macrophages with higher *Tnf, Il1b*and *Il23*expression by GPR35-positive macrophages. *Gpr35* expression is regulated by the microbiota as antibiotic-treated zebrafish and mice as well as germ-free mice have reduced GPR35 expression. Conversely, TNBS-colitis in zebrafish, DSS-colitis in mice induced GPR35 expression in macrophages, and increased numbers of GPR35-positive macrophages were present in inflamed regions of UC patients. Potential agonistic ligands of GPR35, were screened with a Chinese Hamster Ovary (CHO)-K1 GPR35 Gi cell line, that stably overexpressed human GPR35 coupled to an inhibitory G protein which inhibits forskolin-induced cAMP accumulation in response to GPR35 agonists. LPA and CXCL17 but not KYNA inhibited forskolin-induced cAMP production, and the potential candidate LPA was further tested in *Gpr35.2*-deficient zebrafish. As macrophages express other lysophophospatic acid receptors bone marrow-derived macrophages from GPR35Ko mice were stimulated with GPR35. LPA induced *tnf,Il1b*and *Il1a* production in macrophages and induced macrophage migration in a GPR35-dependent manner. Increased expression of autotaxin, which converts lysophosphatidylcholine into LPA, was observed in zebrafish and mice undergoing intestinal inflammation. In agreement with the potential activation of GPR35 during colitis, GPR35-deficient mice have increased DSS-colitis severity. The deletion of GPR35 in CX3CR1+ macrophages in-

dicated that GPR35 signaling in macrophages is critical for the increased severity of DSS colitis. GPR35 deletion in macrophages resulted in reduced *tnf* production by macrophages. As TNF regulates *CYP11A1* and *CYP11B1* expression required for extraadrenal corticosterone synthesis, the silencing of GPR35 in macrophages was associated with reduced intestinal *CYP11A1* and *CYP11B1* expression.

Conclusion: LPA-induced GPR35-signalling in macrophages modulates cytokine responses and colitis. The depletion of GPR35 in macrophages resulted in increased DSS colitis severity associated with reduced *CYP11A1* and *CYP11B1* expression involved in extraadrenal corticosterone synthesis.

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OP208 EFFICACY AND SAFETY OF UPADACITINIB AS AN INDUCTION THERAPY FOR PATIENTS WITH MODERATELY-TO-SEVERELY ACTIVE ULCERATIVE COLITIS: COMBINED RESULTS FROM 382 SUBJECTS IN THE PHASE 2B STUDY U-ACHIEVE

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Introduction: The efficacy and safety of upadacitinib (UPA), an oral Janus Kinase 1-selective inhibitor, were assessed in an 8-week double-blind, placebo-controlled, dose-ranging phase 2b induction study (part 1) in patients with moderately-to-severely active ulcerative colitis (UC) who had inadequate response, loss of response, or intolerance to corticosteroids, immunosuppressives, or biologic therapies.[1,2] During the analysis of part 1, additional patients were enrolled in part 2 to avoid interrupting the study activities and to provide a sufficient number of clinical responders for the maintenance portion of the study.

Aims & Methods: We present the efficacy and safety of the combined results of part 1 and part 2 of U-ACHIEVE.

Adult patients with moderately-to-severely active UC (Adapted Mayo Score 5-9 points and centrally-read endoscopy subscore 2-3) were randomised in a 1:1:1:1:1 ratio to receive extended-release UPA 7.5, 15, 30, 45mg once daily (QD) or placebo for 8 weeks (N=250). In part 2, an additional 132 patients were randomised to UPA 30 or 45mg QD with 1:1 allocation for 8 weeks. Pairwise comparisons between UPA doses and placebo for the primary endpoint of clinical remission per Adapted Mayo Score at Week 8 (defined as stool frequency subscore ≤1, rectal bleeding subscore =0, and endoscopic subscore ≤1) and ranked secondary endpoints were conducted using the Cochran-Mantel-Haenszel test stratified by previous biologic use, baseline corticosteroid use, and baseline Adapted Mayo score. No multiplicity adjustments were applied. Non-responder imputation was utilized for missing values in 13% of patients. Treatment emergent adverse events (AEs) were reported from first dose of study drug to up to 30 days after last dose.

Results: A total of 382 patients were randomised with a mean (SD) age of 42.7 (14.3) years and a disease duration of 8.4 (7.4) years. The primary endpoint of clinical remission, and secondary endpoints of endoscopic improvement, clinical response per Adapted Mayo score, clinical response per Partial Mayo score, endoscopic remission, and histologic improvement were significantly higher with UPA doses ≥30mg QD compared to placebo (Table). Incidences of AEs and AEs leading to discontinuation were similar across UPA groups, and numerically higher in the placebo group. Rates of serious AEs were 10.9%, 0%, 4.1%, 4.3% and 4.9% for placebo and UPA 7.5, 15, 30, and 45mg QD, respectively. Serious infections occurred in patients receiving placebo (4.3%, n=2), 15mg QD (2.0%, n=1), 30mg QD (0.9%, n=1), and 45mg QD (1.6%, n=2). One case of herpes zoster and one case of pulmonary embolism (PE)/deep vein thrombosis (DVT) with UPA 45mg QD were reported. The case of PE/DVT was reported 26 days after study drug discontinuation due to UC worsening and hospitalization. No deaths were reported.

Endpoints, n (%)	Placebo N=46	UPA 7.5 mg QD N=47	UPA 15 mg QD N=49	UPA 30 mg QD N=117	UPA 45 mg QD N=123
Clinical remission per Adapted Mayo Score (SFS ≤1, RBS=0, and ES ≤1) at Week 8[a]	0	4(8.5)	7(14.3)*	25(21.4)***	22(17.9)**
Endoscopic Improvement (ES ≤1) at Week 8[b]	1(2.2)	7(14.9)*	15(30.6)***	40(34.2)***	42(34.1)***
Clinical response per Adapted Mayo score (decrease from baseline ≥2 points and ≥30% and in RBS ≥1 or an absolute RBS ≤1) at Week 8[b]	6(13.0)	13(27.7)+	22(44.9)***	63(53.8)***	65(52.8)***
Clinical response per Partial Mayo score (decrease from baseline ≥2 points and ≥30% and in RBS ≥1 or an absolute RBS ≤1) at Week 2[b]	7(15.2)	11(23.4)	18(36.7)*	52(44.4)***	63(51.2)***
Endoscopic remission (ES=0) at Week 8[b]	0	3(6.4)+	2(4.1)	19(16.2)**	20(16.3)**
Histologic improvement (any decrease from baseline in Geboes score) at Week 8[b]	3(6.5)	16(34.0)**	25(51.0)***	55(47.0)***	62(50.4)***

[a]Primary Endpoint; [b]Ranked Secondary Endpoints

***, **, *, and + significant at 0.001, 0.01, 0.05, and 0.1 levels, respectively compared with placebo

UPA=upadacitinib; QD=once daily; SFS=stool frequency subscore; RBS=rectal bleeding subscore; ES=endoscopic subscore

[Table]

Conclusion: In this combined analysis, primary and ranked secondary endpoints consistently met statistical significance with UPA doses ≥ 30mg QD compared with placebo in patients with moderately-to-severely active UC. These results are consistent with the part 1 intention-to-treat analysis.[1,2] UPA was well-tolerated, and no new safety signals were identified compared to previous studies of UPA.[3]

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OP209 PROMINENCE OF ILEAL MUCOSA ASSOCIATED MICROBIOTA TO PREDICT POST-OPERATIVE ENDOSCOPIC RECURRENCE IN CROHN´S DISEASE

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Introduction: Following ileal resection for Crohn's disease (CD), recurrence is very frequent. Although several clinical risk factors of recurrence have been identified, predicting relapse remains challenging. Performing an ileocolonoscopy within the first year after surgery is currently recommended to assess endoscopic recurrence and adjust the treatment.

Aims & Methods: We took advantage of a large prospective multicentric cohort to investigate the role of the ileal mucosa-associated microbiota in post-operative endoscopic recurrence. This is a prospective study performed in 9 centers of the REMIND group, collecting clinical and biological data at time of surgery and of endoscopy (performed at 6 months). Ileal mucosa-associated microbiota was analyzed by 16S sequencing (MiSeq, Illumina) at the time of surgery and/or of endoscopic evaluation in 201 patients (288 samples in total) prospectively recruited in France. The obtained sequences (rarefied to 5000 read/sample) were analyzed using the Qiime pipeline to assess composition, alpha and beta diversity. Linear discriminant analysis effect size (LEfSe) pipeline was used to identify bacterial taxa differentially represented. We used logistic regression and Random Forest to evaluate the role of the gut microbiota at the time of surgery to predict endoscopic recurrence (defined by a Rutgeerts score >i1).

Results: Among the 201 patients included: 98 (49%) were male, mean age at surgery was 35 years (SD 12), 66 patients (33%) were active smoker at time of surgery, 39 patients (19%) had a previous resection, and 47 patients (23%) had perianal lesions. Indication for surgery was stricturing disease (116), penetrating disease (71). After surgery, 48 patients received thiopurines, and 68 patients received anti-TNF therapy. The microbiota was composed of bacteria from the Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria and Fusobacteria phyla. As expected, antibiotics treatment within one month before surgery had a dramatic impact on microbiota composition (Anosim, p < 0.0001) and diversity (Shannon index mean 4.3 ± 0.1 vs 3.7 ± 0.2, p=0.006). Ileal mucosa-associated microbiota exhibits profound changes following surgery in CD. Compared to non-recurrence setting, endoscopic recurrence was associated with strong changes in ileal mucosa-associated microbiota that were highly reminiscent of those observed generally in ileal CD compared to healthy subjects with a reduction in alpha diversity, increase in several members of the Proteobacteria phylum and decrease in several members of the Lachnospiraceae and the Ruminococcaceae families within the Firmicutes phylum. At the time of surgery, we identified several bacterial taxa associated with endoscopic recurrence and that can better predict relapse than usual clinical risk factors (ROC Curve, Area under the curve, AUC: 97.1% [93.8%-100%] and 81.0% [60.8%-100%] in the whole population and in the validation set respectively).

Conclusion: Surgery has an important impact on ileal-mucosa associated microbiota. Post-operative endoscopic recurrence is associated with changes in microbiota composition and alpha diversity. The gut microbiota has the potential to predict post-operative evolution and recurrence.

OP210 MULTICENTER PROSPECTIVE RANDOMIZED STUDY TO COMPARE ENDOSCOPIC TREATMENT OF STRICTURES IN CROHN´S DISEASE: SELF-EXPANDING METAL STENTS VS ENDOSCOPIC BALLOON DILATION. PROTDILAT STUDY

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Introduction: Endoscopic Balloon Dilation (EBD) is the established endoscopic treatment for short strictures in Crohn´s Disease (CD). Self-expanding metallic stents (SEMS) have been used for the treatment of refractory strictures with good results in patients that failed to dilation.

Hypothesis: Endoscopic treatment of strictures in CD by placing a SEMS is more effective than EBD.

Aims & Methods: Objectives:

1)To compare the efficacy and safety of endoscopic treatment (SEMS vs EBD) in CD patients with stenosis;

2) To perform a comparative cost study.

Methods: Randomized, prospective, multicenter clinical trial of patients with CD and obstructive symptoms with stenosis < 10 cm and refractory to medical treatment. We exclude patients with stenosis previously treated with SEMS and/or EBD in the previous year and with stenosis no accessible to colonoscopy. The main outcome was to determine the efficacy of the endoscopic treatment defined by the percentage of patients free of a new therapeutic intervention (EBD, SEMS or surgery) due to symptomatic recurrence at one year of follow-up. Those who failed the endoscopic primary treatment were crossed over to the other endoscopic option. A direct cost study was done.

Results: A total of 99 patients from 19 Spanish hospitals were randomized, 19 were excluded because they did not fulfil the inclusion criteria. Eighty patients, 39 women, with a median age of 45 (IQR: 38-54.7) were finally included. The primary treatment was 39 SEMS and 41 EBD for ITT analysis. In 42.5% of the cases the stenosis was in the anastomosis site whereas in 57.5% were *de novo* strictures. The median length of the strictures was 3.4 cm (IQR: 2-5.5). No differences related to demographic, disease, treatment and stenosis characteristics were found between the two groups. The success rate of EBD and SEMS was 80.5% and 51.3%, respectively (Adjusted OR, 3.5; 95% CI, 1.3-9.6; p=0.016). In a subanalysis of patients with strictures >3 cm differences between the 2 endoscopic procedures disappeared (EDB: 66.7% vs SEMS: 63.6%). In multivariate analysis of patients with EBD, the only variable associated with the success was the length of the stricture (OR, 1.05; 95% CI, 1.01-1.10; p=0.038). A 6.3% adverse events were reported without differences between the two treatments. Only 3 complications were related to endoscopic procedure (1 perforation in each therapy arm, 1 mild self-limited hemorrhage in EBD group). The average

cost for EBD patient was 802.83 euros (average 1.3 dilations) and for SEMS patients was 1827.06 euros (cost analysis of first 55 randomized patients). A total of 20 patients were crossed over to the other endoscopic option; 13 patients completed the follow-up (10 SEMS and 3 EBD initial failure crossed over to EBD and SEMS respectively) with a final success of 10/10 in rescue EBD treatment and 1/3 in rescue SEMS treatment.

Conclusion: The EDB is more effective than SEMS for CD strictures, with a good safety profile of both treatments. In addition, EBD is a more cost-effective than SEMS. The length of the stricture is the only factor related to EBD success. The clinical scenario in which SEMS could be useful is strictures >3 cm. ClinicalTrials.gov NCT 02395354.

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OP211 RIFAMYCIN SV-MMX® FOR ACUTE UNCOMPLICATED DIVERTICULITIS? RESULTS OF INNOVATIVE ANTIBIOTIC THERAPY FROM A PROSPECTIVE DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Introduction: Traditionally, guidelines recommended bowel rest and an up to 10-day treatment regime with a broad-spectrum antibiotic in acute uncomplicated diverticulitis (AUD). Recent studies have questioned this common strategy. However, placebo-controlled studies are lacking, and if effective, the duration of treatment is unclear. We conducted a double-blind trial, studying therapeutic benefits of the novel broad-spectrum, poorly absorbed antibiotic Rifamycin SV multi-matrix (MMX®) in comparison to placebo.

Aims & Methods: The aim was to compare efficacy and safety of two doses of Rifamycin SV-MMX® versus placebo (PLC) in the oral treatment of AUD. This was an exploratory, double-blind, double-dummy, randomized multi-center trial, with three treatment groups: (I) Rifamycin SV-MMX® 400mg BID (RIF800), (II) Rifamycin SV-MMX® 600mg TID (RIF1800) and (III) placebo (PLC). Out-patients with AUD proven by cross-sectional imaging and biomarkers were randomly assigned to one of the three treatment groups for a 10-day oral treatment. The primary endpoint was treatment success (required absence of fever, left lower quadrant pain, CRP improvement and absence of complications) at day 10. Key secondary endpoint was complete treatment success (required a normalization of CRP in addition) at days 0, 3, 7 and 10.

Results: A total of 201 patients qualified for the full analysis set (FAS). Main baseline characteristics were: 60% female, mean age 58.6 years, mean BMI 29.1 kg/m², mean CRP 40.5 mg/l and intensity of abdominal left lower quadrant pain of 5.6 cm (on a 10 cm visual analogue scale). The proportion of patients with treatment success at day 10 was numerically higher in the RIF800 group (62.2%) than in the PLC group (47.5%) (p=0.06) (Table 1). In a subgroup of patients with > 3 days of symptoms prior to start of the therapy both Rifamycin groups reached higher complete treatment success rates at day 10 compared to placebo, which was statistically significant for the RIF800 group (Table 1). In addition, both Rifamycin groups achieved statistically significant higher complete treatment success rates at day 3 compared to placebo (p< 0.05) (Table 1). It is to be noted that none of the placebo treated patients had complete treatment success at day 3. No unexpected side effects occurred and the rate of adverse events did not differ among groups.

	Number (%) of patients		
	RIF800 (n=82)	RIF1800 (n=79)	Placebo (n=40)
Treatment Success at day 10	51/82 (62.2%) / p=0.06	39/79 (49.4%) / p=0.42	19/40 (47.5%)
Complete Treatment Success at day 10 for subgroup with >3 days of symptoms	16/30 (53.3%) / p=0.01	16/42 (38.1%) / p=0.08	1/12 (8.3%)
Complete Treatment Success at day 3	9/82 (11%) / p=0.03	10/79 (12.7%) / p=0.02	0/40 (0%)

[Table 1: Results from clinical efficacy endpoints (FAS)]

Conclusion: Overall, antibiotic treatment with Rifamycin SV-MMX® trended to demonstrate therapeutic superiority over placebo in acute uncomplicated diverticulitis. It was faster than placebo in achieving complete treatment success, with most pronounced effect already at day 3. The subgroup of patients with more than 3 days of symptoms of AUD benefitted most from the Rifamycin treatment. The preferred dosis of Rifamycin seems to be 400mg BID. Rifamycin SV-MMX® was safe and well tolerated.

Disclosure: The following authors have financial relationship with a commercial interest: Wolfgang Kruis received lecture fees and travel costs by Dr. Falk Pharma GmbH. Roland Greinwald and Tanju Nacak received salary (employment) by Dr. Falk Pharma GmbH.

OP212 PRECLINICAL AND CLINICAL EFFICACY OF OLORINAB, A PERIPHERALLY RESTRICTED, HIGHLY SELECTIVE FULL AGONIST OF THE CANNABINOID TYPE 2 RECEPTOR FOR THE MANAGEMENT OF VISCERAL PAIN IN INFLAMMATORY BOWEL DISEASE

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Introduction: Abdominal pain is common in patients with inflammatory bowel diseases (IBDs), including Crohn's disease (CD), and available treatments often fail to relieve this pain. Cannabinoid receptors can modulate visceral pain; however, clinical development of non-selective agonists is limited by unwanted psychoactive effects. Olorinab is a highly selective full agonist of the cannabinoid type 2 receptor (CB_2) and showed low blood-brain barrier penetration in rodents. Reported here, preclinical evaluation assessed whether olorinab reduced visceral hypersensitivity in a rat model of IBD (colitis), and a randomized, open-label, multi-centre, phase 2a study evaluated olorinab in patients with quiescent CD experiencing abdominal pain.

Aims & Methods: In preclinical study, colitis was induced using 12 mg 2,4,6-trinitrobenzene sulfonic acid (TNBS) in 35% ethanol in rats, applied rectally. Vehicle or olorinab (3 or 30 mg/kg) was given twice daily for 5 days in control or colitis rats beginning 1 day after TNBS. Visceral mechano-sensitivity was measured *in vivo* as visceromotor responses (VMR) to colorectal distension (CRD; distension pressures 0-80 mm Hg). Colonic nociceptor firing was measured *ex vivo*.

In the phase 2a study, subjects aged 18-66 years with quiescent CD (simple endoscopic score-CD < 10 or faecal calprotectin < 500 µg/g) experiencing abdominal pain, defined as weekly average abdominal pain score (AAPS) ≥4 on a scale of 0 (no pain) to 10 (worst possible), were randomly assigned 1:1 to 25 or 100 mg oral olorinab 3 times a day (TID) for up to 8 weeks. Primary objectives were safety and tolerability. Efficacy endpoints included change in AAPS from baseline week (BL) to weeks 4 and 8, change in AAPS from pre-dose to 1.5 hours post-dose, and proportion of clinical responders (≥30% reduction in weekly AAPS from BL).

Results: Visceral hypersensitivity was observed in vehicle-treated colitis rats with higher VMR to CRD vs healthy controls ($P< 0.05$ at 20 mm Hg; $P< 0.01$ at 40-80 mm Hg). Colitis rats treated with olorinab had lower VMR to CRD vs their vehicle-treated counterparts ($P< 0.001$, N=9/group). Control rats treated with olorinab did not show altered VMR to CRD ($P>0.05$, N=8-11/group). Olorinab reduced colonic nociceptor hypersensitivity in a concentration-dependent manner via CB_2.

In the phase 2a study (N=14), AAPS significantly improved at weeks 4 and 8 from BL. Change in AAPS from BL to the time of peak concentration

(1.5 hours post-dose) during week 8 was -4.6 on an 11-point scale (N=11; $P< 0.001$). The proportion of clinical responders was 85% (11/13) at week 4 and 100% (11/11) at week 8 among evaluable subjects. Adverse events (AEs) occurred in 4/6 (67%) and 6/8 (75%) subjects who received 25 mg and 100 mg TID, respectively, and were generally mild to moderate with limited duration. AEs in ≥2 subjects included drug hypersensitivity, pain in extremity, and hypomagnesaemia; 2 serious AEs (pneumonia, worsening interstitial pneumonia) occurred in 1 subject and were not considered treatment related. There were no discontinuations due to AEs, and no clinically significant changes in vital signs or laboratory results were observed.
Conclusion: Olorinab, a highly selective full agonist of CB_2, showed preclinical efficacy in reducing visceral hypersensitivity in a rat model of IBD. Olorinab-treated subjects with quiescent CD experiencing abdominal pain had an improvement in AAPS without psychoactive effects in phase 2a. These preclinical and clinical results support further clinical development of olorinab for the treatment of abdominal pain.
Disclosure: B.Y. has received grant support from Merck and advisory board honoraria for Arena; S.M.B. is a consultant to Arena Pharmaceuticals; B.L., J.A., B.E., and K.S. are employees and shareholders of Arena Pharmaceuticals; P.D.R.H. has received grants from NIH, CCF, AbbVie, Janssen, Takeda, Genentech, and Pfizer and advisory board honoraria for Lycera, and Arena Pharmaceuticals.

Paradigm shifts in IBD treatment
14:00-15:30 / B2

OP213 TOFACITINIB, AN ORAL JANUS KINASE INHIBITOR, IN THE TREATMENT OF ULCERATIVE COLITIS: AN INTERIM ANALYSIS OF AN OPEN-LABEL, LONG-TERM EXTENSION STUDY WITH UP TO 5.5 YEARS OF TREATMENT

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Introduction: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). Tofacitinib safety and efficacy were demonstrated in patients (pts) with moderate to severe UC in 3 Phase 3, randomised, placebo-controlled studies,[1] and are being further evaluated in an ongoing open-label long-term extension (OLE) study.[2]
Aims & Methods: We present an update (as of Sep 2018) on previously presented safety and efficacy data[2] from the ongoing OLE study (NCT01470612; database not locked) in pts who completed or demonstrated treatment failure in OCTAVE Sustain (NCT01458574) or were non-responders in OCTAVE Induction 1/2 (NCT01465763/NCT01458951). Eligibility was determined per Week (Wk)8 data from OCTAVE Induction 1/2, or Wk52 (for completers) or early-termination data from OCTAVE Sustain. Pts in remission (total Mayo score ≤2, no individual subscore >1, rectal bleeding subscore 0) at Wk52 of OCTAVE Sustain (per central read) were assigned tofacitinib 5 mg twice daily (BID) in the OLE study; all others were assigned 10 mg BID. At Month 2, all pts underwent endoscopy, and induction non-responders were mandated to withdraw if they did not show clinical response. Incidence rates (IRs) for adverse events (AEs) of special interest were calculated as the number of unique pts with events per 100 pt-years (PY). Efficacy endpoints were derived from Mayo score per local read, with non-responder imputation for missing data at all visits but last observation carried forward after a pt advanced to the next study (NRI-LOCF).
Results: Of 944 pts who received ≥1 dose of study drug (for up to 5.5 years), 175 (18.5%) received tofacitinib 5 mg BID and 769 (81.5%) received tofacitinib 10 mg BID (total PY exposure 454 and 1550, respectively). In total, 337 (35.7%) pts discontinued due to insufficient clinical response, and 78 (8.3%) discontinued due to AEs excl. worsening UC. AEs, serious AEs and severe AEs occurred in 764 (80.9%), 162 (17.2%) and 109 (11.5%) pts, respectively (Table). The most frequent AE classes were infections and infestations (52.1%) and gastrointestinal disorders (43.3%). The most frequent AEs were nasopharyngitis (20.3%), worsening UC (19.5%) and increased blood creatine phosphokinase (10.8%). IRs (95% confidence interval) in the 'Tofacitinib All' group were: serious infections 1.61 (1.10, 2.27); herpes zoster (all) 3.35 (2.58, 4.27); major adverse cardiovascular events 0.15 (0.03, 0.44); malignancies excl. non-melanoma skin cancer (NMSC) 0.85 (0.50, 1.36); and NMSC 0.81 (0.46, 1.32), with no clustering of malignancy type; IRs by dose are shown in the Table. No new safety risks were identified. At Month 36 (NRI-LOCF) in the 5 and 10 mg BID groups, respectively, 55.9% and 32.2% of pts were in remission, 62.5% and 35.8% had mucosal healing, and 65.8% and 38.9% showed clinical response.
Conclusion: In pts with moderate to severe UC in the OLE study with up to 5.5 years of treatment, no new safety risks emerged vs those observed in earlier analyses of the OLE study[2] or with tofacitinib in rheumatoid arthritis. Efficacy data from the OLE study continue to support long-term efficacy with tofacitinib 5 or 10 mg BID up to 36 months beyond Wk52 of OCTAVE Sustain.

	Tofacitinib 5 mg BID (N=175; 454 PY)		Tofacitinib 10 mg BID (N=769; 1550 PY)		Tofacitinib All (N=944; 2004 PY)	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Serious infections[a]	6 (3.4)[b]	1.33 (0.49, 2.89)	26 (3.4)[c]	1.69 (1.10, 2.48)	32 (3.4)	1.61 (1.10, 2.27)
Herpes zoster (all)[a]	11 (6.3)	2.49 (1.24, 4.45)	53 (6.9)[d]	3.61 (2.70, 4.72)	64 (6.8)	3.35 (2.58, 4.27)
MACE[e,f]	2 (1.1)[g]	0.44 (0.05, 1.59)	1 (0.1)[h]	0.06 (0.00, 0.36)	3 (0.3)	0.15 (0.03, 0.44)
Malignancies excluding NMSC[e,f]	5 (2.9)[i]	1.11 (0.36, 2.58)	12 (1.6)[j]	0.78 (0.40, 1.35)	17 (1.8)	0.85 (0.50, 1.36)
NMSC[e,f]	5 (2.9)	1.12 (0.36, 2.61)	11 (1.4)	0.72 (0.36, 1.29)	16 (1.7)	0.81 (0.46, 1.32)

Data are as of Sep 2018, database not locked
IRs were calculated as the number of unique patients with events per 100 PY
[a]Events that occurred >28 days after the last dose of study drug were excluded for calculation of proportion and IR; [b]Three events were reported as severe (number of events): appendicitis (1), gastroenteritis norovirus (1), necrotising fasciitis (1); [c]Thirteen events were reported as severe (number of events): appendicitis (3), arthritis bacterial (1), atypical pneumonia (1), herpes zoster (2), herpes zoster meningitis (1), mastoiditis (1), meningitis viral (1), osteomyelitis (1), sinusitis (1), wound infection (1); [d]Four events were reported as severe; [e]All events, including those outside the 28-day risk period, were included for calculation of proportion and IR; [f]Adjudicated events; [g]MACE (number of events): acute myocardial infarction (1), cerebellar haemorrhage (1); [h]An event of cerebrovascular accident; [i]Malignancy (number of events): breast cancer (2), cervical dysplasia (1), diffuse large B-cell lymphoma (1), pulmonary mass (1); [j]Malignancy (number of events): acute myeloid leukaemia (1), adenocarcinoma of colon (2), cervical dysplasia (1), cholangiocarcinoma (1), cutaneous leiomyosarcoma (1), Epstein-Barr virus-associated lymphoma (1), essential thrombocythaemia (1), hepatic angiosarcoma (1), invasive ductal breast carcinoma (1), malignant melanoma (1), renal cell carcinoma (1)
AE, adverse event; BID, twice daily; CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular events; N, number of patients who received ≥1 dose of study drug; n, number of patients with the specified event within the given category; NMSC, non-melanoma skin cancer; OLE, open-label, long-term extension; PY, patient-years

[Table. Proportions and IRs of AEs of special interest in the OLE study]

References: 1. Sandborn WJ et al. N Engl J Med 2017;376:1723-1736.
2. Lichtenstein GR et al. Am J Gastroenterol 2018; 113 (Suppl 1): Abstract 571.
Disclosure: GR Lichtenstein has received research support and consultancy fees from Celgene, Salix/Valeant, Shire and UCB; research support from Janssen Orthobiotech; consultancy fees from Abbott/AbbVie, Cellceutix, Ferring, Gilead, Luitpold/American Regent, Merck, Pfizer Inc, Prometheus, Romark and Takeda; and other fees from Am J Gastroenterol: ACG, Clin Adv Gastroenterol and Gastroenterol Hepatol: Springer Science and Business Media, University of Pennsylvania, Janssen Orthobiotech, Pfizer Inc, Takeda, Luitpold/American Regent, Merck, Romark, McMahon Publishing, Up-To-Date and SLACK Inc.
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A Soonasra, N Lawendy, G Chan, H Zhang, W Wang and AJ Thorpe are employees and shareholders of Pfizer Inc. S Bloom has received advisory board fees from AbbVie, Janssen, Pfizer Inc and Takeda.

OP214 INTERLEUKIN-6 TRANS-SIGNALLING INHIBITION WITH OLAMKICEPT (SGP130FC) IN ACTIVE IBD RESULTS IN EARLY UNIQUE MOLECULAR SIGNATURES PREDICTING CLINICAL REMISSION AND DIFFERENTIATING FROM REMISSION INDUCTION BY VEDOLIZUMAB OR INFLIXIMAB

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Introduction: The cytokine interleukin-6 (IL-6) regulates many important immunological processes. Many IL-6-mediated effects are attributed to classic IL-6 signalling, *i.e.*, binding of IL-6 to a membrane receptor complex consisting of the specific IL-6 receptor (IL-6R) expressed mainly on hepatocytes and leukocytes and the ubiquitously expressed signal-transducing co-receptor gp130.In contrast, chronic inflammation is mediated by trans-signalling, in which a complex of circulating soluble IL-6R isoforms (sIL-6R) together with IL-6 can engage virtually every body cell by binding to the ubiquitous gp130 co-receptor. The fusion protein olamkicept (sgp-130Fc, FE 999301, ola) is a cytokine trap that selectively neutralizes IL-6/sIL-6R complexes and hence intercepts trans-signalling.

Aims & Methods: The aim of this study was to i) identify early molecular response patterns in Ola treated IBD patients and ii) to compare these with response patterns from Infliximab or Vedolizumab treated patients in order to identify ola-specific signatures of clinical response.

Samples were obtained from a multi-centre, open-label, Phase IIa, exploratory proof-of-concept trial administering ola over 12 weeks by intravenous infusion in patients with active IBD. 16 patients with IBD (CD=7, UC=9) received 600 mg ola every 2 weeks from week 0 to a maximum of 12 weeks. For multi-modal molecular assessment, blood, stool, and biopsies from the sigmoid colon were collected twice before (screening, week 0) and at several time points (+4 h, +24 h, 2 weeks, 6 weeks, and 14 weeks) after ola infusion. Phosphorylation of STAT3 was assessed in colonic biopsies by immunohistochemistry and with an in vitro PBMC stimulation assay to investigate target engagement. Integrated omics analysis was based on RNA sequencing (blood, sigmoid colon) and 16s rRNA/DNA (stool) data sets. Ola-induced mucosal transcriptome signatures were compared with mucosal transcriptome signatures from anti-TNFa(infliximab, IFX, n=12) and anti-a4b7 integrin (vedolizumab, VDZ, n=18) treated patients undergoing the same protocol to identify drug-specific signatures of clinical remission.

Results: RNAseq analysis revealed compartment-specific transcriptomal response (blood vs. sigmoid colon) to ola exposure. Ola induced pronounced downregulation of inflammation-associated transcripts starting at +4 h after initial drug infusion in PBMCs coinciding with inhibition of *in vitro*pSTAT3 phosphorylation induced by stimulation with a IL-6/sIL-6R fusion protein (hyper-IL6). Importantly, mucosal STAT3 phosphorylation and expression of inflammatory transcripts in the intestinal mucosa showed significant downregulation at week 2 timepoint, being highly predictive of later clinical and endoscopic remission. By comparing ola-induced transcriptomal signatures associated with clinical remission with mucosal signatures in remission induced by IFX- (n=12) or VDZ- (n=18), we could define common as well as olamkicept-specific mucosal transcriptional signature of clinical remission.

Conclusion: The study demonstrates the utility of molecular response mapping in early drug development by comprehensive multi-omics assessments using mucosal biopsies and peripheral blood samples. In-depth molecular analysis of IL-6 trans-signalling inhibition in humans represents a novel therapeutic principle for the management of IBD. The delineation of drug-specific remission signatures in the intestinal mucosa may early identify patient populations with differential response to specific anti-cytokine classes of drugs.

Disclosure: Nothing to disclose

OP215 MAINTENANCE OF REMISSION AMONG PATIENTS WITH INFLAMMATORY BOWEL DISEASE AFTER VEDOLIZUMAB IS STOPPED: A MULTICENTER COHORT STUDY FROM THE GETAID

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Introduction: It is unclear whether vedolizumab therapy can be discontinued in patients with inflammatory bowel disease (IBD) after achieving clinical remission. The aim of this study was to assess the risk of relapse after vedolizumab therapy was discontinued in patients with IBD.

Aims & Methods: We performed a retrospective observational study, collecting data from 21 tertiary centers in France affiliated to the GETAID from January 2017 to April 2019, on consecutive patients with IBD treated with vedolizumab in clinical remission for at least 3 months who discontinued vedolizumab therapy. Disease activity was assessed using the Harvey-Bradshaw Index for Crohn's disease (CD) and the partial Mayo Clinic score for ulcerative coliits (UC). Relapse was defined as partial Mayo Clinic score ≥ 3 and/or a stool frequency or rectal bleeding subscores of >1 for UC and Harvey-Bradshaw index >4 for CD and the initiation of second line therapy. Relapse-free survival was studied with Kaplan-Meier method, log-rank test and Cox regression model. Patients were censored when vedolizumab was reintroduced despite persistence of clinical remission.

Results: 95 patients (24 male; median age: 32.5 [IQR 27.3-42.4] years; 58 with CD) were included in the present study. Before discontinuation, the median duration of vedolizumab therapy was 17.5 [10.6-25.4] months. Patients discontinued vedolizumab therapy for pregnancy in 37 cases (38.9%), adverse events in 26 (27.4%), by their own choice in 24 (25.3%) and reimbursement issue in 8 (8.4%). At baseline, Harvey-Bradshaw index and partial Mayo Clinic score was 1.7 ± 1.4 and 0.9 ± 1.1, respectively. Only 6 (6%) were still treated with immunomodulator when they discontinued vedolizumab therapy. After a median follow-up period of 11.2 (5.8-17.7) months, 61 of the 95 patients experienced a relapse. Four patients were retreated with vedolizumab after pregnancy in three cases and ovarian cyst work up in one, with a mean delay of 0.7 ± 0.5 years. The probabilities of relapse-free survival were 83%, 59% and 36% at 6, 12 and 18 months, respectively. The multivariate analysis demonstrated that patients with CRP level < 5 at the time of vedolizumab discontinuation (OR = 0.56, CI95%[0.33-0.95], p = 0.03) and patients who discontinued vedolizumab by their own choice (OR = 0.41, CI95%[0.21-0.80], p = 0.009) were less likely to experience relapse. Among the 61 relapsers, vedolizumab was re-introduced in 24 cases permitting to re-induce steroid-free clinical remission after 14 weeks in 71%. After a median follow-up of 11.0 [5.4-13.3] months, 15 (62.5%) patients were still in clinical remission on vedolizumab therapy.

Conclusion: Almost two thirds of patients with IBD who discontinued vedolizumab therapy while achieving clinical remission experienced a relapse within 1 year after discontinuation of vedolizumab. Normal CRP level

(< 5 mg/L) and patients' choice rather than pregnancy, adverse events and reimbursement issues was associated with a lower probability of relapse. After re-introduction of vedolizumab therapy, more than two thirds of patients achieved steroid-free clinical remission after 14 weeks.

Disclosure: Nothing to disclose

OP216 HIGH VERSUS STANDARD ADALIMUMAB INDUCTION DOSING REGIMENS IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS: RESULTS FROM THE SERENE-UC INDUCTION STUDY

Panés J.[1], Colombel J.-F.[2], D'Haens G.R.[3], Schreiber S.[4], Panaccione R.[5], Peyrin-Biroulet L.[6], Loftus, Jr E.[7], Danese S.[8], Louis E.[9], Armuzzi A.[10], Ferrante M.[11], Vogelsang H.[12], Lefebvre J.[13], Doan T.[13], Kwatra N.V.[13], Mostafa N.M.[13], Xie W.[13], Huang B.[14], Petersson J.[15], Kalabic J.[16], Robinson A.M.[13], Sandborn W.J.[17]

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Introduction: Adalimumab (ADA) is effective and well tolerated in inducing and maintaining clinical remission in adult patients (pts) with ulcerative colitis (UC).[1-3] We report results from the 8 wks induction period of SE-RENE-UC (NCT02065622), comparing two ADA dosing regimens: a higher induction dosing regimen (HIR) and a standard induction dosing regimen (SIR).

Aims & Methods: SERENE-UC is a Phase 3, double-blind, randomized multicenter study of higher versus standard ADA dosing regimens for induction and maintenance therapy in adult pts with moderately to severely active UC. Pts were randomized 3:2 to receive either the HIR (160 mg at Wks 0, 1, 2, and 3, followed by 40 mg at Wks 4 and 6) or the SIR (160 mg at Wk 0 and 80 mg at Wk 2, followed by 40 mg at Wks 4 and 6) of ADA.
At randomization, pts were stratified by baseline corticosteroid use and previous infliximab (IFX) use. All pts who entered the study on oral corticosteroids were mandated to begin steroid taper at Wk 4.
The primary efficacy endpoint for the induction study was the proportion of patients in the intent to treat population achieving clinical remission, defined as full Mayo Score ≤2 with no subscore >1, at Wk 8. The endoscopic component of the Mayo Score was scored via a central reading protocol. ADA trough serum concentrations were measured at Wks 2, 4, and 8. Exposure-response (ER) modelling was performed using NONMEM 7.3 for the overall population and the ER relationship (ERR) was compared with the ULTRA 2 study.[3] Non-responder imputation was used for missing values. Safety assessment included collection of adverse events (AEs), vital signs, and laboratory data.

Results: In total, 852 pts were randomized, 512 and 340 into the HIR and the SIR, respectively. Baseline demographics were generally balanced across the two treatment groups; overall, mean UC disease duration was 7.2 (7.1) years, 87.1% of pts were biologic-naïve (12.9% had prior IFX experience with initial response and subsequent inadequate response or intolerance), and 58.7% of pts were receiving corticosteroids. There was no significant difference in clinical remission rate at Week 8 between the HIR and SIR (13.3% vs 10.9%, respectively; p=0.273).
The Table displays results for secondary efficacy endpoints. ADA trough concentrations were higher in the HIR versus the SIR (mean [SD] = 39.2 [20.7] and 10.8 [5.2] μg/mL at Wk 4 and 19.3 [9.5] and 8.0 [4.9] μg/mL at Wk 8, respectively) and the levels for the SIR were comparable to those previously reported in ULTRA 2. Higher ADA concentrations were associated with higher clinical remission rate; however, modeling results indicated shallower ERR in this study compared with ULTRA 2. The observed safety

profile was similar between the HIR and SIR groups, including AEs of special interest (< 1% across both groups).

Conclusion: In SERENE-UC, there was no additional benefit of the HIR at Wk 8 beyond the approved SIR. Both induction dosing regimens of ADA demonstrated similar clinical and endoscopic efficacy. Both dosing regimens were generally safe and well tolerated. The maintenance portion of the study is ongoing.

Endpoints (Wk 8), n (%)	Adalimumab HIR (n=512)	Adalimumab SIR (n=340)	p-value
1. Endoscopic improvement[a] (endoscopic subscore of 0 or 1)	159 (31.1)	92 (27.1)	0.182
2. Fecal calprotectin < 150 mg/kg	115 (22.5)	67 (19.8)	0.283
3. IBDQ response (increase of IBDQ ≥ 16 from BL)	342 (66.8)	207 (60.9)	0.063
4. Clinical response per full Mayo Score[a,b]	241 (47.1)	136 (40.0)	0.034*
5. Endoscopic remission[a] (endoscopic subscore of 0)	67 (13.1)	34 (10.0)	0.162

*Nominal p-value < 0.05. [a]Endoscopy scored via a central reading protocol. [b]Clinical response per full Mayo Score: Decrease from baseline in the full Mayo Score ≥ 3 points and ≥ 30% from baseline, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. BL, baseline; HIR, higher induction dosing regimen; IBDQ, Inflammatory Bowel Disease Questionnaire; RBS, rectal bleeding score; SIR, standard induction dosing regimen

[Ranked secondary efficacy endpoints]

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OP217 VEDOLIZUMAB EFFICACY, SAFETY AND PHARMACOKINETICS WITH REDUCED FREQUENCY OF DOSING FROM EVERY 4 TO EVERY 8 WEEKS IN PATIENTS WITH ULCERATIVE COLITIS AND CROHN'S DISEASE

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Introduction: Ulcerative colitis (UC) and Crohn's disease (CD) are chronic diseases generally requiring long-term maintenance therapy. Vedolizumab (VDZ) is a humanised monoclonal antibody targeting $\alpha_4\beta_7$ integrin to reduce lymphocyte migration to the gut. VDZ was effective and well tolerated with 8-wk (Q8W) and 4-wk dosing (Q4W) in CD and UC in the GEMINI Phase 3 studies and with Q4W dosing in the GEMINI long-term safety (LTS) study. After GEMINI LTS, an extended access program (XAP) with Q8W dosing was initiated. Data from patients (pts) who reduced VDZ dosing from Q4W to Q8W are limited. From the XAP pharmacokinetics (PK) substudy, we report clinical efficacy, PK, and safety for pts who reduced VDZ frequency from Q4W to Q8W.
Aims & Methods: VDZ XAP (NCT02743806) is a prospective, open-label, multinational, interventional study to provide pts access to VDZ and monitor safety. Eligible pts were on VDZ 300mg IV Q4W during GEMINI LTS with continued clinical benefit. In XAP, VDZ frequency was reduced to 300mg IV Q8W and pts were followed for 56 wk; return to Q4W dosing was allowed based on physician's assessment of pt clinical status and Medical Monitor approval. Blood samples for PK analyses were obtained at enrolment (last Q4W dosing visit) and wks 8, 16, and 56; serum VDZ was measured using a validated ELISA. Clinical remission was defined as Harvey-Bradshaw Index (HBI) ≤4 for pts with CD and partial Mayo score ≤2 with no subscore >1 for pts with UC. Clinical response after restarting Q4W dosing was defined as decreased HBI of ≥3 from XAP baseline, or decreased partial Mayo score of ≥2 and ≥25% from baseline with a decrease of ≥1 point in rectal bleeding subscore (RBS) from baseline or an RBS of ≤1 point.
Results: A total of 167 pts (88 CD, 79 UC) enrolled in the XAP-PK substudy. Overall, pts had a median of 6.5 y (range, 4.4-10.0) of prior VDZ use; 69% of pts were anti-TNF naïve at VDZ initiation in prior studies. Of pts with CD and UC, 91% and 92%, respectively, completed the 56-wk substudy, with 86% and 90% remaining on Q8W dosing. Rates of clinical remission and corticosteroid (CS)-free clinical remission in pts remaining on Q8W were stable through wk 56 (Table). Four pts with CD and 2 pts with UC returned to Q4W dosing; 3 of 4 CD pts regained clinical response. Pts remaining on Q8W VDZ through wk 56 had low CRP levels that were stable over time; 2.2 mg/L and 1.7 mg/L at baseline and wk 56 for CD pts and 2.2 mg/L and 1.2 mg/L for UC pts. Median trough VDZ was 43.6 µg/mL at baseline and 10.4 µg/mL at wk 56 in pts with CD and 42.4 µg/mL and 13.3 µg/mL in pts with UC. Adverse events (AEs) related to VDZ were infrequent; no new or serious AEs related to VDZ were reported.

	Baseline		Week 8		Week 16		Week 56	
	CD	UC	CD	UC	CD	UC	CD	UC
Clinical remission, %	84.0	95.8	84.2	91.5	83.8	91.2	82.7	94.4
CS-free remission, %	78.7	91.5	78.9	87.3	78.4	86.8	76.0	91.5
CRP, median, mg/L	2.4	1.8	1.9	1.6	2.2	1.2	2.6	1.2
Trough VDZ, median, µg/mL	43.6	42.4	16.2	18.6	12.6	14.2	10.4	13.3

CD, Crohn's disease; CRP, c-reactive protein; CS, corticosteroid; Q8W, every 8 weeks; UC, ulcerative colitis; VDZ, vedolizumab.

[Table. Efficacy, Safety and PK in CD (N=76) and UC (N=71) Patients Who Remained on Q8W Dosing for 56 Weeks]

Conclusion: In a clinically stable cohort, high pt persistence was observed after reducing dose frequency from VDZ Q4W to Q8W. High clinical and CS-free remission rates were maintained for 56 wk. Return to Q4W dosing was necessary in only a few pts and half of them regained clinical response afterwards. VDZ trough concentrations decreased from baseline as expected. AEs were consistent with previous reports.

Frontiers in pancreatic neoplasia
14:00-15:30 / B3

OP218 A RANDOMISED PROSPECTIVE COMPARISON OF LIQUID-BASED CYTOLOGY WITH CONVENTIONAL SMEAR CYTOLOGY FOR ENDOSCOPIC ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION OF SOLID PANCREATIC MASSES

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Introduction: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) cytology is a widely used method for the diagnosis of pancreatic neoplasms. Liquid-based cytology (LBC) analysis has been developed to overcome the disadvantages of conventional smear cytology (CS) in which contaminants such as blood, mucin, necrosis and artefactual aggregation of lymphoid cells, block the background of cytology slides [1]. The aim of this study was to evaluate the efficacy of LBC in the diagnosis of pancreatic neoplasms compared to CS.
Aims & Methods: We randomly assigned patients with suspected pancreatic cancer who required histologic confirmation to receive EUS-FNA cytology by either LBC or CS for the first pass. Nineteen to 25G needles (median 22G) were used at the discretion of each echoendoscopist. The second pass was performed with the technique not used for the first pass, and the last pass was allocated to core biopsy. The cytology slides were independently reviewed by two pathologists, and the diagnostic accuracy of the CS and LBC method was assessed for the primary outcome. Secondary outcomes included the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each method. Gold standard was defined as the final diagnosis of combined results from CS, LBC, core biopsy, and surgically obtained histology or at least 6 months follow-up for benign lesions. The sample size was calculated to determine the noninferiority of LBC compared to CS regarding diagnostic accuracy with acceptable margin of 10%. The reported accuracy of CS was approximately 90% [2]. With an alpha level of 5%, 90% power, and a dropout rate of 15%, the planned sample size was 170 cases.
Results: From April 2018 to March 2019, a total of 170 patients were enrolled in this study. Mean age was 64.8 years (range 37 - 88), and 95 patients (55.9%) were male. The median size of masses was 3.0cm (range 1.3-11.0), and the lesions were located as follows: 59 (34.7%) in the head, 24 (14.1%) in the uncinated process, 38 (22.4%) in the body, 40 (23.5%) in the tail, and 8 (4.7%) in the junction of the body and tail. Of the 170 cases, 165 lesions were malignant: pancreatic ductal adenocarcinoma (n = 163), neuroendocrine carcinoma (n = 2), and 5 lesions were benign conditions associated with chronic pancreatitis. No statistically significant differences were observed in age, sex, needle gauges, tumor size, and tumor location

between the two groups. The diagnostic accuracy, sensitivity, specificity, PPV, and NPV of LBC versus CS were 87.4% versus 83.9%, 87.1% versus 83.3%, 100% versus 100%, 100% versus100%, and 16.0% versus 16.1% (Table 1). When LBC combined with core biopsy, the diagnostic accuracy for pancreatic cancer was higher than that of LBC only (95.3% versus 87.4%, p = 0.01). There were 3 (1.76%) and 9 (5.29%) unsatisfactory samples for diagnosis in LBC and CS, respectively. Blood clots were much less observed in LBC than in CS (0.59% versus 64.1%), and the nuclear feature was similarly preserved in two groups.

Conclusion: Our study shows diagnostic utility of LBC was comparable to that of CS. Cytomorphologic features of ductal adenocarcinoma in LBC did not significantly differ from those in CS, and less frequent bloody backgrounds allow better visibility in LBC method.

Characteristic	Accuracy % (n/N)	Sensitivity % (n/N)	Specificity % (n/N)	PPV % (n/N)	NPV (%) (n/N)
LBC	87.4 (146/167)	87.1 (142/163)	100 (4/4)	100 (142/142)	16.0 (4/25)
CS	83.9 (135/161)	83.3 (130/156)	100 (5/5)	100 (130/130)	16.1 (5/31)
p value	0.37	0.34	0.99	0.99	0.99

[Table 1. Comparisons of operative characteristics]

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Disclosure: Nothing to disclose

OP219 ROLE OF HISTOLOGICAL SUBTYPES ON THE RISK OF HIGH GRADE DYSPLASIA CANCER IN OPERATED IPMNS: A LARGE SINGLE CENTER STUDY

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Introduction: Intraductal papillary mucinous neoplasms (IPMNs) suffer from low preoperative diagnostic accuracy. No method is available to accurately predict the grade of dysplasia of an IPMNs before surgery. Branch duct IPMNs (BD-IPMNs) and main duct-involving IPMNs (MD IPMNs) display different risks of progression to cancer and have different managements according to guidelines. IPMNs can also display different histological subtypes such as pancreatobiliary (PB) gastro foveolar (GF) oncocitic (O) and intestinal (I). The influence of such subtypes on the risks of harboring high-grade dysplasia cancer (HGD/C) in relation to different kinds of IPMNs is unknown.

Aims & Methods: To investigate the risk of HGD/C according to different histological subtypes. Single center, retrospective study on a prospectively collected cohort of patients operated for suspect malignant IPMN between 2007 and 2017 at HPB Disease Unit, Karolinska Hospital, Stockholm. Data about demographics, known risk factors for PDAC, pathological features were recorded. The inclusion criterion was the presence of histologically proved IPMNs. The exclusion criteria were the presence of a synchronous PDAC, positive margins for high grade dysplasia/cancer, or unknown histological subtype. Chi square and fisher test were used to analyze categorical variables, and statistically significant results were evaluated through sex and age adjusted univariable and multivariable logistic regression analysis. A sub-analysis was performed in BD and MD-IPMNs to assess the prevalence of different subtypes and the risk of harboring HGD/C.

Results: Among the 273 operated patients, 176 were included in the final analysis. In the BD-IPMN displaying HGD cancer the prevalence of GF subtype was significantly lower when compared to other subtypes (3.8% vs 100%, p=0.007). PB subtype was much more prevalent (66.7% vs 4%, p=0.02). The prevalence of HGD/cancer was not significantly higher for cyst dimension above 40 mm (25% vs 44%, p=0.62).
At univariable logistic regression analysis PB phenotype was associated with an increased risk of displaying HGD/C (OR 47.21; 95% CI 1.8-1184.7, p=0.01). In the MD-IPMN group displaying HGD/C the prevalence of GF subtypes was significantly lower when compared to other subtypes (45.4% vs 74.4%, p=0.001), while I subtype was much more prevalent (70.7% vs 46.2%, p=0.007).
No statistically significant differences were found for PB and O subtypes. At univariable logistic regression analysis GF was associated with a decreased risk of displaying HGD/C (OR 0.29; 95% CI 0.12-0.66, p=0.003) while I subtype was associated with higher risk (OR 2.85 95% CI 1.29-6.28, p=0.009). At multivariable logistic regression analysis adjusted even for MPD diameter GF subtype was confirmed to be associated to a decreased risk (OR 0.37 95% CI 0.15-0.95, p=0.03).

Conclusion: GF subtype associated with a decreased risk of HGD/C in BD-IPMN and in MD IPMN irrespectively from cyst dimension and MPD diameter. Intestinal subtypes might be associated to an increased of HGD/cancer risk in MD IPMNs and pancreatobiliary might be associated to an increase risk of HGD/cancer in BD IPMNs

Disclosure: Nothing to disclose

OP220 UPDATED INTERNATIONAL CANCER OF THE PANCREAS SCREENING (CAPS) CONSORTIUM GUIDELINES ON THE MANAGEMENT OF PATIENTS WITH INCREASED RISK FOR FAMILIAL PANCREATIC CANCER

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Introduction: The international Cancer of the Pancreas Screening (CAPS) Consortium has recommended specific guidelines for the management of individuals with increased risk of pancreatic cancer (high-risk individuals; HRI) arising from a familial clustering of the disease or associated with germline mutations.

Aims & Methods: Our aim was to update the 2013 CAPS consensus guidelines on the management of HRI. A modified Delphi approach was used, consisting of a systematic review of the literature, an international multi-disciplinary development workgroup meeting, and two rounds of online voting. Based on pre-defined criteria, experts in the field of familial pancreatic cancer were invited to vote on statements using a 7-point Likert scale. An *a priori* threshold of 75% agreement ('Strongly agree' or 'Agree') was used to establish consensus statements.

Results: 76 experts, from 7 disciplines, 11 countries and 4 continents, completed two rounds of voting (response rate 84%). Consensus was reached on more statements than the previous guidelines (55 versus 34). The goals of surveillance (to identify T1N0M0 margin-negative pancreatic cancer and high-grade dysplastic precursor lesions) remained unchanged.

Experts now also agreed that surveillance should commence at least by the age of 50 or 10 years younger than onset in the family, or when diabetes develops. There was still no agreement on the age to stop surveillance. Added as eligible for surveillance were *CDKN2A* p16 mutation carriers without a pancreatic cancer family history, and *ATM* mutation carriers with one affected first-degree relative. Experts also agreed that baseline surveillance should still include both endoscopic ultrasound (EUS) and MRI/MRCP, and not CT, ERCP, or abdominal ultrasound.

Both modalities should also be used for follow-up, but there was no consensus on whether to alternate these modalities, or on the optimal surveillance intervals when lesions are detected. Serum carbohydrate antigen 19-9 was recommended when worrisome features are found on imaging. Fasting blood glucose testing should be performed routinely, a new diagnosis of diabetes should prompt for immediate investigations. In HRI below 50 years of age, a new diagnosis of diabetes should lead to initiation of surveillance.

The surveillance interval in case of no or low-risk findings should be 12 months. EUS-fine needle aspiration is recommended for detected cysts with worrisome features, solid lesions ≥5 mm, or main pancreatic duct strictures (with or without associated mass). Main areas of disagreement included if and how surveillance should be performed for hereditary pancreatitis, and the management of indeterminate lesions.

Conclusion: Surveillance is recommended for selected HRI to detect early pancreatic cancer and its high-grade precursors, and should be performed in expertise centers, by multidisciplinary teams, preferably within a research setting.

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OP221 METHODOLOGY OF PANCREATIC JUICE COLLECTION FROM THE DUODENUM FOR BIOMARKER DISCOVERY AND EARLY DETECTION OF PANCREATIC CANCER

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Introduction: Pancreatic cancer (PC) is a deadly disease for which early detection of high-grade precursor lesions provides the only chance of cure. Surveillance by imaging (even EUS and MRI combined) in individuals at risk to develop PC does not enable timely detection[1]. Hence, there is an urgent need for reliable biomarkers. Pancreatic juice (PJ) is a promising biomarker source as it is in direct contact with the pancreatic ductal epithelial lining from which PC arises.

Aims & Methods: We aimed to determine the technique and duration of duodenal PJ collection after secretin stimulation that results in the highest yield of cell-free DNA, exosomes for miRNA analysis, proteins and cells (organoid growth).

PJ from patients suspected of sporadic PC and high-risk individuals, under surveillance for hereditary predisposition for PC (FPC), was collected from the duodenum during EUS after secretin stimulation. For each subject, two collection techniques (i.e. suction by a through-the-scope catheter positioned close to the ampulla or the endoscopic channel) and two time periods (i.e. the first and second four minutes) were compared. PJ

was snap frozen < 10 minutes after collection and stored at -80°C. DNA extraction was compared between the NucleoSpin and Maxwell cfDNA kit. The yield of DNA (Quant-iT dsDNA Assay), the cfDNA/gDNA-ratio (i.e. 75bp/300bp-ratio; qPCR) and %mutated KRAS (dPCR; KRAS Multiplex Kit) were compared. Exosomes were isolated and analyzed with Nanoparticle Tracking Analysis (NTA). Total protein, cytokine and (pancreas specific) PLA2G1B concentrations were quantified with Lowry assay and ELISA. Organoids were grown, based on Broutier et al.[2], from cellular content of PJ. Also, usefulness of a protease or superase inhibitor was tested. For statistical analysis, either a Friedman's or Wilcoxon signed-rank test was performed.

Results: Presence of pancreatic content was confirmed by PLA2G1B in all PJ collection methods (32 samples, 8 individuals), with exception of 6 FPC samples that were collected with a catheter. The NucleoSpin kit resulted in a higher DNA concentration and cfDNA/gDNA-ratio (p=0.025, p< 0.0001) than the Maxwell kit. Collection through the endoscopic channel during the second time period resulted in the highest yield of DNA (p=0.017, p=0.039), albeit with a lower cfDNA/gDNA ratio (p=0.039). cfDNA/gDNA ratio was highest in the first four minutes (P=0.002); independent of collection technique. Mutated KRAS was detected in all samples (%mutated KRAS: 0.09-1.01); indiscriminate of DNA extraction technique, collection technique or duration.

Exosomes (size range: 81.6-244.6 nm, 2 FPC kindreds) were present in all 8 analyzed samples. Yields were highest in samples collected with a catheter. The overall protein concentration of PJ collected through the endoscopic channel during the first four minutes was highest (64 samples, p=0.02). IL-8, IL10, IFN-γ and TGF-β concentrations did not differ between the collection methods. IL-6, IL-13 and TNF-α were not detectable. 16/65 (25%) PJ samples that were seeded for organoids grew into organoids, of which 85% had been collected in the first four minutes. The addition of inhibitors to PJ during collection did not improve any of the biomarkers tested.

Conclusion: We show feasibility of DNA, exosome and protein quantification and organoid growth from PJ. Duodenal collection during EUS in the first four minutes after secretin injection resulted in a high yield of cfDNA, exosomes, proteins and organoids. According to PLA2G1B concentrations, the use of a catheter did not result in higher yields or a more concentrated collection of PJ.

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OP222 NEW THERAPEUTIC METHOD FOR UNRESECTABLE PANCREATIC CANCER - THE IMPACT OF HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) THERAPY

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Introduction: Even with recent advances in the diagnostic imaging technology, most cases of pancreatic cancer (PC) are diagnosed at an unresectable stage. The therapeutic effect of chemotherapy and chemoradiotherapy for unresectable PC was not satisfactory. High-intensity focused ultrasound (HIFU) is expected as new advanced therapy for unresectable PC. HIFU therapy with chemotherapy is being promoted as new method to control local advance by ablation tumor.

Aims & Methods: We have evaluated the therapeutic effect of HIFU therapy in locally advanced and metastatic PC. We treated PC patients by HIFU as optional local therapy as well as systemic chemo / chemo-radiotherapy, with whom an agreement was obtained in adequate IC, from the end of 2008 in our hospital.

This study took approval of member of ethic society of our hospital. HIFU device used is FEP-BY02 (Yuande Bio-Medical Engineering Co.LTD., China). The subjects were 176 PC patients, i.e. 88 cases in stage III, 88 cases in stage IV. Performance status (PS) was PS:0 ; 85, PS:1; 87, and PS:2; 4 cases. Gender ratio was 90 male and 86 female. Mean age was 64.0±11.8 years, The details of therapy before HIFU treatment (overlap) was radiochemotherapy in 42, chemotherapy in 97, arterial infusion chemotherapy in 5, immunotherapy in 8, operation in 22, Irreversible electroporation (IRE) in 3 ,and BSC in 13 cases.

Results: All tumors were visualized by HIFU monitor system. Tumor location was head in 49, uncus in 21, body in 73, body~tail in 7, tail in 4, and others (recurrence) in 22 cases. Treatment data was followed; mean tumor size before and after therapy was 33.3±10.9 and 33.8±11.7 mm, mean treatment sessions: 2.1±0.7 times, mean total treatment time: 89.4±66.8 min, mean total number of irradiation: 1709.6±1125.7 shots.

The effects of HIFU therapy were the following; the rate of complete tumor ablation was 90.3 %, the rate of symptom relief effect was 63.8%, the effectiveness of primary lesion was CR:0, PR:21, SD:105, PD:47 cases, primary disease control rate (DCR) more than SD was 71.0%. The therapy after HIFU treatment was operation in 8, chemotherapy in 143, immunotherapies in 4, and best supportive care (BSC) in 22 cases. MST after diagnosis in HIFU with chemotherapy and chemotherapy alone (100 patients in our hospital) was 772.3 vs 346.6 days, respectively (*p*< 0.05).

The mean duration to HIFU therapy from the diagnosis (including the pretherapy period) was 391.5 ± 390.0 days (median: 288.5 days). MST after HIFU therapy was 379.8 days. Combination therapy of HIFU with chemotherapy was better result than common chemotherapy alone.

Conclusion: This study suggested that HIFU therapy has the potential of new method of combination therapy for PC.

Disclosure: Nothing to disclose

OP223 PREDICTING CONDITIONAL SURVIVAL DURING FOLLOW-UP AFTER RESECTION FOR PANCREATIC CANCER: A POPULATION-BASED STUDY

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Introduction: Pancreatic ductal adenocarcinoma is one of the most lethal cancers. Survival estimates are traditionally calculated from the time of diagnosis or at the time of surgery. Since many patients with pancreatic ductal adenocarcinoma decease within the first year, 5-year overall or relative survival estimates change considerably when surviving the first years postoperatively. Conditional survival (CS) accounts for the time already survived after resection and may be more informative for patients. This population-based study aims to assess CS and to develop a nomogram predicting 5-year survival at a predefined period after resection of pancreatic ductal adenocarcinoma.

Aims & Methods: Patients with resected pancreatic ductal adenocarcinoma were included from the Netherlands Cancer Registry (2005-2016). Conditional survival was calculated as the probability of 5-year survival in patients who already survived 1, 2, 3 and 4 years after resection of pancreatic

ductal adenocarcinoma using the Kaplan-Meier method. The Cox proportional hazards model was used to evaluate known predictors of overall survival. A prediction model, based on tumor differentiation, resection margin, lymph node ratio and adjuvant therapy, was constructed.

Results: Overall, 3,082 patients were included with a median age of 67 years (IQR 60-73). Median overall survival was 18 months (95%CI 17-18 months) with a 5-year survival of 15%. The probability of 5-year survival after resection increased from 15% directly after resection to 23%, 42%, 61% and 82% per additional year survived (1, 2, 3 and 4 years, respectively, Table 1). The created nomogram had an optimism-adjusted C-statistic of 0.64 (95% CI 0.63-0.65). The probability to achieve 5-year survival, when measured 1 year after surgery, varied from 1 to 58% depending on the patient- and tumor characteristics included in the nomogram.

	Survival probability to reach X years								
Given years of survival	0	1	2	3	4	5	6	7	8
Number at risk	3082	2054	1001	585	367	246	176	125	88
0	100	67	37	25	18	15	13	12	10
1		100	55	38	28	23	20	17	15
2			100	68	50	42	36	31	28
3				100	74	61	53	46	41
4					100	82	71	62	55
5						100	86	75	67

Each column represents the years survived from surgery and each row represents the percentage to reach a certain total survival time from that point of survived years. For example, if a patient has survived 2 years after surgery, the probability to achieve 3-year survival after surgery is 68% and to achieve 5-year survival after surgery is 42%.

[Table 1. Conditional survival from the time of pancreatic resection in 3,082 patients, given 1 to 5 years survival after surgery]

Conclusion: This nationwide study showed the added value of conditional survival for patient who underwent resection for pancreatic ductal adenocarcinoma. A nomogram was created to provide insight to patients regarding their survival probabilities during follow-up. It could be recommended to inform pancreatic cancer patients about CS, especially those who survive the first year after resection.

Disclosure: Nothing to disclose

IBD: Basic Science I
14:00-15:30 / B5

OP224 THE BRANCHED-CHAIN AMINO ACID TRANSPORTER CD98 HEAVY CHAIN FACILITATES THE DEVELOPMENT OF COLONIC MACROPHAGES ASSOCIATED WITH DECREASED APOPTOSIS IN MACROPHAGE PROGENITORS

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Introduction: Monocytes and macrophages maintain the integrity of the gut by clearing apoptotic cell bodies and microorganisms that have crossed the epithelial barrier (1,2).A comprehensive macrophage development is critical for gut macrophages, which evolve from blood monocytes through a 'monocyte waterfall'-developmental trajectory (3,4). The underlying mechanisms of the macrophage development in the gut remains elusive.

Aims & Methods: To assess the role of branched-chain amino acids for the development of gut macrophages, we generated an inducible knock-out mouse model for the branched-chain amino acid transporter CD98hc in CX3CR1[+]intestinal macrophages.

Results: CD98hc is highly expressed on monocyte-macrophage dendritic cell progenitors, the common monocyte progenitors, and the monocytes in the bone marrow. In the gut, extravasated monocytes, intermediates of the 'monocyte waterfall'-development and macrophages express CD98hc. Stimulation of bone marrow-derived macrophages with LPS + IFN-γ (M1 conditions) or with IL-4 + IL-13 (M2 conditions) did not change CD98hc

expression. As tissue-resident macrophages develop from the yolk sac, the CD98hc expression was determined in the embryonic yolk sac (E8.5), Kupffer cells and Langerhans cells. The macrophages of the yolk sac revealed a lower CD98hc expression compared to the tissue-resident Kupffer cells and Langerhans cells. We next generated an inducible knock-out mouse system. CD98hc$^{\Delta CX3CR1}$ mice were generated by breeding Cx3cr-1^{CreER} mice with CD98hc$^{flox/flox}$ mice for the tamoxifen-inducible silencing of CD98hc. Tamoxifen-injection into CD98hc$^{\Delta CX3CR1}$ mice lead to the deletion in colonic macrophages and liver Kupffer cells but not in Langerhans cells. The deletion of CD98hc in macrophages attenuated the severity of dextran sodium sulfate (DSS) induced-colitis clinically, endoscopically, and histologically. After quality filtering, a total of 3,213 (1863 control and 1,350 CD98hc cKO) cells were obtained for scRNA-seq.

The observation of cells on a principal component analysis (PCA) or tSNE visualization, patterns of expression of cluster-specific genes, hypervariable genes and arbitrarily chosen monocytes and macrophages marker genes suggested a differentiation trajectory from monocytes to macrophages. The calculation of the relative proportion of control and CD98hc-deficient cells, across clusters and across the PCA space, indicated an enrichment of CD98hc-deficient cells in monocyte clusters, which was also apparent when the relative proportions of control and CD98hc-deficient cells projected on the nodes of FlowSOM trees.

These results indicate a block in the 'monocyte waterfall'-development to mature macrophages in the colonic lamina propria of tamoxifen-treated CD98hc$^{\Delta CX3CR1}$ mice. To further gain insights into molecular mechanisms involved in the developmental arrest in CD98hc deficient macrophages, we looked for genes differentially expressed between tamoxifen- or corn oil-treated CD98hc$^{\Delta CX3CR1}$ mice within each cluster along the developmental trajectory. The "pseudo-bulk" samples used for this analysis indicated an enrichment of apoptosis-associated genes, such as *Bcl2l11*, *Tnf*, and *Osm* in tamoxifen-treated CD98hc$^{\Delta CX3CR1}$ mice. Consequently, the numbers of macrophages but not monocytes were significantly reduced after CD98hc silencing, which is highly expressed in biopsies of patients with quiescent and active ulcerative colitis or Crohn's disease.

Conclusion: Our results demonstrate that the deletion of CD98hc results in a developmental arrest of intestinal macrophages. CD98hc plays a pivotal role in the development of intestinal macrophages.

References: 1. Smythies, LE et al. J Clin Invest 115, 66-75 (2005). 2. Kamada, N et al. J Clin Invest 118, 2269-2280 (2008) 3. Bain CC et al. Mucosal Immunol 6, 498-510 (2013) 4. Schridde A et al. Mucosal Immunol 10, 1387-1399.
Disclosure: Nothing to disclose

OP225 MITOCHONDRIAL IMPAIRMENT IN CROHN'S DISEASE DRIVES INTESTINAL STEM CELL TRANSITION TOWARDS DYSFUNCTIONAL PANETH CELLS

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Introduction: Altered intestinal epithelial cell (IEC) homeostasis is associated with chronic intestinal pathologies like inflammatory bowel diseases (IBD). Paneth cells (PC) reside in close proximity to Lgr5$^+$ intestinal stem cells (ISC) localized at the crypt base, supporting epithelial renewal/homeostasis. PC produce antimicrobial peptides and niche factors necessary for the maintenance of Lgr5$^+$ ISCs. Impaired PC function contributes to the ileal pathogenesis of Crohn's disease (CD). The aim of this study was to characterize the role of mitochondrial function on the ISC niche including PC.
Aims & Methods: To determine the impact of mitochondria on the ISC niche, we used a mouse model for CD-like ileitis (TNF$^{\Delta ARE}$ mice), and ileal tissue samples from CD patients. Impact of mitochondrial impairment on ISC and PC was evaluated in mice with a tamoxifen-inducible ISC specific knockout for the mitochondrial chaperone Hsp60 (Hsp60$^{\Delta ISC}$). Small intestinal organoids from mice and humans were generated to illustrate alterations of stem cell and PC phenotypes after treatment with dichloroacetate (DCA) and oligomycin. In addition, we performed transcriptional analyses, *in situ* hybridization, and immunostaining (IHC and IF) in tissue sections and organoid cultures to dissect molecular mechanisms.

Results: In TNF$^{\Delta ARE}$ mice, ileal inflammation correlated with reduced PC granularity and diffuse lysozyme (Lyz) staining. Impaired PC function was further indicated by diminished expression of the ISC-niche factor (*Dll4*) and antimicrobial peptides (*Ang4*, *Defa5*). Ileal tissue sections from CD patients confirmed distorted PC appearance in inflamed regions. Most importantly, the appearance of a low-granular PC and re-localization of Lgr5+ cells in non-inflamed tissues predicted disease recurrence of CD patients after surgical resection. Parallel to PC dysfunction, the intestinal epithelium developed signs of an activated mitochondrial unfolded protein response and loss of stemness indicated by reduced expression levels of *Lgr5* in the crypt base of TNF$^{\Delta ARE}$ mice as well as CD patients. ISC-specific deletion of HSP60 led to elevated numbers of dysfunctional PC and transient reduction of *Lgr5* expression, confirming the importance of mitochondrial homeostasis in regulating PC function and ISC maintenance. Increased numbers of *Lgr5*$^+$-Lyz$^+$ cells and HSP60$^-$-Lyz$^+$ cells together with absence of apoptosis or necrosis at the crypt base indicated differentiation of ISC into dysfunctional PC upon mitochondrial impairment.
Underlining the importance of mitochondrial function for ISC niche maintenance, inhibition of mitochondrial respiration using oligomycin in murine and human intestinal organoids decreased expression of *Lgr5* and antimicrobial peptides (*Lyz* and *Defa5*). In line with reduced stemness *in vivo*, TNF$^{\Delta ARE}$ mice-derived crypts were not able to give rise to organoids *ex vivo*. However, DCA-mediated inhibition of glycolysis, forcing cells to shift to mitochondrial respiration, reverted the oligomycin-mediated distortion of PC functions in organoids and rescued TNF$^{\Delta ARE}$ mice-derived crypt cultures to form sustainable organoids.
Conclusion: We provide evidence that mitochondrial impairment drives the stem cell niche towards a dysfunctional PC phenotype, and is predictive for disease recurrence of CD patients after surgical resection. Maintenance of mitochondrial respiration may represent a novel drug target to antagonize PC dysfunction in the pathogenesis of CD.
Disclosure: Nothing to disclose

OP226 ULCERATIVE COLITIS IS CHARACTERIZED BY AN INTENSE AND DYSFUNCTIONAL MUCOSAL AND SYSTEMIC B CELL RESPONSE

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Introduction: The lack of clear B-cell associated drivers of mucosal inflammation and the failure of the Rituximab trial in ulcerative colitis (UC) has largely dampened the enthusiasm for B-cell focused research in Inflammatory Bowel Diseases. However, emerging data as well clues in existing literature suggest that the humoral immune system participates in and perhaps drives the pathophysiology of UC.
Aims & Methods: In the present study, we systematically examined the B cell phenotype and function in patients with UC.
Blood and colonic biopsies were collected from UC patients as well as healthy controls at the Mount Sinai hospital. B cells were characterized using multiparameter flow cytometry and immunohistochemistry. In a subset of patients we examined the heavy chain immunoglobulin gene (IgH) repertoire at the single-cell level. We also deciphered the B cell transcriptomic profile and key B-cell clusters as well as their interactions with other cell types using single-cell RNA sequencing (10x genomic) in the colonic mucosa.
Results: We enrolled 65 active UC patients, 15 patients with quiescent disease and 30 healthy controls from whom we obtained blood samples. 58% of the patients were not under any immunomodulator. Whereas there were no changes in the frequency of CD19+ B cells and B cell subsets in blood, circulating plasmablasts (CD19+/intCD27+CD38hi) were markedly expanded in active UC patients (0.56% vs 0.12%, p< 0.0001). They up-regulated the β7-intregrin and CXCR3 while down-regulating β1-integrin. Both IgA and IgG plasmablasts were expanded in circulation. Expansion of β7+plasmablasts correlated with disease activity and systemic inflammation. Subsequent analyses of plasma cells in the colonic mucosa, from 20 inflamed mucosa, 19 non-inflamed mucosa from UC patients and 13 healthy colonic biopsies,

revealed the reshaping of the B cell landscape in the inflamed mucosa. Indeed, short-lived plasma cells (CD45+CD19+CD27+CD38hi) and Ki67+ plasmablasts were massively expanded in the inflamed mucosa along with an increased frequency of naïve and germinal center B cells. The study of the IgH gene sequencing from single-cell sorted short-lived plasma cells showed the skewing of isotype toward an increase of IgG and a decrease of IgA2 in UC. In addition, their repertoire diversity was significantly reduced. Further, clones sequenced from UC patients presented more somatic hypermutations and a longer complementary-determining region 3 (CDR3) suggesting a reduced maturation state.

Single-cell RNA sequencing of lamina propria cells demonstrated the highly proliferative state of colonic plasmablasts during active UC that were also increased in frequency while virtually absent in healthy controls. IgG plasma cells expressing the chemokine receptors CXCR4 were also found in greater frequency in the inflamed mucosa. These changes in the antibody-secreting cells compartment were accompanied by an increase in naïve and germinal center B cells as well as in a cluster of CXCL13-expressing T cells.

Conclusion: We show that an intense and acute B cell response is ongoing in active UC as evidenced by the expansion of circulating β7+plasmablasts that leads to an increase of short-lived PC and highly proliferative plasmablasts in the colonic mucosa. This B cell response likely participates in the inflammatory process as they have skewed isotype usage, they differentially express chemokine receptors and they have modified IgH gene features. This study, along with key recent works, suggests a potential interest in targeting specifically intestinal antibody-secreting cells as a therapeutic strategy in UC.

Disclosure: Nothing to disclose

OP227 MUTATIONS IN THE X-LINKED INHIBITOR OF APOPTOSIS PROTEIN PROMOTE SUSCEPTIBILITY TO MICROBIOTA-INDUCED INTESTINAL INFLAMMATION

Gopalakrishnan S.[1], Zeissig Y.[2,3], Strigli A.[1], Basic M.[4], Muders M.[3,5], Baretton G.[3], Baines J.[6], Bleich A.[4], Hampe J.[1,3], Zeissig S.[1,3,7]

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Introduction: Mutations in the gene encoding the X-linked inhibitor of apoptosis protein (XIAP) form the basis for one of the most common Mendelian forms of Crohn's disease. However, the mechanisms which link *XIAP* mutations to CD are poorly understood.

Aims & Methods: We investigated *Xiap*^{-/-} mice and wildtype (WT) littermates under constitutive conditions in a specific pathogen-free (SPF) environment as well as upon exposure to dextran-sodium sulfate (DSS) or the pathobiont *Helicobacter hepaticus*.

Results: Deficiency in XIAP was associated with a selective loss of Paneth cells as a result of increased Paneth cell death. Remaining Paneth cells showed ultrastructural defects, including aberrant positioning of granules, nuclear condensation and fragmentation, and loss of mitochondrial structure.

This was associated with reduced abundance of Paneth cell-derived antimicrobial peptides and impaired bacterial control associated with dense colonization of intestinal crypts by commensal bacteria, increased abundance of mucosa-adherent bacteria and an altered intestinal microbial composition. Under SPF conditions, these alterations were not sufficient to elicit spontaneous intestinal inflammation.

However, upon exposure to the pathobiont *Helicobacter hepaticus*, *Xiap*^{-/-} mice showed impaired clearance of *Helicobacter hepaticus* and developed granulomatous ileitis, which was not observed in WT littermates. Reconstitution of antimicrobial activity by adenoviral delivery of alpha defensin 5 restored the clearance of *Helicobacter hepaticus* in *Xiap*^{-/-} mice and prevented ileal granuloma formation.

Moreover, in accordance with long range effects of Paneth cell-derived antimicrobial peptides in the colon, *Xiap*^{-/-} mice showed increased susceptibility towards DSS compared to WT mice. Intriguingly, DSS also elicited ileal pathology such as villus blunting in *Xiap*^{-/-} mice, which was not observed in WT mice.

Conclusion: Defects in XIAP are associated with loss of Paneth cells and increased susceptibility to chemical and microbiota-induced intestinal inflammation. As such, these data provide novel insight into the mechanisms that link XIAP mutations to intestinal inflammation and highlight the microbiota as a potential therapeutic target in patients with *XIAP* mutations and CD.

Disclosure: Nothing to disclose

OP228 THE TRANSCRIPTOMIC LANDSCAPE OF HUMAN COLONIC ORGANOIDS AND ITS REMODELLING BY CANONICAL CYTOKINES PROVIDES KEY FUNCTIONAL AND CLINICAL INSIGHTS INTO INFLAMMATORY BOWEL DISEASE

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Introduction: The immune- epithelial interactions are central in our current understanding of inflammatory bowel disease (IBD) pathogenesis. Cytokines have been shown to play an integral part in this cross-talk, with some considered pro-inflammatory (e.g. IFNγ, TNFα) and others protective (e.g. IL22).

Aims & Methods: Since most of the work informing our current understanding of cytokine mediated epithelial responses is based on pre-clinical models we set out to define and compare the transcriptional programmes regulated by the canonical cytokines IFNγ(TH1), IL13 (TH2), IL17A(TH17), IL22 (TH22) and TNFα, as a pro-inflammatory control, in human colonic organoids (colonoids) and associate them to disease phenotypes and therapeutic trajectories in IBD.

Whole transcriptome profiling of cytokine treated human colonoids (n=4) was performed using the Illumina platform. Pathway analysis was performed using the Ingenuity database while gene set variation analysis (GSVA) and weighted gene correlation network analysis (WGCNA) were used to associate cytokine regulated modules to phenotypes by interrogating whole biopsy transcriptomic profiles of our own UC cohort (n=16) and reposited datasets (GSE16879, n=73, GSE23597, n=206). Flow cytometry of human intestinal lamina propria mononuclear cells (LPMC) corroborated our transcriptomic analysis while the functional relevance of our findings was confirmed by using the TRUC model of colitis.

Results: A large functional overlap was found between IFNγ, IL22 and TNFα transcriptional programmes with key pathogenic pathways upregulated by all three cytokines (e.g. IL6, NF-kB, TREM1, TLR signalling, acute phase response, neutrophil chemotaxis). GSVA revealed enrichment of all cytokine regulated transcriptional modules in active inflammation while there was no difference in activated module number or type between UC and colonic CD. Intriguingly, patients with the same endoscopic activity had a gradient of activated cytokine regulated modules. Those with ≥2 modules enriched had a higher risk of non-response to anti-TNFα therapy in both IBD phenotypes [relative risk: 2.9, 95%CI(1.7, 6)]. A strong, positive correlation was seen between IL22, IFNγ and TNFα enrichment scores which was also validated by identifying a population of polyfunctional CD4+ T cells being enriched in the mucosa of IBD patients with active disease producing all three cytokines. WGCNA revealed a neutrophil chemotaxis chemokine module to be the pathway most strongly associated with anti-TNFα non-response. This module was primarily upregulated by IL22 and TNFα. In a TNFα and IL22 dependent model of colitis IL22 blockade downregulates the same chemokine module and improves colitis while the use of a neutrophil chemokine receptor (CXCR2) blocker abrogates disease.

Conclusion: Our study provides novel insights into the human gut immune-epithelial interactome and paves the way for a more granular immunophenotyping of IBD. It highlights that the simultaneous activation of modules regulated by multiple canonical cytokines is associated with non-response to anti-TNFα. Targeting of these shared pathogenic pathways may hold the key to overcoming non-response to biological therapies.

Disclosure: Nothing to disclose

OP229 IDENTIFICATION OF A CYTOTOXIC CD127^{+} INNATE LYMPHOID CELL SUBSET THAT IS EXPANDED IN PATIENTS WITH CROHN'S DISEASE

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Introduction: Crohn's disease is an inflammatory disorder within the intestines as a consequence of dysregulated immune responses. Innate Lymphoid Cells (ILCs), including helper ILCs and Natural Killer (NK) cells, regulate intestinal homeostasis and provide protective immunity, but also contribute to pathology when not properly controlled.

Previously we demonstrated that the increased frequency of non-cytotoxic IFN-γ-producing ILC1s in Crohn's disease resection specimen inversely correlated with a decreased frequency of ILC3s, while the frequency of NK cells were not altered[1,2] .

Aims & Methods: Combining flow cytometry, *ex vivo* culture methods, and whole transcriptomic analysis methods of human fetal, non-inflamed and Crohn's disease resection specimen, we demonstrate here the identification of a previously unrecognized population of cytotoxic IFN-γ-producing ILC in the intestinal lamina propria, that are distinct from NK cells.

Results: These cells are characterized by the expression of the ILC-defining markers CD127 (also known as IL7Rα) and CD200R1.

In addition, these cells express CD94, a marker that was previously thought to be restricted to NK cells. This ILC population is highly increased in inflamed intestinal resection specimen when compared to non-inflamed tissue and was virtually absent in fetal intestines or peripheral blood. *Ex vivo* cloning experiments demonstrated that conventional helper ILCs, including ILC3s and ILC1s, acquired the cytotoxic, IFN-γ-producing CD94^{+} phenotype when exposed to IL-12, a cytokine that is prominently abundant in inflamed intestines of Crohn's disease patients.

We furthermore demonstrated that the identified cell population induced cell death of K562 target cells at a similar degree as NK cells whereas CD94^{-} ILC1 and ILC3 failed to kill these target cells

Conclusion: Taken together, we have identified a population of cytotoxic and IFN-γ-producing ILCs that is expanded at the expense of ILC3s in inflamed intestines of Crohn's disease patients where they may contribute to pathology.

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Disclosure: Nothing to disclose

How to improve the diagnosis of GORD
14:00-15:30 / E1

OP230 INCREASED SENSITIVITY OF COUGH REFLEX IS NOT THE MECHANISM OF COUGH ATTRIBUTED TO LARYNGOPHARYNGEAL REFLUX

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Introduction: Coughing is often attributed to laryngophayngeal reflux (LPR). It is assumed that acid in the gastroesophageal reflux (GER) that reaches the laryngopharyngeal area stimulates or sensitizes respiratory nerve terminals mediating cough. This premise allows for formulation of several testable hypotheses. If the stimulation of respiratory nerves by acidic LPR is responsible for coughing then a) acidic LPR should correlate with coughing, b) proton pump inhibitor (PPI) treatment should reduce both coughing and acidic LPR. On the other hand, if sensitization of respiratory nerves by acidic LPR is responsible for coughing then a) cough sensitivity should correlate with coughing, b) PPI treatment should reduce both coughing and cough sensitivity. Here we addressed these hypotheses.

Aims & Methods: Consecutive patients referred for suspected LPR were evaluated and those with positive reflux symptom index (RSI>13) and/or reflux finding score (RFS >7) were enrolled. LPR was inferred from pharyngeal reflux. Pharyngeal reflux was evaluated by simultaneous pharyngeal and distal esophageal 24-hour pH/impedance. Pharyngeal reflux events with the maximum drop of pH at levels 6.0, 5.5, 5.0, 4.5, and 4.0 were determined to perform analysis independent of the assumption how acidic pharyngeal reflux is required to influence cough. Cough reflex sensitivity was determined as the lowest concentration of capsaicin causing at least 2 coughs (C2) by single breath capsaicin inhalation challenge using doubling capsaicin concentrations (0.49-1000μM). For statistical analysis C2 values were -log transformed. Troublesome coughing was evaluated on the scale 0-5.

Results: 27 patients diagnosed with LPR were enrolled. The number of pharyngeal reflux events (median[interquartile range]) with pH 6.0, 5.5, 5.0, 4.5 and 4.0 was 14[8-21], 4[2-7], 1[0-2], 1[0-1] and 0[0-1], respectively. There was no correlation between coughing and the number of pharyngeal reflux episodes at any pH level (Pearson coefficients R ranged from -0.17 to 0.23, P=NS). There was also no correlation between coughing and the cough reflex sensitivity C2 (R=-0.1, P=NS). 17 patients completed PPI treatment. In 11 patients RSI was normalized by PPI (PPI-responders). In PPI-responders the troublesome cough was substantially reduced by >60% (2.3±0.6 vs. 0.9±0.1, P< 0.01). However, strikingly, there was no change in cough reflex sensitivity in PPI-responders. The capsaicin C2 threshold was 13[1.6-32]μM vs. 7.8[3.1-19]μM before and after PPI (P=0.11). Furthermore, PPI treatment did not appreciably reduce acidic pharyngeal reflux.

Conclusion: The lack of correlation between the cough sensitivity and coughing and the lack of change in cough sensitivity despite substantial improvement of coughing by PPI strongly argue that an increased cough reflex sensitivity is not the mechanism of cough attributed to LPR. Dual pharyngeal and distal esophageal 24-hour pH/impedance monitoring did not identify simple relationship between acidic reflux and coughing suggesting that this relationship is more complex. Supported by VEGA 1/0304/19.

Disclosure: Nothing to disclose

OP231 RISK FACTORS OF FUTURE ONSET OF REFLUX ESOPHAGITIS: A LONGITUDINAL CASE-CONTROL STUDY USING LONG-TERM HEALTH CHECKUP RECORDS IN JAPAN

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Introduction: Reflux esophagitis (RE) is a disease in which the reflux of gastric contents into the esophagus causes superficial erosion of the mucosa of the lower esophagus, and its prevalence and burden have recently increased Risk factors of RE proposed in previous studies included obesity, being male, hiatal hernia, absence of atrophic gastritis, advanced age, diabetes drinking smoking, metabolic syndrome, *Helicobacter pylori* (*H. pylori*) negative, However, these risk factors of RE have been investigated in many cross-sectional studies, little is known about predictive factors associated with future onset of RE. We investigated time courses of clinical parameters before RE onset by a longitudinal case-control study using long-term health checkup records.

Aims & Methods: We conducted a retrospective study using to investigate factors associated with future RE onset using long-term health checkup records in Japan. We used health checkup records between April 2004 and March 2014 at nine institutions in Japan. Subjects who were newly diagnosed as RE between April 2009 and March 2014 were included in the analysis as case subjects. For each case subject, two subjects who had no RE diagnosis between April 2004 and March 2014 and were matched for age, sex, and participating institutions with the corresponding case were included as control subjects. The time courses of clinical parameters of RE subjects were compared with those of control group by the restricted maximum likelihood method for repeated measures or multivariate logistic analysis. We also implemented cross-sectional comparisons for each of the five years prior to RE onset.

Results: Initial data were obtained from 230,056 individuals, and 2,066 RE subjects and 4,132 control subjects were finally included in the analysis. The time courses of body mass index (BMI) (p < 0.001), abdominal circumference (AC) (p < 0.001), fasting blood sugar (FBS) (p = 0.039), serum triglyceride (TG) (p = 0.010), glutamate oxaloacetate transaminase (p = 0.044), glutamic pyruvic transaminase (GPT) (p = 0.005), γ-glutamyl transpeptidase (p < 0.001), and percentages with acid reflux symptoms (p = 0.004), feeling of fullness (p = 0.019), and hiatal hernia (p < 0.001) in the RE group were significantly worse than in the control group. In cross-sectional comparisons at the year of RE onset, BMI (p < 0.001), AC (p < 0.001), FBS (p = 0.006), systolic blood pressure (p = 0.011), TG (p < 0.001), uric acid (p = 0.002), GOT (p < 0.001), GPT (p < 0.001), γ-GTP (p < 0.001), amount of alcohol (p < 0.001), smoking (p = 0.008), and percentage with acid reflux symptoms (p < 0.001), feeling of fullness (p = 0.046), hiatal hernia (p < 0.001), hypertension (p = 0.003), and hyperlipidemia (p = 0.044) in the case group were higher than in the control group, and high-density lipoprotein cholesterol (p = 0.007) and percentage with atrophic gastritis (p < 0.001) in the case group were lower. Among them, BMI, AC, TG, GPT, and percentages with acid reflux symptoms and atrophic gastritis showed significant differences for five years prior to RE onset consecutively between the groups.

Conclusion: The RE group displayed a more rapid worsening of the clinical parameters associated with lifestyle diseases, including obesity, diabetes, hyperlipidemia, and fatty liver compared with the non-RE group. These results suggest that RE is a lifestyle disease and thus lifestyle guidance may help to prevent RE onset.

Disclosure: Nothing to disclose

OP232 EXACERBATION OF GASTROESOPHAGEAL REFLUX SYMPTOMS AFTER DISCONTINUATION OF PROTON PUMP INHIBITORS IS NOT ASSOCIATED WITH INCREASED ESOPHAGEAL ACID EXPOSURE

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Introduction: Almost universally, proton pump inhibitors (PPIs) are used for initial management of heartburn symptoms. After an initial PPI course, there is often an attempt to stop medication. However, it is a very common complaint that reflux symptoms exacerbate on stopping PPIs. Mechanisms have been postulated as resumption of esophageal acid exposure and rebound acid hypersecretion, however data on this are limited.

Aims & Methods: We aimed to study the impact of stopping long-term PPIs in patients with heartburn, and its association with esophageal acid exposure on objective testing.

We prospectively evaluated patients with heartburn on long-term PPIs (>8 weeks), referred to the Royal London Hospital Upper GI Physiology Unit. All completed an online questionnaire following a minimum of a 7-day PPI discontinuation. The questionnaire addressed presence and exacerbation of symptoms (heartburn, regurgitation, epigastric pain/burn, and excessive belch/bloating) since stopping PPI. Patients were asked if heartburn symptom had exacerbated since stopping PPI (yes/no). In those who had exacerbation, symptom intensity and frequency were assessed on a 10 point Likert scale (0 = no exacerbation of symptoms; 10 = extreme symptom exacerbation). Then, all patients underwent High Resolution Manometry (HRM) and 24-hour multichannel impedance pH study (MII-pH) based on our standard protocol. We measured esophageal acid exposure time (AET), the number of total reflux and proximal extent episodes, esophageal bolus exposure time%, and gastric pH < 4 time %. All data are presented as median with interquartile range. We used Fisher exact test for comparison of ratios, Mann-Whitney U test for the comparison of continuous variables, and Spearman´s Rank Correlation Coefficient for investigating correlations.

Results: 28 patients were studied. After stopping PPIs, 21 patients (75%) had exacerbation of heartburn ("exacerbation group"), 7 patients had no exacerbation of heartburn ("non-exacerbation group"). Heartburn exacerbation severity in the exacerbation group was rated as mean 6.72 out of 10 on the Likert scale. These patients also reported similar exacerbation of epigastric pain, bloating and belching. AET in the exacerbation group was not significantly higher than in the non-exacerbation group (3.5% [1.7-8.7] vs 3.4% [1.6-7.5], NS). The proportion of patients with physiological

acid exposure (< 4.2%) was not different between the exacerbation and non-exacerbation groups (11 of 21 patients vs. 4 of 7 patients respectively). Similarly, gastric pH< 4 time% was not different between groups (88.6% [77.4-92.7] vs 85.9% [78.8-90.6]). There were no significant correlations between AET/gastric pH< 4 time% and the severity of the exacerbation of each symptom on stopping PPIs. Other MII-pH parameters (the number of reflux episodes, proximal extent, and bolus exposure time%) did not show significant difference.

Conclusion: Our study shows that exacerbation of reflux symptoms after the discontinuation of PPIs occurs in the majority of patients. However, this appears to occur regardless of whether there is excessive esophageal acid exposure, and in at least half is associated with completely normal AET. Not just heartburn, but all recorded upper GI symptoms exacerbated on stopping PPI in most patients. The results suggest that acid-independent mechanisms may have a role in symptom exacerbation on stopping PPI. One potential hypothesis is that sudden withdrawal of PPI-related anti-inflammatory effects induce hypersensitivity of the GI viscera. Further studies are required.

Disclosure: Daniel Sifrim receives research grants from Reckitt Benckiser UK, Jinshan Technology China and Alfa Sigma, Italy. Philip Woodland receives research grants from Reckitt Benckiser UK, and consultancy fees from Reckitt Benckiser UK and Dr Falk Pharma UK

OP233 ABNORMAL POST REFLUX SWALLOW INDUCED PERISTALTIC WAVE (PSPW) INDEX ON PH-IMPEDANCE MONITORING ASSOCIATES WITH HYPOMOTILE ESOPHAGEAL MOTOR PATTERNS ON ESOPHAGEAL HIGH RESOLUTION MANOMETRY (HRM)

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Introduction: Post-reflux Swallow-induced Peristaltic Wave (PSPW) participates in reflux clearance through primary peristalsis, and abnormal PSPW index is a marker for higher reflux burden on pH impedance monitoring. Impaired primary esophageal body peristalsis on HRM also associates with abnormal reflux burden; peristalsis can augment following multiple rapid swallows (MRS), termed contraction reserve. The relationship between PSPW and esophageal body contraction metrics on HRM in the context of reflux disease remains unknown.

Aims & Methods: Our aim was to determine whether a relationship existed between PSPW and esophageal body contraction patterns on HRM in patients being evaluated for reflux disease. Clinical presentation, HRM, and ambulatory pH-impedance studies performed on patients with persisting reflux symptoms were reviewed from five centers (4 in Europe and 1 in US) for this preliminary report. Incomplete studies, achalasia, esophageal outflow obstruction, and prior foregut surgery were exclusions. HRM studies were analyzed according to CC 3.0, and proportions of intact (distal contractile integral, DCI>450 mmHg.cm.s), fragmented (intact with ≥5 cm breaks), ineffective (DCI< 450 mmHg.cm.s), and failed (DCI< 100 mmHg.cm.s) were recorded. The ratio of MRS esophageal body contraction vigor (using distal contractile integral, DCI) to mean contraction vigor from single swallows >1 defined presence of contraction reserve. Total, upright and supine acid exposure time (AET) were extracted from pH-impedance studies (abnormal when total AET>6%, upright AET>6% and supine AET>2%). PSPW was defined as an antegrade swallow within 30 s of completion of an impedance detected reflux episode, and PSPW index was calculated as the proportion of reflux episodes with PSPW on the 24 hour pH impedance study. Univariate comparisons, ANOVA, and linear regression were utilized to investigate potential correlations between PSPW index and contraction patterns.

Results: Of 269 patients (53.1 ± 0.9 yr, 62% F), abnormal AET proportions were found in 77 (28.6%), 111 (41.2%), and 108 (40.1%) for total, upright and supine AET, respectively. Median PSPW index was 0.50, range 0.04-0.89. PSPW index declined progressively with increasing proportions of hypomotile patterns (p< 0.001 for each comparison by ANOVA, Table); there was corresponding increase in AET (p< 0.001 for each comparison by ANOVA). MRS data was available for 140 patients, of which 76.4% had contraction reserve. There was no direct correlation between PSPW index and presence or absence of contraction reserve. However, within ineffective esophageal motility, PSPW was more robust when post MRS DCI was ≥1000 mmHg.cm.s compared to < 1000 mmHg (0.50±0.02 vs. 0.43 ±0.3, respectively, p=0.049) When controlling for physiologic acid burden, regression analysis demonstrated positive correlation between AET and PSPW index (p≤0.02 for each comparison).

	100% intact	<50% ineffective	50-70% ineffective	≥80% ineffective	Absent contractility
PSPW index*	0.60±0.02	0.54 ±0.02	0.52±0.14	0.46±0.03	0.42±0.44
Total AET* (%)	4.5±0.90	5.0±0.5	6.4±1.7	6.9±1.1	12.3±3.7
Upright AET* (%)	4.5±0.6	5.6±0.1	6.5±1.8	7.7±1.0	11.6±3.6
Supine AET* (%)	3.8±1.3	4.3±0.8	5.7±1.9	6.1±1.7	13.2±6.0

*p < 0.001 across groups by ANOVA

[Comparison of PSPW index and acid burden across esophageal body motor patterns]

Conclusion: PSPW index correlates with esophageal body motor pattern, and both associate with abnormal reflux burden. Abnormal PSPW index demonstrates a corresponding gradient of hypomotility on HRM, suggesting that both PSPW and HRM complement evaluation of neuromuscular integrity of esophageal motor function.
Disclosure: Nothing to disclose

OP234 EXTENDED BRAVO STUDIES (UP TO 96HOURS) INCREASES DIAGNOSTIC YIELD OF GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD) IN PATIENTS WITH NORMAL MULTICHANNEL INTRALUMINAL IMPEDANCE-PH (MII-PH) STUDIES

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Introduction: MII-pH catheter studies measure both acid and non-acid reflux and are considered nowadays to be the gold standard in the diagnosis of GERD. Wireless pH capsule (Bravo) may increase the diagnostic yield of standard 24hr catheter-based studies with prolonged monitoring by overcoming the limitation of day-to-day reflux variability and patients are able to perform activities of daily living without the discomfort of the nasal catheter. This study aims to assess the additional diagnostic yield of extended Bravo recordings (up to 96 hours) in patients with negative 24hr MII-pH results.
Aims & Methods: A total of 44 patients with typical GERD symptoms but negative 24hr MII-pH studies off proton pump inhibitor(PPI) were referred for Bravo capsule studies. Bravo studies were performed off PPI over an extended period beyond 48hrs (up to 96hrs). Bravo cases positive for AET were analysed using the Bravo 'Worst Day Analysis' (WDA) and 'Average Day Analysis' (ADA). Reference values for MII-pH and Bravo equivalent were adopted from internationally established studies (Table 1). Subgroup analyses were subsequently made on cohorts whose MII-pH showed normal AET with (A) normal number of total reflux events (TRE), (B) normal number of non-acid reflux (NAR) events and (C) increased number of NAR events. Subgroups (B) and (C) have normal number of acid reflux events. Statistical analysis was performed using SPSS.
Results: study group (male=14, female=30) with a mean age of 48 years, successfully completed Bravo studies up to 96 hours in 77.3% and beyond 48 hours in 97.7%. Using the WDA and ADA respectively, Bravo (AET cut-off >4.2%) captured an additional 59.1% and 43.2% of patients with increased AET (p< 0.001) in cases with normal AET on MII-pH. In MII-pH subgroups (A), (B) and (C), Bravo WDA was able to reveal an additional positive AET of 61.8%(p< 0.001), 60.9%(p< 0.001) and 50.0%(p=0.016) respectively compared to MII-pH while Bravo ADA showed a similar albeit smaller additional yield of 44.1% (p< 0.001), 43.5% (p< 0.002) and 35.7% (not sig-

nificant). Results were similar using other internationally published Bravo AET limits of >4.4% and >5.3%. Inclusion of symptom reflux association in Bravo cases with increased AET also showed additional diagnostic yield over MII-pH ranging from 42.9-47.7% (p≤0.031) across all subgroups.
Conclusion: Extended Bravo studies managed to procure a diagnosis of GERD in more than half of cases with an initial normal MII-pH but persistent symptoms. Half of the patients with increased NAR events on MII-pH also showed positive acid reflux on prolonged testing using Bravo. This additional yield has the potential to alter diagnosis from functional heartburn/hypersensitive esophagus to GERD in difficult cases and affect management by intensifying acid suppression therapy.
Disclosure: Nothing to disclose

OP235 ROLE OF REFLUX IN THE PATHOGENESIS OF EOSINOPHILIC ESOPHAGITIS -COMPREHENSIVE APPRAISAL WITH OFF- AND ON-PPI IMPEDANCE-PH MONITORING

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Introduction: The relationship between eosinophilic esophagitis (EoE) and gastroesofageal reflux disease (GERD) has not been fully elucidated, as well as the mechanisms of response to proton pump inhibitor (PPI) therapy. Comprehensive assessment of reflux by impedance-pH monitoring could clarify these issues
Aims & Methods: A prospective multicenter study comparing EoE and GERD patients with healthy controls was carried out. Patients were evaluated off- and on- PPI; impedance-pH appraisal included chemical clearance, assessed with post-reflux swallow-induced peristaltic wave (PSPW) index, and mucosal integrity measured with mean nocturnal baseline impedance (MNBI) in the distal and mid esophagus
Results: Sixty consecutive EoE patients entered the study, and were compared to 60 age- and sex-matched healthy controls and to 60 typical GERD cases. Number of total and acid refluxes were higher while PSPW index and distal MNBI were significantly lower in EoE than in healthy controls. On therapy, all reflux parameters and MNBI improved in the 40 PPI-responsive EoE cases but PSPW index was the only variable independently associated with PPI responsiveness (OR 1.143, 95% CI 1.049-1.247, *P*=0.002). In PPI-refractory patients, number of total refluxes and PSPW index were not modified by therapy. Distal MNBI improved much more in PPI-responsive than in PPI-refractory cases. Off-PPI, MNBI values in mid and distal esophagus were comparably low in PPI-refractory but not in PPI-responsive EoE
Conclusion: Reflux plays a role in the pathogenesis of EoE, more relevant in PPI-responsive cases. PPIs mainly act by improving chemical clearance, i.e. by an anti-reflux action, thus supporting their long-term prescription in PPI-responsive EoE
Disclosure: Nothing to disclose

Big data to robotics
14:00-15:30 / F2

OP236 A THREE-DIMENSIONAL PRINTED PELVIC MODEL IS USEFUL FOR LATERAL PELVIC NODE DISSECTION IN RECTAL CANCER

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Introduction: In patients with advanced lower rectal cancer, the complex pelvic anatomy renders lateral pelvic node dissection (LPND) challenging. Though laparoscopic and robotic surgery have decreased the invasiveness of LPND, the absence of tactile sensation increases the risk of blood vessel and nerve injury. Recently, three-dimensional (3D) printing of models for preoperative simulation or intraoperative navigation has been described for liver [1], kidney [2], and pancreas surgery [3]. Subjective assessments have confirmed the utility of 3D-printed models for understanding spatial anatomy.

Aims & Methods: We evaluated the utility of printing a 3D pelvic model for LPND.

We included 22 patients who underwent LPND for rectal cancer between June 2017 and February 2019. Using CT scans, 3D pelvic images and models were constructed and printed, respectively. Thirty colorectal surgeons subjectively evaluated the utility of 3D pelvic models based on a 5-point Likert scale questionnaire (1 = strongly disagree to 5 = strongly agree).

Production of the 3D pelvic model

A colorectal surgeon constructed a 3D image from 0.5-mm thin-slice images obtained using an enhanced multi-detector CT. The organ structure was manually segmented to define the region of interest on each CT slice in the axial view and converted into a stereolithography file to generate the 3D virtual model. The 3D models were printed with white polylactic acid of 2.85-mm diameter using an 3D Printer. The models were finalized by removing the support filament and were coloured manually.

Results:

Patient characteristics: The patients included 13 males and nine females; of these, five underwent open surgery, 12 underwent laparoscopic surgery and five underwent robotic surgery. LPND was performed on the left side in eight patients, right side in seven patients and bilaterally in seven patients. Lateral pelvic lymph node metastasis was observed in 19 sides.

Questionnaire results: The average Likert score for the question 'Would a 3D model be useful for understanding pelvic anatomy?' was 4.7. Cases with enlarged pelvic lymph nodes (4.8 ± 0.44) scored higher than those without metastasized lymph nodes (4.4 ± 0.77, p = 0.02). For spatial comprehension of pelvic anatomy, 3D models scored higher (4.83) than 3D images (4.36, p < 0.001). The ease of use of 3D models and images were scored 4.20 and 4.60, respectively (p = 0.015).

Production time of 3D pelvic models: With experience, the 3D image reconstruction time decreased to 150 min. The printing time for the model was approximately 22 h, and the finalizing time was approximately 1 h. In total, it took about a day to produce one 3D pelvic model.

Conclusion: 3D pelvic models helped to understand pelvic anatomy for LPND.

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Disclosure: Nothing to disclose

OP237 ARTIFICIAL INTELLIGENCE IDENTIFIES BARRETT'S NEOPLASIA WITH HIGH ACCURACY USING NBI-ZOOM VIDEOS: A MULTICENTER INTERNATIONAL STUDY

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Introduction: The endoscopic diagnosis of Barrett's esophagus (BE) neoplasia generally consists of primary detection in overview, followed by targeted inspection using Narrow Band Imaging (NBI). Endoscopists have difficulties evaluating NBI-zoom imagery, resulting in suboptimal diagnostic accuracy and poor inter-observer agreement. Computer-aided diagnosis (CAD), using deep learning techniques, has shown promising results in gastrointestinal endoscopy. Therefore, we envisioned that CAD might be able to assist endoscopists in the interpretation of NBI-zoom imagery. Aim To demonstrate feasibility of a deep-learning CAD system for the evaluation of unaltered NBI-zoom videos in BE.

Aims & Methods: We used a step-wise approach using 4 different endoscopic datasets to train our deep learning network (ResNet-UNet hybrid architecture). First, our CAD system was pre-trained using 494,364 labelled images of a variety of endoscopic imagery, named GastroNet. Next, 690 BE neoplasia and 557 non-dysplastic (ND)BE white light endoscopy overview images were used for refinement training. To further improve the CAD system, we used 71 NDBE and 112 neoplastic NBI-zoom *images* from 50 non-dysplastic and 50 neoplastic patients. Finally, the CAD system was trained and validated with a fourth prospectively-collected, and histologically-confirmed, dataset of 77 NDBE and 37 neoplastic (high grade dysplasia/adenocarcinoma) unaltered NBI-zoom *videos*. Performance was evaluated using fourfold cross-validation. Majority voting by the CAD system was applied in our automated video analysis, in which a video was classified as neoplastic if more than 50% of its sequential frames were suspicious for neoplasia. The primary outcome was reported as diagnostic accuracy of the CAD system for classification of neoplastic BE in NBI-zoom images and videos.

Results: The CAD system demonstrated an accuracy, sensitivity and specificity for detection of BE neoplasia using NBI-zoom *images* of 84%, 88%, and 78%, respectively. In total, 18873 individual video frames were analyzed by the CAD system. Accuracy, sensitivity and specificity for BE neoplasia detection using NBI-zoom *videos* were 93% (106/114), 86% (32/37), 97% (75/77). Mean assessment time per video was 0.64 seconds (SD ± 0.02), corresponding to 391 frames per second.

Conclusion: We are the first to report high diagnostic accuracy on prospectively-collected and histologically-confirmed unaltered NBI-zoom *videos* with fast corresponding assessment time, thereby showing feasibility of neoplasia characterization in BE using CAD systems. Future work will focus on optimizing our current CAD system and validation using separate prospectively-collected datasets.

Disclosure: J.J. Bergman: NinePoint Medical, Fuji Film, Olympus, Pentax, CDx diagnostics, Cernostics, Medtronic, Erbe, Boston Scientific, Cook.

Evidence-based improvements in surgical outcomes

14:00-15:30 / Barcelona

OP238 PRETREATMENT TUMOR-DNA SEQUENCING OF KIT AND PDGFRA IN ENDOSONOGRAPHY-GUIDED BIOPSIES OPTIMIZES THE PREOPERATIVE MANAGEMENT OF GASTROINTESTINAL STROMAL TUMORS

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Introduction: Down-sizing tyrosine kinase inhibitor (TKI) therapy increases the chance of organ-preserving, radical resection in selected patients with gastrointestinal stromal tumor (GIST). We aimed to evaluate systematic, immediate DNA-sequencing of *KIT* and *PDGFRA* in pretreatment GIST-tissue to guide downsizing TKI-therapy and optimize pre-operative tumor response.
Aims & Methods: All patients being candidates for downsizing therapy of a suspected GIST [the study cohort (SC)] were prospectively included January 2014 – March 2018. Patients were subjected to pretreatment, endosonography-guided fine-needle biopsy (EUS-FNB) or transabdominal ultrasound-guided needle biopsy (TUS-NB) followed by immediate tumor-DNA-sequencing (< 2 weeks). A historic (2006-2013) reference cohort (RC) underwent work-up without sequencing before downsizing imatinib (n=42). The rate of optimal downsizing therapy (Thera$_{OPT}$) was calculated and the induced tumor size reduction (TR$_{max}$, %) was evaluated by CT-scan.
Results: The success rate of pretreatment tumor-DNA-sequencing in the study cohort (n=81) was 77/81 (95%) [EUS-FNB: 71/74 (96%); TUS-NB: 6/7 (86%)] with mutations localized in *KIT* (n=58), in *PDGFRA* (n=18), or neither gene, WT, (n=5). In patients with a final indication for down-sizing therapy, the Thera$_{OPT}$ was higher in the SC compared with the RC, 61/63 (97 %) *vs* 33/42 (79 %), p=0.006, leading to a significantly higher TR$_{max}$ (32 %) *vs* (19 %), p=0.001, among patients treated with standard dose imatinib.
Conclusion: Pretreatment endosonography-guided biopsy sampling followed by immediate tumor-DNA sequencing of *KIT* and *PDGFRA* is highly accurate and valuable for the guidance of downsizing TKI-therapy in GIST. This approach minimizes the maltreatment with inappropriate regimens and leads to improved tumor size reduction before surgery.
Disclosure: Nothing to disclose

OP239 IMMUNONUTRITION TO IMPROVE THE QUALITY OF LIFE OF UPPER GASTROINTESTINAL CANCER PATIENTS UNDERGOING NEOADJUVANT TREATMENT PRIOR TO SURGERY (NEOIMMUNE): DOUBLE BLIND RANDOMIZED CONTROLLED MULTI-CENTER CLINICAL TRIAL

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Introduction: Malnutrition, is very frequent in oesophagogastric cancers, and is associated with negative outcomes including increased morbidity, poor tumour response, poor tolerance to treatment and decreased quality of life (QOL). Immunonutrition in gastro-intestinal cancer surgery has been shown to efficient in perioperative period in reducing the risk of infectious complications.
Aims & Methods: The aim of this randomized controlled trial was to evaluate if immunonutrition during neoadjuvant treatment prior to surgery will improve patients' QOL, reduce postoperative morbidity and reduce haematological and mucosal toxicities.
Study Design: Double blind randomized controlled multi-center clinical trial. Included patients had untreated non-metastatic Upper GI tumor, aged 18 ≥years with a life expectancy of >3months. The study was powered for 80% power to detect a difference in EORTC-QLQC30 with standard deviation of 15 between the groups, permitting 179 randomized to received

immunonutrition with IMPACT® formula and 179 randomized to receive an isocaloric control during neoadjuvant therapy. The primary end-point for the study was QOL as measured by the EORTC-QLQ-C30. Secondary end-points included diarrhoea, mucositis, haematologic toxicity, nutritional status, compliance and response to neoadjuvant therapy, postoperative morbidity and length of hospital stay.
Statistical Analysis: An intention-to-treat analysis will be employed, and univariate analysis (ANOVA) was performed to compare scores, with an analysis of co-variance using ANCOVA also performed.
n° EUDRACT: 2011-A00716-35
Results: The study was terminated prior to completion of recruitment at the interim analysis stage, as reviewers felt the sample size was underestimated given the true effect of IMPACT formula. 300 patients were randomized; 148 to the IMPACT group and 152 to the control-formula group. Patient groups were well balanced in terms of age, sex, ethnicity, BMI, clinical tumour stage, utilisation of neoadjuvant therapy and medical co-morbidities.
No significant differences between groups in changes, at diagnosis and 30 days postoperatively, were identified in global health score (p=0.112) and time to global health deterioration (p=0.527), physical functioning (p=0.976), role functioning (p=0.777), emotional functioning (p=0.545), cognitive functioning (p=0.207), social functioning (p=0.968) and fatigue score (p=0.920). No significant differences in changes, at diagnosis, after neoadjuvant therapy and 30 days postoperatively were seen in pain, nausea and vomiting, dyspnea, insomnia, appetite loss and change in bowel habit. Analysis of EORTC-OG25 in changes 30-days postoperatively showed with IMPACT® improvements in time to pain and discomfort (p=0.007). Multivariate analysis for global health score deterioration showed no significant effect of IMPACT® administration (Hazard ratio = 1.18; 95% confidence interval 0.843 to 1.652).
Within the IMPACT® group toxicity during neoadjuvant treatment, tumor regression, postoperative complications, length of hospital stay and survival were unaffected.
Conclusion: The results of this large multi-center blind RCT fail to demonstrate any large benefit in terms of HRQOL to the utilization of immunonutrition during neoadjuvant therapy in patients with esophageal or gastric cancer. Furthermore no significant improvements were observed in secondary outcomes including 30-day postoperative complications.
Disclosure: Nothing to disclose

OP240 LAPAROSCOPIC VERSUS OPEN GASTRECTOMY FOR GASTRIC CANCER, RESULTS OF A MULTICENTER PROSPECTIVELY RANDOMIZED CONTROLLED TRIAL (LOGICA-TRIAL)

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Introduction: Open gastrectomy is the preferred surgical approach for gastric cancer worldwide. This procedure is associated with considerable morbidity. Meta-analyses have shown an advantage in short-term outcomes of laparoscopic gastrectomy compared to open procedures, with similar oncologic outcomes. However, the included series are mostly from Asia with early gastric cancer. It is unclear whether these results can be extrapolated to the Western population with mostly advanced gastric cancer. In this randomized controlled multicenter trial from the Netherlands, we assessed the outcomes of laparoscopic versus open gastrectomy.
Aims & Methods: Between 2015-2018, patients with resectable (cT1-4a, N0-3b, M0) gastric adenocarcinoma were randomly assigned to either laparoscopic (105 patients) or open (105 patients) gastrectomy, in 10 participating

centers in the Netherlands. Inclusion criteria were age ≥18 years, European Clinical Oncology Group performance status 0, 1 or 2 and informed consent. The primary outcome was postoperative hospital stay (days). Secondary outcome were postoperative morbidity and mortality, oncologic outcome, readmissions, quality of life and cost-effectiveness.

Results: This is a late breaking abstract. The last study patient was operated on in November 2018. The data are not yet mature at the moment of writing this abstract. We would like to present our primary endpoint and secondary endpoints at the UEGWEEK 2019

Conclusion: See above

Disclosure: Nothing to disclose

OP241 RANDOMIZED CONTROLLED TRIAL ASSESSING THE EFFECTIVENESS OF 5-HT$_3$ RECEPTOR ANTAGONIST (RAMOSETRON (IRRIBOW®)) FOR THE TREATMENT OF ANTERIOR RESECTION SYNDROME IN MALE PATIENTS WITH RECTAL CANCER

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Introduction: Anterior resection syndrome, including fecal urgency, frequency and incontinence can develop after sphincter-saving surgery for rectal cancer in 60-90% of the patients, but there has been no effective treatment.

Aims & Methods: We performed a randomized controlled trial to assess the effectiveness of ramosetron (Irribow®), a 5-HT$_3$ receptor antagonists, for the treatment of anterior resection syndrome.

Male patients with symptoms of anterior resection syndrome after rectal cancer surgery (after ileostomy take-down if ileostomy was performed) were enrolled and randomly assigned to take the ramosetron (Irribow®) 5mg daily (n=48) or conservative treatment (n=50) for 1 month. Low anterior resection syndrome (LARS) score[1] was calculated by questionnaire before and after 1 month after treatment. Primary endpoint was the difference in proportion of severe LARS. The study design was a superiority test with 30% of difference margin, 80% of power and 5% type I error. Analyses were based on the intension-to-treat population. Secondary endpoint was the difference of patients' quality of life by the questionnaire of EORTC QLQ-C30. This study is registered with ClinicalTrials.gov, number NCT02869984.

Results: The mean age was 61.4±9.3 and 59.9±9.9 years in the ramosetron and control group, respectively (p=0.927). Tumor distance from the anal verge was 6.9±3.8 and 7.9±4.3cm (p=0.254) and stage of the tumor was not different between the two groups (Stage III/IV, 20 (41.7%) vs 17 (34.0%), p=0.434). The mean LARS score (36.0±5.9 vs 34.4±6.8, p=0.215) and stool frequency (12.6±7.7 vs 12.6±7.2, p=0.987) before treatment were also similar.

All patients had more than 4 times/day of stool frequency before treatment. The LARS score significantly decreased to 29.6±9.3 after 1 month in ramosetron group (p< 0.001) and the LARS score after 1 month in the ramosetron group was significantly lower than control group (29.6±9.3 vs 34.6±7.6, p=0.004). The mean changes in LARS score (1 month - baseline) was -6.48 in ramosetron, compared to 0.16 in control group (p<0.001).

The proportions of severe LARS (LARS score, ≥30) after 1 month was 58.3% (n=28/48) in ramosetron group vs 82.0% (n=41/50) in the control group, with the difference of 23.7% being statistical significance (95% CI=5.58~39.98%, p=0.011). The stool frequency after 1 month was 7.1/day and 10.5/day in the ramosetron and control group (p=0.004), and the patients who had the stool frequency less than 4 times/day were 13 (27.1%) in ramosetron compared to only 1 (2.0%) in the control group (p< 0.001). The quality of life after 1 month was significantly better in ramosetron group in terms of general health status (70.7±18.6 vs 62.7±17.5, p=0.031), physical functioning (88.6±11.25 vs 82.4±17.18, p=0.038), emotional functioning (90.5±11.78 vs 81.5±20.98, p=0.011) and cognitive functioning (91.7±12.4 vs 85.0±17.6, p=0.032).

Conclusion: Although we did not reach the intended superiority margin of 30% with ramosetron (Irribow®) treatment for anterior resection syndrome, our results showed significantly better LARS score and quality of

life in the ramosetron treatment group. Ramosetron (Irribow®) treatment may be applied for selective patients who had severe symptoms of anterior resection syndrome after rectal cancer surgery.

References: 1. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg 2012;255:922-8

Disclosure: This study was supported by the Grant of Clinical Research Institute, Seoul National University Hospital (Grant No: 0620164120) from Dona-A Parmaceutical Co. Kore

OP242 MULTICENTER, RANDOMIZED CONTROLLED TRIAL OF NASOGASTRIC TUBE WITH WATER-SOLUBLE CONTRAST AGENT *VERSUS* LONG TUBE FOR SMALL BOWEL OBSTRUCTION

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Introduction: Small bowel obstruction (SBO) is a frequently occurred gastrointestinal emergency and the most frequent cause is adhesion after abdominal surgery, accounting for 50-80%. Gastrointestinal decompression is applied to SBO without any findings of strangulation and ischemia. Decompression with nasogastric tube (NGT) is a standard treatment for SBO in Western countries based on the old small trial that showed no significant differences between NGT and long tube (LT). On the other hand, LT seemed to be more effective than NGT in a recent Asian trial. Moreover, some studies have reported that administration of water-soluble contrast, gastrografin, thorough NGT (NGT-G) is useful for determining indication of surgical treatment and it is more effective treatment than NGT alone. However, there have been no comparative studies between LT and NGT-G. We thus conducted a randomized controlled trial to evaluate the efficacy of NGT-G for patients with SBO.

Aims & Methods: In this multicenter, open label, randomized controlled trial, patients with SBO from 11 Japanese institutions were randomly assigned by a computer-based randomization to receive LT or NGT-G between July 2016 and November 2018. Patients who assigned to the NGT-G group could receive LT placement appropriately, when SBO is not improved over 24 h. The primary end point was non-inferiority of NGT-G to LT for non-surgery rate (treatment success rate). According to pre-planned protocol, efficacy analysis was on the basis of initially randomized group (intention-to-treat analysis). Based on the results of previous studies, we estimated 85% non-surgery rate of both groups, and 95.3% CI lower limit of -15% non-surgery rate would be accepted as a lower margin for inferiority with NGT-G to LT because the previous lowest success rate of LT was 70%. According to O'Brien Fleming type α spending rule, 1 sided α levels of 0.0015 and 0.0235 were defined for the interim and final analysis, respectively. Hence, pre-planned sample size was 220 overall 1-sided-α and β errors of 0.025 and 0.20, and allowing an approximate 10% dropout rate.

Results: In total, 224 patients with SBO were enrolled to this trial and 223 patients after exclusion of 1 consent withdrawal were finally analyzed including 111 patients in the LT group and 110 patients in the NGT-G group. Baseline characteristics including laboratory data and physical findings were well balanced between 2 groups. The treatment success rate without non-surgical management was 87.4% in the LT group and 91.1% in the NGT-G group, and difference between LT and NGT-G was 3.7% (95.3% CI; -5.55 to 12.91; non-inferiority *P*= 0.00002923). Among 112 patients in the NGT-G group, 86 patients improved by NGT-G alone (86.7%), 16 patients did by NGT-G followed by LT and 10 patients underwent surgery. Non-surgery rate of NGT-G alone was significantly lower than LT (*P*=0.039).

Expectedly, median insertion time was much shorter in the NGT-G group than in the LT group (1 min vs. 25 min; *P*= 0.0001). No significant differences were found for relief time of abdominal symptoms and duration of hospitalization between 2 groups. In the LT and NGT-G arms, adverse event rates ≥ grade 3 were 1.8% and 0% (*P*=0.247) and the mortality rates were 0.91% and 0% (*P*=0.498), respectively.

Conclusion: NGT-G is an effective alternative to LT as the first-line treatment for SBO. Sequential strategy, NGT-G followed by LT, would be a novel standard treatment for SBO.

(University Hospital Medical Network Clinical Trials Registry, Number: UMIN000022669)

Disclosure: Nothing to disclose

OP243 ENDOSCOPIC ULTRASOUND VS PERCUTANEOUS MANAGEMENT OF POST-OPERATIVE PANCREATIC FISTULA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Post-operative pancreatic fistula (POPF) is a difficult to manage complication with significant morbidity and mortality. Mortality rates as high as 40% have been reported. Surgical and percutaneous drainage (PCD) are the usual first line of treatment. Studies have reported endoscopic ultrasound and/or standard endoscopy (END) guided management of POPF with conflicting results. Data comparing the outcomes of END vs PCD in POPF management is limited.

Aims & Methods: We conducted a comprehensive search of multiple electronic databases and conference proceedings (earliest inception through September 2018) to identify studies that reported on the clinical outcomes of END and PCD in the management of POPF. Our goal was to estimate and compare the pooled rates of technical success, clinical success, adverse events and POPF recurrence with END and PCD. The collected data was matched between the END and PCD management groups. The baseline patient characteristics, symptomatology, indication for surgery, time-to-drain placement, and the number of drains used were comparable between the groups. Meta-analysis was conducted using the comprehensive meta-analysis software.

Results: 4 studies (99 patients) reported outcomes with EUS and/or endoscopy (END) in POPF management, and 4 studies (225 patients) reported outcomes with PCD in POPF management.1.
Technical success: The pooled rate of technical success in END-POPF was 97.6% (95% CI 88.4-99.5, I²=0) and in PCD-POPF was 95.2% (95% CI 84.1-98.7, I²=63.4%). The difference was not statistically significant, p=0.52.2.
Clinical success: The pooled rate of clinical success in END-POPF was 90.8% (95% CI 82.3-95.5, I²=0%) and in PCD-POPF was 78.0% (95% CI 70.5-84.0, I²=0%). The difference was statistically significant, p=0.02.3.
Adverse events: There were a total of 2 adverse events and 7 recurrences in END-POPF group, and a total of 8 adverse events and 17 recurrences in PCD-POPF group.The pooled rate of adverse events in END-POPF was 4.9% (95% CI 1.7-13.1, I²=0%) and PCD-POPF was 5.9% (95% CI 3.4-10.0, I²=0%). There was no statistical significance to the difference, p=0.74. Data was insufficient to calculate pooled rates of recurrence in the groups.

POPF (95% CI, I2)	EUS/END	PCD	P-value
Technical Success	97.6% (88.4-99.5, 0)	95.2% (84.1-98.7, 63.4)	0.52
Clinical Success	90.8% (82.3-95.5, 0)	78% (70.5-84, 42.5)	0.02
Adverse Events	4.9% (1.7-13.1, 0)	5.9% (3.4-10, 0)	0.74

[Summary of pooled results. POPF(pancreatic post-operative fistula), EUS(endosonography), END (endoscopy) PCD (percutaneous drainage)]

Conclusion: Our meta-analysis shows that endoscopic ultrasound and/or standard endoscopy guided management of POPF gives significantly better clinical success as compared to PCD. Use of standard endoscopy in the management of pancreatic fistula is outdated. Well-conducted direct-comparison studies are needed evaluating endoscopic ultrasound to PCD in the treatment of POPF. Indirect comparison, variability in the type of stents used, variability in the number of repeat procedures, and heterogeneity were the limitations of our study.

Disclosure: Nothing to disclose

Duodenal flat mucosa: Coeliac and beyond
16:00-17:30 / A2

OP244 USE OF MICRO-CT IMAGING OF INTESTINAL BIOPSIES TO IMPROVE THE DIAGNOSTICS OF CELIAC DISEASE

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Introduction: Traditional histopathology is too inaccurate for early stage mucosal injury and short-term challenge studies in celiac disease, and the often misoriented biopsies are prone to wrong interpretation. X-ray microtomography (micro-CT) is an imaging technique which could provide freely orientable 3D images for accurate measurements of mucosal morphometry and surface areas. We investigated the use of micro-CT in the examination of small-bowel biopsies.

Aims & Methods: Duodenal samples from 12 endoscopies were selected for the micro-CT imaging. The specimens represented celiac disease patients with different stages of injury and nondiagnosed subjects with morphologically normal mucosa. The micro-CT procedure was tested with variable staining solutions, source voltages and filters to optimize the practicability and resolution. The data were reconstructed into digital 3D images and virtually cut for measurement of villous length crypt depth ratios. Mucosal surface areas were measured utilizing computer-assisted point cloud analysis. The results were compared with routine histopathology and quantitative histomorphometry performed with paraffin-embedded biopsies.

Results: Practical staining and imaging protocol with optimal resolution was accomplished using specific I$_2$E-solution, 100 kV acceleration voltage and 10W source power. Micro-CT imaging was feasible both for previously taken paraffin biopsies and fresh biopsies. It was also possible to do routine histopathology after the imaging. The formed 3D images allowed freely orientable digital images for exact morphometry and demonstrated duodenal injury in samples interpreted as normal in traditional histology. Furthermore, micro-CT enabled reproducible measurements of the mucosal surface areas, which makes it possible to detect previously indistinguishable differences between samples e.g. minor changes during gluten-free diet.

Conclusion: We established a unique micro-CT method for digital analysis of duodenal biopsies. The improved diagnostic accuracy and possibility to measure biologically meaningful surface areas provide a powerful tool for future clinical and pharmaceutical studies.

Disclosure: Nothing to disclose

OP245 DIAGNOSTIC ACCURACY OF THE COELIAC INTRAEPITHELIAL LYMPHOGRAM ASSESSED BY FLOW CYTOMETRY FOR COELIAC DISEASE (CD) DIAGNOSIS IN PATIENTS WITH SERONEGATIVE VILLOUS ATROPHY (SNVA)

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Introduction: Causes of SNVA can be grouped as CD- and non-CD related. Despite several sets of international guidelines on CD, there is no consensus on how to approach subjects with seronegative CD. Coeliac lymphogram has been advocated as a useful tool in doubtful CD cases.

Aims & Methods: To evaluate the accuracy of the increase in $CD3^+$ T-cell receptor gamma delta$^+$ (TCRγδ) intraepithelial lymphocytes (IEL), with or without the concomitant decrease of $CD3^-$ IEL, in samples of duodenal mucosa for the diagnosis of CD in patients with SNVA.

Seventy-four consecutive patients with SNVA were included (45.3±2.5 years; 67% women). Serum anti-TG2 was negative in all cases. In all of them, duodenal biopsies to assess TCRγδ$^+$ and $CD3^-$ IEL by flow cytometry were obtained at the index endoscopy. The increase in TCRγδ$^+$ *plus* decrease in $CD3^-$ IEL defined the coeliac lymphogram. CD was diagnosed on the basis of a clinical and histological remission after a GFD. Sensitivity (S), specificity (Sp), positive and negative likelihood ratios (LR) were calculated. Values of +LR >10 and -LR < 0.10 were associated with a convincing diagnostic evidence.

Results: CD was diagnosed in 46 patients, and non-coeliac SNVA in 28. Non-coeliac causes of SNVA were: olmesartan (8), giardiasis (4), Crohn's disease (2), other enteropathies (6), and idiopathic (8). CD patients were younger (39±3 vs. 55±3 yrs; p=0.001), more often showed HLA-DQ2/8 (97.6% vs. 61%; p=0.002), and had a more severe histology (61% vs. 32% Marsh 3b-c; p=0.056), as compared to non-coeliac SNVA. Coeliac lymphogram was associated with a S of 87% (95% CI, 73-95), Sp of 96.4% (CI, 80-100), +LR of 24.3 (CI, 3.5-167) and -LR of 0.13 (CI, 0.06-0.28). Evaluating only TCRγδ$^+$ yielded a S of 91% (CI, 78-97), Sp of 86% (CI, 66-95), +LR of 6.4 (CI, 2.6-16) and -LR of 0.10 (0.04-0.26). Two olmesartan enteropathies and 1 giardiasis had an isolated increase in TCRγδ$^+$ and another olmesartan enteropathy presented with the coeliac lymphogram.

Conclusion: The coeliac lymphogram assessed by flow cytometry in duodenal biopsy samples was associated with a high level of diagnostic evidence either against or in favour of CD in patients with SNVA.

Disclosure: Nothing to disclose

Trends in treatment and detection of upper GI bleeding
16:00-17:30 / B2

OP246 OUTCOMES OF UPPER GASTROINTESTINAL BLEEDING ARE SIMILAR BETWEEN DIRECT ORAL ANTICOAGULANTS AND VITAMIN K ANTAGONISTS: A SUB-GROUP ANALYSIS OF A FRENCH PROSPECTIVE MULTICENTER STUDY

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Introduction: Management of oral anticoagulants remains challenging during upper gastrointestinal bleeding (UGIB). Outcomes of UGIB are not worse in patients treated with vitamin K antagonists (VKA) but a reversion of the anticoagulation can be easily done contrary to direct oral anticoagulants (DOACs) (1). DOACs belong to a new therapeutic class with conflicting results on the associated risk of UGIB that might be increased (2). Later studies showed a different bleeding risk according to the type of DOACs (3,4), but data are mostly retrospective with a low level of evidence. This study aimed to describe epidemiology, endoscopic management and outcomes of UGIB in patients treated with anticoagulants.

Aims & Methods: From November 2017 to October 2018 a prospective multicenter study in French general hospitals enrolled all consecutive patients with UGIB. Data were collected with an e-CRF. All patients treated with an anticoagulant at the time of the UGIB were retrieved from the cohort and assessed. Main outcomes were mortality at 6 weeks, rebleeding during the first 6 weeks and need for non-endoscopic treatment (surgery, radio-embolisation).

Results: Among the 2498 patients included, 475 (19%) had an oral anticoagulant: 267 (56.2%) with VKA (Warfarin 67 (25%), Fluindione 200 (75%)) and 208 (43.8%) had DOACs (Dabigatran 21 (10%), Rivaroxaban 114 (55%), Apixaban 73 (35%)). This subgroup of patients consisted of 65% men, mean age was 78.2 and mean Charlson score was 3.2. Aspirin was ongoing for 100 patients (21%), and 55 (11.6%) had other antiplatelets agent (APA). Baseline characteristics were broadly similar between VKA and DOACs except for the association of kidney failure and cirrhosis. Gastroscopy was performed in 470 patients (98.9%), described as normal in 73 (15.3%) and showed active bleeding in 117 (24.9%). The aetiology of UGIB was peptic for 289 (60.8%) patients, portal hypertension for 43 (9%), vascular and tumoral for 41 (8.6%) and 27 (5.7%), respectively, without difference between VKA and DOACs. Endoscopic treatment was performed in 128 (26.9%) patients; bleeding resolution was possible in 95 (20%). The mortality rate at 6 weeks was 12.4% (59 patients) (VKA 16.1%, DOACs 7.8%, p< 0,01). Factors associated with mortality by univariate analysis were Charlson index ≥5, anticoagulation by VKA, presence of shock at admis-

sion, peptic lesion in endoscopy, Rockall Score >2 and Blatchford ≥14; only Charlson index remained significant in the multivariate analysis (OR 4.14, p< 0.0001). Re-bleeding happened in 56 patients (11.8%) (VKA 30 (11.2%/), DOACs 26 (12.5%), p=0.71). By multivariate analysis: co-medication with APA was associated with a higher risk (OR 2.72, p=0,009) whereas beta-blockers were protective (OR=0.41, p=0,0072). Non-endoscopic treatment was performed in 18 (3.8%) patients (VKA 10 (2.1%), DOACs 8 (1.6%) p=0.95).Tumoral origin of the bleeding was the only factor associated by multivariate analysis (OR=6.66, p=0.0064).

Conclusion: DOACs do not alter outcomes of UGIB as compared to VKA. Comorbidities and associated treatment seem to be the most important factors worsening prognosis of UGIB.

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Disclosure: Nothing to disclose

OP247 OUTCOMES ON THE USE OF HEMOSPRAY IN UPPER GASTROINTESTINAL BLEEDS SECONDARY TO TUMOURS: OUTCOMES FROM THE MULTICENTRE INTERNATIONAL HEMOSPRAY REGISTRY

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Introduction: Upper gastrointestinal bleeding (UGIB) is a leading cause of morbidity with a 7% mortality in the United Kingdom (UK). Upper GI tumours account for 2-4% of UGI bleeds. These patients are often challenging to treat due to the diffuse nature of the neoplastic bleeding lesions, high bleeding recurrence rates and the significant transfusion requirements with a resultant poor quality of life. Hemospray (Cook Medical, North Carolina, USA) is a novel haemostatic powder for GI bleeding.

The primary aim was to look at the outcomes of all UGIBs secondary to tumoural bleeding who had Hemospray therapy in 14 centres worldwide.

Aims & Methods: Data was prospectively collected on the use of hemospray from specialist centres in the UK, France, Germany and the USA (Jan'16-March'19). Hemospray was used during emergency endoscopy for UGIBs secondary to upper GI tumours at the discretion of the endoscopist as a monotherapy, dual-therapy with standard haemostatic techniques or rescue therapy once standard methods have failed. Haemostasis was defined as the cessation of bleeding within 5 minutes of the application of hemospray. Rebleeding was defined as a sustained drop in Hb (>2g/l), haematemesis or melaena with haemodynamic instability after the index endoscopy.

Results: 84 patients with UGIB secondary to tumours of the GI tract were recruited (57 males, 27 females, 24/84 (29%) oesophageal, 56/84 (67%) gastric, 4/84 (5%) doudenal). The median Blatchford score at baseline for all patients was 10 (IQR, 7-12). The median rockall score was 8 (IQR,7-9). The median size of lesions was 25mm (IQR, 11-40mm).

Immediate haemostasis was achieved in 81/84 **(96%)** of patients, 11/70 (16%) patients had a rebleed, 2/73 (3%) patients died within 7 days, 14/73 (19%) patients died within 30 days (all-cause mortality). Based on the baseline average total rockall score, the expected rebleed rate is 25-40%, and expected mortality rate was 40-45% in our cohort.

Haemostasis was achieved in 51/51 (100%) patients in the hemospray monotherapy group, 16/19 (84%) patients in the combination therapy group and 8/8 (100%) of patients in the rescue therapy group (Table 1).

	Monotherapy (n=57)	Combination therapy (n=19)	Rescue therapy (n=8)
Haemostasis	57/57 (100%)	16/19 (84%)	8/8 (100%)
Median Rockall score	8 (IQR,7-9)	8 (IQR, 7-9)	7 (IQR, 5-8)
Median Blatchford score	10 (IQR, 7-12)	9 (IQR, 7-15)	11 (IQR, 10-13)
Rockall 7 and 8: Predicted re-bleed rate: 25-40%			
Re-bleed	7/49 (14%)	3/13 (23%)	1/8 (13%)
Rockall 7 predicted mortality rate: 20-30%, Rockall 8 predicted mortality rate: 40-45%			
7-day mortality	2/49 (4%)	0	0
30-day mortality	10/49 (20%)	4/16 (25%)	0

[Outcomes in the different hemospray subgroups]

100% (4/4) haemostasis was achieved in the duodenal tumour cohort, 98% (55/56) in the gastric cohort and 92% (22/24) haemostasis in the oesophageal tumour group. The highest rebleed rate was in duodenal tumours, 1/4 (25%), and highest all cause 30-day mortality in the oesophageal tumour group, 7/20 (35%).

Conclusion: Hemospray is an effective endoscopic tool for achieving immediate haemostasis in UGIBs secondary to upper GI tumours, which are generally considered difficult bleeds to treat, with 100% haemostasis levels and lowest re-bleed levels in the monotherapy group.

When considering average rockall score the rebleed and mortality rate is better than predicted rates. Haemostasis is achieved in the majority allowing for patient stabilization and thereby providing time for patients to have urgent surgery or radiotherapy to treat the underlying tumour.

Disclosure: Nothing to disclose

OP248 NOVEL HEMOSTATIC ADHESIVE POWDER APPLICATION IN NONVARICEAL UPPER GASTROINTESTINAL BLEEDING

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Introduction: A new hemostatic adhesive powder (UI-EWD) was developed to improve the high re-bleeding rate and technical challenge in application of current available hemostatic powders.

Aims & Methods: The aim of current study was to assess the performance of UI-EWD in nonvariceal upper gastrointestinal bleeding (NVUGIB).

A total of 56 consecutive patients receiving UI-EWD for endoscopic hemostasis in NVUGIB were retrospectively reviewed. UI-EWD was used as a monotherapy. The main outcomes were success rate of immediate hemostasis and rate of re-bleeding within 30 days. Outcomes were analyzed by reviewing patient medical records.

Results: The etiology of bleeding was post-endoscopic therapy bleeding in 46 (82.1%), peptic ulcer in 8 (14.3%), tumor in 1 (1.8%) and other in 1 (1.8%). The UI-EWD was successfully applied at bleeding site in all

cases. The success rate of immediate hemostasis was 96.4% (54/56). Re-bleeding within 30 days occurred in 2/54 (3.7%) of patients who achieved immediate hemostasis. The adverse event related to use of UI-EWD was not occurred.

Conclusion: UI-EWD had a high success rate for immediate hemostasis in NVUGIB when used as monotherapy and showed promising result in prevention of re-bleeding.

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Disclosure: Nothing to disclose

OP249 RANDOMISED CONTROLLED TRIAL OF EARLY CAPSULE ENDOSCOPY VERSUS COLONOSCOPY FOLLOWING NEGATIVE GASTROSCOPY IN ACUTE GASTRO-INTESTINAL BLEEDING

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Introduction: A proportion of patients with suspected acute upper gastrointestinal bleed (UGIB) characterised by malaena or malaena and haematemsis, have a negative initial gastroscopy. The traditional approach is to perform colonoscopy as the second investigation, however diagnostic yield is low.[1,2] Small bowel bleeding is likely in this cohort. Capsule endoscopy can safely and effectively visualise small bowel bleeding with high sensitivity in the acute setting.[3,4] The aim of this study is to investigate whether capsule endoscopy is superior to colonoscopy as a second investigation in patients with suspected UGIB but negative initial gastroscopy.

Aims & Methods: This is a single centre randomised control trial, which commenced in June 2017. Local ethics approval was obtained (ID 31035). Informed consent was obtained from all patients. All patients admitted to our hospital with acute bleeding as defined above but with negative gastroscopy were considered for the study. Patients who consented for the study were then randomised to either capsule endoscopy or colonoscopy as the second investigation. If the test was not diagnostic, the patient underwent the other investigation or other interventions as clinically required. Our primary outcome was the diagnostic yield of each modality. Secondary outcomes measured were length of stay, transfusion requirements and number of diagnostic tests required. We also recorded baseline patient characteristics.

Results: 20 patients have been randomised to date, 12 males and eight females. Mean age was 69 years and baseline patient characteristics were similar in both groups. 11 patients received capsule endoscopy and nine patients received colonoscopy as the second investigation after negative gastroscopy. Diagnostic yield was 91% in the capsule endoscopy arm and 22% in the colonoscopy arm. Six out of nine patients in the colonoscopy group underwent subsequent capsule endoscopy, which was normal in four cases and in the other two revealed mid small bowel angioectasia and a jejunal diverticulum. Table 1 highlights secondary outcome data. 12-month data was available for four patients from the colonoscopy group and four patients from the capsule group. One patient from each group was readmitted to hospital with recurrent GI bleeding, though neither required further investigation. Regrading complications in our cohort, one patient had capsule retention without obstruction due to strictures. Two had incomplete capsule studies with capsule passing within 48 hours. One diagnosed a gastrointestinal stromal tumour in the gastric antrum and the second temporarily retained in a small bowel diverticulum.

Conclusion: Data from our study suggests capsule endoscopy has a significantly higher diagnostic yield than colonoscopy in patients with suspected acute UGIB and negative gastroscopy. It is well established that an early capsule study is crucial in making a timely diagnosis of small bowel bleeding and allows early intervention. This is expected to decrease overall morbidity and mortality, particularly in the elderly and those with co-morbidities in whom capsule endoscopy is well tolerated. To our knowledge, this is the first randomised controlled trial in this context.

Outcome	Capsule endoscopy (n=11)	Colonoscopy (n=9)
Packed Red Blood Cells (n), Mean (SD)	2.0 (2.4)	2.9 (3.1)
Length of stay (days), Mean (SD)	8.7 (3.9)	8.3 (2.7)
Number of other investigations required, Mean (SD)	1.2 (0.4)	0.9 (0.6)

[Table 1. Secondary Outcomes]

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Disclosure: Nothing to disclose

OP250 ARTIFICIAL INTELLIGENCE USING A CONVOLUTIONAL NEURAL NETWORK FOR AUTOMATIC DETECTION OF SMALL-BOWEL ANGIOECTASIA IN CAPSULE ENDOSCOPY IMAGES

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Introduction: Although small-bowel angioectasia is frequently diagnosed via capsule endoscopy (CE) in patients with obscure gastrointestinal bleeding, a computer-aided detection method has not been established. We aimed to construct an artificial intelligence system with deep learning that can automatically detect angioectasia in CE images.

Aims & Methods: We retrospectively examined 169 patients (training image set: 141 patients, validation image set: 28 patients) with small-bowel angioectasia diagnosed via CE and 20 patients with no abnormal findings on CE at Hiroshima University Hospital, the University of Tokyo, and Sendai Kousei Hospital. CE was performed using a Pillcam™SB2 or SB3 CE device (Covidien Japan Inc., Tokyo, Japan). We trained a deep convolutional neural network (CNN) system based on Single Shot Multibox Detector, using 2,237 CE images of angioectasia. For a validation image set, 10,488 independent images were prepared. Of these, 488 images showed angioectasia in the small-bowel, and 10,000 images showed normal mucosa in the small-bowel. We manually annotated all of angioectasia with rectangular bounding boxes in the validation set. The trained CNN also shaped the region of angioectasia with rectangular bounding boxes in the validation set and outputted the probability score of angioectasia (range, 0-1). We evaluated the ability of CNN to discriminate between whether each image included angioectasia or not using the probability score. In addition, we evaluated the ability of CNN to identify angioectasia correctly. The receiver operating characteristic (ROC) curve was plotted by varying the threshold of the probability score, and the area under the curve (AUC) was calculated for assessing the discrimination. The sensitivity, specificity, positive predictive value, and negative predictive value of CNN's ability to detect angioectasia were calculated, using cut-off values for the probability score according to the Youden index.

Results: The AUC of CNN used to detect angioectasia was 0.999. The cut-off value for the probability score was 0.36. At this cut-off value, the sensitivity, specificity, positive predictive value, and negative predictive value of

CNN were 98.8%, 99.1%, 84.3%, and 99.9%, respectively. The sensitivities of CNN for angioectasia Type 1a and Type 1b were 83.3% (15/18) and 99.4% (467/470). The detectability of small-bowel angioectasia Type 1b by CNN is significantly higher than the detectability of type 1a ($P<$ 0.001). False-negative images (n=6) were classified into two categories based on the cause of the false-negative read: poorly focused (67%, 4/6) and laterality or partialness (33%, 2/6). On the other hand, false-positive images (n=90) were classified into five categories based on the reason as follows: vascular dilation of normal mucosa (40%, 36/90), foam (30%, 27/90), fold (18%, 16/90), debris (9%, 8/90), and normal mucosa (3%, 3/90). The trained CNN required 323 seconds to evaluate the images, with an average speed of 32.5 images per second. The correct discrimination rate was 83.3% (15/18) in Type 1a and 98.9% (465/470) in Type 1b. The cause of incorrect discrimination for angioectasia was bleeding from angioectasia Type 1b. The correct discrimination rate for small-bowel angioectasia Type 1b by CNN is significantly higher than the detectability of Type 1a (P=0.002).
Conclusion: We developed and validated a new system based on CNN to automatically detect angioectasia in CE images. This may be the crucial step for a daily-use diagnostic software for CE images to reduce the burden on the physicians and oversight.
Disclosure: Nothing to disclose

OP251 CLINICAL PERFORMANCE OF A NEW SOFTWARE TO AUTOMATICALLY DETECT ANGIOECTASIAS IN SMALL BOWEL CAPSULE ENDOSCOPY

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Introduction: Video Capsule Endoscopy (VCE) revolutionized the diagnosis and management of obscure gastrointestinal bleeding, though the rate of detection of small bowel lesions by the physician is still disappointing. Our group developed a novel algorithm (CMEMS-Uminho[1]) to automatically detect angioectasias which display greater accuracy in VCE static frames than other methods previously published.
Aims & Methods: We aimed to evaluate the algorithm overall performance and assess its diagnostic yield and usability in clinical practice. Algorithm overall performance was determined using 54 full-length VCE recordings. To assess its diagnostic yield and usability in clinical practice, 38 VCE examinations with the clinical diagnosis of angioectasias consecutively performed (2017-2018) were evaluated by three physicians with different experiences. CMEMS-Uminho algorithm was also applied. The performance of CMEMS-Uminho algorithm was defined by a positive concordance between a frame automatically selected by the software and a study independent capsule endoscopist.
Results: Overall performance in complete VCE recordings was 77,7% and diagnostic yield was 94,7%. There were significant differences between physicians in regard to global detection rate (p< 0,001), detection rate per capsule (p< 0,001), diagnostic yield (p=0,007), true positive rate (p< 0,001), time (p< 0,001) and speed viewing (p< 0,001). The application of CMEMS-Uminho algorithm significantly enhanced all readers' global detection rate (p< 0,001) and the differences between them were no longer observed.
Conclusion: CMEMS-Uminho algorithm detained a good overall performance and was able to enhance physicians' performance, suggesting a potential usability of this tool in clinical practice.
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Cirrhosis and liver cancer
16:00-17:30 / B3

OP252 LONG-TERM EVOLUTION OF HEPATOCELLULAR ADENOMAS AT MR IMAGING FOLLOW-UP

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Introduction: Hepatocellular adenomas (HCAs) are rare benign liver tumors. Guidelines recommend continued surveillance for patients diagnosed with HCAs, but these recommendations are mainly based on small series or experts' opinion. The aims of this study were to analyze the long-term course of evolution of HCAs including solitary and multiple lesions, and to identify predictive features of progression.
Aims & Methods: We retrospectively included consecutive patients with pathology-proven (i.e., biopsy or surgery) and subtyped solitary and multiple HCAs between January 2004 and December 2015. Exclusion criteria were:
(a) preoperative or follow-up MR imaging was not available;
(b) patients treated with locoregional therapies or transplantation, and lack of pretreatment MR imaging follow-up;
(c) inadequate MR imaging protocol.
Reference standard was pathologic analysis. For each patient the following information were assessed:
(a) aspect of non tumoral liver;
(b) subtype of HCA according to the updated classification published by Nault J et al;
(c) hemorrhage and malignant foci within the lesion.
All MR exams performed by each patient were analyzed by two radiologists with expertise on liver imaging.
Tumor evolution was evaluated using the Response Evaluation Criteria in Solid Tumors (RECISTv1.1) thresholds.
Results: Our final study population consisted of 118 patients (mean age, 40 ± 10 years; range 18-69 years, 10 men and 108 women), including 41 patients with a solitary HCA and 77 patients with multiple HCAs.
In 44 HCAs with micro- and/or macroscopic hemorrhage detected at pathology, 26 were inflammatory, 8 were HNF-1α inactivated, 5 were sonic-hedgehog, 4 were ß-catenin mutated exon 3 and 1 was ß-catenin mutated exon 7-8. Malignancy was detected among ß-catenin mutated HCAs in five patients with ß-catenin mutation -four with ß-catenin mutation in exon 3 and one with ß-catenin mutated in exon 7-8 HCA -, and two patients with inflammatory HCAs.
Median follow-up of the entire study population was 5.0 years, and it was not significantly different between the solitary and multiple HCAs cohorts (5.1 years vs. 4.9 years, respectively, p= 0.624).
Overall, 37 of 41(90%) patients with solitary HCAs and 55 of 77 (71%) patients with multiple HCAs showed stable or regressive disease (i.e. >30% size decrease). After resection of solitary HCAs, new lesions appeared only in 2 of 29 (7%) patients, both with HCAs at-risk of malignancy (i.e. ß-catenin mutated HCAs or foci of malignancy within the tumor).
Patients with multiple HNF-1α inactivated HCAs showed a higher rate of progression compared to patients with multiple inflammatory HCAs (11 of 26 [42.3%] vs. 7 of 37 [18.9%], p= 0.043).
Patients with progressive disease had a lower weight and BMI at diagnosis. Of note, neither surgery nor presence of ß-catenin mutated subtype had an impact on progression (p= 1.000, p= 0.667), while presence of multiple HCAs was associated with higher probability of progressive disease compared to solitary HCAs (22/77 [28.6%] vs. 4/41 [10.8%], respectively; p= 0.020). However, the number of lesions at diagnosis in patients with multiple HCAs was not significantly associated with progressive disease (p= 0.541).
Conclusion: Seventy-eight percent of HCAs showed long-term stability or regression. After resection of solitary HCAs, tumor progression occurred only in HCAs at-risk of malignancy. Patients with multiple HCAs were more

likely to show progressive disease, with HNF-1α inactivated HCAs being the most common subtype showing progression.

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Disclosure: None related to this study Dominique Valla discloses the following not related to this study: Laboratoire Servier : "Liver safety committee for Agomelatine"

OP253 HEPATOCYTE-SPECIFIC DELETION OF MTOR ACCELERATES LIVER TUMOR GROWTH

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Introduction: The mTOR protein is an essential component of mTORC1 and mTORC2, two multi-protein complexes of central importance for the regulation of cell proliferation, metabolism and autophagy. Activation of the mTOR pathway is frequently found in cancer, resulting in the notion that targeting mTOR represents a useful approach for cancer therapy. Of note, mTOR inhibitors have thus far failed to demonstrate significant antiproliferative efficacy in the majority of cancer types. It is therefore of pivotal importance to better understand the functional significance of the mTOR protein for the pathogenesis of cancer.

Aims & Methods: We sought to characterize the cell type-specific role of mTOR for the pathogenesis of primary and secondary liver tumors. To this end, we established a liver epithelial cell (LEC)-specific knock-out (KO) of mTOR via the Cre/loxP-system (termed mTOR^{LEC} mice). We characterized the growth of primary (non-alcoholic steatohepatitis-associated hepatocellular carcinoma (NASH-HCC)) and secondary (colorectal cancer liver metastasis (CRC-LM)) liver tumors in mTOR^{LEC} mice compared to wildtype controls.

Results: mTOR^{LEC} mice were viable and developed normally, arguing for a non-essential role of mTOR in LECs for hepatic development. Strikingly, tumor nodules in both the NASH-HCC as well as the CRC-LM model were significantly larger in mTOR^{LEC} mice compared to controls. As both primary and secondary liver tumors were affected, we hypothesized that the KO of mTOR in LECs resulted in the formation of a pro-tumorigenic microenvironment in the liver. To further analyze this, we determined the expression of pro-inflammatory genes in WT versus KO livers. While the expression of COX-2, HIF-1a, TNF-a and IL-6 was not affected, IL-1b gene expression was found to be significantly higher in the livers of mTOR^{LEC} mice. Furthermore, mTOR^{LEC} mice displayed periportal leukocyte accumulation that was absent in livers from wildtype mice. The functional relevance of this finding for the accelerated liver tumor formation in mTOR^{LEC} mice is currently being evaluated by us.

Conclusion: We show an unexpected acceleration of liver tumor growth upon functional deletion of mTOR specifically in liver epithelial cells. These results argue against the widely accepted perception of mTOR as an eligible target for cancer therapy. Our results add a further layer of complexity to the biology of mTOR and suggest that cell and tissue type-specific factors need to be considered in order to comprehend the complexity of mTOR.

Disclosure: The authors declare no competing interests

OP254 MIR-21 IS INCREASED IN EXPERIMENTAL AND HUMAN NASH-ASSOCIATED HCC, CONTRIBUTING TO HEPATOCARCINOGENESIS

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Introduction: The molecular mechanisms governing the progression of non-alcoholic steatohepatitis (NASH) towards hepatocellular carcinoma (HCC) remains elusive. We have recently shown that concomitant miR-NA-21 (miR-21) ablation and farnesoid X receptor (FXR) activation prevents NASH development in mice.

Aims & Methods: Here, we aimed to evaluate the role of miR-21 in NASH-associated carcinogenesis. miR-21 expression was evaluated in two independent cohorts of patients. In the San Sebastian cohort (n=160), RNA was isolated from formalin-fixed, parafin-embbeded liver biopsies obtained from obese patients. miR-21 expression was measured by qPCR and correlated with histopathological and serological findings. In the TCGA cohort, miR-21 expression was evaluated by miRNA sequencing (miRseq) using liver samples from patients with NASH-associated HCC obtained after surgical resection (n=19) and compared with surrounding liver tissue (n=50). In parallel, wild-type (WT) and miR-21 KO C57BL/6N mice were fed either a choline-sufficient, amino acid-defined control diet (CSAA; n=28) or a choline-deficient, amino acid-defined diet (CDAA; n=28) for 32 and 66 weeks. Serum was collected for biochemical analyses and liver samples processed for histological analysis and measurement of miR-21, its targets and metabolic relevant genes, as well as pro-inflammatory/pro-fibrogenic cytokines. A profiler PCR array was used to evaluate the expression of liver cancer-related genes.

Results: miR-21 levels were increased with disease severity (steatosis, lobular inflammation, ballooning, fibrosis and NAS score) while no correlation with serum data was observed in the San Sebastian cohort. Noteworthy, miR-21 levels were markedly increased in the tumor tissue of patients with NASH-HCC, when compared with surrounding liver in the TCGA cohort. WT mice fed the CDAA diet for 32 weeks developed macrovesicular steatosis, hepatocyte ballooning, NASH and fibrosis, concomitantly with accumulation of perivascular lymphoid cells and macrophage agglomerates. CDAA-fed miR-21 KO mice exhibited increased activation of PPARalpha target genes, augmented mitochondrial activity and decreased fatty acid serum levels, compared with WT mice. After 66 weeks, all WT mice on the CDAA diet developed at least one preneoplastic nodule (~5.2 nodules/animal), with one animal developing trabecular HCC. miR-21 expression was increased in CDAA-fed mice and further increased in HCC, concomitantly with decreased expression of its targets (PTEN, PDCD4, CDK2AP1 and PPARalpha). In addition, livers presented with mitochondrial dysfunction, hyperplastic foci and anisokaryosis, as well as phenotypically altered and highly proliferative (Ki-67 positive) hepatocytes. Increased levels of pro-inflammatory/fibrogenic markers were particularlly evident in pre-neoplastic liver tissues, alongside higher activation of oncogenic pathways.

Strikingly, CDAA-fed miR-21 KO mice for 66 weeks displayed serum ALT levels similar to control animals and, compared with CDAA WT-fed mice, the NAS score (< 5); number of liver nodules (~2.3 nodules/animal); hepatocyte profliferation and expression of oncogenes were all significantly reduced, with the pro-inflammatory/fibrogenic milleau reversed to almost baseline controls.

Conclusion: Overall, activation of the miR-21 pathway appears to contribute to NASH-associated carcinogenesis, with its inhibiton halting HCC development. Targeting miR-21 may constitute an appealing therapeutic approach to ameilorate NASH and its progression towards HCC. (PTDC/BIM-MEC/0895/2014, PTDC/MED-PAT/31882/2017, SFRH/BD/88212/2012, SAICTPAC/0019/2015 FCT, PT).

Disclosure: Nothing to disclose

OP255 GENOME-WIDE ASSOCIATION STUDY OF LIVER CORRECTED T1 MAGNETIC RESONANCE IMAGING IDENTIFIES A MISSENSE VARIANT IN SLC39A8 AND YIELDS NEW INSIGHTS INTO MECHANISMS UNDERLYING LIVER INFLAMMATION AND FIBROSIS

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Introduction: Steatohepatitis and subsequent fibrosis affect approximately one in ten middle-aged adults, and are progressive conditions which in turn may lead to cirrhosis, hepatocellular carcinoma and death.[1] The genetic background of steatohepatitis and fibrosis is unknown since liver biopsy is an invasive procedure with significant risks.

A promising, non-invasive proxy measure of liver inflammation and fibrosis is corrected T1 (cT1) magnetic resonance imaging (MRI). cT1 MRI measures are associated with histological liver fibrosis and liver disease outcomes. cT1 MRI has already been used as a non-invasive outcome in randomised controlled trials for NASH,[2] and is an established technique for the assessment of myocardial fibrosis.

Aims & Methods: In this study, we aimed to explore the genetic susceptibility underlying hepatic cT1 MRI measures as a proxy for underlying steatohepatitis and fibrosis.

We used data from the UK Biobank study which is a prospective study of 500,000 individuals recruited at age 40-69 years old across the UK. We derived cT1 measures from abdominal MRI scans in 2,501 unrelated participants. We divided our data into a discovery set of 2,289 white British individuals and a validation set of 212 European but not white-British individuals.

We performed a genome-wide association study (GWAS) in 2,289 white British individuals from UK Biobank using 11,977,111 imputed variants. We adjusted for age, sex, BMI and principal components. We performed a sensitivity analysis where we adjust for all the covariates except BMI. We validated the GWAS significant variants (p-value < 5×10^{-8}) in our validation set of 212 European but not white-British individuals.

Results: The GWAS of liver cT1 MRI measures in 2,289 unrelated individuals of white British ancestry identified one independent variant that reached GWAS significant threshold (rs13107325 in *SLC39A8*, p = 3.44×10^{-32}). The missense G > T variant (rs13107325) was associated with 0.67 standard deviations (SD) higher cT1 measures (95% confidence interval [0.56, 0.78]). In our validation set, the association between rs13107325 and cT1 measures was replicated (p = 0.002).

The same missense G > T variant has been shown previously to be associated with higher alcohol intake, higher blood pressure, higher body-mass index, lower brain grey matter volume, less diverse human microbiome composition, higher risk of schizophrenia and higher risk of Crohn's disease.[3-5]

Conclusion: We identified a highly significant, novel association between a G > T missense variant in *SLC39A8* and cT1 MRI liver measures, a non-invasive marker of fibrosis and inflammation, in an unselected, prospective, population-based cohort. Validation is required in larger independent cohorts.

SLC39A8 encodes ZIP8, a divalent cation importer capable of transporting zinc, iron, manganese and selinate, and is one of the most pleiotropic genes in the human genome. Hepatic ZIP8 deficiency in mice was previously associated with liver inflammation and fibrosis, as well as neoplastic changes consistent with hepatocellular carcinoma.[6]

Future studies are needed to determine whether interventions targeting pathways regulated by *SLC39A8* might be attractive therapeutic options to prevent liver disease in at risk individuals.

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Disclosure: RB and HW are shareholders in Perspectum Diagnostics. RB is an employer of Perspectum Diagnostics.

OP256 VOLUMETRIC-CT ASSESSMENT OF SARCOPENIA IN LIVER TRANSPLANT RECIPIENTS

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Introduction: Today, sarcopenia is widely considered as a factor influencing the prognosis in the liver transplant. Among the various available methods, the analysis of muscle mass on a single CT slice at L3 level is currently considered the gold standard for the diagnosis while other methods are currently a matter of investigation.

Aims & Methods: Our aim was to evaluate the prognostic role of sarcopenia assessed through the analysis of muscle mass of the whole abdomen by means of a volumetric-CT analysis.

We evaluated 101 pre-transplant CT scans (venous phase) of adult patients with cirrhosis who underwent LT between 01/01/2016 and 31/10/2018 at our centre. We measured the muscle volume of the abdomen, using a 3D method, from the iliac crests to the base of the heart, excluding visceral content by segmentation. Images were analyzed with Volume Viewer software (GE Medical Systems). Abdominal muscle volume was indexed by height squared (cm3/m2). The lower quartile of indexed muscle volume in the analyzed population was set as a cut-off for significantly reduced muscle mass. A Cox proportional regression-model was used for post-LT survival analysis.

Results: 80 subjects were male (79.2%). The mean age of the study population was 54.8 ± 10.3 years. The prevalent etiology was alcoholic liver cirrhosis (31.7%) followed by HCV (21.8%), cholestatic liver disease (11.9%) and HBV (10.9%). HCC was present in 41.6% of subjects. The mean MELD score was 16.8 ± 7.4. Volumetric cut-offs for lower quartile of indexed abdominal muscle volume were 583.7 cm3/m2 for women and 629.9 cm3/m2 for men. A statistically significant difference in post-LT survival was found using these cut-offs in the study population as an indicator of significant sarcopenia (HR 7; 95% CI 2.3-21.6, *p* = 0.001).

Conclusion: Muscle mass estimate assessed by volumetric analysis appear to be a reliable predictor of post-LT mortality. 3D analysis has the advantage of analyzing a wider portion of the body compared with the standard single-CT slice methods so providing a more reliable estimate of whole-body muscle mass. This method should be further investigated in larger cohorts to confirm its diagnostic performance compared with the standard bi-dimensional analysis.

Disclosure: Nothing to disclose

OP257 LIVER DISORDER DUE TO PD-1 INHIBITORS IN THE CLINICAL SETTING

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Introduction: Recently, cases in which immune checkpoint inhibitors are administered as a new option for the treatment of cancer have been increasing. They are known to lead to immune-related adverse events (hereafter referred to as 'irAEs'), but the actual state of liver disorders as irAEs in clinical settings are not clear. We studied the liver disorders in cases where Nivolumab and Pembrolizumab were administered in our hospital.

Aims & Methods: The subjects were 103 patients (male, 74; female, 29) who were given Nivolumab and/or Pembrolizumab from July 2015 to February 2019. Seventy patients were given Nivolumab (hereafter 'group N'), 31 patients were given Pembrolizumab (hereafter 'group P'), and 2 patients were given the two drugs separately (hereafter 'group NP'). Carcinomas studied were 65 cases of lung cancer, 7 cases of renal cancer, 6 cases of stomach cancer, 5 cases of malignant melanoma, and 20 cases of other cancers. We reviewed whether or not there was presence of liver disorder after the administration of the drugs, and on how they were managed after the liver disorder manifested.

Results: Liver disorder was found in 5 patients in group N (7.1%); 2 of them had grade 1, and 3 of them had grade 3. In the 2 patients with grade 1, Nivolumab was continued but the liver disorder remitted spontaneously. In 2 patients with grade 3, Nivolumab was discontinued and the liver disorder remitted. In the 1 patient with grade 3, mPSL was given with Nivolumab continued, but the liver disorder did not improve, but when Nivolumab was discontinued, the liver disorder improved. In group P, liver disorder was found in 3 patients (9.7%); 2 of them had grade 1 and 1 had grade 3.

In 1 patient with grade 1, Pembrolizumab was continued, but the liver disorder remitted spontaneously. In the other patient with grade 1, Pembrolizumab was discontinued because of another severe irAE, and with the administration of PSL 1mg/kg, the disorder remitted. As the patient with grade 3 did not remit rapidly after administering PSL 60mg (1mg/kg), mycophenolate mofetil (hereafter MMF) was added, with which the disorder remitted. After then, MMF was discontinued, and PSL was decreased to 10mg, after which the liver disorder relapsed. MMR 1g was resumed, and the liver disorder improved. Liver disorder was not found in the NP group. None of the 8 patients who developed liver disorder had history of autoimmune disease.

Conclusion: Among patients with mild liver disorder, there were many in whom administration of PD-1 inhibitors could be continued. In patients with severe liver disorder, discontinuation of the drugs was required in all of them, but all of them remitted by the discontinuation of the drug and administration of immunosuppressive agents. There were also patients whose liver disorder relapsed by a decrease in the dosage of the immunosuppressive agents.

Disclosure: Nothing to disclose

Intestinal epithelium in health and disease

16:00-17:30 / B5

OP258 DUODENAL MUCOSAL RESURFACING (DMR) COMBINED WITH GLP-1-RA MAY ELIMINATE INSULIN THERAPY AND IMPROVE METABOLIC HEALTH IN TYPE 2 DIABETES

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Introduction: Duodenal mucosal resurfacing (DMR) is an endoscopic intervention in which the duodenal mucosa is ablated by hydrothermal energy. DMR improves glycemic control in type 2 diabetes (T2D) through altered metabolic signaling from the duodenum causing insulin sensitization. We studied the feasibility of eliminating insulin therapy in T2D by combining DMR with GLP-1r agonism (liraglutide) and lifestyle counseling.

Aims & Methods: Single arm, single center study in 16 insulin treated T2D patients (HbA1c ≤64 mmol/mol; basal insulin < 1U/kg/day, c-peptide ≥0.5 nmol/l). Day 1, DMR is administered and insulin therapy discontinued. Day 14, liraglutide is introduced (titrated to 1.8 mg/day) and life style counseling is administered throughout. Primary endpoint: percentage of patients free of insulin and HbA1c ≤59 mmol/mol at 6 months.

Results: Enrolment has been completed (n=16) and 12 patients have reached 6 months with 10/12 (83%) insulin-free and able to maintain glycemic control (HbA1c -6.2 mmol/mol, p=0.002, FPG -2.5 mmol/l, p=0.086, AUC glucose MMT -916 mmol/l*min, p<0.001, iAUC glucose MMT -332 mmol/l*min, p< 0.001, peak glucose MMT -3.9 mmol/l, p<0.001), with

improvement across multiple metabolic parameters (weight -5.0 kg, p<0.001, BMI -2.4 kg/m², p<0.001, HOMA-IR -4.7, p=0.003, ALT -7.9 U/l, p=0.008, MRI-PDFF -44.2%, SBP -4.0 mmHg, p 0.344, DBP -2.0 mmHg, p=0.475)(Table 1).

Conclusion: Single endoscopic DMR, combined with liraglutide and lifestyle counseling, may effectively eliminate the need for insulin therapy in T2D while improving glucose regulation and overall metabolic health. This treatment approach is a promising alternative that appears to shift insulin-treated T2D patients to a state of better overall metabolic health.

Disclosure: Nothing to disclose

	Baseline (n=12)	6 months (n=10)*	p-value
Age	61 ± 8		
Daily insulin dose (IU)	37 ± 28	0	
Weight (kg)	96 ± 23	91 ± 22	<0.001
HbA1c (mmol/mol)	58.5 ± 5.4	52.3 ± 6.2	0.002
Insulin (pmol/l)	120 ± 60	64 ± 49	0.011
HOMA-IR	8.1 ± 4.4	3.4 ± 3	0.003
ALT (U/l)	25.9 ± 8.7	18 ± 4.8	0.008
MRI-PDFF % (change)†	8.5 ± 4.6	5.2 ± 3.2 (-44.2)	0.064

Data are mean ± standard deviation. Data represent measurements at baseline and 6 months after initiation of the combined approach of DMR (Duodenal Mucosal Resurfacing), liraglutide and lifestyle counselling instead of basal insulin. BMI: Body Mass Index, HbA1c: Glycated hemoglobin A1c, FPG: Fasting Plasma Glucose, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, AST: Aspartate Transaminase, ALT: Alanine Transaminase, ABPM: 24-hour ambulatory blood pressure monitoring, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MMT: Mixed Meal Test, AUC: Area under the curve, iAUC: Incremental area under the curve. P-values based on paired student's t-tests (n=10 vs. n=10). *Two subjects were excluded in whom insulin was reintroduced based on high HbA1c levels at 6 months. †Data at 6 months from 7 patients

[Table 1. Baseline characteristics and 6 months follow-up measurements]

OP259 DECREASED INTESTINAL ACETYLCHOLINESTERASE IN PATIENTS WITH DIABETES: AN *IN VIVO* STUDY WITH ¹¹C-DONEPEZIL PET/CT

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Introduction: Gastrointestinal (GI) neuropathy is a serious complication to diabetes mellitus (DM). Most intrinsic and extrinsic neurons controlling GI motility are cholinergic with nerve endings located within the myenteric plexus. Radioactive Donepezil binds with high affinity to acetylcholinesterase in the synaptic clefts and thereby serve as an *in vivo* marker of cholinergic innervation.

Aims & Methods: Nineteen patients with DM type 1 and GI symptoms were compared to nineteen age and gender-matched HC by means of ¹¹C-Donepezil PET/CT scan and validated questionnaires for assessment of GI symptoms.

In the present study we aimed to compare the density of cholinergic innervation of the gut in patients with DM and healthy controls (HC) by means of ¹¹C-Donepezil PET/CT.

Results: All Patients had severe GI symptoms when assessed by standard questionnaires. Compared to HC, the DM patients had significantly larger volumes of the small intestine (DM: median 557 cm³ interquartile range (IQR 446-697) vs. HC median: 448 cm³ (IQR 341-518) (*p*< 0.01)) while their ¹¹C-Donepezil PET signal was lower (DM: median 7.09 SUV (IQR 5.94-7.99) vs. HC: median 9.51 SUV (IQR 7.48-10.85) (*p*= 0.04)).In the colon, differences did not reach statistical significance (DM: median 1064 cm³ (IQR 882-1312) vs. HC: median 939 cm³ (IQR 785-1008) (*p*= 0.13)) (DM: median 1.20 SUV (IQR 1.05-1.36) vs. HC: median 1.33 SUV (IQR 1.19-1.57) (*p*= 0.07)). Furthermore, DM patients had reduced pancreatic volume (DM: median 53 cm³ (IQR 41-69) vs. HC: median 98 cm³ (IQR 82-110) (*p*< 0.01)) and ¹¹C-Donepezil PET signal of the pancreas (DM: median 13.14 SUV interquartile range (IQR 9.58-15.82) vs. HC: median 21.46 SUV (IQR 18.97;24.06) (*p*< 0.01)).

Conclusion: We found that patients with DM and severe bowel symptoms had distended small intestines and reduced cholinergic innervation of the gut. ^{11}C-Donepezil PET/CT holds promise as a non-invasive method for *in vivo* assessment of dysmotility and intestinal neuropathy in DM.
Disclosure: Nothing to disclose

OP260 MEMBRANE MUCIN MUC17 IS A NOVEL INTESTINAL BARRIER COMPONENT REGULATED BY BACTERIAL SIGNALS

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Introduction: Intestinal epithelium defends the host against environmental insults while permitting nutrient extraction and grafting of microbiota. Contact with bacteria and bacterial products at early stages of life is necessary for intestinal maturity and priming of intestinal epithelial cells (IECs) as well the host immune system[1]. However, there is critical knowledge gap concerning how the host senses the gut microbiota. Membrane mucin Muc17 is a dynamic glycoprotein expressed on apical membrane of IECs, where it extends up to 1 μm into the intestinal lumen[2]. We suggest that Muc17 is an ideal docking site for gut bacteria and could act as a novel epithelial immune receptor in intestine. However, the regulation of Muc17 remains unknown.
Aims & Methods: The aim of this work is to determine the role of Muc17 in intestinal barrier function. Ileum of wild type postnatal mice, human enterocyte-like Caco-2 cells and intestinal organoids were used as experimental models. Expression of Muc17 and epithelial barrier genes were investigated using immunofluorescence, quantitative RT-PCR and western blot.
Results: Establishment of an adult microbiota is a critical event in postnatal intestinal development. Consequently, we asked if the emergence of an adult-type microbiota upon weaning regulates Muc17. In adult mice with a conventional microbiota, Muc17 covers the apical membranes of IECs in the small intestine and colon.
In stark contrast to adult animals, Muc17 was restricted to intracellular vesicles in the ileum of neonatal mice, and localized to apical surfaces only after the suckling-weaning transition, at postnatal day P21. In order to gain insight in the epithelial program(s) underlying Muc17 maturation, we assessed expression of epithelial barrier genes and cytokines during postnatal development (P9-P33). We observed a specific increase in Muc17 expression with age, reaching a peak at P24.
Other upregulated genes were the cytokines Il-22 and Ifn-γ and antimicrobial proteins such as Reg3-β, Reg3-γ and Zg16. However, Toll-like receptors (TLRs) and downstream regulators were unaffected in ileum during the suckling-weaning transition.
Next, we investigated the signaling pathways downstream of Il-22 and Ifn-γ in epithelial-only intestinal organoids. Only stimulation of organoids with Il-22, Ifn-γ or the combination of Il-22 and Ifn-γ upregulated Muc17, whereas ligands for TLRs did not elevate Muc17 levels.
Conclusion: In summary, our study shows that Muc17 is associated with important genes that form the epithelial barrier in the small intestine. Expression of Muc17 and antimicrobial peptides is regulated by cytokines Il-22 and Ifn-γ produced by immune cells in the lamina propria, generating a robust epithelial barrier against the gut microbiota. We suggest that the establishment of this epithelial barrier, including membrane mucin Muc17, requires environmental signals from an adult-type consortium of microbiota.
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Disclosure: Nothing to disclose

OP261 XBP1 GOVERNS ENDOPLASMIC RETICULUM STRESS DRIVEN STING SIGNALING IN THE INTESTINAL EPITHELIUM

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Introduction: Endoplasmic reticulum stress (ER-stress), defective autophagy and a dysbiotic microbiota are hallmarks of inflammatory bowel disease (IBD) pathophysiology. Recent findings indicate that Stimulator of Interferon Genes (STING) might be involved in IBD pathophysiology in a mechanism involving excessive IFN-I secretion and consecutive necroptotic cell death[i][ii][iii]. To which extent IBD risk genes involved in the ER-Stress axis such *as XBP1* are necessary to coordinate intrinsic STING activation is not known.
Aims & Methods: We hypothesized that STING signaling might be dysregulated in context of ER-stress and inflammation in the intestinal epithelium. We therefore investigated the crosstalk between ER-stress and the STING pathway, focussing on the IRE1/XBP1 branch of the unfolded protein response (UPR) as hypomorphic *XBP1* variants have been shown to cause ER-stress and thereby confer risk for IBD[i]. Intestinal organoids were derived from IBD patients and tested on their ability to induce ER-stress driven STING signaling. RNA sequencing data from biopsies were analysed for correlation of ER-stress and STING singaling signatures in context of IBD. Mice with a conditional epithelial deletion of *Xbp1* and/or *Atg16l1* (*Xbp1*[ΔIEC], *Xbp1/Atg16l1*[ΔIEC]) were used to study STING signaling in context of ER-stress and defective autophagy. STING signaling was induced either chemically, via dsDNA or using vita-PAMPs such as L. monocytogenes or cytomegaliavirus.
Results: Analysis of ileal biopsies and human organoids from IBD patients revealed a strong correlation of ER-stress marker genes and STING expression in a disease-dependent manner with highest upregulation in inflamed tissue. Surprisingly, ER-stress induction itself via TM treatment induced robust STING-dependent IFN-I induction. In contrast, chronic ER-stress in *Xbp1*-deficient intestinal epithelial cells lead to STING degradation and subsequently impaired pathogen induced IFN-I production. These finding were confirmed *in vivo*, as the STING/IFN-I pathway was strongly impaired in *Xbp1*[ΔIEC] mice. Mechanistically, we show that impaired STING-dependent IFN-I induction was due to Atg16l1-driven autophagic removal of STING, as STING-dependent IFN-I induction was partially recovered in the *Xbp1/Atg16l1*[ΔIEC] mice and organoids.
Conclusion: Our data suggests that the STING/IFN-I pathway is tightly regulated by ER-stress in intestinal epithelial cells. Mechanistically, acute ER-stress directly induces IFN-I release via STING activation. In contrast, chronic ER-stress, such as in the context of Xbp1 deficiency, induces autophagy-dependent STING degradation and renders epithelial cells vulnerable to bacterial or viral infections. Hence our data implicate a novel mechanism of the IBD risk gene *XBP1* on epithelial defense response against pathogens and provides an interesting link to explain the drastically increased vulnerability of IBD patients towards intestinal viral infections
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Disclosure: no conflict of interest

OP262 HYPERSENSITIVITY TO OXIDATIVE LYSOSOME DAMAGE CAUSES DEATH OF ENTEROCYTES IN MICROVILLUS INCLUSION DISEASE

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Introduction: Microvillus inclusion disease (MVID) is a fatal enteropathy, characterized by intractable diarrhea and malabsorption associated with unexplained villus atrophy. MVID is caused by mutations in MYO5B encoding myosin-Vb, known for its role in the recycling of cell surface proteins. Although recycling and degradation pathways of cell surface proteins are connected, the impact of the loss of myosin-Vb on the degradative route remains unclear.

Aims & Methods: The aim of this study was to investigate the impact of myosin-Vb loss-of-function on the late endo-lysosomal system. Immuno-labeling on tissues of MVID patients with MYO5B mutations and Myo5B knockout mice was performed, together with functional studies in a MVID cell model to address causal relationships between phenotypes and myosin-Vb expression and underlying mechanisms.

Results: Loss of myosin-Vb had a profound impact on the late endolysosomal system, causing

1) alterations in the morphology and spatial distribution of late endolysosomes,

2) the accumulation of iron in lysosomes,

3) an iron-mediated hypersensitivity to oxidative stress-induced lysosome membrane rupture and

4) resultant cell death.

The availability of the small GTPase rab7 was identified as a ratelimiting factor for the development of the late endo-lysosomal phenotype. Iron chelation and antioxidant treatment restored the phenotype.

Conclusion: Myosin-Vb, concurrent with its role in plasma membrane homeostasis, is important for late endolysosomal homeostasis. Hypersensitivity of myosin-Vb-depleted cells to oxidative lysosomal membrane permeabilization and cell death should be considered part of MVID pathogenesis. This property underlies a potential clinically relevant and druggable mechanism to explain the extensive villus atrophy in MVID.

Disclosure: Nothing to disclose

OP263 NEW AND SIMPLE DIAGNOSTIC TEST FOR INCREASED INTESTINAL PERMEABILITY BASED ON PLATELET COUNT

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Introduction: The main pathological process associated to increased intestinal permeability is the translocation of toxic products, predominantly endotoxins/lipopolysaccharides (LPS) from the intestinal tract into the microcirculation (1).

In the bloodstream, LPS is distributed in varying proportions bound by LPS-binding protein, several other acute phase proteins, lipoproteins, soluble CD14, and even more relevant for our study, by cells bearing TLR4 such as platelets (2,3). LPS leads to preactivated platelets that have a lower threshold to be aggregated in presence of the physiological agonists, thrombin and collagen, but also by other molecules such as heparin (4,5).

Aims & Methods: The aim of this study was to validate a simple, fast and reliable test for screening LPS-loaded platelets as an indirect biomarker for increased intestinal permeability. This test named PANDA (acronym for PlAtelet's Number in Different Anticoagulants) consists in the measurement of the mean platelet number in blood samples collected into EDTA and heparin.

To explore this issue, we analyzed the platelet number from patients with gastrointestinal diseases and a group of healthy persons in blood samples anticoagulated with EDTA or heparin, but also in presence of hirudin or citrate in order to investigate the contribution of Ca^{2+} in platelet's aggrega-

tion. Finally, we also evaluated whether the PANDA test can be used for monitoring the gut barrier function in 30 patients under treatment with a new oxygenated simethicone emulsion (6).

Results: A notably lower number of platelets was found in heparinized blood compared to EDTA-anticoagulated blood from patients with a gut barrier dysfunction but not from healthy volunteers. These results suggested that when LPS translocates into blood, it binds to platelets leading to a preactivated state in which they have a lower threshold to be aggregated in presence of heparin. In order to confirm this hypothesis, LPS was added to heparinized and EDTA-anticoagulated blood samples collected from both groups. LPS led to a significant reduction of platelet counts only in heparinized blood samples from control subjects but not in patients where the LPS-binding sites on platelets could already be saturated. LPS did not influence platelet number in EDTA-blood samples at all.

Moreover, platelet's aggregation can not be attributed to the higher Ca^{2+} concentration in heparinized samples compared to EDTA-blood samples. If this were so, how can we explain the lack of aggregation in heparinized blood from control subjects? Furthermore, in blood samples from some patients either the platelet number in citrated blood was very similar to that of heparinized blood or platelet counts found in heparinized blood were even lower than those of hirudin-blood samples in spite of the same external Ca^{2+} concentration in these samples.

Finally, we have investigated whether PANDA test could be useful for monitoring the reconstitution of gut barrier function. We found that the platelet's number in heparinized blood was notably lower compared to EDTA-blood before beginning of treatment.

However, the difference in platelet's number in presence of these both anticoagulants decreased notably during the course of a simethicone treatment.

Conclusion: Our results demonstrated that PANDA test can be used for screening LPS-loaded platelets as an indirect diagnostic biomarker for increased intestinal permeability and also for monitoring the gut barrier function during the treatment of gastrointestinal diseases.

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Disclosure: Nothing to disclose

Improving colorectal cancer screening
16:00-17:30 / C2

OP264 ADENOMA DETECTION RATE IN ASYMPTOMATIC FECAL IMMUNOCHEMICAL TEST POSITIVE COHORTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Adenoma detection rate (ADR) is a well-accepted quality indicator of screening colonoscopy and is defined as the proportion of patients who have one or more adenoma detected while undergoing screening colonoscopy. In a recent guideline, the US multi society task force on CRC prevention proposed an ADR benchmark of >35% for females and >45% for males in fecal immunochemical test (FIT) positive asymptomatic population. This, however, is based out of low quality evidence.

Aims & Methods: We conducted this meta-analysis to estimate the pooled threshold of ADR in FIT-positive asymptomatic population undergoing colonoscopy. We conducted a comprehensive search of several databases and conference proceedings including PubMed, EMBASE, Google-Scholar, LILACS, and Web of Science databases (earliest inception to January 2019). We followed the Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, by using predefined protocol, to identify studies reporting the detection of adenoma by colonoscopy in FIT-positive population. Random-effects model was used for analysis. Heterogeneity between study-specific estimates was calculated using Cochran Q statistical test and I^2 statistics. Publication bias was ascertained, qualitatively, by visual inspection of funnel plot and quantitatively, by the Egger test.

Results: From an initial total of 480 studies, 73 records were screened and 48 full-length articles were assessed. 21 studies were included in the final analysis. All included patients were aged more than 50 years. In the included 21 studies, 129,975 cases were positive for FIT, of which 105,731 cases underwent a screening colonoscopy. 50,247 cases were identified with a colorectal adenoma, 12,343 cases were diagnosed with advanced adenoma, and 4,211 cases were diagnosed with colorectal cancer. The pooled rate of adenoma detection rate (ADR) in FIT-positive asymptomatic individuals was 45.4% (95% CI 37.3-53.8, I^2=99.8). The pooled rate of advanced adenoma detection rate (aADR) was 19.4% (95% CI 14.2-25.8, I^2=99.6) and the pooled rate of colorectal cancer detection rate (CDR) was 3.8% (95% CI 2.8-5.0, I^2=97.9). Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was no evidence of publication bias (Egger's p-value=0.37).

Conclusion: From a total of 21 good quality studies that evaluated 129,975 participants, we report a pooled adenoma detection rate (ADR) of 45.4%, a pooled advanced-ADR of 19.4%, and a pooled CDR of 3.8% in FIT-positive asymptomatic individuals. To the best of our knowledge, this study is the largest and most up-to-date meta-analysis reporting on the pooled results of colonoscopy findings in FIT-positive asymptomatic population.

Disclosure: Nothing to disclose

OP265 THE PREDICTIVE EFFECT OF A HIGH-QUALITY SINGLE NEGATIVE SCREENING COLONOSCOPY IN INDIVIDUALS WITH FAMILY HISTORY OF COLORECTAL CANCER EXCEEDS 10 YEARS

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Introduction: Despite limited evidence, current guidelines recommend to repeat screening colonoscopy in individuals with family history (FH) of colorectal cancer (CRC) every 5 years.

Aims & Methods: To assess the long-term risk (>5 years) of CRC and CRC death in individuals with and without a family history of colorectal cancer (at least one first-degree relative with CRC) after high- and low-quality single negative screening colonoscopy, as compared with the general population.

We conducted an analysis of the database records of all colonoscopies performed between October 1st 2000, and December 31st 2011 as part of the Polish CRC screening program.

All subjects with and without FH of CRC who underwent a single negative colonoscopy (defined as the absence of any neoplastic lesions) were identified and followed for CRC and CRC death through the National Cancer Registry over the median of 10.2 years and up to 17.4 years. High-quality colonoscopy was defined as an examination with cecal intubation, adequate bowel preparation (very good, good or sufficient per the Aronchick scale) performed by an endoscopist with an adenoma detection rate ≥20%. Standardized incidence and mortality ratios (SIRs and SMRs) were calculated by comparing the observed values against the values for the general Polish population.

Results: Out of 206,685 individuals who underwent screening colonoscopy with a negative result, we identified 40,798 individuals with FH of CRC. Overall, throughout a 17.4-year period following a high-quality single negative colonoscopy there was no significant difference in risk of CRC and CRC death between subjects with FH of CRC and those without FH of CRC (high-quality screening colonoscopy yielded SIR of 0.33 (95% CI, 0.19-0.53) and SMR of 0.04 (95% CI, 0.00-0.24) in subjects with FH of CRC and SIR of 0.24 (95% CI, 0.19-0.30) and SMR of 0.17 (95% CI, 0.11-0.25) in subjects without FH of CRC. Among individuals with FH who underwent high-quality colonoscopy, the risk of colorectal cancer and colorectal cancer death between 5 and 10 years after examination did not differ significantly from the earlier period of observation (Table 1).

	Years following negative colonoscopy					
	0-5.0	5.1-10.0	Entire follow-up period	0-5.0	5.1-10.0	Entire follow-up period
	Individuals with family history of CRC			Individuals without family history of CRC		
High-quality colonoscopy						
SIR (95% CI)	0.23 (0.08-0.50)	0.40 (0.17-0.79)	0.33 (0.19-0.53)	0.19 (0.13-0.27)	0.30 (0.22-0.42)	0.24 (0.19-0.30)
SMR (95% CI)	0.08 (0.00-0.46)	0.00 (0.00-0.41)	0.04 (0.00-0.24)	0.09 (0.04-0.18)	0.21 (0.11-0.36)	0.17 (0.11-0.25)
Low-quality colonoscopy						
SIR (95% CI)	0.57 (0.39-0.81)	1.04 (0.77-1.37)	0.79 (0.64-0.96)	0.36 (0.30-0.43)	0.63 (0.54-0.72)	0.52 (0.47-0.57)
SMR (95% CI)	0.24 (0.09-0.52)	0.82 (0.48-1.29)	0.50 (0.33-0.72)	0.17 (0.11-0.24)	0.51 (0.40-0.64)	0.38 (0.32-0.45)

[SIRs and SMRs of individuals with and without FH of colorectal cancer according to the quality and the time from single negative screening colonoscopy]

Conversely, low-quality screening colonoscopy was not associated with a significant reduction in colorectal cancer risk among the individuals with FH of colorectal cancer between 5 and 10 years after colonoscopy.

Conclusion: Our results suggest that 5-year screening interval for individuals with FH of CRC could be safely prolonged to 10 years providing that the quality of baseline colonoscopy was high.

Disclosure: JR received honoraria/consultation fees from Ipsen, Polpharma, Takeda, Alfa Sigma, Krka, Promed, and travel grant from Abbvie and Alfa Wassermann. MFK recived honoraria/consultation fees from Olympus, Fujifilm, Alfa Sigma and Norgine.

OP266 SHOULD ADENOMA DETECTION RATES BE AGE BASED?

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Introduction: Adenoma detection rate (ADR) is a measure of the quality of the colonoscopic examination, and in the UK a minimum target of 15% has been set for the whole population. Given the pathogenesis of adenomas, colonoscopists who examine a higher proportion of younger patients might be expected to encounter fewer adenomas, and as such not produce equivalent ADRs to those dealing predominantly with older patients.

Aims & Methods: We set out to establish ADRs in patients of different age groups. We interrogated the endoscopy reporting system at a District General Hospital in South London over a 3-year period. We divided the patients into three age groups, and then determined the crude rate of polyp detection for each. From each age group we selected a sample of 100 consecutive patients who had polyps on their colonoscopy, and reviewed the histological diagnoses to determine the proportion of polyps which were clinically important i.e. adenomas, sessile or serrate lesions, and carcinomas. Chi-square testing was used to compare the different age groups for: the crude polyp detection rates, the rate of clinically important lesions in our samples, and the extrapolated number of clinically important lesions for the 3-year data set.

Results: A total of 7928 colonoscopies were performed in this time period. Table 1 below summarises the lesion detection rates in the three age groups examined.

	20-39 year old	40-59 year old	60-90 year old
Total number of colonoscopies performed	639	2519	4770
Number of colonoscopies in which polyps were detected	102	605	1662
Crude rate of polyp detection	16.0% p value (20-39yo vs. 40-59yo) <0.001	24.0% p value (40-59yo vs. 60-90yo) <0.001	34.8% p value (20-39yo vs. 60-90yo) <0.001
Number of adenomas, sessile or serrated lesions, and carcinomas in a sample of 100	49	67	76
Predicted rates of clinically important polyps	7.8% p value (20-39yo vs. 40-59yo) <0.001	16.1% p value (40-59yo vs. 60-90yo) <0.001	26.5% p value (20-39yo vs. 60-90yo) <0.001

[Table 1]

Conclusion: Our data suggests there is a significant difference in ADRs in different age groups, and that clinically important polyps are more likely to be found in older people. This adds to the body of evidence that ADRs increase with age. Future key performance indicators for colonoscopies should take this into account.

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Disclosure: Nothing to disclose

OP267 EFFICACY AND TOLERABILITY OF SINGLE DOSE *VS.* SPLIT DOSE POLYETHYLENE GLYCOL FOR COLONIC PREPARATION IN CHILDREN: A RANDOMIZED CONTROL STUDY

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Introduction: Polyethylene glycol (PEG) solution is the most effective colon cleansing agent but volume related adverse effects are common. Though split-dose PEG is used in adults, there is no pediatric study so-far comparing split-dose with single-dose PEG.

Aims & Methods: The aim of this study was to find the efficacy and tolerability of split-dose as compared to single-dose PEG for bowel preparation in pediatric patients.

Consecutive children (1-18 years) were randomized into either single-dose or split-dose PEG. Single-dose group received 4000mL/1.73m^2 PEG solution day before colonoscopy while split-dose group received half dose day before and the remaining half on the day of colonoscopy. Effectiveness of bowel preparation was assessed on Aronchik scale, by the endoscopist who was blinded to the type of preparation. Inter-observer variability was analyzed by comparing with independent scoring by the blinded trained endoscopy-nurse. The trial was registered with Clinical Trials Registry of India. (Trail number 2017/08/009303).

Results: Of the 220 randomized children, 179 completed the study (split-dose: 93, single-dose: 86) The mean age of the study population was 138.12 (57.84) months (72.6% males). Age, gender distribution, body surface area (BSA), volume of PEG solution ingested, proportion of in-patients and previous history of colonoscopy were comparable between the single-dose and split-dose PEG groups. The efficacy of bowel preparation was better with split-dose (satisfactory preparation: 76.34% *vs.* 43.02%, p< 0.001) with almost perfect inter-observer agreement (k=0.803). Nausea, vomiting and sleep disturbance were significantly less in split-dose than single-dose group (p< 0.05). Split-dose patients were able to drink PEG solution faster (p=0.002). Total sleep duration and uninterrupted sleep duration was also better in split-dose group as compared to single-dose (p=0.001).

Parameters	Single dose PEG (N=86)	Split dose PEG (N=93)	P value
Mean duration of drinking (SD) in hours	5.15 (1.18)	4.65 (0.93)	0.002
Pain abdomen, n (%)	7 (8.1)	3 (3.2)	0.199
Abdominal distension, n(%)	6 (7)	2(2.2)	0.156
Vomiting, n (%)	36(41.9)	21(22.6)	0.007
Sleep disturbance,n(%)	49(57)	13(14)	0.001
Mean duration uninterrupted sleep (SD) in hours	4.23 (1.83)	6.05 (1.34)	0.001
Last stool liquid consistency, n (%)	72(83.7)	90(96.8)	0.003
Satisfactory preparation (Excellent and Good on Aronchik score), n (%)	37(43.02)	71(76.34)	<0.001
Ileoscopy, n(%)	83(96.5)	93(100)	0.109

[Comparisons of tolerability and efficacy between single dose versus split dose Polyehylene glycol]

Conclusion: Split-dose PEG is more effective than single-dose for colonoscopic preparation in pediatric population. At the same time it causes lower volume related side effects of bowel preparation and improved sleep quality which are of paramount importance for children.

Disclosure: Nothing to disclose

OP268 WATER EXCHANGE (WE) SIGNIFICANTLY INCREASES DETECTION RATE OF SESSILE SERRATED POLYPS COMPARED WITH AIR (AI) OR CARBON DIOXIDE (CO2) INSUFFLATION - POOLED DATA ANALYSIS OF THREE RANDOMIZED CONTROLLED TRIALS

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Introduction: Important advances were made in understanding the impact of water exchange (WE) colonoscopy in the past decade. The cardinal feature and key to the success of WE is, during the insertion phase, the near-complete suction removal of infused water used to aid insertion.[1] A network meta-analysis in 2018 summarized the data and reported that WE provided the highest adenoma detection rate[2]; but the impact on the detection rate of sessile serrated polyps was not addressed. These lesions can be found anywhere in the colon and are more common in the proximal and right colon. The endoscopic features of sessile serrated polyps make their real-time identification challenging. Given their subtle appearance and their definite potential for transformation to malignancy, a method that enhances their endoscopic detection is desirable.

The finding of sessile serrated polyps was mentioned in several randomized controlled trials (RCTs) comparing WE with air (AI) or carbon dioxide (CO2) insufflation.

Aims & Methods: By pooling the data in three RCTs[3-5] to minimize the pitfall of type II error, the aim of this report is to assess the impact of WE (vs. AI or CO2) on detection rate of sessile serrated polyps. Three RCTs with data on sessile serrated polyps when the standardized WE method was compared with AI or CO2 insufflation were identified. Demographic and procedural data were tabulated. Data on sessile serrated polyps were pooled and analyzed.

Results: Table 1 summarizes the studies selected for pooled analysis based on available data. WE significantly increased detection rate of sessile serrated polyps from 3.2% to 4.9% (*P=0.0054, Fisher Exact test).

Conclusion: The pooled data show WE significantly increased detection rate of sessile serrated polyps. The improved outcome adds value to colonoscopy performed with the WE method. The enhanced value justifies incorporation of WE into colorectal cancer screening programs, to set the stage for future studies to assess the impact of WE on minimizing the development of colorectal cancers.

Pooled Data of References 3, 4, 5		
Method	Water Exchange	Air Insufflation
No. of patients	2053	2043
No. of colonoscopists	20	20
Mean age, year	57	57
Male, no. (%)	1088 (53%)	1121 (55%)
Screening, no.(%)	865 (42%)	919 (45%)
Cecal intubation no. (%)	2020 (98%)	2001 (98%)
Withdrawal time (min)	7.1 to 20	7.2 to 22
Bowel prep regimen	Split-dose	Split-dose
Sessile polyp detection rate	101/ 2053 (4.9%)*	65/2043 (3.2%)

[Table 1: Details of randomized controlled trials selected for analysis]

References: 1. Leung FW, et al. Water infusion without near-complete removal during insertion by any other name is still water immersion (WI). Gastrointestinal Endoscopy 2019;89(3):599-601. 2. Fuccio L, et al. Water exchange colonoscopy increases adenoma detection rate: a systematic review with network meta-analysis of randomized controlled studies. Gastrointest Endosc. 2018;88(4):589-597. 3. Garborg K, et al. Water exchange versus carbon dioxide insufflation in unsedated colonoscopy: a multicenter randomized controlled trial. Endoscopy. 2015 Mar;47(3):192-9. 4. Jia H, et al. Water exchange method significantly improves adenoma detection rate: a multicenter, randomized controlled trial. Am J Gastroenterol. 2017;112(4):568-576. 5. Leung JW, et al. A prospective RCT comparing combined chromoendoscopy with water exchange (CWE) vs. water exchange (WE) vs. air insufflation (AI) in adenoma detection in screening colonoscopy. United European Gastroenterology J. 2019 Feb. https://doi.org/10.1177/2050640619832196
Disclosure: Nothing to disclose

OP269 FACTORS ASSOCIATED WITH MECHANICAL AND SYSTEMIC ADVERSE EVENTS AFTER COLONOSCOPY (FRANCE, 2010-2015)

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Introduction: More than one million colonoscopies are performed every year in France. They are associated with risks of mechanical and systemic serious adverse events (SAEs).

Aims & Methods: In this study, we attempted to identify the factors associated with mechanical (colonic perforation, gastrointestinal bleeding, splenic injury) and systemic (shock, myocardial infarction, stroke, pulmonary embolism, acute renal failure, urolithiasis) SAEs after colonoscopy. We analysed data from the French national claims databases (SNDS). A total of 4,088,799 patients, 30 years or older, undergoing a first screening or diagnostic colonoscopy between 2010 and 2015 were identified. SAE rates were estimated, and risk factors associated with SAEs were identified using multilevel logistic regression models, adjusted for patient, colonoscopy, endoscopist, and facility characteristics.

Results: Perforation rates ranged from 3.5 (stringent definition) to 7.3 (broad definition) per 10,000 procedures, bleeding rates ranged from 6.5 to 23.1 per 10,000 procedures, and splenic injury rates ranged from 0.20 to 0.34 per 10,000 procedures. The 5-day SAE incidence rate was 2.8/10,000 procedures for shock, 0.87/10,000 for myocardial infarction, 1.9/10,000 for stroke, 2.9/10,000 for pulmonary embolism, 5.5/10,000 for acute renal failure, and 3.3/10,000 for urolithiasis.

Increasing age was associated with an increasing incidence of mechanical and systemic SAEs. Cancer andcardiovascular comorbidities were associated with mechanical SAEs. A higher number of pre-existing conditions was associated with shock and acute renal failure. Polypectomy, especially of polyps larger than 1 cm, was associated with an increased risk of perforation (OR=4.1; 95% CI, 3.4-5.0) and bleeding (OR=13.3; 95% CI, 11.7-15.1). Mechanical SAEs were associated with the endoscopist's experience, while systemic SAEs were more frequent in public hospitals than in private clinics.

Conclusion: SAEs related to colonoscopy are more frequent in older patients and in those with comorbidities. Systemic SAEs are more frequent in public hospitals, reflecting patient selection processes. The risk of both mechanical and systemic SAEs should be taken into account when deciding colonoscopy, particularly in elderly patients with multiple pre-existing conditions

Disclosure: Franck Carbonnel received personal fees from Medtronic for board participation

New ways to predict response in IBD

16:00-17:30 / E1

OP270 EARLY DYNAMICS OF PERIPHERAL BLOOD GENE EXPRESSION AND DNA METHYLATION PREDICT RESPONSE TO ANTI-TNFA THERAPY IN A PROSPECTIVE MULTI-OMICS ANALYSIS IN IBD PATIENTS

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Introduction: Biologics targeting tumor necrosis factor α (TNFα) are successfully used to treat chronic immune mediated diseases including inflammatory bowel disease (IBD). However, the utility of these therapies is significantly impacted by high primary and secondary non-response rates. Hence, it is crucial to find biomarkers that could predict therapeutic response before or in the initial stages of the treatment. Here, we aim to understand the dynamic molecular changes that lead to remission in IBD patients newly receiving anti-TNFα therapy.

Aims & Methods: In total 14 biologic-naïve IBD patients, who underwent first time anti-TNFα treatment with infliximab, were recruited into a molecular medicine study with a dense sampling scheme at the University Hospital Kiel for hypothesis generation and 45 patients for confirmation of findings. Clinical response was assessed using symptom based clinical disease scores (HBI/MAYO) and endoscopy. In the hypothesis generation cohort, 7 patients attained remission within a time frame of 14 weeks. Whole blood from the patients before and 4, 24, 72 hours, 2, 6 and 14 weeks after therapy was collected. RNA and DNA isolated from the 98 blood samples were used for systematic multi-OMICS profiling including RNA sequencing and DNA methylation profiling by EPIC arrays, respectively.

Results: We found that target engagement of anti-TNFα led to fast and drastic downregulation of overall gene expression in the whole blood transcriptome irrespective of therapy outcome. Pairwise comparisons and impulse-modelling identified a higher number of differentially expressed genes in patients who later attained remission. Co-expression analysis identified gene modules involved in innate immune response and inflammatory response showing different expression profiles in remission and non-remission groups. These modules were characterized by decrease in expression in the early timepoints (24h to 2 weeks) in the remission group. 763 out of 3889 remission associated genes correlated significantly with differentially methylation variable positions (MVPs), indicating a potential epigenetic control of remission-associated gene modules. The identified methylation sites were enriched for binding motifs of transcription factors related to immune and inflammatory processes such as BATF, NFKB, STAT3 and CEBPB. Selected pairs of differentially expressed transcripts and MVPs were verified in a confirmatory cohort of 45 IBD patients receiving first time treatment with infliximab or vedolizumab, demonstrating overlapping and unique signals between biologics.

Conclusion: We show that successful induction of remission through anti-TNFα therapy drastically alters the whole blood transcriptome and methylome in the first 2 weeks during therapy initiation. Our results suggest that transcriptional changes associated with remission are highly dynamic in nature and might be partially regulated by epigenetic mechanisms. The contrast of gene modules integrated across Omics-layers can be used to decipher predictive molecular signatures of remission. Further clinical studies are required to evaluate the utility of such signatures for clinical decisions between continuation of therapy and early switching to other MOA.

Disclosure: Nothing to disclose

OP271 TERMINAL ILEUM THICKNESS IS A PREDICTIVE MARKER FOR INFLIXIMAB THERAPY IN CROHN´S DISEASE

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Introduction: While achieving mucosal healing has been associated with long-term response to therapy of Crohn's disease (CD), little is known about the significance of terminal ileum (TI) transmural thickness in predicting of clinical outcomes.

Aims & Methods: In this retrospective chart review, we examined the correlation between transmural TI thickness during maintenance phase (week 14 and above) and the clinical outcome of CD in a cohort of patients treated with infliximab. Intestinal ultrasonography (IUS) was used in all patients to determine TI transmural thickness. TI transmural response was defined as TI< 4mm. Treatment failure was defined as treatment discontinuation due to inefficacy, dose escalation, or surgery. IUS parameters and clinical data were assessed during follow up.

Results: Sixty CD patients receiving infliximab therapy (60% male, mean age 32.6 years, mean duration of disease-9.6 years, 92% anti-TNF-naïve) were included in the study. All patients had ileal or ileo-colonic disease. Thirty nine patients (65%) achieved transmural response. The mean duration of follow-up was 11.2 months. After a median follow-up of 9.5 months, 22(36.6%) patients developed treatment failure. On univariate analysis, the only variables associated with treatment failure were: TI thickness of 3.1 (3.62-6.72) mm vs 1.4 (1.8-3) mm, p value <0.0001 in patients with and without treatment failure, respectively, and IFX trough level (IFX-TL) of 6.6 (0.13-6.97) mcg/ml vs 3.9 (3.9-7.8) mcg/ml level, p = 0.008. There was a significant correlation between failure to achieve transmural response and treatment failure (18/24 (75%) vs 4/36 (11.1%)) in patients with treatment failure and without treatment failure, respectively (OR-17.55 95%, CI -4.0-76, p=0.02). Other than IFX-TL and TI- thickness there were no clinical or demographic parameter that were associated with the risk of treatment failure.

On multivariate analysis, only terminal ileum thickness> 4 mm was associated with the risk of treatment failure (p= 0.002); IFX-TL did no retain statistical significance on multivariate analysis (P= 0.695)

Conclusion: Our findings suggest that failure to achieve transmural response to infliximab can predict subsequent treatment failure in CD patients, indicating transmural response as a potential novel valuable therapeutic target.

Disclosure: Nothing to disclose

OP272 TRANSMURAL HEALING ASSESSED USING MRI IS ASSOCIATED WITH BETTER OUTCOMES AND IS A POTENTIAL THERAPEUTIC TARGET IN PATIENTS WITH CROHN´S DISEASE

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Introduction: The poor acceptability of repeated colonoscopies limits the use of endoscopic mucosal healing as therapeutic target in patients with Crohn's disease (CD). MRI is better accepted than endoscopy, is able to perform a concomitant transmural assessment of ileocolonic inflammation and to detect CD complications.

Aims & Methods: We aimed to evaluate whether transmural healing assessed using MRI scores was associated with decreased risk of surgery, hospitalization and therapeutic intensification in patients with CD.

From a database including all the consecutive patients who performed anMRI to assess luminal CD between January 2012 and June 2018 in our IBD unit, we selected all the patients with CD (> 18 yearsold) who underwent two MRI with:

1) objective signs of inflammation on the 1st MRI,

2) the second MRI performed to assess therapeutic efficacy,

3) follow-up > 6 months and no surgery between the two MRI.

All the patients underwent MRI assessing the small bowel and the colon using a standardized protocol (no bowel cleansing the day before and no colonic distension). Complete transmural healing was defined as normalization of MRI. Partial transmural healing was defined as a decrease of at least 25 % of Clermont score or MaRIA in each active segment. Results were expressed as Hazard Ratio (HR) and 95% confidence interval [95% CI].

Results: Overall, 443 patients undergoing 889 MRI were screened for the study. Among them 274 patients were included (mean age 33.1 ± 15.8 years, median CD duration = 7.0 [2.013.0] years, 36.4 % smokers, 31.4 % prior intestinal resection, L1 = 51.5 %, L2 = 5.5 % and L3 = 43.1 %, 25.9 % perianal lesions, 35,4 % stricturing CD and 31.0 % fistulizing CD). At the time of the second MRI, the patients received one or several medications among: steroids (6.3 %), immunosuppressants (45.2 %), antiTNF agents (65.7 %) or ustekinumab (2.6 %). The median interval between the 2 IRM was 9.2 months [6.0 - 14.1].

Overall, 53 patients had a CD-related bowel resection, 72 patients (26.3 %) required CD-related hospitalization and 163 patients (59.5 %) needed therapeutic intensification (median follow-up = 14.9 mois [4.3 - 31.4]). In multivariate analysis (Cox model), complete or partial transmural healing was associated with reduced risk of surgery (HR = 0.13 [0.05 - 0.38] ; p < 0.001), of subsequent hospitalization (HR = 0.25 [0.11- 0.56] ; p = 0.001) and therapeutic intensification (HR = 0.08 [0.03 - 0.20] ; p < 0.001). Complete transmural healing showed a lower risk of therapeutic intensification compared to partial transmural healing (p < 0.05).

Conclusion: Transmural healing assessed using MRI scores is associated with favourable outcomes in patients with CD and should be used as therapeutic target both in daily practice and clinical trials.

Disclosure: Nothing to disclose

OP273 MOLECULAR TRAJECTORIES OF REMISSION IN BIOLOGICS THERAPY OF IBD: PRIVATE DRUG SPECIFIC-SIGNATURES VS. COMMON TRANSCRIPT MODULES

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Introduction: Inflammatory bowel disease (IBD) is characterized by inadequate destructive immune responses fueled by a complex dysregulation of the mucosal cytokine network. Targeted therapies block pivotal pathophysiological principles (e.g. cytokines, signalling, leukocyte adhesion). Currently, no biomarkers for predicting or defining molecular remission across therapies are available, although it can be assumed that disease control with mucosal healing -regardless of the drug-specific MOA- is characterized by a shared molecular signature across therapies. Currently, the dynamics of shared gene expression networks (e.g. remodelling of extracellular matrix, epithelial regeneration) associated with molecular remission is unclear. A blueprint of unifying principles of molecular remission is needed to disentangle drug-specific immunological network alterations associated with existing and novel compounds. The aim of this study thus was to identify a drug-independent core expression signature in mucosal biopsies that might be applicable for an early prediction of molecular remission.

Aims & Methods: Patients with IBD that were treated with various biologics, including anti-TNFa (Infliximab, IFX), a4b7-integrin antagonist (Vedolizumab, VDZ) were enrolled into a prospective clinical and molecular characterization program with multiple planned endoscopies (up to 10 endoscopies over 14 weeks) and RNASeq from intestinal biopsies. In addition, Additional data were included from Phase IIa molecular medicine following the same setup and clinical trial in which Olamkicept (OLA), a sgp130Fc fusion protein specifically inhibiting the IL-6 trans-signaling pathway was administered open label. In all cases, biopsies from the sig-

moid colon were collected before (0h) and at several time points (+4h, +24h, 2 weeks, 6 weeks, and 14 weeks) after drug exposure. In total 55 patients were analyzed (UC: 29, CD: 26) and were exposed to the following biologic therapies (IFX: 19, VDZ: 20, OLA: 16). 36% of patients achieved clinical remission, whereas 21% were clear failures

Results: All investigated biologic treatments downregulated genes starting at 2 weeks after treatment. Importantly, this downregulation preceded the attenuation of clinical response parameters (HBI, Mayo). The majority of early downregulated genes were highly drug-specific and showed little overlap between the different biologic treatments; with only 1% of downregulated genes being shared amongst treatments at week 2, 2% at week 6, while at week 14 21% of all downregulated genes detected were shared between one or more treatments.

We identified a core set of eight differentially expressed genes, which were downregulated in mucosal tissues at week 14 in all remission patients in a drug-independent manner. These genes comprised e.g. Toll-like receptor 2 (TLR2), chemokine receptor 2 (CXCR2) and a cytokine receptor (CSFR). Importantly, using this 8-gene score, we were able to define a threshold of the dynamic behavior of the marker set that was able to predict clinical remission status already at week 2.

Conclusion: Our data indicate that different biologic therapies produce private transcriptomal signatures. However, changes also comprise drug-independent longitudinal changes of specific transcript modules, which were already detectable at an early timepoint (i.e. week 2) and were predictive of clinical remission at week 14. A prospective multicenter clinical study is ongoing to evaluate whether this information can be used to develop a "treat and test" strategy to decide already at early timepoints of exposure, which therapy is best for a patient.

Disclosure: Nothing to disclose

OP274 INTEGRIN EXPRESSION CHANGES ON THE T CELL SUBSETS INFLUENCE THE RESPONSE TO VEDOLIZUMAB IN INFLAMMATORY BOWEL DISEASE PATIENTS

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Introduction: Vedolizumab is a gut-selective alpha4beta7 integrin inhibitor approved for the treatment of Ulcerative Colitis (UC) and Crohn's disease (CD). The exact mechanism of action remains to be unraveled and there is no consensus whether the response to vedolizumab is associated with integrin expression profiles of the innate, adaptive immunity or both. Response prediction to vedolizumab is particularly relevant since it is a rather slow-acting molecule.

Aims & Methods: We investigated whether baseline levels and/or early changes in the integrin-expressing T cell subsets during the induction phase can predict the response to vedolizumab in inflammatory bowel disease (IBD) patients.

In this prospective multi-centric study, 71 patients with CD (n=28) or UC (n=43) with moderate-to-severe disease were included at the start of vedolizumab treatment. The response to vedolizumab was determined on a clinical, biochemical and endoscopic level at the end of the induction phase (week (W)14). The clinical response was defined as a drop in the Harvey Bradshaw index (HBI) of at least 3 points for CD and a reduction in Mayo score of at least 3 points with no rectal bleeding for UC. The biochemical response was defined as a 50% reduction of CRP or when the CRP normalized (< 10 mg/l) for CD and a 50% reduction or normalization (< 250mg/g) of calprotectin for UC. The endoscopic response was evaluated positive when there was a drop of at least 1 point in the SES-CD score for CD or the endoscopic Mayo score for UC. During the induction phase, peripheral blood mononuclear cells (PBMCs) were collected at W0, W2,

W6, W10 (only CD) and W14, before vedolizumab administration. Variation between the different centers was reduced by isolating the cells 6h after blood collection. The PBMCs were analyzed by flow cytometry to evaluate the CD4+/CD8+ Alpha4Beta7+, Alpha4Beta1+, AlphaEBeta7+ and Alpha-EBeta1+ T cell populations. Based on the distribution of the data, statistics were performed by an independent sample t-test or a Mann-Whitney U test.

Results: The flow cytometry analyses revealed that only the CD4+ Alpha-4Beta7+ T cell subset at baseline was significantly increased in UC patients with a favorable clinical (P= 0.042), biochemical (P=0.025) and endoscopic response (P= 0.054). This was not the case in CD. In CD, the baseline number of CD4+ Alpha4Beta1+ T cells was lower in clinical (P= 0.094) and biochemical responders (P= 0.004). In addition, lower baseline CD4+ AlphaEBeta1+ T cells and the CD8+ AlphaEBeta1+ T cells were also associated with a biochemical response in CD (P= 0.032 and P= 0.025), respectively. No other significant baseline or delta change differences were identified between the responders and non-responders in the other investigated T cell subsets in both UC and CD.

Conclusion: This prospective cohort study showed that in UC patients, clinical, biochemical and endoscopic response to vedolizumab treatment is associated with a high number of CD4+ Alpha4Beta7+ T cells in circulation at baseline. In CD patients, the relationship is less clear and the response is rather linked to a low number of Beta1+ T cells. A second cohort is being recruited to confirm our findings. The final aim is to build a predictive model that is feasible for use in clinical practice.

Disclosure: Support provided by Takeda.

OP275 GUT MICROBIAL METABOLIC FUNCTIONS ARE ASSOCIATED WITH ANTI-TNF EFFICACY IN IBD PATIENTS

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Introduction: An impaired interplay of the mucosal immune system and gut microbiota plays a critical role in the pathogenesis of human chronic inflammatory bowel disease (IBD).The impact of targeted cytokine blockade on intestinal microbial communities is still poorly understood. Here, we investigate the effect of anti-TNFα treatment on gut microbial community structure and functional properties in a prospective, longitudinal two-step study. We correlate our findings to therapeutic outcome and investigate fecal metabolite patterns associated with microbiota shifts upon therapy initiation.

Aims & Methods: We recruited two cohorts of patients initiating anti-TNFα therapy. Cohort #1 included IBD (n=12) and rheumatic disease (RD; n=17) patients who were exposed to anti-TNFα therapy were enrolled for longitudinal stool sampling at baseline and 2, 6 and 30 weeks after therapy induction. Specificity of the findings was assessed in an independent cohort #2 of 23 IBD patients (13 UC, 10 CD) treated with anti-TNFα or anti-α4β7 integrin. Intestinal microbial community structures were studied by V3-V4 16S rRNA gene amplicon sequencing. In-silico analysis of metabolic interactions among microbial species were performed to identify key metabolites indicative of clinical remission status. Stool metabolomics was performed in a subset of samples to validate functional predictions associated with therapy outcome.

Results: anti-TNFα treatment restores microbial diversity in IBD patients, but not RD patients. Assessment of microbial diversity indices is not suitable for the differentiation between remission and non-remission status in IBD patients. In contrast, in-silico analysis of microbial metabolite ex-

change shows an extensive perturbation of microbial metabolic cooperativity, which discriminates between anti-TNFα remitter and non-remitter. Inferred microbial metabolite exchange indicates e.g. altered inter-microbial metabolism of SCFA. Stool metabolomics validated increased butyrate to be associated with remission status.

Conclusion: We show that anti-TNFα treatment increases the gut microbial diversity and coupling of cross-feeding metabolic interactions towards the state of healthy individuals. Assessment of metabolic interactions in responders and non-responders to therapy may identify predictive microbial metabolite markers as well as aid our understanding how the intestinal microbiota modulates therapy outcome in IBD.

Disclosure: Konrad Aden has received funding from Pfizer to execute parts of this study. The grant did not affect study design at any time point. All other authors have nothing to disclose

New frontiers in pancreatic neoplasias
16:00-17:30 / F2

OP276 AGE, OVERWEIGHT AND INITIAL CYST SIZE ARE ASSOCIATED WITH THE RISK OF PROGRESSION OF BD-IPMN UNDERGOING FOLLOW-UP

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Introduction: Current guidelines do not suggest personalizing the follow-up of BD-IPMN without suspicious signs of malignancies according with their initial features of with patients' characteristics. Furthermore, the need to maintain follow-up (FU) in the long-term is debated.

Aims & Methods: To investigate the occurrence of progression of the cystic lesions and of Worrisome Features (WF) constituting a relative indication for surgery and analyse factors associated with them in a prospective cohort of IPMN-BD under FU. Data on BD-IPMNs diagnosed 2003-2017, without any indication for surgery at diagnosis and under FU in two institutions, were input in a prospective database containing initial patients' and cysts' characteristics. The primary outcome was the progression of the cyst defined as either an increased cyst's size (>2 mm), development of a new cyst or appearance of any indication for surgery. Occurrence of WF was separately considered as a secondary outcome. Fisher test and Student's t-test were used to analyze categorical and continuous variables. Survival probability was calculated with the Kaplan-Meier curve and Cox analysis employed to calculate hazard ratios (HR). A p< 0.05 was considered statistically significant.

Results: Of 530 BD-IPMN with mean age of 65.2 years, 62.4% were female, 54.7% were multifocal and the initial mean size of the largest cyst was 14.3 mm. The mean length of FU was 58.9 months. 32 deaths were recorded, of which 3 pancreas-related. 265 patients had any progression (50%) and 82 (15.5%) developed WFs or HRS; 13 patients were operated (2.8%) of whom 5 had a carcinoma. The rate of progression and occurrence of WFs were 101.9/1000 p-y and 31.5/1000 p-y. The mean time to any progression was 43.7 months and the mean time to WFs was 54.2 and 14% of patients developed the first progression event and 4.5% WF or HRS after 60 months. A ROC curve identified the cut-off of 15 mm as best discriminator of progression (sensitivity 67.9%, specificity 44.5%) and of WF/HRS appearance (sensitivity 64.6%, specificity 67.2%). In a multivariate Cox regression analysis, among initial patients' and cysts' characteristics: age (HR 1.01 per year; 95%CI 0.99-1.02; 0.060), BMI>25 (HR=1.32; 95%CI 1.02-1.71; 0.030), and cyst diameter >15mm (HR 1.32; 95%CI 1.03-1.69; 0.025) were associated with any progression. Only age (HR 1.026; 95%CI 1.00-1.048; 0.022) and

initial cyst diameter>15mm (HR 3.35; 95%CI 2.12-5.30; < 0.0001) were associated with development of WFs or HRS during follow-up. Sex, smoking, family history of any cancer or of pancreatic cancer, alcohol intake and multifocal cysts were not associated with progression risk, while previous diabetes was significant only at the univariate analysis.

Conclusion: In this cohort of BD-IPMNs, the rate of progression and of occurrence of WFs were 10% and 3% per year. A quote of these events occurred after 5 years of negative FU. Age, overweight and initial cyst size>15mm are predictors of progression. These data support the role of metabolic factors in determining progression of BD-IPMNs and offer the opportunity to tailor follow-up intervals based on simple criteria available at diagnosis.

Disclosure: Nothing to disclose

OP277 OXALIPLATIN AND 5-FLUOROURACIL (FOLFOX) IN ADVANCED WELL-DIFFERENTIATED DIGESTIVE NEUROENDOCRINE TUMORS: A MULTICENTER NATIONAL RETROSPECTIVE STUDY FROM THE FRENCH GROUP OF ENDOCRINE TUMORS (GTE)

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Introduction: Oxaliplatin-based regimens have shown promising antitumor activity in digestive neuroendocrine tumors (NETs), however the available data are limited. Our aim was to assess the tumor response and survival in a large series of patients treated with oxaliplatin and 5-fluorouracil (FOLFOX) for advanced digestive NETs.
Aims & Methods: All patients with advanced well-differentiated digestive NETs treated with at least 3 cycles of FOLFOX between 2004 and 2018 in 12 centers of the French GTE, were retrospectively included. Best response according to the RECIST 1.1 criteria, progression-free survival (PFS) and overall survival (OS) were evaluated. The prognostic factors for PFS were investigated by multivariate analysis using a Cox proportional hazard model including variables with a p value ≤ 0.20 in univariate analysis.
Results: One hundred and forty-nine patients were included. Primary tumor location was pancreas (n=88), small intestine (n=37), stomach (n=7), rectum (n=4) and unknown without lung tumor at CT scan (n=13). Partial response rate was of 31% for pancreatic NETs, 13% for small intestine NETs, 14% for gastric NETs, 25% for rectal NETs and 38% for unknown primary NETs. Median PFS were, respectively, 9, 9, 14, 4 and 6 months, and median OS were 30, 28, 31, 25 and 15 months. Significant poor prognostic factors for PFS after FOLFOX in digestive NETs were: progressive disease (HR=2.5, p=0.018), hepatic involvement > 50% (HR=1.8, p=0.009), prior targeted therapy (HR=1.5, p=0.048) and rectal primary tumor (HR=4.2, p=0.01). Among pancreatic NETs, the 9 insulinomas had a 22 months PFS versus 9 months for the others (p=0.025), and serum glucose normalization was obtained in 8 out of 9 cases.
Conclusion: FOLFOX has a promising clinical activity, especially in insulinomas.
Disclosure: Nothing to disclose

Bile duct stone management
16:00-17:30 / F3

OP278 ENDOSCOPIC MANAGEMENT OF DIFFICULT BILE DUCT STONES: RESULTS OF A RANDOMIZED TRIAL

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Introduction: Although ERCP is the reference standard, the optimal approach to efficient treatment of difficult bile duct stones is not standardized. While single operator cholangioscopy-guided laser lithotripsy (SOC-LL) and large balloon sphincteroplasty (LBS) are effective rescue techniques, their precise roles in the treatment algorithm is unclear.
Aims & Methods: To evaluate the role of SOC-LL and LBS for the treatment of difficult bile duct stones.
Patients with difficult bile duct stones were randomized to undergo SOC-LL or LBS. Difficult bile duct stones were defined as stones (≥12mm) that failed retrieval attempts using balloons or baskets and required advanced interventions. The main outcome measure was procedural efficiency defined as the ability to achieve ductal clearance without the need to cross-over to alternate treatment modality or require adjunctive mechanical lithotripsy. The secondary outcome measure was treatment costs.
Results: 66 patients were randomized equally to either cohort over a 2-year period. There was no significant difference in stone size (median, 15mm [IQR 12-18] vs. 14mm [IQR 12-15], p=0.097), number of stones (median, 3 [IQR 1-4] vs 3 [IQR 1-4, p=0.92]) or stone-duct size ratio (stone size/diameter of distal common bile duct in mm; median, 1.5 [IQR 1.0-1.8] vs. 1.3 [IQR 1.0-1.3], p=0.098) between the SOC-LL and LBS cohorts, respectively. More patients randomized to LBS required mechanical lithotripsy (33.3 vs. 3.0%, p=0.001) or cross-over to SOC-LL (27.3 vs. 6.1%, p=0.021) to achieve ductal clearance. On multivariate logistic regression analysis, after adjusting for patient demographics, stone characteristics and procedure details, not using SOC-LL (OR 13.5 [95% CI, 3.11-58.4], p=0.001) and stone-duct size ratio ≥1.2 (Odds ratio (OR) 5.0 [95% CI, 1.21-20.6], p=0.026) were significantly associated with procedural inefficiency. Although the procedural cost for SOC-LL was higher, there was no significant difference in total treatment costs between cohorts by generalized linear models (SOC-LL $16,684 vs. LBS $10,626; p=0.097).
Conclusion: When standard maneuvers fail, utilizing SOC-LL for the treatment of difficult bile duct stones should be the preferred first-line approach, particularly when size of the stone exceeds that of the distal bile duct.
Disclosure: Ji Young Bang, Shyam Varadarajulu and Robert Hawes are Consultants for Boston Scientific Corp. and Olympus America Inc.

OP279 EUS-DIRECTED TRANSGASTRIC ERCP (EDGE) VS LAPAROSCOPIC ASSISTED ERCP (LA-ERCP) VS ENTEROSCOPY ASSISTED ERCP (E-ERCP): A SINGLE CENTER EXPERIENCE

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Introduction: EUS-directed Transgastric ERCP (EDGE) is a novel technique for managing pancreaticobiliary diseases in patients with a history of Roux-en-Y Gastric Bypass (RYGB). Laparoscopic-assisted ERCP (LA-ERCP) and Enteroscopy-assisted ERCP (E-ERCP) are the current standard of care and these procedures can be challenging with limited success.
Aims & Methods: The aim of this study was to compare outcomes of EDGE, LA-ERCP and E-ERCP at a single tertiary-care academic center. Patients with a history of RYGB who underwent these procedures between January 2015 and March 2019 were included. Patient demographics, procedure time, technical success and complications of each group were recorded. Technical success was defined as cannulation of the intended duct. 'Difficulty of procedure' was defined as level of difficulty documented by per-

forming endoscopist or defined as difficult if there was performance of precut sphincterotomy or >2 failed attempted cannulations of intended duct. Statistical analysis was performed using SPSS 23 (IBM, Armonk, NY). **Results:** Forty-eight patients (18 EDGE, 19 LA-ERCP and 11 E-ERCP) were included in this study. Mean procedure time for EDGE patients was 72 ± 27 minutes, compared to 150 ± 58 and 108 ± 39 minutes for LA-ERCP and E-ERCP, respectively (p= < 0.01). The difficulty level was recorded as 'not difficult' for 100% (18/18) of EDGE procedures, compared to 79% (15/19) for LA-ERCP and 45% (5/11) for E-ERCP patients (p=< 0.01). Technical success for EDGE was 100% (18/18) compared to 89% (17/19) and 82% (9/11) for LA-ERCP and E-ERCP, respectively (p=0.21). While none of the EDGE patients developed post-procedure pancreatitis, this was observed in 5% (1/19) of LA-ERCP and 9% (1/11) of E-ERCP patients (p=0.47). The hospital length of stay was shorter for EDGE patients at 1.09 days, compared to 2.35 and 3.47 days for LA-ERCP and E-ERCP, respectively (p=0.04).

	EDGE (n=18)	LA-ERCP (n=19)	E-ERCP (n=11)	p-value
Age (mean)	61.78 +/- 11	61.52 +/- 13	68 +/- 16	0.39
Gender (F)	78% (14)	68% (13)	64% (7)	0.69
Indications:				0.96
Choledocholithiasis	39% (7)	68% (13)	27% (3)	
CBD Dilation	28% (5)	0% (0)	9% (1)	
PD Dilation	11% (2)	0% (0)	0% (0)	
Biliary leak/sludge/stricture	28% (5)	0% (0)	27% (3)	
Cholangitis	0% (0)	5% (1)	18% (2)	
Pancreatitis	0% (0)	11% (2)	18% (2)	
Papillary stenosis	0% (0)	5% (1)	0% (0)	

[Baseline Characteristics of patients]

Conclusion: Our study indicates that EDGE is characterized by significantly shorter procedure time and lower rates of procedural difficulty when compared to LA-ERCP and E-ERCP. We also observed non-statistically significant trend towards superior safety and efficacy profile of EDGE.
Disclosure: Nothing to disclose

Risk assessment, diagnosis and management in colon cancer
16:00-17:30 / Barcelona

OP280 EUS-GUIDED PORTAL VENOUS BLOOD ACQUISITION FOR CIRCULATING TUMOUR CELLS IN PATIENTS WITH COLORECTAL CANCER

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Introduction: Analysis of circulating tumour cells (CTCs) has potential to be a prognostic marker for metastasis in different types of cancer (1). As opposed to peripheral blood collection, the use of endoscopic ultrasound (EUS) to acquire portal venous blood (PVA) for circulating tumour cells (CTC) enumeration has only been described for pancreatic cancer. The role of EUS- PVA in enumerating CTC's for other types of cancer is uncertain.
Aims & Methods: Hence, the aim of the current study is to perform a feasibility study on EUS PVA for enumerating and characterising CTC's in patients suffering from colorectal cancers. We hypothesise that EUS-guided PVA is safe, feasible and effective in obtaining CTC.
Patients suffering from stage 2 to 4 colorectal carcinomas were recruited. Recruited patients had one 9 ml aliquots of peripheral blood collected at the same time of the EUS procedure. The patient then underwent EUS-PVA and two sets of 9 ml aliquots of portal venous blood were collected (PVB). During EUS-PVA, the liver was first assessed for presence of occult metastasis from the duodenum (right lobe) and also the stomach (left lobe).

Under EUS-guidance, the left and right PVs were identified. After verifying flow signal by Doppler, a 19-gauge EUS-FNA needle was advanced transhepatically into the portal vein and two sets of 9 ml aliquots of blood were aspirated. The puncture site was then be monitored under EUS for 3 minutes to observe for any bleeding before the needle was withdrawn. Epithelial-derived CTCs were sorted magnetically based on expression of epithelial cell adhesion molecules. Only those with a proper morphology and found to be CD45 negative and positive for cytokeratins 8 and 18 were considered to be CTCs.
Results: This prospective, single-centre study was performed in the Prince of Wales Hospital in Hong Kong between December 2016 and March 2019. 56 patients with stage 2 and 3 colorectal carcinomas were recruited. Technical success was 100% and none of the patients suffered from adverse events. The colonic tumors were located in the ascending colon (11%), transverse colon (11%), descending colon (7%), sigmoid colon (50%), rectum (21%). 85% of the patients had T2 and T3 tumours and 42.9% were node positive. CTCs were obtained in 80.5% of the PVA and 37.5% in peripheral blood. The mean (S.D.) of CTCs obtained by EUS-guided PVA was significantly higher than that in peripheral blood samples [154.6 (213.4) vs 6.78 (11.2), P< 0.0001].
Conclusion: This study has shown that EUS-guided PVA to be a safe, feasible and effective method in collecting CTCs for enumeration and characterisation in colonic cancer. More CTC's were obtained from the portal vein and the numbers were significantly higher than that of peripheral blood. Further studies are required to be performed to evaluate its potential as a prognostic marker for survival and liver metastasis in colorectal cancer patients.
References: 1. Cristofanilli M, Budd G, Ellis M et al. Circulating Tumor Cells, Disease Progression, and Survival in Metastatic Breast Cancer. New England Journal of Medicine. 2004;351(8):781-791. doi:10.1056/nejmoa040766 2. Catenacci D, Chapman C, Xu P et al. Acquisition of Portal Venous Circulating Tumor Cells From Patients With Pancreaticobiliary Cancers by Endoscopic Ultrasound. Gastroenterology. 2015;149(7):1794-1803.e4. doi:10.1053/j.gastro.2015.08.050
Disclosure: Nothing to disclose

OP281 CLINICAL IMPORTANCE OF COLONOSCOPY IN PATIENTS WITH EARLY GASTRIC CANCER TREATED BY ENDOSCOPIC SUBMUCOSAL DISSECTION (COMPARISON WITH PATIENTS WITH POSITIVE FECAL IMMUNOCHEMICAL TEST RESULTS)

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Introduction: Second primary cancers are a leading cause of morbidity and mortality among cancer survivors all over the world. Colorectal neoplasms are the most commonly observed tumors in patients with gastric cancer.
Aims & Methods: We examined the usefulness of colonoscopy (CS) for patients undergoing gastric endoscopic submucosal dissection (ESD). Of the 312 patients who underwent ESD for early gastric cancer in the 3 years between January 2015 and December 2017, 143 patients receiving CS were included (ESD group) in this study. And 874 asymptomatic patients who underwent CS because of positive fecal immunochemical test (FIT) during the same period were selected (FIT group). Propensity score matching was used to adjust baseline characteristics (BMI, alcohol, smoking, diabetes mellitus, hypertension, hyperlipidemia, liver disease, renal failure and other organs cancer) between two groups. In this study, we compared with the background of two groups and statistically analyzed.
Results: The total number of colorectal neoplasm were found in 90 cases (62.9%) in the ESD group, on the other hand, 81 cases (56.6%) in the FIT group (p=0.012). Advanced adenoma and carcinoma (AAC) were found 30 cases (20.1%) of ESD group and 16 cases (11.2%) of FIT group (p< 0.01).
Conclusion: In patients undergoing gastric ESD, CS appears to be necessary for detecting synchronous double neoplasms.
Disclosure: Nothing to disclose

OP282 BACTERIAL ALTERATIONS IN POST-CHOLECYSTECTOMY PATIENTS ARE ASSOCIATED WITH COLORECTAL CANCER

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Introduction: Previous studies showed that cholecystectomy increased the enterohepatic recirculation rates and the secretion rate of bile acids, which made an increased exposure of the bile acid pool to gut bacteria. However, what kind of alteration after cholecystectomy in patients was unclear. Moreover, many meta-analyses also indicated inconsistent incidences of colorectal cancer (CRC) in patients after cholecystectomy. Thus, our study was to investigate the changes and roles of bacterial microbiota after cholecystectomy and tried to clarify the clinical significance of the changes.

Aims & Methods: 104 subjects were recruited for two groups, post-cholecystectomy patients (PC, n=52) and healthy controls (HC, n=52). 9 of PC patients had precancerous lesions and CRC (preCA_CRC), which confirmed by colonoscopy mucosal pathology. The demographic data and basic clinical data of each group were recorded. Qualified stool samples were collected for 16S rRNA gene V3-4 region amplicons seqencing to profile the overall structure of the bacterial microbiota. Based on the Operational Taxonomic Units (OTUs), bacterial composition, functional annotation, and the correlation with environmental factors were analyzed respectively.

Results: The species richness of gut bacterial microbiota was increased in PC patients, and the composition was quite changed. At the genus level, the abundance of *Bacteroides, Parabacteroides* which took part in bile acid metabolism and *Prevotella* which could promote inflammation increased; the abundance of *Faecalibacterium* which participated in butyrate and short-chain fatty acids biosynthesis and *Bifidobacterium* which could inhibit inflammation decreased. *Megamonas funiformis* and *Lactobacillus mucosae* were characteristic species which could distinguish PC patients from HC. Functional analysis showed that pathways in cancer, especially in CRC, were enriched in PC group. We collected about 10 kinds of indexes as environmental factors for correlation analysis with bacterial composition. Furthermore, the duration after cholecystectomy was the critical factor, which mainly affected the composition of the bacterial microbiota. Although there was no statistical difference, preCA_CRC patients had lower species richness than the subjects of the cancer-free patients after cholecystectomy. The abundance of *Sutterella* and *Flavonifractor*, two protective genera further decreased in preCA_CRC patients, additionally, the abundance of *Megamonas funiformis* was significantly negatively correlated with the progression of CRC.

Conclusion: Our study showed a specific alteration in PC patients, and the duration after cholecystectomy was the critical factor which affected the bacterial composition. *Megamonas funiformis* was not only the characteristic species of PC patients, but also associated with the progression of CRC. These findings suggest that it is necessary to pay more attention to the long-term follow-up of PC patients, and *Megamonas funiformis* may play a pivotal role in related-disease studies.

Disclosure: Nothing to disclose

OP283 COLORECTAL CANCER DRIVES LOSS OF SIRP ALPHA AND INCREASED CD103 ON LAMINA PROPRIA DENDRITIC CELLS IN MACROSCOPICALLY HEALTHY COLONIC MUCOSA: A PATHWAY FOR IMMUNE EVASION?

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Introduction: Dendritic cells (DC) are the major antigen presenting cells of the immune system and orchestrate downstream cellular immune responsesorchestrate the cellular immune response. Within the colonic mucosa, DC populations can be subdivided based on expression of SIRP-alpha (CD172a) and CD103 (alpha E integrin). SIRP-alpha inhibits Fc receptor mediated functions in cells bearing its receptor (CD47) and in doing so recognises the CD47 expressing cell as "self". SIRP-alpha expressed on myeloid cells (DCs and macrophages), via the CD47/SIRP-alpha axis, plays an essential role in "self" recognition, protecting healthy cells from phagocytosis.

CD103 is a mucosal tissue marker and CD103+DC play a vital role in maintaining intestinal immune homeostasis by promoting protective immune responses, including upregulation of gut-homing markers on T cells thus inducing a "tolerogenic" immune response. CD103 expressing DCs are responsible for upregulating CCR9 and $\alpha 4 \beta 7$ - cell surface markers on T cell subtypes essential for homing to mucosal surfaces including the gut.

Aims & Methods: The aim of this study was to explore the effect colorectal cancer has on this important immunological axis in the gut and in doing so identify a further pathway by which cancer evades the immune system. Colonic biopsies were taken from macroscopically healthy mucosa in disease free subjects (n=12) at colonoscopy and colorectal cancer (CRC) patients (n=8) at the time of surgery. Lamina-propria leucocytes were isolated by enzymatic tissue digestion which was performed in a two stage process with DTT and EDTA followed by collagenase and liberase. Cell surface staining was performed using fluorochrome antibodies for SIRP-alpha and CD103. Expression of SIRP-alpha and CD103 on DCs was examined by flow cytometry.

Results: Proportions of CD103-veSIRPa+ve and CD103+SIRPa+ DC populations were significantly reduced in the CRC group (p< 0.0001 and p< 0.0002) whilst CD103+veSIRPa-ve and CD103-veSIRPa-ve DC populations were significantly increased in the CRC group (p< 0.0015 and p< 0.0001).

Conclusion: Many cancers themselves highly express CD47 which allows evasion of the cellular immune response. Herein we demonstrate changes to DC signalling in cancer perhaps reducing an appropriate aggressive response to CRC by loss of SIRP-alpha expression. Notably these immunological changes are taking place in what appears "healthy" bowel tissue away from the tumour site.

Disclosure: Nothing to disclose

OP284 WITHDRAWN

OP285 IS DECOMPRESSING STOMA BETTER THAN STENT AS BRIDGE TO SURGERY FOR LEFT-SIDED OBSTRUCTIVE COLON CANCER? A NATIONWIDE, PROPENSITY-SCORE MATCHED ANALYSIS

Veld J.[1], Amelung F.[2], Borstlap W.[1], van Halsema E.[1], Consten E.[2], Siersema P.[3], ter Borg F.[4], van der Zaag E.[5], de Wilt H.[3], Fockens P.[1], Bemelman W.[1], van Hooft J.E.[1], Tanis P.[1]
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Introduction: Bridge to elective surgery with self-expandable stent (SEMS) placement is still a debated alternative to emergency resection of left-sided obstructive colon cancer (LSOCC) because of oncological concerns. Another bridge to surgery strategy is decompressing stoma construction. However, studies comparing decompressing stoma and SEMS are scarce. If we could directly compare these two methods, we may improve treatment and consequently health-related outcomes such as mortality and morbidity in patients with LSOCC.
Aims & Methods: Our aim was to directly compare decompressing stoma and SEMS as bridge to surgery strategies for LSOCC. All patients with LSOCC who were treated with curative intent between 2009 and 2016 were included from the Dutch ColoRectal Audit, a prospective, (mandatory) national registry. Additional diagnosic, procedural, and long-term outcome data were retrospectively collected through individual patient files. Patients with locally advanced tumours were excluded from the analysis. Following propensity-score matching, patients treated with a decompressing stoma were compared with patients treated with SEMS placement as bridge to surgery.
Results: Seventy-five of 77 Dutch hospitals completed data of 345 decompressing stoma and 229 SEMS patients treated with curative intent. Propensity-score matching resulted in two groups of each 121 patients. Median follow-up was 36 (IQR 15-59) months and 31 (IQR 15-56) months, respectively (p=0.593). Decompressing stoma patients showed more primary anastomoses (86% versus 75%, p=0.024), more stomas after resection (67% versus 29%, p< 0.001), fewer major resection-related complications (6% versus 15%, p=0.023), and more reinterventions including stoma reversal (58% versus 28%, p< 0.001). Following decompressing stoma and SEMS, 3-year locoregional recurrence was 12% and 19% (HR 0.62, 95% CI 0.30-1.28, p=0.200), 3-year disease free survival 64% and 57% (HR 0.90, 95% CI 0.61-1.33, p=0.600), and 3-year overall survival 78% and 72% (HR 0.77, 95% CI 0.48-1.22, p=0.260), respectively.
Conclusion: This nationwide, propensity-score matched study comparing decompressing stoma and SEMS for non-locally advanced LSOCC revealed both advantages and disadvantages of either of the two bridging techniques. Based on the currently available evidence, there is no scientific basis to recommend one over the other.

HPB on fire
16:00-17:30 / Hotspot

OP286 DEVELOPMENT AND VALIDATION OF A PATIENT REPORTED OUTCOME MEASUREMENT IN ACUTE PANCREATITIS: THE PAN-PROMISE STUDY

de-Madaria E.[1], Sánchez-Marin C.[1], Carrillo I.[2], Chooklin S.[3], Mejuto R.[4], Mauriz V.[4], Márta K.[5], Hegyi P.[6], Barbu S.[7], Lauret-Braña E.[8], Gomes A.P.[9], Martins R.[9], Lourenço L.C.[9], Nunes V.[9], Matia R.[9], Ruiz-Rebollo L.[10], Garcia-Rayado G.[11], Lozada-Hernández E.E.[12], Pereira J.A.[13], Negoi I.[14], Espina S.[15], Bernal V.[15], Bajador-Andreu E.[15], Kamal A.[16], Hollenbach M.[17], Litvin A.[18], Marra-Lopez Valenciano C.[19], Bolado F.[19], Vargas R.D.[20], Czako L.[21], Gasiorowska A.[22], Fraile-González M.[23], Abando-Zurimendi A.[23], Cheon Y.K.[24], Triantafyllou K.[25], Gatos C.[25], Romero-Mosquera B.[26], Rodríguez-Oballe J.A.[27], Miguel-Salas I.[27], Pascual-Moreno I.[28], Singh V.K.[16], Mira J.J.[2]
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Introduction: The development of clinical trials in acute pancreatitis (AP) is limited by the absence of adequate outcome variables. Organ failure (OF) and mortality are infrequent, so thousands of patients are needed to detect differences among treatment arms. Despite being the patients the center of the medical act, their assessment is rarely considered.
Aims & Methods: PAN-PROMISE aims to develop and validate a Patient Reported Outcome Measurement scale (PROMS) in AP. Reliability, content validity, apparent, construct and empirical validity indexes were calculated. Firstly, a qualitative study was carried out in patients and gastroenterologists from 2 centers; 7 symptoms were retrieved and the PROMS instrument was designed (PROMISE scale).
Afterwards, an international prospective multicenter cohort (29 centers from 15 countries, 527 patients) was performed to validate the instrument. PROMISE scale was measured in the 1st 24h, 48h, 5th and 7th day, at discharge and 15d after discharge.
Results: The 7 items of PROMISE are grouped into a coherent measure giving rise to a single dimension with factor saturations of the items that exceed the minimum of 0.50: between 0.63 and 0.75, explained variance 45.1% in the mild cases and 0.57-0.73, variance explained 43.3% in the moderate-to-severe cases. The internal consistency of the relationships between the items exceeds the degree of adjustment required for a new instrument of this type: Cronbach's Alpha= 0.77 in mild cases and 0.76 in moderate-to-severe. The stability of the measurement calculated by test-retest (at discharge and 15d after discharge) confirms the reproducibility of the measurement with values in the Student's T statistic without statistical significance, p> 0.05 (the clinical improvement at discharge is sustained after an adequate temporary period). The total PROMISE score was directly related to the health status score of the EORTC QLQ-C30 quality of life scale (beta -1.34, 95% CI -2.55, -0.13). PROMISE allows detecting changes in the clinical evolution of patients during hospital admission: total value

of the scale (maximum 35) at admission 33.1 48h 19.6, 5ºd 11.1, 7ºd 7.7, at discharge 5.3 (p < 0.0001). Mild cases presented lower scores in the evolution than moderate-to-severe severe ones (p < 0.001) except at discharge.

Conclusion: The PROMISE scale satisfies standardized criteria of reliability and validity. PROMISE can be used to test new therapeutic interventions in AP to detect differences in the patients´ assessment of their symptoms.

Disclosure: Nothing to disclose

OP287 PRELIMINARY DATA OF THE PINEAPPLE-P STUDY: 30-80% OF ACUTE PEDIATRIC PANCREATITIS IS NOT DIAGNOSED DUE TO THE LOW AWARENESS

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Introduction: Abdominal pain is one of the most common complaints in childhood and it is responsible for 10-20% of emergency visits. One of the causes of abdominal pain in children is acute pancreatitis (AP). Our retrospective data collection shows that the prevalence of acute pediatric pancreatitis (APP) depends on the diagnostic awareness, hence ranges between 0.2-1.14% in children with abdominal pain.

Aims & Methods: The aim of the PINEAPPLE-P study is to estimate the real worldwide incidence of APP in children with abdominal pain. Furthermore, we would like to develop an EBM guideline to establish a scoring system in order to evaluate the necessity of diagnostic steps for APP in children with abdominal pain. Patients were divided into two groups: 1) abdominal pain with APP (APP group) 2) abdominal pain without APP (non-APP group). PINEAPPLE (Pain In Early phase of Pediatric Pancreatitis) is a registered (ISRCTN35618458), observational, multinational clinical trial (http://www.ncbi.nlm.nih.gov/pubmed/26641250). In the PINEAPPLE-P subtrial detailed patient data are collected, serum pancreatic enzyme measurement (sPEM) and abdominal imaging are performed prospectively for children with abdominal pain turning up at ER units. Until now 769 patients have been enrolled.

Results: 1.7% (13/769) of the children with abdominal pain was diagnosed with APP. The diagnosis was based on the fulfilment of all three diagnostic criteria (abdominal pain, sPEM elevation more than three times upper limit of normal, alteration on imaging characteristic for AP) in 6 patients (46.2%). Beside the abdominal pain in 5 cases (38.5%) the sPEM elevation and in 2 cases (15.4%) the imaging were positive for APP. Epigastric (46.2%) and left upper abdominal pain (23.1%) occurred significantly more often in children with APP than in non-APP group (p=0.004, p=0.01). Patients with APP had abdominal pain for significantly longer period of time than non-APP patients (151.4±256.8 hours vs 70.2±140.9 hours; p=0.0043). Significantly more patients had positive family history for pancreatitis in APP group compared to non-APP group (53.8% vs 13.8%; p< 0.0001). Positive family history of pancreatitis and upper abdominal pain outstanding more than 3 days were characteristic for APP.

Conclusion: The real incidence rate of APP is 1.7%. Diagnostic workup for APP should be performed in children with upper abdominal pain outstanding more than 3 days and positive family history for pancreatitis.

Disclosure: Nothing to disclose

OP288 THE ROLE OF HBSAG LEVELS IN THE OUTCOMES OF NON-CIRRHOTIC PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B WHO DISCONTINUE LONG-TERM ANTIVIRAL THERAPY

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Introduction: HBsAg serum levels at the end of treatment (EOT) have been associated with subsequent HBsAg loss in patients with HBeAg- negative chronic hepatitis B (CHBe-) who discontinue long-term nucleos(t)ide analogues (NA). However, their prognostic value for predicting post-NA relapse remains uncertain. This study assessed relapse, retreatment and HBsAg loss rates based on HBsAg levels at EOT in a large cohort of non-cirrhotic CHBe- patients from 4 liver clinics in Greece.

Aims & Methods: The study included 136 patients (M/F: 87/49, age: 55±23 years) who discontinued NA therapy after a minimum on-NA virological remission of 5.65± 2.39 years and had at least 12 months of post-NA follow-up. Patients with coinfection, cirrhosis, cancer or liver transplantation were excluded. Patient characteristics before therapy as well as ALT, HBV DNA and HBsAg levels at EOT and post-NA were recorded. Patients were divided in 3 groups based on EOT HBsAg levels: A:≤100 IU/mL, B:>100-1000 IU/mL, C:>1000 IU/mL. Study endpoints were virological relapse (HBV DNA>2000 IU/mL), clinical relapse (HBV DNA>20,000 IU/mL & ALT>ULN), retreatment and HBsAg loss.

Results: The median post-NA follow-up was 20 (IQR: 14-66) months. Cumulative rates of virological relapse did not differ significantly among patients of group A, B, C being 46%, 62%, 46% at 6 and 51%, 67%, 77% at 12 months, respectively (log-rank, P=0.25). Cumulative rates of clinical relapse were significantly different among groups A, B, C and were 16%, 30%, 36% at 6 and 16%, 30%, 44% at 12 months, respectively (log-rank, P=0.03). No new case of clinical relapse was observed after 12 months and only two cases of virological relapse were observed between 12 and 24 months of post-NA follow-up. Cumulative retreatment rates differed significantly between group A, B, C being 8%, 18%, 29% at 6 and 8%, 22%, 32% at 12 months, respectively (log-rank, P=0.01). Finally, cumulative rates of HBsAg loss also differed significantly among groups A, B, C being 40%, 9%, 7% at 12 months, respectively (log-rank, P< 0.001).

Conclusion: Post-NA outcomes differ significantly in CHBe- patients with different EOT HBsAg. Patients with EOT HBsAg ≤100 IU/mL have significantly lower risk of clinical relapse or retreatment and higher probability of HBsAg loss. Therefore, non-cirrhotic CHBe- patients with HBsAg ≤100 IU/mL can safely stop antiviral therapy and often achieve post-NA functional cure (HBsAg loss) in the first 12 months after discontinuation.

Disclosure: Nothing to disclose

OP289 SIMULTANEOUS BARIATRIC SURGERY AND LIVER TRANSPLANT ASSOCIATED WITH WORSE OUTCOMES

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Introduction: Obesity is directly linked with development of non-alcoholic steatohepatitis (NASH), which is one of the leading indications for

liver transplantation (LT). Bariatric surgery (BS) in the pre-LT setting has emerged as a successful treatment option for obesity, which improves transplant-free survival and other outcomes, or is used as a way to decrease the BMI and positively influence the patient's transplant candidacy status. BS at the time of transplant (i.e. Sleeve Gastrectomy) has been argued to decrease costs, length of stay (LOS), stress and pain in small studies. To date, larger studies examining outcomes lack.

Aims & Methods: The aim was to determine inpatient outcomes of patients undergoing simultaneous BS and LT compared to LT alone. Case-control study using the 2012-2016 NIS. All patients with ICD9-10CM procedural codes for LT were included. Patients who did not undergo BS with a BMI< 30kg/m², and patients undergoing LT after having undergone BS during the same admission were excluded. The cohort was stratified into two groups depending on whether they had undergone simultaneous BS at the time of LT or not. Primary outcome was determining the odds of inpatient mortality in patients undergoing simultaneous BS at the time of LT compared to patients who underwent LT alone. Secondary outcomes included determining inpatient morbidity, resource utilization, hospital length of stay (LOS), and inflation-adjusted total hospital costs and charges. Multivariate regression analyses were used to adjust for age, gender, Charlson Comorbidity Index, income in patient zip code, hospital region, location, size and teaching status.

Results: A total of 32,580 patients were identified as having LT in the study period, of which 255 underwent simultaneous BS. The mean patient age was 30.1 years in patients who underwent simultaneous BS compared to 55.7 years in patients who underwent LT alone (49% and 39% were female, respectively). For the primary outcome, patients undergoing simultaneous BS had adjusted mortality odds of 14.01 (p< 0.01) compared to patients undergoing LT alone.

For the secondary outcomes, patients with simultaneous BS also had increased odds of shock and total parenteral nutrition (TPN), compared to LT alone. Patients undergoing simultaneous BS had increased additional adjusted hospital costs, additional hospitalization charges and LOS (Table 1).

Variable	Adj. OR / Adj. Mean	95%CI	p-value
Inpatient Mortality	14.05	4.76-41.49	<0.01
Shock	5.73	2.36-13.91	<0.01
TPN	9.42	2.58-34.34	<0.01
AKI	0.73	0.37-1.43	0.36
Multi-organ failure	1.04	0.56-1.98	0.89
ICU	1.55	0.75-3.24	0.24
Additional Adjusted Costs	$177,698	93309,262088	<0.01
Additional Adjusted Charges	$555,072	283609,826536	<0.01
Additional Adjusted LOS (days)	29.1	16.7,41.4	<0.01

[Adjusted odds ratio and additional adjusted means in patients undergoing simultaneous BS at the time of LT compared to patients undergoing LT alone.]

Conclusion: Patients undergoing simultaneous bariatric surgery at the time of liver transplant display increased odds of inpatient mortality, morbidity, hospital costs, charges and length of hospitalization during the index admission for liver transplant. The outcomes may vary significantly with existing studies, as not only sleeve gastrectomies were included in this study, but all varieties of bariatric surgical procedures. This may reflect the burden that an additional surgical procedure may impose on patients undergoing a liver transplant. Large prospective studies are needed to better elucidate the outcomes of patients not only during the index admission for liver transplant, but also in the longer term.

Disclosure: Nothing to disclose

OP290 ITALIAN MULTICENTRIC SURVEY ON DAILY PRACTICE FOR AUTOIMMUNE PANCREATITIS: CLINICAL PRESENTATION, DIAGNOSIS, TREATMENT AND EVOLUTION TOWARD PANCREATIC INSUFFICIENCY

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Introduction: Autoimmune pancreatitis (AIP) is a peculiar form of chronic pancreatitis of presumed autoimmune etiology. Several guidelines have been published in recent years. An attempt to unify the different guidelines have hesitated in the International Consensus Diagnostic Criteria (ICDC) guidelines for AIP. However the application of these guidelines can be complex and articulated. Furthermore the natural history, the best treatment strategy and the final evolution of this relatively new disease is not well known.

Aims & Methods: The aim of this study is to analyze, in a large cohort of patients from several Italian centers, representative of all national area, the daily practice in "real lyfe" regarding AIP, in terms of diagnosis, treatments, relapses, long-term outcomes and adherence to the ICDC guidelines. This observational multicenter retrospective survey was promoted and coordinated by the Italian Association of Hospital Gastroenterologists (AIGO), and was endorsed by AISP (Italian Association for the Study of the Pancreas). Data from 173 AIP patients from 14 different institutions in Italy, distributed along the entire national territory, were retrospectively analyzed.

Results: 106 patients were classified as type 1 AIP, 48 as type 2 AIP and 19 as AIP-Not Otherwise Specified. Epidemiological, clinical, radiological, serological characteristics, relapses and outcome were similar to the previously reported ones for different types of AIP. However, in our cohort endoscopic histology was available merely in 86/173 (49.7%). Pancreatic EUS-FNA/B cyto-histology was obtained more frequently in AIP1 (57/106 patients, 53.8%) compared with AIP2 (13/48 patients, 27.1%) (p< 0.01), and was judged diagnostic for AIP in 43/57 (75.4%) AIP1, 10/13 (76.9%) AIP2 (p= 0.91). EUS-FNA/B of the pancreas was performed mostly in the focal form of AIP (85% of cases).

In the overall cohort an endoscopic histology diagnostic for AIP was obtained in only 61/173 (35.2%) of patients.

Most patients (123/173, 71.1%) were initially treated with steroids with a success rate of 92%. A maintenance steroid therapy was administered in 31/123 (25.2%).

Immunosuppressant drugs were rarely used (10.9%) and Rituximab in only 1.7%.

Steroid trial for diagnosis of AIP was performed in only 75/173 patients (43.3%) of patients and it was considered positive, in accordance to ICDC criteria, in 70/75 (93.3%).

Applying the ICDC criteria to our cohort of patients, a diagnostic mismatch in sub-classification between type 1 and type 2 AIP was founded in about one-third of cases, and 26 (15.2%) patients did not have enough diagnostic criteria for any type of AIP.

Fecal elastase-1 was evaluated in 31.2%, and it was pathologic in 59.2% of cases.

Conclusion: In our cohort of AIP patients, although diagnosis and classification for subtype was frequently possible, the low use of histology and steroid trial for diagnosis of AIP is probably responsible for a mismatch in subclassification. These findings showed that the ICDC Criteria for AIP are difficult to apply in daily-clinical practice, confirming what previously observed by other authors, and the need for modification and simplification of such criteria.

The majority of patients received steroids as initial treatment and as maintenance therapy, with a very high response rate. Immunosuppresants and Rituximab were rarely used.

Finally, the rate of exocrine pancreatic insufficiency development is not routinely investigated during the follow up of AIP, but is rather common in AIP patients. Fecal elastase test is inexpensive, non-invasive, and largely available, its use should be recommended.

Disclosure: Nothing to disclose

OP291 PRECISION ONCOLOGY IN PANCREATOBILIARY CANCERS: A LONGITUDINAL STUDY

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Introduction: Next-generation sequencing is widely used to identify therapeutic options for advanced cancer patients, but its utility in patients with pancreatobiliary cancer is not fully understood. We evaluated the rate of biologically actionable mutations and their impact on therapeutic decision-making in patients with pancreatobiliary cancers.

Aims & Methods: We conducted a retrospective cohort study of patients seen at Taussig Cancer Institute, Cleveland Clinic between 2013-16 with incurable solid tumor malignancies, in whom FoundationOne™ (Cambridge, MA) tumor genomic profiling was ordered. Genomics tumor board (GTB) recommendations and treatment decisions (on label, off label, or clinical trials) based on said recommendations were reviewed.

Results: Six hundred patients with solid tumor malignancies were included, of whom 53 had pancreatobiliary malignancies. For these, median age was 59.6 years, 62.2% (33/53) of patients were female, 86.8% (46/53) were Caucasian, and 11.3% (6/53) were African American. Eight samples (15.1%) had inadequate tissue. Twenty-seven (60%) had biologically actionable alterations. Of these, 21 were recommended treatment including clinical trials (N=19) or off-label drugs (N=2). The most common actionable targets for therapy were FGFR (5/21) and CDKN2 (3/21). Of patients with recommendations, only two (9.5%) received genomics-driven therapy compared to 31.7% (86/271) of patients with other solid tumor malignancies (p=0.03). One received an IDH1 inhibitor and a second received dabrafenib and trametinib for a BRAF alteration; both on clinical trials. At time of last follow-up, best responses were unknown and partial response, respectively.

Unavailability of local clinical trials (9.5%) and clinical trial ineligibility (9.5%) (i.e. low performance scores, other co-morbidities) were common reasons for lack of actionability.

Conclusion: Benefit from next-generation sequencing in the pancreatobiliary population is low with only 4.4% of tested patients eventually receiving genomics-based therapy. Benefit to patients will not improve until access to clinical trials is enhanced and/or patients are evaluated for these trials earlier in the course of their disease, when their functional status is likely to be higher.

Disclosure: Nothing to disclose

OP292 CANCER RISK IN PRIMARY SCLEROSING CHOLANGITIS

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Introduction: Primary sclerosing cholangitis (PSC) is a rare inflammatory bile duct disease closely associated to inflammatory bowel disease (IBD). The lifetime risk for cholangiocarcinoma is 10-20%. The risk for gallbladder cancer and colorectal cancer is also increased. The risk for extra intestinal cancer is less studied.

Aims & Methods: The aim of the present study was to evaluate risk of all cancers in a large well-defined cohort of PSC patients in Sweden. We have performed a national prospective matched cohort study of 1769 PSC patients from six university hospitals in Sweden. All patients were diagnosed according to accepted criteria. The cohort was linked to the national registers of cancer, death and the patient register. Through Statistics Sweden we were provided with up to ten controls for each PSC patient matched for sex, age and residence at time of diagnosis.

Patients were followed from one year after date of PSC diagnosis (index date) until date of first cancer diagnosis, liver transplantation, death, emigration date or the 31st of December 2016.

Kaplan Meier method was used to evaluate the cumulative risk of the different subgroups of cancer in PSC patients and their controls. In addition, we calculated sub distribution hazard ratio (SHR) using competing risks regression model.

Results: After exclusion, using index date, end of follow up or censoring events, 1430 PSC patients remained for final analyzis. Mean patient follow up time was 15.3 years (range 0.02-47.0). A concomitant IBD diagnosis was present in 88 % of the PSC patients. The hazard ratio for any cancer was 3.3 (95 % CI 2.9-3.7) in PSC patients compared to their matched controls. The risk of hepatobiliary cancer (cholangiocarcinoma, hepatocellular cancer and gallbladder cancer), pancreatic cancer, colorectal cancer, ventricular cancer, non-melanoma skin cancer and lymphoma was increased in PSC patients compared to their matched controls.

Conclusion: In this large cohort of well-defined PSC patients from Sweden we show, for the first time, an increased risk of ventricular cancer, non-melanoma skin cancer and lymphoma. The previously known high risk of hepatobiliary and colorectal cancer was confirmed.

Disclosure: Nothing to disclose

OP293 THE DIAGNOSTIC YIELD OF MAPPING BIOPSY AND ITS IMPACT ON SURGICAL CURABILITY IN EXTRAHEPATIC CHOLANGIOCARCINOMA

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Introduction: Surgery with negative tumor margin (R0 resection) offers survival benefits in patients with extrahepatic cholangiocarcinoma (ECC). Accurate preoperative diagnosis, especially for longitudinal cancer spread is required to plan an optimal surgery to achieve R0 resection. However, the diagnostic yield of transpapillary mapping biopsy (MB) for possible surgical ductal margins (PSDMs) and its impact on the operative curability remains unclear.

Aims & Methods: Between 2003 and 2018, 190 patients with ECC (85 perihilar and 105 distal) who underwent surgical resection after preoperative evaluation with ERCP were retrospectively examined. PSDMs were determined according to the planned surgery, and the diagnostic yield of MB for PSDMs was assessed based on the resected specimens as the gold standard. We also compared the operative curability in patients with and without preoperative MB for PSDMs.

Results: A total of 186 preoperative MB procedures were performed in 75 patients, and 242 samples were obtained from PSDMs under fluoroscopic

or cholangioscopic guidance. Among them, 88% (177/201) of samples obtained under fluoroscopic guidance included sufficient materials for the diagnosis (86% and 96% at the possible proximal and distal margin, respectively). On the other hand, 80% (88/110) of samples obtained under cholangioscopic guidance included sufficient materials (79% and 100% at the proximal and the distal margin, respectively). When MB for 75 proximal and 24 distal margins after radical surgical resection (33 pancreaticoduodenectomy, 24 hepatectomy, and 18 hepatopancreatoduodenectomy) was evaluated, MB under fluoroscopic guidance provided the diagnostic accuracy of 65% and 67% at proximal and distal margins, respectively. On the other hand, MB under cholangioscopic guidance provided the diagnostic accuracy of 61% and 72% at proximal and distal margins. Macroscopic residual cancer was observed in 20% (17% at the proximal margin, 6% at the distal margin) and R0 resection rate was 48%. MB for PSDMs was associated with an improved R0 resection rate (56% vs 43%, P = 0.08) and a lower incidence of macroscopic residual cancer at the surgical ductal margins (12% vs 20%, P = 0.10).

Conclusion: MB for PSDMs improved the possibility of curative resection in patients with ECC. Insufficient sampling for the proximal margin may result in the limited accuracy of the MB, especially under the cholangioscpoic guidance. The dedicated devices for MB should be developed.

Disclosure: Nothing to disclose

OP294 13 YEARS OF PROSPECTIVE PANCREATIC CANCER SURVEILLANCE: RESULTS OF THE DUTCH NATIONWIDE PROGRAM IN HIGH-RISK INDIVIDUALS

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Introduction: Surveillance of individuals at high risk for pancreatic ductal adenocarcinoma (PDAC) may reduce pancreatic cancer-related mortality.
Aims & Methods: Our aim was to determine the yield of a nationwide pancreatic cancer surveillance program in high-risk individuals in the Netherlands during a 13-year follow-up. From 2006 through 2019, asymptomatic individuals with an estimated more than 10-fold increased lifetime PDAC risk were enrolled. Surveillance commenced at the age of 50 or 10 years younger than cancer onset in the family, and ended at the age of 75. Surveillance was performed every 12 months with both MRI and EUS. For worrisome features the surveillance interval was shortened to 3 or 6 months or surgery was performed.
Results: 344 individuals from 229 families were enrolled (mean age 54 (SD 10.0) years, 44% male). 156 (45%) were germline mutation carriers and 188 (55%) were familial pancreatic cancer kindred. They were followed for a median of 44 (IQR 74) months and a total of 1616 person-years. Cystic lesions were found in 185 (54%) participants, which were ≥1 cm in 43 (13%). 14 (4.1%) participants underwent surgery for a suspect lesion (3 at baseline, 11 during follow-up). Pathological results in these patients revealed PDAC in 4 patients, low-grade precursor lesions in 7, a 5-mm neuroendocrine tumor in 1, autoimmune pancreatitis in 1, and no lesion in the resected specimen in 1. In total, 7 (2%) patients developed PDAC (median age 56 years, IQR 23). Two were diagnosed at baseline and underwent resection. Histology revealed a margin negative T2N1M0 and T1N0M0. Both patients died after 32 months. Another 5 individuals developed PDAC during follow-up, all of whom had prior abnormalities visible on both EUS and MRI (presumed side branch IPMN in 4, an indeterminate lesion in 2, a moderately dilated common bile duct in 1, and a main pancreatic duct stricture without visible mass in 1 case). Of the 5 PDACs detected at follow-

up, 3 (60%) were irresectable (survival 1-4 months), two of which had presented as symptomatic interval carcinomas, of which one appeared to have arisen separately from the known side branch IPMN. One of the 5 underwent an irradical resection (T3N1M0, survival 18 months), and one was radically resected (T1N0M0, alive, 18 months after diagnosis). The overall median survival for the 6 deceased PDAC patients was 11 (IQR 30) months.
Conclusion: In this relatively young cohort of individuals at high risk for PDAC, timely identification of relevant resectable lesions proved challenging with surveillance based on imaging alone with EUS and MRI. The quantitative effect of surveillance on resectability rates and survival remain difficult to assess because of the limited number of cases and possible lead-time bias. Biomarkers may hold better promise to improve the outcome of surveillance in individuals at high risk for PDAC.
Disclosure: PF is a consultant to Olympus, Cook Medical, Ethicon Endosurgery and received research funding from Boston Scientific. DLC is a consultant to Tramedico. JEH received research funding from Abbott and Cook Medical. She is a consultant to Boston Scientific, Cook Medical, and Medtronics. MJB received research funding from Boston Scientific, Cook Medical, Pentax Medical, 3M. He is a consultant to Boston Scientific, Cook Medical, Pentax Medical, Mylan, MediRisk, and Medicom. The other authors have nothing to disclose.

What's hot in cold snaring

OP295 REAL TIME DIAGNOSTIC ACCURACY OF BLUE LIGHT IMAGING WITH MAGNIFICATION (BLI) IN THE CHARACTERISATION OF SESSILE SERRATED POLYPS (SSPS) AND ADVANCED HISTOLOGY WITHIN COLO-RECTAL POLYPS

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Introduction: Blue light imaging (BLI) is a novel modality for image enhanced endoscopy. Using the short wavelength of the absorption spectrum of haemoglobin and specific white light spectral colours emitted by 4 LED lights enhances the visualisation of vascular and surface pattern morphology within colonic polyps. In addition, magnification endoscopy with BLI is expected to enhance characterization and detection of advanced pathology such as high grade dysplasia (HGD) or submucosal invasion. Our study aims to assess the accuracy of BLI in characterizing SSPs and its ability to accurately predict advanced pathology.

Aims & Methods: A retrospective analysis was performed of a prospectively collected database in a single tertiary hospital. Hospital ethical board approval was obtained and informed consent was attained from all patients. Data from all colonoscopy utilising BLI and magnification were collected for 12 months from October 2017.Data was collected on polyp location, size, morphology and polyp type and presence of advanced pathology. Mucous cap, indefinite margins, type 2 open pits and dilated branching vessels were used as additional criteria for predicting SSPs. Endoscopic prediction was compared to histology to determine accuracy.

Results: 155 polyps were assessed in 68 procedures during the study period. Of these, 112 (72%) were in the proximal colon, 28 in the distal colon (18%) and 15 (10%) in the rectum. 62 polyps were diminutive (40%) and 17 were 6-10 mm (11%). 76 polyps were >10mm in size (49%) of which 43 were between 20-50 mm and 12 were >50 mm in size. 65 polyps were of Paris 1s morphology (41.9%), 80 were Paris 2a (50.3%) and 10 had combined morphology. BLI with magnification detected 55 SSPs of which 54 were confirmed at pathology (sensitivity 98.1%, specificity 99%, PPV 98%, NPV 99%, accuracy 98.7%). Adenomas were predicted in 100 polyps with HGD in 11 polyps and submucosal invasion in 6 polyps. Pathology confirmed submucosal invasion in all predicted polyps but did not detect HGD in 2 lesions. Pathology identified an additional 2 proximal colon polyps with focal HGD and 1 small focus of early submucosal invasion in a >50 mm polyp where endoscopy predicted HGD. Detailed results are in table 1.

Polyp characterisation	Sensitivity	Specificity	PPV	NPV
SSP	98.1(90-99)	99 (94-99)	98 (89-99)	99 (95-100)
Advanced pathology(HGD + SM invasion)	88 (62-97)	98 (94-99)	88 (62-97)	98 (94-99)
SM invasion	85 (42-99)	100 (96-100)	100 (51-100)	99 (95-99)

[Table 1]

Conclusion: As a novel modality, BLI with magnification has enhanced ability to visualise and characterize vascular and pit pattern morphology of colo-rectal polyps. Our study utilised these features and specific criteria for SSPs for accurate prediction of polyp type and advanced pathology. The results indicate high diagnostic accuracy for BLI in differentiation of SSPs as well as prediction of HGD and submucosal invasion. Prediction of advanced pathology is crucial in determining the ideal therapeutic strategy. Our study highlights the potential use of BLI and magnification in this regard.
Disclosure: Nothing to disclose

OP296 CONTINUOUS ANTICOAGULATION AND COLD SNARE POLYPECTOMY VERSUS HEPARIN BRIDGING AND HOT SNARE POLYPECTOMY IN PATIENTS ON ANTICOAGULANTS WITH SUBCENTIMETER POLYPS: A RANDOMIZED CONTROLLED TRIAL

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Introduction: Management of anticoagulants for patients undergoing polypectomy is still controversial, and cold snare polypectomy (CSP) is reported as a less hemorrhagic procedure.

Aims & Methods: To investigate the efficiency of continuous administration of anticoagulants with CSP (CA+CSP) compared to periprocedural heparin bridging with hot snare polypectomy (HB+HSP) for subcentimeter colorectal polyps. Patients taking anticoagulants (warfarin or direct oral anticoagulants) and having at least one non-pedunculated subcentimeter colorectal polyp. Patients were randomly assigned to undergo HB+HSP or CA+CSP. Follow-up of patients was performed 28 days postoperatively. The primary endpoint was incidence of polypectomy-related major bleeding: i) poorly controlledintra-proceduralbleedingor ii) post-polypectomy bleeding requiring endoscopic hemostasis.

Results: A total of 184 patients were enrolled, with 90 allocated to the HB+HSP group, 92 to the CA+CSP group, and 2 refusals. The occurrence of polypectomy-related major bleedingin the HB+HSP and CA+CSP groups was 12.0% [95% confidence interval (CI), 5.1 to 19.1] and 4.7% [95% CI, 0.2 to 9.2], respectively. Inter-group difference for the primary endpoint was +7.3% with the lower limit of two-sided 90% CI of 0.4% [95% CI, -1.0 to 15.7], which demonstrated non-inferiority of CA+CSP. The mean procedure time for each polypand hospitalization periodwere longer in the HB+HSP group than in the CA+CSP group.

Conclusion: CA+CSP for subcentimeter colorectal polyps in patients taking anticoagulants did not increase the incidence of polypectomy-related major bleedingcompared with HB+HSP, with a shorter procedure time and hospitalization period.
Disclosure: Nothing to disclose

OP297 THE SAFETY OF COLD SNARE POLYPECTOMY FOR PATIENTS ON ANTITHROMBOTIC THERAPY

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Introduction: Cold snare polypectomy (CSP) is a more efficacious and safer polypectomy technique without electrocautery, therefore it is widely used for the removal of subcentimeter polyps. Recent studies have revealed that delayed post-polypectomy bleeding (DPPB) and perforation are few observed in CSP. The use of antithrombotic agents for prophylaxis or treatment of thromboembolic events is expected to increase with the aging of the population. The management of antithrombotic agent use in patients undergoing CSP is a very important issue in clinical practice. However the safety of CSP in patients who are currently on antithrombotic therapy haven't been fully evaluated.
Aims & Methods: The aim of this study was to elucidate the safety of CSP in patients who are currently on antithrombotic therapy. 3341 consecutive patients with colorectal polyps were removed by CSP between March 2016 and March 2019. We retrospectively assessed the characteristics of polyps, the histological results, the rates of DPPB. DPPB was defined as significant bleeding requiring endoscopic treatment within 2 weeks after CSP.
Results: 6236 polyps in 3341 patients (male/female; 2511/830) were removed by CSP. There were 1310 polyps (21.4%) in 621 patients (antiplatelets agent users 403, anticoagulants agent users 172 and both agent users 64) in the antithrombotic group, and this group was divided into two groups: the continuation group (group A; 637 polyps, 339 patients) and the interruption group (group B; 569 polyps, 282 patients). And there were 5030 polyps (79.6%) in 2720 patients in the non-antithrombotic group (group C). The baseline characteristics of the lesions (size, location, morphology, resection number, and institution) in three groups weren't significantly different in univariate or multivariate analyses. As for adverse events, the overall rate of DPPB was 0.18% (6/3341). DPPB occurred 0.59% (2/339) in group A, 0.35% (1/282) in group B, 0.11% (3/2720) in group C, showing no significant differences from three groups (p = 0.09). In the rates of DPPB of the antithrombotic group (group A and group B), there were no significant differences depending upon the antithrombotic agents used (warfarin group, DOAC group, antiplatelet group, multiple antithrombotic group). Of the 6 cases of DPPB in CSP, 3 cases were located in sigmoid colon, all polyps were more than 5mm in diameter. Patients in the antithrombotic group in whom DPPB occurred included 2 aspirin users with 2 polyps and 1 aspirin plus rivaroxaban user with 2 polyps. All DPPB occurred within 24 hours, and transfusion and surgery were not necessary. In all cases, no perforation and fetal adverse events were occurred.
Conclusion: It is noteworthy that continued use of all of the antithrombotic agents in patients undergoing CSP didn't increase the risk of DPPB, even in patients receiving multiple antithrombotic agents. Thus, CSP can be performed with a high level of safety, even in patients receiving antithrombotic agents. In addition, there were no significant differences of rates of DPPB between the continuation group and the interruption group. So our results suggest that we may not be necessary for cessation of the antithrombotic therapy in CSP, and it is possible to reduce the risk of thromboembolism. In the future, prospective, randomized studies are necessary to confirm our results.
Disclosure: Nothing to disclose

OP298 INCOMPLETE RESECTION OF 4-20MM COLORECTAL POLYPS WHEN USING COLD SNARE POLYPECTOMY

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Introduction: Cold snare polypectomy has been recently been recommended as preferred polypectomy approach for up to 10mm colorectal polyps. We were interested to evaluate expansion of cold snare polypectomy for up to 20mm colorectal polyps and associated efficacy and safety.
Aims & Methods: This prospective studyincluded adults (age 45-80) presenting for a screening, surveillance or diagnostic colonoscopy at one academic center. The primary endpoint was the Incomplete Resection Rates (IRR) for 4-20mm neoplastic colorectal polyps. Secondary outcomes included technical feasibility of cold snare polypectomy and associated complication rates. "Easy" polypectomy was defined as immediate polyp resection upon first closure of the snare while "difficult" was defined as having to open and close the snare multiple times and/or using mechanical force (e.g. guillotine technique)to complete the cold snare polyp removal. Incomplete resection was defined by the presence of remnant tissue in marginal biopsies after polypectomy.
Results: The study included 413 patients (mean age 63; female 48.2%). Polyp and adenoma detection rates were 54.5% and 36.4%, respectively. A total of 182 colorectal polyps 4-20mm were found and initial removal was attempted using cold snare. In 75.3% cold snare resection was easy, in 12.1% difficult and in 9.9% conversion was required. The IRR for adenomatous polyps was 14.8%. The IRR for neoplastic polyps was 16.8%. Among neoplastic polyps incomplete resection was more frequent for SSP (36.4%) than for adenomatous polyps (14.8%, p=0.018). The IRR for hyperplastic polyps was 20.0%. The IRR for all 4-20mm polyps (combining neoplastic and hyperplastic polyps) was 17.6%. The risk of incomplete resection varied with polyp size (15.8% for 4-5 mm, 22.2% for 6-9 mm and 15.8% for 10-20 mm) and incomplete resection occurred more frequently when immediate polyps resection was difficult (IRR 42.1%). Intraprocedural bleeding requiring endoscopic intervention (treatment with clip or injection) occurred in 4.4%.
Conclusion: In this multi-endoscopist study using systematic cold snare polypectomy for up to 20mm colorectal polyps IRR was found more often than in other recent studies reporting outcomes for cold snare polypectomy. Technical difficulty to resect the polyp was associated with higher IRRs.
Disclosure: Daniel von Renteln is supported by a "Fonds de Recherche du Québec Santé" career development award and has received research funding from ERBE, Ventage and Pentax and is a consultant for Boston Scientific and Pendopharm.

OP299 CLINICAL IMPORTANCE OF COLD POLYPECTOMY DURING INSERTION PHASE IN LEFT SIDE COLON AND RECTUM: A MULTI-CENTRE RANDOMISED CONTROLLED TRIAL (PRESECT STUDY)

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Introduction: Although small and diminutive colorectal polyps are often found unintentionally during insertion phase (IP) of colonoscopy, removal of polyps during IP is not common in the current practice. These polyps, especially in the left side colon are often challenging to re-detect during withdrawal phase (WP) and may even become undetectable. As time-consumption of the re-inspection process is not negligible, instant resection of polyps should be considered. With the global spread of cold polypectomy and carbon dioxide (CO_2) gas insufflation, polypectomy during IP became less of a burden to endoscopists.

Aims & Methods: The aim of this prospective multi-centre randomized trial was to investigate the clinical benefits of instant removal of polyps upon scope insertion. We have set the primary outcome as total procedure time to confirm that polypectomy during IP facilitates the entire colonoscopy procedure and improves time efficiency. Secondary outcomes include the number of missed or 'hiding' polyps. Hiding polyp is defined as a polyp detected during insertion, however lost in withdrawal phase which was eventually found after re-inspection.

Patients with at least one target lesion (adenomas or SSAP < 10mm, hyperplastic polyps 6mm < 10mm in left side colon) detected during IP were divided into two groups and received cold snare or forceps polypectomy under CO_2 gas insufflation: study group removed polyps during both IP and WP, where control group removed polyps during WP only. Patients were randomized into the two groups as soon as a target lesion is detected during IP. 20 senior endoscopists from 7 institutions were involved in this trial.

Results: A total of 1451 patients were recruited for the trial from April 2018 to March 2019. 300 (26.2%) patients had at least one detectable target lesion during IP, and 220 patients (120 in study group, 100 in control group) were eligible for full assessment. Mean total procedure time was significantly shorter (18:51 vs 22:18, -15.4%, p=0.0004) and mean pure cecal intubation time was similar between two groups (7:25 vs 7:33 p=0.9318). Mean number of polyps resected per patient was 2.1 in both groups. In the control group, out of 107 polyps found during IP, 48 polyps (44.8%) were not found in the first withdrawal action and 7 (6.5%) polyps were completely lost. Time consumption for re-searching these hiding or missed polyps was 2:54 in average. One case (1%) of delayed post-polypectomy bleeding in control group was reported as an adverse event.

	Polypectomy upon insertion and withdrawal	Polypectomy upon withdrawal only	P-value
n	120	100	NA
Total number of polyps	254	210	0.9011
Mean number of polyps per patient	2.1	2.1	NA
Mean total procedure time (min:sec)	18:51	22:18	0.0004
Mean pure cecal intubation time (min:sec)	7:26	7:27	0.9318
Mean polypectomy time (min:sec)	2:03	1:59	0.7562
Number of ,hiding' polyps	NA	41(38.3%)	NA
Number of missed polyps	NA	7 (6.5%)	NA

[Main outcomes of PRESECT study.]

Conclusion: Polypectomy during IP in the left side colon improves the time efficiency of colonoscopy and reduces total procedure time without experiencing any disadvantages.
Disclosure: Nothing to disclose

OP300 COLD SNARE POLYPECTOMY VS HOT SNARE POLYPECTOMY VS (APC) FOR SMALL(5-9MM) LEFT-SIDED COLORECTAL POLYPS: A PROSPECTIVE RANDOMIZED TRIAL

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Introduction: The optimal technique for the removal of small colorectal polys is debatable. We aimed to compare the recurrence rates among three endoscopic treatment modalities for 5-9mm left-sided colorectal polyps.
Aims & Methods: Consecutive adults referred for elective colonoscopy (1/2015-1/2018) who had at least one polyp of eligible size (5-9mm) located distally to the splenic flexure were randomly assigned (1:1:1) to one of three treatment modalities: 1) cold snare polypectomy (CSP), 2) hot snare polypectomy (HSP) and 3) APC ablation (50-60W, flow: 2lt/min). The polyp site was marked with endoscopic tattoo and a follow-up colonoscopy with scar biopsies was performed 6-18 months after the index procedure. Outcomes were the polyp recurrence rate and the occurrence of complications.
Results: A total of 119 patients were enrolled, of whom 112 (62.5% males, mean age 61.1±9.9 years) with 121 polyps (CSP: 39, HSP: 45, APC: 37) returned for follow-up colonoscopy. The mean polyp size was 6.7±0.91mm, 58% were located in the sigmoid, 33% in the rectum and 8% in the descending colon. The majority of polyps resected by CSP or HSP were histopathologically proven to be neoplastic (tubular adenomas: 25.9%, tubulovillous adenomas: 11.1%, sessile serrate adenomas/polyps: 17.5%). No cases of delayed bleeding or perforation occurred in the study. Scar biopsies at follow-up colonoscopy (performed after a mean interval of 13.4 ±3.8 months) revealed a total of 6 (4.96%) cases of polyp recurrence, showing no significant difference among the three treatment groups [CSP: 3/39 (7.7%), HSP: 1/45 (2.2%), APC: 2/37 (5.4%), P=0.51).
Conclusion: CSP, HSP and APC ablation are effective and safe treatment modalities for 5-9mm left-sided colorectal polyps. The present randomized study could not detect any differences in the polyp recurrence rates among the three endoscopic techniques.
Disclosure: Nothing to disclose

What causes (recurrent) acute pancreatitis?
08:30-10:00 / B2

OP301 ETIOLOGY OF CHRONIC PANCREATITIS IN CHILDREN - ANALYSIS OF 423 CASES

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Introduction: Chronic pancreatitis (CP) is of a rare occurrence in childhood. The etiology of CP in children is varied and includes anatomic anomalies, gene mutations, metabolic disorders and others.
Aims & Methods: The aim of this study was to investigate the etiological aspects of CP in children from well-defined homogenous single-centre cohort. 423 children with CP (aged: 0.6-18 years; mean 10; F-220, M-203)

hospitalized between 1988 and 2019 were enrolled into the study. The diagnosis of CP was established according to INSPIRE recommendations. Clinical and epidemiological data were recorded and analyzed. All patients were screened for mutations in the high-risk genes associated with CP (*CFTR, CTRC, PRSS1, SPINK1, CPA1, CEL-HYB*). All children had preceding imaging studies, including US, CT, MRCP and/or ERCP.

Results: Gene mutations were found in 279 children **(66%)** (*SPINK1* mutation in 118 children, *CTRC* in 108 patients, *CFTR* in 61 patients, *PRSS1* in 55 children, *CEL-HYB* in 8 and *CPA1* in 4; 75 pts (17.7%) have 2 or more mutations).

Anatomic anomalies of pancreatic duct were diagnosed in 69 patients (16.3%) (43-pancreas divisum, 9-ansa pancreatica, 7-ABPU, 2-two main pancreatic ducts, 8-other).

Toxic-metabolic risk factors were found in 63 children (14.9%) with chronic pancreatitis, with dominance of lipid disturbances. Hyperlipidemia was present in 35 patients (8.3%), including isolated in 15 patients (3.5%) and coexisting with obesity/metabolic syndrome in 20 (4.7%) patients. CP associated with medication was present in 15 (3.5%) children (mostly with anti-epilepsy drugs). Alcohol abuse history was present in 7 (1.7%) patients. Smoking (>5 cigarettes/day) history was present in 8 (1.8%) children. Five patients (1.2%) from these groups had history of both- alcohol abuse and cigarettes smoking. Chronic renal failure was present in 4 (1%), mitochondrial cytopathies in 2 (0.5%) and hypercalcemia (hyperparathyroidism) in 2 (0.5%) patients with CP.

CP was associated with biliary tract diseases in 38 patients (8.9%). Autoimmune pancreatitis was diagnosed in 14 children (3.3%). Idiopathic CP was diagnosed in 37 children (8.7%).

Conclusion: 1. Gene mutations and anatomic anomalies of pancreatic duct are the most common etiologic factors of CP in children.

2. CP is a multifactorial disease.

3. Our data demonstrate the need for genetic testing in children with CP.

Disclosure: Nothing to disclose

OP302 METABOLIC SYNDROME FACTORS WORSEN THE OUTCOME OF ACUTE PANCREATITIS

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Introduction: Several studies have confirmed the effect of obesity (OB), hyperlipidemia (HL) and diabetes mellitus (DM) on the outcome of acute pancreatitis (AP). However, there is no data regarding the association between hypertension (HT) and the outcome of AP. Furthermore, no study has examined yet the independent effects of these four factors, neither the effect of their different combinations.

Aims & Methods: Our aim is to understand how these four factors of metabolic syndrome (MetS) and their combinations effect the outcome of AP. The Hungarian Pancreatic Study Group has prospectively collected clinical data from AP patients between 2012 and 2017. Our cohort contains 1257 cases from 28 centers of which 906 cases had information on all four examined factors of MetS. For the individual effect analysis, patient groups were formed based on the WHO classification of BMI and the presence of other MetS factors, namely HT, HL and DM. Logistic regression was performed to analyze the independent effects of these four factors. For the joint effect analysis, patient groups were defined according to the combinations of the MetS factors.

Results: OB and HT significantly increased the risk for severe AP (OR=2.153 and OR=2.3861 respectively). OB and HT patients stayed significantly longer in the hospital (10.4d vs. 12.1d, p=0.008 and 10.5d vs. 11.8d, p=0.020) and had increased risk for systemic complications (OR = 1.993 and OR=2.830

respectively). HL increased the risk for moderately severe AP, for local complications (OR = 1.552) and for renal failure (OR = 2.166). DM increased the risk of systemic complications, though, the difference was not significant. In the independent effect analysis, only HT was an independent risk factor for mortality and severity (OR=5.900, p=0.020 and OR=3.895, p=0.001 respectively). OB is an independent risk factor for renal failure (OR=2.968, p=0.007), HT for respiratory failure (OR=2.667, p=0.024) and renal failure (OR=7.565, p=0.007) and HL for fluid collections (OR=1.415, p=0.037) and diabetes as a complication (OR=2.373, p=0.013).

In the joint effect analysis, the rate of severe AP elevates with the number of MetS factors (2.6%, 4.7%, 6.1%, 8.5% and 6.0% with 0, 1, 2, 3 and 4 factors respectively).

Conclusion: MetS factors increase the risk of mortality, severe AP and complications. Hypertension proved to be an independent risk factor for mortality and severity of AP. The more MetS factors are present, the higher is the risk of worse outcome in AP.

Disclosure: Nothing to disclose

OP303 QUANTIFYING THE RISK OF DRUG INDUCED PANCREATITIS WITH ACE INHIBITORS AND STATINS USING A LARGE ELECTRONIC MEDICAL RECORD PLATFORM

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Introduction: Acute pancreatitis (AP) is one of the most common causes of gastrointestinal-associated hospitalizations in the United States, with mortality rates as high as 30% for acute severe pancreatitis. Angiotensin-converting enzyme inhibitors (ACEi) and hydroxymethylglutaryl-coenzyme A reductase inhibitors, also known as 'statins', are often prescribed to patients with hypertension and hyperlipidemia and have been implicated in causing AP. The quantitative risk for AP and incremental risk when used together is unknown.

Aims & Methods: Using IBD Explorys (1999-2019), a HIPAA-enabled web platform that includes clinical data from over 63 million unique individuals with accompanying lab data, we aimed to quantify the risk for drug-induced AP with ACEi and statins. AP cases were identified using a combination of ICD and SNOMED codes, and AP episodes secondary to alcohol, gallstones, triglycerides or common class 1 drugs associated with AP were excluded. Odds ratios (OR) with corresponding 95% confidence intervals (CI) are reported.

Results: A total of 280,740 patients with AP meeting our inclusion criteria were identified, the majority of which had been exposed to statin alone (32%), ACEi alone (31%), or both (19%). Among all patients exposed to these medications, AP was observed in 1.5% (n=90,120/5,959,500) of patients exposed to statin alone, 1.9% (n=86,870/4,705,640) of patients exposed to ACEi alone, and 1.9% (n=54,590/2,879,850) of patients exposed to both a statin and ACEi. Compared to the general population, exposure to these medications conferred a 5-6 fold increased risk for AP not related to alcohol, gallstones, triglycerides, or common class 1 drugs associated with AP. (Table 1)

Medication	Odds Ratio	Confidence interval (95%)
HMG-CoA reductase inhibitor (statin)	4.97	(4.93, 5.01)
ACE inhibitor	6.12	(6.07, 6.17)
ACEi + Statin	5.72	(5.67, 5.78)

[Table !: Odds ratio (with 95% confidence intervals) for acute pancreatitis with exposure to a statin, ACE inhibitor, or both]

Conclusion: Approximately 1.5-2% of patients exposed to a statin or ACEi develop AP, and exposure to these medications is associated with a 5-6 fold increased risk for developing AP not attributed to alcohol, gallstones, triglycerides, or other drugs commonly associated with AP.

Disclosure: Nothing to disclose

OP304 DEVELOPMENT OF A MODEL TO DETERMINE THE RISK OF RECURRENCE OF ACUTE BILIARY PANCREATITIS BEFORE CHOLECYSTECTOMY: A MULTICENTRE, RETROSPECTIVE COHORT STUDY

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Introduction: International guidelines of acute pancreatitis (AP) recommend cholecystectomy during the index admission of patients with acute biliary pancreatitis (ABP). This recommendation is not consistently followed, thus increasing the risk of recurrence of ABP.

Aims & Methods: Our aim was to develop a model to determine the risk of recurrence of ABP to prioritise patients on surgical waiting list.

Multicentre, retrospective cohort study of patients with a first episode of ABP from January 2010 to December 2015. Biliary aetiology was defined by the presence of stones, or sludge/microlithiasis in the CBD or gallbladder at abdominal ultrasound, EUS or MRCP, together with the absence of AP relapse after cholecystectomy. Laboratory liver tests (AST, ALT, AP, GGT and bilirubin) at admission were recorded. Primary outcome was the risk of ABP recurrence during the six-month period after the first episode. Survival analysis was performed using the Kaplan-Meier method. Cox regression analysis was performed to calculate hazard ratios (HR). Significant risk factors associated with the risk of ABP recurrence were scored accordingly and three risk categories (low, intermediate and high) were defined.

Results: 498 patients with a first episode of ABP were included. Median time to cholecystectomy was 136 days (range 72-206 days). Patients waiting more than 6 months for cholecystectomy were excluded. 352 patients were finally included (mean age 67.6 years, range 51.6 to 77,4, 199 female). ABP relapsed in 89 patients (25.3%). Serum alkaline phosphatase (AP), previous endoscopic sphincterotomy (EE) and the severity of the first episode of ABP were significantly associated with ABP recurrence. Scores assigned identified patients with ABP who recur with a c-statistic of 0.59 (95% CI, 0.55-0.64, p<0.001), HR 2.64 (95% CI 1.61-4.32). Patients in the high, intermediate and low risk group had a recurrence rate of 30.7%, 18.7% and 0%, respectively.

Level of Alkaline Phosphatase	Points
0 to 263 (Normal limit)	5
264 to 526 (2 ULN)	4
527 to 789 (3 ULN)	3
790 to 1052 (4 ULN)	2
> 1052	0
Severity of AP	
Mild AP	4
Moderate AP	2
Severe AP	0
ERCP	
No	4
Yes	0

Low risk: 4 to 8 points Intermediate: 9 to 11 points High risk: 12 to 13 points

[RABP Score]

Conclusion: A score system (recurrence acute biliary pancreatitis -RABP-score) based on serum levels of AP at admission, EE and severity of AP allows identifying patients with ABP at low, intermediate and high-risk groups of recurrence. This score might be used to prioritise patients in surgical waiting list for cholecystectomy.

Disclosure: Nothing to disclose

OP305 INVESTIGATING THE EARLY PHASE OF CHRONIC PANCREATITIS: THE GOULASHPLUS TRIAL PROTOCOL AND THE RESULTS OF THE FIRST 14 MONTH

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Introduction: Acute pancreatitis (AP) is an inflammatory condition, which can lead to late consequences. In 20 % of patients recurrent AP (RAP) develops and in 7-12 % chronic pancreatitis (CP) will occur. However, we do not have sufficient information to establish an evidence-based statement to define early CP, or how to prevent its development.

Aims & Methods: The aim of the GOULASH-PLUS study is to understand the influencing factors and to determine, which parameters should be measured to detect the early phase of CP.

This is an observational prospective follow-up study of the GOULASH-trial. Patients' selection: individuals enrolled in the GOULASH study will be approached and asked to join this longitudinal study. Participants will be followed up at 1-2-3-4-5 and 6 years after the episode of AP. Anamnestic data will be collected by the following questionnaires: i) FFQ ii) SF-36 iii) physical activity questionnaire iv) stress questionnaire. Genetic tests will be performed for the genes already known to be associated with CP. The exocrine pancreatic, liver and kidney functions will be determined by several laboratory tests, stool sample analyses and imaging will be performed. The endocrine function will be measured by an oral glucose tolerance test (OGTT) and HbA1C. Blood and stool samples will be stored in the biobank for later measurements. Now, the participation in the first 14 months and the changes in the endocrine function were analyzed.

Results: During the first 14 months 93 out of the 126 patients attended the first year control, thus the enrolment rate was 73.8 %. Their mean age was 54+13.3 years and 57 (61.2%) were male. Mild, moderate and severe AP was observed in 69 (74%), 19 (21%) and 5 (5%) patients during their index admission. Out of 18 (19.4%) of them was admitted with recurrent AP episode. At the first year follow-up, 9 patients were newly diagnosed with diabetes, and 21 patients had impaired glucose tolerance. The incidence of diabetes increased after the first year of AP from 12.9% to 22.7%, at 45.3% of the patient´s carbohydrate metabolism disorder could be detected. Patients who were admitted with moderate or severe AP were more likely to develop diabetes (5 from 24 patients; 20.8%) than patients with mild AP (4 from 69 patients; 5.8%).

Conclusion: The development of carbohydrate metabolism disorder is frequent in AP, it shows correlation with the severity of AP, therefore the follow-up of these patients is likely to be beneficial.

Disclosure: Nothing to disclose

OP306 ACUTE PANCREATITIS AND MUCIN PHENOTYPE OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM OF PANCREAS

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Introduction: Acute pancreatitis (AP) occasionally occurred in patients with intraductal papillary mucinous neoplasm (IPMN). The influence of mucin phenotype of IPMN on the occurrence of AP remains controversial.

Aims & Methods: We investigated the relationship between mucin phenotype of IPMN and AP, including pancreatic hyperenzymemia. This study included 163 patients with IPMN who had surgery at our hospital between January 2000 and December 2016. The relationship between mucin phenotype of IPMN and AP (or pancreatic hyperenzymemia) was investigated. Mucin phenotype of IPMN was classified as Gastric type (G type: N=101), Intestinal type (I type: N=45), Pancreatobiliary type (PB type: N=11) and Oncocystic type (O type: N=2).

Results: 11% (18/163) of IPMN cases developed AP and 55.6% (10/18) of AP cases have recurrent episode (2-4 times). Age, gender, BMI, diabetes, alcohol consumption (more than 50g/day), drinking habits, and smoking status (current smoking) were not associated with the incidence of AP. In addition, there was no association of the incidence of AP with the diameter of main pancreatic duct, mural nodules, and the diameter of IPMN. In mucin phenotype, AP was significantly more frequently occurred in pancreatobiliary type (PB type: with AP vs. without AP, 27.8% [5/18] vs. 4.1% [6/145], P = 0.003) and intestinal type (I-type: with AP vs. without AP, 50.0% [9/18] vs 24.8% [36/145], P = 0.046). In the 5 cases of PB type with AP, 4 cases were intraductal mass in the main pancreatic duct, and 1 case had the compression of the main pancreatic duct by the intraductal mass in the branch pancreatic duct. In Intestinal IPMN cases with AP, 88.9% (8/9) had dilated main pancreatic duct by hyper mucin production. The elevation of serum pancreatic enzymes (serum amylase, serum lipase, serum elastase-I) was not significantly related to mucin phenotype of IPMN.

Conclusion: PB type and intestinal type IPMN were significantly associated with AP. PB type sometimes display intraductal mass with poor mucin production in the main or branch pancreatic duct, while intestinal type is characterized by abundant mucin production. These mucin phenotype might be closely associated the occurrence of AP in IPMN.

Disclosure: Nothing to disclose

From bench to bedside in pancreatic cancer
08:30-10:00 / B3

OP307 A MULTI-INSTITUTIONAL STUDY ASSESSING PREVALENCE OF DELETERIOUS GERMLINE MUTATIONS IN PANCREATIC CANCER

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Introduction: Pancreatic cancer is being increasingly associated with germline implications. Some large single-center studies have reported results ranging from 3.9% to 19.8% of patients found to have germline variants [Shindo, JCO 2017; Lowery, JNCI 2018].

Aims & Methods: We aim to further delineate prevalence of deleterious germline mutations in pancreatic cancer using a multi-institutional data set. We also aim to analyze predictive factors such as mutant allele frequency (MAF, in %) in germline versus somatic calls. We sequenced 23 genes in DNA prepared from clinical tissue and blood specimens submitted to Tempus Labs. Germline variants and somatic variants were processed separately. Germline variants were determined to be deleterious through the sum effect of a combination of in silico predictors, population databases, and internal evaluations. Tumor-normal comparisons were used to define somatic versus germline, and MAFs were calculated for each.

Results: A total of 234 patient samples from 17 institutions were analyzed. Of these, 12 (5.1%) had predicted deleterious germline variants involving 8 different genes: BRCA1 (n = 3), CHEK2 (n = 3), ATM (n = 1), MLH1 (n = 1), MUTYH (n = 1), PALB2 (n = 1), SMAD4 (n = 1), TP53 (n = 1). For most somatic alterations, the MAFs were found to be greater than the germline deleterious alterations, with the latter approaching ~50% in most cases.

Conclusion: This multi-institutional study identifies 5% of patients with pancreatic cancer to have deleterious germline alterations. Somatic variant testing, particularly when paired with germline, can be used as a screening method for genetic counseling referrals, especially with MAF analyses of paired tumor-normal samples.

Disclosure: Nothing to disclose

OP308 GENE CO-EXPRESSION NETWORK ANALYSIS OF PRECURSOR LESIONS IN FAMILIAL PANCREATIC CANCER

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Introduction: An estimated fraction of up to 10% of all pancreatic cancers is attributed to familial pancreatic cancer (FPC) with an accumulated lifetime risk of up to 38.5% for pancreatic ductal adenocarcinoma (PDAC) (1). The process of progression from pre-malignant lesions to the formation of invasive PDAC is thought to take around 10 years (2). High grade Pancreatic Intraepithelial Neoplasia (PanIN) are aggressive pre-malignant lesions, associated with elevated risk for progressing to PDAC (3-5). To date, no genetic mutations with strong association to FPC related PanIN lesions are known. A thorough depiction of dysregulated gene activity in high grade PanIN lesions in patients with FPC can help to characterize the molecular events during the development and progression of familial PanIN lesions to PDAC.

Aims & Methods: We performed weighted gene co-expression network analysis (WGCNA) to identify genes associated with FPC related PanIN lesions using gene expression profiles of 33,000 genes measured by Affymetrix GeneChip HG-U133 arrays on 13 pancreatectomy specimens with PanIN lesions (stage 2-3) from FPC patients, 6 pancreatectomy specimens with PDAC from sporadic pancreatic cancer (SPC) patients, and 4 specimens of normal donor pancreatic tissue (6). Microarray data were analyzed using R package WGCNA.

Results: WGCNA detected co-expressed genes as modules/clusters and summarized each module by a representative gene: the module eigengene. Correlation analysis identified 2 up-regulated modules or co-expressed gene clusters (p< 1e-05) and 2 down-regulated modules (p< 1e-05) in FPC compared to SPC. The upregulated gene modules include 5 significant genes (p< 1e-06) consisting of FMO4, FMO2, CORO1B, TPP1, CIB4.
The down-regulated gene modules include 170 significant genes (p< 1e-06), among them 13 highly significant genes (p< 1e-10) consisting of: COL10A1, SAMD9, PLPP4, COMP, POSTN, IGHV4-31, THBS2, MMP9, FNDC1, HOPX, TMEM200A, INHBA, SULF1. The down-regulated modules are significantly enriched for Gene Ontology (GO) terms functionally related to: extracellular structure organization, cell-substrate junction, focal adhesion, collagen binding, extracellular vesicle, etc. In addition, we identified common modules shared by both FPC and SPC - with 2 commonly up-regulated modules (p< 4e-12) and 1 commonly down-regulated module (p< 1e-17) as compared with normal pancreatic tissue.
The common up-regulated modules include 1054 highly significant genes (p< 1e-06) with 14 top significant genes (p< 1e-16) consisting of: ID2B/ID2, OGFOD1, COL3A1, HOPX, SULF1, ELK3, HLA-DRB1, PMP22, CYAT1, PLPP4, COL1A2, SFRP4, SPARC, THBS2. In the common down-regulated module, 214 genes were differentially expressed in comparison with normal pancreatic tissue (p< 1e-06), among them 15 were top significant genes (p< 1e-12) consisting of: UTP14A, PGM3, SLC1A4, PHGDH, MRM3, GMPPA, SNORD14D, NSA2, NUBP1, CCT4, IGBP1, FMOD, AADAC, ASNS, LANCL2. The common down-regulated module is enriched for GO terms related to functions in: cotranslational protein targeting to membrane, peptide metabolic process, structural constituent of ribosome, etc.

Conclusion: The differential molecular pathology of FPC and SPC involves multiple co-expressed gene clusters significantly enriched for GO terms including functions in extracellular activities and focal adhesion. Meanwhile, both FPC and SPC share strong gene co-expression patterns functionally related to intracellular activities. These findings provide reference for genomic characterization of the molecular events during the development and progression of PanIN lesions to PDAC in FPC.

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Disclosure: Nothing to disclose

OP309 GASTROKINE 1 AND 2 IN PANCREATIC CARCINOGENESIS: ONE FAMILY WITH TWO DISTINCT ROLES?

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Introduction: Late detection of pancreatic ductal adenocarcinoma (PDAC) and limited treatment options lead to poor survival of PDAC patients. A better understanding of the pathomechanism of PDAC development will help identify new therapeutic approaches. An early event during tumorigenesis is the development of pre-malignant lesions such as pancreatic intraepithelial neoplasia (PanIN). While studying a K-Ras driven mouse model (KC mice) of PDAC, which recapitulates the stepwise progression of pancreatic cancer, we serendipitously identified Gastrokine 1 (GKN1) and Gastrokine 2 (GKN2) in early PanIN lesions. Importantly, we confirmed the presence of GKN1 and GKN2 in human pancreatic premalignant lesions. GKNs are proteins derived from gastric epithelium, where they maintain gastric homeostasis and act as tumor suppressors. Therefore, we aim to investigate the function of this PanIN-specific GKN1 and GKN2 expression, to understand the early events that underlie the development of premalignant lesions leading to pancreatic carcinogenesis.
Aims & Methods: We intercrossed KC mice with GKN1-/- or GKN2-/- mice. GKN1-/- KC, GKN2-/- KC and GKN+/+ KC pups were analyzed at the age of 3- and 9 months to quantify PanIN lesions and assess tumor development via histology. Furthermore, qRT-PCR and western blots were used to analyze genes and proteins (relevant for apoptosis, EMT or tissue remodeling and stroma composition) involved in tumorigenic processes. For all compared groups we analyzed the proliferation index and measured differences in pancreatic cyst sizes. In vitro, acinar transdifferentiation experiments were performed with cells isolated from all groups. A lentiviral construct overexpressing mouse GKN1 or GKN2 was generated to transduce Panc02 mouse pancreatic cancer cells to confirm the results in-vitro.
Results: Absence of GKN1 or GKN2 dramatically accelerated the development of PanIN lesions in KC mice. 3 months old GKN1-/-KC and GKN2-/-KC mice showed more extensive ADM and PanIN lesions compared to GKN+/+ KC mice, coinciding with significant upregulation of genes involved in PanIN development, cytokine and chemokine expression as well as tissue remodeling. Interestingly, the mRNA expression analysis also revealed a significant difference in apoptosis regulation in GKN1-/- KC mice. Analysis of cleaved Caspase-3, FAS protein and activated cleaved Caspase-8 point towards a decreased apoptosis in the absence of GKN1 and suggests a possible involvement of GKN1 in the activation of the extrinsic apoptotic pathway. The histological comparison at 9-months showed that GKN1-/- KC mice developed a collagen-rich dense stroma around the pancreatic lesions compared to sparse stroma in KC animals. GKN1-/- KC mice showed an increased tumor incidence (40.7% vs 13%) and a more differentiated

tumor phenotype. On the other hand, the histological evaluation shows that 9 month old GKN2-/- KC mice display a change of pancreatic tissue architecture resulting in big cystic lesions. In context of tumor incidence, GKN2-/-KC mice reveal a comparable incidence to GKN+/+ KC mice.
Conclusion: We conclude that the absence of GKN1 or GKN2 leads to accelerated PanIN development. Based on our results, we suggest that GKN1 influences apoptosis avoidance at an early age through the extrinsic apoptosis pathway. Apoptosis avoidance and development of a dense stromal reaction in later stages leads to an increased tumor incidence. GKN2 plays an important role in maintaining pancreatic architecture during PanIN formation, especially influencing the cyst size and proliferation.
Disclosure: Nothing to disclose

OP310 HOW DOES INTESTINAL TYPE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM EMERGE?

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Introduction: Intestinal intraductal papillary mucinous neoplasms (IPMNs) are often concurrent with gastric type components, and gastric IPMNs are assumed the origin of intestinal IPMNs. However, the molecular mechanism underlying the development and evolution of intestinal IPMN is not known.
Aims & Methods: To establish the molecular progression model of intestinal IPMN, we performed triple staining for CDX2, MUC2, and alcian blue, as intestinal differentiation markers, and double immunostaining for p21 and Ki-67, as cell cycle regulatory markers, on 61 intestinal IPMNs. Mutation analyses of KRAS and GNAS of intestinal and gastric components, individually, were performed using droplet digital PCR (QX200, Bio-Rad) and targeted amplicon sequencing (Ion S5, Thermo Fisher) in 25 cases.
Results: Histologically, intestinal features appear gradually in gastric type neoplasms those being IPMNs (n=32, 54%) or incipient PanIN-like lesions (n=20, 30%) in size. Triple staining for CDX2, MUC2 and alcian blue revealed that CDX2 expression appeared to precede MUC2 expression and morphological changes into intestinal phenotypes in gastric type epithelia. With MUC2 expression, intestinal morphological features, such as elongated nuclei, high-columnar epithelia, and nuclear stratification, became obvious. Cytoplasmic alcian blue-positive mucin and papillary growth seemed to become prominent as MUC2 expression increased. These results suggest that CDX2 may induce the characteristic biochemical and morphological transition of gastric-type epithelia into intestinal-type epithelia.
Expression of p21 and Ki-67 seemed to be accelerated by CDX2 expression as follows: the labeling index of p21 was 17.9±24.0% in gastric IPMNs and 52.4±22.1% in intestinal IPMNs (p< 0.05). The labeling index of Ki-67 was 4.3±1.9% in gastric IPMNs and 34.0±16.8% in intestinal IPMNs (p< 0.05). Double immunostaining for p21 and Ki-67 revealed that p21 positive cells tended to distribute in apex while Ki-67 positive cells did base of papillae, which resembles those in normal intestinal mucosa. Hence, intestinal IPMNs may have an adenomatous phase, in which the balance of differentiation and proliferation of neoplasm is regulated. This regulated trend seemed to disappear with the progression of grade and development of invasion (low-grade IPMN versus high-grade IPMN, p< 0.05, and versus invasive cancer, p< 0.05).
Finally, all intestinal IPMNs concurrent with gastric IPMN (n=18) or with incipient PanIN-like lesions (n=7) shared identical KRAS and GNAS profiles with the gastric type epithelia. Intestinal IPMNs seemed to arise from GNAS/KRAS mutant (n=14, 78%) and GNAS mutant (n=4, 22%) gastric IPMNs. Also, intestinal IPMNs seemed to arise from GNAS/KRAS mutant (n=4, 57%) and GNAS mutant (n=3, 43%) incipient PanIN-like lesions, namely incipient IPMNs. Variant allele frequencies (VAFs) of GNAS and KRAS increased with the transition of gastric IPMNs into intestinal IPMNs as follows: VAFs of GNAS in gastric and intestinal IPMNs were 20.8±15.3% and 40.2±18.4% (p< 0.05, n=18), respectively. VAFs of KRAS in gastric and intestinal IPMNs were 23.1±12.1% and 33.8±12.4% (p< 0.05, n=14), respec-

tively. Moreover, VAFs of *GNAS* and *KRAS* increased from incipient IPMN foci (7.5±6.9% and 3.5±3.7%) to mature intestinal IPMNs (47.1±16.1% and 42.8±13.0%, n=7 and n=3, p< 0.05 and p=0.0702).

Conclusion: Intestinal IPMNs may arise in *GNAS*-mutant gastric type IPMNs, in which CDX2 is supposed to play a critical role in the process of intestinal differentiation and progression by inducing the expression of MUC2 and p21 with some unknown growth-promoting molecules.

Disclosure: Nothing to disclose

OP311 DISCOVERY OF GASTROKINES IN EARLY PANCREATIC CANCER PRECURSORS AND THEIR POTENTIAL UTILITY AS A BIOMARKER

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Introduction: Current diagnostic methods are unable to detect pancreatic ductal adenocarcinoma (PDAC) at early, possibly treatable stages. Such early event in the malignant transformation is the development of pancreatic intraepithelial neoplasia (PanIN), the most common PDAC precursor. PanINs are classified according to their grade of dysplasia into PanIN-1A, PanIN-1B, PanIN-2 and PanIN-3. Molecular events occurring in the stepwise progression from premalignant PanIN lesions to PDAC development are largely unknown. A detailed knowledge of the critical biological changes responsible for pancreatic tumorigenesis is essential for the development of early diagnostic and preventive strategies.

The aim of our project is the identification of such key processes through the characterization of PanINs, focusing on two proteins - gastrokine 1 and gastrokine 2- that has so far not been shown in the pancreas. Gastrokines (GKNs) have been almost exclusively described in the stomach with a suggested role in gastric epithelial homeostasis and as tumor suppressor.

Aims & Methods: First, a comprehensive gene expression analysis was performed in human PanIN samples. The results were validated with qRT-PCR in an independent cohort of pancreatic cancer patients. The presence of GKNs was verified by immunohistochemistry (IHC). The *KRAS* gene driven KC (*p48[+/Cre];Kras[+/G12D]*) mouse model is a well-established model for pancreatic cancer, recapitulating the morphological features of PDAC development. Pancreatic tissues of KC mice were characterized by whole genome microarray analysis, qPCR, western blotting and IHC. Using a 3D mouse primary acinar cell culture model, we induced acinar cell transdifferentiation, to test GKNs expression. GKNs in mouse pancreatic juice were detected with mass spectrometry and in serum by western blot.

Results: Molecular analysis of patient samples and KC pancreas revealed high expression of gastrokines (GKN1 & GKN2) on dysplastic cells. GKN1 and GKN2 are co-expressed specifically on low-grade PanIN lesions (PanIN1B and PanIN2) in human and mice, where their expression is restricted to the cytoplasm of dysplastic epithelium. These proteins are absent in healthy acinar and ductal cells, as well as on tumor cells. Also high grade PanIN lesions are negative for GKNs.

We further assessed if inflammation can drive GKNs expression, however infiltrating inflammatory cells in human and mouse samples do not express GKNs. Furthermore, GKNs are undetectable in mouse models of pancreatic inflammation. Analysis of KC mice revealed continuous increase in GKNs from 4-52 weeks of age corresponding to an increase in the PanIN harboring area. During in-vitro transdifferentiation, expression of GKNs increased progressively parallel to the number of newly formed lesions in the culture. We confirmed secretion of GKNs in the pancreatic juice, and detected GKNs in the serum of KC mice. We further observed the presence of GKN1 in human pancreatic cyst fluid in some IPMNs and PDAC with cystic component.

Conclusion: In this study, for the first time, we report association of gastrokines with early pancreatic cancer precursors in human and mouse pancreatic tissues. Their progressive increase in developing PanIN lesions and their secretion in serum, pancreatic juice and cyst fluid suggest that gastrokines could become promising biomarker(s) in PDAC diagnostic or

screening. Collectively, the discovery of GKNs opens up avenues to test these proteins in patient cohorts and to further study their role in PanIN and PDAC development.

Disclosure: Nothing to disclose

OP312 PANCREATIC CANCER CELLS ACCESS NERVES VIA TGFBETA1-MEDIATED TRANSDIFFERENTIATION OF PERINEURAL EPITHELIAL CELLS INTO MESENCHYMAL-LIKE CELLS

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Introduction: Mechanisms of "neural invasion" in pancreatic cancer are widely unclear. Classically, cancer cells are assumed to actively break or mechanically disrupt the perineural barrier to find access into nerves. However, for this hypothesis to be true, the cancer cells would need to exert destructive-toxic effects on the cells that compose the perineural barrier. Here, we hypothesized an alternative mechanism of cancer cell entry into nerves, i.e. the "transdifferentiation" of perineural epithelial cells of the outermost nerve sheath in the cancer micro-environment.

Aims & Methods: Human perineural epithelial cells were cultured within the supernatants of different human pancreatic cancer cell lines and analyzed for markers of epithelial-mesenchymal-transition (EMT). The integrity of the perineural epithelial cell linings was analyzed in human pancreatic cancer tissues by quantitative immunohistochemistry of circumferential perineural GLUT1 staining. Transcriptomic arrays were performed with perineural epithelial cells to decipher the transcriptomic changes in the cancer-induced transdifferentiation process. Levels of different EMT inducers were analysed by ElILISA within pancreatic cancer cell supernatants. Genetically engineered mice with precursors of pancreatic cancer (p48-Cre;LSL-KrasG12D/"KC") and pancreas-specific TGFbeta1 overexpression (KC;TGFbeta1ov+/) were analysed for the perineural integrity.

Results: Treatment of human perineural epithelial cells (HPEC) with supernatants of three different human pancreatic cancer cell lines resulted in morphological alterations in the perineural cells that were reminiscent of EMT. Accordingly, cancer-conditioned perineural epithelial cells overexpressed Vimentin and N-Cadherine, and downregulated E-cadherine. The transcriptomic analysis of the cancer-conditioned, perineural epithelial cells revealed expression changes that pointed out towards an EMT signature. Among the different potential mediators of EMT, the only factor that was specifically enriched in the supernatants of human pancreatic cancer cell lines was TGFbeta1. Accordingly, increasing concentrations of TGFbeta1 in the culture medium of human perineural epithelial cells resulted in prominent EMT-like changes in the perineural cells. In human pancreatic cancer tissues, GLUT1-expressing perineural epithelial barrier cells were widely lost as opposed to the intact barrier around nerves in normal pancreas. Moreover, analysis of the perineural integrity in KC;TGFbeta1ov+/ revealed prominent loss of perineural integrity upon TGFbeta1 overexpression when compared to KC mice.

Conclusion: Cancer cell-induced transdifferentiation of perineural epithelial cells seems to be the initial mechanistic event that enables pancreatic cancer cell access into nerves. In this context, TGFbeta1 signaling seems to be of paramount importance in mediating neural invasion in pancreatic cancer and is thus of potential therapeutic relevance.

Disclosure: Nothing to disclose

Towards early diagnosis of gastric cancer

08:30-10:00 / E1

OP313 COMPREHENSIVE BIOINFORMATIC ANALYSIS OF ABERRANTLY EXPRESSED PROFILES OF MIRNAS AND LNCRNAS WITH THE ASSOCIATED CERNA NETWORK IN GASTRIC CANCER

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Introduction: Increasing evidence has highlighted the critical roles of miRNAs as biomarkers and therapeutic targets for cancer. MiRNAs are also regarded as a major part of competing endogenous RNA (ceRNA) network due to its regulation on protein-coding gene expression by acting as sponges. However, functional roles of miRNA-mediated ceRNAs in gastric cancer (GC) remain unclear.

Aims & Methods: To clarify relevant potential mechanisms, we comprehensively compared the expression profiles of mRNAs, lncRNAs and miRNAs between 55 GC tissues and 55 non-tumor tissues, based on GEO databases. Then, we selected most relevant genes through GO and pathway analysis, together with target gene prediction. We also set up a ceRNA network through the certain algorithm.

Results: 299 lncRNAs and 1118 mRNAs were identified as aberrantly expressed in all of the four databases (GSE67354, GSE78775, GSE79973 and GSE19826). After screening by GO and pathway analysis, 364 significant mRNAs were selected (p< 0.05) and they had correlations with tumorigenesis and/or progression of GC. Further screening was performed using targeting gene prediction and 179 mRNAs were chosen. Then, a dysregulated miRNA-associated ceRNA network was successfully constructed, which inculdes 70 lncRNAs, 11 miRNAs and 112 mRNAs. Finally, 2 out of the 11 dysregulated miRNAs functioned as prognostic biomarkers for GC patients according to the overall survival analysis, which is a higher expression of hsa-miR-125-5p and hsa-miR-130-3p represented a lower prognosis rate (P=0.0259 and 0.0236, respectively). We then examined the miRNAs' expression in our 30 GC tissues and 30 controls. MiR-125 and miR-130 were both decreased in GC tissues.

Conclusion: Our study identified novel miRNAs as candidate prognostic biomarkers and potential therapeutic targets for GC, based on large-scale sample size. More importantly, the newly identified ceRNA network will be beneficial for improving the understanding of miRNA-mediated ceRNA regulatory mechanisms in the pathogenesis of GC.

Disclosure: Nothing to disclose

OP314 POTENTIAL OF URINARY MICRORNA BIOMARKER PANEL FOR THE EARLY DETECTION OF GASTRIC CANCER

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Introduction: Gastric cancer (GC) is one of the most common malignancies in the world. Although endoscopy is a gold standard for the diagnosis of this disease, comprehensive screening endoscopy would be invasive, expensive and could result in significant complications. To date, there is a significant lack of useful GC biomarkers. We thus conducted this study to discover non-invasive biomarkers for the early diagnosis of GC, consisting of urinary microRNAs (miRNAs).

Aims & Methods: A cohort of 306 patients composed of 153 patients with GC and 153 age- and sex-matched healthy controls (HCs) were randomly divided into three groups: the discovery cohort (4 pairs); the training cohort (95 pairs); the validation cohort (54 pairs). Moreover, age- and sex-matched 32 pairs with serum samples were also enrolled in the serum cohort.

Results: Baseline clinical characteristics were well balanced and no significant differences were noted except for *H. pylori* status. More than 60 % of patients with GC were stage I and around 50 % could undergo curative endoscopic resection in this study.

A miRNA microarray analysis detected 22 urinary miRNAs with significantly aberrant expressions between the two groups in the discovery cohort. Two miRNAs, miR-6807-5p and miR-6856-5p, were found to be highly

expressed in the urine of GC patients compared to HCs in the training cohort. A multivariate analysis has demonstrated that urinary levels of these 2 miRNAs were independent biomarkers for diagnosis of GC, as well as *H. pylori* status

In the validation cohort, urinary miR-6807-5p and miR-6856-5p showed significantly higher expression levels in the GC group, and the combination biomarker panel of miR-6807-5p, miR-6856-5p, and *H. pylori* status also showed excellent diagnostic performance (AUC = 0.885). In addition, serum levels of miR-6807-5p and miR-6856-5p were significantly higher in the GC group.

Conclusion: A novel biomarker panel consisted of urinary miR-6807-5p, miR-6856-5p, and *H. pylori* status enabled early and non-invasive detection of GC.

Disclosure: Nothing to disclose

OP315 DETECTION OF GASTRIC CANCER USING A SERUM MICRORNA ASSAY

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Introduction: High mortality from gastric cancer is related to the late manifestation of its symptoms. A blood-based non-invasive biomarker with the ability to detect all stages of gastric cancer could significantly improve patient outcomes.

Aims & Methods: We aimed to develop a novel serum miRNA assay for diagnosis of gastric cancer.

We developed a multi-target miRNA assay from a discovery study involving 892 gastric cancer and control subjects from Singapore and Korea. Using RT-qPCR, we quantified the expressions of 578 serum miRNAs and constructed a 12-miR biomarker panel through multi-variant data analysis. The results were generated with the use of a logistic-regression algorithm, with the value of 40 or more considered to be positive. We subsequently validated this multi-miR assay in a large prospective cohort. The cohort included subjects of all ethnicities (Chinese, Malay, Indian, and others) age 40 years old and above presenting with an indication for upper GI endoscopy at the National University Hospital and Tan Tock Seng Hospital, Singapore between 2013 and 2016. All participants had undergone endoscopy. In addition to miRNA profiling, sera was routinely assayed for *H. pylori* antibodies with Western Blot Assay (MP BIOMEDICALS, USA), as well as levels of pepsinogen I and II using latex agglutination turbidimetric immunoassay kit (Eiken, Japan). The performance of the miRNA assay was compared with serological markers such as *H.pylori* antibody and Pepsinogen index. A positive serum Pepsinogen index was defined as pepsinogen I level ≤70 ng/ml and a pepsinogen I/II ratio ≤3.0. All participants had given informed consent.

Results: Out of the 4566 subjects with the mean age of 57±10, 53% were male, 76% were Chinese, 55% were *H.pylori* serology positive, and 5.3% were positive for Pepsinogen index. There were 125 gastric cancer cases detected. The 12-miR assay achieved an Area-Under-Curve (AUC) of 0.84, significantly outperforming (p-value< 0.01) that of *H.pylori* (AUC of 0.64) and Pepsinogen index (AUC of 0.57). The sensitivity of the miRNA assay in detecting early (stage 0-2) and late (stage 3-4) stage gastric cancer was 82.6% (95% CI, 68.6% to 92.2%) and 88.4% (95% CI, 78.4% to 94.9%) respectively at a specificity of 70.0% (95% CI, 67.8% to 71.9%). In com-

parison, *H.pylori* showed a sensitivity of 80.4% at a specificity of 44.3% whereas the Pepsinogen index showed sensitivity of 18.2% at a specificity of 95.0%. Using the miRNA assay as a pre-screening tool could potentially reduce number of endoscopy needed by 62% in detecting one case of gastric cancer.

Conclusion: Our serum miRNA panel is a useful, non-invasive screening test for gastric cancer. It can reduce unnecessary diagnostic endoscopy too.

Disclosure: Nothing to disclose

OP316 CELL-FREE DNA AMOUNT AND MUTATION PROFILE ANALYSIS FOR GASTRIC CANCER PATIENTS

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Introduction: Cell-free DNA (cfDNA) is released into the blood stream in various ways including at the death of cells or by active secretion. CfDNA also harbors genetic aberrations from malignant tissue (1). It was shown that cfDNA could be a powerful disease state and relapse monitoring analyte (2). New minimally invasive diagnostic procedures for circulating molecules are in demand because standard diagnostics are not able to analyze the cancer mutation profile changes over the course of treatment. However, there is a lack of comparative studies conducted in gastric cancer comparing tumor tissue DNA and cfDNA mutation profiles.

Aims & Methods: The aim of a study was to compare tumor tissue DNA and cfDNA mutation profiles and evaluate correlation of cfDNA amount and TNM stage for gastric cancer patients.

The study was approved by the Kaunas regional biomedical research ethics committee (No. Nr. BE-2-10). Gastric cancer tissue and blood were collected from 30 patients who were recruited at the Department of Gastroenterology, Lithuanian University of Health Sciences Hospital during the period 2010 – 2018. Tumour tissue was obtained from the primary lesion of the resected specimen or biopsy and stored at -80˚C. Peripheral blood was drawn using a K2EDTA tubes at admission (before surgery). Sequencing libraries were prepared using TrueSeq Nano Libraries and samples of cfDNA pilot study were done in two replicates. Genomic DNA (gDNA) of tumor tissue and cfDNA were analyzed for mutations in cancer related genes using xGen Pan-Cancer Panel (IDT) consisting of 7816 xGen Lockdown Probes spanning 800 kb of the human genome, for enrichment of 127 significantly mutated genes implicated across 12 tumor tissue types for deeper sequencing coverage. Libraries were pair-end sequenced on an Illumina NextSeq 500. Individual reads were mapped to hg19 using BWA mem keeping only primary mappings. Variant calling for stand-alone plasma samples was performed using VarDict which enables scaling linearly to sequencing depth and ultra-deep sequencing application to detect tumor DNA circulating in blood. Strand filter was enabled to reduce false positive variants originating from only one strand. All variants were annotated using Variant Effect Predictor (3) and validated using the Integrative Genomics Viewer (4).

Results: Overall, 16 patients had mutations detected in gastric cancer related genes. Most frequently mutated genes in our study were *TP53*, *BRCA2*, *NOTCH1*, *CHECK2*, ERBB4 and KRAS. Yield of cfDNA is significantly increased for gastric cancer patients compared to healthy controls and generally corelated with gastric cancer TNM stage (R=0.55, p=0.012).

Conclusion: Our results demonstrate moderate correlation of total cfDNA amount and tumor stage. cfDNA reflects mutation profile in gastric cancer tissue DNA therefore may enable cfDNA analysis for monitoring disease stage of gastric cancer patients.

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Disclosure: Nothing to disclose

OP317 ENDOSCOPIC THREE CATEGORICAL DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION USING LINKED COLOR IMAGING AND DEEP LEARNING: A SINGLE-CENTER PROSPECTIVE STUDY

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Introduction: *Helicobacter pylori* (HP) eradication is a critical therapeutic approach to reduce gastric cancer mortality. In Japan, 1.5 million people undergo HP eradication annually. Three categories of HP infection status that coexist in the Japanese society are identified, i.e., non-infection (without a history of infection, HP_0), current infection (HP_1), and after eradication treatment (HP_2). Despite successful HP eradication, the risk of gastric cancer persists for patients who already show progression of mucosal atrophy and intestinal metaplasia[1]. Because each category shows a different risk of developing gastric cancer, diagnosis to stratify examinees into three categories is important. The authors find it beneficial to create a novel computer-aided endoscopic diagnosis (CAD) system for classifying HP infection status using linked color imaging (LCI) and deep learning (DL)[2]. LCI is a new image-enhanced endoscopic technique that enhances slight differences in mucosal color, whereas DL is a machine learning technology that imitates the neural network of the brain.

Aims & Methods: This prospective study aims to create a CAD system that can classify HP infection status into three categories using LCI and DL. The candidate subjects were examinees who underwent esophagogastroduodenoscopy (EGD) and who were tested for serum HP antibodies (HPab) or urea breath test (UBT) at our medical clinic. This study grouped the subjects under three categories: non-infection (HPab < 3 U/ml, n = 121, HP_0), current infection (HP ab ≥10 U/ml, n = 144, HP_1), and after eradication (UBT < 2.5 ‰, n = 119, HP_2). HP eradication treatment was performed at our clinic. All 384 subjects were allocated to a training group (n= 294; HP_0 = 91, HP_1 = 114, and HP_2 = 89) or a test group (n = 90; HP_0 = 30, HP_1 = 30, and HP_2 = 30) to evaluate the diagnostic accuracy of CAD. From the training group, 12,836 LCI pictures linked with HP infection status were generated. The accuracy of CAD was assessed by comparing the output data from the test group with the actual data on HP infection status. The endoscopic equipment was EG-L 580 NW or EG-6400 N (Fujifilm Co.). The DL model with 22 deep convolutional layers for CAD was adopted. R (version 3.3.2.) was used for statistical analyses.

Results: The areas under the curve of receiver operating characteristics of the CAD were 0.90 (HP_0; 95% CI, 0.833-0.959), 0.82 (HP_1; 95% CI, 0.727-0.905), and 0.73 (HP_2; 95% CI, 0.612-0.852).

Conclusion: Patients after HP eradication show negative reaction in most noninvasive HP infection tests; therefore, we cannot distinguish HP_0 from HP_2. In such a case, EGD is the only objective examination to achieve three categorical classifications because EGD recognizes mucosal atrophy and intestinal metaplasia of patients with eradicated HP. The CAD system demonstrated good accuracy in classifying HP infection status into three categories using LCI. In particular, the accuracy of HP non-infection with very low risk of gastric cancer was excellent. The authors infer that reducing EGD examination for HP_0 category can help simplify gastric cancer screening programs.

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Disclosure: Nothing to disclose

OP318 EFFICACY OF LINKED COLOR IMAGING IN SCREENING INTESTINAL METAPLASIA AND EARLY GASTRIC CANCER: A MULTICENTER RANDOMIZED CONTROL CLINICAL TRIAL

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Introduction: Minor mucosal lesions in the stomach are prone to be missed under white light (WL) endoscopy. Linked color imaging (LCI) can improve the endoscopic diagnosis, and LCI-based endoscopic criteria were proposed. We conducted this randomized clinical trial to investigate LCI's diagnostic efficacy for gastric intestinal metaplasia (GIM) and early gastric cancer (EGC)/high-grade intraepithelial neoplasms (HGINs).
Aims & Methods: Consecutive adult patients who had indications for gastroduodenoendoscopy were selected and randomly divided into two groups. In Group A (n=914), the patients received the WL endoscopy followed by LCI endoscopic examination. In Group B (n=914), the patients received LCI, followed by the WL mode for gastroscopy. The diagnostic efficacies of LCI and WL were evaluated and compared.
Results: LCI was superior to WL in diagnosing EGC/HGINs. GIM was manifested as "Purple in Mist" (PIM) under LCI. For GIM, the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) [95% confidence interval] of WL were lower than those of LCI (0.676 [0.654-0.699] vs. 0.877 [0.861-892]; 0.650 [0.612-0.688] vs. 0.870 [0.843-0.896]; 0.693 [0.664-0.721] vs. 0.880 [0.862-0.898]; 0.564 [0.527-0.600] vs. 0.784 [0.753-0.815]; and 0.764 [0.736-0.792] vs. 0.931 [0.916-0.946], respectively). For differentiated EGC/HGINs, the accuracy, sensitivity, specificity, PPV and NPV of LCI were higher than those of WL (0.770 [0.729-0.812] vs. 0.664 [0.626-0.703]; 0.825 [0.726-0.923] vs. 0.632 [0.506-0.577]; 0.761 [0.716-0.806] vs. 0.668 [0.627-0.709]; 0.367 [0.284-0.451] vs. 0.175 [0.122-0.227]; and 0.963 [0.940-0.985] vs. 0.942 [0.918-0.966], respectively).
Conclusion: Our data supported the idea that LCI could improve the endoscopic diagnosis of GIM and EGC/HGINs, which can be used for screening and surveillance (ClinicalTrials.gov ID: NCT03092414).
Disclosure: Nothing to disclose

Biomarker-based classification of IBD
08:30-10:00 / Barcelona

OP319 POLYGENIC RISK SCORES IDENTIFY GENETIC AETIOLOGY OF INFLAMMATORY BOWEL DISEASE PHENOTYPES BEYOND KNOWN DISEASE SUSCEPTIBILITY LOCI

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Introduction: Genome-wide association studies (GWAS) have greatly improved our understanding of the genetic background of inflammatory bowel disease (IBD), with up to 240 genetic susceptibility loci identified. Clinical disease phenotypes are very heterogeneous and are, rather than the disease itself, the main determinant of patient well-being. However, only few genetic contributors to disease phenotypes have been identified through conventional GWAS. Polygenic risk scores (PRS), which aggregate the effects of thousands of trait-associated genetic variants discovered in GWASs, are powerful tools to estimate individual-specific genetic propensities and predict outcomes, even when used in relatively small deeply-phenotyped cohorts. In this present study, we use polygenic risk scores of twelve IBD-affiliated traits to uncover mechanisms which contribute to clinical phenotypes.
Aims & Methods: Detailed clinical characteristics of patients with IBD were obtained from two independent cohorts (cohort A: n=1,097 and cohort B: n=2,697). All patients were genotyped using the Global Screening Array, and over 12 million genetic variants were imputed using the Haplotype Reference Consortium panel. PRS were constructed for CD, UC and ten different traits and their associations with IBD disease phenotypes were evaluated using linear regression models. Significant ($P<$ 0.05 after 10,000 rounds of permutation) PRS-phenotype associations identified in cohort A were put forward for replication in cohort B followed by a meta-analysis.
Results: In total, six PRS-phenotype associations remained significant after permutation and were replicated in the independent cohort. The composite genetic risk for CD susceptibility showed association with the subphenotype fibrostenotic CD (Montreal B2 [R^2 = 4.6%; P = 4.0E-7]) and ileocaecal resection (R^2 = 4.3%, P =6.3E-11), and remained significantly associated after correcting for CD disease location and age at diagnosis, even after excluding known contributing factors (*NOD2, MST1* and *MHC*). The composite UC susceptibility genetic risk (R^2 = 6.5%; P = 2.9E-4) and primary sclerosing cholangitis susceptibility (PSC) genetic risk (R^2 = 1.3%; P = 1.2E-3) were associated with colonic CD (Montreal L2). Moreover, polygenic scoring revealed shared genetic aetiology of affiliated diseases: polygenic risk for rheumatoid arthritis was associated with ulcerative proctitis (Montreal E1) (R^2 = 3.6%; P = 2.3E-4) and coeliac disease genetic risk (R^2= 2.6%; P = 1.4E-4) was associated with PSC. The polygenic risk for development of pulmonary fibrosis was nominally significantly associated with the risk of fibrostenotic CD in both cohorts (R^2 = 1.5%, [cohort A: unadjusted P= 0.018 and unadjusted P = 0.02 [cohort B]).
Conclusion: The cumulative genetic burden of CD is associated with more complicated clinical disease phenotypes, suggesting biological signals beyond known genome-wide significant disease susceptibility genetic variants. We validate the putatively shared genetic aetiology of PSC and UC with colonic CD. Moreover, our results suggest shared genetic aetiology between the development of pulmonary fibrosis and fibrostenotic CD. These results further our understanding of specific IBD phenotypes and might be used to better stratify patients or to provide new therapeutic targets.
Disclosure: Nothing to disclose

OP320 GENOME-WIDE ANALYSES IDENTIFY NOVEL GENETIC VARIANTS THAT INTERACT WITH TOBACCO SMOKE AND AFFECT RISK FOR DEVELOPMENT OF INFLAMMATORY BOWEL DISEASE

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Introduction: Inflammatory Bowel Disease (IBD) is characterized by a complex etiology with an interplay between genetic, environmental, microbial, and immunologic factors. A divergent effect of smoking behavior in the two subtypes of IBD, Crohn's Disease (CD) and Ulcerative Colitis (UC), supports the existence of gene-environment interactions (GxE). Several genetic variants have already been found to interact with tobacco smoke in modifying the risk for IBD. However, in previous studies, gene-smoking interactions in IBD were detected based on genome-wide Immunochip-data with poor coverage. Therefore, we performed a case-only study using over 12 million genetic variants with an excellent genome-wide content from Illumina Global Screening Array (GSA).
Aims & Methods: In this study, we aimed to identify novel gene-smoking interactions that could potentially affect IBD, CD or UC. Genetic data were obtained from 1,097 IBD patients (CD n= 500, UC n = 402) of European ancestry of the University Medical Center Groningen (UMCG) through GSA. After quality control (QC) and imputation 12,130,010 genetic variants were available for genome-wide association studies. Smoking status was defined as 'never smoking', 'ever smoking', 'current smoking' or 'former smoking'. Multivariable logistic regression analyses (age- and sex-adjusted) were performed to compare different groups of smokers (ever vs never

smokers, current vs never smokers, former vs never smokers, and current vs never and former smokers). All analyses were performed in the total IBD cohort, and for CD and UC separately.

Results: We observed an overall number of 2,109 statistically significant (p< 5.0x10⁻⁵) single nucleotide polymorphisms (SNPs). However, some SNPs referred to unknown genes or belonged to the same gene. Five significant SNPs, rs1878558 (*SLCO3A1*), rs6680523 (*RASSF5*), rs7141581 (*SLC25A21*), rs6818043 (*ARHGAP10*), and rs240952 (*REV3L*) were detected within loci that were previously associated with nicotine dependence or differences in smoking cessation. The directions of their odds ratios (ORs) indicated that our phenotype data were reliable. We detected several significant SNPs that refer to immune regulating pathway genes (e.g. rs6680523 *RASSF4*, rs11738246 *LNPEP*, rs74660825 *PRKCB*, rs144226221 *CBLB*, and rs160357 *CREB5*). Many other significant SNPs that we detected refer to dopaminergic signaling genes, calcium-associated genes, and nucleic acid binding genes.

Several nominally significant SNPs (p < 0.01) had an opposite OR direction in CD and UC: 216 SNPs in ever vs never smokers, 97 SNPs in current vs never smokers, 202 SNPs in former vs never smokers, and 98 SNPs in current smokers vs never and former smokers. The results imply that a smoking associated SNP protects against the one subtype of IBD, whereas the same gene-smoking interaction increases the risk for development of the other subtype of IBD.

Conclusion: In this study, we identified multiple novel genetic variants that interact with smoking status and affect the risk for development of IBD, CD or UC. In our cohort of 1,097 IBD patients, we were able to reproduce smoking-associated genetic risk variants that have previously been identified in non-diseased populations. We detected genetic risk variants that yielded an opposite direction in CD and UC, thus indicating a distinct effect of gene-smoking interactions on disease development. Our results, especially the divergent effect of gene-smoking interactions in CD and UC, provide a better insight into the contribution of gene-smoking interactions to the etiology of IBD.

Disclosure: Nothing to disclose

OP321 INTEGRATION OF WHOLE-EXOME SEQUENCING, GENOME WIDE GENOTYPING AND RNA SEQUENCING OF INTESTINAL BIOPSIES IN INFLAMMATORY BOWEL DISEASE IDENTIFIES INFLAMMATION-DEPENDENT EFFECTS

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Introduction: Inflammatory bowel disease (IBD) is a chronic immune-mediated disease, characterized by intermittent inflammation in the gastrointestinal tract. Although currently >240 genetic risk loci are known to be associated with this disease, it is still poorly understood how these genetic variants contribute to disease development. The effect of genetic variation on gene expression (defined as expression quantitative trait loci–*cis*-eQTLs) has mostly been studied by combining GWAS and transcriptome data from peripheral blood. However, the importance of studying these eQTLs in the disease- tissue and in the right disease- context is increasingly being recognized. We set out to examine the effect of genetic variants on gene expression in intestinal mucosal biopsies of IBD patients, in both inflamed and non-inflamed conditions, to identify inflammation-dependent eQTLs.

Aims & Methods: We collected 299 snap-frozen intestinal biopsies from 171 IBD patients, 113 deriving from non-inflamed tissue and 186 from inflamed tissue. Mucosal transcription profiles were determined by RNA-sequencing and genotypes were obtained by Whole Exome Sequencing (WES) combined with Genome Wide Screening Array (GSA) data. In total, 28,746 genes and SNPs located in +/- 500kb genomic regions surrounding these genes were included for identifying *cis*-eQTLs. *cis*-eQTLs were identified using linear mixed models and by regressing out the effect of potential confounding variables as visualized in the first 18 Principle Coordinates. To explore the effect of genetic variants in the context of inflammation, we then assessed the *cis*-eQTLs in inflamed versus non-inflamed tissue.

Results: Overall, 419,858 *cis*-eQTLs were found to be significant in gut tissue, after adjusting for inflammation effect (FDR< 0.05). We replicated 84.22% of these in the publicly available intestinal dataset of the Genotype-Tissue Expression (GTEx) consortium, showing robustness of our method. The inflammation-interaction analysis revealed 1.140 inflammation-dependent *cis*-eQTLs in 157 unique genes (FDR< 0.1). We identified inflammation-dependent *cis*-eQTLs involving known IBD-risk genes (*IL26*, *HLA-DQA1*, *HLA-DQA2*, *TNFSF11*), cytokines and growth factors (*DKK1*, *FGF12*, *PENK*, *STC2*), and genes encoding immune cell receptor (segments) (*IL17RB*, *TRAV34*, *TRAV8*, *TREML4*). Enrichment analyses of the associated genes revealed that inflammation-dependent *cis*-eQTL genes are mainly involved in immune responses and ion transport.

Conclusion: In this study we identify genetic variants that influence mucosal gene expression in patients with IBD, both dependent and independent of inflammation status. We observe that the inflammation-dependent *cis*-eQTL genes are mainly involved in immune responses, which suggests that differences in the genetic background of patients drive differences in the mucosal immune response in IBD. Overall, our results show local and context specific *cis*-eQTLs, which are potential leads for understanding disease pathogenesis and drug target identification.

Disclosure: Nothing to disclose

OP322 MICROBIOME AND FECAL BIOMARKERS CAN DIAGNOSE AND CLASSIFY INFLAMMATORY BOWEL DISEASE

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Introduction: Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Diseases (IBD) are chronic disorders of the gut, with prevalence exceeding 10% in the European population. Currently, these diseases are frequently diagnosed by exclusion of other gastrointestinal disorders using multiple, often invasive, clinical procedures. The only biomarker for IBD currently utilised in clinical practice is fecal calprotectin test (FCal), which has high sensitivity but suffers from moderate specificity. Improvements in metagenomic sequencing have enabled cost-efficient profiling of gut microbiota, opening an opportunity to utilise the gut microbiome for diagnosis of IBD and IBS. In addition, our previous research identified that fecal measurements of human beta defensin 2 (HBD2) and Chromogranin A (ChrA) proteins are associated with composition of gut microbiota and diagnosis of IBS.

Aims & Methods: The primary aim of this study was to use features of microbiome and fecal biomarkers FCal, HBD2 and ChrA to train models for non-invasive diagnosis of IBD and IBS. Secondary aim was to test if gut microbiome can be utilised to classify type of IBD (Crohn's disease vs ulcerative colitis) and clinical parameters of the disease (such as disease activity and location).

We used whole metagenome sequencing to analyse composition and function of microbiome of fecal samples of 181 IBS patient, 380 IBD cases and 859 healthy controls (HC), and measured HBD2, FCal and ChrA in all samples. A total of 521 microbiome features (244 bacterial taxa and 277 biochemical pathways) were used to train machine-learning classifiers (random forests, support vector machines and neural networks) for classification of samples as HC, IBD or IBS cases, and to classify type of IBD (Crohn's disease (CD) vs Ulcerative colitis (UC)), clinical parameters of the disease (based on Montreal classifications), and disease activity. The models were put forward for validation on a dataset generated using 16S sequencing to assess the reproducibility of the approach.

Results: Fecal measurement of HBD2 showed high predictive power for differentiating between IBD vs IBS (Sensitivity = 0.9, Specificity = 0.8, Area under ROC curve (AUC) = 0.89), outperforming FCal (Sensitivity = 0.85, Specificity = 0.6, AUC = 0.79). The ChrA, however, showed low predictive power (Sensitivity = 0.6, Specificity = 0.55, AUC = 0.57). Additionally, combining HBD2 and FCal increased the predictive power above individual biomarkers (Sensitivity = 0.9, Specificity = 0.85, AUC = 0.94).

Models trained using microbiome features demonstrated predictive power in line with HBD2 (AUC = 0.88) with an added advantage classification of

disease location (AUC = 0.82 for classification of colonic vs ileal disease) and type of disease (AUC = 0.88 for classification of UC vs CD). Finally, integration of biomarkers and microbiome features further increased the predictive power of the model (Sensitivity and Specificity > 0.9, AUC > 0.95 for IBD vs IBS). Models build on metagenomic-sequencing data replicated well by using 16S data (and vice-versa), with Sensitivity and Specificity within 10% of the original model.

Conclusion: We demonstrate that HBD2 is a novel biomarker for IBD with potential to improve specificity of IBD diagnosis, especially when combined with FCal. Additionally, we show that features of gut microbiome, in combination with already used fecal biomarkers, are strong predictors for differentiating IBD and IBS, with additional potential of classifying location and type of IBD. These results have a potential to improve non-invasive pre-screening for IBD in clinical practice.

Disclosure: Nothing to disclose

OP323 USEFULNESS OF ACP 353 (ANTI-CROHN´S DISEASE PEPTIDE 353) AS A NEW BIOMARKER IN THE DIAGNOSIS OF INFLAMMATORY BOWEL DISEASE: A MULTICENTER STUDY

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Introduction: We isolated an antigenic peptide (TCP 353) specific for patients with Crohn's disease (CD) from the blood using the phage display method and found that its antibody titer (ACP 353) would be a biomarker specific for CD (Clin Exp Immunol 2011 and J Gastroenterol 2014). In multicenter studies, we have clarified the specificity of TCP for novel serum biomarkers centered on ACP 353. Here, we analyzed the specificity of ACP 353 IgG for CD and the improvement in the diagnostic ability of the combination of ACP 353 IgG and a novel serum biomarker and examined its usefulness in the diagnosis of inflammatory bowel disease (IBD).

Aims & Methods: Subjects were patients with intestinal diseases who visited Kurume University Hospital, Fukuoka University Chikushi Hospital and Kyushu University Hospital between December 2016 and September 2017. ACP 353 IgG, glycoprotein 2 (GP2) IgG and antibodies against Saccharomyces cerevisiae (ASCA) IgG levels were mesured as a marker for CD and proteinase 3- antineutrophil cytoplasmic antibody (PR3-ANCA) and myeloperoxidase (MPO)-ANCA levels as a marker for ulcerative colitis (UC).

Results: There were 334 patients, including 108 with CD, 88 with UC, 23 with IBD-unclassified (IBD-U), 32 with other intestinal diseases (Irritable bowel syndrome, etc.), and 83 healthy people. The cutoff value was positive above the mean human healthy value plus 3 SD. The mean ± SE/positive rates of ACP 353 were as follows: CD, 54.7 ± 34.8 U/mL/34.3%; UC, 1.6 ± 0.15 U/mL/1.1%; IBD-U, 1.41 ± 0.12 U/mL/0%, others, 1 .19 ± 0.1 U/mL/0%; and healthy, 2.14 ± 0.06 U/mL/0%. The sensitivities/specificities of the markers were as follows: ACP 353 IgG, 34.3/97.8; GP2 IgG, 36.1/98.2; and ASCA IgG, 15.7/96.5 for CD, PR3-ANCA, 31.8/96.3; and MPO-ANCA, 0/100 for UC. Next, the specificity of the biomarker was fixed at 95%, and the sensitivity was compared. The sensitivities (%) of the biomarkers were as follows: ACP353 IgG, 34.3; GP2 IgG, 42.6; ASCA IgG, 26.9; ACP 353 IgG + GP2 IgG + ASCA IgG, 41.7; and ACP 353 IgG + GP 2 IgG + ASCA IgG + PR3-ANCA, 63.

Conclusion: The high specificities of the IBD novel biomarkers ACP 353, GP2 and PR3-ANCA were demonstrated. In the future, with the aim of multi-facility joint research on a nationwide scale, we would like to clarify the usefulness of new biomarkers centered on ACP 353 for the Japanese population.

Disclosure: Nothing to disclose

OP324 MYENTERIC PLEXITIS AND POST-OPERATIVE RECURRENCE IN CROHN'S DISEASE: THE ROLE OF ENTERIC GLIAL CELLS AND INTER-CELLULAR ADHESION MOLECULE-1

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Introduction: Half of Crohn´s disease (CD) patients require surgery within 20 years of diagnosis, and post-operative recurrence (POR) is frequent. Among the risk factors of POR, the presence of myenteric plexitis (≥ one immune cell in contact with myenteric ganglia) at the proximal resection margin has been incorporated in the European guidelines. However, this criterion is rarely used, as little is known about the involved mechanisms. Our objectives were to determine which cells of the enteric nervous system interact with T cells, and to identify the molecules responsible for these interactions.

Aims & Methods: Our objectives were to determine which cells of the enteric nervous system interact with T cells, and to identify the molecules responsible for these interactions.

In vivo: 29 patients (20 CD, 9 cancer) who underwent an ileocolonic resection were included. Full-thickness slices of the proximal resection margin were analysed by immunohistochemistry (IHC) to identify enteric glial cells (S100β), neurons (Hu) and T cells (CD3, CD4, CD8). T cells in contact with ganglia of the myenteric plexus were counted on each slide.

In vitro: To analyse neuro-immune interactions, human enteric glial cells (EGC) were co-cultured with T cells which were activated by anti-CD3/CD28 antibodies beforehand. To determine the impact of inflammatory conditions, EGC were pre-treated with lipopolysaccharide (LPS) or IL-1β/TNFα (IT). Immunocytochemistry (ICC) was used to analyse the adhesion of T cells to EGC. The expression of adhesion molecules was determined by qPCR, western blot and ICC.

Results: IHC showed the presence of T cells, CD4^{+} and CD8^{+}, in contact with EGC of myenteric ganglia in both CD and control patients. The number of T cells per ganglion was significantly higher in CD patients (5.6 ± 0.9) as compared to controls (1.2 ± 0.2) (p< 0.001), with a threshold of 1.7 T cell per ganglion, and was twice higher in CD patients suffering from POR (7.1 ± 1.4) as compared to those in whom CD did not recur (3.6 ± 0.9) (p=0.175). POR was systematic above 7.7 T cells per ganglion.

In vitro, pre-treatment of EGC with LPS and IT significantly increased the number of T cells in contact with EGC, respectively by a factor of 2.7 (± 0.7) (p< 0.01) and 2.1 (± 0.3) (p< 0.01) as compared to the control condition. These inflammatory stimuli were associated with an overexpression of ICAM-1 in EGC as measured by qPCR, while the expression of MAdCAM and NCAM was not increased. This upregulation of ICAM-1 was confirmed at the protein level.

Conclusion: Our results indicate that T cells interact with EGC *in vitro* and *in vivo*. These interactions are increased under inflammatory conditions and are associated with an upregulation of ICAM-1. This suggests a role of EGC in the formation of plexitis, possibly through the binding of LFA-1 to ICAM-1. Further experiments will be carried out to confirm this possibility.

Disclosure: Nothing to disclose

Highlights in oesophageal cancer: What's hot?

10:30-12:00 / A1

OP325 DETECTION OF BARRETT'S ESOPHAGUS BY MOLECULAR ENDOSCOPIC IMAGING USING NANOPARTICLES

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Introduction: Barrett's esophagus (BE) is recognized as a premalignant condition of esophageal cancer. Despite recent advancements in treatment strategies its prognosis is still very poor. Early detection may allow for more effective surveillance. Endoscopic surveillance for detecting premalignant lesions in BE is challenging because of their flat appearance without any noticeable morphological change. Molecular endoscopic imaging (MEI) allows for in vivo visualization and characterization of biological processes that occur on a cellular or sub-cellular level. Several MEI studies in the past using fluorescent-labeled antibodies were carried out to detect disease-specific targets. However, antibodies may confer allergic reactions, and their diffusion across epithelial borders and delivery to target structures is slow due to their high molecular weight. In contrast, nanoparticles have high surface area to volume ratio and no apparent toxicity. Therefore functionalizing the surface of nanoparticle with antibodies and stronger fluorophores allow for targeting minute amounts of structures. In addition they can also be loaded with ligands to multiple biomarkers. To date, no data is available on the use of nanoparticles for MEI

Aims & Methods: To assess the diagnostic applicability of MEI with nanoparticles for diagnosis of Barrett's esophagus. In addition, the results were compared with traditional MEI using specific labeled Muc-2 antibodies and standard histopathology.

Patients undergoing endoscopic surveillance of known Barrett's esophagus were recruited for the study. First, careful inspection of the Barrett's segment was performed with high-definition white-light imaging and chromoendoscopy. Then biopsies were collected from the Barrett's mucosa and rinsed in PBS. Afterwards, biopsy specimens were incubated with FITC labeled Muc-2 antibodies or biodegradable, pH sensitive nanoparticles coupled with FITC conjugated Muc-2 antibodies. After washing in PBS to remove unbound antibody, MEI was performed using the probe-based confocal imaging system. Squamous epithelium and gastric tissue samples were considered as controls. Fluorescence intensity from Barrett's mucosa and control specimens were compared, followed by histological confirmation.

Results: 30 specimens were successively analyzed. Squamous epithelium or gastric mucosa showed no antibody binding demonstrating the high specificity of the technique. Fluorescence signals were noted for traditional MEI using Muc-2 antibodies in intestinal type Barrett's metaplasia corresponding to goblet cells in the histopathological examination. A significantly higher fluorescence was found with nanoparticles coupled with FITC conjugated Muc-2 antibodies. MEI with nanoparticles for prediction of Barrett's metaplasia was consistent in all cases with histological analyses.

Conclusion: This is the first study showing the feasibility of using nanoparticles for molecular endoscopic imaging. Highly-specific nanoparticles can visualize Barrett's metaplasia more efficiently than conventional MEI. With the unique potential of nanoparticles allowing coupled to multiple biomarkers, future research is focused to identify different grades of dysplasia in affected patients. In addition, NPs can be loaded with cytotoxic materials to apply for targeted therapy.

Disclosure: Nothing to disclose

OP326 FACTORS PREDICTING MISSED DIAGNOSES OF OESOPHAGOGASTRIC CANCER: A CASE CONTROL STUDY OF PATIENTS HAVING GASTROSCOPY

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Introduction: There are unprecedented pressures facing endoscopy services worldwide. In the United Kingdom, there has been an over 40% increase in gastroscopy and 80% increase in colonoscopy delivery in the last 10 years. Oesophagogastric (OG) cancers diagnosed in patients who have had a gastroscopy within the preceding three years are considered to have had cancers missed and occur in 11% cases in the Western population [Menon and Trudgill, EIO 2014]. We examine patient, endoscopist and service level factors that may affect rates of missed OG cancers.

Aims & Methods: Patients diagnosed with OG cancer who had undergone gastroscopy within the preceding three years (the cases) were identified from endoscopy and OG cancer databases between January 2013 and December 2017 at Sheffield Teaching Hospitals, Sheffield, United Kingdom. Patient factors (age, gender, location of missed cancer and indication for gastroscopy), endoscopist factors (professional background, training status, procedural volume and use of sedation) and service pressures (number, types and time of procedures) at the time of the index procedure (at which a missed cancer is presumed) were examined and compared to two control groups. The first comprised the cases at the time of their subsequent diagnostic gastroscopy to control for patient factors. However, lesions in this group would be more endoscopically obvious than early cancers which are typically smaller, more focal lesions. Therefore a second control group comprised patients diagnosed as having benign focal lesions (of ≤ 10mm) matched (in terms of endoscopist, procedural date, patient age, gender and location of cancer) to each of the cases.

Results: We identified 627 patients diagnosed with oesophageal (50.9%) and gastric (48.8%) cancer of whom there were 48 (7.7%) cases considered to have missed cancers in the preceding three years. Missed gastric cancer was more common in male patients (OR 3.0, 95% CI 1.32- 6.91). There were fewer cases of missed oesophageal cancer amongst those who were examined for dysphagia (OR 0.16, 95% CI 0.05 - 0.50), but more cases amongst those examined for anaemia (OR 5.36, 95% CI 1.87 - 15.41). Univariate analysis suggested that greater total numbers of procedures (on lists including upper and lower endoscopy) or greater number of gastroscopies on a list, or gastroscopy only lists, were associated with missed cancers. However, only greater total numbers of procedures were associated with missed cancers on multivariate analysis (OR 2.16, 95% CI 1.19 - 3.91). When missed cancer cases were compared to the control group in which benign focal lesions were diagnosed, only a greater number of procedures on a list (OR 1.25, 95% CI 1.02 - 1.52) was associated with a risk of a missed lesion. There was no association between use of sedation, endoscopist experience or professional background or time of day and risk of missed cancers.

Conclusion: 7.7% of patients diagnosed with OG cancer could have been diagnosed and treated earlier. Our study suggests that there may be risk of missed pathology during gastroscopy performed on more populated endoscopy lists. The use of sedation, endoscopist background, or time of procedure did not increase the risk of missed cancer procedures.

References: Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. Endosc Int Open 2014; 2(2): E46-50.

Disclosure: Nothing to disclose

OP327 LONG-TERM OVERALL SURVIVAL AFTER ENDOSCOPIC MUCOSAL RESECTION FOR ESOPHAGEAL HIGH-GRADE DYSPLASIA AND EARLY ADENOCARCINOMA: A NATIONWIDE REGISTRY LINKAGE STUDY

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Introduction: Endoscopic therapy, particularly endoscopic mucosal resection (EMR), is recommended by current guidelines for patients with esophageal high-grade dysplasia (HGD) or early adenocarcinoma (EAC). Long-term outcome data based on large cohorts is limited. In this study, we aimed to evaluate the long-term outcome of EMR in patients with esophageal HGD/EAC based on nationwide data from daily clinical practice. We also investigated factors associated with overall survival.

Aims & Methods: Registered patients in the period 2005-2015 with HGD/EAC of the esophagus or gastroesophageal junction treated with EMR were identified from the Netherlands Cancer Registry (NCR). Clinicopathological data, including age at diagnosis, year of treatment, disease stage, surgical resection and vital status were retrieved from the NCR. Through record linkage with the nationwide Dutch Pathology Registry (PALGA), additional pathological data were obtained. Patients with no available pathology reports of an EMR specimen were excluded. The primary outcome was overall survival.

Secondary outcomes were the number of en-bloc resections, R0-resections (margins free from dysplasia/EAC) and proportion having undergone surgical resection. Estimated overall survival rates were compared with log-rank analysis. Multivariable Cox regression models were used to investigate the association between clinicopathological variables and overall survival.

Results: A total of 898 primary EMR procedures for HGD/EAC were included. The mean age at diagnosis was 67 [±10.5] years, median follow-up time 4.8 [IQR 3.0-6.8] years. Local tumor stage after primary EMR was 12% HGD (pTm1), 68% intramucosal (pTm2-3) and 21% submucosal (pTsm1-3) EAC, with 10-year overall survival rates of 73%, 58% and 49%, respectively (p<0.001, see table 1). In total, 118 patients (21%) had an en-bloc EMR with 42% complete resection rate.

Following piecemeal EMR (mean specimens 3.3 [±2.6]), R0-resection of the vertical margins was 73%. R0-resections increased over time from 53% in 2005 to 75% in 2015. After radical EMR without lymphovascular invasion, 28/558 (5%) underwent surgical resection during follow-up (4% intramucosal vs 14% submucosal EAC, (p<0.001). Factors associated with overall survival were pTsm1-3 (HR 2.5, 95% CI 1.4 - 4.4), pTm2-3 (HR 1.9, 95% CI 1.1 - 3.3), presence of signet ring cells (HR 1.7, 95 CI% 1.0 - 2.7), lymphovascular invasion (HR 1.6, 95 CI% 1.0 - 2.5), R1-resection (HR 1.5, 95% CI 1.1 - 2.0), age (HR 1.1, 95 CI% 1.0 - 1.1) and surgical resection (HR 0.5, 95% CI 0.3 - 0.8).

pT stage	Overall 5-year OS	Overall 10-year OS	R0-resection 5-year OS	R0-resection 10-year OS	R1-resection 5-year OS	R1-resection 10-year OS
m1 (HGD)	88%	73%	89%	75%	86%	67%
m2-3	76%	58%	79%	61%	69%	51%
sm1-3	65%	49%	80%	57%	55%	44%

[Table 1. Overall survival (OS) rates according to radicality of primary EMR.]

Conclusion: EMR is a highly effective treatment for esophageal HGD/EAC with excellent long-term survival in daily clinical practice. Pathologic factors, i.e. depth of tumor invasion, presence of signet ring cells and lymphovascular invasion, were the strongest predictors of poor overall survival.

Disclosure: Nothing to disclose

OP328 CONDITIONAL SURVIVAL IN PATIENTS WITH RESECTABLE ESOPHAGEAL CANCER

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Introduction: Most provided survival rates in current literature are static, calculated from the day of surgery. But as time proceeds after surgery, the risk of death in esophageal cancer patients changes. Conditional survival accounts for the time already survived after surgery and may be informative in addition to conventional estimates during follow-up.

Aims & Methods: The aim of this study was to assess conditional survival in esophageal cancer patients and to design a nomogram predicting the conditional probability of survival for esophageal cancer patients after surgery. Consecutive patients with esophageal cancer who received neo-adjuvant chemoradiation followed by an esophagectomy between January 2004 and 2019 in the Amsterdam UMC, location AMC, The Netherlands were included in this retrospective study. Patients with distant metastases, who underwent salvage surgery, or who died within 30 days after resection due to complications were excluded. Conditional survival was defined as the probability of surviving "y" years after already surviving for "x" years. The used formula was: $CS_{(x|y)} = S_{(x+y)}/S_{(x)}$ with $S_{(x)}$ representing the overall survival at "x" years. Cox proportional hazard models were used to evaluate predictors for overall survival. A nomogram was constructed to predict 5-year survival directly after surgery and given 1-, 2-, 3- and 4-years survival after surgery, based on the coefficients of the predictors in the multivariable Cox proportional hazard model, using a penalized LASSO (Least Absolute Shrinkage and Selector Operator) method. C-statistic which is presented with optimism adjusted for by bootstrapping.

Results: 660 patients were included in this study. The median overall survival was 46.4 months (95%CI 39.1 - 53.8). The probability to achieve 5-year overall survival after resection increased from 46% directly after surgery to 55%, 67%, 79% and 88% per additional year survived. The more years patients have already survived, the better their chances of additional years of survival are. This increase flattens after more years have passed. The conditional overall survival probability is shown in table 1. ypN-stage was the strongest predictor for overall survival in multivariable analysis (HR 2.53, 95%CI 1.90 - 3.36; HR 3.17, 95%CI 2.27 - 4.43 and HR 6.50, 95%CI 4.28 - 9.87, respectively for ypN1, ypN2, ypN3 with ypN0 as reference, all p< 0.001), followed by pulmonary complications (HR 1.16, 95%CI 1.88 - 0.002, p=0.002), cardiac comorbidity (HR 1.27, 95%CI 1.01 - 1.60, p=0.040) and ypT-stage (HR for ypT2-3 in relation to ypT0 1.461, 95%CI 1.02 - 2.09, p=0.039). These variables were included in the nomogram. The nomogram predicted 5-year survival using these predictors and number of years already survived with a C-statistic of 0.70.

Total years of survival	Years already survived by patients							
	0	1	2	3	4	5	6	7
1	83							
2	69	83						
3	58	69	84					
4	52	62	75	90				
5	46	55	67	79	88			
6	41	49	60	71	79	90		
7	38	46	55	66	73	83	93	
8	33	40	48	58	64	73	81	88

[Table 1. Conditional survival estimates]

Conclusion: The proposed nomogram showed an accurate prediction of survival in patients after esophageal cancer surgery, taking the years already survived after surgery into account. This nomogram can be helpful in counselling patients in the follow-up after surgery.

Disclosure: Nothing to disclose

OP329 DYNAMICS OF BODY COMPOSITION PARAMETERS IN RESECTED PATIENTS WITH ADENOCARCINOMA OF THE ESOPHAGOGASTRIC JUNCTION TYPE 1 AND 2

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Introduction: Preoperative sarcopenia is a predictor of poor prognosis of esophageal cancer after esophagectomy. and can influence surgical complications. Less is known about the influence of surgical resection on body composition. The aim of this study is to examine the dynamics of body composition parameters of resected patients with adenocarcinoma of the esophagogastric junction (AEJ) Siewert type I and II.
Aims & Methods: 172 patients with AEJ Siewert type I and II who underwent esophagectomy in the Department of Surgery, Klinikum Rechts der Isar, 2007-2009 and 2014-2015, were screened for this retrospective study. Computed tomography (CT) images prior to surgery (timepoint 1, T1) as well as 6 (T2) and 12 months (T3) after esophagectomy were assessed using Slice-O-Matic® software version 4.3. Following body compositions parameters were estimated: subcutaneous adipose tissue area index (SATI), visceral tissue area index (VATI), intramuscular tissue area index (IMATI), total adipose tissue area index (TATI), as well as skeletal muscle mass index (SMAI). 157 patients had CT at T1, and only 59 patients had CTs at T1, T2, and T3. Sarcopenia was defined by consensus thresholds before surgery with the cut-off points for SMI (skeletal muscle tissue area index) < 52.4 cm^2/m^2 for male and < 38.5 cm^2/m^2 for female patients.
Results: Preoperative sarcopenia occurred in 53% of patients. 76% of patients were sarcopenic 6 months and 72% 12 months after surgery. Sarcopenic and non-sarcopenic groups differ in absolute and relative weight loss, BMI, albumin, hemoglobin, SMAI and SATI, but not in cholinesterase, c-reactive protein, TATI, VATI and IMATI. Median survival rate was 3,9 (range: 0.2-11.3) years in the non-sarcopenic group and 2,8 (range: 0.2-11.2) years in the sarcopenic group (p = 0.006). The median values for decrease in body composition parameters 6 months after surgery were for TATI 55 cm/m2 (50%) in non-sarcopenic group and 52 cm2/m2 (51%) in sarcopenic group, for VATI 32 cm/m2 (64%) in both non-sarcopenic group and sarcopenic groups, for SATI 19 cm/m2 (33%) in non-sarcopenic group and 16 cm2/m2 (39%) in sarcopenic group, for IMATI 1 cm/m2 (33%) in non-sarcopenic group and 1 cm2/m2 (20%) in sarcopenic group, for SMAI 5 cm/m2 (9%) in non-sarcopenic group and 2 cm2/m2 (4%) in sarcopenic group.
The median values for decrease in body composition parameters 12 months after surgery were for TATI 60 cm/m2 (55%) in non-sarcopenic group and 46 cm2/m2 (46%) in sarcopenic group , for VATI 35 cm/m2 (70%) in non-sarcopenic group and 31 cm/m2 (62%) in sarcopenic group, for SATI 21 cm/m2 (36%) in non-sarcopenic group and 14 cm2/m2 (34%) in sarcopenic group, for IMATI 1 cm/m2 (33%) in non-sarcopenic group and 1 cm2/m2 (20%) in sarcopenic group, for SMAI 4 cm/m2 (7%) in non-sarcopenic group and 2 cm2/m2 (4%) in sarcopenic group. The significant differences between sarcopenic and non-sarcopenic groups were observed regarding change in SMAI (sarcopenic group lost less skeletal muscle 6 and 12 months after surgery), as well as change in IMATI (sarcopenic group lost less intramuscular adipose tissue 6 months after surgery) and SATI (sarcopenic group lost less subcutaneous adipose tissue 12 months after surgery).
Conclusion: To our knowledge, it is the first study demonstrating dramatical loss of adipose and skeletal muscle tissue 6 and 12 months after esophagectomy in AEJ Siewert type I and II patients. No significant changes in body composition parameters occur between 6 and 12 months after surgery.
Disclosure: Nothing to disclose

OP330 IRRADIATION STENTS PROLONG SURVIVAL COMPARED TO REGULAR STENTS IN END-STAGE ESOPHAGEAL CANCER: META-ANALYSIS AND SYSTEMATIC REVIEW

Tinusz B.[1], Soós A.[1], Hegyi P.[1], Sarlós P.[2], Szapáry L.[1], Erős A.[1], Feczák D.[1], Szakács Z.[1], Márta K.[1], Erőss B.[1]
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Introduction: Esophageal cancer is the eighth most common cancer worldwide and the sixth leading cause for cancer-related mortality. Such high mortality underlines the importance of palliative treatment options. Currently, there are no universally accepted international guidelines on whether additional oncological treatment is required besides stenting in the palliative care of esophageal cancer.
Aims & Methods: Our aim was to compare the effectiveness and safety of stent insertion alone to stent insertion combined with any modality of active oncological treatment in the palliative care of esophageal cancer.
A meta-analysis and systematic review were performed according to the PRISMA Statement. We searched 6 databases (PubMed, EMBASE, the Cochrane Library, Web of Science, clinicaltrials.gov, and the WHO Global Health Library) for papers on the palliative treatment of esophageal cancer. Patients receiving stent insertion only (control group) were compared to patients receiving chemotherapy, radiotherapy, chemo-radiotherapy or brachytherapy in addition to stent treatment (intervention group). Meta-analytical calculations were performed by using STATA v15.1. For mean survival time and grade of dysphagia within 3 days of stenting weighted mean differences (WMD) were calculated. For complications of stenting (such as chest pain, hemorrhage, deaths due to hemorrhage, stent migration and restenosis, tracheoesophageal fistula formation and development of pneumonia) pooled odds ratios (OR) were calculated. WMDs and ORs were interpreted with 95% confidence intervals (CI). The protocol of the study was registered prior on PROSPERO under the registration number CRD42018093921.
Results: Out of 9038 articles yielded by our search, 11 met the pre-defined inclusion and exclusion criteria. These contained a total of 838 esophageal cancer patients, out of which 374 and 464 patients belonged to the intervention and control groups, respectively. Patients in the intervention group had significantly longer mean survival time (WMD, 1.56; 95% CI, 0.66-2.46). This significance was still present when analyzing the subgroup of patients where irradiation stents were utilized as intervention (WMD, 1.93; 95% CI, 0.78-3.09), however, the significance disappeared when only looking at patients receiving other modalities of oncological treatment (WMD, 0.72; 95% CI -1.26-2.70). We found no significant difference in any complications of stenting between the two groups. Our systematic review suggested that additional treatment is more effective in the long-term relief of dysphagia than stenting alone.
Conclusion: Our results indicate that the utilization of irradiation stents prolong the survival of patients in the palliative treatment of esophageal cancers as compared to conventional stent insertion. Moreover, additional oncological treatment may be more effective in the long-term relief of dysphagia as compared to stenting alone. Further studies are warranted.
Disclosure: Nothing to disclose

An integrated view of microbiome in IBD

10:30-12:00 / A3

OP331 FECAL SCFA MEASUREMENT AND MICROBIOME METABOTYPE SHIFTS IN NUTRITIONAL THERAPY OF PEDIATRIC CROHN'S DISEASE

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Introduction: Changes in gut bacterial community structure are associated with Crohn's Disease (CD) and response to therapy. A recently completed randomized controlled trial (RCT) showed improved sustained remission with the Crohn's Disease Exclusion Diet + Partial Enteral Nutrition (CDED+PEN) as compared with Exclusive Enteral Nutrition (EEN)[1]. Whole metagenome analysis paired with metabolite assays can help elucidate how changes in abundance impact microbiome function.

Aims & Methods: To examine changes in the functional network and fecal SCFA concentration in CD patients reaching remission after 6 weeks of nutritional therapy (n=53). Stool samples were collected from patients at weeks 0, 6 and 12 and whole shotgun sequence data were obtained. Stool SCFA analysis was available for 128 samples (48 patients). Mann-Whitney U (unpaired) and Wilcoxon signed rank tests (for paired samples) were used to compare SCFA measurements at different time points.

In total 146 CD patient samples were combined with 26 healthy controls (Lewis et al.[2]), and characterized using HUMAnN2. Reactions, substrates and products for genes with an enzymatic commission were input to an unsupervised Bayesian analysis of community metabolism (BiomeNet). Statistical analysis of community metabolism and SCFA concentrations were performed using R. Non-negative matrix factorization (NMF) and Structural topic models (STM) were used to identify patient-associated microbial metabotypes.

Results: Unsupervised analyses revealed two metabotypes. All healthy controls possessed one metabotype (M1). CD patients possessed a mixture of two metabotypes (M1 & M2), with mixtures related to stage of treatment. CD patients achieving remission showed a steady increase in the M1 contribution as nutritional therapy progressed.

Fecal SCFA concentrations did not change significantly across the 3 timepoints in CDED+PEN, but there was a significant drop in butyrate in the EEN group compared with CDED+PEN at week 6 (p=0.00028).

However, SCFA concentrations were associated with M1 and M2 mixtures in patients. M1 was associated with higher concentrations in butyrate (p=0.012), valerate (p=1.2e-6) and iso-butyrate (p=0.008). Genes involved in the 4-aminobutyrate, and crotonoyl-CoA to butyrate pathways, (p=0.03 to 0.0001) were associated with M1 and a different pattern of associated genes was identified in M2. Changes in fecal SCFA concentrations, though associated with M1, were not associated with clinical remission at week 6 in CDED+PEN. In EEN, there was a significant drop between week 0 and week 6 in butyrate concentration (Mann-Whitney p=0.0018 and Wilcoxon signed rank test p=0.0046).

The butyrate-related change in community function is attributable to shifts in bacterial species abundance, notably *Bacteroides* and *Clostridium*.

Conclusion: Diet-induced remission samples were associated with a metabotype that characterized healthy controls and genes involved in the 4-aminobutyrate pathway, and crotonoyl-CoA to butyrate pathway. Although the higher concentrations of butyrate and other SCFA, associated with M1, agree with past work suggesting that butyrate levels are associated with reduced inflammation, we did not measure an increase in fecal butyrate in the CDED+PEN group.

Conversely, remission achieved with EEN is associated with a decrease in butyrate at week 6. An expansion of Firmicutes and decrease in Proteobacteria was observed in both diets by week 6. This suggests that other metabolic processes are important in the microbiome community function shift associated with achieving remission.

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Disclosure: Nothing to disclose

OP332 WHOLE EXOME SEQUENCING ANALYSES REVEAL GENE-MICROBIOTA INTERACTIONS IN THE CONTEXT OF INFLAMMATORY BOWEL DISEASE

Hu S.[1], Vich Vila A.[1], Gacesa R.[1], Collij V.[1], Stevens C.[2], Rivas M.A.[3], Imhann F.[1], van Dullemen H.M.[1], Dijkstra G.[1], Visschedijk M.C.[1], Festen E.A.M.[1], Xavier R.[4], Fu J.[1], Daly M.J.[2], Wijmenga C.[1], Zhernakova A.[1], Kurilshikov A.[1], Weersma R.K.[1]

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Introduction: A large number of host genetic factors, as well as changes in the gut microbiota, are known to determine etiology and pathogenesis of inflammatory bowel disease (IBD). The knowledge on the interaction between these two factors is, however, still limited. In order to characterize these interactions, in depth determination of the host genetics and gut microbiota is necessary. Here we aimed to identify genetic factors relevant for maintenance of the gut microbiome in the context of IBD.

Aims & Methods: We performed whole exome sequencing of the host genome, and whole genome shotgun sequencing of fecal samples of 524 IBD patients and 939 controls from population-based cohort. The interaction between exonic variants, microbial taxa and metabolic pathways was explored using a four step approach: 1) Bidirectional meta-analysis between the two cohorts to identify common variants 2) A targeted meta-analyses of IBD risk loci and protein truncating variants (PTVs) 3) A gene-based burden test to detect rare mutations that affect microbial features, and 4) an interaction analysis to identify IBD-specific microbial quantitative trait loci (mbQTLs).

Results: We tested 170,000 protein coding variants and 641 microbial features and identified 25 associations between genetic variants and gut microbial features (FDR< 0.05). Among common variants, a strong mbQTL was observed for deletion near the IBD-risk *IL17REL* gene that was correlated to *Alistipes indistinctus* abundance, which is known to be decreased in IBD patients. The gene-based burden test revealed that mutations in an IBD-related gene *CYP2D6*, a major component of phase I drug metabolism, were associated with decreased level of bacterial biosynthesis of vitamin K (PWY-5838). Moreover, *GPR151* gene, known to be protective against obesity and type II diabetes, was found to be associated with a decrease in bacterial degradation of glucose. The interaction analysis revealed another association between *TNFSF15* and *glycogen degradation* specific to IBD.

Conclusion: We performed the largest, high resolution, genome-microbiome association study to date, that utilizes whole exome sequencing and metagenomics sequencing methods. Disease specific interactions were explored in the context of IBD, including the effect of risk loci and protein truncating variants. These results highlight the importance of host genetics in the maintenance of gut microbiome homeostasis critical for prevention of IBD.

Disclosure: Nothing to disclose

OP333 INTEGRATED MICROBIOTA AND METABOLITE PROFILES IN HUMAN AND MICE IDENTIFIED FUNCTIONAL SIGNATURES IN CROHN'S DISEASE WITH A LINK TO SULFATE METABOLISM

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Introduction: Dysbiosis and metabolic alterations of the gut microbiome have been implicated in inflammatory bowel diseases (IBD). The aim of this study is to identify functional microbiome signatures associated with disease outcome or response to therapy in patients with IBD, and to mechanistically characterize their pathogenic potential using gnotobiotic humanized mice and an integrative multi-omics approach.

Aims & Methods: We studied 35 Crohn's disease (CD) patients for a period of 5-years after autologous hematopoietic stem cell transplantation (HSCT) therapy. Fecal samples were collected both at baseline and at different time points during follow-up. To characterize changes in gut microbiome and metabolome, we performed 16S rRNA gene sequencing, global 16S predicted metagenomes, shotgun metagenomic sequencing and untargeted metabolomics. To address the functional impact of microbial dysbiosis, we established a humanized IBD mouse model by colonizing germfree (GF) Il-10$^{-/-}$ mice with selected fecal samples from CD patients at different disease states.

Results: Temporal fluctuations in gut microbiota composition and metabolite profiles reflected the individual patient-related variations and the differences in disease activity. Fecal microbiome of patients with active disease was enriched in microbial taxa involved in sulfur metabolism such as *Eshericia Shigella* and *Fusobacterium* as well as a high proportion of sulfate reducing bacteria such as *Desulfovibrio* and *Campylobacter*. Fecal metabolic profiling confirmed an increased abundance of sulfated metabolites (bile acids, polyphenols and biogenic amines). Predicted metagenomes from 16S rRNA gene profiling revealed enrichment of functional genes associated with sulfate and ion transport system metabolism in IBD patients with active disease. In contrast, increased abundance of several basic biosynthetic processes correlated with remission. Transplantation of microbiota from patients with active or inactive disease was reproducibly sufficient to recreate disease phenotype in recipient Il-10$^{-/-}$ GF mice. Humanized mice reflected the dysbiotic features of their respective human donors and inflammation was driven by a variety of individual community profiles. Using a machine-learning algorithm, we identified a microbiome signature that discriminates inflamed from non-inflamed humanized mice characterized by an overabundance of B*acteroides fragillis* and *Desulfovibrio*. In accordance with the signature identified in humans, enrichment of sulfated metabolites was indicative for inflamed phenotypes, together with an abundance of genes mapping to sulfate metabolism, Type II, IV and VI secretion systems. Integration of microbiota and metabolite profiles from human and mice improved the predictive modelling of disease outcome significantly and identified a network of functionally relevant bacteria-metabolite interactions linked to disease activity in CD.

Conclusion: Our data prove that despite the heterogeneity of CD patients gut microbiome at the taxonomic level, shared functional signatures correlate with disease severity. Multi-omics data integration improved the clinical outcome prediction and identified a signature involving sulfur metabolism and detoxification to be relevant in disease outcome.

Disclosure: Nothing to disclose

OP334 IMPACT OF 41 COMMONLY USED DRUGS ON THE COMPOSITION, METABOLIC FUNCTION AND RESISTOME OF THE GUT MICROBIOME

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Introduction: The human gut microbiota composition is influenced by numerous factors including medication. Moreover, there is increasing evidence that the gut ecosystem plays an essential role in drug responses and efficacy. To further understand these drug-microbiota interactions in the context of polypharmacy, we studied the relations between commonly used drugs and gut microbial changes in the general population as well as in patients affected by gastrointestinal disorders.

Aims & Methods: We performed metagenomics sequencing of 1883 fresh frozen fecal samples from three independent cohorts:
1) a population-based cohort,
2) patients with inflammatory bowel disease and
3) patients with irritable bowel syndrome intermixed with healthy controls. Taxonomic and potential metabolic profiles were predicted for all samples. In each cohort, we investigated differences between drug users and non-users in two steps: first, by looking at the effect of single medication use, and second, considering the use of multiple drugs per participant. Finally, cohort-specific results were combined in a meta-analysis using an inverse-variance-based approach.

Results: Out of 41 drugs categories, 18 were associated with changes in gut microbiota composition and/or function, with proton-pump inhibitors (PPIs), metformin, antibiotics and laxatives having the largest impact. After correcting for polypharmacy, seven drug categories remained significant (FDR< 0.05), and associated to changes in 46 taxa and pathways. For example, the abundance of *Eubacterium ramulus* was associated with the use of SSRI antidepressants. The gut microbiota of PPI users was characterized by an increased abundance of upper gastrointestinal tract bacteria and by the increase of fatty acid biosynthesis pathways. While these changes in microbial functions were mainly driven by the expansion of *Streptococcus* species in the fecal samples of PPI users, in metformin users an enrichment of *Escherichia coli*-derived metabolic pathways was observed. The use of oral steroids was associated with an enrichment of methanogenic bacteria. Methanogenic bacteria have been associated with obesity and an increase in BMI, a known side effect of oral steroids use. Finally, we identified an increase in antibiotic resistance mechanisms related to eight different medication categories

Conclusion: We provide evidence for extensive changes in taxonomic structure, metabolic activity and resistome in relation to commonly used drugs. Changes in the gut microbiota can increase the risk of enteric infections, obesity and other disorders, therefore, these associations need to be functionally investigated given the importance of the gut microbiota in health and the widespread use of many drugs.

Disclosure: Nothing to disclose

OP335 *BACTEROIDES FRAGILIS* IS MORE PREVALENT IN CROHN'S DISEASE EXACERBATIONS WHILE STRENGTHENING THE INTESTINAL EPITHELIAL BARRIER IN A STRAIN-DEPENDENT MANNER

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Introduction: Crohn's disease (CD) is a chronic relapsing inflammatory gastro-intestinal disease with a high disease burden. Until today, the pathophysiology is not completely understood. Next to host genetics and environmental factors, impaired intestinal barrier function and microbiota seem to play a role in the onset and course of CD. Among others, *Bacteroides fragilis* has frequently been associated with CD. In addition, recombinant *B. fragilis* toxin (Bft) was found to disrupt the intestinal epithelial barrier *in vitro* by cleaving the adherens junction protein E-cadherin. Furthermore, Ubiquitin was found as a potential virulence factor, acting on host immune response.
Aims & Methods: This study aims to investigate the role of *B. fragilis* in the pathophysiology of CD, focusing on prevalence and its interaction with the intestinal epithelial barrier.
To investigate the presence of *B. fragilis*, *B. fragilis* toxin (Bft) and Ubiquitin, we selected 183 CD patients with active or remissive state from our extensive population-based IBD South Limburg cohort. Disease activity was determined by faecal calprotectin levels (< 100 μg/g = remission; ≥250 μg/g = exacerbation) and faecal DNA was investigated by qPCR. Data were analysed using Chi-square test.
To examine the impact of *B. fragilis* on the intestinal epithelial barrier, we subsequently cultured and isolated six *B. fragilis* strains with various genetic profiles of *bft* and *ubiquitin* from two healthy subjects, three CD patients and one ATCC strain (25285). Differences in coding sequences and secreted metabolites between bacterial strains were examined by whole-genome sequencing using MiSeq and Nuclear Magnetic Resonance (NMR) Spectroscopy, respectively. Next, bacteria-free culture supernatant as well as outer membrane vesicles (OMVs) were isolated and luminally applied to colonic adenocarcinoma-derived Caco-2 cell monolayers. After 24 h incubation, the difference in transepithelial electrical resistance (TEER) was determined and compared to the vehicle control.
Results: *B. fragilis* prevalence was 15 % higher (p<0.023) in active CD patients compared to remission. *Bft* and *ubiquitin* prevalence was comparable in both groups. Interestingly, TEER results demonstrate that luminally applied concentrated culture supernatant of *bft* positive *B. fragilis* strains increased the TEER (p<0.001) compared to *bft* negative strains or vehicle control, suggesting an improved epithelial integrity. This effect even overruled tight junction-dependent barrier disruption by TNF-α and IFN-γ. However, isolated OMVs of *bft* positive or *bft* negative strains did not show any alterations in TEER. Among the *B. fragilis* genomes 160 to 18875 SNPs were observed (Split Kmer Analysis). *bft* positive and *bft* negative strains cannot be discriminated by other known coding sequences than the pathogenicity island, containing *bft* and Metalloprotease II. NMR analysis did not reveal clear differences in metabolic profiles between the supernatants of the strains.
Conclusion: This study confirms in a large well-defined patient cohort that *B. fragilis*, but not *bft* or *ubiquitin* positive strains specifically, is more prevalent in active CD, suggesting that it might play a role in exacerbations. Surprisingly, *B. fragilis* components did not impair the epithelial barrier and components of *bft* positive strains even improved intestinal barrier function, which warrants further investigation. This unexpected finding stresses the relevance of extending current research on the functional role of relevant microorganisms.
Disclosure: Nothing to disclose

OP336 GUT MICROBIOTA IN PRIMARY SCLEROSING CHOLANGITIS IS CHARACTERIZED BY SPECIFIC COMPOSITION OF FUNGI

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Introduction: Primary sclerosing cholangitis (PSC) is a progressive disorder of biliary tree which can lead to end-stage liver disease, liver transplantation or even death. Colitis accompanying PSC (in up to 80% of patients) is considered to be a phenotype of IBD inflammatory bowel disease (IBD) distinct from ulcerative colitis (UC) and is often referred to as PSC-IBD. Gut microbiota presumably plays an important role in both PSC and IBD pathogenesis. Several recent studies described the features of gut bacterial microbiota composition in PSC. However, disruption of gut fungal microbiota (mycobiota) has not yet been properly investigated.
Aims & Methods: The aim of this study was to characterize gut mycobiota composition in patients with PSC, PSC-IBD and UC. Stool samples were prospectively collected and relevant clinical data obtained from 109 study participants: 50 PSC patients with (n = 38) or without (n = 12) concomitant IBD, 32 controls with UC and 27 healthy controls (HC). After standardised DNA extraction, amplification and library preparation, sequencing of the ITS1 gene was performed using Illumina MiSeq platform. Acquired data were processed in QIIME employing MaAsLin and LEfSe tools for analysis of the output results.
Results: Mycobial profiles did not reveal significant shifts between the study groups when calculated for various alpha - diversity indices (Shannon, Chao 1, Simpson, Observed OTUs). Furthermore, there was no statistically significant distinction among phenotypes when describing beta - diversity with both Bray - Curtis and Binary Jaccard index. However, PSC was characterized by high relative abundance of several genera as compared to healthy controls: *Candida* (5.2% vs 2.5%), *Lysurus* (20.7% vs 11.7%) and *Cladosporium* (1.2% vs 0.6%). Furthermore, relative abundance of genus *Rhodosporidium* clearly distinguished PSC-IBD from UC (14.4% vs 2.8%). Such differences were further tracked down to the species level, identifying major taxa responsible for respective shifts: *Candida albicans*, *Lysurus cruciatus*, C*ladosporium herbarum* and *Rhodosporidium Babjevae*. Subsequent multivariate analysis determined high abundance of *Cladosporium herbarum sp.* to be tightly associated with presence of PSC (p ≤ 0.05).
Conclusion: PSC is characterized by specific features of gut fungal microbiota composition. Intestinal mycobiota profiles differ between IBD subphenotypes (PSC-IBD and UC). High abundance of *Cladosporium herbarum sp.* (exceedingly common plant pathogen) in PSC may suggest an association with certain dietary habits.
Disclosure: Nothing to disclose

Seeing is believing: Improving polyp detection
10:30-12:00 / B2

OP337 IMPROVED ADENOMA DETECTION WITH ENDOANGEL: A RANDOMIZED CONTROLLED TRIAL

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Introduction: Colonoscopy is a pivotal procedure in the detection and diagnosis of lower gastrointestinal lesions. However, there are significant variations in colonoscopy performance among endoscopists, impairing the discovery of colorectal cancers and precursor lesions. The aim of this study was to construct a real-time quality improving system, ENDOANGEL, to monitor real-time withdrawal speed, time colonoscopy insertion and withdrawal, and remind endoscopists of blind spots caused by scope slipping, and evaluating its effectiveness in improving the adenoma yield of everyday colonoscopy.
Aims & Methods: ENDOANGEL system was developed using the methods of deep neural networks and perceptual hash algorithm. Patients referred because of health examination, symptoms, surveillance were recruited from Renmin hospital of Wuhan University. Enrolled patients were ran-

domly assigned to ENDOANGEL-assisted colonoscopy (EAC) and normal colonoscopy (NC). The primary end point was the adenoma detection rate (ADR) in colonoscopy with or without ENDOANGEL.

Results: 388 and 391 patients were analyzed in EAC and NC respectively. ADR was significantly higher in EAC compared with the NC (13.56% vs 21.91%, P = 0.049). Polyp detection rate (PDR) was significantly increased from 37.08% to 51.29% with the assistance of ENDOANGEL (P < 0.001). Mean withdrawal was 2.32 minute longer with EAC (P < 0.001), with no difference in caecal intubation rate or insertion time. There was no significant adverse event.

Conclusion: ENDOANGEL significantly improved adenoma yield in colonoscopy and could be used to improve the quality of everyday endoscopy.

Disclosure: Nothing to disclose

OP338 ENDOCUFF-ASSISTED COLONOSCOPY VS STANDARD COLONOSCOPY ON ADENOMA DETECTION RATE IN ROUTINE PRACTICE: A CLUSTER-RANDOMIZED CROSSOVER TRIAL ON 2058 PATIENTS

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Introduction: Endocuff Vision (ECV) is a device supposed to improve polyp detection. This device has recently changed with the marketing of a second generation (ECV) very different from the first (Endocuff Device). If interest of the first generation of this device is still debated, little data is available on the second generation. The aim of this study was to evaluate the interest of ECV on adenoma detection rate (ADR) in routine colonoscopy. The secondary aim was to determine in which endoscopists the ECV is the most useful.

Aims & Methods: This cluster-randomized crossover trial compared endocuff-assisted (ECV+) to standard colonoscopy (ECV-). Randomization determined which team (of 11 endoscopists each, matched on ADR, age and activity volume) started with ECV + and which team by ECV-. A switch of the 2 teams was made at half of the inclusions.

The main criterion was ADR. Secondary objectives were polyp detection rate (PDR), advanced neoplasia detection rate (ANDR) and serrated polyp detection rate (SPDR).

Results: 2058 patients were included (1032 ECV- vs 1026 ECV+). Both groups were comparable except for age (58.5±13y vs. 59.25±12y, P=0.001). ADR was significantly improved in ECV group in multivariate analysis (OR 1.49, CI95% 1.2-1.82, P=10^{-5}). Benefit of ECV was significant for PDR (46.2% vs 37.7%, P< 0.001) but not for ANDR (11.1% vs 9.2%, P=0.17) nor SPDR (12.5% vs 11.9%, P=0.74).

Regarding ADR upon physicians, ECV significantly improved ADR in the medium (42 vs. 30%, P=0.005) and high detectors (46 vs 32%, P< 0.001) groups but not in the low detectors group (31 vs. 26%, P=0.16).

Conclusion: We showed a significant increase in ADR and PDR in ECV group with a gain of approximately 10%. This benefit was significant in medium and high detectors, but not in low detectors. In contrast, we did not show significant impact of ECV on ANDR and SPDR.

Trial registered at ClinicalTrials.gov (NCT03344055)

Disclosure: Nothing to disclose

OP339 IMPACT OF DIGITAL PATIENT REINFORCEMENT ON HIGH QUALITY COLONOSCOPY PREPARATION IN CRC SCREENING: RESULTS FROM THE MULTI-CENTER COLOPRAPP-STUDY

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Introduction: Sufficient bowel preparation is crucial for successful screening and surveillance colonoscopy. However, the rates of inadequate preparation are still high. We investigated the effects of reinforced patient education using a smartphone application for colonoscopy preparation in CRC-screening.

Aims & Methods: In this prospective, endoscopist-blinded, multi-center study standard instructions pertaining to split-dose preparation were provided orally and in a written format to all patients during the initial appointment. Patients (n=500) were randomly assigned (1:1) to group that received reinforced education starting 3 days before the colonoscopy (APP group) or control group without further education. The primary outcome was quality of bowel preparation according to the Boston Bowel Preparation Scale (BBPS). The secondary outcomes included polyp and adenoma detection rate (PDR, ADR), compliance with low fibre diet and split-dose laxative intake and patients' perceived discomfort of the preparation procedure.

Results: The mean BBPS score was significantly higher in the APP group (7.6±0.1) than in the control group (6.7±0.1) (p< 0.0001). The percentage of patients with insufficient bowel preparation was significantly lower in the APP group (8%) than in the control group (17%) (p=0.002). The ADR was significantly higher in the APP group (35 vs. 28%) (p=0.0081). Significantly more flat adenomas were detected in the right colon in the APP group (p=0.004). Using the smartphone application was accompanied by a lower level of discomfort during preparation and a higher rate of compliance regarding correct laxative intake and diet restrictions.

Conclusion: Reinforced patient education using a smartphone application for optimized bowel preparation during the final 3 days before colonoscopy increased bowel cleanliness, adenoma detection and reduced discomfort in CRC screening and surveillance patients.

Disclosure: B. Walter: Consultancies for Norgine Pharma

OP340 LINKED COLOR IMAGING IMPROVES DETECTION RATE OF SESSILE SERRATED ADENOMA/POLYP IN THE COLON: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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Introduction: Colorectal cancer (CRC) is one of the leading causes of cancer deaths worldwide. Endoscopic surveillance for premalignant polyps in the colorectum is a crucial strategy for reducing CRC-related mortality. It has been reported that colorectal polyps in the right-side colon are often missed during conventional colonoscopy. Sessile serrated adenoma/polyp (SSA/P) predominantly occurs in the right-side colon, and is a precursor lesion of the cancer with microsatellite instability. It is more difficult to detect SSA/P with conventional colonoscopy than adenomatous lesion because SSA/P commonly presents as a flat and faded color lesion. To improve endoscopic sensitivity in detection of SSA/P is putative for reduction of mortality of CRC. Linked color imaging (LCI) is a novel image-enhanced endoscopy that emphasizes color contrast between red and white areas and has been widely used for the diagnosis of gastrointestinal diseases including neoplastic lesions.

Aims & Methods: This study aimed to evaluate the utility of LCI for SSA/P detection in a prospective randomized controlled trial (RCT) and was conducted at Tokushima University Hospital between 2015 and 2018. Patients underwent modified back-to-back colonoscopies with white light image (WLI) and LCI. Patients were randomly allocated to 1 of the 2 arms at a 1:1 ratio using a sealed envelope method: (A) WLI-LCI group: first inspection with WLI followed by a second inspection with LCI; (B) LCI-WLI group: first inspection with LCI followed by a second inspection with WLI. Polyps detected during the first inspection were removed by snare or biopsied. Polyps detected during the second inspection were classified as additional polyps, and were also removed or biopsied. The primary outcome of the study was the additional SSA/P detection rate in WLI-LCI and LCI-WLI groups. The secondary outcomes were the positive detection rate for additional SSA/P lesions in the second inspection per subject and the morphological features of additionally detected SSA/P.

Results: A total of 60 patients participated the clinical trial and 52 were eligible; 26 each in the WLI-LCI and LCI-WLI groups. There was no statistically significant difference in inspection time, bowel preparation score, patients´ characteristics between the 2 groups. In the WLI-LCI group, 32 SSA/P were detected in the first inspection and 9 were additionally detected. In the LCI-WLI group, 34 SSA/P were detected in the first inspection and 1 was additionally detected. The additional detection rate of SSA/P in the second inspection in the WLI-LCI group was significantly higher than that in the LCI-WLI group (21.9% vs 2.9%, p< 0.05). The prevalence of additional SSA/P lesions in the second inspection per subject was significantly higher in the WLI-LCI group versus the LCI-WLI group (30.8% vs 3.8%, p< 0.05). The SSA/P lesions of smaller, non-mucus, same color as the background mucosa, and located at the transverse colon were detected more frequently in the second inspection with LCI. It was indicated that hyperplastic polyp and adenoma in the right colon were also additionally detected in the second inspection in the WLI-LCI group by the sub-analysis.

Conclusion: This RCT results demonstrated the superiority of LCI to WLI in SSA/P detection by highly improved additional detection rate of SSA/P. Our data will be warranted by a multicenter, larger-scale trial recruiting a more general patient population to compare detectability of SSA/P with LCI and WLI. The study was registered at the University Hospital Medical Information Network-Clinical Trials Registry (UMIN 000017599).

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Disclosure: Tetsuji Takayama received a research grant from FUJIFILM Co. The financial sponsor was not involved in the design of the study, analysis and interpretation of the data.

OP341 MICROVESSELS OBSERVATION IN COLORECTAL ENDOCYTOSCOPY IS USEFUL IN PREDICTING PATHOLOGICAL DIAGNOSIS

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Introduction: To date, narrow-band imaging (NBI) could make it possible to analyze the surface microvessels of colorectal lesions for differentiating neoplasms from non-neoplasms and for predicting the histropathological diagnosis. Endocytoscopy (EC) is the next generation of ultra-magnification endoscopy that allow visualization of the glandular structure and cellular atypia *in vivo*. In addition, when using EC with NBI (EC-NBI), it enables *in vivo* observation of blood vessels in more detail compared to conventional magnification power without the use of any dye solution.

Aims & Methods: The study included 502 patients who underwent complete colonoscopy and endoscopic or surgical treatment between April 2006 and June 2016. A total of 669 lesions (61 Non-neoplastic polyps, 372

adenomas, 75 intramucosal cancer, 21 slightly invasive submucosal cancer (SMs) and 140 massively invasive submucosal cancer.) were retrospectively evaluated. We used the Kudo classification for the degree of submucosal invasion and classified cancers accordingly(1). SMs cancer without vessel permeation does not metastasize. In contrast, SMm lesions show a substantial proportion (~10%) of lymph node metastasis. We named the ultra-magnified microvessel findings as endocytoscopic vascular (ECV) pattern and classified into the following 3 groups: EC-V1, the surface microvessels were very fine obscure; EC-V2, the surface microvessels were more clearly seen and showed a regular vessel network, and their caliber and arrangement were uniform; and EC-V3, the surface microvessels were thick, and their caliber and arrangement were non-homogeneous.

Results: The sensitivity, specificity and accuracy of EC-V1 for diagnosis of hyperplastic polyp were 91.8%, 98.7% and 98.1%, respectively. Similarly the sensitivity, specificity and accuracy of EC-V3 for diagnosis of SMm were 82.1%, 98.3% and 94.9%, respectively

Conclusion: Endocytoscopic vascular pattern was useful for predicting the histopathology of colorectal lesions.

Disclosure: Nothing to disclose

OP342 EFFECT OF PRECEDING BIOPSY ON THE RESULTS OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR COLORECTAL LATERALLY SPREADING TUMOR

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Introduction: Forceps biopsies are usually performed before endoscopic submucosal dissection (ESD) for colonic laterally spreading tumors (LSTs). However, preceding biopsy is commonly believed to possibly inhibit complete tumor resection by causing blurring of tumor borders and tissue fibrosis.

Aims & Methods: The aims were to investigate whether the preceding biopsy of colorectal LST affects complete endoscopic tumor resection and increases the risk of complications. We retrospectively reviewed the medical records of patients with colorectal LSTs who underwent ESD at our center during an 8-year period. Patients were divided into two groups according to whether they underwent biopsy of the tumor before ESD. In addition, the characteristics of patients and tumors, including the completeness of tumor resection, were investigated.

Results: Of 288 patients (174 men) enrolled in this study, 194 (67.4%, preceding biopsy group) underwent biopsies before ESD, whereas 94 (32.6%, no biopsy group) did not. There were no significant differences in age, sex, comorbidity, medication history, tumor location, and final pathologic result between both groups. Tumor size was larger (*p*=0.002) and LST-G tumor was more common (*p*=0.003) in the preceding biopsy group than in the no biopsy group. No significant difference was seen in ESD outcomes, including procedure time, hospitalization period, incidence of complications, en bloc resection rate, resection margin status, and incidence of surgical operation, between both groups.

Conclusion: Biopsy of LST is commonly performed before endoscopic resection. Contrary to popular belief, it does not increase the incomplete tumor resection rate and incidence of complications.

Disclosure: Nothing to disclose

Enteropathies: From bench to bedside
10:30-12:00 / B3

OP343 DIAGNOSTIC ACCURACY OF SERUM FIBROBLAST GROWTH FACTOR 19 (FGF19) AND TOTAL FECAL BILE ACIDS AS BIOMARKERS FOR BILE ACID MALABSORPTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES, MICROSCOPIC COLITIS AND IRRITABLE BOWEL SYNDROME

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Introduction: Excessive amounts of bile acids (BAs) entering the colon due to bile acid malabsorption (BAM) cause chronic bile acid diarrhoea (BAD). The [75]Selenium homocholic acid taurine (SeHCAT) test is the "gold standard", but is not generally available. Fibroblast growth factor 19 (FGF19) is the ileal hormone providing feedback inhibition of BAs and one possible biomarker of BAM that demonstrate a correlation with SeHCAT, but little is known about the mechanisms of dysregulation in patients with inflammatory bowel disease (IBD), IBD after ileal resection (IBD-IR), irritable bowel syndrome with diarrhea (IBS-D) and microscopic colitis (MC).

Aims & Methods: The aim was to evaluate the diagnostic accuracy of serum levels of FGF19, total free faecal bile acids (TFFBA) for finding BAM in patients active IBD, IBD in remission, IBD after ilea resection, IBS-D and MC. Methods: We enrolled 109 adult patients with chronic diarrhoea and 11 healthy controls who underwent standard laboratory tests, colonoscopy, serum FGF19, fecal calprotectin (FC), TFFBA. Patients were divided into six groups: 30 patients with active IBD, 21 patients with IBD in remission, 21 patients with IBD after surgery (IBD-IL), 23 patients with IBS- D, 14 patients with MC and 11 healthy control subjects. Fasting serum FGF19, TFFBA were measured by ELISA test and FC by the quantitative immunochromatographic method

Results: Diagnosis of BAM based on levels of FGF19 below 30 pg/ml was confirmed in 65 of 109 patients (59,6%) and excluded in 44 (40,4.%) compare to healthy controls. Mean levels of FGF19 in patients with IBD active were 263.06 pg/mL, IBD remission were 367.2 pg/mL, IBD-IR were 57.1 pg/mL, IBS-D were 447,5 pg/mL, MC were 403,7 pg/mL and healthy controls were with 585,6 pg/mL (p- 0,003, Welch test). A cut-off concentration of FGF19 of 136,7 pg/mL or lower identified patients with active IBD and diarrhea attributable to BAM with 70.9% sensitivity, 72,7% specificity and an AUROC 0.79 (p-0,005). The number of IBD patients in remission with up to 4 bowel movements daily was 16 (76.2%) and concentration of FGF19 below 136,7 pg/ml were in 76,2% of the patients, which corresponds with BAD as a co-factor in the diarrhea pathogenesis in these IBD patients. A cut-off concentration of FGF19 of 32,88 pg/mL or lower identified patients with IBD-IL and MC with diarrhea attributable to BAM with 90,5% sensitivity, 81,8% specificity and an AUROC 0.93 (p< 0.01).
The overall sensitivity and specificity of FGF19 for finding BAM in patients with IBD and MC compare to healthy controls were 76.2% and 72,7%, respectively for a cut-off value of 136,7 pg/ml., which will lead to accurate prediction of BAM in 72% of the IBD and MC patients. In patients with IBS-D, serum concentration of FGF19 shows no significant difference compare to healthy controls (p-0,71). TFFBA shows no significant difference between all the groups and compare to healthy controls.

Conclusion: BAM is common and very under-diagnosed condition in patients with chronic diarrhea. FGF19 could be used for screening biomarker for BAM in patients with IBD, IBD after surgery (ileal resection) and MC, because there is effective additional treatment with bile acid binder's for this patients. We observed significantly lower serum concentrations of FGF19 in patients with IBD with IR, compared to healthy controls. A cut-off concentration of FGF19 below of 30,04 pg/mL identifies patients with diarrhea likely attributable to BAM with an AUROC value of 0.93. Further bigger studies are needed to establish the efficacy of FGF19 in patients with suspected bile acid malabsorption.

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Disclosure: Nothing to disclose

OP344 CYTOKINE RESPONSES TO GLUTEN AND GLIADIN IN MUCOSAL IMMUNE CELL POPULATIONS FROM FUNCTIONAL DYSPEPSIA PATIENTS

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Introduction: Non-coeliac gluten or wheat sensitivity (NCWS) describes a condition by which ingestion of wheat products induce gastrointestinal symptoms, in the absence of coeliac disease or wheat allergy. Symptoms of epigastric pain and post-prandial fullness are often described by these patients, demonstrating some overlap of symptomology with functional dyspepsia (FD). In addition, an association between FD and foods containing wheat components have been reported in a number of observational studies; however, the mechanism behind this link has not been elucidated.

Aims & Methods: This study aimed to examine whether antigens present in gluten or gliadin could provoke an immune response from duodenal mononuclear cells isolated from patients with FD.
Lamina propria mononuclear cells (LPMCs) were isolated from duodenal biopsies taken from patients with FD diagnosed by Rome III criteria (n=14) and non-dyspeptic controls (n=8). The cells were cultured and exposed to gluten (1 mg/mL) or gliadin (1mg/mL) for 24 hours. The supernatant was collected and a cytometric bead array used to analyse the concentrations of Th1, Th2 and Th17 cytokines (IL-2, IL-4, IL-6, IL-10, TNF, IFN-γ, and IL-17a).

Results: When LPMCs were stimulated with gliadin, a significant increase in the concentration of IL-17a was produced from FD patient cells compared to non-FD controls (*p*=0.047). There was no significant response observed for IL-17a in response to gluten for FD or control. When the cohort was classified by self-reported NCWS, FD patients with NCWS had increased IL-17a concentrations when compared to non-FD controls with no NCWS (*p*=0.0001). Interestingly, FD patients without NCWS had significantly increased IL-17a levels when compared to the NWCS positive FD group when treated with both gluten (*p*=0.002) and gliadin (*p*=0.009).
Stimulation with gluten produced a decreased TNF level trending towards significance (*p*=0.061) in FD patients when compared to controls. FD patients with NCWS had significantly decreased levels of TNF compared to controls with NCWS (*p*=0.006) and controls without NCWS (*p*=0.030). An increase in TNF level in FD patients without NCWS compared to FD patients with NCWS was approaching significance (*p*=0.052).There was no change in TNF level following exposure to gliadin.

Conclusion: Gluten and gliadin, components of wheat, stimulate immune responses from duodenal LPMCs from FD patients, characterised by an increase in IL-17a concentration and a decrease in TNF levels in cell culture supernatants.
These results indicate that NCWS may be a subtype of FD, and that dietary antigens from wheat products may induce symptoms of FD in some. The increased IL-17 concentration in cells from FD patients following stimulation with gliadin suggests Th17 immune pathways warrant further inves-

tigation in NCWS and FD. Further characterisation of these antigens as potential triggers for a subset of FD could allow for the elucidation of the immune mechanisms driving symptom onset and subtle inflammation in patients.
Disclosure: Nothing to disclose

OP345 MAST CELL DENSITY AND MAST CELL-NERVE INTERACTIONS CORRELATE WITH SEVERITY OF ABDOMINAL PAIN AND BLOATING IN PATIENTS WITH NON-CELIAC GLUTEN / WHEAT SENSITIVITY

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Introduction: Non-celiac gluten/wheat sensitivity (NCG/WS) is characterized by gastrointestinal (GI) and extra-intestinal symptoms triggered by gluten-containing foods. Hitherto, despite many efforts, different aspects of this disorder, i.e. epidemiology, pathophysiology, diagnostic biomarkers and mechanisms underlying symptom generation remain unsolved. Furthermore, the overlap of clinical signs with functional GI disorders, including functional dyspepsia (FD) and irritable bowel syndrome, make the diagnosis of NCG/WS challenging in daily practice. Based on the hypothesis that innate, more than adaptive, immunity is involved in NCG/WS, we designed this study aimed to investigate the role of neuro-immune interactions in GI symptom generation in patients with NCG/WS, focusing on the upper gut, specifically on duodenal submucosal neurons and mast cells (MCs).

Aims & Methods: Patients with self-reported NCG/WS (n=34), celiac disease (CD; n=28), FD (n=13) and healthy controls (HC; n=24) were recruited and examined with upper GI endoscopy to obtain routine duodenal biopsies. NCG/WS and CD patients were recruited according to the diagnostic work-up, including serological and genetic tests and histopathological evaluation, while FD patients were selected based on Rome IV criteria. All subjects were invited to fill an appropriate symptom questionnaire (modified GI symptom rating scale). Submucosal whole-mount preparations were analyzed by immunohistochemistry to obtain quantitative data on neuronal and MC density and the percentage of MC in close vicinity to submucosal nerve endings. Appropriate statistical tests were applied to compare the three groups in terms of symptoms, neuronal and MCs density and MCs-nerves distance (D). These results were correlated to the clinical features.

Results: There were significant differences among the three pathological groups in terms of the number of GI symptoms (P< 0.0001) and the presence and severity of bloating and abdominal pain (P< 0.0001), with NCG/WS groups showing the highest scores. Bowel habit changes were similar among the three groups (P=0.08). Immunohistochemistry showed absence of neuronal cells abnormalities in the enteric submucosal plexus of all the three pathological groups. In NCG/WS, MCs density was not different from HC, while was slightly increased vs. CD (P=0.07), and significantly decreased vs. FD (P< 0.05). The percentage of MCs close to nerves (D< 15 mm) was similarly increased in all three pathological groups *vs.* HC (P< 0.001). Specifically, we identified that in NCG/WS, CD, and FD patients, 60% of the total MCs present in the tissues were localized in the range of 15 mm from the closest nerve fiber.

Moreover, 45% of the total MCs were localized in the range of 5 mm, as opposed to the 20% found in HC. In NCG/WS, MCs infiltration correlated to bloating (P=0.001) and abdominal pain severity (P=0.03), and the per-

centage of MCs in proximity to neurons correlated with the number of GI symptoms (D< 5 mm; P=0.05), bloating and abdominal pain severity (D< 15um; P=0.01). In FD MC density correlated to the number of GI symptoms (P=0.03) and with the presence of pain (P=0.05). In NCG/WS, CD and FD, MCs density and MC-nerve spatial relation did not correlate to bowel habit.

Conclusion: This study provided a morphological basis indicating that submucosal MCs infiltration and MCs-nerve interactions in the upper GI tract of NCG/WS patients contribute to patient reported GI symptoms generation and maintenance, i.e. abdominal pain and bloating severity.
Disclosure: Nothing to disclose

OP346 THE IMPACT OF CLINICAL PRESENTATION OF COELIAC DISEASE ON DIAGNOSTIC DELAYS IN CHILDREN IN CENTRAL EUROPE

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Introduction: Due to a broader use of serological screening tests, more coeliac disease (CD) patients with non-classical presentation have been diagnosed during the past decades. However, limited awareness of the diversity of clinical presentation of CD among health care professionals (HCP) contributes to continued frequently missed diagnoses.

Aims & Methods: The aim of our study was to assess the impact of the clinical presentation on diagnostic delays in children with CD in Central European (CE) region.

Paediatric gastroenterologists (PaedGI) in five CE countries retrospectively submitted anonymised medical records of all their symptomatic patients aged < 19 years with CD diagnosis in 2016. Based on clinical presentation, patients were classified as classical CD (presenting with signs and symptoms of malabsorption), non-classical CD (any other symptoms) and dermatitis herpetiformis Duhring (DHD). Classical CD patients were subdivided into those with and those without diarrhoea, and non-classical CD into those with gastrointestinal and those with non-gastrointestinal symptoms (appetite loss, fatigue, irritability, headache, joint pain, skin rash (not DHD)).

We analysed diagnostic delays in relation to clinical presentation at diagnosis. Diagnostic delays were calculated as the time gap between first CD related symptoms to confirmed CD diagnosis, and subdivided into the duration between first symptoms and first visit to the PaedGI, and from this visit to final diagnosis. Kruskal-Wallis H test with post hoc tests were used for the analysis (IBM SPSS Statistics 22.0 for Windows).

Results: Data from 393 symptomatic children (65% female) from Croatia, Hungary, Germany, Italy and Slovenia were included (Table 1). Median age at diagnosis was 7 years (range 7m-18.5y). Patients with classical CD tended to have a slightly shorter median diagnostic delay (6m) compared to those with non-classical CD (7m) and DHD (8m) (NS). Further analysis showed that the median duration from first symptoms to the first visit to the PaedGI was the same (5m) in children with classical CD (n=264) and non-classical CD (n=122) whereas it tended to be slightly longer (7m) in children with DHD (n=7) (NS). Median duration from the first visit to the PaedGI to the confirmation of CD was found to be significantly longer in non-classical compared to classical presentation (p< 0.05).

Within classical CD group longer diagnostic delay was found in patients without diarrhoea (8m) compared to those with diarrhoea (5m) (NS), which can be attributed to significantly longer duration from symptoms to PaedGI in patients without diarrhoea (6m) compared to those with diarrhoea (4m) (p< 0.05).

In patients with non-classical CD, diagnostic delay with GI symptoms was slightly longer (7m) compared to non-GI symptoms (6m) (NS).

	Classical CD	Non-classical CD	Skin DHD
Number of patients N=393 (%)	264 (67.2%)	122 (31.0%)	7 (1.8%)
Time from first symptom until first visit to PaedGI Median (range)	5m (0-10y)	5m (0-6y)	7m (1m-1.5y)
Time from first visit to PaedGI until diagnosis* Median (range)	1m (0-2.5y)	1m‖ (0-5y)	1m (0-1m)
Time from symptoms to diagnosis (diagnostic delay) Median (range)	6m (0-10y)	7m (0-6y)	8m (1m-1.5y)

*PaedGI - paediatric gastroenterologist; m - month; y - year; DHD - dermatitis herpetiformis Duhring *p<0.05 ‖significance (p<0.05) vs Classical CD*

[Diagnostic delays and clinical presentation of coeliac disease]

Conclusion: Clinical presentation at CD diagnosis has some, although relatively small effect on diagnostic delays. Delays were longer in patients presenting with non-classical symptoms or dermatitis herpetiformis Duhring compared to malabsorption. Lack of awareness about different clinical presentations of CD may contribute to prolonged delays. Further efforts to raise the awareness and knowledge among HCPs appear necessary.
*Study was co-financed by Interreg CE programme (CE 111, Focus IN CD)
Disclosure: Nothing to disclose

OP347 CELIAC FACTS - ONLINE COURSES ON CELIAC DISEASE FOR HEALTH CARE PROFESSIONALS AND PATIENTS AND WEB-APP IMPLEMENTING THE UPDATED DIAGNOSTIC GUIDELINES

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Introduction: Celiac disease (CD) requires a life-long gluten-free diet to treat symptoms and avoid long-term health consequences. A correct and early diagnosis is of utmost importance. However, many health-care professionals (HCPs) have poor knowledge of CD, leading to impaired patient care. Most patients seek more details on CD online with the risk of misinformation. To improve this situation we developed online courses on CD within the „Focus IN CD" project (Interreg Central Europe Projekt CE111).
Aims & Methods: Twelve project partners from Germany, Slovenia, Hungary, Italy & Croatia developed free, autodidactic online-courses with comprehensive, understandable, varied and evidence-based content, tailored to the target group. Project partners and external reviewers revised the drafts before the online implementation. Adult patients, parents of pediatric patients, and HCPs are currently evaluating the courses before and after their use by completing anonymous online questionnaires. A Web based App was planned to provide detailed pathways and explanations for physicians to diagnose CD during childhood and adolescence.
Results: The courses contain written explanations illustrated by graphics, interactive elements, explain movies, self-tests and a dictionary. The HCP's course comprises two units (background & diagnosis, treatment & follow-up), published in parallel to diagnostic guidelines of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) updated in 2019. The patient's course includes four units (background, diagnosis, treatment, living with CD) and explains the medical background in lay terms. Furthermore, the Web-App provides two separate pathways for the generalist (GP/ paediatrician) and the specialist (pediatric gastroenterologist) according to the new ESPGHAN guidelines. Therefore the physician can easily follow the diagnostic flow scheme by choosing the relevant options while getting background information and advice how to proceed

and make the correct diagnosis. The courses and Web-App are accessible via www.celiacfacts.eu (English), www.zoeliakie-verstehen.de (German), www.coeliakia.info (Hungarian), www.poznam-celiakijo.com (Slovenian), www.sveocelijakiji.hr (Croatian) and www.celiachia-info.it (Italian). Preliminary data of the evaluation show a significant knowledge improve and high user satisfaction.
Conclusion: The online courses "Celiac Facts" increase the knowledge of celiac disease among health care practitioners and patients while the Web-App facilitates a correct diagnosis. These innovative tools may improve patient care. More language versions are intended.
Disclosure: The Focus IN CD project was funded by Interreg CENTRAL EUROPE (European Regional Development Fund), project no. CE111

OP348 A DURUM WHEAT VARIETY-BASED PRODUCT IS EFFECTIVE IN REDUCING SYMPTOMS IN PATIENTS WITH NON-CELIAC GLUTEN SENSITIVITY: A DOUBLE-BLIND RANDOMIZED CROSS-OVER TRIAL

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Introduction: Patients with non-celiac gluten sensitivity (NCGS) do not have celiac disease but their symptoms improve after a gluten-free diet. However, to date, it is uncertain if the gluten or other components of the wheat are responsible for these symptoms.
Aims & Methods: The aim of this study was to compare the effects of an organic durum wheat variety and of a standard commercial wheat in patients with known NCGS.
We performed a double-blind randomized cross-over trial of 42 patients (mean age 45 years, 8 men) with NCGS diagnosed according to the Salerno criteria and adherence to GFD for at least 12 weeks from screening. Enrolled subjects were randomly assigned to one the following groups of treatment: A) a 2-week diet with Senatore Cappelli wheat variety pasta; B) a 2-week diet with standard commercial pasta. Then, after a 2-week washout period on gluten-free diet, each patient crossed over to the other treatment group. Symptoms were assessed through a modified version of the Gastrointestinal Symptom Rating Scale (GSRS), tailored on NCGS.
Results: Between April 2018 and July 2018, 42 patients with NCGS were enrolled in the study (70.6% female) 34 patients completed the study. Patients reported lower overall symptoms scores after eating Senatore Cappelli pasta than standard pasta (p=0.03), and also significantly lower scores in several specific gastrointestinal and extra-intestinal symptoms after eating Senatore Cappelli pasta than standard pasta specifically bloating (p=0.04), abdominal distention (p=0.004), eructation (p=0.01), flatus (p=0.02), feeling of incomplete evacuation (p=0.001), dermatitis (p=0.01) and limb numbness (p=0.03).
Conclusion: In our study patients with NCGS experienced lower gastrointestinal and extra-intestinal symptom scores after eating the Senatore Cappelli wheat variety than a standard commercial wheat. Should our preliminary results be confirmed by further studies, new dietary alternatives may be available to patients with NCGS, with consequent health, economic, and social benefits
Disclosure: Nothing to disclose

Video Case Session
10:30-12:00 / F1

OP349 GEL IMMERSION ENDOSCOPY FOR COLONIC DIVERTICULAR BLEEDING

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Introduction: Diverticular bleeding(DB) is most common cause of lower gastrointestinal bleeding. Despite 75% of diverticular bleeding achieve hemostasis naturally, 25% of DB have the stigmata of recent hemorrhage(SRH)

and need treatment such as Endoclips and Endoscopic Band Ligation(EBL). SRH includes active bleeding, non bleeding visible vessels and adherent clots. Compared with left sided DB, right sided DB tends to be massive bleeding.[1)] In Asia, right sided DB is more common than left sided DB.[2)] In massive bleeding cases, it's difficult to identify the SRH due to inappropriate endoscopic view with a large amount of bleeding and clot. Therefore to achieve hemostasis in DB, to get clear endoscopic filed is important. Although water jet endoscopy was one of the good device, active bleeding and flesh clot make water muddy immediately and disturb good visual filed.Gel immersion endoscopy has been reported to achieve hemostasis besides difficult visual filed in gastrointestinal bleeding.[3)]

Aims & Methods: Our aim is to confirm the effectiveness of gel immersion endoscopy for the massive DB case.

Results: The case was 72 year old female who admitted our hospital with massive hemotochezia. CT scan revealed the extravasation at hepatic flexure. Urgent colonoscopy was performed after bowel preparation.Because of massive bleeding and clot, it was difficult to identify SRH. So Gel(OS-1 jelly: Otsuka Pharmaceuticals Factory, Tokushima, Japan) was used to get clear view. We injected the OS-1 gel through the BioShield irrigator(US Endoscopy, Mentor, Ohio).Gel clean the visual filed instead of clot.After Gel injection, bleeding source was seen clearly. Small non bleeding visible vessel was identified. Then marking clip was done. Colonoscopy was re-inserted with Endoscopic Band Ligation(EBL) device.EBL was successfully done and hemostasis was achieved. At the top of EBL lesion, visible vessel was confirmed.

Conclusion: Gel immersion endoscopy was effective technique in massive diverticular bleeding.

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Disclosure: Nothing to disclose

OP350 ENDOSCOPIC RESECTION OF A CHOLEDOCOCELE

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Introduction: Coledococele is a very rare finding in upper GI endoscopy and it is liable to endoscopic resection only in a few times.
Aims & Methods: A 17 years old caucasian man referred to our endoscopic unit for a recent episode of pancreatits. A MRCP showed regular caliber of the common bile duct, with an isolated cystic-like dilatation of its distal part. Our preliminary duodenoscopy and EUS detected a pre-papillary choledococele of 25-30 mm containing 3 biliary stones and ascribable to the biliary dilatation type III, according to the Todani classification.
Results: The choledococele was handled like an ampulloma and removed en-bloc with the hot snare; it was too large to pass through the oesophageal lumen, so we cut it in the stomach and took it out in two parts. At the cut edge the biliary and pancreatic orifice could be clearly seen: we performed both sphinterotomies and decided to proctect the Wirsung orifice against the risk of pancreatitis using a plastic stent. At the end of the procedure, the cut edge was closed by two clips.
Conclusion: The control after 2 months showed the spontaneous expulsion of the pancreatic stent and a regular scar of the papillary area.
Disclosure: Nothing to disclose

OP351 HOW TO MODIFY THE AXIS OF A SEMS PLACED FOR GASTRIC ANTRAL NEOPLASIA: A SIMPLE TRICK

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Introduction: Self-expandable metallic stents (SEMSs) may be used to effectively palliate malignant gastric outlet obstructions (GOOs), but their utility and efficacy in patients with gastric antral neoplasia in not completely clear. One of the reason why gastric SEMS can be inefficacy is possibly due to the impact of the proximal end of the stent to the great curvature of the gastric body.
Aims & Methods: .The aim of our treatment was the modification of the proximal part of the SEMS, to restore the normal anatomy of the stomach. Three patients unfit for surgery underwent SEMS placement for gastric antral neoplasia (two F of 25 and 56 years old and one M 57 years old). In the first patients a SEMS 22 x 90 mm was placed, in the second a 22 x 60 mm and in the third patient a 22 x 90 mm was placed inside a previous 22 x 60 mm
Results: Because of the normal anatomy of the stomach, after placing a SEMS for gastric antral neoplasia, the proximal end of the stent can bit on the great curvature of the gastric body. This can results in a GOO due to the impact of the stent. With a standard clip we catch the upper part of the proximal end of the stent, closing the clip inside the mesh of the body of the SEMS. This trick allow to the upper part of the stent the completely modification of the axis, restoring the normal anatomy of the stomach. All of the patients restart oral intake the day after without any complication or vomiting.
Conclusion: In presence of gastric antral neoplasia causing GOO undergone SEMS placement, the modification of the axis of the stent with a standard clip is a simple trick to restore the normal anatomy, allowing to the patients a correct oral intake.
Disclosure: Nothing to disclose

OP352 ACETIC ACID IN COMBINATION WITH BLUE LIGHT IMAGING: A NEW METHOD TO IMPROVE THE DETECTION OF RECURRING SESSILE SERRATED LESIONS IN THE COLON

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Introduction: Sessile serrated lesions (SSLs) have a high risk of incomplete endoscopic resection, and any recurrent lesion at the site of resection is often difficult to delineate due to the development of mucosal scars in the area.[1] Our previous experience have demonstrated that acetic acid (AA) spray along with indigocarmine is of substantial benefit for the delineation of SSLs.[2] Recently, a new image enhanced endoscopy technique, blue light imaging (BLI), has been developed and the benefits in assessing colonic polyps has been reported.[3] Nevertheless, the combined use of AA and BLI has not yet been presented.
Aims & Methods: The aim is to describe the first experience of AA and BLI in two recurrent SSLs.
Colonoscopy with a magnifying function and BLI (EC-760ZP-VM, Fujifilm Co., Tokyo, Japan) was used. The acetic acid (5%) was diluted in lukewarm water to derive a solution with a concentration of 1.7%. The solution was sprayed directly through the working channel of the endoscope on to the suspicious lesions. Thereafter the polyps were assessed and characterized prior to endoscopic removal.
Results: Acetic acid improved the visibility of the recurrent SSLs in both cases. In combination with BLI, the delineation of the lesion was more easily performed, and thus facilitated precise and radical resection, which was achieved in both cases. The use of acetic acid in a concentration of less than 2% was safe and no adverse events were recorded.
Conclusion: The combination of acetic acid and BLI could be an excellent method to improve the visualization of recurrent SSLs and thereby increasing the possibility to perform complete endoscopic resections. The acetic acid spray was both easy to prepare and use.

References: 1 Pohl H, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology. 2013;144:74-80. 2 Yamamoto S, et al. Acetic acid-indigocarmine mixture for evaluating the margins of sessile serrated adenomas/polyps. Dig Endosc. 2017;29:817-8. 3 Bisschops R, et al. BASIC (BLI Adenoma Serrated International Classification) classification for colorectal polyp characterization with blue light imaging. Endoscopy. 2018;50:211-20.
Disclosure: Nothing to disclose

OP353 SALINE-IMMERSION THERAPEUTIC ENDOSCOPY (SITE) FACILITATED UNROOFING OF A LARGE, SYMPTOMATIC ILEAL LIPOMA AT DOUBLE-BALLOON ENTEROSCOPY (DBE)

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Introduction: Lipomas of the gastrointestinal (GI) tract are common, benign and usually present as innocuous findings. Larger ones (>2cm in diameter), particularly those involving the ileum, may present with clinical symptoms such as abdominal pain (caused by intussusception) and iron deficiency anaemia (IDA) or obscure GI bleeding (OGIB) (caused by overlying mucosal ulceration); these cases warrant intervention and often end up being referred for surgery. We describe a minimally invasive endoscopic alternative to surgical resection for the management of these lesions.
Aims & Methods: A 60-year-old man presented with recurrent, cramping abdominal pain and OGIB. A magnetic resonance enterography (MRE) revealed a 2.5 cm submucosal lesion in the distal ileum, in keeping with a large lipoma. In light of these findings and the clinical presentation, we perform a saline-immersion retrograde DBE under conscious sedation, for further evaluation and minimally invasive, definitive endotherapy.
At DBE the lesion was identified at around 40cm proximal to the ileocaecal valve. The endoscopic appearances revealed a 2.5 cm sessile submucosal, lumen-filling lesion with a positive 'pillow sign'. Although the overlying mucosa appeared mostly unremarkable, a small, healed ulcer (which would account for the patient's IDA and OGIB) was identified on the medial surface of the lesion.
Endotherapy was deemed feasible and this was facilitated by the buoyancy properties provided by SITE. In order to reduce the risk of perforation and bleeding, an endoscopic loop ligating device was first deployed tightly at the base of the lesion. A ball-tip, needle-type endoscopic submucosal dissection (ESD) knife was then used to incise and unroof the lesion. This allowed for exposure and spontaneous extrusion of the lipomatous tissue (already under pressure from the loop-lighting device). Saline-immersion allowed for maintenance of a clear visual field, through avoidance of clouding of the endoscopic lens and flotation of extruded micelles of fatty tissue. A submucosal tattoo and a clip were placed as endoscopic and radiological markers, respectively. The procedure was performed under antibiotic cover. No significant immediate, early or late adverse events were encountered.
Results: Histopathological examination of retrieved tissue showed mature adipocytes with fibrofatty submucosal changes, in keeping with a submucosal lipoma. No dysplasia or sarcomatous transformation was identified. The patient's symptoms have resolved completely post-endotherapy.
Conclusion: Our case demonstrates the safety and usefulness of minimally invasive endotherapy of symptomatic large ileal lipomas. The combination of DBE with SITE-facilitated unroofing, after securing the lipoma's base with a loop-ligation device, allows for safe, spontaneous extrusion of the benign lipomatous tissue and avoids the need for operative surgery in symptomatic patients.
Disclosure: Dr Despott and Dr Murino receive research/ education support from Aquilant Medical, Fujifilm, Olympus, Pentax Medical, Boston scientific and GI supply. All others authors have no conflicts of interest to disclosure.

OP354 MUCOSAL ENTRY DEHISCENCE AND ESOPHAGEAL LEAK AFTER POEM

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Introduction: Per-oral endoscopic myotomy (POEM) has been a minimally invasive technique for the treatment of achalasia. While most of the cases in the Northern are performed for idiopathic achalasia, in our country the majority of the patients treated with POEM are Chagasic patients. Many of them have per-oral endoscopic myotomy after recrudescence of dysphagia many years after surgical esophagogastric myotomy with partial fundoplication.
Aims & Methods: To present the case and the treatment of mucosal entry dehiscence and esophageal leak after a per-oral endoscopic myotomy.
Results: A 49 years old female with advanced Chagas achalasia presenting recurrence of dysphagia (Eckardt 6) 15 years after a cardiomyotomy and partial fundoplication was submitted to POEM. Control esophagogram the next day showed no leak. However, she presented a severe vomiting episode. Liquids were introduced the following day, and the patient discharged asymptomatic on the postoperative day 3. After 48 hours, she returned complaining about chest pain and vomiting. Physical examination and leukogram were normal. Computed tomography (CT) with oral contrast showed dehiscence of the mucosal entry (mucosotomy) in the esophagus and esophageal blocked leakage to the posterior mediastinum. Broad-spectrum antibiotics, proton-pump inhibitor (PPI) and placement of nasoenteric feeding tube were adopted. Follow-up CT after 10 days showed the persistence of the esophageal leakage. Upper gastrointestinal endoscopy (UGE) showed a proximal mucosotomy on the mucosal entry topography with fibrin clots and an hemoclip inside it. The hemoclip was pulled-out and then the endoscope advanced inside the tunnel. A distal orifice communicating the submucosal tunnel to the esophageal lumen was identified 3 centimeters forward, guiding the drainage of the esophageal leakage and preventing the formation of fluid collection. Section of the mucosal flap over the submucosal tunnel was the therapeutic choice as previous surgery fibrosis and inflammatory tissue around blocked the leakage and contained the infection. PPI and sucralfate were prescribed. Liquid diet was introduced 2 days after and the patient discharged with semi-liquid diet 4 days after. The patient was asymptomatic 30 days after the new procedure, and UGE revealed a small amount of fibrin over the blocked wall. PPI was maintained and pasty diet introduced. UGE after 90 days showed the blocked wall almost wholly re-epithelialized and Los Angeles B esophagitis. Due to improving but still present reflux the patient is still on PPI and will have a 6-months UGE control.
Conclusion: Mucosal flap section could be safely performed as the leakage was blocked. Avoiding severe vomiting after POEM is an important step to prevent mucosal entry dehiscence. Previous surgery for achalasia may be a factor that helps block esophageal leakage in case of mucosotomy.
Disclosure: Nothing to disclose

OP355 MULTIPLE BULBAR NEUROENDOCRINE TUMORS RESECTED BY PRE-PYLORIC TUNNELING ESD

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Introduction: A 61 years-old patient underwent an esophagogastroduodenoscopy (EGD)for epigastric pain. It revealed multiples sub-mucosal lesions of the duodenal bulb, between 5 and 16 mm, the two largest being juxta-pyloric. Biopsies revealed grade I neuroendocrine tumors (Rindi I, Ki67< 2%). Work-up included an endoscopic ultrasound that showed a T1 tumor with no regional lymphadenopathies and a positron emission tomography-computed tomography (PET/CT) scan using ^{68}Ga-DOTA-TATE (somatostatin [SST]-analog)that came back negative.

Aims & Methods: After discussion in the multidisciplinary oncological board, a decision was made to perform an endoscopic submucosal dissection (ESD) of the largest tumors, followed by an endoscopic mucosal resection (EMR) for the remaining small lesion.

Results: Knowing the close contact between the two largest bulbar NETs and the pylorus, the procedure was started with gastric submucosal tunneling 2 cm proximal from the pylorus according to the pocket-ESD method, to be able to reach the deep submucosa of the juxta-pyloric bulb in a tangential axis with the ESD knife. The dissection was conducted alongside the pylorus sphincter before digging under the Brunner glands under the NET lesions. A clip and thread traction system was set up on the flap after lateral opening, followed by distal incision. En-bloc, complete endoscopic resection was achieved with a tiny bulbar muscular tear easily closed by clips.

The patient had no symptoms after the resection. Histopathological examination of the specimen showed 3 grade I neuroendocrine tumors. Lateral margins were free from malignancy, while one of the vertical margins was in contact with the tumor cells. There was no lymphovascular invasion and the lesion was classified pT2mNx. Given the well differentiation of the tumor, endoscopic follow-up was proposed. The patient underwent control EGD at three months and resection of the small remaining lesion by cap-band-assisted EMR. At that time no recurrence was discovered.

Conclusion: Pre-pyloric tunneling ESD is feasible and safe for bulbar submucosal lesions.

Disclosure: Nothing to disclose

OP356 ENDOSCOPIC SUTURING TO REDUCE THE RISK OF COMPLICATIONS AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION OF A RECURRENT RECTAL POLYP

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Introduction: Recurrent colorectal polyps present a challenge for the endoscopist due to the presence of submucosal fibrosis. In these cases, endoscopic mucosal resection (EMR) is often unsuccessful thus submucosal dissection (ESD) is the preferred technique. The risk of muscle layer damage and subsequent perforation is increased in performing ESD for recurrent colorectal polyps. As such, wound closure after resection may reduce the risk of complications.

Aims & Methods: This video demonstrates closure of a rectal ESD defect using an overstitch device designed for use with a flexible endoscope. A 74 year-old man presented with a recurrent laterally-spreading tumor (LST) in the mid-rectum (initial size 65mm with pathology showing focal high-grade dysplasia). Previous piecemeal EMR had been performed but at follow-up endoscopy 6 months later a large recurrent adenoma was identified. We anticipated significant submucosal fibrosis particularly in the scarred center of the lesion.

Furthermore, the previous histology and location of the lesion predicted an increased risk for covert submucosal invasion thus ESD would likely be the best option for a complete en bloc resection. If indeed the center of the lesion was tethered to the muscle layer, we further anticipated some degree of muscle injury during ESD so we were prepared to close the defect via endoscopic suturing.

Results: A detailed examination of the lesion under high-definition white-light, linked-color imaging and blue-light imaging in addition to optical zoom + under water magnification revealed a mid-rectal 40x30mm granular-type LST with Paris type IIa+IIc morphology and Kudo IIIL/IV pit pattern. Standard ESD was then performed using a HybridKnife (ERBE Elektromedezin, GE) by incising the mucosa around the lesion followed by stepwise ESD. As anticipated, the center of the lesion was adherent to the muscularis propria thus very careful dissection was required with cutting of some superficial muscle fibres in this area to preserve an en bloc resection. No major bleeding or intra-procedural perforation occurred.

After ESD was completed, further examination of the resection bed revealed no definite signs of deep muscle injury or perforation. However, given there was intentional incision of the muscle layer in the center of the lesion, wound closure was optimal. The resected area was too large to attempt clip closure therefore we elected to perform endoscopic suturing using an overstitch device (Apollo Endosurgery Inc., USA). Two running sutures were completed to tightly appose the edges of the resection

bed and completely seal the mucosal defect. Total procedure time was 165 minutes. No delayed complications occurred. Final pathology revealed low-grade dysplasia only.

Conclusion: Endoscopic suturing is a viable option when full closure of a mucosal defect is desired.

Disclosure: Nothing to disclose

OP357 ENDOSCOPIC MECHANICAL LITHOTRIPSY FOR SIGMOID GALLSTONE ILEUS

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Introduction: Gallstone ileus is an uncommon condition accounting for 1-4% of all causes of mechanical intestinal obstruction. The usual site for stone impaction is the terminal ileum or ileo-caecal valve. Intestinal obstruction caused by gallstone impaction in the large bowel is a very rare entity. We present a case of colonic gallstone ileus, at the level of sigmoid colon, which was successfully treated with endoscopic mechanical lithotripsy.

Aims & Methods: A 60 year old man was admitted with a 5 day history of upper colicky abdominal pain, high grade fever and darkening of urine. Initial blood tests showed, WBC 9.8 x10^9/L, CRP 270 mg/L, Bilirubin 44mmol/L, ALT 48 iu/L, and Alkaline phosphatase 170 iu/L (NR< 130). An ultrasound scan of abdomen and MRCP showed multiple stones in the gallbladder and in the common bile duct. Hence, an ERCP was performed 2 days later and strangely, 4 litres of fluid was seen in the stomach despite a prior overnight fast. After aspirating the fluid, the pylorus was found to be widely patent and two small ulcers were noted in the duodenum just proximal to the normal looking ampulla. After a wire guided biliary cannulation, the cholangiogram confirmed common bile duct stones. A sphincterotomy was performed and the bile duct stones were extracted with a balloon catheter. However, the final occlusion cholangiogram showed a possible cholecysto-duodenal fistula. Despite a successful ERCP, the patient failed to show clinical improvement and developed vomiting and abdominal distension with a rise in the WBC to 28x10^9/L. A CT scan 2 days after the ERCP confirmed a cholecysto-duodenal fistula together with dilated small bowel loops and a large gallstone impacted in the sigmoid colon. Hence, a flexible sigmoidoscopy was performed confirming the presence of a 3cm gallstone obstructing the narrow sigmoid colon. Initially, a large polypectomy snare was used to grasp the stone but it was not possible to extract the stone through the narrow sigmoid colon. Therefore, a 3cm diameter Olympus Lithocrush Basket was used to crush the gallstone into smaller pieces, which then passed spontaneously.

Results: The patient recovered and went home two days later.

Conclusion: Gallstone ileus involving the large bowel is an uncommon condition. The stone usually fistulates from the gallbladder directly to the colon rather than to the duodenum as in this case. Colonic gallstone ileus is usually seen in old age and in patients with multiple co-morbidities where surgical intervention is associated with an increased risk of morbidity and mortality. Hence, less invasive techniques such as colonoscopy with mechanical lithotripsy of the impacted gallstone should be tried prior to considering surgical intervention.

Disclosure: Nothing to disclose

Oncology: Basic mechanisms

10:30-12:00 / Barcelona

OP358 THE CHICK EMBRYO CHORIOALLANTOIC MEMBRANE ASSAY: *IN OVO* MODEL FOR PERSONALIZED ASSESSMENT AND EVALUATION OF THE MOST EFFECTIVE THERAPEUTIC APPROACH IN CANCER THERAPY

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Introduction: "Personalized medicine," is tailoring and maximize medical treatment to a single person.
Aims & Methods: To generate a personalized, quick and reliable screening system for effective evaluation of different therapeutic options using 3D tumors in a „humanized egg".
At day 3, 2ml of albumin was pulled out from fertilized eggs to separate the CAM from the eggshell and a small window in the eggshell has been made. On day 6-7, single cells suspension or tissues, derived from cancer patients, were transplanted onto the CAM and visible tumors were developed („CAM-PDX"). Human immune cells were inoculated on day 9-10 and then drugs, mAbs and Immuno/chemo-therapy, were applied via the yolk sac. Tumor growth was measured, weighted, stained and monitored by caliper and IVIS imaging platform.
Results: Histology and IHC analysis confirmed that the established tumors retained their characteristics. Positive Ki-67 staining confirmed that cancer cells proliferate while the treated tumors showed reduced staining. Anti-CD24 mAb, FOLFOX and cetuximab, given as single agent or combinations, successfully inhibited CRC cells growth (by 70-75%). Detection of active caspase-3 confirmed these results. Biopsies from human specimens, were successfully established and expanded by serial passages allows generation of bio-bank. The stimulated human PBMCs demonstrated enhanced proliferation *in vitro* and *in ovo*, even after 5 days in the egg.
Conclusion: The CAM is an ideal, effective, economical and powerful avatar-based precision medicine approach to predict the best protocol for cancer therapy.
Disclosure: Nothing to disclose

OP359 METHYLATION ANALYSIS OF NON-AMPULLARY DUODENAL PRECANCEROUS LESIONS

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Introduction: Because duodenal epithelial tumors are rare, their biological and clinical characteristics are not yet fully understood.
Aims & Methods: To clarify the molecular and clinicopathological characteristics of non-ampullary duodenal lesions, we assessed DNA methylation of cancer-associated genes in a cohort of non-ampullary duodenal

precancerous lesions. One-hundred and two non-ampullary duodenal premalignant lesions including 95 intestinal-type tumors (90 intestinal-type adenomas and 5 intestinal-type non-invasive carcinomas) and 7 gastric-type tumors (2 pyloric gland adenomas and 5 non-invasive carcinomas) as well as adjacent normal tissues (n = 15) from 102 individuals were investigated. According to the revised Vienna classification, intestinal-type tumors were classified as 32 Category 3 tumors (low grade adenomas) and 63 Category 4 tumors (high grade adenomas and non-invasive carcinomas).
Also, gastric-type tumors were classified as 2 Category 3 tumors (pyloric gland adenomas) and 5 Category 4 tumors (non-invasive carcinomas). After extracting DNA from formalin-fixed paraffin embedded (FFPE) sections, we assessed the methylation status of CpG island methylator phenotype (CIMP) markers including *CACNA1G*, *IGF2*, *NEUROG1*, *RUNX3*, and *SOCS1* as well as *MLH1* using bisulfite pyrosequencing. A cutoff value of 15% was used to define genes as methylation-positive. Tumors were defined as CIMP-positive when methylation was detected in two or more out of five methylation markers.
Results: Tumors with CIMP were seen in 20 intestinal-type tumors (21.1%) and 3 gastric-type tumors (42.9%), respectively. In intestinal-type tumors, prevalence of CIMP-positive lesions was higher in non-invasive carcinomas (40%) than in adenoma (20.2%) or normal mucosa (0%, P < 0.01). In gastric-type tumors, CIMP was detected more frequently in non-invasive carcinomas (60%) than in normal mucosa (0%, P < 0.01). As for intestinal-type tumors, prevalence of CIMP-positive lesions was significantly higher in Category 4 tumor than in normal mucosa (25.8% vs. 0%, P = 0.03). As for methylation levels of each cancer-associated gene, we found that the methylation levels of *CACNA1G*, *NEUROG1*, *RUNX3*, and *SOCS1* were significantly higher in intestinal-type non-invasive carcinomas than in intestinal-type adenomas or normal mucosa. However, there were no significant differences when intestinal-type tumors were classified according to the revised Vienna classification.
Conclusion: Genome-wide hypermethylation of cancer-associated genes estimated by CIMP were associated with development of non-invasive carcinomas other than adenoma formation during carcinogenesis of non-ampullary duodenal precancerous lesions. Especially for intestinal-type tumors, epigenetic silencing of *CACNA1G*, *NEUROG1*, *RUNX3*, and *SOCS1* was significantly associated with development of non-invasive carcinomas from adenomas.
Disclosure: Nothing to disclose

OP360 TLR4-DRIVEN SPONTANEOUS TUMORIGENESIS IS MEDIATED BY MICROBIAL-INDUCED EPITHELIAL PRODUCTION OF REACTIVE OXYGEN SPECIES

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Introduction: Duodenal adenocarcinoma (DA) is a rare malignancy with a poorly defined pathogenesis. Previous studies have identified histopathological similarities between DA and colorectal cancer (CRC) as well as an increased risk in CRC patients to develop DA. We have shown that toll-like receptor 4 (TLR4), a receptor for Gram negative bacteria, is overexpressed in intestinal epithelial cells (IECs) of CRC patient adenomas. To mimic over-activation of epithelial TLR4 in an animal model, we developed the villin-TLR4 mice, which express a constitutively active form of TLR4 under the promoter of villin.
In this model, we have demonstrated that epithelial TLR4 signaling induces gut dysbiosis, production of reactive oxygen species (ROS), and increased susceptibility to colitis-associated cancer. Furthermore, we have also reported that these mice develop spontaneous duodenal adenomas before 12 weeks of age.
Aims & Methods: Here, we took advantage of this spontaneous model of DA to test the hypothesis that epithelial TLR4 activation promotes tumor initiation by shaping the microbiome and inducing reactive oxygen species (ROS). Villin-TLR4 mice and their wild-type (WT) littermates were either rederived into germ-free conditions or treated with the ROS scavenger apocynin from birth. At 12 weeks, mice were euthanized and tumor area in vilin-TLR4 mice was measured. IECs from non-involved areas were iso-

lated by EDTA chelation and analyzed for H_2O_2 production by means of Amplex Red and expression of NADPH oxidase 1 (Nox1) and dual oxidase 2 (Duox2) transcripts by means of qPCR.

Results: Constitutive activation of epithelial TLR4 significantly increased the expression of Nox1, p22 phox, Duox2, and DuoxA2 transcripts in villin-TLR4 IECs when compared to those of WT littermates. Rederivation of villin-TLR4 into germ-free conditions significantly reduced the epithelial expression of DuoxA2, which was accompanied by a significant reduction in the production of H_2O_2. In the absence of a microbiota, duodenal tumor initiation was abrogated in 5 out of the 6 mice and the tumor area was dramatically reduced in the only mouse that developed DA. Chronic administration of apocynin did not inhibit epithelial NADPH oxidase activity or expression, but significantly reduced the tumor area in 5 out of the 8 mice and prevented tumor formation in 3 out of the 8 mice, demonstrating that ROS play an important role in this model of tumorigenesis.

Conclusion: Our findings demonstrate that TLR4-driven spontaneous tumorigenesis is dependent on the presence of a microbiota that induces DuoxA2 upregulation and the release of ROS. In addition, our observations suggest that similar to CRC, DA is also dependent on the microbiota. We speculate that TLR4 activation induces dysbiosis, which in turn feeds forward ROS production by IECs, leading to tumor initiation.

Disclosure: Nothing to disclose

OP361 YAP/TAZ PLAYS A POTENTIAL ROLE IN TUMOR INITIATION IN THE INTESTINE AND CAN BE REGULATED BY THE MICROENVIRONMENT

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Introduction: The stromal microenvironment plays a key role in regulating adult stem cell niches and can play a dual role in tumor development. Depending on the tissue context, stromal cells may either promote or inhibit tumor growth, however the precise cellular and molecular mechanism remain largely unknown.

Aims & Methods: We aimed to identify tumor initiation signaling pathway(s) that is regulated by the stromal microenvironment. To study this, we employed wild type and mutated (Apc+/1638N) murine intestinal organoid cultures and crypt-myofibroblast co-cultures, microarray analysis, real-time PCR and immunohistochemistry staining of human colorectal cancer samples.

Results: Microarray analysis revealed that genes associated with YAP signaling are upregulated in both mutated intestinal organoids and wild type organoids from an indirect crypt-myofibroblast co-cultures, that was confirmed with real-time PCR. Inhibition of YAP signaling with cytochalasin D resulted in reduced number and decreased diameter of tumor-like crypts (spheroids). Immunohistochemistry staining of human colorectal cancer samples showed that strong activation YAP/TAZ in dysplastic epithelium correlated with strong infiltration of aSMA+ stromal cells.

Conclusion: We discovered that YAP/TAZ signaling in the intestinal epithelium can be regulated either intrinsically by an oncogenic mutation or extrinsically by secreted factors from the stromal microenvironment. This study highlights the important role of the microenvironment in regulating epithelial cell plasticity and suggests that aSMA+ stromal cells can contribute to tumor initiation. Therefore, aSMA+ stromal cells should be considered in the future as cellular targets for anti-cancer therapies.

Disclosure: Nothing to disclose

OP362 COMPREHENSIVE MOLECULAR ANALYSIS IDENTIFIES DRIVER MUTATIONS IN METASTASES OF SPORADIC WELL-DIFFERENTIATED NEUROENDOCRINE TUMOURS OF THE SMALL INTESTINE

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Introduction: Small intestinal neuroendocrine tumours (SI-NETs) represent a heterogeneous group of rare tumours. At present, the genetic make-up of SI-NETs is poorly elucidated. In contrast to adenocarcinomas and neuroendocrine carcinomas (NECs), well differentiated SI-NETs are relatively indolent tumours. NECs share oncogenic pathways with adenocarcinomas whilst SI-NETs are mutationally quiet. The prognosis and treatment of SI-NETs is currently based on traditional criteria, which do not predict clinical outcomes for individual patients nor provide a rationale for targeted therapy.

Aims & Methods: The aim is to perform a comprehensive genetic characterization of metastatic SI-NETs. This study, which is largely based on genomic tumour data collected as part of the Center of Personalised Cancer Treatment (CPCT) study from patients of the Netherlands Cancer Institute, entails whole genome sequencing (WGS) of 29 metastasized SI-NETs (group 1) and next generation panel sequencing (NGS) of 7 SI-NET liver metastases (group 2). Diagnosis was confirmed by histopathological examination according to the WHO classification of neuroendocrine tumours (NETs) 2018. For group 1, WGS included assessment of somatic mutations in all cancer related driver genes (>500), somatic copy number variations, gene disruptions (including gene fusions), tumour mutational burden (TMB) and microsatellite status. In group 2, NGS was performed in a diagnostic setting with a cancer hotspot mutation panel of 58 genes. Our cohort consisted of metastatic well-differentiated SI-NETs of which 19% (7/36) were grade 1, 69% (25/36) grade 2 and 11% (4/36) grade 3. Association between tumour grade and genetic features was assessed using the Man-Whitney U test.

Results: Somatic mutations were identified in 66% of SI-NETs by WGS (n=29) and 43% by NGS (n=7). Of SI-NET metastases (n=36), 36% showed driver mutations in tumour suppressor genes (e.g. TP53, RB1, ATM, CDKN1B, CTNNB1, SMAD2) and 8% of metastases showed mutations in proto-oncogenes (KRAS, NRAS, MET). In group 1 (N=29), allelic loss of chromosome 18 was present in 63%. Other recurrent events were complete loss of CDKN2A and CDKN1B (both 7%). All tumours in group 1 were microsatellite stable (median 0.029, IQR 0.022-0.046) and showed low TMB (median 1.10, IQR 0.86-1.33). Solely 13% of all driver mutations unveiled by WGS would have been detected using panel NGS. No association between tumour grade and genetic characteristics was found.

Conclusion: Metastasized SI-NETs are mutationally quiet tumours and allelic loss of chromosome 18 is common, which is in accordance with earlier studies on primary SI-NETs. Surprisingly, 44% of metastasized well differentiated SI-NETs harbour driver mutations in proto-oncogenes and tumour suppressor genes. Thus, the presence of driver mutations is not exclusive to neuroendocrine carcinomas or adenocarcinomas and does not contribute to the distinction between well differentiated NETs and poorly differentiated NECs during pathological assessment. Targetable genetic alterations were detected in 19% of patients, including the BRCAness, the cyclin D/cyclin-dependent kinases 4 and 6 -retinoblastoma protein and the HGF/MET pathway, rendering these patients eligible for targeted therapy which provides them with new treatment options. These mutations may be missed in the routine clinical setting when hot-spot NGS panels are used. In the immediate future, we will continue to assess the additional value of WGS in SI-NETs in terms of biomarker identification, additional standard treatment options and eligibility for trial inclusion.

Disclosure: Nothing to disclose

OP363 REGULATION OF LYMPHANGIOGENESIS BY PANETH CELLS IN NORMAL PHYSIOLOGY AND EXPERIMENTAL PORTAL HYPERTENSION

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Introduction: The mesenteric lymphatic network contributes to the transport of fluid and intestinal mucosal associated immune cells along the gut-liver axis. We have previously reported a decrease in intestinal vascularization and number of Paneth cells along with diminished lymphangiogenesis in absence of intestinal microflora [1]. However, the association of Paneth cells with the regulation of lymphatic vascular development is unknown.
Aims & Methods: We hypothesized that Paneth cells, as part of the innate intestinal immune system, regulate the development of lymphatic vessels and affect portal pressure under the control of intestinal bacteria.
We induced Paneth cell depletion in Math-1 Lox/LoxVillcre^{ERT2} mice by injecting three consecutive doses of tamoxifen and performed partial portal vein ligation (PPVL) to induce portal hypertension. After 14 days, intestinal and mesenteric lymphatic vessels were assessed by immunohistochemistry (IHC) using lymphatic vessel endothelial hyaluronic acid receptor 1(Lyve-1) antibody. The lymphatic vessels were quantified using Metamorph to calculate pixel ratio. Expression of genes involved in the regulation of lymphatic vessels was evaluated by RT^2 profiler PCR array in intestinal tissue. Additionally, the expression of specific genes involved in lymphangiogensis was evaluated separately by quantitative PCR. Intestinal organoids from control and Paneth cell depleted mice were exposed to different bacterial derived products. Proteomic analysis of conditioned media was performed using MaxQuant to analyse differentially regulated proteins in lymphangiogenesis in the absence of Paneth cells and/or in portal hypertension.
Results: Portal pressure was significantly attenuated in Paneth cell depleted mice compared to control mice after PPVL (n=11/group, 9.78±1.23 cmH$_2$O vs 11.45±1.41 cmH$_2$O, respectively, p<0.002). Depletion of Paneth cells resulted in a significantly decreased density of lymphatic vessels compared to control as assessed by IHC (n=5, pixel ratio), in the intestine (0.176% ±0.12 vs 0.367%±0.15, p=0.01) and in the mesentery (0.160%±0.06 vs 0.404%±0.20 p=0.001). Quantitative PCR showed a decreased expression of genes involved in the regulation of lymphangiogenesis, including VEGF-C, VEGF-D, VEGF-A, Nrp2, Angpt-2, Tie-1, Tie-2, TGF-α, HGF and CXCL-1 in Paneth cell depleted mice. Moreover, the expression of specific markers of lymphangiogenesis such as transcription factor Prox-1 or growth factor VEGFR3 and protein FOX-C2 were significantly decreased in Paneth cell depleted mice after PPVL. In the absence of Paneth cells, proteomic analyses showed a significant downregulation of several proteins involved in lymphatic vessel development and morphogenesis, as well as in processes of lipid metabolism and transport.
Conclusion: In the absence of Paneth cells, the intestinal and mesenteric lymphatic vessel networks were significantly underdeveloped. This was associated with an attenuated portal hypertension. These findings suggest that Paneth cells not only play an antimicrobial role in the intestine, but also contribute to the regulation of lymphatic vessels and portal pressure.
References: 1. Moghadamrad S, McCoy KD, Geuking MB, et al. Attenuated portal hypertension in germ-free mice: Function of bacterial flora on the development of mesenteric lymphatic and blood vessels. Hepatology 2015;61:1685-95.
Disclosure: The authors declare no conflict of interest. These data has been presented as an e-poster in ILC-2019 in Vienna.

Hot topics in gastric cancer
10:30-12:00 / Hotspot

OP365 EVALUATING THE ACCURACY OF DISCHARGING PATIENTS FROM SURVEILLANCE FOR GASTRIC PREMALIGNANT LESIONS ACCORDING TO THE MAPS GUIDELINE IN A LOW RISK POPULATION: A PROSPECTIVE COHORT STUDY

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Introduction: Intestinal type gastric cancer follows a cascade of premalignant lesions which makes gastric cancer suitable for screening and surveillance. The Management of epithelial precancerous conditions and lesions in the stomach (MAPS) guideline (first published in 2012 and revised in 2019) advises an histological-led diagnosis by performing random biopsies, in order to stage the extent and severity of premalignant gastric lesions, and determine if surveillance is recommended. No surveillance is deemed necessary for atrophic gastritis (AG) or intestinal metaplasia (IM) limited to either antrum or corpus. However, random biopsies may not properly reflect the extent of the lesions. The aim of this study was to assess the appropriateness of discharging patients from further surveillance according to the guideline in daily practice.
Aims & Methods: Patients were included from the multicenter, prospectively followed PROREGAL cohort initiated in 2009 in which patients were identified with AG, IM and/or dysplasia of the gastric mucosa at index endoscopy (t0). In the PROREGAL protocol each patient underwent a first surveillance endoscopy with random biopsies one year after the index endoscopy (t1), and in case no high or low grade dysplasia was present, a second surveillance endoscopy was performed three years after the index endoscopy (t2). Further surveillance interval was in accordance with the MAPS guideline. For the current study, patients excluded from further surveillance according to MAPS-2012 were re-invited to undergo a follow-up endoscopy after three years (t3). Patients were included in the current study 1) if they met the MAPS-2012 or MAPS-2019 guideline recommendations to stop surveillance based on the outcome of the latest endoscopy (t1 or t2), and 2) underwent a subsequent follow-up endoscopy (t2 or t3) not included in the guideline recommendations. An inappropriate discharge from follow-up was defined if premalignant gastric lesions were present at t2 or t3 that gave reason to resume surveillance.
Results: The PROREGAL cohort comprises 334 patients. Between 2009 and 2019,113 patients were supposed to be discharged according to MAPS-2012 but underwent follow up endoscopy according to the PROREGAL protocol. In 38/113 (33.6%; 95%CI 25.2-43.2) patients (progressions of) gastric lesions for which surveillance is recommended were found at t2 or t3. If MAPS-2019 was followed, inclusion increased to 173 patients who were supposed to be discharged from surveillance. In 62/173(35.8%; 95%CI 28.8-43.5) of these patients, gastric lesions for which surveillance is recommended were present at t2 or t3. In two cases high grade dysplasia (both corpus) and in one case gastric adenocarcinoma of the angulus was diagnosed.
Conclusion: 1/3rd of patients who are discharged from gastric cancer surveillance according to MAPS recommendations appeared to be misclassified as low risk according to results found at follow-up endoscopy. Three of them had developed high grade dysplasia or gastric cancer. Therefore improvement of endoscopic and histological staging of premalignant gastric lesions is warranted.
Disclosure: Nothing to disclose

OP366 DIFFERENTIAL EXPRESSION OF LONG NON-CODING RNA HOTAIR IN GASTRIC CANCER AND PRENEOPLASTIC CONDITIONS

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Introduction: HOTAIR is long non-coding RNAs that plays an important role in gene regulation and has been shown to be upregulated in various tumors, including gastric cancer (GC). Recent studies reported that high expression of HOTAIR can promote tumor growth in vitro influencing patient prognosis including worse survival.

Aims & Methods: The aim of this study was to evaluate HOTAIR expression in preneoplastic gastric conditions and GC as well as to assess the clinicopathological and prognostic value of HOTAIR in GC patients. HOTAIR expression was analyzed in tissue samples of 81 GC patient (paired samples from tumor and corresponding adjacent gastric mucosa), 50 atrophic gastritis (AG) patients, 22 chronic gastritis (NACG) patients, and 16 controls. In addition, HOTAIR expression was evaluated in serum of 23 GC patients. Samples were obtained from 2 University hospitals in Lithuania and Germany. Total RNA was extracted using RNeasy Plus Universal Mini Kit. Quantitative HOTAIR expression analysis was performed using SYBR Green assay. HOTAIR expression was further correlated with genome-wide methylation using surrogate LINE-1 methylation by bisulfite pyrosequencing. GC patient's survival was evaluated using Kaplan-Meier analyses.

Results: HOTAIR was undetectable in histologically confirmed normal gastric mucosa samples from control group and NACG. HOTAIR expression was found in 24% of patients with AG. The HOTAIR positivity was strongly related to intestinal metaplasia (64.7%) and expression was positively associated with the grade of intestinal metaplasia (p< 0.001). Paired GC samples analysis revealed higher positivity rate of HOTAIR in tumor tissue compared to adjacent gastric mucosa (65.4% vs 8.6%, p< 0.001). HOTAIR was only sporadically detectable in serum samples of GC patients; however, with very low level of reproducibility.

Overall, tumor positivity for HOTAIR expression was associated with shorter overall survival in GC patients compared to patients without detectable HOTAIR expression; however, the difference did not reach statistical significance (p=0.074). HOTAIR positive tumors showed lower genome-wide LINE-1 methylation level compared to HOTAIR negative tumors (p=0.024).

Conclusion: Our data provide a novel evidence for a distinct expression pattern of HOTAIR in gastric mucosa. HOTAIR expression increases in stepwise manner in correlation to progression of preneoplastic condition of Correa´s cascade. These results indicate that HOTAIR might be involved in the development of GC.

Disclosure: Nothing to disclose

OP367 INVESTIGATION OF MECHANISTIC ROLE OF HOTAIR AND PCDH10 IN GASTRIC CARCINOGENESIS

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Introduction: Long non-coding RNA (LncRNA)s are rapidly emerging as new players in cancer biology and contribute to epigenetically to regulate DNA methylation. HOX transcript antisense intergenic RNA (HOTAIR) is one of the well-studied lncRNAs that regulate gene expression by mediating the modulation of chromatin structure. Protocadherin 10 (PCDH10) is well-known tumor suppressor genes and aberrant methylation of the PCDH10 is a frequent event in gastric cancers.

Aims & Methods: We aimed to investigate the epigenetic mechanism of lncRNA HOTAIR related with PCDH10 in gastric cancer.

Materials and methods: We collected 30 fresh gastric cancer tissue and paired adjacent gastric tissue samples and we used gastric cancer cell lines. We investigated mechanism of HOTAIR on apoptosis, cell proliferation, cell cycle analysis as indicators of carcinogenesis and metastasis of gastric cancer. We analyzed expression of HOTAIR and PCDH10 in gastric cancer tissues and paired adjacent gastric tissue and perform methylation-specific PCR to identify the interaction between HOTAIR and PCDH10 in cancer cell line.

Results: The expression of HOTAIR was found to be higher in gastric cancer tissue compared with adjacent non-tumor gastric tissue. Using MKN 28 and MKN 74 cells, we demonstrated that HOTAIR repressed apoptosis, was associated with cell cycle progression, and controlled the invasion and migration of gastric cancer cells. PCDH10 expression was significantly decreased in gastric cancer tissues compared with adjacent non-tumor gastric tissue. The treatment of siHOTAIRs increased the transcriptional level of PCDH10, furthermore, PCDH10 protein was also upregulated by siHOTAIRs in gastric cell lines. We observed that HOTAIR induced PCDH10 methylation in gastric cell lines via methylation-specific PCR.

Conclusion: We identified a novel epigenetic mechanism involving the methylation of PCHD10 by lncRNA HOTAIR in gastric cancer and demonstrated that the HOTAIR modulated cell proliferation and the invasion and migration of gastric cancer cell We identified a novel epigenetic mechanism involving the methylation of PCHD10 by lncRNA HOTAIR in gastric cancer and demonstrated that the HOTAIR modulated cell proliferation and the invasion and migration of gastric cancer cell.

Disclosure: Nothing to disclose

OP368 CLINICAL AND MOLECULAR CHARACTERIZATION OF EARLY ONSET GASTRIC CANCER (≤ 50 YEARS): ANALYSIS OF A NATIONAL MULTICENTRE STUDY

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Introduction: Gastric adenocarcinoma (GC) is a common tumour with high morbidity and mortality. Although most GCs are sporadic, familial aggregation can be observed in approximately 10% of cases and hereditary GC, i.e. in the context of a germline mutation, accounts up to 5% of all cases. Only 7% of patients are diagnosed before age 50. The clinical and molecular characteristics of early onset GC had been poorly described.

Aims & Methods: To describe the clinical, histological and molecular characteristics of early onset GC (≤ 50 years old).

From 1999 through 2018, patients with early onset GC were retrospectively recruited at 4 Spanish centres. Personal and, family history, tumour-related information and tumour immunohistochemistry (IHC) of DNA mismatch repair proteins (MMR) (MLH1, MSH2, MSH6 and PMS2) status were registered. Germinal genetic analysis was performed in patients who met criteria of a hereditary syndrome associated with GC (ie. hereditary diffuse gastric cancer, Peutz-Jeghers syndrome, Lynch syndrome, familial adenomatous polyposis, hereditary breast and ovarian syndrome, juvenile polyposis and Li -Fraumeni syndrome).

Results: 308 patients were included, 118 (38%) were women. The median age at diagnosis was 43 years (range 17-50). The tumours were located mainly at body and antrum, 55% and 25% respectively. Histologically, 75% were diffuse, 17% intestinal and 18% mixed or unclassifiable. An advanced stage (III/IV) at diagnosis was present in 78% cases. With regard to environmental risk factors: and *Helicobacter pylori* infection was detected in 24/82 (29%) cases, 78/167 (46%) patients had regular smoking habit and 51/105 (20%) were moderate/severe alcohol consumers.

Family history was available in 108 cases: familial aggregation of GC was present in 15 (13.8%) cases and 5 (4.6%) met criteria for familial GC. IHC of MMR was performed in 88 (28.5%) tumours: 3/88 (3.4%) showed loss of expression in MLH1/PMS2, without an associated germline mutation. Fifteen genetic analyses were performed, detecting a germline mutation in 3 (20%) cases: *BRCA2*, *TP53* and *CDH1* (Table 1).

Conclusion: Most of early-onset GCs are histologically diffuse and diagnosed at an advanced stage. In this subgroup of patients, DNA mismatch repair system deficiency is an infrequent event and likely not very useful. Familial aggregation is present only in 13% of cases; however, in 20%

of the patients who meet criteria for genetic study, a germline mutation is found (*BRCA2, CDH1, TP53*). These results demonstrate that early-onset GC has a marked genetic heterogeneity, reinforce the importance of an adequate genetic counselling (complete family history) and enhance the emerging use of multigene panels.

Disclosure: Nothing to disclose

Age at diagnosis	Gender	Family history of GC	Family history of other tumours	IHC	Germline gene mutation
40	Female	No	Breast Ovarian	MMR+	BRCA2
38	Male	Yes	No	MMR+	CDH1
34	Male	No	Breast Colon	MMR+	TP53

[Table 1: Characteristics of patients with germline gene mutation]

OP369 CHARACTERISTICS AND RISK FACTORS OF INTERVAL GASTRIC NEOPLASMS DETECTED IN SCREENING ENDOSCOPY AMONG ASYMPTOMATIC HEALTHY ADULTS

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Introduction: In Korea, where gastric cancer is highly prevalent, regular upper endoscopy every other year is recommended for gastric cancer (GC) screening among individuals over 40 years old. However, even under such regular screening endoscopy, some are still diagnosed to have advanced gastric neoplasms.

Aims & Methods: This study was designed to identify characteristics and risk factors of interval gastric neoplasms detected in screening endoscopy. Medical records of individuals who were newly diagnosed with gastric neoplasms in screening upper gastrointestinal endoscopy between January 2004 and May 2016 were reviewed. Among them, those who had previous endoscopy within 2 years were enrolled. Their endoscopic finding, family history of GC, cigarette smoking, and *Helicobacter pylori* (*H. pylori*) infection status were analyzed. Those with positive results in anti-*H. pylori* IgG, CLO test or histologic findings of *H. pylori* were considered to have *H. pylori* infection.

Results: During the study period, 625 patients were newly diagnosed with gastric neoplasm. Among them, 300 patients underwent previous endoscopy within 2 years (median 12 months; Interquartile range: 11-15 months). Three patients with previous gastrectomy or unclear final pathology were excluded. Among the 297 neoplasms, 246 were endoscopically treatable gastric neoplasms (ET-GN) and 51 were endoscopically untreatable gastric neoplasms (EUT-GN) according to the criteria for endoscopic submucosal dissection. About 80% of EUT-GNs were undifferentiated cancers (40/51) and about 30% of them showed submucosal invasion (13/40). EUT-GN were less commonly located at the antrum compared with ET-GN (29.4% vs. 58.1%, p < 0.001) and their median size was 2.0 cm. In multivariable analysis, EUT-GN was highly related with age < 60 (OR, 2.091; 95% CI, 1.028-4.255, p = 0.042), *H. pylori* infection (OR, 2.814; 95% CI: 1.195-6.625, p 0.018), and absent or mild atrophic gastritis (OR, 2.673; 95% CI, 1.251-5.724, p = 0.011). Overall and disease-free survival were not significantly different between the two groups, however, EUT-GN showed a tendency of short disease-free survival.

Conclusion: Current screening interval of 2 years seems unsatisfactory to detect rapid-growing gastric neoplasms, such as undifferentiated cancers, early enough. Those neoplasms tended to develop in young adults with current *H. pylori* infection without severe atrophic gastritis. More intense screening is warranted for subgroup of young adults with *H. pylori* infection even if they do not have gastric atrophy.

Disclosure: Nothing to disclose

OP370 ENDOSCOPIC TREATMENT OF EARLY GASTRIC NEOPLASIA IN THE WEST : EXPERIENCE FROM THREE EUROPEAN TERTIARY CENTRES

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Introduction: Endoscopic submucosal dissection (ESD) is a technique first developed in Japan to enable en-bloc endoscopic resection of early gastric neoplasia. The high prevalence of gastric neoplasia allowed for greater opportunity to train and refine the technique in the Far East. The same is not applicable to the West where the prevalence of gastric neoplasia is low.

Aims & Methods: We aim to review the efficacy and safety of ESD for early gastric neoplasia from three large European referral centres. Data was prospectively collected on an electronic database. We analysed this database and patient's electronic record. Parameters related to ESD outcome were collected.

Results: A total of 175 gastric neoplasia were resected between 2009 and 2017 (152 ESD, 23 hybrid ESD), 51.4% were in proximal stomach. Mean size was 29mm. Only 13 (7.42%) were sub-epithelial lesions. Table (1) shows outcomes and procedure-related complications. The overall en-bloc resection, R0 (deep), and R0 (deep and lateral) rates were 92.5%, 83.4%, and 61% , respectively. Proximal location of the lesion was a predictor for R1 outcome (p value 0.011). Size of the lesion was not significantly related to the R0 rate. The overall adverse event rate was 11.3%. There was no 30-day procedure related mortality. Recurrence at 3 months occurred in 7 patients (4%).

Conclusion: This is the largest western gastric ESD series, demonstrating the feasibility and safety of this technique in an European setting. Despite the low R0 rate, our recurrence rate is low and comparable to Japanese data.Reasons behind good clinical outcome (very low recurrence) despite an average technical outcome (R0) remains uncertain.This raises a possibility that in the west, R-1 should not automatically be considered as an indication for surgery.

Disclosure: PB received research grants and honorarium from Pentax, Boston, Fuji, Olympus, and 3D Matrix.

OP371 SHORT- AND LONG-TERM OUTCOMES OF GASTRIC ENDOSCOPIC SUBMUCOSAL DISSECTION FOR ABSOLUTE-INDICATION LESIONS AND EXPANDED-INDICATION LESIONS

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Introduction: Endoscopic submucosal dissection (ESD) is an effective treatment method for early gastric neoplasms, and its indication is being expanded. According to 2018 Japanese gastric cancer treatment guidelines, for differentiated-type gastric cancer (>2 cm without UL, ≤ 3cm with UL) treatment, expanded-indication of ESD became absolute-indication. Expanded-indication for undifferentiated-type gastric cancer (≤2 cm) is also expected to become an absolute-indication. These claims were based on evidence from high-volume centers, and it is important to check their applicability to actual clinical practice.

Aims & Methods: Our study aimed to evaluate and compare the clinical outcomes of ESD to early gastric cancers for absolute-indication lesions and that for expanded-indication lesions. The subjects were 490 patients who collectively presented with 574 early gastric cancers diagnosed with absolute-indication lesions or expanded-indication lesions. All patients underwent ESD at our hospital between June 2007 and August 2018. The

patients were segregated into two groups: absolute-indication lesions (group A: 294 patients with 331 collective lesions) and expanded-indication lesions (group B: 233 patients with 243 collective lesions). We evaluated the clinicopathological findings, and short- and long-term outcomes including the local and distant recurrence rates, and overall survival (OS) and disease-specific survival (DSS) rates.

Results: The patients' mean ages were 72.9 years (group A) and 71.4 years (group B), and the male-to-female ratios were 232/62 (group A) and 177/56 (group B). The mean tumor size in group B (22.9 mm) was significantly larger than that of group A (10.2 mm) (p < 0.01). Histopathological findings revealed that the rates of differentiated-type were 100 % (331/331) in group A and 88.9 % (216/243) in group B (p < 0.01). Regarding tumor depth, intramucosal carcinomas were 100 % (331/331) in group A and 81.9 % (199/243) in group B, and shallow submucosal invasive carcinomas (< 500 μm) were 0 % (0/331) in group A and 18.1 % (44/243) in group B (p < 0.01). The *en bloc* resection rates were 99.7 % (330/331) in group A and 95.9 % (233/243) in group B (p< 0.01), and the curative resection rates were 98.5 % (326/331) in group A and 93.8 % (228/243) in group B (p< 0.01). Regarding adverse events, postoperative hemorrhage rates were 2.42 % (8/331) in group A and 4.94 % (12/243) in group B, and perforation rates during the procedure were 0.30 % (1/331) in group A and 0.82 % (2/243) in group B. There were no significant differences in adverse events. Regarding long-term outcomes, the local and distant recurrence rates were 0.30 % (1/331) and 0 % (0/331) in group A and 0.41 % (1/243) and 0 % (0/243) in group B, respectively (n.s.). Regarding survival analysis, the mean follow-up periods in group A and group B were 55.1±35.6 and 47.0±35.4 months, respectively. The 3- and 5-year OS rates were 92.7 % and 90.1 % in group A, and 94.1 % and 88.7 % in group B (using the Kaplan-Meier method and long-rank test), respectively. The 5-year DSS rates were 100 % in both groups. No significantly difference was observed in the survival rates.

Conclusion: The short-term outcomes of expanded-indication lesions were inferior to those of absolute-indication lesions, despite both being acceptable. In addition, expanded-indication lesions had excellent long-term prognosis, equivalent to absolute-indication lesions. Therefore, expansion of the indication of gastric ESD to actual clinical practice is appropriate.

Disclosure: Nothing to disclose

OP372 DO THE SUPPRESSION OF PROLIFERATIVE CAPACITY OF GASTRIC CANCER CELLS DUE TO *HELICOBACTER PYLORI* ERADICATION AFFECT THE FINDINGS OF MICROSURFACE PATTERNS ON MAGNIFYING ENDOSCOPY WITH NARROW-BAND IMAGING?

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Introduction: In Japan, *Helicobacter pylori* (HP) eradication therapy is already spread, but gastric cancer is frequently detected, even after eradication (post-eradication gastric cancer). The detection of lesions or the diagnosis of the margin of the lesions is considered to be more difficult in post-eradication gastric cancer than in HP-uneradicated gastric cancer. Regarding the underlying reason, it has been reported that the Ki-67 index is low in post-eradication gastric cancer, indicating that the proliferative capacity of tumor cells is suppressed [1-3]. However, whether differences in cell proliferative capacities between post-eradication and uneradicated gastric cancer are associated with the microsurface pattern (MSP) has not been determined.

Aims & Methods: This study included 122 lesions of differentiated early gastric cancer (63 lesions of post-eradication gastric cancer and 59 lesions of uneradicated gastric cancer) treated with endoscopic submucosal dissection (ESD) at our hospital between January 2014 and December 2017. Under magnifying endoscopy with narrow-band imaging (M-NBI), all lesions were resected in an en bloc fashion by using ESD. The middle sections of the resected specimens were immunostained for Ki-67 (MIB-1). The Ki-67 index was then calculated and compared to determine whether it was different between post-eradication and uneradicated gastric cancer. In addition, according to the MSP using the vessel plus surface classification system, the lesions were divided into the following 4 groups: group A of post-eradication gastric cancer with a regular MSP, group B of post-eradication gastric cancer with an irregular MSP, group C of uneradicated gastric cancer with a regular MSP, and group D of uneradicated gastric cancer with an irregular MSP. In each group, the Ki-67 index was calculated and analyzed using the Tukey-Kramer test to determine whether the

cell proliferative capacity was associated with M-NBI findings.The Ki-67 index was defined as a value calculated using the following formula: Ki-67-positive cell count / total epithelial cell count per magnification of 200 times. To match the result for the visible range of NBI, the index was calculated in an area that was located 200 μm from the superficial portion of the mucous membrane.

Results: The mean Ki-67 index score of all the lesions was 24.8% for post-eradication gastric cancer and 38.2% for uneradicated gastric cancer. The score was significantly lower for the former (P < 0.001), suggesting that eradication suppressed the proliferative capacity of tumor cells. According to the MSP findings, there were 20 lesions in group A (31.7%), 43 lesions in group B (68.3%), 5 lesions in group C (8.5%), and 54 lesions in group D (91.5%). The mean Ki-67 index scores were 19.6% in group A, 27.1% in group B, 31.6% in group C, and 38.8% in group D. The Ki-67 index scores in groups A and B were significantly lower than the score in group D (P < 0.001 and P < 0.01, respectively), whereas no significant difference in the scores was observed between groups A and B. No association was detected between decreased Ki-67 index scores due to eradication and MSP findings.

Conclusion: In post-eradication gastric cancer, the Ki-67 index was generally lower than in uneradicated gastric cancer, and the proliferative capacity of the tumor cells was suppressed. However, M-NBI did not show any association between different MSP findings and the cell proliferative capacity. The previously reported view appeared unlikely.

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