ABSTRACTS

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Contents

Belgian Association for the Study of the Liver (BASL) / Belgian Liver Intestine Committee (BLIC)

A01

The impact of rifaximin on the hospital burden and infections in patients with hepatic encephalopathy: a retrospective observational study

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Introduction: Hepatic encephalopathy (HE) is a potentially severe complication of cirrhosis. Overt HE imposes a substantial quality-of-life and socioeconomic burden on patients. Rifaximin is a gut-selective, oral antimicrobial agent shown to reduce the recurrence of overt HE.

Aim: We aim to evaluate the use of rifaximin and the evolution in hospital admissions in patients with HE over a period of 6 months before and after initiation of rifaximin in a real-world population.
Methods: In this retrospective, observational and monocentric cohort study, we include patients with liver cirrhosis who were treated with rifaximin for HE, at a dose of 550 mg twice daily. Demographic data were collected and we evaluate the number of HE-related hospital admissions and bed days on a general ward and the intensive care unit (ICU); number of liver-related hospitalisations and bed days; number of emergency department and outpatient clinic visits; number and type of infections. Safety was assessed (adverse events, clinical laboratory parameters) for all patients. Patients were followed for at least 6 months after rifaximin initiation or until death, liver transplantation, or permanent discontinuation of rifaximin.
Results: A total of 66 patients with HE who initiated rifaximin between October 2014 and January 2020 were included. Demographic data showed that 65.2% of the population consisted of males, the mean age (standard deviation (SD)) was 67.2 (±9.25) years and a median (inter quartile range (IQR)) model for end-stage liver disease (MELD) of 20.5 (13.7 – 28.0), the etiology of the underlying cirrhosis was predominantly (post) alcoholic (80.3%) and NASH (13.6%). All patients were treated with lactulose simultaneously and 15.2% received prophylactic antibiotics. The mean (SD) exposure to rifaximin was 285 days (± 402 days). At time of rifaximin initiation, 68.2% of patients were scored as having a HE West Haven grade 2 and 30.3% a West Haven grade 3. All scores significantly decreased after 6 months of treatment with rifaximin (51.2% grade 1, 16.7% grade 2 and 1.5% grade 3, $p<0.001$). When comparing the first 6 months after rifaximin initiation with the prior 6 months, the mean number of HE-related hospital admissions per patient decreased (1.55 (±1.18) to 0.42 (±0.88) admissions, $p<0.00$), as well as the liver-related admissions (1.01 (±1.44) to 0.39 (±0.72), $p<0.02$) and ICU liver-related admissions (0.87 (±0.99) to 0.32 (±0.87), $p<0.00$). Likewise a significant reduction in the mean number of hospital bed days per patient was observed for HE-related hospitalisations (23.07 (±23.46) to 7.29 (±23.7), $p<0.02$), ICU liver-related admissions (3.8 (±0.28) to 0.23 (±1.25), $p<0.04$), but not for liver-related admissions (4.10 (±5.80) to 6.03 (±13.44), $p=0.41$). Furthermore, a significant reduction of the mean number of visits to the emergency department was seen per patient (1.94 (±2.09) to 0.94 (±1.44), $p<0.01$), but not for the outpatient clinic visits (6.35 (±5.56) to 4.39 (±3.28), $p=0.13$). Finally, a significant decrease in the mean number of total infections per patient was recorded (0.90 (±1.02) to 0.32 (±0.63), $p<0.001$), as well as for those with a respiratory focus (0.18 (±0.38) to 0.03 (±0.17), $p<0.03$). The mean number of gastrointestinal infections per patient (0.14 (±0.42) to 0.04 (±0.21), $p=0.08$) and spontaneous bacterial peritonitis (0.15 (±0.36) to 0.06 (±0.24), $p=0.08$) showed a non-significant decrease. Only 2 patients (3.03%) reported rifaximin related side effects (nausea, itching).
Conclusions: This study provides 'real-world' data demonstrating the potential value of rifaximin in reducing hospital admissions, length of stay in the hospital, emergency department attendances and the total number of infections in cirrhotic patients with HE.

Compared with previous studies, this is the first study providing this evidence in an advanced cirrhotic population with a high MELD score.

A02

NOX1 inhibition attenuates the development of a pro-tumorigenic environment in experimental hepatocellular carcinoma

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Introduction: The poor prognosis of advanced HCC and limited efficacy of current systemic treatments emphasize the need for new or combined targeted therapies. The development of HCC is a multistage process in which liver injury appears in a complex microenvironment associated with oxidative stress. NOX enzymes are the main source of ROS during hepatocarcinogenesis and NOX1 in particular has shown correlation with poor prognosis of HCC patients.

Aim: This study evaluates the effect of pharmacological NOX1 inhibition on the development and progression of HCC and its effect on the tumor microenvironment.

Methods: The in vitro cytotoxic effects of the NOX1 inhibitor GKT771 (Genkyotex) on human Huh7 and Hep3B and murine Hepa1-6 HCC cell lines, the human THP1 monocyte cell line and mouse macrophages were evaluated via MTT, LDH activity and CaspGlo® assays. In order to induce in vivo HCC, male SV129 wild-type mice received weekly IP injections of diethylnitrosamine (DEN) (35 mg/kg) for 20-25 weeks. Mice were treated with vehicle or GKT771 (30 mg/kg) via oral gavage, daily or twice daily, in preventive and therapeutic studies. The liver damage was evaluated for inflammation, angiogenesis, fibrosis and HCC development via histology, RT-qPCR, multiplex analyses and ROS levels.

Results: A concentration-dependent reduction in cellular activity of the human HCC cell lines without cytotoxicity was observed. GKT771 treatment reduced LPS-induced pro-inflammatory bone-marrow derived macrophage polarization. DEN injections resulted in 100% tumor formation and the induction of HCC markers which could be reduced by twice daily dosing of GKT771 at early onset of advanced HCC. DEN-induced HCC resulted in an upregulation of pro-inflammatory, angiogenic and fibrotic markers which was less pronounced in GKT771 treated mice in all treatment regimens. In line, liver fibrosis was induced in HCC mice and this to a lesser extend upon GKT771 treatment.

Conclusions: NOX1 inhibition showed to be safe and well tolerated and was able to attenuate the induction of a pro-inflammatory, angiogenic and pro-fibrotic microenvironment suggesting that this might be a promising adjuvant therapeutic strategy in the treatment of advanced HCC.

A03

Human and mouse precision-cut liver slices as a dynamic tool to model liver fibrosis

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Introduction: Chronic liver disease, including liver fibrosis, accounts for two million deaths worldwide each year. Besides causal treatments, which can slow down fibrosis progression, no anti-fibrotic liver therapies are currently available, mainly due to the lack of robust and representative in vitro models. The most representative in vitro model of human liver disease could be the use of precision-cut liver slices (PCLS), as these maintain the architecture and microenvironment as found in vivo. However, the major drawback of this model is that slice preparation results in cut surfaces, which eventually triggers the induction of spontaneous fibrosis progression in culture, as hepatic stellate cells (HSC) will activate within 96 hours upon slicing.

Aim: To establish stable PCLS cultures that allow direct and as well as hepatocyte-damage induced HSC activation in a reciprocal way (induction and inhibition).

Methods: Human and mouse liver tissues were sliced with a Leica vibrating blade microtome VT1200S. Slices were eventually punched into 3mm diameter discs (PCLS). PCLS were cultured during a period of 5 days in the presence or absence of valproic acid (VPA). RNAseq analysis was performed on PCLS cultured in the presence or absence of VPA over a time period of 5 days. In the presence of VPA, PCLS were exposed on day 3 for 48 hours to a direct trigger of 10ng/mL TGFβ or an indirect trigger of 20mM acetaminophen (APAP), a known hepatotoxic compound.

Results: In this study, we established stable mouse and human PCLS culture conditions demonstrating sustained viability, sustained albumin protein expression and low levels of culture-induced fibrosis for at least 5 days by the addition of VPA to the culture medium. More insight into the mechanisms by which VPA inhibits this PCLS culture-induced fibrosis will obtained by the RNAseq analysis. Direct HSC activation could be induced by treatment with TGFβ, which could be blocked by simultaneous exposure to an Alk5 inhibitor. Hepatocyte-damage dependent HSC activation was established in mouse PCLS by the exposure of APAP. This HSC activation could be blocked by N-acetylcysteine, a compound used in the clinic to treat acetaminophen overdose or verteporfin, a YAP inhibitor. HSC activation and fibrosis induction by both compounds could be confirmed on both transcriptional and translational level.

Conclusions: The obtained results demonstrate the potential of both human and mouse PCLS as a reliable model to mimic inducible liver fibrosis. In the future, this model allows to perform mechanistic studies and offers the opportunity to model other chronic human liver diseases, such as non-alcoholic fatty liver disease or cholestasis.

A04

Hypoxia-induced angiogenesis rescues survival upon extended hepatectomy in mice

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Introduction: After hepatectomy, hepatocytes proliferate first and before the proliferation of sinusoidal endothelial cell (SEC) causing a transient imbalance between cell populations and a transient perturbation of the lobular architecture with proliferating hepatocytes forming avascular, hypoxic, clusters. The larger the liver resection, the highest the portal hyperperfusion and the more hepatocytes proliferate. Hence, the larger the liver resection, the larger the avascular, and thus non-functional, hepatocyte islands. Hypoxia is, thus, considered at the origin of liver dysfunction, also called a "small-for-size syndrome" (SFSS). The new surgical technique called “Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy” (ALPPS) allows for a rapid remnant hypertrophy with high resection rates compared to the more conventional techniques. Recent work from our lab on rats showed that ALPPS rescued survival compared to a standard SFSS-setting hepatectomy. Also, ALPPS was associated with hypoxia in the remnant. Confirmatory, induction of hypoxia after a SFSS hepatectomy rescued survival. Hypoxia also activated HIF pathways and triggered a pro-angiogenic response. We hypothesize that hypoxia-induced angiogenesis helps to maintain the lobular structure and thus liver function during liver regeneration.

Aim: The aim of the present study is to analyze the remodeling of the liver sinusoidal network during SFSS-hepatectomy with of without exposure to hypoxia.

Methods: Directly after a SFSS-setting hepatectomy (where 80% of the liver is removed) (referred to as time T), mice were housed in a gas tight chamber and exposed to a controlled hypoxic environment (11% FiO2) (PHx80 HC) or to ambient air (20,9% FiO2) (PHx80). We sacrificed mice at T+24H, T+48H, T+72H and T+7days. Survival was assessed twice a day. Endothelial cell proliferation was assessed by double immunofluorescence to detect the proliferative marker Ki67 and CD31/PECAM-1 to endothelial cells: proliferative endothelial cells were Ki67+/CD31+. CD31- cells were divided by their size as such: $<45\mu m^2$ = non-parenchymal cells (except endothelial cells); $>45\mu m^2$ = hepatocytes. Feret's diameter of liver sinusoids and sinusoidal area were assessed manually and semi-automatically respectively on x20 images of CD31 immunostained liver sections. Mitosis were counted on x20 fields on H&E staining.

Results: In Animals with SFSS hepatectomy, mortality was high with only 30% of survival at T+7days with most of the deaths occurring in the first 3 days. Exposure of the animal to the hypoxic environment directly after the surgery dramatically improved their survival as 95% of the mice survived at T+7days. Liver cells' proliferation was assessed by immunofluorescence. Proliferative hepatocytes were hardly present in the regenerating livers at T+24H while hypoxia chamber slightly but not significantly increased their numbers at T+48H (0.36 ± 0.38 in PHx80 vs 4.55 ± 5.77 in PHx80 HC, p

value= 0.08). Mitosis counts confirmed these results, as hardly any mitosis were found at T+24H. At T+48H, mitosis count increased in both groups. As so, liver weight was not different between PHx80 and PHx80 HC during the course of liver regeneration. On the other hand, endothelial cell proliferation was greatly enhanced with hypoxia: differences between PHx80 and PHx80+HC were already seen at T+24H (0.52±0.39 vs 5.56±2.87, p = 0.0018) and even larger at T+48H (0.71±0.88 vs 8.81±4.07, p value< 0.0001). The vascular bed (as the mean sinusoidal diameter) was increased at T+24H in PHx80 HC compared to PHx80 (6.19±0.47 vs 4.94±0.21, p value= 0.001). Also, the sinusoidal area was larger in PHx80 HC compared to PHx80 at T+48H (54055±10850 vs 19864±9201, p value= 0.0007).
Conclusions: Our data demonstrate that hypoxia rescues survival after a SFSS-setting hepatectomy. Hypoxia had no effect on hepatocyte proliferation but accelerated LSEC proliferation, increased the diameter of liver sinusoids and the overall vascular sinusoidal areas. Our results are compatible with the hypothesis that hypoxia triggers and angiogenic response as to ensure proper blood supply to regenerating hepatocytes, hence supporting liver function.

A05

Intensive lifestyle management improves steatosis and fibrosis in pediatric non-alcoholic fatty liver disease

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Introduction: Childhood obesity, with associated comorbidities such as insulin resistance and non-alcoholic fatty liver disease (NAFLD), is a growing global health problem. As pharmacological interventions for pediatric NAFLD are lacking, lifestyle management is the mainstay of treatment. Nonetheless, its efficacy on liver fibrosis has not been established.
Aim: To investigate the efficacy of weight loss and lifestyle management on the severity of pediatric NAFLD.
Methods: Children and adolescents admitted for severe obesity at the Zeepreventorium between July 2019 and January 2020 were invited to participate in this prospective study. Intensive lifestyle therapy in a residential multidisciplinary setting encompassed caloric restriction, physical activity, education about a healthy lifestyle and psychosocial support. At baseline and after 6 and 12 months, liver ultrasound and transient elastography with controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were performed to assess liver steatosis and fibrosis. Fibrosis was defined as an LSM ≥7kPa for F2, ≥9kPa for F3, and ≥11kPa for F4 fibrosis; CAP values

≥240 dB/m were considered elevated. These data were compared with clinical, anthropometric and biochemical patient characteristics.
Results: 94 patients (52.1 % male, median age 14.5 years, BMI 35.5, BMI Z-score 2.7) had data available at baseline and at 6 months. At admission, NAFLD on ultrasound was present in 75.5%, whereas 76.6% had CAP values ≥240 dB/m. 35.1% of patients had at least F2 fibrosis, including 10.6% with LSM ≥9kPa. After 6 months, median body weight loss was 16.0%. Steatosis and fibrosis improved in 66.2 and 66.7% of patients ($P < 0.001$), respectively, with 18/33 patients with baseline ≥F2 fibrosis now falling below this threshold. Baseline severity of liver fibrosis and steatosis, but not percentage weight loss after 6 months, were significantly correlated with fibrosis resolution. 53 patients had reached the 1-year timepoint. The improvements were sustained, as fibrosis regressed at least one stage in all patients with baseline fibrosis, and resolved in 83.3% ($P < 0.001$).
Conclusions: NAFLD and associated fibrosis are highly prevalent in children and adolescents with severe obesity. An intensive multidisciplinary lifestyle management program which causes significant weight loss not only improves liver steatosis, but also fibrosis.

A06
Relative in vivo antiviral potency of pegIFN-lambda vs -alpha against HEV
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Introduction: Hepatitis E viruses (HEV) are an underestimated global burden and an important enterically transmitted cause of viral hepatitis. The treatment options for chronic HEV infected immunocompromised patients are limited to dose reduction of immunosuppressive drugs, ribavirin monotherapy, or pegylated IFNα (pegIFNα) as the last available option.
Aim: In the present study, we assess the in vivo antiviral potential of pegIFNλ as an alternative to pegIFNα, which is known to increase the risk of acute rejection in HEV-infected transplant patients.
Methods: Primary hepatocytes and hepatoma cell line HEPG2 cells were used to examine the relative in vitro ISG induction (STAT1, ISG15, Oas1, Mx1) by pegIFNλ and pegIFNα. uPA-NOG and TK-NOG mice were transplanted with primary human hepatocytes and inoculated iv with a feces derived HEV gt3c clinical isolate (6-8 log HEV RNA/mouse) upon establishment of a stable hepatocyte graft. Successful infection was confirmed using fecal materilas. Thereafter animals were treated either with a range of doses up to 300µg/kg pegIFNλ for different durations (n=9) or 30µg/kg pegIFNα as a positive control for two weeks, as previously shown (n=5). Upon treatment completion, animals

were sacrificed and liver, bile and feces samples were collected for viral load determination by multiplex qPCR. A liver fragment was stored in RNAlater for ISG mRNA expression analysis or in formalin for immunofluorescent staining.
Results: Based on our previous data on the relative IFNλ potency forISG induction in B cells, HepG2 and primary hepatocytes were incubated with a 10-fold higher pegIFNλ dose at 100 ng/ml compared to pegIFNα at 10 ng/ml. These doses resulted in a similar ISG induction in hepG2 cells, but higher ISG mRNA levels in human hepatocytes. Upon in vivo pegIFNλ treatment of HEV infected humanized mice for upto 8 weeks and 120 ug/kg, HEV loads in feces were rapidly suppressed, but persisted in bile and liver (n=18). A complete sterilization of HEV liver titers was only obtained after applying pegIFNlambda at 300 ug/kg for 2 weeks (n=8/9). As previously demonstrated, pegIFNα was able to clear the in vivo HEV infection using 10-fold lower doses at 30 ug/kg for 2 weeks (n=5).
Conclusions: pegIFNλ is able to fully clear an HEV infection in a humanized mouse model, but requires a 10-fold higher dose compared to pegIFNα.

A07
Restoration of altered bile acid pool inhibits the development of nonalcoholic steatohepatitis
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Introduction: We have previously shown that foz/foz mice with nonalcoholic steatohepatitis (NASH, NAFLD Activity Score (NAS) $\geq$ 7) and associated metabolic features have an altered bile acid pool with a reduction in secondary bile acid deoxycholic acid (DCA) in bile and portal blood compared to wildtype mice that do not develop liver disease (NAS $\leq$ 1). These alterations in bile acid pool result in a reduction of Takeda G-protein coupled receptor 5 (TGR5) activation, a receptor mainly activated by secondary bile acids regulating lipid and glucose homeostasis, energy expenditure, inflammation and fibrosis. Reduced TGR5 agonism and resulting low TGR5 signaling could thereby contribute to NASH pathogenesis in this experimental model.
Aim: We thus aimed to determine whether a modulation of bile acid pool and a restoration of secondary bile acids inhibit NASH development.
Methods: Foz/foz mice were separated in three groups: a reference group received high fat diet (HFD) and the two treated groups received a HFD containing 0.03% or 0.1% (w/w) of deoxycholic acid (DCA, a secondary bile acid) for 12 weeks. Foz/foz mice were compared to wildtype mice fed a HFD for 12 weeks (n=7/group) designated as controls. Portal and systemic blood and tissues were sampled after 12h fasting and 4h refeeding. Bile acid profile was established by LC-MS/MS. We used a cell reporter assay, HEK293T

cells overexpressing TGR5 and expressing a CRE luciferase reporter to quantify TGR5 ligand activity in portal plasma.
Results: A HFD supplemented with 0.1% of DCA, but not 0.03%, increased total bile acids as well as cholic and deoxycholic acids concentrations in foz/foz mice, normalizing the concentrations at wildtype mice's level. TGR5 ligand activity of the portal blood was low in foz/foz mice fed a HFD (2.7-fold lower than wildtype) or fed 0.03% DCA supplemented HFD (1.4-fold lower than wildtype). By contrast, 0.1% DCA in the HFD successfully raised the concentration of TGR5 ligands in foz/foz mice (1.7-fold higher than wildtype controls). We then looked at the consequences of these modulations of the bile acid pool on liver disease and NASH associated metabolic features. While 0.03% DCA did not improve metabolic features in HFD-fed foz/foz mice, 0.1% DCA supplementation significantly reduced body weight gain and fat mass, despite an increased food intake. Glucose intolerance, fasting glycemia and HOMA index were also reduced by DCA 0.1%. Regarding liver disease, supplementation of the HFD of foz/foz mice with 0.03% of DCA did not significantly change hepatic steatosis, inflammation and liver weight. NAS was slightly reduced compared to HFD-fed foz/foz mice, but 85% of the treated mice still presented NASH. On the contrary, supplementation with 0.1% of DCA reduced liver weight, hepatic steatosis and ballooning. Although gene expression of pro-inflammatory markers was not downregulated in 0.1% DCA fed-foz/foz mice, the treatment significantly decreased NAS such as six mice out of the seven foz/foz mice treated with 0.1% of DCA did not present NASH.
Conclusions: In conclusion, supplementation of the HFD with a secondary bile acid restored bile acid pool and TGR5 activation and in consequence, inhibited the development of NASH, obesity and glucose intolerance in this mouse model of NASH.

A08
Multicellular primary mouse liver spheroids for DILI, MAFLD and fibrosis studies
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Introduction: Sustained liver disease independent of the etiology leads to liver fibrosis. Drug induced liver injury (DILI), metabolic (dysfunction) associated fatty liver disease (MAFLD), fibrosis and subsequently cirrhosis are a great health burden and a major cause of death worldwide, for which currently no therapies are available. During chronic liver disease hepatic stellate cells (HSCs) become activated and will obtain a myofibroblast phenotype and produce extracellular matrix that accumulates in the liver giving rise to scar tissue. However, not only HSCs but also other non-parenchymal cells respond to liver injury such as liver sinusoidal endothelial cells(LSECs) and Kupffer cells(KCs). These cells produce molecules that can lead to and aggravate HSCs activation and fibrosis. Currently, there are no robust in vitro culture models available that can recapitulate the complex fibrotic response upon hepatocyte damage or MAFLD, and thus animal studies remain necessary to test and screen drugs.

Aim: Our aim was to develop a multicellular spheroid in vitro model with primary isolated mouse HSCs, KCs, LSECs and hepatocytes that can be used to model DILI, fibrosis and MAFLD and for research into its mechanism of action and the development of new anti-fibrotic/MAFLD therapies.
Methods: Multicellular liver spheroids were generated by the co-culture of freshly isolated primary mouse hepatocytes, isolated by Percoll gradient isolation, and LSECs, HSCs and KCs isolated by FACS. DILI was induced by 24h exposure of DILI compounds and toxicity was determined by an ATP cell viability assay. Chronic injury was induced by 72h exposure with Acetaminophen(APAP) and MAFLD induction was obtained by culturing spheroids in lipogenic media (oleic and palmitic acid) for 9 days. Furthermore, treatment of the fibrotic response in both chronic liver injuries was done by addition of PPAR agonists Pioglitazone, Elafibranor and Lanifibranor to the medium. Intracellular fat accumulation in the spheroids was assessed by bodipy staining, mRNA expression monitored by RT-qPCR and protein changes detected with immunohistochemistry and Enzyme-Linked Immuno Sorbent Assay.
Results: We established 3D co-cultures with freshly isolated liver cells from mice that can be cultured for at least 14 days without significant change in cellular composition or induction of HSC activation. Stellate cells could be activated directly by exposure to TGFβ as shown by a significant upregulation of HSC markers like Acta2 and Col1a1 at the mRNA level and as well as Collagen protein levels determined by ELISA. DILI was induced by an acute or chronic exposure of APAP and chronic exposure of APAP generated a fibrotic response with an upregulation of Acta2 and Collagen genes, specific for HSC activation, as well as collagen deposition in the spheroids and secretion of the protein in the culture media. Exposure of spheroids to high amounts of free fatty acids resulted in MAFLD induction evidenced by an intracellular lipid accumulation and change in pro-fibrotic (Acta2, Col1a1, Col3a1, Col5a2) and inflammatory genes (Il-1 and Il-6). Interestingly, preliminary data indicates that the fibrotic response in APAP-exposed spheroids could be inhibited by PPAR agonists and anti-fibrotic/MAFLD drug candidates Pioglitazone, Elafibranor and Lanifibranor.
Conclusions: We established a robust multicellular in vitro spheroid culture model from primary mouse liver cells that can display a fibrotic response upon chronic exposure to APAP or under MAFLD conditions. Moreover, this model faithfully represents characteristics of MAFLD. In addition, these primary liver spheroids can potentially be used to assess novel anti-fibrotic/MAFLD compounds and for the development of novel therapies. *two first authors contributed equally **last two authors contributed equally

A09

Acute liver decompensation following bariatric surgery in patients without cirrhosis: clinical presentation, histological findings and management

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Introduction: Obesity is a growing problem with multiple complications, such as metabolic dysfunction-associated fatty liver disease (MAFLD). Bariatric surgery (BS) has shown efficacy in long-term weight loss achievement. Numerous reports have described MAFLD related cirrhosis at the time of BS, complicated by further liver decompensation, in particular in patients with ancient BS techniques. The exact mechanism is unknown. Sometimes, cirrhosis may be absent. Fatal outcome, liver transplantation and reversal surgery have been reported in those patients.
Aim: We wanted to describe the clinical characteristics, histological findings and clinical management of patients without cirrhosis who developed acute hepatic decompensation after BS for severe obesity.
Methods: We collected clinical, biological, histological and follow-up data from patients without cirrhosis with acute hepatic decompensation after BS.
Results: From December 2014 to October 2019, 6 patients (5 females and 1 male) underwent a transvenous liver biopsy for acute liver decompensation after BS. Four patients had a Roux-en-Y gastric bypass, one patient had a biliopancreatic diversion according to Scopinaro and one patient had a distal gastric bypass. At the time of BS, the mean age was 36 years (31-56), all patients were severely obese (mean body mass index 45 kg/m^2) and there was no argument for cirrhosis (FIB-4 score < 1.3). The time between surgery and the onset of acute liver decompensation varied widely (min. 8 months, max. 17 years). Three patients consumed alcohol occasionally and only one patient had a chronic alcohol abuse. All patients described limited oral intake. The mean weight loss at the time of acute liver decompensation was 54.5 kg (31-76). The clinical presentation was as follows: fatigue and jaundice in 3 patients, edema of the lower limbs in 3 patients, ascites in one patient and altered coagulation in all patients. Blood tests showed an acute increase in transaminases (mean ALAT 47 UI/L, mean ASAT 81 UI/L), bilirubin (mean 3.75 mg/dL) and INR (mean 1.43) with a low albumin level (mean 24 mg/dL). The hepatic venous pressure gradient was high (mean 9.5 mmHg). Histology revealed severe steatosis (predominantly macrovesicular) in 5 patients and moderate steatosis in 1 patient. Hepatocyte ballooning was present in 4 patients. Mean fibrosis score was 2 (no patient with a F4 score). Interestingly, histological analysis also revealed cholangitis and bile duct alterations in all patients. There was no other cause of acute liver injury. All patients were treated with aggressive nutritional therapy (intravenous albumin supplements, parenteral and/or enteral nutrition, vitamins) as well as diuretics. The clinical course was favorable in all cases (mean time of hospitalization was 29 days), without the need for surgery or transplantation. All patients are still alive with a mean follow-up of 36 months.
Conclusions: Acute liver decompensation in the absence of cirrhosis can occur after bariatric surgery (with a highly variable delay). Hepatic injury is characterized histologically by a unique feature of steatoheptitis with bile duct alterations. Severe

protein malnutrition and bacterial overgrowth are possible candidates for the development of this alarming complication. Substantial clinical improvement with appropriate refeeding seems to be effective.

A10

Altered gut adaptive immune surveillance favors microbial translocation and correlate with progressive alcoholic liver disease in humans

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Introduction: A minority of patients with alcohol use disorder (AUD) develop progressive alcoholic liver disease (ALD) potentially associated with increased microbial translocation (MT), duodenal dysbiosis and gut barrier dysfunction. Gut mucosal T cells act as local gate keepers to protect against microbial invasion. However, their role during ALD in humans is still unknown.

Aim: We aimed to assess the links between gut mucosal T cells, gut adaptive immunity, microbial translocation and ALD progression in AUD patients.

Methods: We included 76 actively drinking AUD patients who follow a highly standardized rehabilitation program and 26 matched healthy controls. Fasting blood samples were obtained at admission and duodenal biopsies within 48 hours that were used to study duodenal T lymphocytes by immunohistochemistry, flow cytometry analysis and RNA Sequencing in sorted T cells. Systemic microbial translocation was measured by ELISA assessing Gram – (soluble CD14) and Gram + (peptidoglycan recognition proteins) serum markers. ALD was clinically staged by Fibroscan® (liver stiffness, controlled attenuation parameter) combined with serum AST, ALT, and CK18-M65. ALD severity was clinically defined as: non-progressive ALD, i.e. no liver disease (normal AST, ALT, CAP $<$ 250 dB/m, no fibrosis, CK18-M65 $<$ 300 U/l); simple steatosis (normal AST, ALT, CAP $>$250 dB/m, no fibrosis, CK18-M65 $<$ 300 U/l) and progressive ALD, i.e. steato-hepatitis, SH (elevated AST, ALT, CAP $>$ 250 dB/m, no fibrosis, CK18-M65 $>$ 300 U/l); steato-fibrosis (SH and significant fibrosis (kPa $>$ 7.6)).

Results: CD3+ T cells were reduced in the duodenal mucosa of AUD patients compared to controls. Within the T cell pool, CD8+, KLRG1- tissue-resident memory cells (TRM) decreased significantly (55% vs 39%; p=0.026) while no changes were observed for CD4+ T cells. Number of CD8+ T cells inversely correlated with serum levels of soluble CD14 (r=-0.6147; p$<$0.05), suggesting their role in microbial immunosurveillance, and their reduction was linked to increased proportion of lymphocytes in end-stage apoptosis (AnnexinV+/DAPI+; 5.1% vs 9.6%; p=0.0069). Presence of apoptotic CD8+ T cells in the duodenal mucosa was confirmed by a TUNEL assay . Remarkably, apoptosis of intestinal CD8+ T lymphocytes increased specifically in the sub-group of patients with progressive liver disease. Principal component analysis revealed different

transcriptomic profiles in TRM in the sub-group of AUD patients with progressive ALD. Interestingly, gene ontology (GO) and KEGG analyses showed enrichment of different gene sets associated with apoptosis, lysosomes, immune regulatory responses and lipid metabolism in AUD with progressive forms of liver disease. Changes in expression of top-ranked genes playing a role in e.g. transcriptional or metabolic regulation of immune cells correlated with increased levels of microbial translocation markers (all $r>0.55$ with $p<0.01$).

Conclusions: Our results point to an impairment of gut adaptive immunity in progressive ALD. They suggest the presence of functional alterations in CD8+ TRM cells in the intestinal mucosa that possibly contributes to gut barrier dysfunction favoring microbial translocation in particular in the sub-set of AUD patients with progressive ALD.

A11

Feasibility of systemic treatment after progression following radioembolization in patients with hepatocellular carcinoma: a retrospective cohort study

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Introduction: Radioembolization (RE) with yttrium-90 resin microspheres for unresectable hepatocellular carcinoma (HCC) can provide clinical benefit for well selected patients, despite disappointing results of recent randomized trials. At the same time, new potent systemic treatment options are emerging, leading to a clinical significant benefit in overall survival.

Aim: We aimed to determine the exact role of RE for HCC in the era of new systemic treatment options by (1) identifying the clinical factors associated with prolonged progression free survival (PFS) following RE and (2) analysing post-progression treatment strategies.

Methods: All patients who underwent RE for unresectable HCC at the University Hospitals Leuven between January 2009 and December 2018 were evaluated retrospectively. Patient and disease characteristics before RE and at time of disease progression were analysed, as well as subsequent treatments. A univariate and multivariable cox regression model was used to test the association between clinical variables and PFS. Survival analysis was done using the Kaplan-Meier method and log-rank test.

Results: 130 patients treated with RE were included in the study with a median follow-up of 5.5 months. Disease control rate using mRECIST was 63.6%. 17 patients got orthotopic liver transplantation. Median PFS was 6.3 months (95% confidence interval (CI) 4.15-8.7), which varied significantly ($p < 0.001$) with ECOG performance status (ECOG 0 20.9 months [95% CI, 8.6-33.2 months]; ECOG 1, 8.5 months [95% CI, 6.1-10.9 months]; ECOG 2, 1.4 months [95% CI, 1.6-7.2 months]). This association remained significant after multivariable testing, together with disease burden as assessed by the number of HCC lesions (HR 1.16 [95% CI 1.03-1.30] ($p = 0.012$)).

Progressive disease after RE occurred in 85 patients, of whom only 41 (48.2%) got a systemic treatment. Again, ECOG PS (and not Child-Pugh or MELD score) at time of progression was significantly better for patients that did receive systemic treatment versus those that did not (p = 0.003). Systemic treatments in first line included sorafenib (n = 30), checkpoint inhibitors (n = 4), chemotherapy (n = 1) and other options.

Conclusions: Patients with unresectable HCC in a good general condition with a limited number of lesions have superior outcomes after radioembolization. After RE, close monitoring of patient performance, liver function and cancer control is warranted to allow timely initiation of systemic treatment options when indicated.

A12

Muscle fat content is strongly associated with NASH and decreases upon NASH resolution: a longitudinal biopsy-proven study in obese patients

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Introduction: Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disease in the world. Non-invasive scores or imaging techniques are increasingly validated to assess steatosis or fibrosis, but cannot distinguish NASH from NAFL. Hence, we need additional tools to assess or delineate patients with or being at-risk for NASH, irrespectively of the fibrosis stage. A large body of literature supports that muscle alterations (i.e. sarcopenia and fatty infiltration) are associated with an increased incidence of non-alcoholic fatty liver disease (NAFLD) and increased NAFLD severity.

Aim: To evaluate the association between sarcopenia, muscle fatty infiltration and biopsy-assessed NAFLD severity in obese patients before and after a therapeutic intervention.

Methods: At inclusion (n=184) and 12 months after a dietary intervention (n=15) or a bariatric surgery (n=22), we evaluated NAFLD with NASH-CRN-scored liver biopsy, skeletal muscle mass index with computed tomography (CT-SMI) and bioelectrical impedance analysis (BIA). We developed an index to evaluate muscle absolute fat content (skeletal muscle fat index or SMFI) from CT-based psoas muscle density and area (SMFI_Psoas).

Results: In the overall cohort, muscle mass was higher in patients with NAFLD than in those without (CT-SMI 56.8±9.9 vs 47.4±6.5 cm^2/m^2, $p<0.0001$). SMFI_Psoas was higher in NASH ≥F2 and also early NASH F0-1 than in NAFL (78.5±23.6 and 73.1±15.6 vs 61.2±12.6 respectively, $p<0.001$). One point in scores for any of the individual cardinal NASH features (i.e. steatosis, inflammation or ballooning) associated with an increased SMFI_Psoas (all $p<0.05$). The association between SMFI_Psoas and NASH was highly significant even after adjustment for multiple confounders in multivariate analysis (all $p<0.025$). After intervention, NASH resolution, achieved in 24 out of 30 patients (80%), associated with a significant decrease in SMFI_Psoas ($p<0.0001$). Strikingly, all patients who had ≥11% reduction in SMFI_Psoas achieved NASH resolution (13/13, $p=0.012$) or ≥2 point reduction in NAS score (15/15, $p<0.025$).
Conclusions: Muscle fat content as evaluated with SMFI_Psoas, but not muscle mass, is strongly and independently associated with NASH. All individuals who achieved a ≥11% decrease in SMFI_Psoas after intervention resolved their NASH. These data prompt us to explore muscle fatty infiltration as a potential marker and perhaps a pathophysiological contributor of NASH.

A13

A profibrotic role for the orphan G-protein coupled receptor 176 during hepatic stellate cell activation

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Introduction: Hepatic stellate cells (HSC) are the major scar forming cells in liver fibrosis. During liver fibrosis, quiescent, vitamin-A-storing, HSCs (qHSC) transdifferentiate to an activated myofibroblast-like phenotype (aHSC) who exert fibrotic characteristics. In recent years, transcriptional profiling of HSCs has provided new insight into the dysregulated transcriptional program of these cells at different stages of disease and etiology. Despite these advances, HSC-targeting drugs are still not used in the clinic, leaving an unmet need.
Aim: In this study we set out to further characterize the transcriptional dysregulation in mouse HSCs during fibrosis by including experimental reversal of liver fibrosis. The inclusion of reversal allowed us to more stringently define genes involved in the pro-fibrotic phenotype of aHSC. From said dysregulated program, we aimed to identify candidate targets for HSC-based anti-fibrotic treatment.
Methods: Experimental fibrosis development was induced by injecting Balb/c mice with carbon tetrachloride (CCl4) twice a week for a total of 4 weeks. Reversal was accomplished by an additional 2 weeks recovery. HSCs were collected from healthy, 4 weeks CCl4-treated and 2-week recovery mouse livers by FACS-based sorting for UV positive cells. Subsequently, RNA was processed for RNA sequencing analysis. Differential gene expression was performed using DESeq2 package in R. For 2D in vitro culture, mouse HSCs were isolated using Nycodenz density gradient. Gpr176 knockdown on cultured mouse HSCs was carried out using Gpr176 specific siRNAs on

days 1 and 5 using scramble siRNAs as a control. Mouse precision cut liver slice (mPCLS) cultures were performed by slicing liver tissue with a vibratome followed by punching into 3mm discs. At the start of the cultures, mPCLSs were transfected with Gpr176 specific siRNAs using scramble siRNAs as a control.
Results: The RNA sequencing analysis shows that after 2 weeks of recovery, HSCs have reverted to a quiescent like phenotype showing upregulation of qHSCs markers Gfap and Ngfr and downregulation of HSC activation markers Acta2, Col1a1 and Lox when compared to 4 weeks CCl4. Only 311 genes were differentially expressed between HSCs from a recovered liver and HSCs from a healthy liver, while activated HSCs (isolated from 4-weeks-CCl4-treated mouse livers) had 1231 differentially expressed genes. Next, we generated a gene set defining the transcriptional dysregulation in mouse aHSCs by including genes that are downregulated during recovery. By excluding genes that remain upregulated during recovery, we pinpoint the dysregulated transcriptional program that, at least, has to be targeted in any future therapeutic experiment. From this gene set, we identified the orphan G protein coupled receptor (GPCR) 176 (Gpr176) as a marker of HSC activation and show that it is conserved in both human and mouse HSC, and across different models of experimental liver disease. Notably, follow up experiments showed that Gpr176 is expressed at a remarkably early timepoint after HSC activation both in vivo and in vitro in mouse (24hours after one CCl4 injection and 10 hours after start of 2D in vitro culture). Additionally, we noted reduced expression of HSC activation markers Acta2, Col1a1, Col3a1 and Lox when performing RNA interference for Gpr176 mRNA in 2D in vitro model of mouse HSC activation as well as in mPCLS cultures.
Conclusions: We provide new insight in an orphan GPCR for which, currently, only limited information exists and place it in a context of chronic liver disease. Gpr176 could potentially exert pro-fibrotic characteristics which marks it as a potential novel target for liver fibrosis. In vivo experiments using Gpr176 knock-out mice are currently ongoing to confirm this hypothesis.

A14
Contribution of monocytes to systemic inflammation in alcohol use disorder patients
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Introduction: Systemic inflammation, increased plasma levels of pro-inflammatory cytokines IL-1β, IL-8, IL-18, IL-6 and TNF-α and an increased microbial translocation of both gram+ and gram- bacteria have been previously reported in subjects with an alcohol use disorder (AUD) compared to healthy volunteers. Activation of PBMCs could contribute to the development of systemic inflammation by reacting against gut-derived bacterial products. Among those cells, monocytes hold the highest potential to secrete in high amount the pro-inflammatory cytokines IL-1β, IL-8, IL-18.

Aim: We aimed to assess the potential role of monocytes in the development of the systemic inflammation and whether this might relate to liver disease especially at early stages.
Methods: We included 27 AUD patients (they are non-cirrhotic and actively drinking) and 10 healthy subjects matched for their age, weight, height, BMI and gender. We determined the total number of monocytes in the blood, separated the peripheral blood mononuclear cell (PBMCs) fraction and then isolated monocytes by magnetic cell sorting (MACS). The proportion of each subpopulations of monocytes was determined by fluorescence activated cell sorting (FACS) according to their expression of specific surface markers CD14 and CD16. Serum PGRPs and sCD14 levels were measured by ELISA as surrogate markers for microbial translocation of gram+ and gram- bacteria, respectively. Gene expression of pro-inflammatory cytokines was measured in isolated monocytes by qPCR and their serum levels using a customized multiplex assay kit. We analysed correlations between monocytes, cytokines, bacterial translocation and liver disease stages. Liver disease stages were determined based on clinical parameters taking into account AST, ALT, controlled attenuation parameter (CAP), liver elasticity measured by Fibroscan™, as well as the serum liver damage marker K18-m65.
Results: The number of blood monocytes significantly increased in AUD patients compared to healthy subjects ($p < 0.0001$). Among the 3 monocyte subpopulations identified by FACS, the proportion of intermediate (CD14++,CD16+) and non-classical (CD14+,CD16++) monocytes significantly increased while the proportion of classical monocytes (CD14++,CD16+/-) decreased in AUD patients compared to controls. Remarkably, monocytes from AUD patients express higher mRNA levels of the proinflammatory cytokines IL-1β and IL-8 compared to monocytes from healthy subjects, while gene expression of IL-18, TNF-α and IL-6 did not change significantly. Serum bacterial translocation markers, PGRPs and sCD14, were higher in AUD patients compared to controls. Intriguingly, transcription of IL-1β positively correlated with the total number of monocytes and serum sCD14 levels while the proportion of intermediate monocytes positively correlated with the systemic translocation of gram+ bacteria. Finally, we assessed levels of circulating IL-8, IL-6 and TNF-α and found an increased levels of these pro-inflammatory cytokines in AUD patients compared to controls. Interestingly, the serum levels of IL-8, IL-6 and TNF-α positively correlated with the serum level of sCD14. No correlations between the number, proportions or cytokine production of monocytes and different stages of liver disease were found.
Conclusions: The results support the implication of monocytes in AUD induced systemic inflammation. AUD patients have increased number of circulating monocytes, alterations in the proportion of the different subsets and activation by gram+ products as well as upregulation of IL-1β and IL-8. Each and all of these features may contribute to systemic inflammation. By contrast, they did not correlate with liver disease stages.

A15
Characterization of the inflammatory microenvironment and hepatic macrophage subsets in experimental hepatocellular carcinoma models

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Introduction: Hepatocellular carcinoma (HCC) typically develops on a background of chronic inflammation and fibrosis with tumor associated macrophages (TAMs) playing an important role in chronic inflammation-induced HCC and progression.

Aim: In this study, we assessed the time-dependent characteristics of the inflammatory micro-environment in two frequently used HCC mouse models, with an emphasis on the differential transcriptional profile of liver macrophage (Mϕ)subsets and the sequential changes in phenotype during the progression of HCC. The resulting understanding of Mϕ function and the implicated immune and metabolic pathways pave the way for targeting these Mϕ in the treatment of HCC, which is a field of considerable interest

Methods: Diethylnitrosamine (DEN) was administered weekly to male 129/Sv mice for 30 weeks. C57BL/6J mice were injected subcutaneously with 200 µg streptozotocin 2 days after birth and were fed a high-fat, high-sucrose, high-cholesterol diet from 4 to 16 weeks of age. The hepatic Mϕ population was analyzed by flow cytometry and the transcriptional profile of liver-isolated Kupffer cells (KCs), monocyte-derived macrophages (Mo-Mϕ) and infiltrating monocytes (Mo) and full liver tissue was evaluated by RNA sequencing at different time points.

Results: A gradually increased expression of inflammatory, immune regulatory, fibrotic and cell proliferation pathways and markers was observed during DEN- and non-alcoholic steatohepatitis (NASH)-induced HCC development. The transcriptional phenotypes of isolated hepatic Mϕ subsets were clearly distinct, with mixed pro-inflammatory and tumor-promoting expression profiles. There were marked differences between the models as well, with Mϕ in NASH-HCC exhibiting a more immunomodulatory phenotype, in conjunction with an upregulation of lipid metabolism genes.

Conclusions: Resident KCs and infiltrating Mo and Mo-Mϕ have divergent phenotypes that change during HCC progression with mixed expression of markers linked to TAMs. These insights are useful to further unravel sequential pathogenic events during hepatocarcinogenesis and direct future development of new treatment strategies for HCC.

A16

Has the 5-year mortality of patients with alcoholic cirrhosis changed during the last 20 years? … The reality is that patients die just as much, but in a different way

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Introduction: Patients with alcoholic cirrhosis have a poor short-term prognosis. Indeed, 5-year mortality may exceed 50%.

Aim: The aim of this study was to determine whether the 5-year mortality of alcoholic cirrhosis has changed over the past two decades.

Methods: From January 1995 to December 2014, 932 cirrhotic patients who attended the hepatology outpatient clinic of our institution were consecutively listed in a registry. From this registry, 565 patients had alcoholic cirrhosis (61%). 16 patients were excluded because they were loss to follow-up and 114 patients were excluded because the diagnosis of cirrhosis was made more than 2 years before the inclusion in the registry. We separated the 435 remaining patients into two cohorts 10 years apart: the cohort C1 (C1), patients included in the registry between 1995 and 2004 (n= 206) and the cohort C2 (C2), patients included from 2005 to 2014 (n= 229). Epidemiologic data and 5-year mortality were retrospectively compared between both cohorts.

Results: The sex ratio was similar between both cohorts (C1: male 68% vs C2: male 71%) as well as the Child Pugh score at inclusion in the registry (C1: 7,28 vs C2: 7). By contrast, the mean age at diagnosis of cirrhosis was significantly higher in the cohort C2 than in the cohort C1 (C1: 52,8 ± 11 years vs C2: 56,5 ± 9,3 years, $p<0.0001$). From the 206 patients in the cohort C1, 80 died within 5 years after diagnosis of cirrhosis compared to 83 patients from the 229 patients in the cohort C2 (C1: 39% vs C2: 36%, p= 0.6). When the circumstances of 5-year mortality were compared between the 80 patients from the cohort C1 (Group A) and the 83 patients from the cohort C2 (Group B), the liver-related mortality rate was similar between both groups (Group A: 64 of 80 patients (80%) vs group B: 65 of 80 patients amongst whom the cause of death was known (81%), p=0.8). Among those patients who died from their cirrhosis, liver-related mortality by end-stage liver disease without precipitating event was not statistically different between both groups (Group A: 36% vs Group B: 29%, p=0.4). However liver-related mortality precipitated by an acute event was different according to the underlying precipitating event. Patients in Group A died more often from gastrointestinal bleeding than patients in Group B (Group A: 30% vs Group B: 9% p=0.003). Patients in Group A died less by sepsis than patients in Group B (Group 1: 1,5% vs Group 2: 14% p=0.009). There were no statistically differences concerning liver-related death precipitated by alcoholic hepatitis (Group 1: 17% vs Group 2: 18% p=0.8) or hepatocellular carcinoma (Group 1: 9% vs Group 2: 15%, p=0.3)

Conclusions: Our study demonstrated that the 5-year mortality rate in patients with alcoholic cirrhosis has not changed over the past two decades. It remains around 40% and 80% of these patients die from their liver disease. The mortality rate by end-stage liver disease without precipitating event has not changed and is around 30%. By contrast, the type of precipitating events which lead to liver-related death has changed

with a rarefaction of mortality provoked by acute gastrointestinal bleeding, but an increase of mortality by sepsis. Mortality by severe alcoholic hepatitis and hepatocellular carcinoma has not changed.

A17

Comparison of clinicobiochemical risk scores versus ultrasound for steatosis detection in subjects with type 1 diabetes

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Introduction: Data are limited concerning the value of scores based on clinical and biochemical parameters to diagnose NAFLD in type 1 diabetes (T1D).

Aim: We aimed to evaluate the effectiveness of controlled attenuation parameter (CAP), Hepatic Steatosis Index (HSI) and Fatty Liver Index (FLI) compared to conventional ultrasound (US) as reference method in a study of 407 subjects with T1D.

Methods: Adult T1D subjects were screened for NAFLD using simultaneously US, CAP (criterion for NAFLD diagnosis: ≥215 dB/m on M probe or ≥250 dB/m on XL probe according to skin-liver capsule distance), FLI (criterion for NAFLD diagnosis ≥60) AND HSI (criterion for NAFLD diagnosis ≥36). We subtracted 2 points from each HSI score to correct for diabetes, since it gives weight to the presence of diabetes.

Results: 407 adult subjects were included (male sex proportion: 56.8%, age 46 (IQR: 29) years, HbA1c 7.5 ± 1.0 %, BMI 25.5 ± 4.0 kg/m2, diabetes duration 26.3 ± 14.2 years, metabolic syndrome proportion: 31.7%). The prevalence of NAFLD was 20.4% based on US, 52.1% based on CAP, 43.8% based on HSI and 18.3% based on FLI. There was strong correlation between HSI and FLI (r:0.724, p<0.001), moderate correlation between FLI and CAP (r:0.578, p<0.005) and between HSI and CAP (r:0.400, p<0.001) and weak correlation between US and CAP (r: 0290, p<0.001). FLI and HSI (k: 0.395, p<0.001), HSI and CAP (k: 0.246, p<0.001) and US and CAP (k: 0.228, p<0.001) showed fair agreement, while FLI and CAP showed slight agreement (kappa: 0.177, p<0.001). Sensitivity of CAP versus US was 81%, specificity: 55%, PPV: 32%, NPV: 92%. AUROC for CAP yielded 0.77 [0.71-0.82], p<0.001. Sensitivity of FLI versus US was 52%, specificity: 90%, PPV: 58%, NPV: 88%. AUROC for FLI yielded 0.79 [0.73-0.85], p<0.001. Sensitivity of HSI versus US was 76%, specificity: 64%, PPV: 35%, NPV: 92%. AUROC for HSI yielded 0.74 [0.68-0.80], p<0.001. All tests correlated moderately with the metabolic syndrome (HSI r:0.433, p<0.001, CAP r:0.135, p<0.001), except the FLI, which correlated more strongly (FLI r:0.568, p<0.001). In logistic regression analysis, adjusting for age, gender, systolic and diastolic blood pressure or antihypertensive drug use, HDL-c and triglycerides levels, FLI (OR:1.04 [1.03-10.6];p<0.001), CAP (OR:1.02 [0.01-1.02], p<0.001) and HSI (OR:1.17 [1.11-1.24], p<0.001) were all associated with US-determined NAFLD.

Conclusions: Based on US, NAFLD seems prevalent in T1D. Clinicobiochemical scores show moderate diagnostic accuracy compared to US to determine NAFLD in this pilot

study. Mutual agreement between diagnostic tools is moderate, stressing the need for more specific diagnostic tools in subjects withT1D.

A18

The prevalence of NAFLD in a cohort of type 1 diabetes subjects based on non-invasive assessment and its association with macrovascular complications

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Introduction: The association between NAFLD and cardiovascular disease has been observed in type 2 diabetes but data in type 1 diabetes mellitus (T1DM) are scarce.
Aim: This study aimed to compare the prevalence of NAFLD according to ultrasound (US), fatty liver index (FLI) and controlled attenuation parameter (CAP) within the same cohort and evaluate the association of fatty liver disease with prevalent macrovascular cardiovascular disease (CVD).
Methods: Adult T1DM subjects were consecutively screened for NAFLD using US, FLI and CAP. Cardiovascular events were defined as prevalent ischemic coronary, peripheral arterial or cerebrovascular events. Causes of secondary liver disease including excess alcohol intake were systematically excluded.
Results: 400 adult subjects with T1DM were included (age 47±30y, HbA1c 7.4±1.0%, BMI 26.2±5.2kg/m2, diabetes duration 27±14y). The prevalence of NAFLD was 22.8% (US), 22.3% (FLI≥60), and 34.6% (CAP≥248dB/m). Furthermore, 27 (6.8%) coronary, 18 (4.5%) peripheral arterial, 9 (2.3%) cerebrovascular and 44 (11.0%) composite events were documented. NAFLD defined by either US (OR 2.18 [1.07-4.44], p=0.032) or FLI (OR 2.78 [1.39-5.56], p=0.004), but not by CAP was independently associated with composite cardiovascular events, besides diabetes duration (OR:2.18 [1.08-4.44], p<0.001(US) and OR:2.78 [1.39-5.56], p=0.004 (FLI)) and HDL (OR:0.97[0.95-0.99]; p=0.006 (US only)) when including these variables and age, HbA1c, hypertension and waist circumference in the regression model.
Conclusions: Non-invasive tools diagnose NAFLD in T1DM in 22-23% using US or FLI. CAP suggested a higher prevalence, illustrating the need to further explore the diagnostic accuracy of this tool in T1DM patients. Presence of NAFLD diagnosed based on US and FLI, but not on CAP, is independently correlated with prevalent cardiovascular events in T1DM patients, corroborating data in T2DM and metabolic syndrome patients about the potential independent role of NAFLD in the development of CVD.

A19

The effects of oral bosentan treatment on the increased intrahepatic vascular resistance and disease severity in high fat high fructose diet-fed Zucker fatty rats with hepatic steatosis

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Introduction: The intrahepatic vascular resistance (IHVR) is increased in early non-alcoholic fatty liver disease (NAFLD), impairing hepatic blood flow and potentially causing tissue hypoxia and disease progression. We previously demonstrated that this increase in IHVR is in part mediated by vascular hypersensitivity to endothelin-1 (ET-1) and the ability of Bosentan (BOS, a dual ET receptor antagonist) to decrease the transhepatic pressure gradient (THPG) in methionine-choline-deficient (MCD)-fed Wistar rats (Van der Graaff et al., AGEB 2020;83(1):A24; Van der Graaff et al., J Hep 2020;73(1):SAT012).
Aim: The aim of this study was to analyse the potential benefit of BOS on liver haemodynamics and concurrent severity of disease in a different model of early NAFLD.
Methods: The effects of ET-1 inhibition were studied in Zucker Fatty rats (ZFR) (n=8/group) fed a HFHFD during 4 weeks, which develop severe hepatic steatosis, or lean Zucker rats after 4 weeks of control diet. Rats were gavaged daily with 100 mg/kg BOS or placebo during the complete 4 weeks of diet. The IHVR was studied by measuring the transhepatic pressure gradient (THPG) in an in situ ex vivo perfusion model at different flows (10-50 mL/min). Blood samples were collected before liver perfusion to determine transaminase levels. At the end of the experiment, the liver was weighed and harvested for histology.
Results: The baseline THPG in ZFR was significantly increased compared to controls independent of flow (ZFR 7.4±0.5 mmHg vs. controls 5.1±0.6 mmHg at 30 mL/min, $p<0.01$). After preventive BOS treatment, the THPG in ZFR showed lower values at higher flows compared to placebo-treated ZFR, most prominent at 45 mL/min, but without reaching statistical significance (BOS-treated 9.9 ± 0.6 mmHg vs. placebo-treated 11.4 ± 1.0 mmHg, $p=0.162$). After 4 weeks of HFHFD, body and liver weight increased significantly compared to controls (ZFR 468.1 ± 10.3 g vs. controls 294.4 ± 8.9 g, $p<0.001$; liver/total body weight-ratio: ZFR 4.6 ± 0.1% vs. controls 3.9 ± 0.2%, $p<0.05$. BOS treatment did not affect liver nor total body weight. ALT and AST levels were significantly increased in ZFR compared to controls (ALT: ZFR 119.2 ± 12.1 vs. controls 31.0 ± 7.0, $p<0.05$; AST: ZFR 257.0 ± 40.1 vs. controls 70.5 ± 5.1, $p<0.001$). Preventive BOS treatment significantly decreased AST levels to the level of controls (BOS-treated ZFR 69.0±9.0 U/L, $p<0.001$ compared to placebo-treated ZFR and $p=1.00$ compared to controls) and induced a non-significant decrease of ALT levels. Histology in ZFR demonstrated moderate hepatic steatosis without features of NASH or fibrosis. The degree of steatosis (% fat of total liver surface) was significantly lower in preventively BOS-treated ZFRs compared to ZFR with placebo treatment.
Conclusions: In hepatic steatosis, a significantly increased THPG was observed, which could be attenuated by BOS treatment. This effect goes along with a decrease in steatosis and a decrease of transaminase levels in the absence of any effect on body weight. These data replicate our previous observations in another model and corroborate the role of ET-1-related vascular alterations in NASH pathogenesis and its

potential as a therapeutic target. These findings hence support the concept that the intrahepatic vascular changes and the effects of BOS are disease-related phenomena and not model-specific.

A20

Lower abundance of Clostridium sensu stricto is associated with liver steatosis and fibrosis severity in a prospective cohort of obese patients with metabolic dysfunction-associated fatty liver disease

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Introduction: There is an increasing evidence for the role of the gut microbiota in the pathogenesis of obesity, insulin resistance and metabolic dysfunction-associated fatty liver disease (MAFLD). Deciphering the bacterial signature associated with liver alterations would be interesting as a new indicator for MAFLD pathogenesis.

Aim: Here, we describe the microbiome composition of a cohort of obese patients well characterized for MAFLD severity (i.e. steatosis and fibrosis degree) and link them with other obesity-related extra-hepatic alterations.

Methods: Obese patients recruited prospectively at St-Luc Hospital (FOOD4GUT project) were included. Liver stiffness (LSM) and controlled attenuation parameter (CAP) measurements were performed using liver transient elastography (TE). Physical examination, blood and stool samples and computed tomography (CT) were also assessed. The fecal gut microbiota was analyzed by Illumina sequencing of the 16S rRNA gene.

Results: Stool samples were available for 37 patients. Liver TE allowed us to classify the patients in three groups based on CAP and LSM: LS (low steatosis defined as CAP < 296 dB/m, n=10), HS (high steatosis defined as CAP ≥ 296 dB/m, n=18) and HS+F (high steatosis + fibrosis defined as CAP ≥ 296 dB/m and LSM ≥ 7.8 kPa with M probe or ≥ 6.4 kPa with XL probe, n=9). Both α- and β- diversity indices of the overall gut microbiota composition were not different between the three groups. Moreover, no changes in the gut microbiota composition were observed at the phylum level between the three groups. At the taxa level, only Clostridium sensu stricto significantly decreased with the severity of liver steatosis and fibrosis ($p=0.021$ for HS+F vs HS and $p=0.002$ for HS+F vs LS). Microbes discriminant for liver alterations were determined through a pairwise comparison using linear discriminant analysis effect size (LEfSe) analysis. For the LS-HS comparison, Flavonifractor and Faecalibacterium are more represented in the HS group. Regarding the HS and HS+F comparison, we interestingly

found that Clostridium sensu stricto characterized the HS group (without fibrosis) whereas Escherichia/Shigella are more represented in the gut microbiota from subjects with fibrosis. An analysis based on amplicon sequence variants (ASV) revealed 19 bacterial sequences significantly affected according to liver steatosis and/or fibrosis. Among them, Spearman's correlations showed that C. sensu stricto was significantly negatively associated with LSM, CAP, the waist to hip ratio and muscle fat infiltration evaluated by muscle density on CT.
Conclusions: Our study allowed us to elaborate the link between MAFLD severity and extra-hepatic alterations incriminating adiposity, skeletal muscle dysfunction and the gut microbiome. We identified Clostridium sensu stricto as the only genus decreasing with the development of steatosis and fibrosis. This genus also negatively correlated abdominal adiposity and muscle fat infiltration. Those data suggest a gut-liver-muscle axis in the pathogenesis of MAFLD complications.

A21
Endothelin receptor antagonist bosentan improves microvascular structural disruption in a rat model of early NAFLD
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Introduction: The intrahepatic vascular resistance (IHVR) is increased in early non-alcoholic fatty liver disease (NAFLD), impairing hepatic blood flow and potentially causing tissue hypoxia and disease progression. We previously demonstrated that this increase in IHVR is partially dynamic, mainly mediated by hyperreactivity to vasoconstriction, which could be attenuated by the dual endothelin receptor antagonist bosentan, the cyclo-oxygenase 2-inhibitor celecoxib and the angiotensin receptor blocker valsartan. We also demonstrated structural alterations of the sinusoidal vascular bed. Whether the drugs also affect these structural alterations, is to date unknown.
Aim: The aim of this study was to analyse the structural effects of vasoconstrictor antagonism in early NAFLD.
Methods: Male Wistar rats (n=8/group) were fed either a methionine-choline-deficient (MCD) or control diet, the former inducing severe steatosis after 4 weeks of diet. Rats were gavaged daily with 100 mg/kg bosentan, 30 mg/kg celecoxib, 30 mg/kg valsartan or placebo during the complete 4 weeks of diet. Corrosion casts of the intrahepatic vasculature were constructed. Briefly, animals were anaesthetized, underwent median laparotomy and a 26G catheter was inserted into the ileocolic vein. Twenty millilitre of freshly prepared Batson's no. 17 solution was subsequently injected. Animal bodies were immersed for 30 min in tepid water during polymerization and were macerated overnight in 25% potassium hydroxide. The vascular corrosion casts were rinsed and

samples of the casts were then mounted on a metal stub, coated with platinum and examined systematically with scanning electron microscopy (SEM).
Results: SEM of vascular corrosion casts demonstrated a sinusoidal pattern that was well-organised with a regular pattern in lobules in livers of control rats. In steatosis (MCD diet-fed rats), all livers demonstrated a disruption of the regular sinusoidal pattern, resulting in a disorganised tangle of vessels. Furthermore, many vessels appeared to branch into dead-ending dilated vessel stumps, known as blebs. None of the 3 treatments affected the microvascular structure in controls. In MCD diet-fed rats, when treated with bosentan, the disorganisation caused by the steatosis improved remarkably, compared to what was observed in placebo-treated MCD-fed rat livers. The pattern regained regularity, was less tangled and was strongly reminiscent to that of the livers of control diet-fed rats. Likewise, a clear decrease in the number of blebs was observed. Neither celecoxib nor valsartan treatment improved the disrupted structure of the hepatic microvasculature in MCD diet-fed rat livers.
Conclusions: The hepatic microvascular structure in severe steatosis is extensively disrupted compared to controls, confirming previous observations. Besides the beneficial effects on the increased IHVR, bosentan restores these structural disturbances in the vascular organisation that develop under steatosis. Thus, blocking ET receptors tackles different disease features simultaneously and is therefore a potentially promising therapeutic target in early NAFLD.

A22

The prevalence of disorders of the gut brain axis in type 2 diabetes mellitus with non-alcoholic fatty liver disease: preliminary results from an observational study.

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Introduction: While the exact pathophysiology of disorders of gut-brain axis (DGBI) remain unclear, alterations of the gut microbiome are regarded as a potential treatment target. As dysbiosis has been described in non-alcoholic liver disease (NAFLD), it was hypothesized that the prevalence of DGBI would be higher in patients with NAFLD.
Aim: To determine the prevalence of disorders of the gut-brain axis (DGBI) in non-alcoholic fatty liver disease (NAFLD) patients.
Methods: In this observational study consecutive patients with type 2 diabetes (T2DM) aged 18 - 75 years old were prospectively included and categorized according to the presence (S+) or absence (S-) of steatosis on imaging. Functional dyspepsia (FD) and irritable bowel syndrome (IBS) were defined according to the ROME IV criteria. Demographics, T2DM related specifics and liver test results were recorded. Fibrosis-4 score (FIB-4) was calculated. Quality of life and presence of anxiety and depression were evaluated by resp. the IBS-QOL and the Hospital anxiety and depression scale (HADS). Prevalence was compared by Fisher exact test and continuous variables by t-test.
Results: Till now, sixty seven patients are included in our study (S+ 41, S- 26), with a male predominance (S+ 61,0% vs. S- 61,5%, p=ns). ALT was found to be significantly

higher in the S+ vs the S- group (36.1±18.8 vs. 23.4±9.1, p=.001). There were no differences in age, body mass index (BMI), waist circumference, FIB-4, HbA1c levels or metformin use between the 2 groups. When combining FD and IBS, DGBIs were significantly more prevalent in women (38.5% vs. 14.6%, p=.039). DGBIs were significantly more frequent in S+ vs. the S- group (34,1% vs. 7.7%, p=.018), with a tendency to more frequent IBS in S+ vs. the S- group (22.0% vs. 3.8%, p=.075), but not FD. Scores on the HADS and the overall IBS-QOL remained comparable, while QOL sub scores for health worry and food avoidance were significantly higher in the S+ vs. the S- group (resp. 15.7±23.2 vs. 5.4±15.3, p=.034 and 21.7±25.1 vs. 8.3±21.0, p=.021).
Conclusions: These preliminary results underscore a higher prevalence of DGBI in the presence of steatosis in T2DM patients, with impact on specific quality of life subscales. While higher levels of ALT were confirmed in the steatosis group, anxiety and depression scores remained comparable. Further inclusion should confirm these results in IBS and FD separately. Future studies should focus on the underlying mechanisms, which could include microbiome alterations.

A23

Local control of hepatocellular carcinoma and colorectal liver metastases after microwave ablation only without concomitant hepatectomy

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Introduction: Microwave ablation (MWA) is an accepted alternative to hepatectomy in the treatment of hepatocellular carcinoma (HCC) and colorectal liver metastases (CRLM), within certain clinical and anatomical contexts. The advantage of being less cumbersome comes at the cost of a higher local recurrence rate. The evaluation of the local efficacy is challenging, particularly when MWA is combined with hepatectomies or other surgeries which is a source of heterogeneity between studies.
Aim: The primary endpoint of this single-centre retrospective study was to evaluate the local efficacy of MWA.
Methods: Laparoscopic and open MWA for HCC and CRLM were considered. In order to better evaluate the ablative outcomes, combined procedures were excluded.
Results: A total of 47 patients and 70 tumours were treated. After a median follow-up of 26 months (interquartile range: 12-40) incomplete ablation rate was 8.6% and local recurrence rate was 29.4% on the analysis per tumour. By multivariable analysis, vascular proximity (OR3.4; 95% CI 1.26-9.22; p=0.016) was a predictor of incomplete ablation or local recurrence, while superficial location of the tumour had a protective effect (OR0.32; 95%CI 0.11-0.96; p=0.041).
Conclusions: MWA is a useful tool for the treatment of hepatic malignancies but local tumour recurrence remains an issue.

A24

Retrospective Audit of the Quality of Intraoperative Cholangiogram during Laparoscopic Cholecystectomy

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Introduction: Intraoperative cholangiograms are performed during laparoscopic cholecystectomy to identify bile duct stones, delineate biliary anatomy, and prevent bile duct injuries. The quality of intraoperative cholangiograms has never been previously audited and there are currently no standardized criteria to achieve this.

Aim: The primary aim is to assess the quality of intraoperative cholangiograms performed at a secondary center using consensus criteria. The secondary aim is to determine the interobserver reliability of the criteria used to assess the quality of intraoperative cholangiograms.

Methods: A retrospective audit of patients who underwent laparoscopic cholecystectomy and intraoperative cholangiogram in 2016 at a single secondary center was performed. De-identified images were downloaded and interpreted independently by two final year trainee surgeons using consensus criteria. Descriptive statistics were used to determine percentage fulfilment of each criteria. Interobserver reliability was assessed using percentage agreement and Cohen's kappa.

Results: Over this period, 123 out of 243 (50.6%) laparoscopic cholecystectomies were performed with intraoperative cholangiogram. The most fulfilled criteria as determined by the two trainee surgeons was the observation of terminal narrowing of the common bile duct (95.9%) and the presence of the cystic duct (99.2%) respectively. Both observers determined that having no instruments obstructing the view of the ducts was the least fulfilled criteria (56.1% and 49.6% respectively). The criteria with the greatest interobserver reliability was the visualization of free-flowing contrast into the duodenum (97.6% agreement; $k=0.759$, $p<0.001$).

Conclusions: The quality of intraoperative cholangiograms is currently suboptimal and can be improved. Our audit criteria has good interobserver reliability and can also be used to establish the quality of intraoperative cholangiograms at other hospitals.

A25

The role of estimated glucose disposal rate (eGDR) as a predictor of insulin resistance, NAFLD and cardiovascular complications

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Introduction: Subjects with type 1 diabetes (T1D) have an increased risk of cardiovascular disease (CVD), which may be accelerated by insulin resistance and/or nonalcoholic fatty liver disease (NAFLD), both classically associated with type 2 but not type 1 diabetes, the latter normally being insulin sensitive. Estimated glucose disposal rate (eGDR) correlates well with the euglycaemic clamp, which is the gold standard to assess insulin resistance but is unsuited for use in routine clinical practice.

Aim: We aimed to assess the association between eGDR, NAFLD and macrovascular CVD in patients living with T1DM.

Methods: Adult T1D subjects were consecutively screened for NAFLD using ultrasound (US), Fatty Liver Index (FLI) and controlled attenuation parameter (CAP). Secondary causes of liver disease where excluded. The eGDR was calculated based on a validated formula including hypertension, HbA1c and waist circumference in the equation. CVD was assessed based on prevalent ischemic coronary disease, peripheral artery disease or cerebrovascular disease.
Results: Macrovascular CVD was present in 34 out of 355 eligible subjects. Divided into tertiles (<5.39,5.39-7.79,>7.79), 36.6% expressed low eGDR; 32.7% intermediate eGDR and 30.7% high eGDR. There was moderate correlation between eGDR and FLI ($r=0.68, p<0.001$) and weak correlation with US ($r=0.33, p<0.001$) and CAP ($r=0.50, p<0.001$). In the low eGDR group (=insulin resistant group) not only steatosis (38.5% vs. 11.2% (intermediate eGDR) and 12.8% (high eGDR)) but also composite CVD (18.5% vs. 6.0% and 2.8%) were significantly more present ($p<0.001$ for both). Low eGDR (OR:4.2[2.2-8.2],$p<0.001$), but not BMI or dyslipidaemia, was independently associated with fatty liver disease based on US. Low eGDR was also independently associated with FLI-determined steatosis (OR:5.5[1.7-17.6],$p=0.004$) together with BMI (OR:1.6[1.4-1.9],$p<0.001$). Low eGDR (OR:8.0[2.3-27.4],$p=0.001$) and liver steatosis (OR:2.7[1.2-6.1],$p=0.022$ (US-defined), OR:2.9[1.4-6.0],$p=0.005$ (FLI-defined)) were independently associated with composite CVD, but presence of metabolic syndrome, dyslipidemia and BMI were not.
Conclusions: Insulin resistance is not uncommon in patients with T1D. eGDR correlates with the presence of liver steatosis. Both eGDR and liver steatosis correlate with prevalent CVD independently of other classical CVD risk factors, suggesting their independent contribution to the development of CVD.

A26

Ascitic fluid infection in patients with chronic liver disease: A single center study

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Introduction: Ascites is a common problem in patients with chronic liver disease. About 60% of patients with cirrhosis will develop ascites. Patients with chronic liver disease and cirrhosis frequently develop ascitic fluid infection.
Aim: The aim of this study is to assess the frequency, clinical profile, bacteriologic patterns and outcome of ascitic fluid infections in patients with chronic liver disease admitted to Ain Shams University hospital. The study will also investigate the bacterial isolates and antibiotic sensitivity and resistance patterns in patients with ascitic fluid infections
Methods: The current study included a cross-sectional component to assess the prevalence, etiology and clinical presentation of ascitic fluid infections at Ain Shams University hospital and a longitudinal component to investigate the antibiotic sensitivity and outcome of ascitic fluid infections. All patients were subjected to detailed history taking, clinical examination, biochemical assessment and imaging studies.

Results: A total of 87 Egyptian patients with chronic liver disease and ascites were enrolled and followed during a 12-months period. The prevalence of infected ascites among the studied patients with chronic liver disease and ascites was 31%. The main symptoms and signs of patients with infected ascites were abdominal pain (37%), lower limb edema (81%) and fever (30%). Almost one third of the ascitic patients developed at least one attack of spontaneous bacterial peritonitis or bacterascites. Monomicrobial bacterascites is more frequent than polymicrobial bacterascites and E coli is the most common isolated organism. Among patients with infected ascites, 12 patients (44%) responded to the third generation cephalosporins and nine patients (33%) responded to Meropenem.
Conclusions: Ascitic fluid infection is frequent among patients with chronic liver disease. E coli is the most frequent organism associated with ascitic fluid infection. Third-generation cephalosporins is an efficient initial therapy for patients with different forms of infected ascites. Alternative antibiotics such as Meropenem and pipercillin-tazobactam should be considered for patients who do not respond to cephalosporins.

A27

Increased prevalence of hepatitis C in patients admitted in psychiatric centres

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Introduction: Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infections are common causes of chronic liver injury worldwide, leading to significant morbidity and mortality. HIV has similar routes of transmission. Major advances have been made during recent years in the prevention and treatment of these blood-borne viruses (BBV). We have vaccinations for HBV and effective suppressive antiviral drugs for HBV and HIV. Recent development of direct-acting antivirals (DAA's) made HCV a curable disease. In 2016, the World Health Organization set the target to eliminate viral hepatitis as a public health threat by 2030. The biggest barrier to HBV and HCV elimination results from the high proportion of undiagnosed patients with chronic HBV and HCV, accounting for more than half of them. Although risk factors for transmission and infection are well known and we have guidelines on testing strategies, it seems hard to reach and detect infected patients. In Europe, especially people who inject drugs (PWID) and men who have sex with men (MSM), migrants and incarcerated people remain at high risk for HBV and HCV infection. Several recent data indicate that, although not mentioned as a high-risk group, people with serious mental illnesses (SMI) are at increased risk for infection with BBV. Presence of a SMI is not an isolated risk factor, but has a potentially confounded association with poor socioeconomic background, drug or alcohol abuse. Data on this subject, especially in Europe, are scarce.
Aim: The primary objective of this study is to document the prevalence of HBV, HCV and HIV in psychiatric patients in a hospital setting and forensic psychiatric centers.

Prevalence data will be compared to data from the general Belgian population. The secondary objective is to explore risk factors associated with these viral infections, hereby elucidating a need for selective or general screening strategy for the psychiatric population.

Methods: Between 2018 and 2020, all adult patients hospitalized in 5 Belgian psychiatric hospitals were approached and offered BBV tests. All participants were provided with an information leaflet and a written account and questioned on behavioral risk factors for BBV infection (history of drug abuse, unsafe tattoo or piercing, sexual risk behavior, living with infected people). Serological data from patients residing in 2 Belgian forensic psychiatric centres (FPC) between 2017 and 2019 were collected as well. Data on 881 patients were analyzed, of which 421 residing in a FPC. Prevalence data on HBC, HCV and HIV were compared to data in the general Belgian population. Possible differences in prevalence were analyzed, depending on psychiatric diagnoses, risk factors, demographic data. New infections were referred for further examination and management.

Results: A total of 881 patients aged between 18 and 83 years (mean 42,2) were included, mostly being male (74,6%). 9/833 were HBsAg + (1,1%) and 282/833 were HBsAb+ (33,9%), 55/832 were HBcAb + (6,6%). Seroprevalence for HCV was 5,1% (43/836), with viremia in 37,5 % of the cases (15/40, unknown for 3 patients). HIV antibodies were found in 4/825 (0,5%). Prevalence of chronic HBV (1,1%) was not significantly higher compared to the general Belgian population (0,7%) (p=0,099). HIV seropositivity was significantly higher (0,5% compared to 0,17%, p=0,038) in the overall group, but not after exclusion of FPC (p=0,178). Conflicting data exist on HCV seroprevalence in the general Belgian population (between 0,12 and 0,71%), though in this psychiatric population a statistically siginificant higher seroprevalence was found (5,1%, p<0,001), even after exclusion of patients residing in FPC (p<0,001). HCV seroprevalence was higher (6,0%) in male compared to female patients (2,4%) (p=0,044). No significant differences in HBV, HIV or HCV prevalence could be found between different psychiatric diagnoses. A history of unsafe tattooing or piercing (p=0,012) and living with someone with BBV (p=0,028) were found to be related to significant higher prevalence on HCV, sexual risk behavior and intravenously or intranasally drug abuse were not.

Conclusions: Psychiatric patients show a higher prevalence of HCV infection, unrelated to the psychiatric diagnosis. Based on these result, we recommend a general screening on HCV in all psychiatric hospitalized patients.

Belgian Network on Gastrointestinal Regulatory Mechanisms (GIREM)

B01

Enteric glia cell and macrophage interaction in health and disease

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Introduction: In the gut, neuro-immune interactions between muscularis macrophages (MMs) and enteric neurons (ENs) are well reported. More in detail, the MMs secrete factors like BMP2 to support the EN functioning, while the ENs produce CSF1 to maintain the local MMs (1). However, the enteric nervous system (ENS) also comprises another player, the enteric glia cells (EGCs), which support the ENs and are involved in gastro-intestinal (GI) functioning (2). Relatively little attention has so far been paid for the interaction between MMs and EGCs, neither in health nor in disease. Post-operative ileus (POI) is a common side-effect of abdominal surgery and is defined by impairment of the functioning of the enteric nervous system (ENS). Here, neuro-immune interactions are involved in both the onset and resolution of post-operative ileus (POI) (3–5). Therefore, POI could be an interesting model to uncover a neuro-immune interaction between EGCs and gut macrophages. In case of the resolution of POI, our previous work showed that the recruitment of monocytes to the muscularis was important for the restoration of gastrointestinal (GI) motility (3). However, how these monocytes are recruited and by which mechanisms they resolve the GI functions remains unknown.

Aim: Our main aim is to understand the EGC and MM crosstalk in health and disease. Moreover, related to the EGC-macrophage interaction in inflammation, our aim is twofold. First, we aim to investigate if the EGCs are responsible for the observed monocyte recruitment towards the muscularis. Second, we aim to uncover how the recruited monocytes can promote the repair of the damage to the ENS in POI.

Methods: Taking advantage of the Ribotag-technology (6), we were able to identify the interactions between resident muscularis macrophages and EGCs during homeostasis. Moreover, this technology allowed us to perform RNA sequencing (RNAseq) of EGCs isolated from different time points during murine POI disease. To investigate the different macrophage populations in POI, we collected single-cell RNAseq data at different time points in both WT and CCR2 KO mouse diseased with POI. Targets of interest in the EGC-macrophage crosstalk were predicted by combining the collected RNAseq and scRNAseq data of both cell types. The functioning of these targets in the EGC-macrophage neuro-immune interaction were further confirmed by performing different in vitro assays.

Results: Using the methodologies described above, we observed a possible crosstalk between MMs and EGCs, both in health and in disease. During homeostasis, MMs secreted neurotropic factors with proliferative effects on EGCs in vitro. The same neurotropic factors were highly expressed in CCR2 positive monocyte-derived macrophages in our disease model, POI. These CCR2+ macrophages were essential for the resolution of the inflammatory response and reestablishing of the intestinal motility upon POI. Moreover, CCR2+ monocyte-derived macrophages also showed an inflammation-specific increased expression of other neurotropic factors. Therefore, the

increased expression of these neurotropic factors in CCR2+ monocyte-derived macrophages could explain the importance of the CCR2+ monocyte recruitment for the resolution of the damage to the ENS seen in POI. On the other hand, inflammatory EGCs seemed responsible for the recruitment of the CCR2+ monocytes towards the muscularis and for the differentiation of these monocytes towards pro-resolving macrophages. During the resolution phase of POI, the expression profile of EGCs showed the secretion of several monocyte chemoattractant molecules and molecules responsible for the differentiation of alternative activated macrophages.
Conclusions: In conclusion, we have collected evidence of a neuro-immune interaction between EGCs and macrophages in the muscularis both in heath and in disease. During homeostasis, MMs could support EGC maintenance by secreting neurotropic factors. On the other hand, during inflammation, EGCs secreted factors to recruit monocytes towards the muscularis both to modulate the inflammatory response and to protect the ENS from further damage. References: 1. Na, Y. R. Nat. Rev. Gastroenterol. Hepatol. (2019). 2. Gulbransen, B. D. Nat. Rev. Gastroenterol. Hepatol. (2012). 3. Farro, G. Gut (2017). 4. Boeckxstaens, G. E. Gut (2009). 5. Hupa, K. J. Sci. Rep. (2019). 6. Sanz, E. Proc. Natl. Acad. Sci. (2009). 7. Mhatre V. Ho and Kelsey C. Martin, J.-A. L. Bone (2012).

B02

Extracting neuronal activity signals from ENS microscopy recordings of contractile tissue: a cell tracking approach using B-spline Explicit Active Surfaces (BEAS)

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Introduction: Ca2+ imaging is a widely used microscopy technique to study cellular activity simultaneously in many cells. The desired information in Ca2+ imaging is a number of time series of pixel intensity values representing cellular activity during the recording time period. Novel techniques have been developed for delineation and signal extraction from Ca2+ imaging recordings but each of them requires complete frame alignment . If cells move or their tissues deform, which is sometimes unavoidable, the recorded data is unusable unless motion correction algorithms completely correct the endogenous movement. Multiple analysis challenges, including moving scenes, are present in microscopy recordings of the enteric nervous system (ENS), a layer of critical neurons embedded within the muscular layers of the gut wall. The complexity of these recordings reduces the applicability of classical segmentation techniques as well as traditional regions of interest (ROIs) selection. Registration techniques struggle against some contraction related tissue movement and the rapid temporal intensity changes of cell-belonging pixels .
Aim: Therefore, there is a clear need for a delineation and signal extraction method that is capable to deal with moving cells and is insensitive to large intensity changes in consecutive recording frames. Here we propose and implement an active contour cell

tracking method to delineate neuronal cell bodies based on local and global energy terms and track them despite intensity changes due to cell activity, overlap between neighboring neurons and, most importantly, tissue movement to efficiently extract Ca2+ activity.
Methods: We develop a novel approach designed specifically to accommodate popular Ca2+ genetic indicator (GECI) expressing cells by creating a coupled double-contour method that tracks the nucleus' boundaries as well as the cytoplasmic contour providing a stable delineation of neighboring, overlapping cells despite movement and intensity changes. We also incorporate a technique to automatically move manually-selected ROIs throughout recordings, using the tracked cell contours as landmarks for tracking ROIs throughout a recording, improving the yield of efficacious cell tracking and allowing signal extraction from other cell compartments like neuronal processes.
Results: Compared to manual delineation and other segmentation methods, the proposed cell method can track cells during large tissue deformations and high-intensity changes such as during neuronal firing events, while preserving the shape of the extracted signal.
Conclusions: The analysis package represents a significant improvement to available Ca2+ imaging analysis workflows for ENS recordings as well as for other systems where movement represents a challenge to the traditional Ca2+ signal extraction workflow.

B03

The enteric nervous system (ENS) responds to host-derived and bacterial amyloids by activating a pro-inflammatory gene circuit

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Introduction: Mounting evidence suggests a role for the microbiome-gut-brain axis in amyloid-driven neurodegeneration, yet the specific pathogenic changes induced by amyloids in the gut are not fully understood.
Aim: To obtain a comprehensive view on the early response of ENS cells to amyloid exposure.
Methods: We challenged primary myenteric networks with host- (Aβ1-42 vs Aβscrambled) and microbial-derived (curli vs medium) amyloids and performed bulk RNA-Seq and hit/pathway validation.
Results: We unveiled a transcriptional signature pointing to an inflammatory response, increased oxidative stress and DNA damage that is shared between both amyloid types. Amyloid-induced release of pro-inflammatory cytokines into the cell culture medium was confirmed by multiplex ELISA, and validation of the oxidative stress and DNA repair pathways is ongoing. To this end, we perform live cell ROS imaging on dissociated myenteric cultures and quantify SOD2 and γH2AX marker abundance in whole mounts prepared from colon at different time points post-intramural amyloid injection.

Conclusions: Together, these results shed new light on the intrinsic vulnerability of ENS cells to both amyloid species.

B04

Study on the role of muscularis macrophages in aging-associated neurodegeneration and constipation

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Introduction: Thanks to the increasing quality of medical care, life expectancy of the Western population has increased exponentially, resulting in an aging society. The downside of this evolution however is that aging results in a significant increase in patient morbidity and economic costs. Of note, 35-40% of geriatric patients and up to 80% of long-term care residents are affected by gastrointestinal (GI) complaints every year, most commonly constipation. Constipation is a debilitating disorder in the ageing population, associated with loss of enteric neurons (neurodegeneration). Macrophages in the muscularis externa are critical for the homeostasis and survival of enteric neurons. Importantly, depletion of neuron-associated macrophages led to loss of enteric neurons and delay in gastrointestinal transit, a phenotype resembling that of constipation. Insoluble protein aggregates, including α-Synuclein, are a hallmark of neurodegeneration in the brain and dysfunction of resident macrophages in the brain, microglia. We hypothesise that dysfunction of neuron-associated macrophages in the muscularis externa may underlie neurodegeneration and constipation with age.

Aim: We evaluated whether changes in muscularis macrophages are associated with ageing-related constipation/neurodegeneration.

Methods: Whole gut intestinal transit time (WGTT) was evaluated via carmine red gavage and total faecal output over 2 hours and faecal water content were measured in male and female mice of 3, 12 and 20 months. Colonic Cx3cr1+ macrophages were isolated from the colonic muscularis externa for flow cytometry and scRNAseq via 10X genomics. Colonic muscularis externa was collected for immuno-histochemical staining (IHC) of enteric neurons. Insoluble protein aggregates were stained using Amytracker dye.

Results: WGTT was significantly increased in females at 12 (184±36 min) and 20 months (169±28 min) compared to 3 months (108±9 min; $p<0.0001$; $n=10$). Faecal output was significantly decreased in females at 20 months (0.075±0.031 g) compared to 3 months (0.286±0.089 g, $p<0.0001$, $n=10$), but not in males. Faecal water content was significantly decreased in females at 20 months (2.3±7.3%) compared to 3 months (44.1±7.6%, $p<0.0001$, $n=10$), but not in males. Neuronal density was decreased in the myenteric plexus of the proximal and distal colon of 20-month-old (680±179 neurons/mm2 proximal; 457±155 neurons/mm2 distal, $n=10$) mice compared to 3-

month-old mice (995±212 neurons/mm2 proximal; 633±109 neurons/mm2 distal, n=10) in females but not in males. Furthermore, we detected insoluble protein aggregates in the muscularis externa of 12-month and 20-month old female mice, and in 20-month old male mice. Flow cytometry analysis revealed a significant reduction in the percentage of Cx3cr1+ macrophages with age in males (0.5±0.2%; p=0.02; n=4) and females (0.8±0.2%; p=0.0005; n=4). scRNAseq revealed subpopulations of macrophages of which some showed gender-specific age-related differential representation and upregulation of inflammatory signalling pathways. Additionally, we identified marker genes and showed differential activity of regulatory networks for these populations.
Conclusions: Female mice develop age-related constipation accompanied by neurodegeneration and deposition of insoluble protein aggregates. We identified gender-specific age-related alterations in the transcriptome of macrophage subpopulations in the muscularis externa, which may underlie enteric neurodegeneration and constipation. These findings shed light on the role of muscularis macrophages in neurodegeneration, unveiling novel and exciting therapeutic targets for the management of age-related constipation.

B05
Tyramid-amplified immunostaining reveals amyloid in the gut
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Introduction: The gut may represent an entry point for neurodegeneration. In Parkinson's disease, the protein alpha-synuclein becomes misfolded and aggregates within the enteric nervous system, after which it spreads to the central nervous system through the vagal nerve. Whether a similar mechanism takes place in Alzheimer's disease (AD) is not known. While the gut has been shown to produce amyloid beta (Aβ) and is also exposed to bacterial-derived amyloids, there is as yet little convincing data showing amyloid depositions in the gut.
Aim: To evaluate different labelling procedures for amyloid in the gut.
Methods: For in vitro benchmarking, bacterial-derived amyloids (Curli) and human amyloid oligomers (Aβ1-42) were plated into a 96-well plate and fixated. Next, ileum of 12 weeks old WT Black6 mice was injected with Curli, Hilyte555-conjugated Aβ1-42 or sterile PBS. 2 hours post-injection, animals were sacrificed and tissue was fixed and cryosectioned. As positive control samples, brain sections of 15-months old transgenic (3xTg) AD mice were taken along. For labelling amyloids, we compared different amyloid dyes (pFTAA, bromophenol blue, and Congo red) with several validated antibodies (clones D54D2, 6E10, 4G8 for Aβ, and anti-CsgA for Curli). It is known that dyes typically only stain the dense core of larger aggregates, while antibodies are more specific and therefore able to stain more diffuse forms of amyloid aggregates. In an attempt to increase the sensitivity of the detection, we combined both 4G8 (frequently used in AD research) and anti-CsgA antibody with tyramid signal amplification (TSA).

The latter relies on Alexa fluorTM tyramides and the catalytic activity of horseradish peroxidase for signal enhancement.
Results: The in vitro evaluation revealed that pFTAA and Congo red stain both Curli and Aβ1-42, while bromophenol blue and anti-CsgA only stain Curli. Antibody clones D54D2, 6E10 and 4G8 stain Aβ1-42 with no cross-reactivity towards Curli. No signal was observed for any marker in PBS-injected ileum, yet the overlap of amyloid dyes and antibody signals with injected Aβ1-42-Hilyte555 was incomplete, indicating lack of sensitivity to stain amyloids in gut tissue. In contrast, amyloid plaques in the brain of 3xTg-AD mice could be visualized with both amyloid dyes and antibodies. To boost the staining sensitivity in gut tissue, we implemented TSA which resulted in near-perfect co-localisation of the amyloid antibody signal with injected Aβ1-42-Hilyte555. Where no signal was obtained with the anti-CsgA antibody when using a standard immunofluorescence protocol, we found clear deposits in Curli-injected ileum upon TSA amplification. However, a reference staining is required to assess the sensitivity.
Conclusions: We have shown that TSA amplification increased the sensitivity of amyloid staining in the gut. Currently, we are investigating whether there are differences in amyloid abundance in the gut in young and old WT black6 and 3xTg-AD mice using the optimized TSA protocol.

B06

Dissecting TLR-mediated immune responses to amyloids in the enteric nervous system

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Introduction: The presence of extracellular amyloid-β (Aβ)-containing plaques is one of the pathological hallmarks of Alzheimer's disease (AD). Yet, the exact role of these aberrant protein deposits to pathology development remains unclear. Recent evidence has shown that the innate immune system, and more precisely Toll-like receptors (TLRs) play an important role in the recognition of Aβ, leading to the activation of downstream signalling pathways such as the NLRP3 inflammasome response. Given that the gut is continuously exposed to both human and bacterial-derived amyloids, and is vulnerable to inflammatory stimuli that compromise its integrity, prevailing research is focusing on whether the gut and its enteric nervous system (ENS) also become affected in AD.
Aim: To characterize TLR-mediated signaling in primary myenteric cultures exposed to amyloids.
Methods: Myenteric neuronal networks, isolated from the colon of WT Black6 mice, were incubated for 24h with bacterial-derived amyloid aggregates (Curli), human amyloid oligomers (Aβ1-42), or peptides with a scrambled sequence (Aβscr). After Illumina NextSeq 500 mRNA sequencing, differentially expressed genes and dysregulated pathways were explored using standard bioinformatic pipelines. Expression of TLRs and downstream sensor molecule NLRP3 were validated using qPCR. NLRP3 inflammasome activation is considered to be a two-step mechanism. As benchmark for detecting its

activation, THP-1 monocytes were first challenged with 100 ng/mL lipopolysaccharide (LPS) for 3.5h. Next, either ATP or nigericin were added for 30 min at a final concentration of respectively 5mM and 20 µM. After stimulation, medium was collected and IL-1β release was measured using a IL-1β/IL-1F2 DuoSet ELISA.
Results: Exposure of myenteric networks to Curli induced specific transcriptomic alterations in a subset of genes (Tirap, Ptges, Sod2, Cxcl2 and Cxcl5) involved in TLR-mediated immune responses. Additionally, we found that Tlr2-Tlr7 are expressed in primary myenteric cultures, and that a pro-inflammatory cytokine cocktail (TNFα, IL1β and IFNγ) induced upregulation of Tlr2, Tlr3 and Tlr7 as well as the Nlrp3 gene, a crucial factor in inflammasome activation. As myenteric cultures are heterogeneous cultures composed of both neurons and immune cells, and the latter are known to respond to pro-inflammatory stimuli, we used a monocyte line (THP-1) to query inflammasome activation. During benchmark experiments, we found that exposure of THP-1 cells to LPS and nigericin resulted in a significant higher release of IL-1β in the medium, indicative of inflammasome activation.
Conclusions: We have shown that TLR-mediated immune responses can be induced by Curli and pro inflammatory components in an in vitro setting of the ENS. We also confirmed that inflammasome activation can be measured (albeit indirectly) in THP-1 cells after dual stimulation. We are now using this model to investigate their sensitivity to amyloids and we are extending our measurements to query the response in neuronal cells, so as to gain a cell-type resolved view on inflammasome signaling in the gut.

B07

Characteristics of a population visiting a patient centred informative website: prevalence of Rome IV criteria for irritable bowel syndrome and red flag symptoms

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Introduction: Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterised by abdominal pain and changes in stool pattern. Based on dominant stool pattern we can subtype into IBS-D (diarrhoea), IBS-C (constipation), IBS-M (mixed), or IBS-U (unspecified). Many undiagnosed patients experiencing chronic abdominal complaints do not immediately visit a health care professional but turn to the internet for advice. Therefore, we probably underestimate the prevalence of disorders like IBS. Furthermore, when these patients do not visit a doctor, red flag symptoms are not noticed, and more serious diseases could be missed.
Aim: The aim of this study was to assess the prevalence of Rome IV criteria for IBS and red flags in a population visiting an IBS patient centred informative website (www.ibsbelgium.org).
Methods: Visitors of the website had the opportunity to participate in a questionnaire combining the Rome IV criteria and red flag symptoms (blood in stool, weight loss, start symptoms after 50 years of age, family history of colon cancer, unexplained fever). Afterwards, they received the results via mail. These results described the presence of

IBS according to the Rome IV criteria, the subtype and the presence of red flag symptoms. When red flag symptoms were present advice to visit the general practitioner was given. After informed consent, the data was extracted, and the prevalence of positive Rome IV criteria and red flags was calculated.
Results: 412 visitors completed the questionnaire, and 383 visitors (93.0%) gave permission to use the data for research purposes. Of these 383 visitors, 257 fulfilled the Rome IV criteria (67.1%). Based on stool pattern 98 visitors have IBS-D (38.1%), 31 IBS-C (12.1%), 119 IBS-M (46.3%) and 9 IBS-U (3.5%). Of the visitors not fulfilling the Rome IV criteria this was due to (multiple reasons possible): insufficient abdominal pain (27.0%), insufficient changes in stool pattern (45.2%) or duration of symptoms less than 6 months (52.4%). 159 visitors had red flag symptoms (41.5%): 12.5% had bloody stools, 14.1% unexplained weight loss, 4.4% unexplained fever, 18.3% a positive family history for colon cancer and 7.0% were older than 50 years when symptoms started. Patients fulfilling the Rome IV criteria had a similar percentage of red flags compared to Rome IV negative patients (41.2% versus 42.1%).
Conclusions: Since the COVID-19 pandemic, there has been an increasing interest in telemedicine. Based on our research results, we believe digital questionnaires could aid in the screening of patients presenting with abdominal symptoms. Since almost half of our population has at least one red flag symptom we think that a patient centered website could also help raise awareness and direct patients at risk towards consulting a health care professional.

B08

Aerosol-generating and droplet spread in nasogastric intubation in the COVID-19 era

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Introduction: Insertion and extraction of nasogastric catheters is a common practice in routine patient care. Procedures such as catheter positioning for High Resolution Manometry (HRM) and 24h multichannel intraluminal impedance-pH monitoring (MII-pH) are believed to generate aerosol and droplets, which may contain respiratory pathogens and pose an occupational risk of infection to health care workers (HCW). However, there is a lack of scientific evidence on the spread of aerosol (particles $\leq$5 µm) and droplets while performing these interventions.
Aim: To quantify the generation and spread of droplets and particles in the air near the patient during naso-gastric intubation for gastrointestinal motility investigations.
Methods: Patients undergoing HRM or MII-pH, and who confirmed negative for COVID-19 by PCR, were invited to participate. They wore a surgical mask over the mouth during nasogastric intubation by a HCW, positioned sideways behind the patient. Quantification of aerosol (0.3µm, 0.5µm, 1.0µm, 3.0µm, 5.0µm, and 10µm) was done using the

Lasair® II Particle Counter. For both probe positioning and removal, measurements were taken before and 1 and 5 minutes after. For droplet visualization, fluorescein (Fluorescein Faure; diluted to 1%) was applied to nasal cavity at the beginning of the investigation. Patients were covered with a white sheet and HCW wore an apron allowing quantification of droplet spread. After the procedure, fluorescent drops on the sheet and apron were visualized with a Woods UV light, photographed and analysed using ImageJ. Aerosol particle counts are logarithmically transformed and presented as particles-per-cubic-meter. Statistical analyses were performed using repeated one-way ANOVA with stepdown Bonferroni adjustment (Padj). Data are presented as mean±SD and significance was set at $P<0.05$. Fluorescent droplet spread data were presented as total amount of detected spots and total surface per body region.

Results: The spread of aerosol particles HRM procedure (n=21) One minute after catheter placement, there was a general significant reduction in aerosol particles of all sizes compared to baseline except for 0.3 and 0.5µm (Padj=0.71; Padj=0.36; Padj=0.01; Padj=0.01; Padj=0.002; Padj=0.003, in ascending size order respectively). Five minutes after placement, the number of particles was further reduced except for 0.3µm (Padj=0.54; Padj=0.04; Padj=0.01; Padj=0.008; Padj=0.006; Padj=0.007, respectively). The removal of the HRM catheter did not affect particle spread within 5 minutes (Padj=0.053; Padj=0.75; Padj=1.00; Padj=0.75; Padj=0.77; Padj=0.77, respectively). pH-MII procedure (placement n=12, removal n=10) The placement of the pH-MII probe did not affect aerosol counts of any size, except for a decrease of 1.0µm-sized particles 5 minutes after placement (from 11.25±0.32 to 11±0.31; Padj=0.026). For every particle size, except 0.3µm, probe removal was followed by a reduction in aerosol particle numbers. For sizes 0.5; 1.0 and 3.0µm this occurred 1 minute after (Padj=0.003; Padj=0.004 and Padj=0.017, respectively), while for the two bigger sizes 5.0 and 10µm, the reduction occurred after 5 minutes (Padj<0.0001 and Padj=0.001, respectively). The spread of fluorescent droplets HRM procedure (n=15) The highest contamination on the patients' sheet was found in the neck, counting 25 spots with a total surface of 50.90mm². The other regions had remarkably less spots and surface contamination. pH-MII procedure (n=12) With insertion of a pH-MII (n=6), the amount of spots and surface areas on the sheet for the neck , chest, leg, upper left flank, lower left flank, upper right flank and lower right flank were as follows: 8 (0.97mm²); 1 (0.01mm²); 14 (0.42mm²); 5 (0.24mm²); 1 (0.03mm²); 1 (0.35mm²) and 3 (0.10mm²) spots, respectively. The numbers of spots for the apron were the following (neck, chest, leg, upper left flank, lower left flank, upper right flank and lower right flank): 3 (0.51mm²); 5 (0.14mm²); 3 (0.06mm²); 0; 8 (0.25mm²); 2 (0.03mm²) and 2(0.05mm²) spots, respectively. The removal of the 24-hour pH-MII probe (n=6), in the same order as previously described: 7 (10.88mm²); 10 (175.78mm²); 12 (11.31mm²); 1 (0.01mm²); 3 (0.04mm²); 0 and 1 (0.01mm²) spots on the sheet and only 2 spots (0.13mm²) on upper left flank region of the apron.

Conclusions: Nasogastric intubation and probe removal, with a mask covering the patients' mouth, and the patient seated in a lower position in front of the HCW, does not induce significant aerosol spread and only generates sporadic droplets. For such

procedures, besides a gown, gloves, and protective eyewear, FFP1 masks seem sufficient for protecting medical staffs.

B09

Bismuth-based vs. standard triple therapy for the eradication of Helicobacter pylori in Belgium: final results of a multicentre, non-blinded randomized, prospective study.

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Introduction: H. pylori (HP) infection is related to malignant and non-malignant diseases like peptic ulcer, atrophic gastritis and gastric cancer warranting eradication. In Belgium, resistance rates for clarithromycin range between 10 and 15%, being just acceptable for standard triple therapy (STT: 14 days of pantoprazole 40mg bid, clarithromycine 500mg bid, amoxicilline 500mg bid). Since 2015, bismuth-based quadritherapy (BQT: 10 days of bismuthsubcitrate 140mg qid, tetracycline 125mg qid, metronidazole 125mg qid, pantoprazole 40mg bid) became commercially available.
Aim: The aim of this study is to evaluate the eradication rates (ER) of BQT over STT.
Methods: Multicentre, non-blinded randomized, prospective study comparing ER in treatment-naïve HP positive patients. Comparison of eradication rate (confirmed by urea breath test at least 6 weeks following treatment) was performed by intention to treat (ITT) and per protocol (PP) analysis. Based on estimated ER of 90% for BQT and 75% for STT and 10% loss to follow-up, sample size of 125 patients per group is required.
Results: Overall 232 patients were included (STT 115, BQT 117). 18 patients were lost to follow-up (8%). No significant difference in ER between BQT and STT was observed in ITT (75% vs 70%, p= 0.41) neither in PP analysis (83% vs 76%, p= 0.23). Logistic regression showed no significant influence of gender or site allocation.
Conclusions: In a head-to-head comparison, bismuth-based quadritherapy failed to demonstrate superior eradication rates as compared to standard triple therapy. Lower ER in the BQT arm, with preserved ER in the STT arm owing to the intensive follow-up in this study, could partly explain these results and questions the cost-effectiveness of BQT. A continuous nationwide monitoring of resistance patterns, maximal investments in treatment adherence as well as a detailed follow-up of the changing treatment landscape will provide opportunities to optimise ER in Belgium.

B10

Duodenal mucosal gene expression is associated with duodenal permeability and affected by proton pump inhibitor therapy in functional dyspepsia

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Introduction: Duodenal low-grade inflammation has consistently been reported in functional dyspepsia (FD) and we have previously linked this to increased duodenal mucosal permeability (Vanheel et al. Gut 2014). However, the role of local mediators

including cytokines, and the effect of proton pump inhibitors (PPI), the first line therapy in FD, remain unclear.
Aim: We aimed to study duodenal inflammatory gene expression in FD patients compared to healthy volunteers (HV), as well as the effect of PPI on mucosal gene expression. In addition, we aimed to evaluate associations between duodenal inflammatory gene expression and symptoms, barrier function and eosinophil infiltration.
Methods: FD patients fulfilling the Rome IV criteria and HV underwent upper-GI endoscopy with duodenal biopsies. Procedures were repeated after PPI-therapy (pantoprazole 40mg OD for 4 weeks). Expression of mucosal inflammatory genes (IL33, CCL5 (coding for RANTES), CCL11 (coding for eotaxin-1), CCL24 (coding for eotaxin-2), IL1RL1, TSLP) in snap-frozen duodenal biopsies was quantified using TaqMan RT-qPCR and normalised to ACTB and PPIA housekeeping genes. Mucosal integrity was assessed by measuring paracellular passage of a fluorescein-labelled dextran (4kDa, Fd4) and by recording transepithelial electrical resistance (TEER) in Ussing chambers. Eosinophils were counted on H&E-stained biopsy sections. Symptoms were scored using the Patient Assessment of GI Disorders Symptom Severity Index (PAGI-SYM). Changes in clinical (PAGI-SYM scores) and mucosal (Fd4-passage, TEER, eosinophils, gene expression) factors were analysed with linear mixed models. Spearman correlations were performed for off- and on-PPI visits, as well as for changes (Δ) in variables on- vs. off-PPI.
Results: In total, 30 HV (21 female, mean ± SE age 31 ± 2 years) and 29 FD patients (24 female, 31 ± 2 years) were included. Despite higher PAGI-SYM scores (β= 2.08 ± .19, p< .001), Fd4-passage (β= .76 ± .32, p= .02) and duodenal eosinophil counts (β= 15.29 ± 1.54, p< .001) in FD patients vs. HV off-PPI, baseline cytokine expression was similar (all p> .05). PPI-therapy significantly reduced PAGI-SYM scores (β= -.65 ± .11, p< .001), Fd4-passage (β= -.75 ± .25, p= .004) and eosinophilia (β= -10.54 ± 1.88, p< .001) in FD patients. Interestingly, PPI treatment increased IL33-expression in both HV (β= .12 ± .05, p= .03) and FD (β= .15 ± .04, p= .003), without between-group differences. In FD patients, mucosal IL33-expression correlated with Fd4-passage off- (r= 0.56, p= .004) and on-PPI (r= 0.57, p= .002), while it correlated inversely with TEER on-PPI (r= -0.61, p= .001). Although CCL11-expression correlated with duodenal eosinophil counts in HV off-PPI (r= 0.41, p= .02), no association was found between eosinophil counts and the expression of inflammatory genes in FD patients. Interestingly, ΔIL33-expression correlated inversely with ΔPAGI-SYM in FD patients (r= -0.48, p= .02), implying decreased symptoms with a higher increase in IL33-expression on- vs. off-PPI.
Conclusions: Here we show that PPI-therapy affects duodenal IL33-expression in both health and FD. The association of duodenal permeability and gene expression of IL33, a primarily epithelial-derived cytokine, suggests a link between IL33 and the barrier defect observed in FD. Importantly, increased IL33-expression was also associated with decreased symptoms after PPI in FD. Despite the basal chemotactic effect of CCL11 (eotaxin-1) on eosinophils in health, the absence of any correlation with eosinophils in FD suggests that other mechanisms contribute to duodenal eosinophilia in FD.

B11

Prevalence of double incontinence in patients with fecal incontinence and associated factors

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Introduction: Double incontinence (DI) is the concomitant presence of incontinence for urine and stool. Studies report a prevalence of DI between 3 to 5% among adults, with consistently higher numbers in women. The prevalence of faecal incontinence (FI) is higher, between 7% and 18% in community-dwelling adults and similar in men and women.

Aim: The aim of this study is to assess the prevalence of DI in patients with FI and to identify associated factors at a tertiary care centre.

Methods: The medical records of consecutive patients referred for Ano-Rectal Manometry (ARM) for FI were reviewed. Results from ARM, presence of diarrhoea, diseases from recto-anal or peri-anal region, prior abdominal, proctologic or urological surgery and neurological comorbidities were recorded.

Results: Of 101 enrolled patients, 77.2% suffered from solitary FI (61.5% women), and 22.8% from DI (87.0% women). Diarrhoea was more common in DI vs. FI (43,5% vs. 15,4%, p=.008), as was the presence of neurological comorbidities (34.8% vs. 10.3%, p=.009) and urological interventions (21.7% versus 1.3%, P = .002). Presence of diabetes mellitus, proctologic and abdominal surgery was comparable between groups. In respect to women only, significantly more urological interventions were performed (20% vs. 0%, p=.006) and more pathologies of rectum, anal canal or perineal region were encountered in DI vs. FI (35.0 % vs. 12.5 %, p= .045). In men, neurological disorders were significantly more common in DI vs FI (100.0% vs 3.3%, p=.002). Results from ARM were comparable between DI and FI within gender.

Conclusions: In patients with FI, despite comparable ARM parameters, gender-specific comorbidities associated with an increased prevalence of DI were identified. Insight into these factors could identify patients in need for a multidisciplinary approach at an early stage. A prospective study should corroborate these results.

B12

EFFICACY OF A NEW APPROACH TO THE REINTRODUCTION PHASE OF THE LOW-FODMAP DIET IN IBS PATIENTS

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Introduction: Irritable Bowel Syndrome (IBS), characterized by recurrent abdominal pain associated with defecation and/or changes in bowel habits in the absence of an

underlying organic cause, is highly prevalent in the general adult population. To date, pharmacological treatment strategies are only effective in subgroups of patients. Several studies have established efficacy of a low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAP) diet for symptom control in IBS. The diet starts with an all FODMAP elimination phase, followed by a reintroduction phase to determine personalized triggers.

Aim: As the latter phase is poorly established, nonblinded, and remains highly subjective, our aim was to develop a blinded reintroduction phase using FODMAP containing powder sugars instead of food items. In addition, we aimed to investigate weight loss and the impact of the low-FODMAP diet on somatization, depression, and anxiety.

Methods: After a 2-week baseline period, a trained dietitian explained the low FODMAP elimination phase to IBS patients recruited from a tertiary care clinic. The Irritable Bowel Severity Scoring System (IBS-SSS) was used to score symptom severity at baseline and throughout the elimination phase. Responders to the elimination phase, defined by a drop of $\geq$50 on the IBS-SSS, entered a 9-week reintroduction phase during which patients were challenged with 6 FODMAPs (daily intake of 20 g fructans or 60 g fructose or 12 g galacto-oligosaccharides or 60 g lactose or 15 g mannitol or 15 g sorbitol) or glucose (30 g) as a control in a randomized blinded order, administered as a powder. The powders were dissolved in water 3 times daily during meal intake for 7 consecutive days followed by 2 days of wash-out. A rise of IBS-SSS of $\geq$50 points over the score in the elimination phase defined a trigger FODMAP. In addition, changes in body weight, somatization, depression and (visceral specific) anxiety were assessed by the Patient Health Questionnaire (PHQ), and Visceral Sensitivity Index (VSI) respectively. Patients filled out daily diaries throughout the study and questionnaires at baseline, after 2, 4, 6 weeks of the FODMAP elimination phase and at the end of each reintroduction week. Data were compared using paired Student's t-tests.

Results: Twenty-eight IBS patients (32.8$\pm$0.4 years, 86% females, BMI 24.5 kg/m2) were recruited. The IBS-SSS score improved significantly after 2, 4, and 6 weeks of the FODMAP elimination phase compared to baseline (195$\pm$3, 140$\pm$3, 101$\pm$3 vs. 318$\pm$3, all $p<0.0001$). No significant difference in body weight was observed at the end of the elimination phase (65.1 vs. 64.4 kg, p=NS). In addition, somatization (7.9$\pm$0.2 vs. 12.9$\pm$0.4, p=0.0004) and depression (4.4$\pm$0.3 vs. 6.6$\pm$0.3, p=0.05) improved significantly after the elimination phase compared to baseline, while anxiety levels did not differ significantly (59.3$\pm$1.5 vs. 56.5$\pm$1.5, p=NS). Twenty-seven responders (96%) started the reintroduction phase. During blinded reintroduction, symptom recurrence was triggered in all patients by an average of 2.9$\pm$0.1 different FODMAPs per patient. The most prevalent triggering FODMAPs were fructans (67%) and mannitol (53%). A lower proportion of patients reacted on sorbitol, lactose, galacto-oligosaccharides and fructose (respectively 33%, 47%, 47% and 40%). On average, in the entire patient group, the IBS-SSS score increased significantly compared to the end of elimination phase (142$\pm$4.4) with intake of mannitol (217$\pm$8.6, p=0.04) and fructans (232$\pm$8.6, p=0.03),

while no significant increase was observed for sorbitol (150±9.8), fructose (173±5.8), lactose (171±8.8), GOS (199±10.4), and glucose (149±9.2).
Conclusions: This study confirms the significant benefit for symptom severity, somatization, and depression in tertiary care IBS patients started on a low-FODMAP diet. A blinded FODMAP reintroduction phase revealed a highly personalized pattern of symptom recurrence, with fructans and mannitol as the most prevalent triggering FODMAPs. We conclude that the blinded reintroduction phase using powders allows the most objective identification of individual FODMAP triggers.

B13
Efficacy and safety of spore-forming probiotics in functional dyspepsia: a randomised placebo-controlled trial

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Introduction: Acid suppressive or first-line therapy with proton pump inhibitors (PPI) for functional dyspepsia (FD) has limited efficacy and potential long-term side effects. Spore-forming bacteria or sporebiotics may be effective for postprandial distress (PDS) and epigastric pain (EPS) symptoms, offering benefits which may differ in relation to PPI-intake.
Aim: To study the efficacy and safety of sporebiotics in FD patients, both on- and off-PPI.
Methods: FD patients (off- or on-PPI) were randomised to sporebiotics (Bacillus coagulans and subtilis, 2.5 x 109 CFU) or placebo consumed twice daily for 8 weeks, followed by an open-label phase of sporebiotics for 8 weeks. Symptoms were assessed using the daily Leuven Postprandial Distress Scale (Carbone et al., APT 2016) diary. In FD patients on-PPI, a 14C-glycocolic or bile acid breath test (BT) was used to detect small intestinal bacterial overgrowth at baseline and after 8 weeks. The primary outcome was a decrease (Δ) > 0.7 for weekly PDS symptoms at 8 weeks (clinical response) in patients with baseline PDS >1 (mild). Secondary outcomes were minimal clinical response (ΔPDS >0.5), changes in cardinal PDS, epigastric pain and burning (EPS) or individual symptoms. Adverse events were graded using CTCAE v4.0. Intention-to-treat analysis was done for between-group comparisons of proportions (chi-square test) and changes from baseline (linear mixed models) in FD patients on- and/or off-PPI.
Results: In total, 68 FD patients (51 female, mean age 40.1 ± 1.74 years, 34 on-PPI) were included with similar baseline characteristics between groups. The proportion of clinical responders was 48% (12/25) in all patients with sporebiotics vs. 20% (6/30) with placebo (p= .03). A greater proportion of minimal clinical responders (56% vs. 27%, p=

.03) and (greater) decrease in the cardinal PDS (β= −.3 ± .15, p< .05) and EPS (β= −.28 ± .14, p< .05) symptoms was found with sporebiotics vs. placebo. Individual symptoms of postprandial fullness (β= −.37 ± .17, p= .03), upper abdominal bloating (β= −.32 ± .18, p= .07) and pain (β= −.42 ± .18, p= .02) significantly decreased in sporebiotics vs. placebo. Sporebiotics administered in the open-label phase decreased PDS (β= −.36 ± .11, p= .002) symptoms in the original placebo group, whereas PDS symptoms in the original sporebiotics group remained stable (p= .98). The proportion of positive bile acid BT was similar for both groups at baseline (18% vs. 25%, p= .29) but significantly reduced after sporebiotics vs. placebo (7% vs. 36%, p= .04). During the first 8 weeks, a trend for a lower incidence of all (16% vs. 33%, p= .09) and similar GI-specific (3% vs. 15%, p= .2) side effects was found with sporebiotics vs. placebo.
Conclusions: Spore-forming probiotics are effective and safe in patients with FD, decreasing both postprandial distress and epigastric pain symptoms. In FD patients on-PPI, sporebiotics decrease the percentage of positive bile acid breath tests, suggesting a reduction of small intestinal bacterial overgrowth.

B14

Symptoms and duodenal mucosal integrity and are improved by a dietary intervention in functional dyspepsia

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Introduction: The majority of functional dyspepsia (FD) patients experience symptoms such as early satiation, fullness, or epigastric pain/burning triggered or worsened by meal ingestion. The pathophysiology of FD remains poorly understood, but recent studies have shown increased duodenal mucosal permeability and loss of tight junction molecule expression in the duodenum as possible key players. As confirmed in several series, this occurs in the presence of increased numbers of activated mast cells and eosinophils in the duodenal submucosa. The trigger for these changes is not identified, but adverse reaction to nutrients is an important candidate mechanism. Previously, the low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAP) diet showed its efficacy in patients with irritable bowel syndrome (IBS), probably through decreased fermentation and osmotic actions in the bowel. However, intragastric infusion of FODMAPs induced symptoms reminiscent of FD, with a rapid onset that precludes involvement of fermentation in the bowel (Masuy 2018).
Aim: Therefore, our aim was to evaluate in FD patients the effect of a low FODMAP diet on symptom severity and duodenal mucosal permeability.
Methods: Patients with predominant meal-related FD symptoms (postprandial distress syndrome, PDS) were recruited from tertiary care. Subjects were also allowed to report

non-predominant IBS-like symptoms. After a 2-week baseline period, an experienced dietitian explained the low FODMAP diet, which the patient followed for 6 weeks. Throughout the study, patients filled out the validated Leuven PDS (LPDS) daily diary, from which the severity score is calculated as the average of scores for early satiation (ES), postprandial fullness (PPF), and upper abdominal bloating (Bl) (absent to very severe, 0-4). A difference of 0.5 points in the composite LPDS score is clinically meaningful. Before and after the low FODMAP diet, patients underwent an endoscopy with duodenal biopsies. Duodenal mucosal integrity was evaluated in adapted mini-Ussing chambers and defined by transepithelial electrical resistance (TEER) and paracellular permeability for FITC dextran (4kDa). In case of clinically meaningful improvement on LPDS, the FODMAP elimination phase was followed by a blinded reintroduction phase during which patients were challenged by adding one of 7 powders (fructans, fructose, galacto-oligosaccharides, lactose, mannitol, sorbitol and glucose) to each meal, to determine personalized triggers. Results are given as mean±SEM and compared by Student's t-test and Pearson correlations.
Results: Seventeen FD patients (39±0.8 yo, 82% females, 36% IBS overlap) completed the study. The LPDS score improved significantly after the low FODMAP diet (1.8±0.04 vs. 0.9±0.06, p=0.0004; responder rate 88%), and this was also the case for the individual symptoms of PPF (2.0±0.04 vs. 1.0±0.06, p=0.0002), ES (1.7±0.05 vs. 0.9±0.05, p=0.0002), and Bl (1.8±0.05 vs. 1.0±0.06, p=0.0009). The symptom improvement was associated with a trend towards a decreased macromolecular flux across the duodenal mucosa during low FODMAP diet (597±28 vs. 382±10, p=0.059) while TEER was not altered (p=0.55). During the reintroduction phase, a large variety of FODMAPS were able to induce recurrence of higher LPDS (≥0.5) scores, in a highly individualized pattern. Mannitol was the most prevalent triggering FODMAP (40%, mean LPDS score 1.3±0.06, p=0.02), followed by lactose, sorbitol, fructans and fructose (all 20%, p=NS). Only 10% of all patients scored higher on LPDS by galacto-oligosaccharides.
Conclusions: A low FODMAP diet significantly improves PDS symptoms, and this is associated with a trend towards restoring mucosal integrity against transmural flux of macromolecules. Reintroduction identifies a large variety in individual FODMAP triggers.

B15
Aberrant MUC13 expression as prognostic marker for gastric cancer.
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Introduction: One of the hallmarks of gastric adenocarcinoma is aberrant mucin expression, with gastric- and intestinal-type mucins widely being expressed in gastric

tumors. Their clinical importance is still controversial in relation to disease progression, outcome and microbiome composition.
Aim: Here, we investigated mucin expression in human gastric adenocarcinomas and its correlation with disease outcome and bacterial taxa.
Methods: Gastric biopsies of tumour and adjacent tissue of two independent cohorts of Belgian (n=45) and Lithuanian (n=43) patients were analysed for mucin expression. One additional Belgian cohort (n=24) is currently being analysed. Relative expression of gastric (MUC1, MUC5AC and MUC6) and intestinal mucins (MUC2, MUC4 and MUC13) was determined by RT-qPCR. The adenocarcinomas were classified by expression leading to gastric (predominantly MUC5AC and MUC6), intestinal (predominantly intestinal and MUC1), mixed (all types) and unclassified/null (neither gastric nor intestinal) mucin phenotypes. The overexpression threshold was defined as a 0.2*MNE increase (mean normal tissue expression) in the tumour compared to normal tissue. Correlation with 5-year survival (Kaplan-Meijer analysis) and other clinical traits (tumour stadia, histology, age, gender, …) was tested. The gastric microbiome is currently being determined using 16s rRNA sequencing on the Illumina platform. Read quality will be assessed, adapters trimmed and further processed using the DADA2 R package to determine sequence taxonomy and community composition. To detect biologically significant differences between mucin phenotypes regarding their microbial communities a linear discriminant analysis effect size (LEfSe) will be determined at multiple taxonomic levels.
Results: Microbial community analysis for the full cohort and the mucin phenotype analysis for the additional Belgian cohort (n=24) are still ongoing. Based on the preliminary analysis of the Belgian (n=45) and Lithuanian (n=43) cohorts, the cancers were classified as gastric (14.5%), intestinal (25.0%), mixed (17.1%) and unclassified (43.4%) mucin phenotypes. MUC13 overexpression was observed in 55.3% of the cases. Interestingly, 30% of the cohort -intestinal and mixed type- had a MUC13 expression exceeding a 1.75*MNE threshold. This correlated with decreased survival (p= 0.017, log-rank test). For the other mucins tested, this association could not be established.
Conclusions: Our results obtained so far highlight a key role for MUC13 in gastric cancer progression and survival. More research is required to understand its exact mechanism.

B16

A role for short-chain fatty acids in the disruption of the circadian clock during chronic jet-lag?

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Introduction: The circadian system enables organisms to optimally adapt their physiology and behavior (activity/rest, feeding/fasting) to the natural light/dark rhythm ensuring that all physiological processes are carried out at the optimal time of the day. Perturbations of the circadian system, also called chronodisruption, caused by rotating shift work or jet-lag lead to desynchronization of various body clocks and favor the development of metabolic, cardiovascular and/or intestinal disorders. Several intestinal

microbiota and their metabolites, most notably short-chain fatty acids (SCFA), display diurnal oscillations that are influenced by feeding rhythms. Diurnal fluctuations in SCFA levels are crucial to orchestrate and maintain proper oscillations of clock genes in peripheral tissue.
Aim: We aimed to investigated if chronodisruption induced by chronic jet-lag in mice affects feeding rhythms and the rhythmicity of microbial production of SCFAs that coordinate oscillations of clock genes in the gut.
Methods: Chronic jet-lag model: C57Bl6/5J mice were assigned either to a control group that was housed under a 12-h/12-h light/dark-cycle (Zeitgeber (ZT) 0 lights-on) or to a jet-lag group that was exposed to an 8h forward and backward shift 3 days a week during 1 month. Body weight and food intake (day vs night) were monitored during jet-lag induction. The expression of clock genes in the colonic mucosa were determined by qPCR and fecal SCFA concentrations were analyzed by gas chromatography-flame ionization detector. Crypt model: Crypts isolated from the distal colonic mucosa of control mice were synchronized for 2h with 200 nM dexamethasone and incubated with either DMEM (Control) or DMEM + SCFAs (24 mM). Samples for qPCR analysis were taken every 4 hours for 36 hours.
Results: Chronic jet-lag enhanced body weight gain ($P < 0.01$) and affected the food intake pattern ($P < 0.001$) without an increase in consumed calories. The alteration of the day/night food intake pattern resulted in a phase-delay of the peak in the rhythm (acrophase) of fecal propionate (5h19, $P < 0.01$) and butyrate levels (2h43, $P < 0.05$). A similar delay in the acrophase in clock gene expression in the mucosa of the colon was found. The acrophase of the mRNA expression of a positive regulator of the circadian clock, Bmal1, was delayed with 4h20 ($P < 0.001$), whereas the expression of the negative regulators Reverbα and Per2 were delayed with 4h53 ($P < 0.001$) and 4h49 ($P < 0.001$), respectively. In addition, Bmal1 mRNA expression (C: ZT 2.31; J: ZT 6.65) peaked together with the fecal propionate (C: ZT 4.79; J: 10.09) and butyrate (C: ZT 3.07; J: 5.78) concentration in both control and jetlagged mice. Stimulation of isolated colonic crypts with a mixture of SCFAs (24 mM) that mimic fecal levels in mice resulted in a phase delay of 2h38 ($P < 0.05$) in Bmal1 mRNA expression, 4h46 in Reverbα ($P < 0.001$) mRNA expression and 4h36 ($P < 0.01$) in Per2 mRNA expression.
Conclusions: Jet-lag abolishes the day/night food intake pattern thereby delaying the rhythms in fecal SCFA concentrations that paralleled the shifts in clock gene expression in the gut mucosa of jet-lagged mice. In isolated crypts, SCFAs mimic the shift in clock gene mRNA expression observed in jet-lag mice. Thus, SCFA possibly play a role in the phase shifts of the peripheral circadian clock during chronodisruption associated with altered feeding rhythms.

B17
Disruption of the gut-liver axis in experimental sclerosing cholangitis and colitis triggers compositional and phenotypical changes in hepatic myeloid cell subsets
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Introduction: Primary sclerosing cholangitis (PSC) is a rare, idiopathic liver disease characterized by sclerosis of the bile ducts, resulting in cholestasis, inflammation and eventually liver fibrosis. Four out of five PSC patients have concomitant colitis (PSC-UC), though milder and often subclinical compared to 'classical' ulcerative colitis (UC). A disturbed gut-liver crosstalk and a dysregulated immune response are increasingly recognized as key mediator in PSC and PSC-UC pathology. However, in depth investigation of the effect of sclerosing cholangitis and colitis on hepatic myeloid cell subsets is lacking.
Aim: To characterize compositional and phenotypical changes in hepatic myeloid immune cells in a mouse model of sclerosing cholangitis and colitis.
Methods: Sclerosing cholangitis was induced in mice by common bile duct ligation (CBDL). Dextran sodium sulphate (DSS) was administered in drinking water to induce acute colitis. Serum, liver and colonic tissue was isolated at 2-, 4- and 6-weeks post CBDL and after 7 days of DSS, alone and in combination with CBDL, to evaluate longitudinal changes during sclerosing cholangitis and colitis. Hepatic immune cell populations were analysed by flow cytometry and myeloid cell subsets were isolated by FACS for transcriptomic analyses.
Results: CBDL resulted in progressive cholestasis, liver inflammation and fibrosis. Flow cytometric analysis showed enrichment of hepatic monocytes (MO) and monocyte-derived macrophages (MoMF), and a depletion of Kupffer cells (KCs), as early as 2 weeks post CBDL, and these changes remained stable until 6 weeks post-surgery. KC core signature genes such as Clec4f, Vsig4 and Cd5l were enriched in KCs compared to MoMF in control and CBDL mice at each time point. Expression of genes involved in immune responses and tissue remodelling was enriched in MoMF compared to KCs and this was most pronounced 2 weeks post CBDL. In KCs, CBDL resulted in a stable downregulation of genes involved in complement activation and endocytosis from week 2 until week 6 post-surgery, while MO showed a pro-immune response profile at 2 weeks post CBDL which decreased over time. MoMF from CBDL mice showed upregulation of genes involved in inflammation, angiogenesis and fibrosis, and this was again most pronounced 2 weeks after CBDL and decreased over time. DSS-induced colitis resulted in increased expression of inflammatory and tissue remodelling genes and monocyte infiltration in the liver. Transcriptomic analyses of isolated MF from mice with acute colitis showed downregulation of genes involved in endocytosis, lipid metabolism and cytokine production and upregulation of cytochrome C release in KCs, whereas genes involved in inflammation, angiogenesis and response to endosymbionts were upregulated in MoMF. The combination of CBDL and DSS resulted in enhanced upregulation of pro-inflammatory and -fibrotic genes in the liver but did not exacerbate histological liver injury and fibrosis compared to CBDL alone. Transcriptional changes observed in hepatic MoMF, including increased expression of Spp1

(osteopontin) and Trem2, indicate a more inflammatory phenotype when colitis is introduced as second hit on end-stage BDL-induced liver damage.
Conclusions: Disruption of the gut-liver interconnection induces compositional and phenotypical changes in the hepatic myeloid cell compartment pointing to MoMF as important mediators in experimental sclerosing cholangitis pathogenesis.

B18

UNPREDICTABLE EARLY LIFE ADVERSITY IN FEMALE RATS DISRUPTS THE EPIGENETIC REGULATION OF STRESS-INDUCED VISCERAL PAIN IN ADULTHOOD.

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Introduction: We previously showed that elevated histone acetylation in the central nucleus of the amygdala (CeA) underlies visceral pain in female rats, exposed to unpredictable early life stress (uELS). Furthermore, chronic stress in adulthood exacerbates uELS-induced visceral hypersensitivity. Here, we employed a dual hit model of uELS and adult stress to investigate central epigenetic mechanisms that drive abnormal stress-induced pain vulnerability.
Aim: To test the role of histone acetylation in the CeA in stress-induced visceral pain.
Methods: Female rats were exposed to either uELS (n = 18) or odor only (n = 18) (single hit) from postnatal days 8-12. In adulthood (day 90-120), indwelling cannulae were positioned on the dorsal margin of the CeA. Subsequently, 500 nl of garcinol (histone acetyltransferase (HAT) inhibitor targeting PCAF and p300, 1ng/nl) or vehicle (50%DMSO-50%ACSF) was microinjected into the CeA for 7 days. In another cohort of rats, garcinol or vehicle was microinjected into the CeA after exposure to water avoidance stress (WAS, 1h/day for 7 days, dual hit). On day 8, visceral sensitivity was assessed in freely moving rats by quantifying the number of abdominal contractions during graded pressures of isobaric colorectal distension (0-60 mmHg). A two-way ANOVA with Bonferroni post-hoc analysis tested statistical significance.
Results: Exposure to uELS (single hit) increased colonic sensitivity (uELS = 33±8 vs. odor only = 16±4 abdominal contractions, $p<0.0001$). Garcinol microinjections into the CeA reversed colonic hypersensitivity to levels resembling odor only controls (19±6 abdominal contractions, $p=0.0030$). In the dual hit model, neonatal stress and WAS in adulthood increased colonic sensitivity (uELS: 45±3, $p<0.0001$; odor only: 30±6 abdominal contractions $p<0.0001$). In the dual hit model, garcinol microinjections into the CeA of uELS females reduced, but did not normalize colonic sensitivity (uELS from 45±3 to 28±5, $p<0.0001$).
Conclusions: Elevated histone acetylation in the CeA underlies visceral pain after uELS. However, in a dual hit model combining uELS and adult stress, the inability of garcinol to normalize colonic hypersensitivity, suggests that two hits activate garcinol-insensitive HATs that contribute to stress-induced visceral pain.

Case Reports

C01

Purtscher’s-like retinopathy associated with acute alcoholic pancreatitis, a case report

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Case Report: Purtscher’s retinopathy is an occlusive microvasculopathy, first described in 1910 by Otmar Purtscher in a patient with post-traumatic loss of vision. When features like Purtscher’s retinopathy presents without the history of trauma, such as acute pancreatitis, renal failure, connective tissue disease, lymphoproliferative disorders, etc... it is called Purtscher’s-like retinopathy. This condition is well documented in the ophthalmological literature but not commonly recognized by gastroenterologists in case of acute pancreatitis. Our case concerns a 46-year-old man without medical history who was referred to the ophthalmologist due to bilateral visual impairment in the last week. His visual acuity was disturbed in both eyes and funduscopic examination revealed typical findings of a Purtscher's-like retinopathy. He was referred to exclude gastro-intestinal or haematologic causes, as no trauma was reported. The patient had no abdominal pain, nausea or weight loss. Recent binge drinking and daily smoking was reported. Clinical examination showed no abnormalities. His laboratory results were notable for leucocytosis 15.300/mm³, platelets 738.000/ mm³, elevated lipase 537 U/l, bilirubin 0.27 mg/dL, AST 28 U/L, ALT 55 U/L, AF 153 U/l, GGT 138 U/L CA19.9 103 kU/L and C-reactive protein (CRP) 53 g/dl. Bone marrow morphology and genetic tests (BCR ABL, JAK-2 mutation) performed by the hematologists were negative. Abdominal computed tomography showed pancreatic inflammation and peripancreatic fluid collections, matching with an acute alcoholic pancreatitis. The patient did not receive specific therapy for Purtscher’s-like retinopathy and he received a supportive treatment for his pancreatitis. He stopped drinking alcohol completely. His visual function and fluoroscopy showed a good evolution. The lipase has normalized. Abdominal computed tomography after 3 months showed regression of the peripancreatic fluid collections and no suspicion of underlying malignancy. Inkeles and Walsh were the first to describe the association between Purtscher’s-like retinopathy and acute pancreatitis. The annual incidence of symptomatic Purtscher's retinopathy has been estimated to be 0.24 cases per million population per year. The incidence off Purtscher’s-like retinopathy is unclear and frequency of Purtscher’s-like retinopathy in the case of acute pancreatitis is even less described. Fewer than 50 cases have been reported to date, probably due to underdiagnosis. Purtscher’s-like retinopathy is a microvasculopathy but the true mechanism has not been well established yet. Most excepted mechanism is that pancreatic damage causes an embolic phenomenon where air, fat, fibrin clots, or leukocyte aggregates clog the retinal arteriole. The diagnosis is clinical with sudden loss of visual acuity associated with typical fundus appearance in the context of a systemic illness such as acute pancreatitis. This severe angiopathy typically begins

within some hours to days after the onset of the pancreatitis. Ophthalmological examination shows typically confluent cotton-wool spots in the posterior pole, intraretinal hemorrhages and Purtscher flecken in the acute phase. The disease is bilateral in the majority of the cases. There is no specific treatment available for Purtscher's-like retinopathy. Observation and treatment of the underlying etiology may be the most reasonable therapeutic option. Studies have suggested the use of systemic corticosteroids and nonsteroidal anti-inflammatory drugs with variable results. Its development is independent of the severity of pancreatitis. The outcome depends probably upon the resolution of the pancreatic disease. We think our case is important because it describes a complication of a very common disease, a complication that is not well-known by many gastroenterologists. It demonstrates that acute pancreatitis may influence different organ systems, including the eye. In this case it was remarkable that the diagnosis of pancreatitis was made by the finding of the Purtscher's-like retinopathy, within a patient who didn't had a history of abdominal pain but had the typical biochemical and CT-graphic findings. This also hints that many patients might experience subclinical pancreatitis. To date, all described cases were about acute pancreatitis followed by acute blindness when the diagnosis of a Purtscher's-like retinopathy was made. Our case suggests that this diagnosis could be easily overlooked or misdiagnosed. It should remind us as well that acute pancreatitis can present with any symptom or systemic manifestations that initially do not lead to suspicion of pancreatic disease.

C02

A case of Secukinumab induced inflammatory bowel disease

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Case Report: Introduction Secukinumab is a human monoclonal antibody that selectively targets Interleukin-17, a pro-inflammatory cytokine involved in the pathogenesis of several immune-mediated inflammatory diseases including psoriasis and inflammatory bowel disease. (1) There is growing evidence suggesting an association between the use of IL-17 inhibiting drugs and an increase in exacerbations and even de novo cases of inflammatory bowel disease. Case description We present a 75 year-old female with a history of type II diabetes, arterial hypertension and multiple basocellular carcinomas. She suffered from severe psoriasis for which she was treated with several drugs in the past including methotrexate, cyclosporine, infliximab and Ustekinumab, all of them without satisfying results. Ultimately, she was started on Secukinumab with spectacular effect on the skin lesions. Six months after initiation of Secukinumab, she presented to the emergency department with complaints of severe watery diarrhea for 6 weeks. This was the first time she experienced gastrointestinal complaints. Lab results showed a mild raise in inflammatory parameters. A colonoscopy was performed demonstrating a mild colitis predominantly at the level of the sigmoid. At this point, the colitis was

presumed to be infectious considering the immunosuppressed status of the patient. However, all cultures remained negative. Upon control consultation symptoms were somewhat less prominent, however diarrhea remained present. Calprotectin was elevated to a level of >1000 µg/g. New ileocolonoscopy showed an erosive inflammation of the terminal ileum, compatible with a terminal ileitis in the context of Crohn's disease. On microscopic examination the diagnosis of chronic erosive ileitis was confirmed. MRI examination, in addition, also demonstrated severe wall-thickening with contrast hypercaptation over the length of 90 cm at the level of the terminal ileum. Treatment with Budesonide was initiated with favorable effect on the patient's complaints. The indication for combined therapy for psoriasis and IBD was established and vedolizumab was associated. Discussion Psoriasis is a multisystem disease which may also include enteropathy. There is some evidence suggesting an increased prevalence of IBD in patients suffering from psoriasis since these conditions share some common inflammatory pathways. In this patient new onset primary IBD seems less likely considering the older age in which the disease manifested itself and the beginning of symptoms shortly after starting Secukinumab. We can therefore assume that the new onset Crohn's disease in this patient is due to Secukinumab use. Increasing evidence exists for an association between IBD and Secukinumab (or IL-17 inhibition in general). Multiple reports demonstrate a greater risk for exacerbations of known IBD in patients using Secukinumab. (2) Initiation of IL-17 inhibiting therapy should therefore be done with caution in patients with existing IBD. Secukinumab was once considered a treatment modality for Crohn's disease, however results of the randomized controlled trial turned out rather unexpected. A higher rate of adverse effects and exacerbations was seen in Crohn patients receiving the treatment compared to placebo. (3) In addition, multiple cases of new onset IBD in patients receiving Secukinumab are already reported in literature. (2) A pooled data analysis including 21 trials showed this adverse effect of Secukinumab to be rare but nevertheless, a new onset Crohn's disease or ulcerative colitis should be considered in patients receiving this treatment and presenting with suggestive complaints and a matching colonoscopic image. (4) This case report aims to supplement existing literature regarding this subject and to raise awareness for this rare but severe adverse effect of Secukinumab. References 1. Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut. 2003;52(1):65-70. 2. Hohenberger M, Cardwell LA, Oussedik E, Feldman SR. Interleukin-17 inhibition: role in psoriasis and inflammatory bowel disease. J Dermatolog Treat. 2018;29(1):13-8. Available from: https://doi.org/10.1080/09546634.2017.1329511 3. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PDR, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 2012 Dec;61(12):1693-700. Available from: https://gut.bmj.com/lookup/doi/10.1136/gutjnl-2011-301668 4. Schreiber S, Colombel JF, Feagan BG, Reich K, Deodhar AA, McInnes IB, et al. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and

ankylosing spondylitis treated with secukinumab: A retrospective analysis of pooled data from 21 clinical trials. Ann Rheum Dis. 2019;78(4):473-9.

C03

Cardiogenic Shock due to Mesalazine-induced Myocarditis in a Patient with Ulcerative Colitis: A Case Report

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Case Report: Background: Mesalazine or five-amino salicylic acids (5-ASA) is widely used in the management of inflammatory bowel disease. This long-established treatment is known to be efficacious in inducing remission and is generally regarded as safe and well tolerated. Although severe complications are described, there are only a couple of cases reported of cardiogenic shock due to mesalazine-induced myocarditis. The mechanism by which Mesalazine causes myocarditis remains unclear. There could be a direct cardiotoxic effect, although a hypersensitivity reaction is more plausible. The few cases that have been published all showed improvement of symptoms after discontinuation of Mesalazine, which supports the idea of a hypersensitivity reaction. Case presentation: We report a case of a 23-year-old Belgian man who was diagnosed with Ulcerative Colitis (UC) after having symptoms of diarrhea and bloody stool for more than 2 months. He was started on a treatment with high dose Mesalazine (2g, twice a day). Three weeks after initiating Mesalazine treatment he was admitted to the intensive care unit (ICU) with cardiogenic shock due to systolic heart failure. The patient showed symptoms of fatigue, shortness of breath, acute chest pain, fever and aphthous stomatitis. Abdominal symptoms of UC were almost completely absent. Cardiac enzymes and white blood cells (with notable eosinophilia) were greatly elevated. Treatment with inotropes and vasopressors was initiated, whilst Mesalazine was discontinued on the hypothesis of a drug reaction with eosinophilia and systemic symptoms (DRESS-syndrome). The diagnosis of myocarditis was made on the basis of cardiac magnetic resonance imaging, which showed clear zones of delayed enhancement of the left ventricle. Other common causes of myocarditis (infectious, autoimmune and other drug-induced) were excluded. After six days, the patient's symptoms improved and he could be weaned off inotropes/vasopressors. Due to an acute flare of UC, seven days after stopping Mesalazine, the patient was started on high dose corticosteroid therapy. Now, one month after hospitalization, patient has made a full recovery and shows no signs of systolic heart failure. Corticosteroids are being tapered and treatment with a tumor necrosis factor (TNF) inhibitor has been initiated. Conclusion: Mesalazine-induced myocarditis is an uncommon but very severe and potentially fatal disease. Notwithstanding the validity and efficacy of Mesalazine as first line treatment in Ulcerative Colitis, it is vital that clinicians are aware of possibly life-threatening side effects such as myocarditis and recognize early cardiac symptoms. This case illustrates the need to recognize early symptoms so that prompt discontinuation of Mesalazine can prevent permanent damage. Keywords: Mesalazine, cardiogenic shock, myocarditis, Ulcerative Colitis, DRESS

C04

ERYTHEMA MULTIFORME IN THE ESOPHAGUS

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Case Report: A 61-year old man was referred to the gastroenterology department with complaints of dysphagia for solid food and odynophagia for one year. The patient had an extensive medical history of diabetes mellitus type 2, chronic kidney disease, ischaemic cardiomyopathy and peripheral vascular disease. Four years ago he experienced similar complaints of dysphagia and was diagnosed with esophagitis on esophagogastroduodenoscopy (EGD). Biopsies from the distal part of the esophagus showed characteristics of both reflux and possible manifestation of erythema multiforme (EM). Proton pump inhibitors (PPIs) were initiated in high dose by which symptoms disappeared. At present, an esophageal manometry showed aperistalsis in the distal two thirds of the esophagus. Barium esophagram revealed stasis of contrast both for solid and fluid substances without evidence for any motility disorders. A new EGD was performed and demonstrated a tortuous distal part of the esophagus with macroscopic signs of candida esophagitis and reflux esophagitis grade B according to the Los Angeles classification despite the use of PPIs in high dose for over three years. Biopsies were taken from the distal part of the esophagus and the stomach. The histopathologic findings of the biopsy specimen from the esophagus were again compatible with EM. Immunohistochemical staining for herpes virus was negative. PAS (periodic acid-Schiff) staining showed no pseudohyphae. The patient had no history of skin disorders. Clinical examination by the dermatology department revealed no mucosal or cutaneous lesions. A course of Fluconazole 200 mg each day during 14 days brought temporary relief but symptoms returned once therapy was stopped. A new EGD four months later showed furrows and multiple concentric rings in the distal third part of the esophagus. New esophageal biopsies confirmed the presence of EM. Around the same time, the patient was diagnosed with small cell lung cancer (SCLC) and sternal metastasis. Metoclopramide 10 mg three times daily was started for diabetic gastroparesis. His symptoms improved slightly. After association of Pyridostigmine 10 mg three times daily, all complaints disappeared. The patient died four months later due to his oncological condition. Erythema multiforme is an immune-mediated mucocutaneous disorder. Mucosal involvement usually affects the oral region, the genitals or the eyes (1). We report a case of esophagitis caused by erythema multiforme in a patient diagnosed with lung cancer. Esophageal manifestation in erythema multiforme is rarely seen (2). Besides esophagitis it can lead to esophageal strictures. Erythema multiforme is mostly triggered by infection or drugs but the association with malignancy has been described (3). In patients with dysphagia, an esophageal manifestation of mucocutaneous disorders should be included in the differential diagnosis, especially in patients with skin diseases. In case of esophageal involvement

in EM, the possibility of a malignancy should be investigated when obvious triggers such as HSV or M. pneumoniae infection are absent. (1) SOKUMBI O., WETTER D.A. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. International Journal of Dermatology, 2012, 51(8) : 889-902 (2) HUFF J.C., WESTON W.L., TONNESEN M.G. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. Journal of the American Academy of Dermatology, 1983, 8(6) : 763-775. (3) TRAYES K.P., LOVE G., STUDDIFORD J.S. Erythema multiforme: recognition and management. American family physician, 2019, 100(2) : 82-88.

C05

Endoscopic lithotripsy for Bouveret syndrome complicated postoperatively by small bowel obstruction from gallstone fragments

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Case Report: Bouveret syndrome refers to gastric outlet obstruction secondary to a gallstone. It is an extremely rare complication of acute cholecystitis, where the formation of a cholecystoduodenal fistula results in migration of gallstones into the duodenum causing a mechanical obstruction. Given the rare occurrence of Bouveret syndrome, there are currently no standardised recommendation for the management of these patients. Endoscopic lithotripsy have been reported to relieve gastric outlet obstruction caused by gallstones. This technique breaks down the obstructing gallstone into smaller fragments, which can then be removed endoscopically. We report a case of Bouveret syndrome treated with endoscopic lithotripsy where not all the gallstone fragments could be removed. Postoperatively, the patient developed a mechanical small bowel obstruction caused by distal migration of the stone fragments and required a laparotomy. This case highlights the importance of retrieving all gallstone fragments following endoscopic lithotripsy to prevent associated complications such as bowel obstruction. To our knowledge, such a complication following endoscopic lithotripsy has never been previously reported. A 90 year old female presented to the emergency department with right upper quadrant pain associated with nausea and vomiting. This was on a background of a previous admission with acute necrotic cholecystitis seven months ago, which was managed non-operatively with intravenous antibiotics and a cholecystostomy tube that was removed eight weeks after insertion. The patient was haemodynamically stable on presentation but had percussion tenderness in the right upper quadrant. Abdominal ultrasound showed air in the gallbladder lumen and biliary tree but this was attributed to the recent cholecystostomy tube removal. A subsequent CT abdomen showed a cholecystoduodenal fistula with a large 60mm gallstone into the third part of the duodenum causing a gastric outlet obstruction, consistent with Bouveret syndrome. A nasogastric tube was inserted for stomach decompression. The patient was assessed to be a poor operative candidate by the anaesthetic and surgical

team given her advanced age, frailty, and multiple comorbidities. To relieve her gastric outlet obstruction, endoscopic retrieval of the gallstone was attempted but the size of the stone prevented it from being captured by the largest retrieval basket available. A decision was made for electrohydraulic lithotripsy but this had minimal effect on the gallstone due to its hard consistency. Holmium laser lithotripsy ensued and this was able to achieve fragmentation of the stone. However, the stone fragments were still of considerable size even after extensive laser lithotripsy, which made it difficult for complete retrieval. Following a lengthy intraoperative time, the procedure was aborted as the obstruction had completely resolved. Postoperatively, the patient was monitored in intensive care. Her nasogastric output continue to increase and she developed obstipation. A progress CT abdomen and pelvis revealed a small bowel obstruction secondary to a gallstone fragment in the left lower quadrant. Further conservative management with bowel rest and total parental nutrition did not improve the patient's clinical state. Following extensive discussion with the patient and family, it was decided that the best course of action would be for the patient to undergo surgery. The patient underwent a laparotomy, where the transition point was identified at 7cm away from the ileocaecal valve. A 5cm gallstone fragment could be palpated at this point. A longitudinal 4cm enterotomy was performed on the anti-mesenteric border and a large gallstone fragment was delivered. The enterotomy was closed transversely with interrupted 3-0 vicryl sutures and patched with omentum. Following this, the patient's diet was gradually uptitrated and her nasogastric tube was eventually removed. She was transferred to the geriatrics rehabilitation unit following completed resolution of her surgical issues. The patient has since been discharged to the community and is doing well at our last follow-up.

C06

EUS-guided radiofrequency ablation for a left adrenal oligometastasis of a gastric adenocarcinoma

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Case Report: EUS-guided radiofrequency ablation (RFA) has proven its safety and effectiveness for targeting focal pancreatic lesions, ranging from pancreatic cystic neoplasms to neuroendocrine tumors and adenocarcinomas. However, when it comes to the treatment of extra-pancreatic lesions, the role of this technique still remains to be determined. We describe the case of a 35 year old female patient with a poorly differentiated Her-2-positive gastric adenocarcinoma. At presentation, the tumor marker CA19-9 concentration was high (17.000 kU/L) and there were already multiple secondary lesions (including locoregional lymph nodes, peritoneal carcinosis, pancreatic, hepatic and bony metastasis), witnessing for the advanced oligometastatic stage of the disease. A systemic chemotherapy treatment was promptly administered, allowing to achieve a morphologic and metabolic partial response, with a CA19-9 dosage decreasing to 81 kU/L. However, after 16 months of treatment, a newly developed hypermetabolic left adrenal lesion was detected. After discussion at the oncology multidisciplinary meeting, a supplementary loco-regional treatment by EUS-

guided RFA targeting the left adrenal metastasis was proposed, as it appeared to be the only lesion progressing under the ongoing systemic treatment. The procedure was performed by an experienced endoscopist, using a linear EUS endoscope (GF-UCT180; Prosound F75 processor; Olympus, Hamburg, Germany). The patient was under propofol deep sedation and antibiotic prophylaxis was administered. With the endoscope positioned in the gastric lumen, it was possible to identify the metastatic 25 mm isoechogenic lesion, surrounded by normal adrenal parenchyma. A EUS-RFA 19G gauge internally cooled electrode with 10 mm exposed tip (EUSRA™) was inserted into the lesion and the radiofrequency generator was then activated to deliver an energy of 50 W during a few seconds, until the development of air bubbles was observed near the tip of the electrode. A post-RFA look showed that the whole nodule had now become hyperechoic. There were no peri-procedural adverse effects and the patient was discharged the next day. She later reported a mild pain at her left flank, which had resolved spontaneously few days after the procedure. No other adverse effect was reported and chemotherapy could be continued as usual. At one month follow-up, an MRI suggested a favorable local response with the development of necrosis at the site of the lesion. The PET-CT revealed an increased hypermetabolism, attributed to the local necrotic reaction. However, there were radiological signs of progression in other locations (including the appearance of new hypermetabolic abdominal and retroperitoneal lymphadenopathies), as well as an increase of the CA19-9 concentration (1400 kU/L). With this in mind, chemotherapy treatment was adapted and a new workup performed one month later (2 months follow-up). This time, the CA19-9 concentration had decreased by more than half (640 kU/L) and the PET-CT showed a complete metabolic response in all previously hypermetabolic sites. EUS-guided RFA is now widely accepted as a safe and feasible technique for the treatment of pancreatic lesions. This case suggests that its use can be safely and successfully extended to other extra-pancreatic lesions, making it an additional treatment option for local control of left adrenal metastatic disease (probably amongst other transluminal accessible lesions). Nevertheless, future multicentric prospective studies are still needed to demonstrate and validate this hypothesis.

C07

Rapid deterioration of a patient in the Emergency Room: No time to waste!

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Case Report: A 56-year-old woman presented at the ER with acute abdominal pain and vomiting. She had been experiencing these complaints for seven hours, with a crescendo decrescendo character. Medical history was notable for a mild stomach herniation due to a traffic accident in 2018 and a recently diagnosed uterus fibroma. Initial clinical assessment showed a healthy nonsmoking middle-aged woman of African

origin with mild tachycardia, stable blood pressure and no fever. Physical examination was unremarkable with no signs suggestive for peritonitis. Blood testing and a thoracoabdominal scan were ordered to exclude an ischemic intestinal event. Awaiting the results, the patient progressively deteriorated, with the onset of fatigue and agitation. An arterial blood gas (ABG) was taken with the finding of a significant high anion gap metabolic acidosis, with pH 7.1 and a lactate level of 7.2 mmol/L. IV fluids and antibiotics were administered to correct the metabolic acidosis with initial good response. Results of the CT scan showed a massive herniation of the entire small intestinal loop and half of the colon in the left hemithorax resulting in a mediastinal shift with compression of the vena cava superior and the left ventricle. An emergency surgical consult was asked. Yet despite ongoing fluid resuscitation while awaiting surgical review, the patient deteriorated further with eventually going into asystole. Immediate CPR was initiated, following the asystole protocol. Regain of spontaneous circulation (ROSC) was obtained after 15 minutes. After a short surgical evaluation, an urgent laparotomy was deemed necessary. During transport to the OR, a second cardiovascular collapse occurred. The incision was done under active CPR and decompression of the heart was reached after 20 minutes, upon which ROSC was obtained. Further exploration led to the finding of necrotic small intestine over a length of 3 meters due to strangulation, which was resected. A relook laparotomy was planned 48 hours later, and the patient was admitted to the ICU under the care of the anesthesiology department. The patient experienced several events of bleeding over the course of the next days with the need for operative intervention. Eight days after the event she was unfortunately declared brain dead by the consulting neurologist. Conclusion: Tension viscerothorax is a rare but serious complication of a diaphragmatic herniation leading to obstructive shock. Recognition is not necessarily straightforward and a past history of a “hiatal hernia” is not always given serious consideration. Literature suggests this condition can present itself several years after the initial trauma, especially when a tear goes unnoticed. The continuous motion of the diaphragm hinders the healing of the initial tear. Because of the cyclic negative intrathoracic pressure viscera are sucked into the tear which causing it to enlarge. This way viscera increasingly protrude the tear, where they eventually may get obstructed or strangulated(1). Doctors should be aware of this possible complication and patients should be encouraged for early surgical correction. In case of a tension viscerothorax, rapid surgery is appropriate. Valuable time was lost here in awaiting the CT scan. More conventional imaging techniques like a plain upright X-ray could have spared some time. Yet while awaiting surgery, and especially in tension gastrothorax, a nasogastric tube, gastroscopic deflation, or as a last resort a percutaneous needle insertion of the stomach may give decompression without spillage of the intestines (2). Ref: 1. MS Al Skaini, A Sardar, H Haroon, SM Al Ghamdi, Abdulla Homran, and M Ezzedien Rabie. Traumatic diaphragmatic hernia: delayed presentation with tension viscerothorax – lessons to learn. Ann R Coll Surg Engl. 2013 Mar; 95(2): e27–e29 2. Takahiro Shoji MD et al. A survival case of tension gastrothorax due to hiatal hernia, the key of life-saving

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C08

An unexpected rectal mass

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Case Report: We present the unusual case of a 48-year-old woman with recurrent painless rectal bleeding and an unexpected rectal mass. Our aim is to emphasize the importance of a correct assessment for the differential diagnosis. The patient was hospitalized at the gastroenterology ward due to recurrent painless rectal bleeding and iron deficiency anemia, known for years but that was attributed to internal hemorrhoids. She had a recent diagnosis of a deep venous thrombosis in her left lower limb, for which treatment with rivaroxaban was started. Afterwards there was an increase of the rectal blood loss and a deterioration of the anemia. The patient had no further clinical or surgical history and no family history of gastrointestinal or oncological diseases. At clinical examination, she was in good general condition with red blood on the finger after rectal examination. Biochemically there was an iron deficiency with a hemoglobin of 7.8 g/dl, without any other abnormalities. Initial sigmoidoscopy revealed a circumferential, contact-fragile rectal mass in rectum. The initial working diagnosis was a rectal carcinoma for which biopsies were taken and staging with MRI, endoscopic ultrasound of the rectum, CEA and abdominal- and chest-CT were scheduled. However, histopathological examination of the biopsies showed normal rectal mucosa, without arguments for a malignancy. CT of the abdomen revealed a rectal mass with submucosal thickening of the rectal wall with calcifications and infiltration of the mesorectal adipose tissue and multiple adenopathies in the mesorectal adipose tissue. The findings at endoscopic rectal ultrasound were also not suggestive for a rectal carcinoma. These findings were suggestive for a submucosal vascular malformation of the rectum. A control ileocolonoscopy showed a diffuse circumferential tortuous dilated vascular lesion with friable mucosa and telangiectasias in the rectum, without any dysplastic or ulcerative mucosal lesions suggestive of malignancy. Cavernous hemangioma is a blood vessel malformation that can be found in the small bowel, colon and rectum. This rare entity used to be called diffuse cavernous hemangioma of the rectum (DCHR). However, according to the International Society for the Study of Vascular Anomalies (ISSVA) this lesion needs to be classified as a venous malformation in the slow-flow lesion category. It can present with painless, overt or occult bleeding from the rectum. The differential diagnosis includes internal hemorrhoids, colorectal carcinoma, colonic angiodysplasia, and inflammatory bowel disease. Management of a venous malformation of the rectum can be challenging. Surgery is the only definitive treatment, with complete resection of the malformation. Alternative treatments such as

radiofrequency ablation therapy, sclerosis, and embolization have shown high recurrence rates. Since our patient was mildly symptomatic, required temporary anticoagulation therapy and did not want to undergo surgery, a conservative approach was decided in a multidisciplinary discussion. During the follow up for 2 months now, the patient has remained clinically stable with only minor blood loss. In conclusion, cavernous hemangioma of the rectum is a rare blood vessel malformation that can present with painless, overt or occult bleeding from the rectum. It is often misdiagnosed due to a lack of knowledge of the clinical, endoscopic and radiological features, and treated inappropriately for years. It can be suspected at endoscopic examination and confirmed radiologically. Biopsies of the lesion should be avoided due to the risk of bleeding, which fortunately was not the case in our patient. A multidisciplinary approach is recommended, knowing that surgery is the only definitive treatment.

C09

Gastric amyloidosis: unusual cause of massive upper digestive bleeding.

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Case Report: We present the case of a 71-year-old man who had nausea, epigastric and retrosternal chest discomfort for 5 months. He had antecedents of gastric ulceration in 2014. The initial gastroscopy performed in March 2018 showed ulcerative gastritis. Biopsies of the stomach were HP negative. An additional gastroscopy in May 2018 because of persistent discomfort confirmed the diagnosis (ulcerative gastritis) but anatomopathological examination revealed no malignancy. RX OMD, CT abdomen, PET CT were negative besides gastritis. EGD examination in October 2018 revealed once more a fine granular appearance of gastric mucosa and polypoid protrusions of the gastric mucosal folds, erosions, deep ulcerations and friability. The latest histological examination revealed a gastric mucosa amyloidosis without Helicobacter pylori or gastric neoplasia. CEA, 24-hours urine collection, ECG all turned out normal. Chest X-ray revealed no abnormalities. In the previous weeks before this admission X-ECG and echo cardio were also normal. Colonoscopy including biopsy in the rectum for Congo red staining was negative. Because of major upper digestive bleeding due to persistent gastric ulceration surgery was inevitable. Partial distal gastrectomy was performed. Anatomopathological examination confirmed deposition of amyloid transmural in the stomach and in the stroma. Depositions of amorphous eosinophilic material, especially surrounding blood vessels were found. These depositions were positive on Congo red coloration. Amyloid A coloration was negative. No lymphadenopathies were involved. Diagnosis of a non-AA amyloidosis was made. Electron microscopy confirmed deposition of typical fibrils. Conclusion: We present a case of non-AA amyloidosis with secondary gastric ulceration and upper digestive bleeding. No other pathological signs of this disease were found during further examination. Amyloidosis is a systemic disease that is capable of targeting the GI tract. Gastric involvement is symptomatic in

only 1% of patients. The accompanying symptoms are non-specific (diarrhoea, bleeding, malabsorption, …). Gastric ulcers resembling carcinoma or ulcerative gastritis can occur. As amyloidosis is a disease with poor prognosis, early diagnosis and treatment are required. To achieve early diagnosis, it is necessary to collect biopsy specimens from gastric zone and duodenum. In patients older than 30 years with unexplained diarrhoea, weight loss, autonomic dysfunction, malabsorption or proteinuria, amyloidosis has to be considered anyway to achieve early diagnosis and treatment.

C10

Unusual cause of low abdominal pain: colon perforation due to a spontaneous migration of an intrauterine device.

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Case Report: Colon perforation due to intrauterine device (IUD) migration is a very rare but possible serious complication of IUD insertion. Clinical presentation can vary from absence or nonspecific symptoms to peritonitis, abcedation, fistulisation or intestinal obstruction with different incidence numbers found in the current literature. In nearly all cases laparoscopic removal of the IUD is necessary. We report the case of a 53-year-old woman, gravida 2 para 2, who was referred to the outpatient clinic by her general practitioner because of longstanding abdominal pain. She had a medical history of appendectomy and constipation. She didn't take any medication and there was no substance use. Abdominal examination revealed localised tenderness in the right lower quadrant without peritoneal signs. Blood analysis was completely normal. To exclude slow transit constipation a pellet study was performed. Plain abdominal radiography on day 1 showed the presence of all (24) ingested pellets and an abnormal, slightly lateralized and angulated position of the IUD. An abdominal computed tomography was also planned on the same day because of the low abdominal pain. These images revealed a partial migration of the intrauterine device, a levonorgestrel intrauterine system called Mirena®, placed five years earlier. One side arm of the IUD was perforating the sigmoid colon while the other arm was embedded in the meso-sigmoidal fat. There were no signs of inflammation nor pneumatosis in the peritoneal cavity. The pellet study was not completed. We referred the patient to the abdominal surgeons and a laparoscopic removal of the intrauterine device with closure of the sigmoid colon wall defect was successfully performed . No antibiotics were started. The postoperative course was uneventful and her complaints quickly disappeared postoperatively. Conclusion: This case illustrates a rare complication of IUD insertion. Extrauterine IUD migration mostly has a silent or low-grade course, but secondary perforation of adjacent organs such as the gastrointestinal and/or urinary tract is possible. Abdominal computed tomography remains the mainstay to reveal the exact location and potential complications of the migrated IUD. Laparoscopic removal of the IUD is necessary in nearly all cases.

C11

Primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue with an underlying chronic hepatitis B virus infection: How about aiming at the virus?

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Case Report: Introduction: Primary hepatic mucosa-associated lymphoid tissue (MALT) lymphoma is an extremely rare disease. Different underlying conditions are described in literature. Little is known about its clinical course and optimal treatment. Case report: A 31-year-old man of African ethnicity presented at our institution with the sole complaint of generalized pruritus since one month. There were no other known comorbidities. There was no use of addictive substances. On clinical examination scleral jaundice and a 15% weight loss was observed. A blood panel demonstrated moderate cholestasis with an important direct hyperbilirubinemia (28.4mg/dL) and discrete cytolysis (2x ULN). Viral serology suggested a chronic hepatitis B virus (HBV) infection with a low count of circulating HBV-DNA (48 UI/mL). Hepatitis delta virus serology was negative, so was auto-immune testing. An abdominal ultrasound (US) showed a heterogeneous aspect of the liver. A magnetic resonance (MR) of the liver suspected tumor infiltration of the left hepatic lobe and showed a diffuse cholangitis pattern with multiple stenosis of the central bile ducts. Introduction of a biliary stent for a substenosis of the common bile duct on ERCP did not improve the clinic. Liver biopsy disclosed a periportal lymphocytic inflammation and septa compatible with HBV related chronic hepatitis. Next to a morphology and immunohistochemistry compatible with a marginal zone lymphoma. But with absence of a monoclonal rearrangement of IgH and IgKappa. PET-CT evaluation revealed several hypermetabolic lymphadenopathy on both sides of the diaphragm, which altogether makes a stage IV B according to Ann Arbor staging. Consequent bone marrow biopsy was normal. A treatment with tenofovir in compassionate use was initiated. A control hepatic MRI at two months showed a significant diminution of the lymphomatoid infiltration of the left hepatic lobe, a normalization of the cholangitis aspect and a diminution of the adenopathy. The biliary stent was removed and the cholangiogram suggested a net structural amelioration. PET-CT evaluation at six months showed ‘partial response’ according to the Deauville five-point scale with complete resolution of the extrahepatic lymphadenopathy. The patient has recovered a normal liver function, his weight normalized and he has completely resumed everyday life without pruritus. Discussion: MALT lymphoma generally arise in the background of chronic inflammation associated with infective agents or autoimmune diseases. In literature several underlying conditions are reported. Inter alia both hepatitis C virus (HCV) and HBV are described in a low number of cases specifically in hepatic MALT lymphoma. The correlation between HBV and hepatic MALT lymphoma remains unclear. Treatment modality should be selected in each case in accordance with tumor size, tumor location and the underlying liver disease. Among the most reported treatment options are surgery, chemotherapy (CHOP regime) and

rituximab. Despite the intrinsically indolent and slowly progressive character of this disease, we opted to initiate a treatment because of the presence of hepatic cytolysis and a B symptom (significant weight loss). Although our patient is an inactive carrier for HBV, we started to treat with an antiviral drug. At one hand to avoid reactivation in case of eventual administration of systemic therapy. At the other hand in analogy with Helicobacter pylori associated gastric MALT where eradication of this underlying infective agent can be sufficient. Conclusion: Described here is a rare case of a primary hepatic MALT lymphoma with an underlying chronic HBV infection which was treated in first intention by an antiviral molecule with achievement of partial response at six months.

C12

Mildly elevated liver enzymes and steatosis: not always NAFLD

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Case Report: We present the case of a 40-year old male seen at our outpatient hepatology clinic because of mildly elevated liver enzymes. His medical history was unremarkable besides a treated Wolff-Parkinson-White syndrome. The patient consumed 2 units of alcohol per week, did not smoke, neither used illicit drugs. He did not take any medication, nor any nutritional supplements. The patient was a manager at human resources. His clinical examination showed no signs of chronic liver disease, he had a BMI of 23.9 kg/m2. Neurological investigation was ongoing because of progressive and unexplained gait disturbances, a pyramidal syndrome, sensational disturbances in the lower extremities and a neurogenic bladder dysfunction for more than 10 years. The brother of the patient had similar complaints but less prominent. Biochemically, mildly elevated transaminases and CK were seen (AST 48 U/L, ALT 66 U/L, CK 514 U/L), no signs of cholestasis (GGT 38 U/L, AF 52 U/L) and no signs of liver dysfunction (total bilirubin 0.4 mg/dl, INR 0.92). An extended lab analysis did not reveal any classical cause of chronic liver disease (e.g. viral, auto-immune, metabolic). On ultrasound mild steatosis (grade 1) and shear-wave elastometry showed no arguments for advanced fibrosis (F0 - F1). MRI of the brain revealed extensive areas of confluent white matter disease in both cerebral hemispheres, cerebellum and brainstem in addition cervical myelum atrophy. Electromyography was consistent with a motoric polyneuropathy, in particular in the right leg. Analysis of the cerebrospinal fluid did not reveal any abnormalities. A diagnostic liver biopsy was performed and revealed a normal architecture without increased cellularity and with quite pronounced micro-macrovesicular steatosis (grade 2). There were no areas with inflammation, nor Mallory bodies, cholestasis or accumulation of iron. Some hepatocytes showed ballooning and limited perisinusoidal fibrosis was observed. Given the combination of liver steatosis

with the neurological problems, liver tissue was analyzed for mitochondropathy, but returned negative. Additionally, lysosomal acid lipase deficiency (LAL-D) was excluded as well. A diagnosis of NAFLD was made. Years went by with persistently elevated transaminases and a persisting image of liver steatosis on ultrasound. Because of slow progression of the neurological symptoms, a whole exome sequencing was performed, in which a compound heterozygote mutation in the glycogen branching enzyme 1 (GBE1) gene was found. The GBE1 gene is linked with a spectrum of autosomal recessive diseases with liver and neuromuscular involvement, called glycogen storage disease type IV (GSD IV) or Andersen disease. Typical for these conditions is the accumulation of polyglucosan bodies in tissues like the liver and the central and peripheral nervous system. Different subtypes of GSD IV have been described: a fatal perinatal neuromuscular subtype, a congenital neuromuscular subtype, a childhood neuromuscular subtype and a hepatic subtype. The hepatic subtype appears to be the most common presentation of GSD IV with a progressive and a non-progressive form. In the progressive form, children may appear normal at birth, but a rapid deterioration with failure to thrive and elevated liver enzymes is seen in the first months of life. Death of liver failure is usually seen before the age of 5 years without transplantation. In the less common non-progressive form hepatomegaly and liver dysfunction develop during childhood, but without further progression of the liver disease. Adult polyglucosan body disease (APBD) is an extremely rare form of GSD IV with an adult onset of progressive neuromuscular disease. The spectrum contains a spastic gait, neurogenic bladder dysfunction, peripheral neuropathy, leuko-encephalopathy on imaging and a gracile presence of the myelum. A disease course similar with that of our patient and currently accounted as explanatory for the hepatological findings. Unfortunately, to date there is no treatment available for this condition. Glycogen storage disorders are very rare and for that reason they are seldom included in the differential diagnosis. Nevertheless, in patients with the combination of elevated liver enzymes and progressive neurological symptoms, inborn errors of metabolism, such as glycogen storage disorders should be looked for.

C13

Recurrent hepatic encephalopathy: beyond infection and GI bleeding.

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Case Report: A 72 years old female patient, known with cirrhosis Child Pugh B secondary to non-alcoholic steatohepatitis (NASH) and alcohol abuse, was admitted repeatedly since April 2020 due to hepatic encephalopathy (HE), with several episodes of deep coma requiring intubation and observation on the intensive care unit (ICU). Further history included hypothyroidism and type 2 diabetes mellitus. Apart from signs of cirrhosis physical examination was not contributive. Active, though minimal, alcohol consumption was reported during the initial hospitalization. Minimal ascites not

amenable to aspiration, was noted by ultrasound. Infection, gastro-intestinal bleeding and portal vein thrombosis were actively and repeatedly excluded. Imaging, lumbar puncture and EEG ruled out central causes of encephalopathy. There was no evidence of hepatocellular carcinoma. Glucose levels were normal, although there was poor metabolic control of type 2 diabetes mellitus. Micronutrient deficiency were excluded. Because of hypothyroidism thyroid substitution was increased accordingly. Vitamin B1 substitution, diuretics and lactulose were initiated in hospital and continued upon discharge. Because of the recurrent episodes rifaximin was added. During a subsequent admission for HE levetiracetam was started because of epileptic activity on EEG. A transfer to a service residence was arranged to improve compliance to treatment. Nevertheless, 2 weeks later, the patient was readmitted for the fourth episode of altered mental state. An abdominal contrast-enhanced CT-scan identified recanalization of the umbilical vena with presence of a shunt between the portal and the deep venous system via the right iliac vena. Partial embolization was performed with subsequent improvement of mental state. HE is a feature of decompensated cirrhosis. It is associated with significant morbidity and mortality. In cases refractory to treatment, assessment of a portosystemic shunt is recommended. Around 60 % of patients remain free of hepatic encephalopathy three months after embolization, and 49-55 % after 1-2 years.

C14

Haematochezia in a patient with liver cirrhosis, a portal hypertensive bleed?

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Case Report: We present a case of a 54 year old woman with a history of severe alcohol abuse, initially hospitalized with icterus and an ALT above 3xULN. This was the first presentation on a hepatology ward. Initial evaluation with extensive lab evaluation and imaging ruled out other cases of acute hepatitis, hence the diagnosis of acute alcoholic hepatitis was put forward, with an underlying cirrhosis and portal hypertension. Treatment with corticosteroids was initiated as the Maddrey score was 57. Two weeks after presentation the patient had severe haematochezia with hemodynamic instability. Initial gastroscopy was negative for an upper GI bleed and a portal hypertensive cause of upper GI bleed. A sigmoidoscopy demonstrated a rectal ulceration. She was referred for urgent interventional angiography due to hemodynamic instability. This was negative for active bleed. Repeat-sigmoidoscopy reconfirmed a circumferential rectal ulceration which was treated with injection of adrenalin and hemoclips. Initial hemostasis was achieved, but due to repetitive bleeding an urgent surgical intervention was acquired. Anal exploration showed a circumferential ulceration in the rectum with

active bleeding. Local haemostasis was achieved through coagulation and sutures and deep biopsies of ulceration were taken. Biopsies showed acute fibropurulent inflammation without any recognizable microorganism, demonstrating no signs of IBD and tissue-PCR of the ulceration was negative for Herpes virus and cytomegalovirus (CMV). Another episode of acute haemorrhage with hemodynamic instability occurred after a few days and a second urgent angiography was performed. This revealed rectal varices in the portal phase without signs of active bleeding. An urgent TIPSS procedure, was performed with haemostasis after coiling of the rectal varices. The portosystemic pressure gradient before TIPSS insertion was 28 mmHg and it was reduced to 8 mmHg after TIPSS. A transjugular liver biopsy was taken during the procedure which confirmed the diagnosis of underlying micronodular liver cirrhosis and severe cholestasis. Corticosteroids were rapidly tapered until stop, given the absence of histological inflammation on liver biopsy. The evolution of the MELD score during hospitalisation was initially 26 and after several weeks admission evolved to 13. Due to active alcohol abuse the patient was not screened for liver transplantation. Despite a TIPSS and additional haemostasis of the rectum, haematochezia continued, for which a new gastro duodenoscopy and a total colonoscopy were performed, which revealed multiple deep ulcerations in the colon and a large ulceration in the cardia of the stomach. New biopsies were positive for Epstein Barr virus (EBV) on PCR. Additional in situ hybridization for Epstein Barr virus (EBV) on the biopsies was positive confirming the diagnosis of EBV colitis, together with positive serum PCR for EBV. The patient was treated with intravenous acyclovir 10mg/kg three times daily. After initial clinical improvement the patient unfortunately passed away. EBV is a double-stranded DNA herpesvirus that infects and persists in more than 90%. (1) Involvement of the gastrointestinal tract is rare, in which this latent infection reactivates, mostly in immunocompromised patients or those with locally impaired antiviral immunity secondary to underlying gastro-intestinal disease (e.g. IBD patients)(2). It manifests as an EBV-associated lymphoproliferative disease. Diagnostic gold standard is identification of EBV in biopsy via in situ hybridization. It is challenging to differentiate an EBV colitis from EBV as innocent bystander in other causes of colitis, which can be done on other pathology findings. In our case there was concomitant chronic liver disease with acute alcoholic hepatitis being treated with corticosteroids, other causes of colitis were excluded, hence the diagnosis of EBV colitis was put forward. This case emphasizes the importance to exclude non-portal hypertensive related origins of severe lower gastrointestinal bleeding. 1. Epstein-Barr virus infection – Cohen 2000 2. EBV-associated colitis mimicking IBD in an immunocompetent individual – Karlitz 2010 3. Rare case of EBV-induced colitis in an immunocompetent individual – Choi 2020 4. Epstein Barr virus-positive mucocutaneous ulcer of the colon associated Hodgkin lymphoma in Crohn's disease – Moran 2015

C15

Cessation of Nucleos(t)ide Analogues in long-term virally suppressed chronic hepatitis B patients – close monitoring is key

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Case Report: Introduction: Increasing evidence suggests that Nucleos(t)ide Analogue (NA) treatment cessation is safe in patients without advanced fibrosis following long-term viral suppression (>2 years). Aim: We report a case of serious liver-related complications following NA cessation in a patient without advanced fibrosis. Methods: Nucleos(t)ide Analogue treatment was stopped in a 69-year old, male, Caucasian, start of treatment HBeAg negative, chronic hepatitis B patient. Apart from chronic hepatitis B, his medical history was insignificant. At the moment of treatment cessation, the patient had been treated with Tenofovir Disoproxil Fumarate for 6 years, with completely undetectable viral loads during the last 5 years. There were no signs of advanced liver fibrosis and all liver tests were normal. Follow-up was foreseen six months after treatment cessation. Results: A little more than five months after treatment cessation, the patient presented to the outpatient clinic with extreme fatigue, epigastric pain and a decreased intake since one week. Diagnostic workup showed a fulminant Hepatitis B flare (ALT >15x Upper Limit of Normal, HBV DNA >4x10^9 IU/mL) with signs of hepatic dysfunction (INR 1.7; Bilirubin 5.9 mg/dL). The patient was hospitalized for surveillance and Tenofovir treatment was immediately restarted. Unfortunately, a rapid deterioration was noted with signs of increasing liver failure (Maximum Bilirubin 22.1 mg/dL, maximum INR 4.14, minimum Factor V: 22%) necessitating a liver transplantation 2 weeks later (MELD score: 37). The explant liver showed a massive collapse (>50% necrosis) but without any sign of fibrosis (F0). Post-transplant follow-up was marked by a Graft Versus Host disease for which the patient was treated with ruxolitinib and recently a severe COVID-19 infection complicated by invasive aspergillosis. Conclusion: This case highlights the need for close follow-up after NA treatment cessation in order to detect relapse early and act accordingly. Recommendations for close monitoring are urgently needed.

C16

Oxaliplatin induced focal nodular hyperplasia of the liver

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Case Report: Case reports: In this abstract, we present two patients with colonic cancer, who developed multifocal liver disease suggestive of liver metastasis, but turned out to have benign chemotherapy related liver lesions. The first patient, a woman of 37, presented in 2016 with an adenocarcinoma of the sigmoid. She underwent a laparoscopic sigmoidectomy and the final staging was pT4N2aMx. Postoperatively she

received 6 months of FOLFOX (leucovorin, 5-FU + oxaliplatin) chemotherapy. In 2018 a metastasectomy in the sixth segment of the liver was performed for a solitary liver metastasis, and after this surgery she received another 3 month course of FOLFOX chemotherapy. A CT-scan in June 2020 was indicative of multifocal liver metastasis, mainly in segment 7 and 8. An MRI of the liver showed even more substantial disease, with nodules in both lobes of the liver. CEA was 8. The lesions showed no FDG-PET avidity, but they were very small and the radiologist found them indeed very suggestive of malignant disease, especially given her history of liver metastasis. Given the young age of the patient, an aggressive surgical approach with curative intent was postulated. She had extensive surgery of the liver, including a left hepatectomy and microwave ablation of the smaller lesions. Anatomopathological examination did not display any signs of malignancy, on the contrary, they were benign lesions found that seemed to be focal nodular hyperplasia (FNH). She recovered well and no further therapy was administered. So far she is doing well. Our second patient, a 50 year old man, was diagnosed with a rectal K-ras mutated adenocarcinoma in 2018. He started 6 cycles of neoadjuvant chemoradiotherapy with 5-FU, followed by an uneventful TaTME procedure. Definitive staging was ycT3N1M0. Afterwards, adjuvant chemotherapy was initiated, and he received 10 cycles of FOLFOX. The oxaliplatin was stopped 2 cycles before the end of the 12 cycles due to grade 2 polyneuropathy. Nine months after the last chemotherapy, follow up imaging showed a new lesion in segment 8 liver that wasn't present before. An R0 resection of the metastasis through segmentectomy of liver segment 8 was performed, without complications. Five months after this surgery, another liver lesion was found in segment 6 and the patient was scheduled for minimally invasive liver surgery. CEA level was normal. Intra-operatively, the lesion did not have the typical aspect of malignant infiltration. A frozen section was subsequently sent to pathology and turned out to be benign FNH. Discussion: Focal nodular hyperplasia is a benign condition, consisting of non-malignant nodules in liver tissue. It probably arises from disturbed local blood flow (1). Oxaliplatin is a platinum-based antineoplastic drug. It is used in the adjuvant treatment of stage III and metastatic colorectal cancer. It has several hepatotoxic effects. Rubbia-Brandt et al investigated several liver resection specimens in patients with colorectal metastatic liver disease (2) A significant number of patients treated with oxaliplatin demonstrated moderate or severe sinusoidal obstruction syndrome. Worldwide there have only been few cases of (either pathologically or radiologically) oxaliplatin induced nodular liver disease described in the past 13 years, which are summarized in a recent review of the literature (3). Another case series by Furlan et al found FNH in fourteen patients on MRI of liver post therapy with oxaliplatin (4). In 7 of them, this was also confirmed via pathological examination. The other seven patients were suspected to have FNH and did not receive surgery. In our patients, there was no evidence of FDG-PET avidity in the first case and CEA was 8 and 1 respectively. In the other patients described in the literature, CEA was negative. In the other cases described in the literature who report CEA and nuclear imaging, there was also no FDG-PET avidity or elevated CEA present. (5) There are some specific characteristics on MRI that can distinguish malignant lesions

from FNH, such as strong, homogeneous hyperenhancement in the arterial phase, lack of washout in the portal venous phase. Furthermore, isointensity or hyperintensity on hepatobiliary phase images after hepatobiliary contrast injection are very suggestive of FNH. (4) Conclusion: Focal nodular hyperplasia of the liver can arise following oxaliplatin use and can mimic metastatic disease on imaging (both CT and MRI). Differential diagnosis includes malignancy, but also cystic lesions, hemangioma and hepatic adenoma. Especially in patients with normal CEA and no FDG-PET avidity, the possibility of FNH should be considered. There are some typical MRI characteristics that can distinguish these lesions from malignancies. Keeping this in mind, we can maybe avoid overtreatment of these patients. Therefore we suggest that in people who received oxaliplatin, liver lesions should be checked for FDG-PET avidity before planning surgery.

Belgian Society for Gastrointestinal Endoscopy (BSGIE)

G01

Prevalence and detection of early adverse events following POEM in a single-center patient cohort – why performing post-procedural imaging or endoscopy can be omitted

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Introduction: Peroral Endoscopic Myotomy (POEM) is an endoscopic procedure that has earned its place in the treatment of achalasia and hypercontractile esophageal disorders. Early adverse events (AEs) of POEM include insufflation-related events, bleeding and infections. In most centers measures are taken in order to rapidly detect immediate post-operative AEs, including repeat endoscopy or a water soluble contrast esophagogram. It is currently not well known to what extent these investigations will influence clinical outcome or guide our therapeutic decision making.

Aim: The goal of this retrospective, single-center cohort study was to characterize the prevalence of early AEs following POEM (within 14 days), and to assess whether early AEs following POEM can be predicted by technical investigations performed post-procedure.

Methods: All patients were contacted 14 days following POEM to inquire about the possible occurrence of AEs (according to the Clavien-Dindo classification). The characteristics of failed procedures were assessed, as were the AEs following all procedures and the findings on repeat endoscopy and esophagogram the following day.

Results: Between August 2011 and October 2020, a total of 352 consecutive POEM-procedures were performed by two experienced endoscopists in our center. 11 of these 352 procedures were unsuccessful (3.13%), 8 due to the presence of extensive submucosal fibrosis, 2 due to loss of orientation in the submucosal tunnel and 1

extensive submucosal hemorrhage who underwent a successful POEM in a second attempt. Fibrosis was present in subjects that underwent radiotherapy for other indications prior to POEM, or following long standing disease (> 10 years). Between August 2011 and August 2016 a barium esophagogram was routinely made the following day in all procedures- in three of these patients (3/162 subjects, 1.85%), a contrast leakage judged by the radiologist as significant was visualized and endoscopic treatment for this was performed. After August 2016, esophagograms were no longer performed, and none of these patients afterwards (0/190) required a repeat endoscopy anymore. Repeat gastroscopy was performed 48h post-POEM in the first 14 consecutive subjects - no repeat interventions were performed based on these findings and therefore aborted as well. Intra-procedural events were observed in 19.89%, with drainage of a capnoperitoneum (22/352, 6.25%) and closure of a distal mucosal perforation (17/352, 4.82%) by additional clipping being the most prevalent ones. No deaths or debilitating AEs were observed.
Conclusions: POEM is a safe procedure, with no severe AE reported in this large retrospective single-center cohort study. Performing an esophagogram post-POEM may trigger obsolete repeat procedures when POEM was performed by highly skilled endoscopists, as none of the patients without mandatory imaging following POEM necessitated repeat intervention.

G02

Impact of endoscopic duodenal and ampullary resection in familial adenomatous polyposis patients: Spigelman classification can be considered as outdated due to a low risk of invasive cancer in patients with regular follow-up and endoscopic resection, even in stage III and IV.

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Introduction: Familial adenomatous polyposis (FAP) is an autosomal dominant polyposis syndrome with varying degrees of penetrance. A dedicated endoscopic surveillance with endoscopic resection (ER) of duodenal and ampullary lesions has been proposed by the European guidelines. Surgery has been traditionally considered as the gold standard according to the Spigelman classification, particularly indicated in patients with advanced pathology or FAP-related polyps not amenable to ER. However, Spigelman IV polyposis may be absent in half of FAP patients with duodenal cancer and ER may prevent the occurrence of cancer. Thus, the optimal approach for management of non-ampullary duodenal tumors (NADTs) and ampullomas in FAP remain to be determined.
Aim: To describe the impact of ER in patients with FAP and ampullomas/duodenal adenomas on occurrence of invasive cancer or need for surgery, and the role played by Spigelman classification on the patient's management.

Methods: This is a national-based observational retrospective study. All consecutive >18 years-old patients with genetically confirmed FAP who underwent endoscopic follow-up for duodenal lesions under the FAPA network in 1998-2020 were included. Demographic variables including age, sex, smoking, NSAIDs use, APC mutation, and personal history of cancer were collected. ER was performed according to the characteristics of the lesions at the discretion of the endoscopist (cold snare resection, EMR, ESD, ampullectomy, ablation, etc). The number of endoscopies, number of NADTs (1-4, 5-20, >20), largest tumor size, ER technique, Spigelman stage, presence of an ampullary tumor and most advanced pathology were noted. The main outcome was to describe the impact of ER in FAP patients by analyzing the occurrence of advanced lesions during endoscopic follow-up. The need for surgery was also evaluated.
Results: One-hundred and eleven patients (mean age: 25 ± 14 years, 49.5% male) were included. The most frequent mutation was APC (n=71, 63.4%). They had a personal history of colorectal cancer (n=17, 15.6%), smoking history (n=23, 21.3%), or NSAID intake (n=40, 37.4%). Sixteen patients were lost to follow-up (14.4%). Ninety-five patients were followed-up during a median of 168 months (range: 6-408) and 10 endoscopies (range: 2-35). The first endoscopy showed 1-4 NADST (n=25, 50%), 5-20 NADST (n=11, 11.6%) and >20 (n=14, 14.7%) of 1-4mm (n=30, 31.6%), 5-10mm (n=7, 7.4%) and >10mm (n=12, 12.6%). The histology confirmed a villous component in one case (1.1%) cases and high-grade dysplasia in 5 (5.3%) cases. The Spigelman stage (median: 1, range:0-4) was classified in 0 (n=38.9%), I (n=5, 5.3%), II (n=13, 13.7%), III (n=19, 20%) and IV (n=21, 22.1%). An ampulloma was treated in 9 patients (9.5%). The last follow-up endoscopy confirmed an advanced Spigelman status (III-IV) in 24 cases (25.3%). Thus, the Spigelman status decreased one point between first and follow-up endoscopy (median: 2, range 0-4 vs. 2, range:0-4, p=0.055) and the difference in advanced Spigelman status was statistically significant (42.1%% vs. 25.3%, p<0.001). Overall, the occurrence of duodenal adenocarcinoma was confirmed in only one case (1.1%) with a 0-stage in initial Spigelman classification. The presence of >20 polyps at first endoscopy was correlated to a higher advanced Spigelman status at the end of the follow-up compared to those patients with <20 polyps (51.6% vs. 23.8%, p=0.041), but there was no increase of need for surgery (p=0.228) or cancer incidence (p=0.632). Six patients (6.3%) required duodenal surgery during the follow-up. Similarly, the initial Spigelman status was not associated to an increased incidence of cancer (p=0.238) or need for surgery (p=0.662).
Conclusions: Duodenal and ampullary endotherapy in FAP patients is effective, the incidence of invasive duodenal or ampullary carcinoma or need for surgery during follow-up are rare. Patients with a high number of NADTs and/or high-grade dysplasia can be safely treated and followed by endoscopy. Spigelman classification seems outdated since not related to invasive cancer or need for surgery, in patients with regular follow-up and endoscopic resection.

G03
Endoscopic dilation of post-sleeve gastrectomy stenosis: long-term efficacy and safety results

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Introduction: Post-sleeve gastrectomy (SG) stenoses occur in about 5% of cases. Hydrostatic dilation (HD) and pneumatic dilation (PD) have been proposed as treatments, but efficacy data remain scarce.

Aim: The objectives of this study were to evaluate the safety and the initial and long-term efficacy of endoscopic balloon dilation for post-SG stenosis according to different mechanisms of post-SG stenosis.

Methods: This retrospective study in a referral endoscopy center included patients with symptomatic post-SG stenosis treated with endoscopic balloon dilation (EBD). Stenosis was defined as “organic” if luminal narrowing was evident, “functional” for a deformation, or “combined”. Endoscopic treatment consisted of ≥1 HD (15-20 mm) and/or ≥1 PD (30-35 mm). Initial success was defined as improvement of stenosis-related symptoms at 1 month and long-term success as persistence of improvement at last follow-up.

Results: Forty-four patients (73% women; mean age 45.5±11 years; mean follow-up 26±23months) underwent EBD between 2013 and 2019. HD and PD were used in 15 (34%) and 29 (66%) patients, respectively, (mean dilation number: 1.8±1.1). Post-SG stenoses were considered organic in 10 (23%), functional in 21 (48%), and combined in 13 (29%) patients. Initial success was achieved in 42 (96%) patients, while 35 (80%) patients had no symptom recurrence at last follow-up. Perforation occurred in one patient. HD was more frequently used in organic stenoses (8/10), while PD in functional and combined stenoses (18/21 and 9/13, respectively; $p<0.001$). Rates of success did not differ by type of stenosis.

Conclusions: Endoscopic dilation is an effective treatment for post-SG stenoses, providing long-term symptom relief. PD should be preferred in cases of functional stenoses, and HD used for organic stenoses.

G04

Pneumatic balloon dilation for the treatment of post-fundoplication symptoms: long-term efficacy and safety results

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Introduction: Post-laparoscopic fundoplication (LF) dysphagia occurs in 5%-17% of patients and its optimal management remains questionable.

Aim: We assessed the safety and efficacy of pneumatic dilation (PD) in patients with post-LF symptoms.

Methods: Medical files of all patients treated with at least one PD for post-fundoplication-associated symptoms were reviewed. Demographic, clinical, radiological and endoscopic data were collected. Long-term clinical success was the primary outcome, while PD-related complication incidence comprised the secondary endpoint.

Results: From 2006 to 2019, 50 patients [76% women, 58.5±11.8 years, median follow-up 665 (304-1566) days] underwent 79 PD (mean: 1.58±0.84) with dysphagia being the most common symptom [78%; mean Eckardt score 4.84±1.88), followed by pain (10%) and vomiting (6%). A 30mm, 35mm and 40mm balloon was used in 45.6%, 43% and 11.4% of the dilations, respectively. Among 49 patients with available follow-up, 39 (79.6%; 95%CI 65.2-89.3) had an initial clinical response, while symptoms recurred in 9 patients (23.1%; 95%CI 11.7-39.7) and 4 of them were effectively treated by a new dilation. Thus, the overall long-term success rate of PD was 34/49 (69.4%; 54.4-81.3). Among 15 non-responders to PD, 12 underwent surgery (24.5% 95%CI 13.8-39.2; Nissen redo 58%). Overall, 4 complications (2 perforations, 1 muscularis dilaceration and 1 severe bleeding) occurred in 4 patients [incidence: 5.1% (95%CI; 2-12.3)]. The first perforation occurred at the level of the plicature (PD at 30mm), the second at the lower esophagus (PD at 40mm), while dilaceration occurred also at the lower esophagus after a PD at 35mm. An intrathoracic slipping of the Nissen was absent in all three cases. They were effectively treated with self-expandable metallic esophageal stents. Significant bleeding followed a PD at 35mm and was ceased using hemostatic clips.
Conclusions: Pneumatic balloon dilation for post-fundoplication-associated symptoms is associated with satisfactory long-term success rate and acceptable safety profile.

G05

ENDOSCOPIC MUCOSAL RESECTION OF COLORECTAL POLYPS: RESULTS, ADVERSE EVENTS AND TWO-YEAR OUTCOME

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Introduction: Endoscopic mucosal resection (EMR) is currently the first-line treatment for large sessile and flat colorectal polyps in Western centres. However, adenoma recurrence after EMR continues to be a challenge. Here we present the results on outcome, recurrence and adverse events of EMR of large sessile and flat colorectal polyps in a Belgian series.

Aim: The aim of this study is to assess the efficacy, safety and recurrence rate of EMR in a tertiary centre and to identify risk factors associated with local recurrence during first surveillance endoscopy (SE1).

Methods: We performed a retrospective study of 165 sessile and flat colorectal lesions measuring ≥15 mm, treated by EMR from October 2017 to October 2019. Subsequent colonoscopy and pathology reports were reviewed until October 2020 to identify recurrence. We used multivariate logistic regression to identify independent risk factors for recurrence at SE1.

Results: EMR was performed for 165 colorectal polyps in 142 patients and successful resection was achieved in 158 cases (95,2%). SE1 data was available for 117 of 135 eligible cases (86,7%) after a median time of 6,2 months (IQR 5-9,9), and showed recurrent adenoma in 19 cases (16,2%). Recurrence was mainly treated endoscopically (78,9%) by EMR, polypectomy or biopsy avulsion. Three patients (15,8%) underwent surgery and one elected a conservative approach due to age and comorbidity. SE2 was

available for 16 cases after a median time of 12,9 months (IQR 11,7–18,2). Persisting adenoma was found in 2 of 3 available cases after endoscopic treatment at SE1. These were managed by polypectomy or surgery. All 13 available cases without recurrence at SE1 remained free of adenoma at SE2. Independent risk factors for recurrence at SE1 were lesion size ≥ 40 mm (odds ratio [OR] 4,03; p = 0,018) and presence of high-grade dysplasia (OR 3,89; p = 0,034). Early adverse event occurred in 4 patients (2,4%) and consisted of 3 bleeding complications and 1 perforation. Twelve patients (7,2%) presented with delayed bleeding of which 3 required transfusion, with radiological intervention in one case. All other complications were managed either conservatively (n = 8) or endoscopically (n = 5) with various combinations of clipping, snare tip soft coagulation, BICAP cautery and submucosal adrenalin injection.
Conclusions: EMR is a safe and effective treatment for large sessile and flat colorectal lesions with low recurrence rates. Lesion size ≥ 40 mm and presence of HGD were identified as risk factors for early recurrence, highlighting the importance of compliance to follow-up in these cases.

G06
Pre-procedural Imaging Does not Predict Technical Failure of EUS-guided Intrahepatic Biliary Drainage: Post-hoc Analysis from a Large Retrospective Cohort
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Introduction: Endoscopic Ultrasound (EUS)-guided intrahepatic biliary drainage (EUS-IBD) is an emerging technique, which may facilitate endoscopic treatment in patients with failed ERCP or post-surgical anatomy. Limited data are available concerning pre-procedure risk assessment for technical failure. A better understanding of factors which influence technical success, might assist the interventional endoscopist in selecting the most optimal approach.
Aim: Our aim was to identify risk factors for technical failure of EUS-IBD and evaluate the usefulness of quantifying peripheral bile duct diameter on pre-procedural cross-sectional imaging for predicting technical failure.
Methods: A post-hoc analysis was performed of a large retrospective tertiary center cohort, in which all consecutive EUS-IBD procedures performed at the University Hospitals Leuven were included. Baseline characteristics, underlying disease characteristics, as well as technical procedural details and outcome were recorded. Left sided peripheral bile duct diameter (PBD) was measured on pre-procedural cross sectional imaging (CT or MRI), using a standardized method by measuring a third of the total liver span from the tip of the left liver lobe. This was used as an universal measuring point for the left sided PBD throughout our database. Variables which revealed a significant association with technical failure by means of univariate analysis where entered into the multivariate Cox regression model.

Results: In total, 124 patients were identified, of which 22 (17.7%), 52 (41.9%) and 48 patients (38.7%) underwent a rendezvous approach, hepaticogastrostomy or antegrade stenting respectively. Technical success was achieved in 108 out of 124 patients (87.1%). When comparing patients with either technical success or technical failure, baseline characteristics, including age, gender, underlying disease stage and disease manifestations, as well as technical approaches were similar. Pre-procedural imaging was available in 46.3% and 66.7% of patients with technical success and technical failure, with an almost identical median PBD of 5.0mm (IQR 4-6) and 5.1 (IQR 4-6) respectively (p=0.726). When stratifying both groups according to PBD, the incidence of PBD <3mm was significantly higher amongst patients with technical failure (2% vs. 20%, p=0.013). When comparing the remaining subgroups of patients with technical success vs. technical failure, a similar distribution of PBD was demonstrated: PBD ≥3 - <4mm (14% vs. 6.7%, p=1.000), PBD ≥4 - <5mm (44% vs. 20%, p=0.499), PBD ≥5 - <6mm (6% vs. 0%, p=1.000) and PBD ≥6mm (34% vs. 20%, p=1.000). When cross-sectional imaging from patients with CT to EUS-IBD-interval <72 hours were compared, similar results were found. All variables with p<0.20 on univariate analysis, which included use of 'rendezvous' approach and 'antegrade stenting', as well as 'PBD <3mm', were entered in the multivariate logistics regression, which yielded no independent risk factors for technical failure.
Conclusions: In patients undergoing EUS-guided intrahepatic biliary drainage, peripheral bile duct dilatation below 3mm on pre-procedural cross-sectional imaging was associated with technical failure. However, no independent risk factors for technical failure were identified, suggesting that in the expert setting, interventional endoscopists should not rely on pre-procedural imaging for patient selection.

G07

Biliary and pancreatic endoscopy in patients with previous Whipple's duodenopancreatectomy: Is enteroscopy-assisted ERCP the first choice?

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Introduction: Whipple's duodenopancreatectomy results in an afferent limb with biliary and pancreatic anastomosis. Endoscopic treatment of subsequent biliopancreatic pathology is challenging due to altered anatomy.
Aim: To evaluate feasibility and safety of single-balloon enteroscopy-assisted ERCP to treat biliary and/or pancreatic pathology in patients with Whipple's duodenopancreatectomy altered anatomy.
Methods: Retrospective analysis of 41 patients with Whipple's anatomic variations who underwent single-balloon enteroscopy-assisted ERCP from October 2014 to October 2020. Technical and clinical success rates and adverse events were evaluated.
Results: There were 29 patients with a biliary indication, 8 pancreatic and 4 both biliary and pancreatic. Biliary ERCP was performed in 33 (73%) and pancreatic ERCP in 12 (27%) patients. In the biliary group male/female ratio was 23/10 with mean age of 66 (32-84)

years. A total of 71 ERCP procedures were performed with a technical success rate of 63/71 (88.7%) procedures and a clinical success rate of 30/33 (90.9%) patients. Endoscopic treatment consisted of recreation or dilatation of the biliary anastomosis, extraction of intrahepatic bile duct stones with cholangioscopy and intraductal lithotripsy, plastic and metallic stent placement. Mild adverse events were self-limiting cholangitis and abdominal pain in 9/71 (13.7%) procedures. There were no serious adverse events. In the pancreatic group male/female ratio was 5/7 with mean age of 63 (53-80) years. A total of 19 ERCP procedures were performed with a technical success rate of 13/19 (68.4%) procedures (p=0.030 Chi-square vs. biliary ERCP) and a clinical success rate of 7/12 (58.3%) patients (p=0.012 Chi-square vs. biliary ERCP). Endoscopic treatment consisted of recreation or dilatation of the pancreatic anastomosis, removal of intraductal surgical drain, pancreatic stone extraction and plastic stent placement. Mild adverse events were self-limiting pancreatitis or abdominal pain in 5/19 (26.3%) procedures (p=0.145 Chi-square vs. biliary ERCP). There were no serious adverse events.

Conclusions: Biliopancreatic pathology in patients with Whipple's duodenopancreatectomy can be dealt with using single-balloon enteroscopy-assisted ERCP. Technical and clinical success rates are high (±90%) for biliary indications, whereas they are lower (<70%) for pancreatic indications. It is a very safe procedure with only mild adverse events. Enteroscopy-assisted ERCP can be considered to treat biliopancreatic pathology in patients with Whipple's duodenopancreatectomy.

G08

Endoscopic management of biliopancreatic pathology in patients with Roux-en-Y gastric bypass: lessons learned from multiple options

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Introduction: Treatment of biliopancreatic pathology is challenging in patients with altered anatomy. Different therapeutic approaches exist for Roux-en-Y gastric bypass (RYGB): device-assisted enteroscopy ERCP (DAE-ERCP), laparoscopy-ERCP (LA-ERCP), EUS-transgastric ERCP (EDGE) and percutaneous transhepatic cholangiography (PTC).

Aim: We evaluated efficacy and safety of single-balloon enteroscopy-assisted ERCP (SBE-ERCP) as first line therapy in RYGB patients. In case of failure, second line endoscopic therapy based on EDGE, PTC or LA-ERCP was performed.

Methods: A monocentric retrospective study of consecutive RYGB patients with biliopancreatic pathology were referred for SBE-ERCP or EDGE between June 2014 and November 2020. SBE-ERCP was considered first line technique because of its safety profile without transmural approach. Multistep EDGE was proposed when multiple and/or complex ERCP procedures were planned or when SBE-ERCP failed. LA-ERCP was proposed when SBE-ERCP failed in a patient who also needed cholecystectomy.

Results: 61 RYGB patients (43 women; mean age 54±8 years) were included. Indications were biliary disease in 51, pancreatic disease in 7 and both in 3 patients. 57 patients underwent first line SBE-ERCP with a total of 71 SBE-ERCP procedures and 4 underwent

first line EDGE. Average procedure time of SBE-ERCP was 87±22 min. Technical SBE-ERCP success rate was 56/71 (78.9%) procedures. Clinical SBE-ERCP success rate was 42/57 (73.7%) patients. Mild adverse events were self-limiting cholangitis, pancreatitis or abdominal pain in 8/71 (11.3%) procedures. There were no serious adverse events. Alternative endoscopic therapy (5 EDGE, 1 LA-ERCP, 2 combined PTC with redo SBE-ERCP) allowed additional successful treatment of 8/15 (53.3%) patients after failed SBE-ERCP, and together with 3/4 (75.0%) first-line EDGE procedures, leading to an overall clinical success rate using endoscopic techniques of 53/61 (86.9%) patients.
Conclusions: Thanks to its good technical and clinical efficacy and excellent safety profile, SBE-ERCP seems to be a good first line option to treat biliopancreatic pathology in RYGB patients. Alternative second line options are EDGE, PTC and LA-ERCP depending on the indication.

G09

About the diagnosis and treatment of suspected bile duct pathology in Roux-en-Y liver transplant patients

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Introduction: Biliary complications after liver transplantation are frequently dealt with by means of endoscopic retrograde cholangiopancreatograpy (ERCP) using a duodenoscope. However, when the bile duct is anastomosed on a Roux-en-Y jejunal limb, the biliary system is out of reach for conventional ERCP, and it is accessed usually via percutaneous transhepatic cholangiography (PTC) or surgery.
Aim: We retrospectively studied the feasibility of single-balloon enteroscopy-assisted ERCP (SBE-ERCP) to evaluate and treat biliary complications in liver transplant patients with Roux-en-Y reconstruction.
Methods: Between 2016 and 2020 all SBE-ERCP procedures in liver transplant patients were analysed for indications, technical and clinical success and adverse events.
Results: A total of 40 patients (26 males) with a mean age of 43±3 years (range 13-81) underwent 69 SBE-ERCP procedures. Indications were suspicion of anastomotic stricture (40%), cholangitis (32.5%), bile duct stones (20%), biliary leak (2.5%), haemobilia (2.5%) and sepsis of unknown origin (2.5%). Technical success rate per patient was 85% (34/40). Failure was due to inability to reach the hepaticojejunal anastomosis. SBE-ERCP was normal in 12/34 (35%), confirmed the anastomotic stricture in 12/34 (35%), bile duct stones in 6/34 (18%), indwelling metallic stent in 2/34 (6%) and biliary leak and bile duct torsion both in 1/34 (3%). Biliary endoscopic interventions: balloon dilatation (6-9 mm), plastic stent insertion (4-7 Fr), stone extraction, bile duct biopsy and direct cholangioscopy in 1 to 6 ERCP procedures per patient. Only minor adverse events (self-limiting cholangitis) were encountered in 5/34 patients (15%). Of all 69 SBE-ERCP

procedures, 54% were considered easy, 27% were difficult or very difficult (9%) and 10% were impossible. Clinical success of therapeutic SBE-ERCP was measured by the evolution of biliary liver function tests before, 1 day after and 30 days after the last SBE-ERCP procedure. There was a significant decrease in gamma-GT serum levels (345±90 U/L before, 257±73 U/L after and 146±27 U/L after 30 days, p=0.023) and alkaline phosphatase levels (337±70 U/L before, 343±89 U/L after and 198±53 U/L after 30 days, p=0.044), whereas the decrease in bilirubine serum levels was not significant.

Conclusions: Endoscopic evaluation of the bile duct system is feasible and safe using single-balloon enteroscopy-assisted ERCP in liver transplant patients with Roux-en-Y reconstruction. It allows close examination of the hepaticojejunostomy and the intrahepatic bile ducts, and endoscopic therapy leads to clinical improvement of liver function tests.

G10

Computer Aided Detection (CADe) in colonoscopy: an end-user experience using two systems.

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Introduction: CADe is a novel technology developed to increase adenoma detection rate (ADR). Recent studies have shown its effectiveness, however data on its acceptance in the endoscopy suite is lacking.

Aim: This study wants to investigate the perception of endoscopists towards CADe.

Methods: We performed a prospective, multicenter study including endoscopists at different levels of experience. No endoscopists had prior experience with CADe. Two different systems were used: Medtronic GI Genius and Fujifilm CAD EYE. For ten weeks, all colonoscopies performed with CADe were prospectively registered and assessed via a questionnaire, using LimeSurvey. In these, using slider bars (0-100), we explored the subjective experience and perceived performance of CADe, as well as the number of detected relevant lesions by the endoscopist and/or CADe. Relevant lesions were defined as adenomas and sessile serrated lesions. The data were analyzed using SPSS v26, normality was tested with a Shapiro-Wilk test and continuous variables were compared with an independent sample T-test.

Results: 791 colonoscopies were performed by 19 endoscopists of whom 3 trainees and 4 young (<5years experience) consultants. In total 720 lesions were detected, 54 thanks to CADe, which entails an increase of 8.1% lesions detected and an increase in lesion detection rate from 41.2% to 43.0%. Endoscopists scored CADe as user-friendly (63.9), not distracting (25.1), nor timewasting (26.6). In contrast, the auditory signal wasn't positively perceived (23.1). While endoscopists state they're triggered to better characterize the polyps (70.6), they don't feel their ADR increases (53.3), nor do they feel more confident (57.8). Overall CADe was experienced as having some added value

(61.9), without significant differences between the two systems. Trainees feel more positive about CADe, giving higher scores for perceived ADR increase (64.9; p=0.002), confidence (65.1; p=0.037) and overall added value (74.5; p<0.001).
Conclusions: The added value of CADe is perceived lower than the increase in lesion detection probably warrants. This might hinder the implementation of CADe in daily practice. More effort will have to be invested in convincing endoscopists to start using this technology.

G11

Semi-automated annotation tool outperforms trained medical students and is comparable to clinical expert performance for frame-level detection of colorectal polyps

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Introduction: Training of deep learning systems requires an enormous amount of labeled data. This data must ideally cover the entire range of polyp appearances in real life, but also the whole possible range of image qualities and polyp locations. Expert labelling of each frame in a polyp video is therefore the most robust way for constructing a training set, but this is very time-consuming and currently represents a major barrier for widespread implementation of AI in endoscopy.
Aim: This study aims to evaluate two alternative approaches for frame-level annotation: an innovative semi-automated labelling tool and manual annotation by trained medical students.
Methods: 20 unique polyp white light videos containing 6282 frames (14 adenomas and 6 sessile serrated lesions confirmed by histopathology, mean size 7mm, Olympus) were annotated with bounding boxes by a clinical expert. These annotations are used as the gold standard for comparison. Two cheaper annotation methods were then applied to evaluate their validity and relative performance: (1) a semi-automated labelling technique – this tool only requires 3 manually annotated video frames, from which a representation of the polyp is learned and transferred automatically to all the other frames in the video; (2) independent manual labelling of each video by three medical students – following a training module with polyp images and videos.
Results: The semi-automated method significantly outperforms all three students on frame-level sensitivity (paired t-test, p-value < 0.05) with 74, 63, 67 and 94% (SD 27, 20, 27 and 6%) respectively for student 1, 2, 3 and the semi-automated method. It also achieves the highest value for positive predictive value (PPV) with 89, 95, 65 and 97% (SD 31, 22, 22 and 6%) respectively and adjudicated PPV (for borderline low-quality frames) with 90, 95, 95 and 99% (SD 15, 7, 12 and 14%). The total time for annotation is also significantly shorter when using the semi-automated method with 264, 1208, 234 and 25 minutes respectively.

Conclusions: A semi-automated labelling tool is a faster, more efficient and valid approach for polyp detection. It outperforms three medical students, specifically trained for polyp recognition and is comparable to clinical expert performance.

G12

Implementation of Aldrete's scoring system significantly reduces recovery time after procedural sedation by more than 20%.

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Introduction: Endoscopic procedures are often performed after administration of procedural sedation and analgesia (PSA) by trained non-anaesthesiologist physicians, followed by monitored observation in a dedicated recovery area. Historically, discharge from this recovery area was based on time parameters (e.g. standard after 1 hour) or clinical assessment by the responsible nurses. The Aldrete's scoring system is a useful tool (5 parameters, 10 points) to objectivate this clinical 'gut feeling' to decide when a patient can be discharged safely.

Aim: In this study the effect of solely implementation of the Aldrete's scoring system on recovery time after procedural sedation was analysed in a real-life setting.

Methods: Between November 21st and December 12th 2019 recovery time after gastroscopy, colonoscopy and endoscopic ultrasound with procedural sedation and analgesia was actively monitored in 231 patients. All procedures were randomly included to represent a real-life situation with different endoscopists, recovery nurses, endoscopy systems and indications. After this observation period all endoscopy nurses were educated to implement the Aldrete's scoring system when discharging patients. The effect of implementation was monitored in 97 patients between February 13th and March 11th 2020.

Results: The average time spent in the recovery area was 59 +/- 22 minutes after procedural sedation with 3.5 +/- 1.3 mg midazolam and 30 +/- 19 mg pethidine. After implementation of the Aldrete's scoring system, the recovery time decreased significantly to 47 +/- 25 minutes ($p<0.01$) with similar doses of procedural sedation (3.5 +/- 1.2 mg midazolam and 32 +/- 19 mg pethidine). The decrease in time was between 19% and 35% for the different endoscopic procedures. No complications related to earlier discharge from the recovery area were observed.

Conclusions: Implementation of Aldrete's scoring system after procedural sedation and analgesia significantly reduces the time spent at the recovery area without increasing complication rate.

G13

Assessment of the clinical impact of postponing endoscopic procedures using risk stratification during COVID-19 pandemic: a prospective systematic multicentric study.

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Introduction: During the COVID-19 outbreak, we adopted in March 2020 our own risk stratification triage policy facing massive cancellation/postponing of all endoscopic procedures not considered urgent or immediately necessary. At the end of the first wave endoscopy activity resumed progressively. We aimed to assess the impact of procedure postponing on patient outcome.

Aim: We aimed to assess the impact of procedure postponing on patient outcome.

Methods: Six weeks after cancellation policy initiation, the endoscopic reporting system of two tertiary hospitals was modified to allow prospective completion of our electronic database. From 01/05/2020 to 30/08/2020, for each procedure, endoscopists were asked to precise whether: 1) the examination was postponed due to the COVID-19 outbreak; 2) the examination revealed a significant diagnosis (SD, e.g: neoplasia diagnosis and management, diagnosis and management of gastrointestinal bleeding lesion, stricture management, management of functional gastrointestinal disease with severe symptomatology, cyst and abdominal collection drainage, resection of large (pre)neoplastic lesions, gastrointestinal leak management, …) and 3) if postponing the examination had a significant impact on patient's management.

Results: During this period, a total of 5283 procedures were performed, including esophagogastroduodenoscopy: 60.3%, colonoscopy: 32.5%, ERCP: 4%, endoscopic ultrasonography: 2.9%, enteroscopy: 0.4%. Among them, 476 (9%) had been tagged as postponed procedures (PP) [esophagogastroduodenoscopy 50.8%, colonoscopy 43.5%, ERCP 2.5%, EUS 2.7%, enteroscopy: 0.4%; median postponing delay 71 (52-91) days]. 8.1% were postponed by the patient and 91.9% by the hospital. Examinations revealed a SD in 70 cases in the PP group (14.7%) and in 672 (14%) in the non-PP group during the same period (p=0.72). In 14 cases (2.9%) postponing the examination had a significant impact on patient management; 4 patients received a delayed diagnosis on management of cancer, 3 patients developed biliopancreatic complications and appropriate management was provided with delay in 2 and 3 patients with severe functional and inflammatory bowel diseases, respectively and 2 had severe esophagitis worsening.

Conclusions: Based on the analysis of PP procedures, the triage policy adopted during first wave COVID outbreak appeared adequate in term of proportion of SD and impact on patient management.

G14

Laparoscopic versus EUS-guided Gastroenterostomy for Gastric Outlet Obstruction: An International Multicenter Propensity Score-Matched Comparison.

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Introduction: In the management of gastric outlet obstruction, EUS-guided gastroenterostomy (EUS-GE) seems safe and more effective than enteral stenting. However, comparisons to laparoscopic gastroenterostomy (L-GE) are scarce.
Aim: Our aim was to perform a propensity score-matched comparison between EUS-GE and L-GE, in the context of both benign and malignant disease.
Methods: An international, multicenter retrospective analysis was performed of consecutive EUS-GE and L-GE procedures in 3 academic centers (Jan-2015 to May-2020). A propensity score-matched design was used in order to minimize selection bias. Age, sex, underlying disease, disease stage, presence of ascites and/or peritoneal carcinomatosis were used as variables, with a standard maximum propensity score difference of 0.1. All EUS-GE were performed using the Wireless EUS-gastroenterostomy Simplified Technique (WEST).
Results: In total, 126 patients were identified, of which 77 patients (61%) were treated with EUS-GE and 49 patients with L-GE (39%). At baseline, ascites (22.1% vs. 4.2%, p=0.009) and pancreatic cancer-induced gastric outlet obstruction (48.1% vs. 29.2%, p=0.037) were significantly more frequent in the EUS-GE group, whereas underlying benign disease was identified significantly less (3.9% vs. 14.6%, p=0.044) when compared to L-GE-treated patients. Technical success was similar in the EUS-GE and L-GE group (95% vs. 100%, p=0.156), while we identified a trend towards lower clinical success amongst L-GE-treated patients (97% vs. 88%, p=0.059). Regarding safety in the overall cohort, the overall adverse event (AE)-rate was significantly lower in the EUS-GE group (7.8% vs. 35%, p=0.003), with significantly more severe AEs in the L-GE group (2.6% vs. 20%, p=0.001). Moderate (2.6% vs. 12%, p=0.055) and mild AE rates (2.6% vs. 2.0%, p=1.000) were similar. By means of propensity score-matching, 37 patients were allocated to both groups, resulting in 74 (1:1) matched patients. No significant baseline differences between both study groups were identified. Technical success was achieved in 35/37 EUS-GE-treated patients (94.6%) vs. 100% in the L-GE group (p=0.493). Clinical success, defined as eating without vomiting or GOO Scoring System ≥ 2, was achieved in 97.1% and 89.2% respectively (p=0.358). When considering safety in this matched comparison, overall AEs (2.7% vs. 27.0%, p=0.007) and severe AEs (0.0% vs. 16.2%, p=0.025) were identified more frequently in the L-GE group. Median time to oral intake (1 (IQR 0.3-1.0) vs. 3 (IQR 1.0-5.0) days, p<0.001) and median hospital stay (4 (IQR 2-8) vs 8 (IQR 5.5-20) days, p<0.001) were significantly shorter in the EUS-GE group. Gastroenterostomy dysfunction rates (none in both groups), distal enteric

obstruction rates (5.4% vs. 2.7%, p=1.000) and evolution in body mass after two months (-0.3 (IQR -2.4-1.1) vs. 0 (-3.0-0.7)kg, p=0.352) did not differ.
Conclusions: For patients with gastric outlet obstruction, EUS-GE and L-GE showed almost identical technical and clinical success. However, reduced time to oral intake, shorter median hospital stay and lower rate of adverse events suggest that the EUS-guided approach might be preferable. While awaiting high-quality prospective confirmation, these findings should guide gastroenterologists, oncologists and surgeons in considering EUS-GE for treating GOO, especially in the setting of malignancy, where patients will benefit from the least invasive technique with the highest expected efficacy.

G15

Technique, safety and feasibility of EUS-guided radiofrequency ablation of pancreatic tumors and oligo-metastatic disease : an observational, prospective multicenter registry

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Introduction: Currently, surgical resection remains the only curative treatment option for the treatment of focal pancreatic and peripancreatic lesions, including pancreatic ductal adenocarcinomas (PDAC), pancreatic neuroendocrine tumors (pNET), pancreatic cystic lesions (PCL) and metastasis from other specific cancers. However, given that the affected patients are often not eligible for surgery, a less invasive and locally ablative technique could be of major interest. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) is an emerging and promising minimally invasive technique, which has already proved to be feasible and safe in this context.
Aim: Our aim was to prospectively register and evaluate the feasibility, safety, technical and clinical success of pancreatic and extra-pancreatic EUS-RFA performed in three academic centers.
Methods: We prospectively collected clinical and technical data regarding all patients submitted to EUS-RFA in three Belgian academic centers, from June 2018 up until September 2020. EUS-RFA was performed using an 19-gauge internally cooled electrode with 10 mm exposed tip (EUSRA™) and a power application of 50 watts, at least once, through a VIVA COMBO* RF generator (Taewoong /STARMED, Koyang, Korea-imported in Belgium by Prion medical). The procedure was considered complete when echogenic bubbles occurred (“steam popping”), meaning that the tissue temperature in the ablation region had increased to more than 100°C. Feasibility, adverse events and follow up were also assessed.
Results: Twenty-four patients were included, counting for thirty-one lesions treated in total. Treatment indications were diverse, ranging from PDAC (4.2%), non-functioning pNET (33.3%) and highly symptomatic pancreatic insulinoma (33.3%), to pancreatic renal and pulmonary cancer metastasis (20.8% and 4.2%, respectively) and, finally, a gastric

cancer left adrenal metastasis (4.2%). Technical success was achieved in 95.8%, with a median of 3 power applications per lesion (range=1-6, n=31). The procedure was aborted in one case, as the RFA needle was not clearly visible at EUS. From the 23 patients that were treated, 14 (60.9%) presented no early collateral effects. Four (17.4%) patients developed non-severe acute pancreatitis and two (8.7%) patients reported post-procedural mild abdominal pain that resolved spontaneously. There was also one case of per-procedural arterial bleeding (with spontaneous resolution at angio-CT and without hemodynamic repercussions), one case of (spontaneously rapid recovering) gastric wall hematoma and one case of post-anesthesia urinary retention. There were no late adverse effects reported. At 6 months follow-up (n=17), 52.9% of patients showed radiological signs of complete response, 29.4% presented a partial response and 11.8% showed signs suggesting a locally progressive disease. Hypoglycemia related to insulinoma was immediately corrected after procedure in all 8 cases.
Conclusions: EUS-RFA is a feasible, safe and effective procedure for the treatment of pancreatic and peripancreatic tumors. Large multicentric prospective studies are warranted to confirm the real clinical benefits of this technique and to establish its role in the management of focal pancreatic lesions. Accuracy of response determination requires further evaluation and longer follow-up. Symptomatic insulinoma currently represent the best indication.

G16

Magnetic Gastrointestinal Universal Septotome: first results of a pilot study in Epiphrenic Esophageal Diverticulum

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Introduction: -

Aim: In absence of motility disorders, treatment of symptomatic epiphrenic esophageal diverticulum (EED) is challenging. We have developed a specific device which provides marsupialization of EED after placement of two magnets on each sides of the septum of the diverticulum, linked by a self retractable suture wire, called MAGUS (Magnetic Gastrointestinal Universal Septotome). Once inserted, magnets and self-retractable surgical wire induce a progressive ischemia, leading to tissue necrosis and ultimately its section. We initiated a prospective human study to evaluate technical success, clinical outcome and safety following MAGUS insertion in patient presenting with symptomatic diverticulum.

Methods: Insertion procedures were done under general anesthesia. MAGUS delivery system is advanced over a guidewire in the esophagus. Under endoscopic guidance proximal magnet is mobilized inside the diverticulum and placed at the bottom of it. Under fluoroscopic guidance the distal magnet is pulled on the esophageal side at the level of the proximal intradiverticular magnet until magnetic apposition occurs. Clinical outcome were followed prospectively.
Results: During September and october2020, two men of 73 and 56 years old displaying symptomatic EED were enrolled. Diverticulum and septum sizes measure 52.5 and 21.5 mm in the first one and 58 and 32 mm in the second patient. Technical implantation was successful in both. Device insertion time took 12 and 15 minutes. No clinical adverse event related to the procedure was observed. The magnets migrated spontaneously in the first patient and required an additional endoscopy for retrieval in the second one. One month after insertion, Eckardt score dropped from 2 to 1 and from 6 to 2 respectively.
Conclusions: Marsupialization of EED using MAGUS system seems to be safe and effective in the two first patients included in a pilot trial, allowing to consider that MAGUS could become one of the endoscopic treatment of symptomatic EED.

G17

Endoscopic management of buried bumper syndrome: the Balloon Dilation Pull (BDP) technique: a case series.

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Introduction: Buried Bumper Syndrome (BBS) is a rare complication of Percutaneous Endoscopic Gastrostomy (PEG) placement. Symptoms include atypical abdominal pain, inadequate feeding and infections at the insertion site. BBS is caused by excessive traction on the inner bumper of the PEG-tube causing necrosis and ulceration of the overlying gastric mucosa, leading to impaction of the bumper into the gastric wall. Generally, the diagnosis is made by endoscopy. Many different strategies for endoscopic treatment have yet been published, although only anecdotical use of the Balloon Dilation Pull (BDP) technique (as mentioned in the “Methods” section) is described. In this case series, we demonstrate the use of the BDP technique for the treatment of BBS, that has a very high success rate in our daily practice.
Aim: To assess feasibility, efficacy and safety of the systematic use of the BDP technique for the treatment of buried bumper syndrome (BBS) and to demonstrate a modification of the endoscopic treatment in case of complete BBS.
Methods: We prospectively collected all data from patients who were diagnosed with BBS between June 2019 and November 2020 and who were treated with the balloon dilation pull (BDP) technique. Primary outcome measures were technical success rate, procedure time and occurrence of adverse events. For the BDP technique, an endoscope with a therapeutic 3.7mm working channel is required. First, the PEG-tube is cut off at the cutaneous side at about 1-2cm. In case of complete BBS (internal bumper completely overgrown by overlying gastric mucosa which precludes the passage of guidewire

through the internal PEG-bumper), a new entry site is made with a stiff metal paracentesis needle through the PEG-tube. Subsequently, a guidewire (type Jagwire) is advanced into the stomach through the PEG-tube (or the metal sheath of the paracentesis needle) and is picked up by the scope with a snare. Thereafter, a dilation balloon (15-18mm) is advanced over the guidewire through the scope and through the PEG-tube. By inflating the dilation balloon to the maximum dilation pressure, the balloon stays solidly impacted into the PEG-tube. In this way, the buried bumper can be mobilized from the gastric mucosa by traction on the endoscope and the balloon catheter together. In the same procedure, a new PEG is inserted at some distance from the old PEG-tract and can be used immediately.
Results: A total of 7 patients with BBS were treated with the BDP-technique; 1 female patient and 6 male patients with a mean age of 72 years (range 60-83). The procedures were performed under enhanced sedation with anaesthetic support in 6 patients. In 1 patient, in whom the anaesthetic risk was deemed very high, the procedure was performed without any form of sedation. The mean procedure time was 14,5 minutes (range 5-27). The technical success rate was 100%. There were no direct complications of the procedure (post-procedural pain or bleeding). One episode of aspiration pneumonia was noted, rather as a complication of the underlying medical condition of the patient and not due to the endoscopic procedure.
Conclusions: Many different strategies for endoscopic treatment of BBS have yet been published. The BDP technique is a simple endoscopic procedure, using endoscopic accessories which are readily available in every endoscopic unit. The procedure time is short and the technical success rate is optimal. In this case series, there were no direct complications linked to the procedure. A new PEG-tube is placed in the same procedure time, so enteral nutrition can be restarted immediately.

G18

Minimally Invasive Treatment of a Bulging Appendiceal Orifice: A Case Report

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Case Report: A 60-year-old patient was referred to our center to undergo colonoscopy following a positive fecal occult blood test. The patient was asymptomatic and declared a negative personal and familial medical history. The endoscopic examination itself revealed two diminutive sessile polyps, macroscopically compatible with sessile serrated lesions (SSLs), which were resected using cold snare polypectomy. Furthermore, a bulging appendiceal orifice (AO) was identified with mucoid appearance. Biopsies were taken and abdominal computed tomography (CT) was scheduled. Surprisingly, CT scan showed a normal appendiceal region, without signs of underlying mucocele or mass. In the end, histopathological analysis revealed a diagnosis of a large SSL without dysplasia, completely involving the AO. For larger SSLs, selection of the most optimal resection technique depends on lesion size, location, shape and skill of the

endoscopist.1 Where both endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) can be considered for large lesions, >50% involvement of the appendiceal orifice has been suggested as a reason to refer patients for surgery in the past.2 However, since recent years, endoscopic full thickness resection (eFTR) has broadened the therapeutic horizon of peri-appendiceal lesions. By providing ease-of-use in complex situations, as well as broad resection margins for when submucosal invasion or early malignancy is suspected, surgery can be potentially averted in such patients. Following a multidisciplinary team meeting, eFTR was proposed to our patient, as the lesion was deemed ineligible for classic endoscopic resection by ESD or EMR owing to the complete invasion of the AO. After relatively easy access into the right colon, the lesion was marked and finally captured using the colonic full-thickness resection device (FTRD) and tissue grasper. Immediately after retracting all the markers into the cap, the over-the-scope-clip (OTSC) was deployed, after which the lesion was completely resected by snare resection (ENDOCUT Q – effect 1). Histopathological analysis confirmed complete resection, with wide horizontal and vertical margins. As illustrated, the endoscopic distinction between a low grade appendiceal mucinous neoplasm and a sessile serrated polyp can be challenging, suggesting that we should involve a pathologist in the diagnostic process. Where a thinned bowel wall, abundant luminal mucin and distention of the appendix are the macroscopic features favoring a diagnosis of low grade appendiceal mucinous neoplasm, SSLs are usually associated with a normal caliber thickness appendix and can easily be confirmed by endoscopic biopsies.3 Although the endoscopic image was quite suggestive of a mucocele, histology of the eFTR-specimen clearly showed complete invasion of the AO by a non-dysplastic SSL, together with a partially resected appendix. When considering the latter, it comes to no surprise that FTRD-induced appendiceal occlusion results in a non-negligible risk of appendicitis or appendicular abscess, occurring in up to 14-20%4,5,6 Little evidence exists regarding the prophylactic use of antibiotics, varying greatly from a 5 day empiric antibiotic regimen to a single prophylactic dose.5,7 Other adverse events such as delayed perforation (predominantly in the left colon) and post-procedural bleeding have also been reported. 6 In our case, no complications occurred and the patient was discharged the morning after the procedure with a short preemptive course (5 days) of broad-spectrum antibiotics. After one month, the patient continued to do well and was free of any symptoms. As wide R0-resection was histologically confirmed, endoscopic follow-up was scheduled 12 months after eFTR. The evidence surrounding eFTR in the context of AO lesions has clearly been increasing since 2020, and although technical success approaches 96%, R0 resection rates of around 64% leave a lot to be desired.4,6 Similarly, a multicenter study reported an overall recurrence rate of 15.6% of cecal polyps involving AO, with >75% involvement of the AO circumference as the only significant risk factor for recurrence.8 These findings clearly suggest that, especially in the area of patient selection, more data is urgently needed. In summary, while diagnosis of a mucocele should be considered in patients with a bulging appendiceal orifice, our case illustrates that invasion by SSLs can lead to a similar presentation and that even in situations with complete involvement of the

appendiceal orifice endoscopic resection can be considered. In the future eFTR may prove itself as a cost-effective and minimally invasive strategy to remove AO polyps, although further research is clearly needed to confirm long-term efficacy and cost-effectiveness.

G19

Where does all the air come from?

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Case Report: An 62 year old man presented to the outpatient clinic for further investigation of excessive belching since one month, sometimes associated with concurrent vomiting, and severely impacting his quality of life. The belching occurred up to ten times a minute, mostly postprandially, while absent during speech or sleep. He denied epigastric pain and heartburn. The patient's symptoms did not respond to Proton Pump Inhibitor therapy. Previous oropharyngeal examination and radiologic evaluation of the oesophagus were normal. Eradication of Helicobacter pylori based on results from pathology from an otherwise normal upper GI endoscopy did not provide any relief. In order to understand the mechanism of belching, High Resolution oesophageal Impedance Manometry (HRIM) before and after a solid meal was performed. Before the meal, normal oesophageal motility was noted. Multiple episodes of belching and a few episodes of vomiting were recorded postprandially. All episodes shared the same characteristics concordant with supragastric belching (SGB): decrease of the intrathoracic pressure with ab-orally propagating rise in impedance, followed by a sudden increase of intrathoracic and intra-abdominal pressure, with orally propagating decrease in impedance. Vomiting followed the same pattern but was accompanied by a higher increase of abdominal pressure. As diaphragmatic breathing (DB) remained unsuccessful, baclofen was associated. While sporadic belching reflects normal behavior, excessive belching becomes bothersome and requires medical care. Uncovering the underlying mechanism with HRIM will direct treatment at an early stage. Despite its benign nature, SGB negatively impacts social interaction and quality of life. Treatment should focus on education and reassurance. Diaphragmatic breathing, behavioral therapy and speech therapy all demonstrated their efficacy, while baclofen should be reserved for refractory cases.

G20

Working under pressure – insufflation-induced gastric barotrauma during esophageal ESD

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Case Report: We describe the case of a 64-year-old female with a history of alcoholic hepatic steatosis and vitamin B12 deficiency with the presence of tissue transglutaminase antibodies. An upper gastro-intestinal endoscopy was performed to rule out celiac disease with an unexpected finding of a well differentiated esophageal

squamous cell carcinoma. The lesion was located in the mid-esophagus (extending 20-25 cm from the incisors, gastroesophageal junction at 38cm) and had an endoscopic type V1-V2 intrapapillary capillary loops pattern (IPCL). Staging showed limited disease (cT1N0M0). She underwent an endoscopic submucosal dissection (ESD) in march 2019. Postoperative pathology report showed a high-grade squamous intraepithelial lesion. During follow up dysphagia developed, caused by a postoperative refractory stricture which was managed with sequential endoscopic balloon dilation. During follow-up two metachronic lesions more distally in the esophagus (28cm from the incisors) with aberrant IPCL pattern type V1 were identified. In march 2020 a second ESD for these lesions was performed. Prior to ESD, during the same session a balloon dilatation of the post ESD stricture was also performed. ESD was successfully conducted using carbon dioxide insufflation with en bloc resection of the suspect lesion (27x15 mm). A few hours after the procedure, the patient developed dyspnea and associated upper abdominal pain. A chest X-ray showed the presence of a pneumoperitoneum. Urgent endoscopy revealed a linear mucosal laceration and perforation of 2cm in the lesser curvature of the gastric upper body. The perforation site was endoscopically closed using six hemoclips. There was no perforation or injury to the muscular layer at the ESD site. Intravenous broad-spectrum antibiotics were started and she resumed oral feeding gradually. The patient was discharged six days after the ESD procedure without any sequelae. The final pathology report showed a high-grade squamous intraepithelial lesion. Discussion: ESD is an organ preserving treatment for patients with gastro-intestinal neoplasms and very low risk for lymph node metastasis. The most common adverse events of esophageal ESD include perforation (0 - 10,7%), bleeding (0 - 22,8%) and stricture formation (1). In this case we demonstrated an exceptionally rare complication of insufflation induced-barotrauma in the stomach during ESD in the esophagus, despite the use of CO2. We assume this perforation was caused by the esophageal stricture proximal to the ESD site. Tight apposition of the endoscope most likely caused air trapping in the stomach impeding air to escape through the esophagus. The perforation at the high lesser curvature of the stomach is an inherent point of weakness together with the left side of the distal esophagus. The preference for this location is related to reduced elasticity, fewer mucosal folds and the presence of a junction between the semicircular and oblique muscle fibers (2,3). As illustrated by this case, esophageal ESD can cause high intra-esophageal and intragastric pressure with suction in the esophagus not effectively reducing gas and pressure in the stomach. General anesthesia also plays a role by reducing the contractile force of the gastric muscles (increased trapping of gastric gas) and the impossibility of the patient to belch. Literature: 1. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European society of gastrointestinal endoscopy (ESGE) guideline. Endoscopy. 2015;47(09):829-854. 2. Merchea A, Cullinane DC, Sawyer MD, et al. Esophagogastroduodenoscopy- associated gastrointestinal perforations: a single-center experience. Surgery 2010;148:876-82. 3. Fung AM, Chan FS, Wong IY, Law S. Synchronous perforations of the oesophagus and stomach by air insufflation: an

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General Gastroenterology

GE01

The DOMINO study: Diet Or Medication in primary care patients with Irritable bowel syndrome

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Introduction: Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders in clinical practice. In primary care, IBS is a condition that generates high diagnostic and therapeutic uncertainty for general practitioners (GPs), and the efficacy of currently available therapeutic modalities is limited. This all leads to repetitive medical consultations, additional “unneeded” technical examinations, and chronic use of multiple drugs with limited therapeutic gain. In Europe, musculotropic agents (e.g. otilonium bromide, OB) are commonly used. Recently, at the level of specialist care, the low FODMAP diet supervised by an experienced dietician, was shown to provide significant improvement in IBS symptoms. The use of dietary treatment in primary care remains to be explored.

Aim: Our aim was to evaluate the effect of a FODMAP lowering diet, administered through a smartphone application, vs. OB on symptoms, quality of life and psycho-social co-morbidity in primary care IBS.

Methods: In this clinical trial, funded by Belgian Health Care Knowledge Centre and supported by the Rome Foundation research Institute, 69 GPs in Belgium recruited 470 IBS patients who were randomized to OB (60 mg t.i.d.) or a FODMAP lowering diet (smartphone application). After a treatment period of 8 weeks, followed up continued until 6 months. Patients fulfilling Rome IV criteria were defined as Rome+. The change in IBS Symptom Severity Score (IBS-SSS) was compared between treatment groups both as a numeric score (bootstrapped t-test) and in terms of proportion of responders for which improvement of 50 points or more was considered a responder (Chi-Square). Additionally, the impact of treatment was explored for the IBS subtype, quality of life (IBS-QoL), anxiety (GAD), depression (PHQ9), and somatization (PHQ15). Finally,

parameters predicting response were analyzed in both treatment groups (logistic regression) with effect sizes reported as odds ratios (OR). Data are shown as mean±SD.
Results: 453 primary care IBS patients (41±15 years, 76% female, 71% Rome+) were randomized to either OB (n=231, 41±15 years, 75% female) or diet app (n=227, 41±15 years, 75% female). The responder rate in the diet group (71%) was significantly higher compared to OB (61%) after 8 weeks of treatment (p=0.03) and this was more pronounced in Rome+ (77% vs. 62%, p=0.005). During the follow-up period, the diet group maintained a significantly higher responder rate (6 months: diet: 74%; OB: 58%, p<0.001). Mean IBS-SSS improved significantly over time in both groups (OB: 267±100 vs 170±109 (p<0.001); diet: 267±96 vs 188±109 (p<0.001)), but with significantly larger improvement in the diet arm compared to OB (p=0.02). Both with OB and diet, significant improvement was observed for IBS-QoL (OB=-7.34 (p<0.001) vs. diet=-8.07 (p<0.001)) and levels of anxiety (OB=-0.99 (p<0.001) vs diet=-1.19 (p<0.001)), depression (OB=-1.09 (p<0.001) vs diet=-1.36 (p<0.001)) and somatization (OB=-1.31 (p<0.001) vs diet=-1.80 (p<0.001)), but without significant difference between treatment groups (p>0.05). Female gender (OR=2.35, p=0.04) was a response predictor for diet-treated patients whereas higher somatization (OR=1.21, p=0.002) was a predictor of OB treatment response.
Conclusions: In primary care IBS, a smartphone app-based diet intervention was superior to standard medical therapy (OB) in improving symptom severity, and in achieving clinically significant response, at the end of treatment and during follow-up. Both treatments improved quality of life and psychosocial co-morbidities. Response to diet is associated with female gender, while response to OB associates with high baseline somatization levels. App-based dietary intervention should be considered the first-line treatment choice for primary care IBS.

Belgian Inflammatory Bowel Disease Research and Development Group (BIRD)

I01
A discriminative metabolic profile in the sera of Crohn's disease patients with fibrostenosis
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Introduction: Crohn's disease (CD) patients are at high risk of developing fibrotic strictures, which significantly affects the patient's quality of life. The accumulation of fibrotic tissue and progression of stricture formation is difficult to assess, leading to

late awareness of stricture formation and surgical resection. Therefore, fibrostenosis-specific biomarker profiles are highly needed.
Aim: Given the increasing evidence of metabolic alterations in activated fibroblasts, we aimed to identify discriminating metabolic markers in the serum of CD patients with and without fibrostenosis.
Methods: In this retrospective study, samples of 66 CD patients with (n=28) and without (n=38) ileal fibrotic strictures at the time of sampling were selected from a local biobank (UZ Gent, BB190100). Fibrostenosis was defined as a narrowing of lumen and prestenotic dilation on CT/MRI at the time of serum collection. Both groups included an equal number of patients in remission or with active disease, based on imaging and/or CRP levels (cut-off at 10mg/L) and were age- and gender-matched. Metabolomics analysis was performed applying UHPLC-Q-Orbitrap™-HRMS. The in-house method for metabolite extraction and mass spectrometry analysis was validated for serum compatibility. Statistical analysis of the untargeted MS data was performed using SIMCA 15.0 and MetaboAnalyst 4.0, allowing multivariate statistical modelling through, amongst others, Principal Component Analysis (PCA) and sparse Partial Least-Squares Discriminant Analysis (sPLS-DA).
Results: Age at diagnosis, exposure to anti-TNF drugs, disease location and disease activity were similar between both groups. Validation of metabolomics analysis of serum samples, including instrumental precision, intra-assay, and inter-day analyses, showed excellent coverage of the measured metabolites with respective coefficients of variance <20% for targeted (>75% of metabolites complied) and <30% for untargeted analysis (compound compliance rate of 80% in positive and 90% in negative ionisation mode). The extraction and analysis of the serum samples yielded a total of 5,959 features. sPLS-DA models were used to determine which features were most discriminating between groups, and 1,000 features were retained. A valid Orthogonal PLS-DA model based on these 1,000 features had R2Y of 0.99 and Q2 of 0.83, suggesting excellent predictivity and fitting of the existent data. The top differentiating features, 47 in total, were retained after further filtering, based on a Variable Influence on Projection score higher than 1, Jack-knifed confidence interval higher than 0 and S-plot with p(corr)-values lower than -0.3 or higher than 0.3.
Conclusions: To our knowledge, this is the first study using a comprehensive metabolomics approach by which we unveiled a discriminative metabolic fingerprint in the serum of fibrostenotic CD patients. Further MS2 measurements to allow the identification of these metabolites and validation are on-going and will allow to prove biomarker potential and gain insight in the functional pathways involved.

I02
Magnetization transfer MRI and T2-weighted MRI texture analysis allow non-invasive detection of intestinal fibrosis in a fibrosis-inducing chronic colitis mouse model.
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Introduction: Differentiation between inflammatory and fibrotic bowel strictures remains a holy grail in Crohn's disease (CD) management, primarily because of the therapeutic implications. Stricture characterisation in CD patients is further hampered by the co-occurrence of inflammation and fibrosis in various degrees. Currently, there are no validated imaging tools to differentiate fibrotic from inflammatory or mixed strictures, but several new techniques, such as magnetization transfer magnetic resonance imaging (MT-MRI) and magnetic resonance texture analysis (MR-TA), seem promising.

Aim: We investigated whether MT-MRI and MR-TA can detect and quantify intestinal fibrosis in an established mouse model of fibrosis-inducing chronic colitis.

Methods: Chronic colitis was induced in C57BL/6 (n=16) mice by three consecutive cycles of administration of the colitis inducing agent dextran sodium sulphate (DSS) for 7 days, followed by a 14-day recovery period. Using a 7.0 Tesla scanner, MT and T2-weighted MR images were recorded for each mouse at baseline and weeks (wk) 1, 3, 4, 6, 7, and 9. Regions of interest were created over the bowel wall on both MT and T2-weighted images. The bowel wall to spine muscle normalized MT ratio was calculated using ImageJ. Textural features, including skewness, kurtosis and entropy, were extracted by a filtration histogram technique, enclosed in the TexRAD software. Masson's trichrome stained colon sections were used as golden standard for the quantification of fibrosis. Multivariate mixed model analysis and receiver operating characteristic (ROC) curves were applied to statistically assess the MR parameters for evaluating intestinal fibrosis.

Results: Conducting mixed model analysis, significant differences in MT-ratio between mixed strictures and pure fibrotic strictures were observed at wk4 vs. wk6 ($p=0,012$) and at wk7 vs. wk9 ($p<0,0001$), whereas the significance for TA-entropy was lower at these compared timepoints ($p= 0,108$ and $p=0,012$, respectively). Nonetheless, TA-entropy performed better when monitoring the increasing proportion of fibrotic tissue in mixed strictures between first and second (wk1 vs. wk4, $p=0,001$) and second and third DSS-cycle (wk4 vs. wk7, $p=0,004$), compared to the MT-ratio. ROC-curve analysis using histopathology as reference score, generated a sensitivity, specificity and area under the curve (AUC) for TA-entropy of 83%, 80% and 0,93 ($p=0,018$) respectively, while MT-ratio outperformed with a sensitivity and specificity of 100% and an AUC of 1 ($p=0,006$).

Conclusions: To our knowledge, we have shown for the first time that MT-MRI and MR-TA can both accurately detect fibrosis in a fibrosis-induced chronic colitis mouse model. Where TA-entropy excels in detecting fibrosis build-up in an inflammatory environment, MT-ratio has higher sensitivity and specificity to detect fibrotic tissue as such. MT-ratio and TA-entropy should be seen as complementing techniques prompting comprehensive fibrosis detection.

Blood proteins linked to immune tolerance, inflammation and cellular junctions reveal a succession of pathophysiological events preceding the relapse in Crohn's disease patients stopping infliximab

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Introduction: In Crohn's disease (CD), biologics well succeeded in inducing mucosal healing and stable remission. When this objective is achieved, treatment de-escalation is considered and the relapse constitutes the main risk of such choice. In the context of biologics withdrawal in CD, risk factors predicting the relapse have been intensively searched. Although these investigations classically respond to a practical need, we recently highlighted that they can also serve to better understand the underlying mechanisms of relapse. Indeed, the comprehension and the prediction of relapse are two sides of the same coin. By stratifying CD patients according to time to relapse, we identified distinct pathophysiological processes associated with the risk of short-term (< 6 months) and mid/long-term (> 6 months) relapse after stopping anti-TNFα treatment. In our previous study, we did not target proteins specifically related to CD since we used the biomarkers discovery workflow which is a hypothesis-free method. This approach combined with the low analytical sensitivity of our measurement method (selected reaction monitoring) led us to mainly measure the highly abundant and liver-produced proteins of the serum. As a complement to this strategy, targeting serum proteins less abundant and more specifically related to the development of CD could improve the understanding and the prediction of relapse after anti-TNFα withdrawal.

Aim: To test whether circulating proteins, implicated in the immune response, can provide novel insights in the comprehension and the prediction of relapse in CD patients stopping anti-TNFα.

Methods: We used a proximity extension assay (PEA) panel (Olink) targeting 92 proteins involved in the immune response. These proteins were measured in the baseline serum of patients belonging to the cohort of infliximab diScon-Tinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors (STORI, n=102). To investigate the dynamic of the markers before the relapse, we stratified the cohort according to a time to relapse of 6 months. All the subsequent analyses were performed in the short-term relapse (<6 months), mid/long-term relapse (>6 months) and non-stratified datasets. Association of markers with the risk of relapse was determined with the univariate Cox model. By using Uniprot, Human Protein Atlas and

literature, we systematically characterised the function and the cellular origin of each measured protein. According to this database and the statistical analysis, we searched for biological patterns differentiating the short-term from the mid/long-term relapsers. To evaluate the capacity of our markers to jointly predict the relapse, we combined them systematically by pairs (with the 'AND' or 'OR' logical operators) and used the log-rank statistic.

Results: The risk of short-term relapse was associated with a decreased circulating level of proteins belonging to the inflammatory pathways while an increased circulating level of those markers was associated with the risk of mid/long-term relapse. The risk of short-term relapse was specifically associated with an increased circulating level of interleukin-6 (IL-6). The risk of mid/long-term relapse was specifically associated with a decreased circulating level of proteins showing anti-inflammatory properties: interleukin-10 (IL-10); corticosteroid 11-beta-dehydrogenase isozyme 1 (HSD11B1). The risk of short-term relapse was specifically associated with a changed circulating level of proteins involved in tolerance and immunity of antigen presenting cells (APCs) (Allergin-1: MILR1; C-type lectin domain family 4 member C: CLEC4C; CLEC4G, CLEC4A; CLEC7A; lysosome-associated membrane glycoprotein 3: LAMP3). The risk of mid/long-term relapse was specifically associated with an increased circulating level of proteins implicated in lymphocytes tolerance (lymphocyte activation gene 3 protein: LAG3; signaling threshold-regulating transmembrane adapter 1: SIT1; SH2B adapter protein 3/SH2B3) and a decreased circulating level of cellular junction proteins (contactin-associated protein-like 2: CNTNAP2; corneodesmosin: CDSN; coxsackievirus and adenovirus receptor: CXADR; integrin α-11: ITGA11). We found 1046 (short-term relapse dataset), 233 (mid/long-term relapse dataset) and 99 (non-stratified dataset) novel marker combinations which showed FDR<0.05 and higher Z-scores than C-reactive protein (CRP) and faecal calprotectin.

Conclusions: By studying blood proteins, we discovered that immune tolerance (in lymphocytes and APCs), inflammation and cellular junctions are dynamically modulated before the relapse of CD patients stopping anti-TNFα. These findings could help to better understand the underlying mechanisms of relapse. Compared to CRP and faecal calprotectin (the current references for relapse prediction), our novel marker combinations showed a high capacity to predict the relapse thus highlighting their potential for a clinical application.

I04

Early prediction of response to vedolizumab in patients with active Inflammatory Bowel Disease: a prospective real-life multicentre cohort study

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Introduction: Vedolizumab is a gut-selective α4β7 integrin inhibitor approved for inflammatory bowel disease (IBD) treatment. Despite its excellent benefit-risk profile, only 40-60% of patients will respond.

Aim: We evaluated whether integrin expression on circulating T cells are potential biomarkers for vedolizumab response and aimed to build a predictive model by adding previously associated clinical and biochemical markers.

Methods: In this prospective multicentre study, 71 IBD patients initiating vedolizumab were included (27 Crohn's disease (CD), 44 Ulcerative colitis (UC)). Peripheral blood mononuclear cells, serum and stool were collected at weeks 0, 2, 6, 10 and 14. The clinical, biochemical and endoscopic response was determined at week 14. Flow cytometry was used to quantify CD4+/CD8+ α4β7+, α4β1+ and αEβ7+ T cells. Additionally, vedolizumab trough levels, soluble MAdCAM-1, retinoic acid and albumin were quantified. Multivariate models were used to screen candidate biomarkers.

Results: Sixty-two percent of patients showed clinical response, whereas the biochemical and endoscopic response rates were 64.0 and 61.0%, respectively. Trough levels, soluble MAdCAM-1, retinoic acid and albumin concentrations were similar between responders and non-responders. Baseline CD4+α4β7+ T cells abundance was positively associated with clinical and biochemical response in UC (respectively; $p=0.037$ and $p=0.046$). In CD, baseline CD4+α4β1+ T cells were negatively associated with biochemical response ($p=0.028$). Despite associations, the prognostic value of integrins in predictive models was not robust.

Conclusions: High abundance of CD4+α4β7+ T cells in UC and low abundance of CD4+α4β1+ T cells in CD are positively associated with vedolizumab response, indicating the predictive potential of integrins.

I05

Long-term environmental hypoxia does not impact experimental Crohn's like ileitis

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Introduction: Environmental hypoxia is an important environmental factor that influences inflammatory bowel disease (IBD) initiation and course, but published data remains contradictory. In particular, IBD patients experience flare-ups more frequently after high altitude flights while short-term hypoxic exposure ameliorates inflammation in colitic mice. However, the impact of environmental hypoxia on ileal inflammation has not been investigated thus far.

Aim: We investigated the long-term effect of environmental hypoxia in a mouse model of ileal Crohn's disease.

Methods: Five-week-old, male TNFΔARE/+ mice (n=16) and wild type (WT) littermates (n=16) were housed in normoxia (21% O2) or in a hypoxic chamber (8% O2) for 10 weeks. Systemic inflammation was quantified via hematology analyzer. The degree of hypoxia in the distal ileum was evaluated by pimonidazole staining. Ileal inflammation was scored on hematoxylin/eosin stained sections by two independent observers. Pro- and anti-inflammatory gene expression was measured in the distal ileum using qPCR.
Results: Environmental hypoxia induced a significant upregulation of red blood cells, hemoglobin and hematocrit in circulation (all $p<0.01$) and a significant increase in pimonidazole intensity in the distal ileum ($p<0.05$). Hypoxia did not significantly impact body weight evolution in WT nor TNFΔARE/+ mice, except for the first five days due to reduced appetite (acclimatization period). Interestingly, hypoxia led to an increase in the number of circulating monocytes ($p<0.05$) in WT mice, while in TNFΔARE/+ mice a significant increase in both monocytes ($p<0.01$) and neutrophils ($p < 0.01$) could be detected. Despite these alterations, no significant difference could be identified on histology between the distal ileum of WT mice housed in normoxia and hypoxia nor between the TNFΔARE/+ mice housed in normoxia and hypoxia. In line with the histological scoring, the mRNA levels of pro- and anti-inflammatory cytokines were not significantly altered in TNFΔARE/+ mice housed in hypoxia versus normoxia.
Conclusions: In this study, we demonstrated for the first time that long-term environmental hypoxia does not have an effect on the development of chronic ileal inflammation in TNFΔARE/+ mice.

I06

Potential Role of Epithelial Protein Disulphide Isomerases in Crohn's Disease Fibrosis

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Introduction: Intestinal fibrosis is a common complication of Crohn's disease (CD) characterized by an accumulation of fibroblasts differentiating into activated myofibroblasts secreting excessive extracellular matrix. In in-vitro experiments, this myofibroblastic differentiation is elicited by a whole series of factors among which transforming growth factor β1 (TGF-β1) seems to play a key role.
Aim: The potential role of the intestinal epithelium in this fibrotic process remains poorly defined.
Methods: We performed a pilot proteomic study comparing the proteome of surface epithelium isolated by laser-capture microdissection in normal and fibrotic zones of

resected ileal CD strictures (13 zones collected in 5 patients). The pro-fibrotic role of selected epithelial proteins was investigated through in-vitro experiments using HT-29 epithelial cells and a CCD-18Co fibroblast to myofibroblast differentiation model.
Results: Proteomic study revealed an endoplasmic reticulum (ER) stress proteins increase in the epithelium of CD ileal fibrotic strictures, including Anterior gradient protein 2 homolog (AGR2), Protein disulphide isomerase A6 (PDIA6) and Endoplasmic reticulum resident protein 44 (ERP44) which are 3 protein disulphide isomerases. In HT-29 cells, tunicamycin-induced ER stress triggered AGR2, PDIA6, ERP44 as well as TGF β1 intracellular expression and their secretion. Supernatant of these HT-29 cells, pre-conditioned by tunicamycin (Tm), led to a myofibroblastic differentiation when applied on CCD-18Co fibroblasts. The application of blocking agents for AGR2, PDIA6, ERP44 or TGF β1 in the supernatant of these Tm-pre-conditioned HT-29 cells, attenuated the myofibroblastic differentiation induced by this supernatant, suggesting a pro-fibrotic role of these secreted epithelial proteins.
Conclusions: The development of CD fibrotic strictures may involve ER stress in epithelial cells, releasing a whole set of proteins into their environment, including AGR2, PDIA6, ERP44 as well as TGF-β1, which could exercise a pro-fibrotic role through a paracrine action.

I07

Ultraproactive therapeutic drug monitoring based on point-of-care testing of infliximab is not superior to reactive drug monitoring in patients with inflammatory bowel disease: 1 year results of a pragmatic clinical trial.

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Introduction: Higher infliximab (IFX) drug levels are associated with better outcomes over time in patients with inflammatory bowel disease (IBD). Algorithm based personalized dosing of IFX may prevent loss of response.1 When incorporating point of care testing (POCT) for IFX, ultraproactive therapeutic drug monitoring (TDM) with ad-hoc dose optimisation is possible.
Aim: We aimed to compare the use of an ultraproactive TDM dosing algorithm based on POCT with the use of reactive TDM, by looking at clinical outcomes at 1 year in IFX-treated patients with IBD.
Methods: This was a pragmatic cluster randomized clinical trial in two large IBD centers. All IBD patients with maintenance IFX treatment were prospectively included between June and August 2018. In cohort A, an ultra-proactive TDM algorithm was applied as follows. All patients had an ELISA TL measurement at baseline, of which the result

determined the follow-up pathway: (A) TL between 3-7µg/mL: continuation at same dose and interval; (B) TL >7µg/mL: interval prolongation allowed; (C) TL <3µg/mL: interval shortening with minimum 2 weeks, with the next IFX TL measured using a POCT. (i) If the POCT showed an IFX TL <3µg/mL, dose was optimized ad hoc using a linear dosing formula (Dosen = (TLtarget * Dosen-1) / TLmeasured), followed by a new POCT test at next visit with the same interval. (ii) If the POCT showed an IFX TL ≥3µg/mL, no additional dose was given and routine TL testing with ELISA was retaken at next visit. This algorithm was repeated at each visit. In cohort B, a reactive TDM approach was applied with TL measurement only at physician's discretion (retrospectively assessed to avoid treatement bias). Primary endpoint was failure of IFX therapy, defined as IFX discontinuation, IBD surgery, IBD hospitalization, add-on IBD treatment, and allergic reaction to IFX. Secondary endpoints included sustained clinical remission (phycisian's global assessement <1 at each visit) and mucosal remission (endoscopy and/or fecal calprotectin) between 6 and 12 months after initiation of the trial.

Results: One hundred eightyseven patients were included (cohort A/B: 115/72, M/F: 95/92, CD/UC: 135/51). Both cohorts had comparable baseline characteristics for disease type, disease duration, IFX duration, and previous treatment. Cohort A had more TL measurements compared with cohort B (8.8/patient/year vs 1/patient/year; p<.0001) leading to a significant higher number of dose optimizations: interval shortening 48% vs 15% (p<.0001), interval prolongation 21% vs 6% (p=.004), bidirectional 13% vs 1% (p=.006). In cohort A, POCT was required in 27% after the first round of ultraproactive TDM and in a mean of 6.3% (SD 1.9%) in the subsequent rounds. Ad-hoc extra dosing was required in 13% of the POCT. After one year of follow-up, no difference was seen in IFX failure 19% vs 10% (p=.08) or IFX discontinuation 11% vs 6% (p=.18) between cohort A and B. Sustained clinical remission rates were comparable in both cohorts (75% vs 83%; p=.17). Mucosal remission data were available in 71 patients (38%). In this subgroup, mucosal remission was more frequently seen in the reactive TDM cohort (79%) than in the ultraproactive TDM cohort (52%) (p=.021).

Conclusions: This is the first clinical trial comparing an ultraproactive TDM dosing regimen including POCT with reactive TDM dosing during maintenance therapy with IFX in IBD. Although ultraproactive TDM dosing leads to more dose flexibility compared with reactive TDM, this does not result in better clinical outcomes. The value of ultraproactive TDM during induction therapy requires further investigation. 1 Strik et al. Journal of Crohn's and Colitis 2019:13(S063)

I08

Quality improvement by benchmarking of a core outcome indicator set in inflammatory bowel disease: a multicentric feasibility study.

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Introduction: Quality of care in inflammatory bowel disease (IBD) is dependent on multiple factors and can be adequately assessed through structure, process and outcome indicators. Structure and process indicators are more static and can easily be measured by an audit. Patient-oriented outcome indicators that impact most on the quality of life of the patient are more difficult to assess.

Aim: The aim of the project was to build a platform that automatically captures key outcome quality indicators and provide benchmarking output to improve quality of care in IBD centres.

Methods: Literature was reviewed for relevant quality indicators in IBD. After two non-anonymized Delphi like review and consensus meetings, twelve quality indicators were selected for implementation. The definitions of the outcomes were aligned in consensus with the available International Consortium for Health Outcomes Measurement (ICHOM). A web-based interface was built in three large volume IBD centres in Belgium to collect data on multiple ways: (i) Patients complete patient-reported outcome questionnaires and disease specific questions when attending the outpatient clinic and/or day clinic; (ii) The software automatically extracts data from the electronic medical files including biochemical and endoscopic reports; (iii) The medical baseline characteristics and outcome indicators for each patient are completed by the healthcare professional at inclusion and after this on a yearly basis.

Results: In total 218 patients were included in the participating IBD centres. Three indicators could be directly extracted from the patient-reported outcome questionnaires (clinical remission, fatigue, work productivity). Two items could be retrieved by use of the bot that automatically extracts biochemical and endoscopic reports from the medical files (anaemia, deep remission). The other items were collected throughout yearly confirmation by a health care professional (colorectal cancer, steroid use [systemic/topical], severe infections, hospital admission, IBD surgery [perianal/abdominal]). All items are benchmarked in an anonymous way on a benchmarking dashboard. Each centre can only see his own position in the benchmarking diagram. Additionally, the case mix per centre (type IBD, severity, demographic data) was added to the benchmarking output to provide a balanced evaluation of the outcome indicators.

Conclusions: This is the first partially automated benchmarking initiative for quality of care in IBD. The data collection is feasible and provides an objective assessment and comparison of the IBD related quality of care in different centres. Further prospective evaluation needs to confirm that implementation of benchmarking improves the performance and quality of IBD management.

I09

Patient perspectives on the role of the IBD nurse and telemedicine during COVID-19 pandemic: results from a Belgian tertiary IBD unit

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Introduction: Many inflammatory bowel disease (IBD) patients experienced additional stress since the start of the COVID-19 pandemic. Concerns for infection and severe COVID-19 disease course increased the risk of immunomodulatory treatment discontinuation. Furthermore, lockdown and travel limitations threatened the continuity of chronic care delivery. To counter this, our IBD unit rapidly adapted and developed new ways of remote communication including specific e-mails, electronic notifications and a monthly newsletter. In addition, most of the face-to-face appointments were replaced by telephone clinics in order to guarantee the continuity of care. In this process the IBD nurse played a pivotal role.
Aim: To assess IBD patients' concerns during the first wave of COVID-19 pandemic and their acceptance of teleconsultation.
Methods: A cross-sectional study was performed using an anonymous electronic questionnaire to assess IBD patients' concerns and satisfaction regarding care delivery at the IBD unit of the Ghent University Hospital during the COVID-19 pandemic. For development of the survey and analysis of the responses, the REDCap software platform was used. All IBD patients with a valid email received a study invitation. Data was collected between 22/10/2020 and 30/11/2020.
Results: Two hundred fifty-eight participants were included. Mean age was 47.18years (SD ±15.61). According to patients' answers, 58.1% suffered from Crohn's disease, 33.9% ulcerative colitis and 8.1% reported 'other'. During the first wave of the pandemic, 44.9% of the patients had contacted the IBD nurse. Their most frequent questions considered medication changes (50.5%), appointment arrangements (46.3%) and risks regarding SARS-CoV2 infection (14.8%). In 98.1%, these contact moments were experienced as sufficiently informative. Of all responders, 70.2% had a scheduled follow-up consultation in the last months. Of this group, at least 30 patients (17.6%) thought about cancelling their consultation because of the pandemic. Twelve patients discussed the need for the appointment with the IBD nurse and seven postponed the appointment. Eighteen patients effectively cancelled their appointment. During the first wave, 78 patients (32.2%) had an appointment for endoscopic investigation. Nine patients postponed or cancelled this investigation and five reported that fear of contracting coronavirus was the main reason. Half of the responders (51.8%) are treated with intravenous biologic infusions at the Day Clinic. Telephonic pre-admission screening the day before treatment was well appreciated by 98.4% of patients. Ninety-four (39%) of the study participants responded to questions on telephone clinics with their IBD specialist during the pandemic. The majority (86.1%) of patients reported that this remote counselling was a good alternative way of guaranteeing care delivery during the pandemic. About one out of three responders (36.2%) thought that important information could be missed due to the absence of clinical examination. The mean level of satisfaction about these remote consultations was 71.06 (±22.84) on a visual analogue scale from 0 to 100. With regards to future follow-up, 60.4% stated that they

would prefer a balanced combination of telephonic appointments and face-to-face consultations.
Conclusions: The COVID19 pandemic resulted in a rapid shift towards remote ways of care delivery for IBD patients. This was generally well received by the IBD patients at the University Hospital of Ghent. Only a minority of patients cancelled appointments without consulting a healthcare practitioner. The most frequent concerns amongst IBD patients were about medication changes and appointments.

I10
One year endoscopic and histologic outcomes to tofacitinib therapy in refractory ulcerative colitis
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Introduction: Long-term real-life data on the efficacy of the pan-Janus kinase inhibitor tofacitinib in moderate-to-severe ulcerative colitis (UC) are limited.
Aim: To report efficacy of tofacitinib in refractory UC patients with an emphasis on endoscopic and histologic remission rates.
Methods: Forty consecutive UC patients (Mayo endoscopic sub-score ≥2) initiating tofacitinib prior to November 2019 were prospectively included. Almost all were refractory to both anti-TNF (97.5%) and vedolizumab (92.5%), and received tofacitinib 10mg twice daily (BID) with tapering to 5mg BID from week 8 (60.0%) or week 16 (40.0%) onwards, upon decision of the treating physician. Steroid-free clinical remission was defined as a partial Mayo score of ≤2 with no single sub-score > 1 and without any steroid exposure at time of assessment. Biological remission was defined as faecal calprotectin <250mcg/g. Endoscopic remission was defined as a Mayo endoscopic sub-score of 0, endoscopic improvement as a Mayo endoscopic sub-score of ≤1, and histologic remission as a Nancy histology index of 0. A combination of endoscopic and histologic remission was referred as mucosal healing. All outcomes were assessed at year 1. Non-responder imputation and last observation carried forward analysis was applied for missing data.
Results: Patients were followed for a median [IQR] of 90.4 [66.8-102.9] weeks, with a median exposure to tofacitinib of 18.8 (12.6-54.8) weeks. By year 1, 32.5% of patients were in steroid-free clinical remission. Biological remission was observed in 28.2% of patients. Endoscopic improvement, as well as endoscopic and histologic remission, were observed in 35.0%, 27.5% and 25.0% of patients, respectively. Mucosal healing was achieved in 19.4% of patients. All patients in endoscopic remission by week 8 (n=5) or week 16 (n=6) remained in remission till week 48. An additional 5 patients (12.5%), who did not achieve endoscopic remission by week 16 but did show a 50% drop in faecal calprotectin compared to baseline, achieved endoscopic remission by week 48. Multivariate analysis identified baseline Mayo endoscopic score (OR 0.033, 95% CI

0.002-0.69, p=0.03); endoscopic improvement by week 16 (OR 36.5, 95% CI 2.6-515.2, p=0.008) and disease extent at tofacitinib initiation (OR 0.11, 95% CI 0.013-0.95, p=0.05) as independent predictors for endoscopic remission at year 1. Patients with histologic remission by week 16 had significant higher endoscopic remission rates by year 1 (p=0.006). Patients with left-sided colitis (n=19) or proctitis-only (n=6) experienced higher endoscopic remission rates (42.1% and 33.3%) than patients with extensive colitis (n=15) (6.7%, p=0.02 and p=0.2 respectively). Ultimately, 62.5% of all patients discontinued tofacitinib therapy after a median of 15.4 [7.7-16.6] weeks, due to primary non-response (n=21), loss-of-response (n=3) or serious adverse events (n=1). Twelve patients (30,0%) required colectomy. During follow-up, we did not observe any venous thrombo-embolisms or cancers. One patient had to be admitted at ICU due to several life-threatening opportunistic infections. No other safety signals were raised.

Conclusions: In this highly refractory cohort of UC patients, tofacitinib induced and maintained endoscopic and histologic remission in up to one quarter of patients. UC patients with moderate left-sided colitis and proctitis had higher likelihood for a sustained effect than patients with extensive colitis.

I11

Efficacy and Safety of Filgotinib as Induction Therapy for Patients with Moderately to Severely Active Ulcerative Colitis: Results from the Phase 2b/3 SELECTION Study

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Introduction: Filgotinib (FIL) is a Janus kinase 1 preferential inhibitor being investigated for several inflammatory conditions, including ulcerative colitis (UC).
Aim: The SELECTION (NCT02914522) Induction Studies aimed to evaluate the efficacy and safety of FIL as induction therapy for patients with moderately to severely active UC who were biologic naïve but failed conventional therapy (Cohort A Induction Study) or who had failed prior biologics (Cohort B Induction Study).
Methods: In both induction studies, patients were randomized 2:2:1 to once daily oral FIL 200 mg, FIL 100 mg or placebo (PBO). The primary endpoint for both studies was endoscopic/rectal bleeding/stool frequency (EBS) remission at Week 10, defined by Mayo endoscopic subscore (ES) ≤1, rectal bleeding subscore = 0, and ≥1-pt decrease in stool frequency subscore from baseline and stool frequency subscore ≤1. Key secondary endpoints included Mayo Clinic Score (MCS) remission, endoscopic remission (ES=0), and Geboes histologic remission at Week 10.
Results: In both cohorts, baseline demographics, UC disease characteristics and concomitant UC medications were generally similar across treatment groups. In Cohort A, 659 patients were randomized and treated. At baseline, mean MCS was 8.6 and 56% of patients had severe endoscopic disease (ES=3). 625 (95%) patients completed treatment; the most common reason for treatment discontinuation was an adverse event (AE). A significantly higher proportion of patients treated with FIL 200 mg in Cohort A achieved EBS remission vs. PBO (26.1% vs. 15.3%, respectively [p=0.0157]). In addition, a significantly higher proportion of patients treated with FIL 200 mg vs. PBO achieved all key secondary endpoints. In Cohort B, 689 patients were randomized and treated. At baseline, mean MCS was 9.3 and 78% of patients had ES = 3. Approximately 86% were prior anti-TNF failures, 52% were prior vedolizumab failures and 43% had failed both. 635 (92%) patients completed treatment; the most common reason for treatment discontinuation was an AE. A significantly higher proportion of patients receiving FIL 200 mg in Cohort B achieved EBS remission vs. PBO; 11.5% vs. 4.2% in Cohort B (p=0.0103). Overall, the incidence of AEs, serious AEs and discontinuations due to AEs were similar across FIL and PBO treatment groups. In Cohort A, serious infections occurred in 0.7%, 0.7% and 0.4% of patients in PBO, FIL 100 mg and FIL 200 mg treated groups, respectively, and in 1.4%, 1.4% and 0.8% of patients respectively in Cohort B; herpes zoster infection occurred in 0%, 0% and 0.8% of patients on PBO, FIL 100 mg and FIL 200 mg respectively in Cohort A and in 0%, 0.4% and 0.4% of patients respectively in Cohort B. One patient on FIL 200 mg experienced an opportunistic infection of mild esophageal candidiasis on Day 15 that resolved with treatment. One patient on FIL 200 mg experienced a serious AE of pulmonary embolism on Day 19; the patient's medical history was significant for hypothyroidism and pulmonary symptoms of unknown origin.
Conclusions: The SELECTION study population included a high proportion of dual-refractory patients, and patients with severe endoscopic disease. Both doses of FIL were

well tolerated. Filgotinib 200 mg was effective as an induction treatment for both biologic-naïve and biologic-experienced patients with moderately to severe UC.

I12

Efficacy and Safety of Filgotinib as Maintenance Therapy for Patients with Moderately-Severely Active Ulcerative Colitis: Phase 2b/3 SELECTION Study

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Introduction: Filgotinib (FIL) is a Janus kinase 1 preferential inhibitor being investigated for several inflammatory conditions, including ulcerative colitis (UC).

Aim: The SELECTION (NCT02914522) Maintenance Study is a global, double-blind, randomized trial of FIL as maintenance therapy for patients with moderately to severely active UC who achieved clinical remission or Mayo Clinic Score (MCS) response after 10 weeks of induction with FIL 200 mg, FIL 100 mg or placebo (PBO) for up to 58 weeks.

Methods: Patients randomized and responding to FIL induction were rerandomized 2:1 to their induction FIL dose or PBO. Patients randomized and responding to PBO during induction continued PBO maintenance. Mandatory steroid tapering was required. Primary endpoint was endoscopic/rectal bleeding/stool frequency (EBS) remission at Week 58, defined by Mayo endoscopic subscore (ES) $\leq$1, rectal bleeding subscore = 0, and $\geq$1-pt decrease in stool frequency subscore (SFS) from baseline and SFS $\leq$1. Key secondary endpoints included 6-month corticosteroid-free clinical remission, sustained clinical remission, MCS remission, endoscopic remission and Geboes histologic remission at Week 58.

Results: A total of 664 patients were enrolled and treated in the Maintenance Study (n=93, 270, and 301 from induction PBO, FIL 100 mg and FIL 200 mg arms, respectively); efficacy analyses included only patients who received FIL during induction (n=558). Baseline demographics and disease characteristics were generally balanced across treatment arms; approx. 40% of patients were biologic experienced. A significantly higher proportion of patients on FIL 200 mg or FIL 100 mg achieved EBS remission vs. PBO (37.2% FIL 200 mg vs. 11.2% PBO [$p<0.025$] and 23.8% FIL 100 mg vs. 13.5% PBO [$p<0.05$]). Significantly higher proportions of patients achieved key secondary endpoints including 6-month corticosteroid-free clinical remission (27.2% FIL 200 mg vs. 6.4% PBO [$p<0.025$] and 13.6% FIL 100 mg vs. 5.4% PBO) histologic remission (38.2% FIL 200 mg vs. 13.3% PBO [$p<0.025$] and 27.9% FIL 100 mg vs. 18% PBO) and MCS remission (34.7% FIL 200 mg vs. 9.2% PBO [$p<0.025$] and 27.9% FIL 100 mg vs. 18% PBO). Overall, the incidences of adverse events (AEs), serious AEs and discontinuations due to AEs were similar across treatment arms (59.6%–66.8% AEs; 4.3%–7.7% serious AEs and 2%–5.6% discontinued due to an AE). Serious infections and herpes zoster infections were infrequent across groups; serious infections were seen in 0% PBO vs. 1% in the FIL 200 mg group; 2.2% PBO vs. 1.7% in the FIL 100 mg group. Herpes zoster infection was only seen in one patient taking FIL 200 mg and one patient taking PBO. No opportunistic infections occurred. There were no venous thromboses, including pulmonary embolism, among FIL-treated patients. Two patients on FIL 200 mg died (one from asthma exacerbation, one from left ventricular failure), both considered unrelated to FIL.
Conclusions: FIL 200 mg and 100 mg were effective as maintenance treatment for patients with moderately to severely active UC who had achieved clinical response to induction treatment with FIL. FIL 200 mg met all key secondary endpoints including endoscopic, histologic and 6-month corticosteroid-free remission. FIL was well tolerated in patients with moderate to severely active UC.

I13

Positioning strictureplasty in the treatment of extensive Crohn's disease ileitis. A comparative study with ileocecal resection.

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Introduction: To obviate the potential risk of repetitive resections and the inherent risk of short bowel syndrome, long atypical strictureplasties have been established as a valid alternative to resection in case of extended small bowel involvement, particularly when multiple fibrotic strictures without signs of penetrating disease (abscess or fistula) are present. To date, no studies have directly compared the short- and long-term outcome

of modified side-to-side isoperistaltic strictureplasty over the valve (mSSIS) to traditional ileocecal resection.
Aim: To assess the short and long-term outcome of the two techniques, with particular focus on postoperative morbidity and surgical recurrence.
Methods: A retrospective, observational, comparative study was conducted in consecutive CD patients operated for extensive involvement of the terminal ileum (≥20 cm). Ninety-day postoperative morbidity was assessed using the comprehensive complication index [CCI]. Surgical recurrence was defined as the need for any surgical intervention related to CD during the follow-up period. Endoscopic remission was defined as ≤i2a, according to the modified Rutgeerts score. Deep remission was defined as the combination of endoscopic remission and absence of clinical symptoms. Perioperative factors related to clinical recurrence were evaluated.
Results: Eighty-seven patients were included [47 (54%) ileocecal resection and 40 (46%) mSSIS]. Median follow-up was 56 (IQR 34.7-94.4) and 72 (IQR 48.3-87.2) months for resection and mSSIS, respectively ($p<0.001$). No mortality occurred. Mean CCI was 9.1 vs 8.5 for ileocecal resection and mSSIS, respectively ($p=0.48$). Throughout the follow-up, 8 patients in the resection (17%) and 5 patients in the mSSIS group (12.5%) experienced surgical recurrence ($p=0.393$). Thirty-seven (92.5%) of patients kept the mSSIS. No difference in deep remission was observed [41% vs 22.5%, $p=0.34$].
Conclusions: Modified SSIS seems to be non-inferior in terms of safety, recurrence and durability to traditional resections with the advantage of mitigating the risk of a short bowel syndrome. Larger prospective studies are required to confirm these findings.

I14
Evaluation of trough level and disease activity after switch from adalimumab originator (Humira®) to biosimilar (Imraldi®) in patients with inflammatory bowel disease: 6 month interim analysis of the SafE-OrBi study.

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Introduction: Biosimilars offer an opportunity to reduce the high economic burden of inflammatory bowel diseases (IBD) and their biologic treatments. Imraldi® (SB5) is approved as a biosimilar to the adalimumab (ADA) originator Humira®. Bio- and efficacy equivalence, as well as comparable safety and immunogenicity for originator and biosimilar have been demonstrated in Phase I and III randomised clinical trials. However, data are still lacking on effectiveness and trough levels over time in patients with IBD after switching from originator to biosimilar ADA.
Aim: The primary outcome measurement was the description of ADA trough level over time after the switch. The secondary outcome measurements were disease activity

scores as well as biochemical measurements to readily monitor potential flares (faecal calprotectin, peripheral blood count and C-reactive protein).
Methods: In 2 Belgian IBD centres, IBD patients on Humira® and in clinical remission or stable response were offered to enter this phase IV, interventional trial. Patients showing stable response or in remission, were switched to Imraldi®. Patients were followed at baseline, at 8 weeks and 6 months post-switch. Therapy type and dose regimen remained unchanged the first 8 weeks. Trough serum ADA concentrations were measured by enzyme-linked immunosorbent assay (ELISA), using the apDia Adalimumab ELISA kit (ref. 710201). The detection range of the ELISA lies between 0.1 and 12 µg/mL.
Results: One hundred and ten patients were enrolled in the study of which 84 had Crohn's disease (CD) and 26 had ulcerative colitis (UC). Eighty four patients were still treated with Imraldi® at month 6 of which 62 CD and 22 UC patients. At week 8, objective assessment (high antidrug antibody levels) resulted in ADA discontinuation in 5 patients. During further follow-up 4 patients stopped ADA as a result of secondary loss of response; 17 patients discontinued due to an adverse event. At baseline, mean (SD) and median (IQR) plasma trough levels of ADA were respectively 9.21 (5.72) and 9.30 (4.80 to 12.00) µg/mL. The mean and median trough levels at week 8 were 9.00 (5.25) and 8.00 (5.10 to 11.90) µg/mL, respectively. At month 6, a mean and median trough level of 8.00 (4.19) and 7.65 (5.00 to 10.90) µg/mL were respectively found. The median value (IQR) at baseline of the Physician Global Assessment Score (PGA), Partial Mayo Score (PMS) and the Crohn's Disease Activity Index were 0.0 (0.0 to 0.0), 0.0 (0.0 to 1.0) and 50.5 (25.5 to 93.0) respectively. No differences were found in disease activity scores from baseline to week 8 and month 6 after switching to Imraldi®.
Conclusions: In this interim analysis we describe the trough levels at baseline and after switch from Humira® to Imraldi® in an IBD population showing stable response or remission. After switch, no differences were found in disease activity scores over time.

I15

Acceptance of switch, patient satisfaction and adverse events after switch from adalimumab originator (Humira®) to biosimilar (Imraldi®) in patients with inflammatory bowel disease: 6-month interim analysis of the SafE-OrBi study.

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Introduction: Biosimilars offer an opportunity to reduce the high economic burden of inflammatory bowel diseases (IBD) and their biologic treatments. Imraldi® is approved as a biosimilar to the adalimumab originator Humira®. Even though bio- and efficacy equivalence, as well as comparable safety and immunogenicity have been demonstrated in phase I and III randomised clinical trials, data on acceptance of switch to a biosimilar,

as well as patient satisfaction, adverse events and nocebo effects are lacking in the IBD population.

Aim: To analyse data on acceptance of switch to a biosimilar, as well as patient satisfaction, adverse events and nocebo effects in a real-life IBD population.

Methods: In 2 Belgian IBD centres, IBD patients on Humira® and in clinical remission or stable response were offered to enter this phase IV, interventional trial. In this study, patients were informed on biosimilars by their gastroenterologists and IBD-nurses before they were offered to switch to the biosimilar. Patients not willing to switch were asked about the reasons. Patients were followed at baseline, at 8 weeks and at 6 months. Therapy remained unchanged until week 8. Patients who agreed to switch, were questioned (Visual Analogue Scale (VAS)) on satisfaction and local discomfort after injection at baseline with Humira® and Imraldi®, and 8 weeks and 6 months post-switch. When patients discontinued Imraldi®, reasons were documented.

Results: One hundred and forty-two patients were screened of which 5 patients (3.5%) refused to take part in the study and 27 patients (19.0%) refused to switch to Imraldi®. Thirteen patients reported in total 18 reasons for refusal; the reasons most frequently given were fear for a flare (n = 6, 33.3%), ease to stay on Humira® (n = 4, 22.2%), absence of trust in biosimilar (n = 3, 16.7%) and negative experiences with disease burden in the past (n = 2, 11.1%). One hundred and ten patients switched to Imraldi® (84 patients with Crohn's disease (76.4%) and 26 with ulcerative colitis (23.6%)). Twenty seven patients discontinued Imraldi® for several reasons: high adalimumab antidrug antibodies at baseline (n = 5), secondary loss of response (n = 4), long-term remission (n = 1) and adverse events like injection site pain (ISP) (n = 6) and adverse events which could not be attributed to the investigational product (n = 11). Furthermore, the median (interquartile range (IQR)) VAS for local discomfort up to 30 minutes after injection was 1 (0 – 2) for Humira®, and 3 (0 – 6) for Imraldi® at baseline, 3 (1 – 7) at week 8 and 3 (1 – 7) at month 6 ($p < 0.001$ for all, compared to Humira®). However, the median (IQR) VAS for local discomfort after 30 minutes after injection up till next injection remained stable over time, 1 (0 – 2) on Humira® at baseline, 0 (0 – 2) at week 8 and 1 (0 – 2) at month 6 ($p > 0.05$ for all, compared to Humira®). Importantly, the satisfaction with the decision to switch to Imraldi® was stable over time with a median (IQR) VAS of 8 (5 – 9) at baseline and of 7 (5 – 9) and 8 (7 – 9) at week 8 and month 6 respectively ($p > 0.05$ for both). Sixteen serious adverse events were reported, none of them were deemed to be causally related to Imraldi®.

Conclusions: Our 6-month interim analysis shows that, after being well informed, the great majority of patients treated with adalimumab originator is willing to switch to biosimilar Imraldi®. The most important reasons to stop Imraldi® were adverse events which could be attributed to the nocebo effect and to ISP. Patients in general report a higher local discomfort in the first 30 minutes after injection with Imraldi®, which then resolves. However, in general patients remain satisfied with their decision to switch.

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Introduction: Recently the therapeutic armamentarium for ulcerative colitis (UC) has been expanded with a JAK inhibitor, tofacitinib (TOFA) and an anti-IL12/IL23, ustekinumab (UST). Both molecules have shown effectiveness in UC. However, no head-to-head trials have compared these 2 molecules and there are currently no guidelines on the position of these agents in the therapeutic algorithm for moderate to severe UC.

Aim: To assess the real life effectiveness of TOFA and UST in UC.

Methods: A retrospective study was performed in patients with UC after initiation of UST or TOFA between December 2018 and July 2020. Clinical and endoscopic response were assessed.

Results: In total 27 patients were evaluated: 12 patients treated with UST and 15 with TOFA. The majority of patients was refractory to anti-TNF and/or vedolizumab: 92.6% of patients had $\geq$ 2 previous lines of treatment. Five patients treated with UST were previously treated with TOFA. All patients had moderate to severe active disease at baseline (endoscopic Mayo 2-3). Baseline characteristics between UST and TOFA were comparable. The follow-up duration was longer in patients treated with TOFA (mean of 45.7 $\pm$ 28.8 weeks compared to 26.6 $\pm$ 14 weeks in UST). Induction with TOFA (10 mg twice daily) was given for 8 weeks in 3 patients (20%), 12 patients (80%) needed prolonged induction, usually for 16 weeks. Treatment was started in combination with corticosteroids in 75% and 86.7% of patients treated with UST and TOFA respectively. In 3 patients treatment was started in combination with an immunosuppressant because of concurrent extra-intestinal manifestation: auto-immune hepatitis in 1 patient treated with UST and spondyloarthropathy in 2 patients (1 in each treatment group). At week 8 clinical response/remission was seen in 83.3% (10/12)/8.3% (1/12) and 61.5% (8/13)/15.4% (2/13) of patients treated with UST (n=12) and TOFA (n=13) respectively. Endoscopic response after 8 weeks of treatment with UST was promising: 85.7% (6/7 evaluated patients) had an endoscopic response. After 8 weeks of tofacitinib 50% (6/12 evaluated patients) had an endoscopic response, 6 patients had no response. After 6 months of UST the response could be evaluated in 7 patients; treatment was stopped in 1 patient due to loss of response (LOR) and 42.9% (3/7)/42.9% (3/7) of patients had clinical response/remission. Corticosteroid free remission was seen in 2 patients. Endoscopic evaluation was performed in 5 patients, endoscopic response/remission was seen in 2 out of 5 patients. In patients under TOFA assessed at 6 months (n=14), TOFA was stopped in 4 patients due to insufficient response. Clinical response/remission was seen in 14.3% (2/14)/50% (7/14). Corticosteroid free remission was seen in 5 out of 14 patients (35.7%). In 11 patients treated with TOFA an endoscopy was performed at 6 months, this showed endoscopic response/remission in 63.9% (7/11)/9.1% (1/11). After 1 year of TOFA treatment (n=13), TOFA was stopped in 1 additional patient, and 7.7% (1/13) /46.2% (6/13) of patients were in clinical response/remission. Five patients were in steroid-free remission. Endoscopy at this timepoint (n=6) showed response/remission in 33.3% (2/6)/50% (3/6) of patients. In

this cohort 4 patients (2 in each group) had an UC flare during treatment and 1 patient treated with TOFA underwent colectomy due to severe, refractory disease. Other side effects included arthralgia (UST: n=2, TOFA: n=2), eczema (UST: n=1, TOFA: n=1), hyperlipidemia (TOFA: n=2) and cystitis (TOFA: n=2). There were no severe infections during the follow-up.

Conclusions: In this tertiary population of refractory UC patients, overall a good clinical evolution is seen both with UST and or TOFA. However, the rates of steroid-free remission and endoscopic remission are still modest and longer follow-up is necessary.

I17

Effects of concomitant steroids on a prognostic blood gene expression biomarker for inflammatory bowel disease

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Introduction: Accurately predicting disease course at diagnosis is critical to facilitate personalized therapy in inflammatory bowel disease (IBD). PredictSURE IBDTM is a whole blood qPCR assay that was developed to predict prognosis in newly diagnosed, treatment-naïve IBD patients – classifying them into IBDhi (high-risk) or IBDlo (low-risk). The current recommendation is that PredictSURE IBDTM not be used in those who have commenced steroids, but whether steroids do impact on test performance is unclear, though they are known to profoundly affect gene expression.

Aim: To determine the impact of steroid therapy on the performance of PredictSURE IBDTM.

Methods: To determine the effect of steroids on PredictSURE IBDTM, whole blood was serially taken from patients admitted with severe IBD requiring intravenous (IV) steroid therapy (pre-steroid, day 3, day 5) and from patients receiving oral steroids as outpatients (pre-steroid, week 1, week 6) (n=10/cohort). To assess the prognostic accuracy of the biomarker, a larger cohort of 43 IBD patients receiving their first corticosteroid treatment (41 systemic and 2 topical) were recruited (all within 3 months of diagnosis). RNA was extracted and analyzed with PredictSURE IBDTM (PredictImmune, UK). Patients were prospectively followed and treated according to routine clinical management by physicians blinded to the test results, and clinically stratified according to one of the original definitions used to construct and validate the test, namely, need for step up to immunosuppressive or biological therapy or surgery (ileocecal resection, hemicolectomy, or colectomy).

Results: Oral and intravenous steroids affected the PredictSURE IBDTM result. Misclassification as IBDlo occurred in 5/8 IBDhi patients receiving oral, and 5/7 IBDhi

patients receiving IV, steroids. In 60% this change was detectable early (within 1 week of oral steroids and 3 days of IV steroids). Steroids did not affect the classification of IBDlo patients. Consistent with this, the prognostic accuracy of PredictSURE IBDTM was limited in patients already receiving steroids. After a median follow-up of 31.8 [IQR 18.7 - 42.1] months, 35 (81%) patients required a step-up in therapy. PredictSure IBDTM correctly classified only 23 (54%) patients with accuracy of 0.53 (sensitivity: 0.51, specificity: 0.63, positive likelihood ratio: 1.38, negative likelihood ratio: 0.77). Seventeen (80%) of the misclassifications were clinically high-risk patients who were predicted as IBDlo. Time to treatment escalation was similar between patients classified as IBDhi or IBDlo after starting steroid therapy (P= 0.47).
Conclusions: The prognostic accuracy of PredictSURE IBDTM is limited if the test is performed after steroid therapy has begun, most likely because of the misclassification of high-risk patients as low risk. Until the effects of other therapies are known, the test should only be performed in patients with active disease who are not receiving immunosuppressive treatment, as currently recommended.

I18

Single-cell RNA sequencing to unravel the cellular heterogeneity, inter-cellular communication and spatial organization in human intestinal tissue remodelling in Crohn's disease

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Introduction: In Crohn's disease, recurrent cycles of intestinal inflammation and tissue repair progressively result in excessive extracellular matrix protein accumulation, tissue fibrosis and luminal obstruction. This is the irreversible end-stage result of excessive fibroblast activation and tissue remodelling that often culminates in luminal stenosis, necessitating surgical intervention, thereby considerably contributing to the socio-economic burden of CD. Until now, the intestinal wall of CD patients is mostly studied using endoscopic-derived mucosal biopsies. It lacks evidence to show the mechanisms of activated fibroblasts and the cellular factors in the deeper bowel wall.
Aim: Current understanding of fibro-stenosis in CD patients have not been sufficient in identifying potential therapeutic targets for prevention of tissue remodelling and fibrosis. Hence, we intend to understand the cellular mechanisms leading to abnormal extracellular matrix protein accumulation during chronic inflammation. This includes phenotyping the cellular origin of ECM deposition and understanding the regulatory mechanism that initiates and sustains ECM secreting cellular phenotypes.
Methods: Full-thickness samples from CD patients undergoing ileocecal resection were collected using transmural biopsies. Ileal tissue from proximal non-inflamed, inflamed and stenotic area of the tissue were profiled using single-cell RNA sequencing (sc-RNA seq) with 10x platform. As an external control, proximal non-tumour tissue was also collected from patients undergoing right hemicolectomy for colorectal cancer. Single-

cell suspensions were obtained by enzymatic digestion. Each sample was run on separate lanes on a 10x chip and library was prepared using 10x 3' v3 kit as per instructions from the manufacturer and sequenced on Illumina platform at the Genomics Core at the UZ Leuven. Read alignment and demultiplexing was performed using 10x Cell Ranger software and integrated using the R package 'Seurat'.
Results: Analysis of sc-RNA seq data from unsorted cells revealed well-resolved compartments of lymphocytes, myeloid cells, endothelial cells, epithelial cells and mesenchymal cells. A specific activated fibroblast population responsible for most ECM transcripts only appeared in the inflamed and stenotic segments of CD samples. We defined this subset of fibroblasts as pro-fibrotic fibroblasts. Intercellular communication studies using Nichenet predicted a set of pro-fibrotic cytokines to be inducing the unique transcriptional profile of the activated fibroblasts. Further analysis revealed that an inflammation specific monocyte cluster is mostly responsible for the secretion of the pro-fibrotic cytokines during inflammation and fibrosis. Motif enrichment analysis also revealed several key transcription factors involved in the possible induction of activated fibroblast phenotype. This finding was validated in vitro using primary human ileum fibroblasts. Upon treatment with the pro-fibrotic cytokine cocktail define via the sc-RNA seq data, normal fibroblasts attained inflammatory and pro-fibrotic signatures and ECM-related genes.
Conclusions: Our study revealed previously unknown characteristics of the fibrotic niche in intestinal fibro-stenotic tissue including the identification of specific pro-fibrotic fibroblasts. It also revealed a crucial pro-fibrotic regulatory role for inflammatory myeloid cells promoting the differentiation of ECM-producing fibroblasts during inflammation. This study, hence, revealed multiple potential therapeutic avenues to prevent/ reduce inflammation-induced fibro-stenosis in CD patients.

Belgian Society for Paediatric Gastroenterology, Hepatology and Nutrition (BESPGHAN)

K01

First experiences with Modulife® in inducing remission in pediatric Crohn patients in Belgium.

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Introduction: ECCO and ESPGHAN recommend exclusive enteral nutrition (EEN) as first-line treatment in the management of mild to moderate Crohn's disease (CD) in children. EEN requires an important patient commitment to adhere to exclusive liquid formula intake for 6 to 8 weeks. Modulife® combines 50% Crohn's Disease Exclusion Diet (CDED) with 50% liquid formula intake. The addition of solid foods aims to improve diet adherence without compromising remission rate. The diet is designed to reduce dietary components with an adverse effect on the microbiome and intestinal barrier.
Aim: The study objective was to evaluate the tolerability of Modulife® and its efficacy in induction of remission in pediatric CD.
Methods: In this retrospective study we collected data from children diagnosed with mild to moderate CD from 4 IBD clinics in Belgium. Endpoints were dietary tolerance and remission at week 6 and 12 defined as PCDAI $\leq$ 10, according to the original study of Levine et al (2019).
Results: Twenty-three children with mild to moderate CD were included in the analysis. Five out of 23 patients (22%) discontinued the Modulife® diet prematurely because of intolerance. Eighteen patients (78%) adhered to the diet. At week 6, 15 out of 18 children (83%) were in remission with PCDAI $\leq$ 10 and with an average decline in PCDAI of 21,5 points. At week 12, 15 out of 17 children (88%) were in remission with an average decline in PCDAI of 24,5 points. One child refused to continue the Modulife® dietary therapy after 6 weeks of use. 16 out of 23 children (70%) received azathioprine simultaneously.
Conclusions: These preliminary retrospective observational results from 4 pediatric Belgian centers demonstrate that Modulife® is generally well tolerated with three quarters of the patients adhering to the diet. 88% of the patients who were able to maintain the diet were in corticoid free remission at week 12 with additional drug treatment. There are 2 important limitations of this study, namely the assessment of remission was based on PCDAI scores alone. We suggest to also take inflammatory markers and fecal calprotectin into account to assess remission in the following results of this study. There are few patients included, further patient enrollment is necessary to confirm these conclusions with longer follow-up.

K02

Child with protein losing enteropathy as presentation of collagenous duodenitis and eosinophilic gastroenteritis.

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Case Report: Background: We describe a child with protein losing enteropathy as presentation of collagenous duodenitis and eosinophilic gastroenteritis. Although, both diseases are rare in children, the combination is extremely rare. Summary: A four-year-old girl presented at the emergency department with non-bloody diarrhea for two months and progressive oedema with an albumin of 16g/dl. The diagnosis of a protein losing enteropathy was made. Extensive investigations withheld only an infectious cause

of the protein losing enteropathy (co-infection of acute cytomegalovirus and adenovirus). Despite supportive treatment with albumin infusions, no spontaneous recovery was seen. Therefore, a new endoscopic work-up was performed. Duodenal biopsies revealed collagen deposition, in association of a high number of eosinophils and mast cells throughout different parts of the gastrointestinal tract. The diagnosis of a diffuse eosinophilic gastroenteritis and collagenous duodenitis was made. Collagenous gastroenteritis can affect multiple parts of the gastrointestinal system. Clinical presentation varies widely, ranging from abdominal pain and diarrhea to more severe clinical picture with malabsorption and protein losing enteropathy. Typical histopathological findings are: collagen band thickness > 10µm in the subepithelial mucosa, increased inflammatory cell infiltration in the lamina propria, and surface epithelial damage (1-2). The underlying pathogenesis is unknown. Several hypothesis are postulated to describe the collagen deposition: (1) as a result of chronic inflammation and/or an autoimmune mechanism, (2) abnormalities of peri-cryptal fibroblast sheath or proteins, and (3) fibrinogen leakage with increased collagen replacement due to primary vascular abnormality with increased vascular permeability (3-4). The immune-mediated hypothesis is the most popular theory because of frequent association with autoimmune disorders and overexpression of HLA-DR by epithelial cells and CD25-positive cells in the lamina propria as a sign of continue inflammation (5-7). These activated immune cells will produce cytokines and growth factors that in turn stimulate the extracellular matrix-producing myofibroblasts. It is presumed that a luminal agent (such as infections or toxins), or allergic reactions to environmental or dietary antigens may act as a trigger for chronic inflammation and will initiate this fibroinflammatory condition. As collagenous gastroenteritis is a scarce disorder, there is no standardized treatment yet. Exclusive amino acid-based diet and oral antihistamine were started to treat the underlying food allergy. In addition, high doses of proton pomp inhibitor (2 mg/kg/day) were added to achieve an anti-inflammatory effect and iron deficient anaemia was supplemented. Clinical improvement was seen rapidly, with normalization of serum albumin within 1.5 weeks, and this remained stable during follow-up without extra albumin infusion. We do not have a histological correlation yet, but literature shows that it takes months, even years before histological improvement is seen. Conclusion: As collagenous gastroenteritis in children is a rare entity, little is known about the triggers, natural course and most effective treatment. In our case, the protein losing enteropathy was caused by a collagenous duodenitis, most likely triggered by an underlying food allergy as represented with infiltration of eosinophils and mast cells in the gastrointestinal tract. Although, this condition is extremely rare, gastroenterologists and pathologists need to be aware of this condition to enable accurate diagnosis, so that appropriate therapy could be started in a timely manner. As more cases will be reported, we will hopefully develop more insight in this disease.

K03

Is there a correlation between symptoms suggestive for gastroparesis and results of gastric emptying breath test in children ?

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Introduction: Gastroparesis Cardinal Symptom Index (GCSI) is the most frequently used validated patient-reported symptom score to assess gastroparesis severity in adults but this score does not always correlates well with the results of gastric emptying (GE) rate. One paediatric study trialed a modified version from the adult GCSI but no association was found between this score and degree of GE emptying delay.

Aim: We performed a prospective cohort study in children with gastrointestinal symptoms (GI) suggestive for gastroparesis to study the relation between a non-validated patient-reported symptom score and GE, measured by 13C-octanoic acid breath test (13C-OBT).

Methods: Prior to the 13C-OBT, a symptom questionnaire, rating abdominal pain and discomfort, bloating, burping, early satiety, epigastric and retrosternal pyrosis, nausea, postprandial fullness and vomiting from 0-3 and assessing the presence of weight loss. GE of a standardized pancake test meal was measured with 13C-OBT. Gastric half emptying time (GE-t1/2) was calculated and defined as normal or delayed according to previously established reference values. Statistical analyses were done using R version 3.1.2. Differences in proportions were analyzed using a chi square or fisher exact test; odds ratio's (OR) were calculated to determine the association between symptoms and delayed GE. Differences between continuous variables were calculated using a Mann Whitney U or t-test . A p-value of <0.05 was considered statistically significant.

Results: A total of 55 patients (35 girls, median (Q1;Q3) age 11.0 (9;13) years) underwent a 13C-OBT, of which 6 patients with delayed GE had follow up testing under prokinetics. The median (Q1;Q3) duration of complaints was 6 (3;12) months, with 44 (81.5%) having more complaints for more than 3 months. Mean (SD) GE-t1/2 was 191 (33.2) min, with no significant sex difference (p=0.926); 19 (34.5%) had delayed GE, with no significant sex difference (p=0.140). Presenting symptoms were abdominal discomfort (n=34, 61.8%) and pain (n=41, 74.5%), bloating (n=34, n=61.8%), burping (n=30, 54.5%), early satiety (n=40, 72.7%), epigastric (n=29, 52.7%) and retrosternal pyrosis (n=20, 36.4%), nausea (n=41, 74.5%), postprandial fullness (n=47, 85.5%), vomiting (n=23, 41.8%) and weight loss (n=22, 40.0%). The median (Q1;Q3) number of symptoms was 6 (5;9), with only two patients having only 1 presenting symptom. Median GE-t1/2 was significantly higher in patients with vs without weight loss (202 vs 180 min, p=0.040) and significantly more children with weight loss had a delayed gastric emptying (OR 4.5, 95% CI 1.4-14.6; p=0.012). No statistically significant associations were found with any of the other symptoms. In 5/6 patients with a follow up 13C-OBT, the test normalized after treatment with prokinetics. Weight increased after treatment for 3/5 patients with normalized GE. No correlation could be found in change in symptoms for patients with a normalized GE on follow up.

Conclusions: We did not find any correlation between GI symptoms suggestive for gastroparesis and GE as assessed by 13C-OBT except for the presence of weight loss. There was no correlation between normalization of GE after treatment and any of the symptoms, although follow-up was available for only six children.

K04

Development of a clinical risk score for significant liver fibrosis in pediatric non-alcoholic fatty liver disease

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Introduction: Childhood obesity, with associated comorbidities such as insulin resistance and non-alcoholic fatty liver disease (NAFLD), is a growing global health problem. NAFLD might progress to steatohepatitis, fibrosis and ultimately liver cirrhosis. Nevertheless, accurate and simple risk scores for the diagnosis of clinically significant liver fibrosis in pediatric NAFLD are currently lacking.

Aim: To identify factors associated with significant liver fibrosis in children and adolescents with obesity, and develop a clinical risk score for fibrosis.

Methods: Children and adolescents admitted for severe obesity at the Zeepreventorium between July 2019 and November 2020 were invited to participate in this study. Liver ultrasound and transient elastography with controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were performed to assess liver steatosis and fibrosis. Fibrosis was defined as an LSM ≥7kPa for F2, ≥9kPa for F3, and ≥11kPa for F4 fibrosis; CAP values ≥240 dB/m were considered elevated. These data were compared with clinical, anthropometric and biochemical patient characteristics. The pediatric NAFLD fibrosis index (PNFI) was calculated using patient age, waist circumference and serum triglycerides.

Results: 162 patients (54.3% male, median age 14.0 years, BMI 36.1, BMI Z-score 2.77) for whom all data were available were included in this analysis. 72.2% of children and adolescents were diagnosed with NAFLD on ultrasound, whereas 75.3% had CAP values ≥240 dB/m. Importantly, 33.3% of patients had at least F2 fibrosis, including 11.1% with LSM ≥9kPa. In univariate analysis, factors associated with ≥F2 fibrosis included anthropometrics (weight and BMI Z-scores, waist and hip circumference), serum ALT and AST, HDL and the severity of steatosis as measured on ultrasound and CAP. Fibrosis was more common in boys (P=0.002) and in patients with hypertension (P<0.001) and girls with polycystic ovary syndrome (P=0.001). The PNFI predicted ≥F2 fibrosis with an area under the receiver operating characteristics curve (AUROC) of 0.70. A new composite formula including gender, weight Z-score, AST, HDL and hypertension had

an AUROC of 0.81 for the diagnosis of fibrosis, while the replacement of AST by the degree of steatosis on ultrasound improved the AUROC to 0.84.
Conclusions: NAFLD and associated fibrosis are highly prevalent in children and adolescents with severe obesity. A risk score incorporating readily available clinical variables is able to diagnose significant liver fibrosis, whereas the utility of the PNFI in this population is limited.

K05
Towards automated scoring of stool consistency in diapers using a digital tool
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Introduction: Accurate stool consistency classification of non-toilet trained children remains challenging.
Aim: This study evaluated the feasibility of automated classification of stool consistencies from diaper photos using a digital tool.
Methods: In total, 2687 usable smartphone photos of diapers with stool from 96 children <24 months were obtained after independent ethical study approval. Stool consistency was assessed from each photo according to the original seven types of the Brussels Infant and Toddler Stool Scale (BITSS) independently by study participants and two researchers. A healthcare professional assigned a final score in case of scoring disagreement between the researchers. A proof-of-concept machine learning (ML) model was built upon this collected photo database, using transfer learning to re-train the classification layer of a pre-trained deep convolutional neural network model. The model was built on random training (n=2478) and test (n=209) subsets.
Results: Agreements between study participants and both researchers were 58.0% and 48.5%, respectively, and between researchers 77.5% (assessable n=2366). The model classified 60.3% of the test photos in exact agreement with the final score. With respect to the four-class grouping of the seven BITSS types, the agreement between model-based and researcher classification was 77.0%.
Conclusions: The automated and objective scoring of stool consistency from diaper photos by the ML model shows robust agreement with human raters and overcomes limitations of other methods relying on caregiver reporting. Integrated with a smartphone application, this new framework for photo database construction and ML classification has numerous potential applications in clinical studies and home assessment.

K06
How to manage constipation: a Belgian national survey
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Introduction: Constipation in children is a frequent problem that can be managed ambulatory for the vast majority. Whenever outpatient treatment fails, admission for a clean-out becomes inevitable. The ESPGHAN/NASPGHAN guidelines for the treatment of functional constipation do not elaborate a disimpaction protocol.

Aim: We aimed to survey Belgian paediatricians on their current practices for the treatment of functional constipation and to compare treatment practices in secondary and tertiary hospitals and across regions in Belgium.

Methods: A Dutch and French version of an electronic survey was sent out to Belgian paediatricians via Groupement Belge des Pédiatres Francophones and the Vlaamse Vereniging voor Kindergeneeskunde. The survey addressed three pillars of constipation management: ambulatory care, in-hospital practices and follow-up. Statistical analysis was performed using R. Differences in proportions between groups were analyzed using χ^2-test or Fisher's exact test. Continuous variables were compared using a Wilcoxon rank sum test. Missing values (nmissing) were reported separately per question. A p-value of <0.05 was considered statistically significant.

Results: A total of 114 paediatricians responded to the questionnaire, of which 104 (91.2%) were used for analysis (Flemish: 76 (73.1%), Walloon: 28 (26.9%)). The median (Q1;Q3) response rate per (not open ended) question was 71.6% (66.1;84.9). Respondents worked primarily in secondary care (68.3%), with no significant difference in proportion of tertiary vs secondary care level between Flemish or Walloon respondents (p=0.139). The median (Q1;Q3) number of in-patient beds amongst respondents from secondary care was 22 (17;26) beds (nmissing: 5). The majority of the respondents had 2-5 admissions for constipation/clean out per month (39/89, 43.8%). The primary choice for the ambulatory treatment of functional constipation was macrogol with (50/89, 56.2%) or without (34/89, 39.3%) electrolytes (secondary vs tertiary care: p = 0.584). When ranking the primary endpoints for successful outpatient treatment, "no more soiling or encopresis" was most frequently ranked as most important (35/89, 39.3%), whereas "daily loose stools" and "daily stools (regardless of consistency)" were attributed the least importance (respectively 27/89, 30.3%, and 26/89, 29.2%). No differences were noted according to the respondent's work setting or region, except for "daily loose stools" which was given less importance in secondary vs tertiary care (p = 0.011). The most popular indications for admission were failure of outpatient macrogol therapy and/or failure of ambulatory treatment of encopresis (both 32/88, 36.4%). The median of the average length of stay was 3.0 days (min 1, max 21; no difference according to setting or region: p-values $\geq$ 0.367; nmissing: 39). The primary endpoint for clean out in hospital was clear stools after PEG treatment (45/68, 66.2%), followed by no more clinical findings of a faecaloma (13/68, 19.1%). A protocol for disimpaction in the hospital was absent for 5/89 (5.6%) respondents, with the majority (34/89, 38.2%) using PEG or a combination of PEG and enema's (25/89, 28.1%). There was no difference in the standard use of enema between Flemish or Walloon respondents (p= 0.670). PEG is given "always" (11/80, 13.8%) or "sometimes"

(55/80, 68.8%) through a nasogastric tube; 37/80 (46.3%) administers PEG during daytime only whilst 31/80 (38.8%) also gives PEG overnight. The amount of PEG is most frequently (61/79, 77.2%) based on weight. The quantity (ranging from 10 to 360 mL/kg/h, nmissing = 65) and rate (ranging from 25 to 60 mL/kg/h or 10 to 1000 mL/h, nmissing = 58) varied considerably among respondents.
Conclusions: Belgian paediatricians "ranked no more soiling or encopresis" as the most important clinical endpoint for successful outpatient treatment for constipation and "clear stools after PEG treatment" or "no more palpable faecaloma" for in-hospital clean-outs, although regional differences across Belgium exist Failure of outpatient macrogol therapy and/or failure of ambulatory treatment of encopresis were judged as primary indications for admission. Despite local protocols being present for the majority of the respondents, wide ranges of PEG dosages and administration rates were present among respondents.

K07

Safety and tolerance of a novel anti-regurgitation formula combining carob bean gum, prebiotics and partly fermented formula with postbiotics: a double-blind, randomized, controlled trial.

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Introduction: Troublesome regurgitation is a frequent FGID in infants.
Aim: To assess the gastrointestinal (GI) tolerance and safety of a new anti-regurgitation (AR) formula.
Methods: This was a 4-week double-blind, randomized, controlled trial in formula fed infants with regurgitation. The new AR (Test) formula contained 0.4 g/100 ml carob bean gum (CBG) as thickener, partly fermented formula with postbiotics, and short chain galacto-oligosaccharides (scGOS) and long chain fructo-oligosaccharides (lcFOS) (0.4 g/100 ml, ratio 9:1). The Control AR formula contained CBG (0.4 g/100ml) with postbiotics and has a history of safe use. The primary outcome was the Infant Gastrointestinal Symptom Questionnaire (IGSQ) score including stooling, spitting-up/vomiting, crying, fussiness and flatulence (range 13-65) after 4 weeks of intervention.
Results: All 182 infants screened were enrolled in the study. The primary analysis showed equivalence of the IGSQ sum scores at Week 4 between the study groups, within pre-defined equivalence margins. IGSQ sum scores improved statistically significantly within 1 week ($p<0.001$). Post-hoc analysis showed a more pronounced improvement of the IGSQ sum score in the Test versus Control group ($p=0.008$) in the subpopulation ($n=82$) with more GI distress. Stool characteristics were comparable between study groups, with low incidences of watery (≤12%) and hard (≤2%) stools. Both study groups showed adequate growth and improvement of regurgitation. Adverse Event data did not result in any safety concerns.
Conclusions: The novel AR formula combining CBG, scGOS/lcFOS and postbiotics is well-tolerated, safe and supports adequate growth. Post-hoc results suggest a better improvement of overall GI health in infants presenting with more GI distress.

K08

Expanding the phenotypic spectrum of mutations in DCDC2 with central nervous system impairment.

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Introduction: Neonatal sclerosing cholangitis (NSC) is a progressive cholangiopathy marked by inflammation and/or fibrosis, ultimately leading to biliary cirrhosis and end stage liver disease demanding liver transplantation in childhood. Biallelic pathogenic variants in DCDC2 are known to cause a ciliopathy presenting primarily as NSC. However, ciliopathies are often syndromes with high pleiotropy. Additionally, nephronophthisis and non-syndromic recessive deafness are also known to result from biallelic pathogenic variants in DCDC2. So far only 15 families have been published.

Aim: Since cilia are a component of cells of various tissues, disruption of the function of this organelle can result in the high pleiotropy seen in some ciliopathies. In this report we aim to expand the known phenotypic spectrum of the DCDC2 ciliopathy.

Methods: Two patients with NSC were enrolled in this study. The subjects were referred to Ghent University Hospital in Belgium where the diagnostic investigations and clinical examination occurred. We further performed a literature search where all the reported patients up to today were reviewed.

Results: We identified two unrelated patients harboring homozygous mutations in DCDC2 with neonatal sclerosing cholangitis, one with histological findings mimicking extrahepatic biliary atresia and one mimicking congenital hepatic fibrosis, along with an impairment of the central nervous system which may present as intellectual disability, global developmental delay, hypotonia, and microcephaly. Moreover, a literature review of all reported patients revealed the presence of arterial aneurysms in multiple patients. Histological findings of our patients can mimic extrahepatic biliary atresia or congenital hepatic fibrosis. We further show that transmission electron microscopy in patients with NSC does not implicate absence of primary cilia.

Conclusions: Biallelic pathogenic variants in DCDC2 were previously related to a ciliopathy with a phenotype confined to neonatal sclerosing cholangitis and nephronophthisis in addition to a single report of non-syndromic recessive deafness. A literature review uncovered the occurrence of arterial aneurysms which warrants consideration to include vascular evaluation following the initial diagnosis. Moreover, we establish that central nervous system impairment is a part of the phenotypic spectrum caused by pathogenic variants in DCDC2, thereby underlining the pleiotropy of this disorder as a ciliopathy.

K09

Postponed analysis of lactose hydrogen breath test samples

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Introduction: Measuring hydrogen in exhaled breath is a reliable and non-invasive method to diagnose lactose malabsorption. The COVID-19 pandemic forced to rethink procedures as breath tests could be seen as potentially aerosol generating procedures.
Aim: The aim was to test if postponed analysis of hydrogen lactose breath test samples was a reliable method.
Methods: Parents and children were instructed by the nurses how to collect breath samples. After providing two baseline breath samples and drinking the lactose solution (2g/kg with a maximum of 50g), the children were asked to exhale in 2 different syringes every 30 minutes for 3 hours. The syringes were brought back to the clinic within 24 hours and the first 7 breath samples were analyzed immediately. The second 7 samples were stored at room temperature and analyzed 1 to 5 days later. All breath samples were analyzed using the QuinTron MicroLyzer (Milwaukee, Wis., USA).
Results: A total of 73 “double” hydrogen breath tests were performed at home during the four-month study period. Mean age of the children was 9.8 years (SD +/- 3.2 years; median age 9.4 years). The early read-outs were performed 4.5 to 30 hours (mean 15.8h, SD 10h) after the beginning of the test. Of 73 tests performed at home, one test was not interpretable, as the child cooperated insufficiently and many samples were invalid. Of 72 remaining breath tests, 33 tests (45.8%) were positive (increase of > 20 ppm)(32 only for hydrogen, 1 for both methane and hydrogen). All second samples were analyzed 20 to 117 hours after the first samples (mean 41.7h, SD 24.3h). All negative tests were again negative. 32 tests were positive for a second time. One test was not conclusive, as the last breath sample was invalid - and this was the only one that was increased during the early read-out. The mean difference in expired hydrogen for all positive test was -0.8 ppm, median of difference was 0. There was a high correlation between the H2 concentration of first and second breath samples (r=0.96, p=0.000). Having performed 73 at-home breath tests over the past months, parents reported that only one child did not drink the lactose solution, while children refusing to drink the solution is a common observation in the clinic.
Conclusions: Hydrogen methane breath testing can be performed at home in a reliable way. More important, results are not influenced by the fact that that the analyses are done after 1 to 5 days. The expired hydrogen level remains stable in these plastic syringes even if they are preserved at room temperature during a couple of days.

Belgian Group for Digestive Oncology (BGDO)

O01

ACROSS THE CROSS: PRIMARY SURGERY NOT INFERIOR TO NEOADJUVANT CHEMORADIOTHERAPY FOLLOWED BY SURGERY FOR LOCALLY ADVANCED OESOPHAGEAL ADENOCARCINOMA

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Introduction: Current gold standard for treatment of locally advanced oesophageal adenocarcinoma (cT1/2N+ or cT3/4N0/+) is neoadjuvant chemoradiotherapy (nCRT) or neoadjuvant chemotherapy followed by surgery. This shift towards nCRT followed by surgery was driven merely by the results of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS). However, firstly these results may overestimate the effect of nCRT in a group of specifically adenocarcinoma patients. Secondly, in 45% of patients, surgery was performed through transhiatal approach with limited lymphadenectomy, which could negatively impact the results of the primary surgery group. Thirdly and lastly, nCRT also has an important morbidity and mortality that shouldn't be neglected.

Aim: This study aimed to reassess the presumed advantage of nCRT followed by surgery on long-term survival compared to primary surgery, in a group of all adenocarcinomas treated through transthoracic approach with extensive lymphadenectomy.

Methods: This retrospective cohort study with propensity score matched analysis included all patients treated with surgery between 2000 and 2018. The same exclusion criteria as the CROSS-trial were applied: age more than 75 years, clinical tumour length more than 8cm, subcardia tumours (gastro-oesophageal junction Siewert 3 class), World Health Organization performance status more than 2 and all chemotherapy regiments other than cisplatin-based (CDDP) schedules or CROSS-schedule in the nCRT treatment. Patients were matched on age, clinical tumour length, clinical lymph node status and Charlson comorbidity score. Overall survival at 5 years was the primary endpoint. In-hospital mortality, 30- and 90-day mortality, postoperative complications, admission to ICU and length of hospital stay were prospectively recorded.

Results: Between January 2000 and December 2018, 473 eligible patients with cT1/2N+ or cT3/4N0/+ staged adenocarcinoma underwent either primary surgery (225 patients) or nCRT followed by surgery (248 patients). After propensity score matched analysis, we defined 149 matched cases in each group for analysis. Transthoracic resection allowed an extensive lymphadenectomy with median of 24 and 30 resected lymph nodes after nCRT followed by surgery and primary surgery respectively, much higher than in the CROSS-trial (15 and 18 respectively). In paradox with the CROSS-trial, there was no significant difference in overall 5-year survival between the matched groups ($p=0.4273$). Compared with primary surgery, nCRT was associated with significantly more postoperative complications (Mean Comprehensive Complications Index: 21.0 versus 30.5 respectively; $p<0.0001$), of which also more major postoperative complications (Clavien-Dindo $\geq$ grade 3B: 11% versus 19%; $p=0.050$). Patients after nCRT had a significantly longer duration of both mean hospital stay (14.0 versus 18.2 days; $p=0.0498$) and of mean ICU stay (11.7 versus 37.7 days; $p=0.0458$). There were no significant differences between both groups in in-hospital mortality, 30- or 90-day mortality.

Conclusions: Based on results of this study, primary surgery, performed through transthoracic approach with extensive lymphadenectomy, can offer a comparable overall survival after 5 years with potentially fewer major postoperative complications and shorter hospital stay and ICU stay compared to nCRT followed by surgery for patients with locally advanced oesophageal adenocarcinoma. Therefore, it could be time to reconsider the place of primary surgery in the treatment of locally advanced oesophageal adenocarcinoma.

O02

Presumed metastatic, but worthwhile to operate: not all clinically positive cervical lymph nodes imply the same prognosis in oesophageal adenocarcinoma – the correct assumption within TNM 8th for oesophageal cancers.

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Introduction: Lymph node metastasis remains one of the important factors determining prognosis of oesophageal cancer. Lymphatic drainage of the oesophagus runs longitudinally over the length of the oesophagus in two communicating systems: a submucosal interconnecting network and an extraoesophageal network connecting separate lymph nodes. These complex networks are the cause of well-known skip-metastases in between lymph node stations. To address this issue, the 8th edition of TNM staging has defined para-oesophageal cervical lymph nodes as locoregional (N) – independent of tumor location – and more lateral or supraclavicular lymph nodes as metastatic (M). Today many patients with clinically positive cervical lymph nodes are still not referred to an expert center to be considered for potential multimodality treatment with curative intent.

Aim: The objective of our study was to determine whether we could detect a survival difference between clinically positive lateral cervical (cNlc+) and medial cervical lymph nodes (cNmc+) in surgically treated oesophageal adenocarcinoma.

Methods: A retrospective data collection was performed between January 2000 and December 2019. Only adenocarcinomas were included; hypopharyngeal cancers, gastric cancers, early staged tumors, clinically node negative tumors (≤ cT2N0) and patients with distant organ metastases and abdominal lymph node metastases caudal to the coeliac artery (including 22 patients with both abdominal and cervical positive lymph nodes) were excluded. All PET-CT scans were reassessed and cNlc+ were defined as clinically positive lateral cervical lymph nodes in positions 100, 102 and 104 according to the Japanese Esophageal Society (JES) classification and cNmc+ as clinically positive medial cervical lymph nodes in positions 101 and 103 according to JES. Overall survival (OS) and disease free survival (DFS) of these groups were compared with “classical” cT3-4N0 and cT3-4N+ (locoregional thoracic and/or abdominal lymph nodes) groups of the same time cohort. A log-rank (Mantel-cox) test was used to determine significant differences, defined as $p<0.05$.

Results: In our study group of 827 patients, 3.6% (N=30) had clinically positive cervical lymph nodes: cNlc+ in 1.4% (N=12) and cNmc+ 2.2% (N=18) Median OS for cNlc+, cNmc+, cT3-4N+ and cT3-4N0 was 14.2 months, 19.0 months, 33.5 months and 44.9 months respectively. OS was not different between cNlc+ and cNmc+ patients (p= 0.212), between cNmc+ and cT3-4N0 patients (p= 0.390) and between cNmc+ and cT3-4N+ patients (p= 0.616). However, OS was significantly different between cNlc+ and cT3-4N0 patients (p= 0.001) and between cNlc+ and cT3-4N+ patients (p= 0.008). Median DFS for cNlc+, cNmc+, cT3-4N+ and cT3-4N0 was 10.6 months, 14.5 months, 19.0 months and 25.2 months respectively. DFS between cNlc+ and cNmc+ patients was not different (p= 0.131), between cNmc+ and cT3-4N0 patients (p= 0.368) and between cNmc+ and cT3-4N+ patients (p= 0.907). However, DFS was again significantly different between cNlc+ and cT3-4N0 patients (p= 0.001) and between cNlc+ and cT3-4N+ patients (p= 0.017).
Conclusions: Our study suggests that clinically positive cervical lymph nodes in oesophageal adenocarcinoma should not always be staged as stage IV metastatic disease, as reflected by TNM 8th. Since some cNmc+ patients have comparable DFS to cT3-4N0/N+ patients. As such, all patients with clinically positive cervical lymph nodes should be discussed in a central multidisciplinary tumor board of an expert center. Optimal personalised treatment, including multimodality treatment with neo-adjuvant therapy followed by oesophagectomy with 3-field lymph node dissection, could be offered to some of these patients, as a strategy with curative intent.

O03

Response prediction of rectal cancer to chemoradiotherapy: a random subspace decision forest analysis

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Introduction: Preoperative chemoradiotherapy is the standard of care in locally advanced rectal cancer and results in an excellent local tumor control. However, the response to preoperative chemoradiotherapy is heterogeneous and remains unpredictable. Patients with a complete clinical remission (CCR) may profit from a watchful-waiting approach (Van der Valk, et al., 2018). The MRIdian is a novel radiation platform that integrates a 0.35 Tesla MRI-scan for daily imaging on the treatment couch and adaptive radiotherapy. Its high precision will allow dose escalation on rectal tumors to increase the CCR rate.
Aim: The aim of the study is to build a statistical model that predicts the response of rectal cancer to preoperative chemoradiotherapy. This will be used as a basis for patient-specific dose prescription on the MRIdian, which is being installed in our center.
Methods: Patients that were treated with 5 weeks of preoperative (chemo)radiotherapy at the UZ Brussel in two consecutive clinical trials were included (De Ridder, 2013; Engels, et al., 2014). Radiomics and clinical parameters were used to build a predictive model

by a random subspace decision forest algorithm. A random forest algorithm is a supervised learning method that is able to select variables and predict outcome. Forests are built by bundling decision trees together (Ho, 1998). For each tree, a random subgroup of predictor variables is drawn and used to predict the outcome by a prediction classifier. The coefficients of these classifiers are called one tree. Multiple trees together generate the random forest, where trees are eliminated when the prediction of the outcome variable is not good enough. The algorithm keeps growing trees and eliminating bad ones to enhance the performance of the random forest and therefore enhance the confidence in the prediction.
Results: 141 patients were included in the study. The Dworak regression grades and 109 radiomics parameters were entered in the algorithm (Van Griethuysen, et al., 2017). Dworak regression grades 0 & 1 were classified as non-response, Dworak 2 as moderate response and Dworak 3 & 4 as major response. The random forest analysis was able to successfully predict the response in 68.8% (std: 2,3%) of the cases. For 27 patients, the Dworak regression grade and a full set of 23 clinical variables were entered in the algorithm, namely gender, age, cT-stage, cN-stage, cM-stage, tumor location, tumor grade, hemoglobin, leukocytes, neutrophils (absolute and %), lymphocytes (absolute and %), neutrophil-lymphocyte ratio, thrombocytes, CEA, CRP, albumin, radiation dose, radiation boost, pre-operative chemotherapy (yes/no), type of chemotherapy, type of surgical resection. The random forest analysis was able to correctly predict 82.1% (std: 1,8%) of the patients based on these clinical parameters.
Conclusions: Clinical parameters are superior to radiomics in our prediction model based on random forest tree analysis. Our algorithm will further be developed and used as a basis for patient-specific dose escalation on the MRIdian. Our goal is to improve the CCR rate and favor a rectum-preserving approach when possible. References: De Ridder, M. (2013). Randomized Trial of Preoperative Radiotherapy With an Integrated Simultaneous Boost Compared to Chemoradiotherapy for T3-4 Rectal Cancer. Retrieved from ClinicalTrials.gov: https://www.clinicaltrials.gov/ct2/show/NCT01224392 Engels, B., Platteaux, N., Van den Begin, R., Gevaert, T., Sermeus, A., Storme, G., . . . De Ridder, M. (2014). Preoperative intensity-modulated and image-guided radiotherapy with a simultaneous integrated boost in locally advanced rectal cancer: report on late toxicity and outcome. Radiotherapy & Oncology, 155-159. Ho, T. (1998). The random subspace method for constructing decision forests IEEE Transactions on Pattern Analysis and Machine Intelligence, vol. 20, no. 8, Aug, 1998, doi: 10.1109/34.709601. IEEE Transactions on Pattern Analysis and Machine Intelligence, 832-844. Van der Valk, M., Hilling, D., Bastiaannet, E., Meershoek-Klein Kranenbarg, E., Beets, G., Figueiredo , N., . . . van de Velde, C. (2018). Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet, 2537-2545. Van Griethuysen, J., Fedorov, A., Parmar, C., Hosny, A., Aucoin, N., Narayan, N., . . . Aerts, H. (2017). Computational Radiomics System to Decode the Radiographic Phenotype. Cancer Research, e104-e107.

O04

Sequential changes of histological growth patterns of colorectal liver metastases during disease progression

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Introduction: The histological growth pattern (HGP) of liver metastases is a strong prognostic factor in patients undergoing surgery for colorectal liver metastases (CRLM). Postoperative outcome is significantly better in patients operated for desmoplastic HGP (DHGP) CRLM, characterized by a peritumoral fibrous rim, inflammation and angiogenesis, as compared with replacement HGP (RHGP), characterized by intra-parenchymal growth of cancer cells, minimal inflammation and vessel co-option. The biology behind different HGPs and their evolution during disease progression remain largely unknown.

Aim: We aimed to evaluate the evolution of HGPs during cancer progression in patients undergoing repeated resection of CRLM.

Methods: In a consecutive series of 357 patients operated for CRLM, we identified 55 patients with ≥2 liver resections for recurrent disease. Demographic and clinico-pathologic criteria were collected. In each patients, HGP of each resected CRLM was scored on hematoxylin-eosin sections, according to consensus guidelines and blinded for outcome. Pure and dominant HGPs were identified when >95% or 50 to 95% of tumor-liver interface, respectively, showed the characteristics of DHGP or RHGP. HGPs were compared between first and second resections and related to outcome.

Results: Pure and dominant RHGP represented 27% of the cases at first resection, increasing to 58% at second resection (p=0.002). None of the clinico-pathological factors related to the primary tumor predicted the HGPs. Pre-surgery chemotherapy did not influence the HGP. Five-years overall (OS) and disease-free survivals (DFS) after first hepatectomy were 60.3% and 24%, respectively. Five-years DFS was significantly better in patients with pure DHGP at first resection as compared with the other patients (37.8% versus 13.3%, p=0.02). The HGP at second resection was not correlated with outcome. Multivariate analyses did not reveal other prognostic factors.

Conclusions: HGP in recurrent CRLM evolve from DHGP to RHGP, suggesting that this parameter may represent a surrogate marker for aggressive tumor behavior during cancer progression. The presence of any RHGP component in CRLM predicts poor postoperative outcome, indicating that this parameter could be considered into predictive models for personalized therapeutic decision in these patients.

O05

The histological growth pattern and the clinico-metabolic characteristics accurately predict the outcome in patients undergoing surgery for colorectal liver metastases

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Introduction: Predictive models for personalized treatment of patients with colorectal liver metastases (CRLM) who are eligible for surgery remain inaccurate. Histological growth patterns (HGPs) of CRLM have been demonstrated to be a strong and independent prognostic factor. Patients undergoing surgery for CRLM with desmoplastic-HGP (DHGP), characterized by a peritumoral fibrous rim with numerous immune cells, have an improved outcome when compared with patients with replacement-HGP (RHGP) CRLM, characterized by cancer cells growing into the liver parenchyma, with minimal inflammation, no angiogenesis and no desmoplastic rim. In parallel, we recently showed that a new prognostic score, defined as the metabolic-CRS (mCRS), may predict the benefit of surgery in patients with CRLM (Duran Derijckere. J Surg Oncol 2019). This mCRS includes the 5 factors of the traditional Clinical Risk Score (Fong. Ann Surg 1999) and 1 additional point: baseline tumor glucose uptake measured by 18FDG/PET scan.

Aim: We aimed to evaluate if the association of HGP and mCRS may improve the prognostication in patients undergoing surgery for CRLM.

Methods: In a consecutive series of 357 patients who underwent curative-intent surgery for CRLM, we identified 108 cases with scorable HGP on hematoxylin-and-eosin-stained tissues of all resected CRLM and available baseline 18FDG/PET scan, performed at the time of CRLM diagnosis before any preoperative chemotherapy. Demographic and clinico-pathological data were collected. In each patient, HGP was defined as DHGP when all the resected CRLM presented $<5\%$ of RHGP at the tumor-liver interface and as non-DHGP in all the other cases. mCRS was defined by adding one point to the standard 5-point CRS when the highest standardized tumor uptake values (SUVmax/SUVmean normal liver) ratio was >4.3, defining low- and high-risk mCRS by scores of 0 to 2 and 3 to 6, respectively.

Results: In the entire series, after a median follow-up of 66 ± 14 months, 3, 5, and 10-years overall survival (OS) and disease-free survival (DFS) were 54.2%, 41.9%, and 25.3%, and 18.4%, 16.6%, and 12.4%, respectively. None of the traditional risk factors, including CRS, was predictive for OS or DFS in multivariate analysis. In patients with DHGP CRLM, 3, 5, and 10-years OS were 73.1%, 68.6% and 45.6%, as compared with

44.3%, 27.3%, and 13.3% in the non-DHGP group (p=0.002), and 3, and 5-years DFS were 35.5% and 35.5%, as compared with 10.3% and 7.7% in the non-DHGP group (p=0.001). Baseline metabolic ratio SUVmax/normal liver mean SUV>4.3 and the mCRS were not predictive for OS and DFS. In contrast, the combination of HGP and mCRS was highly discriminant. In patients with DHGP and low-risk mCRS, 3 and 5-years OS and DFS reached 88.9% and 82.1%, and 51.7% and 51.7%, respectively, thus significantly improved as compared with the 3 other categories (p<0.001). In particular, in patients with DHGP and high-risk mCRS, 3 and 5-years OS and DFS were 45.5% and 45.5% and 0% and 0%, respectively (p<0.001).

Conclusions: The evaluation of baseline clinico-metabolic parameters may discriminate between patients with CRLM with similar HGP but different tumor biology. Models combining HGP with clinico-metabolic characteristics may represent new tools for improving prognostication in patients with CRLM candidate for surgery.

O06

Prognostic value of baseline and early changes of circulating cell-free (cf)DNA in the neoadjuvant setting of early stage colon cancer

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Introduction: Approximately 80 to 95% of stage II-III colon cancer patients do not benefit from adjuvant chemotherapy. For these, oxaliplatin-based chemotherapy will result in substantial toxicities, some of which may be permanent and negatively affect quality of life. Circulating tumour (ct)DNA is a surrogate marker of minimal residual disease and negative prognostic factor in stage II-III colon cancer treated with surgery +/- adjuvant

chemotherapy, and it is currently being studied as a tool to select patients who are most likely to benefit from adjuvant chemotherapy. No study, however, has ever analysed the prognostic value of this biomarker in colon cancer patients treated with neoadjuvant chemotherapy. This evidence gap is worth addressing, especially considering the strong interest that has recently emerged for neoadjuvant treatment strategies in the setting of early stage colon cancer, as shown by the recently reported FOXTROT trial.

Aim: We sought to evaluate the prognostic value of baseline and early, on-treatment changes of cfDNA and ctDNA in stage II-III colon cancer patients who were treated with one cycle of neoadjuvant FOLFOX chemotherapy followed by surgery +/- adjuvant FOLFOX chemotherapy in the PePiTA trial.

Methods: PePITA was a multicentre, single-arm, prospective phase II trial aiming to test in vivo tumour chemosensitivity as assessed by metabolic response using 18F-FDG PET/CT scan of early stage colon cancer and to evaluate its association with survival outcome (NCT00994864). Plasma samples were prospectively collected at baseline and 2 weeks (ie, after one cycle of neoadjuvant FOLFOX chemotherapy). cfDNA was isolated with the QIAmp circulating nucleic acid kit (Qiagen), and quantified with the Qubit fluorometer (Life-Technologies). cfDNA samples were bisulfite converted using the EZ DNA Methylation-Gold™ Kit (Zymo Research), with NPY and WIF1 being selected as universal methylation markers for ctDNA, and analysed with digital droplet (dd)PCR technology. Data from ddPCR were processed with the QuantaSoft V1.6 software (Bio-Rad) to obtain the concentration (reported in copies of target per ml of plasma). The primary outcome measure was 3-year disease-free survival (DFS), while 5-year overall survival (OS) was a secondary outcome measure. Receiver operating characteristics curve analyses, Kaplan-Meier method, Cox proportional hazards models and log-rank tests were used. Statistical analyses were carried out with the SPSS for MacOS version 25.0 software (SPSS Inc.).

Results: 80 trial patients with available plasma samples for cfDNA analysis were included. Following one cycle of neoadjuvant FOLFOX chemotherapy and surgery, 45 patients (56%) had ypStage I-II, and 35 (44%) had ypStage III tumours. All resections were with clear margins (R0). After a median follow-up of 52.5 months, 3-year DFS was 80% (95% CI: 71.2-90.8) and 5-year OS 84% (95% CI: 75.2-94.9) in the whole cohort. Patients with high (≥1.2 ng/µl) baseline cfDNA level had worse 3-year DFS (48% vs 80%; HR 2.72, 95% CI: 1.02-7.25; p=0.036) and 5-year OS (71% vs 90%; HR 5.36, 95% CI: 1.14-25.28; p=0.017) than those with low baseline cfDNA levels. In the multivariable analysis (including sex, ypStage and CEA), baseline cfDNA was the only factor showing a trend towards statistical significance (HR DFS 2.6, 95% CI: 0.96-7.01; p=0.059; HR OS 4.65, 95% CI: 0.97-22.32; p=0.055). Early changes of cfDNA (Δ ≥11%) after one cycle of neoadjuvant FOLFOX chemotherapy failed to predict survival (HR DFS 1.08, 95% CI: 0.42-2.81; p=0.873; HR OS 0.68, 95% CI: 0.19-2.39; p=0.543). ctDNA analyses are ongoing and will be presented at the Meeting.

Conclusions: For the first time, we have shown that baseline cfDNA may predict survival outcome in early stage colon cancer patients treated with neoadjuvant chemotherapy.

Pending confirmation in larger independent series, testing for cfDNA at baseline could help select high-risk patients who may benefit from neoadjuvant, FOXTROT-like, treatment strategies.

O07

INTERIM ANALYSIS OF THE AVETUXIRI TRIAL: AVELUMAB COMBINED WITH CETUXIMAB AND IRINOTECAN FOR TREATMENT OF REFRACTORY MICROSATELLITE STABLE (MSS) METASTATIC COLORECTAL CANCER (mCRC) – A PROOF OF CONCEPT, OPEN LABEL, NON-RANDOMIZED PHASE IIA STUDY.

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Introduction: Immune checkpoint inhibitors have demonstrated poor efficacy in MSS mCRC. Previous research indicates that cetuximab (anti-EGFR chimeric monoclonal antibody) could initiate, independently from RAS mutation, an immunogenic tumor cell death and mediate antitumor immune response.

Aim: In this trial, we aim to explore the clinical efficacy and safety of anti-PDL1 avelumab (AVE) combined with cetuximab (CET) and irinotecan (IRI) for treatment refractory MSS mCRC.

Methods: AVETUXIRI (NCT03608046) is a multicenter academic study recruiting MSS, BRAFV600E wt, mCRC patients (pts) refractory to standard treatment (fluoropyrimidine, oxaliplatin, irinotecan and anti-EGFR treatment if RAS wt tumor) in 2 cohorts (cohort A: RAS wt - cohort B: RAS mut). In both cohorts, patients receive CET (400 mg/m2 W1, 250 mg/m2 W2, 500 mg/m2/2 weeks from W3), IRI (180 - 150 mg/m2/2 weeks from W1) and AVE (10 mg/kg/2 weeks starting from W3). Primary endpoints are safety and overall response rate (ORR), defined as partial or complete response (PR or CR) according (i)RECIST1.1. Secondary endpoints include disease control rate (DCR), PFS and OS. Based on a Simon 2-stage design for ORR in each cohort (cohort A: P0=0.15, P1=0.33 / cohort B: P0=0.09, P1=0.25 / $\alpha = 0.1$, $\beta = 0.2$ in both cohorts), 10 and 13 patients are needed in the first stage of cohort A and B respectively. At least 2 pts have to reach PR in each cohort to allow the continuation of the trial in the 2nd stage. The density of CD3 (T cell) and CD8 (cytotoxic T cell) was quantified on metastases biopsies performed before and during the study treatment and analyzed with a dedicated image analysis software to generate an immunoscore.

Results: Between Oct 2018 and Jan 2020, 23 patients (median age 62 y-old, 86.9% male 78.3% left-sided, 91.3% synchronous mCRC) have been included in the first stage of the trial. No major or unexpected safety events were observed. 21.7% (5/23) of pts presented grade 3 diarrhea, all related to IRI, with complete resolution after IRI dose reduction or interruption. A reduced starting dose of IRI (150 mg/m2) was amended (09/2019) for the last included 8 pts without any grade 3-4 diarrhea occurrence. Grade 1-2 hypothyroidism was the only immune-related side effect. 3 PR were observed in cohort A and none in cohort B. DCR was 60.0% (6/10) and 61.5% (8/13) in cohort A and B respectively. Median PFS and OS were respectively 4.2 and 12.7 months (cohort A) and 3.8 and 14.0 months (cohort B). 6 months-PFS rate was 40.0% and 38.5% in cohort A and B. 12 months-OS rate was 53.3% and 57.7% in cohort A and B. The median follow-up of patients was 9.2 months. Pts with a tumor shrinkage had a high-Immunoscore compared with absence of tumor regression (73% vs 19%, $p<0.0001$)
Conclusions: The AVETUXIRI trial met its preliminary primary efficacy endpoint for RAS wt mCRC pts justifying the study continuation in cohort A (2nd stage). No PR was observed in RAS-mut cohort. Nevertheless, encouraging data of DCR, PFS and OS observed in RAS mut cohort allow the opening of a new cohort for RAS-mut mCRC (cohort C) with PFS as primary endpoint. A high-Immunoscore was associated with treatment benefit.

O08

Randomized Phase 2 study comparing pathological responses of resected colorectal cancer metastases (CRCM) after bevacizumab (BEV) with FOLFOX or FOLFIRI (BEV-ONCO trial).

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Introduction: Pathological response (PR) of resected CRCM after preoperative treatment is a recognized prognostic factor. Retrospective studies reported that BEV + oxaliplatin-based chemotherapy increased PR compared to irinotecan-based chemotherapy.
Aim: In this trial, we aim to demonstrate that preop BEV + FOLFOX would increase PR.

Methods: BEV-ONCO (NCT01858649) is a multicenter prospective randomized (1/1) phase II trial evaluating PR on resected CRCM after 3 to max 6 cycles of mFOLFOX (ARM A) or FOLFIRI (ARM B) + BEV (5mg/kg/2 weeks). Primary endpoint is the major pathological response rate (MPRR) defined as the % of patients presenting CRCMs with a mean tumor regression grade (TRG) <3. Secondary endpoints include DFS, OS, safety, complete PR, R0 resection rate and liver toxicity comprising sinusoidal obstruction syndrome (SOS) and nodular regenerative hyperplasia (NRH). 54 pts (27 per arm) are needed to detect a difference (alpha=0.05; beta=0.2) of MPRR proportion of 0.40 between treatment arms (two-sided Fisher's Exact test).
Results: Among 65 pts included between 06/2013 and 09/2018, 57 pts (28 ARM A / 29 ARM B) have had CRCM resection. Clinical and treatment characteristics were similar in both treatment arms (median age 60 y-old, 51% male, 33% RAS wt, 98% liver CRCM, 75% synchronous, median 2 CRCM/pt, median of 4 chemo cycles and 3 BEV cycles). 11/28 pts presented 1-month postop surgical complications in ARM A (39%, grade 3-4: 17.9%) and 9/29 pts in ARM B (31%, grade 3-4: 6.9%, p=0.58). MPRR was 32% in ARM A and 21% in ARM B (p=0.38). 4 pts presented complete PR (ARM A/B: 14%/0%, p=0.05). No difference between treatment arms was observed for R0 resection (ARM A/B: 89%/93%, p=0.80), SOS (ARM A/B: 54%/38%, p=0.50), NRH (ARM A/B: 21%/17%, p=0.75), DFS (ARM A/B: HR=1.14, 95%CI:0.58-2.21, p=0.71) and OS (ARM A/B: HR=1.38, 95%CI:0.48-4.00, p=0.55). Pts with PR among all CRCM (Max TRG≤3; 44% of pts) had a lower risk of relapse/death (DFS: HR=0.41, 95%CI=0.20-0.82, p=0.01) and death (OS: HR=0.34, 95%CI=0.10-1.11, p=0.07).
Conclusions: This trial fails to demonstrate any significant difference of PR between BEV with FOLFOX or FOLFIRI but confirms PR as a prognostic factor.

O09

Sex and regorafenib toxicity in refractory colorectal cancer: a safety analysis of the RegARd-C trial

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Introduction: Regorafenib is an oral multikinase inhibitor approved for the treatment of refractory metastatic colorectal cancer (mCRC). Despite showing a small but statistically significant survival advantage in two phase III trials, toxicity remains a concern limiting its widespread use in routine practice. A number of strategies have already been investigated to improve patient tolerability in this setting with variable success, but information on risk factors for regorafenib-induced toxicity is still lacking. This evidence gap is especially relevant considering the general prognosis of real-world refractory mCRC patients and the need to carefully balance clinical benefit against treatment-related toxicity which could ultimately have a detrimental impact on quality of life.
Aim: We sought to identify clinical factors and biomarkers associated with regorafenib-related toxicity in a prospective cohort of refractory mCRC patients.
Methods: RegARd-C was an academic, multicentre, single-arm prospective trial enrolling 141 refractory mCRC across 17 Belgian centres (NCT01929616), and aiming to show the prognostic value of early 18F-FDG PET/CT-based metabolic response. Patients received regorafenib at a 160 mg/day dose in a 3-weeks-on/1-week-off schedule until disease progression or unacceptable toxicity. Adverse events (AEs) were graded according to the CTCAE version 4.0. Baseline blood parameters (haemoglobin, conjugated bilirubin, T3, T4), clinico-pathologic factors (sex, ECOG PS, number of metastatic sites, liver or peritoneal metastases), anthropometric features (weight, body mass index [BMI], body surface area [BSA], body mass composition), and ATP-binding cassette transporters (ABCG2, MDR1, and MRP2) were explored for their association with toxicity. Body mass composition parameters were measured through the assessment of the quantity and quality of muscle, subcutaneous, and visceral adipose tissue on baseline 18F-FDG PET/CT scans at the third lumbar vertebra using the Planet Onco software (DOSIsoft, France). ABCG2, MDR1, and MRP2 expression in tumour and normal tissue were evaluated by immunohistochemistry with rabbit monoclonal antibodies (Cell Signaling Technology, USA). The primary outcome measures were grade $\geq$2 toxicity during the first treatment cycle, and grade $\geq$3 toxicity during the whole treatment. Median values, Fisher's exact test, and logistic regression for multivariable analyses were used. A p value of $<$0.05 was considered statistically significant. Statistical analyses were carried out with Graphpad Prism version 7.02 and R version 3.5.1.
Results: 136 eligible patients started regorafenib and were included in the analysis (male/female: 57/43%; median age 67 years; ECOG PS 0/1: 49/51%; median BSA 1.8 m2; median BMI 24). During the first cycle of treatment, grade $\geq$2 toxicities occurred more frequently in women (84% vs 60%, p=0.002), and in patients with a low BSA (79% vs 61%, p=0.035). A similar pattern was observed for grade $\geq$3 toxicities which were reported more frequently in women (51% vs 31%, p=0.033), in patients with a low BSA (48% vs 27%, p=0.017), and in those with lower T3 levels (51% vs 27%, p=0.036).

Women (19% vs 5%, p=0.014), patients with a low BSA (22% vs 1%, p<0.001), and those with a low BMI (17% vs 5%, p=0.044) also suffered early serious AEs more frequently, with early dose modifications being required more often in women (55% vs 37%, p=0.055). In the multivariable analysis, sex was the only independent predictive factor of early grade ≥2 toxicities (odds ratio 3.4; 95% CI: 1.2-11.1, p=0.02). Results of the ABCG2, MDR1, and MRP2 staining and data on toxicities throughout the whole study treatment will be presented at the Meeting.
Conclusions: To the best of our knowledge, this is the first study showing an association between sex and early moderate to severe toxicity from regorafenib in a prospectively treated population of refractory mCRC patients. Our findings are overall in line with previous studies suggesting the importance of this parameter as a predictive factor for adverse events from cytotoxic chemotherapies and other targeted agents. If confirmed in independent series, they could pave the way for the implementation of personalised regorafenib dosing strategies with the potential to optimise oncological outcomes while reducing toxicity and preserving quality of life.

O10

Tumor-Associated Copy Number Alterations in Plasma Cell-Free DNA from Metastatic Gastroenteropancreatic Neuroendocrine Neoplasm patients

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Introduction: Recent studies, including our proof-of-concept study, demonstrated the possibility to detect tumor-derived molecular alterations in cell-free DNA (cfDNA) from plasma of patients with a gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN). The lack of highly sensitive and specific blood-based biomarkers for GEP-NEN patients, therefore, warrants an in-depth evaluation of the biomarker potential of cfDNA.
Aim: Our goal was to detect tumor-associated copy number alterations (CNAs) in cfDNA from GEP-NEN patients to molecularly characterize the tumor and estimate tumor fraction, and to evaluate these parameters over time.
Methods: Metastatic GEP-NEN patients were included within NETwerk, a multi-institutional network of eight hospitals in Belgium. cfDNA was extracted from plasma of all patients and subjected to shallow whole-genome sequencing (WGS). Then, detection of CNAs and estimation of tumor fraction were performed using the R-based tool ichorCNA. Clinicopathological data were collected from all patients to correlate experimental and clinical findings.

Results: In total, 80 samples of 29 metastatic GEP-NEN patients were analyzed using shallow WGS. All patients had a well-differentiated GEP-NEN and primary sites were pancreas (N=15), small intestine (N=10), colon (N=1), caecum (N=1), ileocaecal valve (N=1) and pylorus (N=1). In 32 cfDNA samples from 13 patients (45%), CNAs with a tumor fraction higher than 3% could be detected. CNAs were detected in 60% of included pancreatic NEN (PNEN) patients and CNA patterns were similar to patterns detected in PNEN tumor tissues, e.g. whole-chromosome gains of chromosomes 4, 5, 7, 9, 12, 13, 14, 17, 18, 19 and 20. Tumor fractions changed over time, which could be linked to changes in tumor burden, tumor progression or treatment response according to RECIST1.1 criteria and will be further examined, including in additional samples that are being collected.
Conclusions: Cell-free DNA of metastatic GEP-NEN patients contains CNAs that correspond to CNA patterns seen in tumor tissue samples. CNAs can be used to quantify the tumor fraction in cfDNA over time, which will be linked to tumor evolution in our ongoing study.

O11
First clinical experience with Atezolizumab/Bevacizumab in advanced hepatocellular carcinoma
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Introduction: The IMbrave150 reported improved overall survival and progression free survival in untreated advanced HCC patients receiving the novel combination of atezolizumab/bevacizumab compared to sorafenib. These practice-changing results represent the first positive phase III clinical trial using combination regimens in advanced HCC. Both the European (ESMO) and American (ASCO) clinical practice guidelines have been adapted and now recommend atezolizumab/bevacizumab as first-line therapy for advanced HCC patients.
Aim: To present the first clinical experience with atezolizumab/bevacizumab in advanced HCC patients in a single center in Belgium.
Methods: All advanced HCC patients treated with the combination regimen atezolizumab/bevacizumab at the University Hospital of Leuven were prospectively enrolled in this study. Demographic and clinical data including baseline liver function, previous treatments and subsequent treatment after progression were collected. Clinical and radiological follow-up is done on routine basis. Outcome parameters include best radiological response, progression free survival rate and overall survival rate at 6 months. All treatment-related adverse events are recorded.
Results: Between February and November 2020, twenty-one patients started treatment with atezolizumab/bevacizumab. None of these patients had received prior systemic treatment for HCC. All cases were confirmed by tissue biopsy. Disease control rate, objective response rate, progression free survival and overall survival will be discussed at the meeting to provide the attendees with the most recent update figures. No life-threatening bleeding events occurred. Two patients had mild auto-immune related

thyroid dysregulation. Two patients presented with grade 5 immune-related adverse events. One patient had an early tumor response, but developed an immune-related hepatitis with acute liver failure. The second patient presented with auto-immune encephalitis.
Conclusions: Clinical trials are meticulously controlled treatment settings and do not always mirror daily practice. Our results represent the first real-life, clinical experience with atezolizumab/bevacizumab in advanced HCC patients in Belgium. Extensive biomarker studies on this prospective cohort are underway to unravel the mechanisms of response.

Belgian Pancreatic Club (BPC)

P01
Splenic vascular patency after spleen and vessel preserving distal pancreatectomy: Is the Kimura technique worth the effort?
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Introduction: Spleen-preserving surgical techniques combined with a minimally invasive approach have become increasingly common for benign or borderline malignant lesions of the pancreas. These more challenging procedures have immunologic advantages due to the maintenance of a functional spleen.
Aim: The aim of this study was to evaluate the patency of the splenic vessels and splenic perfusion after spleen and splenic vessel-preserving distal pancreatectomy.
Methods: This retrospective single-centre study included all patients who underwent a spleen and splenic vessel-preserving distal pancreatectomy between April 2009 and October 2018. Patency of the vessels and splenic perfusion were assessed and classified based on computed tomography or magnetic resonance imaging.
Results: Twenty-five patients underwent a spleen-preserving distal pancreatectomy of which 20 patients also had a splenic vessel-preserving surgery. The majority of the patients was operated with a minimal invasive technique (17 via laparoscopy or robot-assisted surgery and 3 via laparotomy). Five patients had no postoperative imaging. Normal patency of the splenic artery and vein was observed in 14 and 9 patients, respectively. Partial occlusion of the splenic vein was observed in 5 patients and total occlusion of the artery and vein was observed in 1 patient. Only 2 of these last 6 patients showed a limited infarction (< 50%) of the total splenic volume although without functional consequences.
Conclusions: Spleen and splenic vessel-preserving distal pancreatectomy is safe and feasible. The patency of the splenic vessel is preserved in the majority of the patients

and the perfusion of the spleen is also maintained, even when the splenic vessels are compromised.

P02

Total pancreatectomy with islet autotransplantation – a new treatment option for chronic pancreatitis patients in Belgium

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Introduction: Pain is the most disabling symptom in chronic pancreatitis (CP) and can be difficult to manage. In some cases of CP with refractory pain or recurrent pancreatitis attacks, eg. small duct CP or hereditary CP with high risk of malignancy, total pancreatectomy (TP) is proposed. To prevent brittle diabetes, TP with islet autotransplantation (TPIAT) is an option. Until recently this treatment modality was not available in Belgium.

Aim: Development of a multidisciplinary approach to select patients for TPIAT and measure impact on pain, quality of life (QoL), beta cell function and diabetes development.

Methods: In 2018 a multidisciplinary team (MDT) was composed in our tertiary hospital, including a pancreatologist, endocrinologist, transplant surgeon, pain care specialist and islet isolation specialist. Patients with CP and >6 months of pain not responding to conservative treatment or endoscopy were evaluated for TPIAT if alcohol and tobacco abstinence and a patent portal vein were present. Patients were evaluated using validated questionnaires on pain (Izbicki, VAS) and QoL (SF-12, EORTC QLQ-C30) and by our pain care specialist. The functional beta cell mass (FBM) was measured with a hyperglycemic clamp test. For TPIAT selection unanimous consent by our MDT was necessary. Total pancreatectomy was performed following organ transplantation principles to reduce warm ischemia time. After short cold preservation of the pancreas, islet isolation was carried out in our islet isolation facility. After overnight culture, the isolated islets expressed as number of beta-cells/kg body weight, were transplanted into the portal vein using an ultrasound guided percutaneous technique. Questionnaires and hyperglycemic clamp test were repeated post-operative.

Results: From 2018 to 2020 six patients were evaluated for TPIAT. All patients suffered from CP: 2 genetic, 2 anatomic variants, 1 alcohol and 1 idiopathic form. Five patients had previous endoscopic treatment and two previous Whipple surgery. The median time of CP was 4,5y (range 3-25). Five patients suffered from chronic pain and one patient had recurrent attacks and was at increased risk for cancer. All patients with pain used

weak opioids on a chronic basis and were intensively evaluated and treated by our pain care specialist. The median preoperative FBM was 69% (range 47-153) compared to normal and median HbA1c was 5,9% (range 5,1-7,7). Two patients with FBM of 72% and 49% were on metformin and small dose of insulin respectively. After MDT evaluation two patients underwent TPIAT, one patient was referred to a foreign expert center, one was treated surgically with a redo-pancreaticogastrostomy, one refused TPIAT and in one pain control was obtained by our pain specialist. Of the two patients selected for TPIAT one had previous Whipple surgery. The surgical procedure in the two TPIAT patients was uneventful, although post-operative pain management was challenging. The pancreatic pain disappeared completely in both patients, and all analgesics could be stopped. However, the second patient had intermittent episodes of subobstruction. QoL improved in the first patient and was stable in the second patient. The first patient had a FBM of 153% and HbA1c of 5,6% pre-operatively and received 4x106 beta-cells/kg body weight (4700 islet equivalent/kg). Three and 12 months after transplantation, FBM was 72% and 55% respectively. The patient started low-dose of insulin (9U/day) with good glycemic control (HbA1c 5,8%) after a corticosteroid treatment for a chronic sinusitis. The second patients had a FBM of 66% pre-operatively and HbA1c of 5,1% and received 2.5x106 beta-cells/kg body weight (1500 islet equivalent/kg). Two months after transplantation, low dose of insulin (6U/day) was started to avoid post-prandial hyperglycemia. Six months after transplantation, FBM was 61% together with an HbA1c of 6,3%.
Conclusions: TPIAT seems a valid treatment strategy in highly selected CP patients using an MDT approach. In the first cases performed in Belgium early data suggest good pain control and tight glycemia control with minimal insulin doses.

P03
Prevalence of non-alcoholic fatty liver disease after extensive pancreatic surgery in a Belgian cohort
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Introduction: Non-alcoholic fatty liver disease (NAFLD) has been reported previously as a post-operative complication after pancreatic surgery. The reported incidence ranges from 7,8 to 55% in studies with a follow up from 3 months to 4,5 years. Most data are found in studies originating from southeast Asia. There are 2 European studies examining NAFLD after pancreatic surgery using CT (computed tomography) images: one Swedish and one Dutch study, the latter focusing solely on pancreatic neuroendocrine tumors.
Aim: The aim of this study is to assess whether NAFLD occurs after extensive pancreatic surgery in the Belgian population and to investigate factors possibly associated with the development of steatosis after pancreatic surgery.
Methods: We performed a retrospective monocentric cohort study in 124 patients who underwent extensive pancreatic surgery between 2005 and 2014. We started from a

database with 472 patients. One hundred and four people were excluded usually because of known liver disease/steatosis or follow-up of less than 2 months. Another 238 patients were excluded because of lack of imaging data pre-operatively and/or post-operatively. Steatosis was assessed using pre- and postoperative Hounsfield units on liver and spleen. Data on imaging, liver function, weight, body mass index (BMI) and other relevant parameters (underlying pathology, type of surgery, use of chemotherapy, remnant volume, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, CA 19.9,…) were gathered 2 months, 6 months, 1 year and 2 year after surgery.

Results: 38 (31%) of 124 patients developed liver steatosis at least at one point in time in the two years following surgery. NAFLD appears to occur mainly relatively fast after surgery, usually within the first 6 months: we see a prevalence of 21,0% at 2 months, 28,6% at 6 months, 16,4% at 1 year. There is a statistically significant association with preoperative ALT and AST values, but also with administration of pancreatic enzyme supplementation as surrogate for pancreatic exocrine insufficiency (PEI). The exact pathophysiological process remains unclear and some suggest that NAFLD post pancreatic surgery is a self-limiting event. We suspect a relationship with maldigestion/ malabsorption, pancreatic insufficiency and pancreatic enzyme substitution. The evolution over time and the association with the intake of pancreatic enzyme supplements supports this hypothesis. There is a difference in evolution of weight after surgery between two groups: the steatosis group continues losing weight, the non-NAFLD group gains weight again. The average weight at 2 years in the NAFLD group is 60,3 ± 21,89 kg (median 53,0 kg) compared with 71,9 ± 13,58 kg (median 72,5 kg) in the non-NAFLD group. The registration in our study is longer than average in other publications. We see a prevalence of NAFLD of 20,8 % at 2 year. A statistically significant association with weight loss at 2 years was also detected.

Conclusions: Also in a Belgian population, NAFLD after extensive pancreatic surgery is not an exception, with an incidence of 31% in this study. NAFLD is more prevalent in the first year after surgery, as was stated by others, but in our cohort some patients don't develop steatosis until late. An association with weight and intake of PEI is most likely.

P04

Pancreatic blunt trauma in children: report from the Belgian Pancreatic Trauma Group

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Digestive Oncology, [8] Cliniques universitaires Saint-Luc, Brussels, Belgium, Gastroenterology and Hepatology
Introduction: Pancreatic trauma is the fourth most frequent cause of abdominal trauma in children. Few studies focused on the impact of trauma severity and therapeutic management (surgery vs endoscopy vs observation) on mid- and long-term outcomes.
Aim: The aim of this study was to determine the mid and long-term outcome of children with grade III-V pancreas trauma and correlate this data with the initial patient management.
Methods: The charts of 47 children aged <18 years admitted in one of the 7 participating Belgian tertiary Hospitals between 01/2010 and 01/2020 for an abdominal trauma involving the pancreas were retrospectively reviewed. Data about trauma characteristics, clinical symptoms, imaging, therapeutic management and short to long-term complications were recorded.
Results: We identified 25 patients (11/22, 50% boys) aged 2-17 years (median: 9,2y; IQR 7-12,4). Fourteen patients had a grade III trauma following AAST, 10 had a grade IV and 1 a grade V. In 8/25 (32%) patients, pancreas trauma was associated to another organ lesion. Clinical symptoms are nonspecific to diagnose pancreatic involvement: pain (23/24, 96%) and nausea/vomiting (18/24, 75%). All children had increased amylase/lipase at admission. Four children were initially managed by endoscopy (1/14 grade III, 3/10 grade IV), 10 (4/14 grade III, 5/10 grade IV and 1/1 grade V injuries) patients had surgical management, while the other 11 children were managed conservatively. Median hospital stay was 17.5 days (IQR 13.5-25) and was neither influenced by trauma grade or by initial management. Mediate complications of pancreatic trauma consisted of pseudocysts; these were exclusively seen in patients managed conservatively (n=6 grade III and n=3 IV traumas) and were the main cause for rehospitalisation. Exocrine pancreatic function was followed (median follow-up: 0.8 years, IQR 0.2-5.5) in 8/14 and 8/10 patients respectively with grade III and IV traumas. Exocrine function tests were partially impaired in 3/24 (13%); all of them complained of intermittent symptoms of abdominal pain and steatorrhea. Instead, endocrine function (median duration of follow-up 2.9 years, IQR 0.4-7.4) was preserved in all of them.
Conclusions: This Belgian multicentric study showed that compared to grade I-II pancreatic traumas, children admitted for pancreatic blunt injury grade III-V were mainly managed surgically. Children managed conservatively had a higher risk of rehospitalisation for pseudocysts drainage, and were more likely to evolve to exocrine pancreatic dysfunction over time. Follow-up of patients with grade III-IV-V pancreatic trauma is important to detect those mid and long-term complications.

P05
ICTERUS CAUSED BY ANNULAR PANCREAS AND ASSOCIATED INTRALUMINAL DUODENAL DIVERTICULUM

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Case Report: A 59-year old woman presented with jaundice and pruritus for two weeks. She underwent a duodenojejunostomy during childhood for duodenal stenosis. There was no other medical history and she was not on any chronic medication. She smoked ten cigarettes a day and denied any alcohol consumption. Abdomen was painless during clinical examination. Blood tests showed an elevated total bilirubin level of 16.97 mg/dL [0.1-1.2], lipase of 202 IU/L [13-60] and CRP of 5.8 mg/L [< 0.5]. Aspartate aminotransferase (AST) were 47 U/L [5-40], alanine aminotransferase (ALT) were 56 U/L [7-56] and y-glutamyl transpeptidases were 97 U/L [9-48]. Computed tomography (CT) revealed strong dilation of the intrahepatic bile ducts and the common bile duct. CT also demonstrated an unclear anatomic variant of the pancreatic tissue and a hypodensity in the duodenal bulb. Esophagogastroduodenoscopy (EGD) was performed and showed a bulging structure in the duodenum suggestive for an intraluminal duodenal diverticulum. Empiric antibiotics (piperacillin-tazobactam) were initiated for escalating C-reactive protein (CRP) levels. Endoscopic ultrasound was negative for malignancy but interpretation of the pancreatic tissue was suboptimal due to the anatomy. At last, magnetic resonance imaging (MRI) showed a constricted distal part of the duodenum surrounded by pancreatic tissue, suggestive for annular pancreas. The intraluminal diverticulum was present in the dilated, proximal part of the duodenum. The common bile duct was dilated up to the level of the major duodenal papilla, most likely caused by a mass effect of the intraluminal duodenal diverticulum. Eventually, percutaneous transhepatic cholangiography (PTC) was performed with stenting of the distal part of the common bile duct. Bilirubin levels progressively decreased after the procedure and all complaints disappeared. Annular pancreas is a rare congenital anomaly characterized by a band of pancreatic tissue encircling the second part of the duodenum (1). It is diagnosed on abdominal imaging (mostly CT or MRI). Approximately two-thirds of patients with annular pancreas remain asymptomatic for life (2). Clinical features mostly present during childhood but may also manifest at adult age with chronic epigastric pain, nausea and postprandial fullness. It is also associated with peptic ulcer disease, acute or chronic pancreatitis, gastric outlet obstruction, jaundice due to biliary obstruction and other congenital disorders such as duodenal atresia and duodenal diverticulum like in our case report (2, 3). In contrast to pediatric patients, both surgery as well as interventional endoscopic procedures have been described as an effective treatment in adult patients with annular pancreas (4). 1. Kozu T, Suda K, Toki F. Pancreatic development and anatomical variation. Gastrointest Endosc Clin N Am 1995; 5:1. 2. Cunha J.E.M., de Lima M.S., Jukemura J., Penteado S., Jureidini R., Patzina R.A., Siqueira S.A.C. (2005). Unusual clinical presentation of annular pancreas in the adult. Pancreatology, 5(1), 81-85. 3. Ameur H.B., Boujelbene S., Affes N., Ghorbel A., Beyrouti M.I. (2011). Duodenal diverticulum associated with annular pancreas: A rare cause of severe cholangitis. Journal of visceral surgery, 148(3), e221-e224. 4. Urayama S., Kozarek R., Ball T., Brandabur J., Traverso L., Ryan J., Wechter D. (1995). Presentation and treatment of annular pancreas in an adult population. American journal of gastroenterology, 90(6).

P06

Differential diagnosis for multiple pancreatic cystic lesions

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Case Report: We report here two cases of patients with multiple pancreatic cysts. Case1. An asymptomatic 73-year-old woman with history of colorectal adenomas performed an abdominal ultrasound in 2006 with hazardous discovery of pancreatic cysts. An MRI was performed in 2012 with presence of multiple small and clustered peripheral cysts without communication with the main pancreatic duct. The largest cyst measured 14.5 mm in the pancreatic isthmus. Radiological follow-up by MRI has been performed annually until October 2020 with mild size progression of the largest cyst up to 18 mm. Three EUS have been performed in 2013, 2015 and 2018 without identification of cystic mural nodules, wall thickness or main pancreatic duct communications without morphological indication for biopsy. Case 2. A 40-year old woman, with history of pituitary adenoma and colorectal adenomas, presented in March 2020 with abdominal pain and postprandial exacerbation with discovery of pancreatic cysts on abdominal computed tomography. The MRI was performed with presence of multiple small and clustered peripheral cysts, mostly located in the head of the pancreas and without communication with the main pancreatic duct. EUS excluded cystic parietal alterations or pancreatic duct dilation. The largest cyst measured 12 mm in the pancreatic tail. For both cases, the small size of the cysts did not indicate FNA, FNB, CLE or biopsy for the differential diagnosis and MRI annual follow-up was suggested. Both cases are suggestive of acinar cystic transformation (ACT) of the pancreas, an uncommon pathology also known as « Acinar cell cystadenoma». It was first described in 2002 and there have been only few case reports with approximately 75 patients on this non-neoplastic entity in the literature up to now. ACT has a tendency to be seen in young adults, mainly in females and are usually indolent. It is accepted as a benign process and the etiology is still unknown. The reported cases of ACT display a benign course with no reports of malignant transformation. Cysts of this entity are lined by epithelium with morphologic and immunohistochemical resemblance to pancreatic acinar cells. The cells are immunohistochemically positive in stains for trypsin, chymotrypsin and CK7. The Ki67-index is low; 1-2 %. Diagnosis of ACT may be difficult making the differential diagnosis between a cystic neoplasm. The cysts are primarily located in the head of the pancreas and are often multilocular with a mean size over 50 mm. In magnetic resonance imaging (MRI) presence of five or more cysts, clustered peripheral small cysts, cyst calcifications and absence of communication with the main pancreatic duct are suggestive for ACT. Nevertheless, synchronous cystic lesions of the pancreas with different pathophysiology in the same patient are a rare occurrence but have been described and have to be considered. Confocal laser endomicroscopy (CLE) probe and a small-caliber biopsy forceps can be passed through a 19-gauge needle during endoscopic ultrasound (EUS) for immunohistochemical stain to differentiate ACT and pancreatic cysts with malignant potential. Surgical treatment of ACT should be based

only on the symptoms of the patient. In conclusion, ACT is a rare and benign lesion that should be considered as a differential diagnosis when dealing with multiple cystic lesions in the pancreas. MRI imaging criteria have a strong predictive value for the diagnosis of ACT. Nevertheless, EUS biopsy seems a promising tool for immunohistochemical stain to distinguish between ACT and cystic lesions with malignant potential and avoid unnecessary surgery in larger lesions.

Belgian Working Group on Digestive Pathology

R01

A unique case of duodenal mass requiring pancreaticoduodenectomy: giant Brunner's gland hamartoma

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Case Report: Brunner's gland hamartoma is a rarely reported lesion of unknown aetiology and pathogenesis. In contrast to the more common Brunner's gland hyperplasia it generally presents as a single polyp, by definition larger than 5 mm. A Brunner's gland hamartoma is an infrequent cause of gastrointestinal bleeding or obstruction. A need for invasive surgical intervention is rarer still. A review of the literature could only find a handful of cases treated by pancreaticoduodenectomy (Whipple procedure). Here we describe the case of a 67 year old female, originally presenting with chronic anaemia resulting in fatigue and shortness of breath. Endoscopy showed an ulcerated sessile tumour in the second portion of duodenum. Subsequent computed tomography revealed an underlying fusiform tumoral mass located in the duodenal wall, radiologically compatible with a gastro-intestinal stromal tumour. Biopsy results were inconclusive, with only granulation tissue in the acquired sample. A complete resection by means of pancreaticoduodenectomy ensued. Histopathological study revealed a mass, measuring 108 x 68 mm, fully composed of hyperplastic Brunner's glands, mature fat and connective tissue. Therefore, a diagnosis of a giant Brunner's gland hamartoma, was made. There was no dysplasia. Postoperative adverse events included haemoptysis and an associated aspiration pneumonia. The patient was free of adverse events at 3 months follow up. Diagnostic modalities such as endoscopy and radiological imaging help in guiding the clinicians towards a correct preoperative differential diagnostic landscape. Our case serves as a reminder of the fallibility of these investigations. Despite a relative low rate of incidence, sources state that Brunner's gland hamartoma's make up approximately 5% of all duodenal masses. Tumours > 100 mm are however a rare entity, generally being pedunculated masses instead of more sessile polyps. We propose that awareness of this rare entity, and the potential giant proportion of these, is vital in order to prevent overtreatment and subsequent intra-

and postoperative morbidity. In light of diagnostic amelioration, we report this case to illustrate the rare benign entity of a giant Brunner's gland hamartoma.

R02

Automatic embedding technique for histopathological examination results in increased R0 resection rates for endoscopic submucosal dissection.

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Introduction: Endoscopic submucosal dissection (ESD) allows « en-bloc » resection of superficial gastrointestinal neoplasia. Standardized macroscopic and microscopic approaches are required to adequately assess the curative status of the resection that determines patient's further clinical management. Nevertheless, margin assessment is sometimes challenging especially if samples are not correctly orientated within paraffin blocks.

Aim: The aim of the study was to compare margin status of ESD specimens embedded using one of two methods: a manual embedding technique (MET) or an automatic embedding technique (AET).

Methods: Data from consecutive ESDs performed between June 2015 and November 2020 in a single center (Erasme University Hospital) were collected. Macroscopic examination of the ESD specimens was realized under supervision of the same pathologist (LV). Briefly, ESD specimens were pinned down on a cork and directly fixed in a 4% buffered formalin solution during at least 24h to 72h depending on the size. Deep margin was inked in black while lateral margins were inked in green. Closest lateral margins were assessed using perpendicular technique. Specimens were sliced at 2-3 mm intervals. ESD specimens were submitted in their totality for microscopic examination. For MET, orientation of slices was realized by a technician within the paraffin while for AET, the pathologist orientated slices using a gel (Tissue-Tek® Paraform® Biopsy Gel-Sakura) and the blocks were embedded using an automate (Tissue-Tek AutoTEC a120-Sakura). Microscopy of all ESD specimens was revised by two pathologists (LV-PD). ESDs were realized for dysplastic lesions or cancer arising from esophagus (32% MET-31% AET), stomach (21% MET-20% AET), duodenum (1% AET), colon (9% MET-6% AET) and anorectal location (38% MET-42% AET) .

Results: 190 ESDs were collected: 100 with MET and 90 with AET. Medians (IQR) of specimen area were 999 (550-1894) and 1332 (675-2587) mm2 for MET and AET, respectively (p=0.06). We observed positive margins in 28% and 6.7% for MET group and AET group, respectively (p=0.00031). In MET group, positive margins were lateral in 22 cases (78.6%) and deep in 6 cases (21.4%) while in AET group, positive margins were lateral in 3 cases (50%) and deep in 3 cases (50%) (p=NS). To avoid an effect of learning curve, analysis of data from 2016 to 2020 only was also performed, again showing a difference in positive margins (25% MET vs 6.7% AET, p=0.001) Less paraffin

blocks were used in the AET compared to MET group: median (IQR) of 4(3-9) vs 13(9-23) paraffin blocks ($p<0.001$).
Conclusions: Automated embedding technique results in improved margin status of ESD specimens, especially with regard to lateral margins. AET is associated with less extensive handling after macroscopy assessment and lower need of paraffin blocks.

R03
Pancreatic medullary carcinoma developed on a Pancreatic Intraductal Papillary Mucinous Neoplasm with loss of MSH2 and MSH6 expression
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Case Report: Herein we report the case of a 73-year-old woman presenting with right iliac fossa pain. MRI revealed a 16 mm diameter mass in the pancreas, leading to a pancreatic duct stricture and upstream a dilatation of the distal pancreatic duct of Wirsung. Endoscopic Ultrasound-Guided Fine Needle Aspiration (19G) was performed, and pathology analysis revealed malignant glandular cells. Immunohistochemistry revealed diffuse expression of MLH1 and PMS2 and a heterogeneous expression of MSH2 and MSH6. G12D mutation of the KRAS gene was detected using Next-Generation Sequencing. The patient underwent distal pancreatectomy without splenectomy, but with cholecystectomy and splenic vessel resection. Gross examination of the surgical specimen revealed a 12 mm indurated white lesion, close to the surgical margin, adjacent to a cystic lesion extending into the rest of the pancreatic body. Microscopically, the cystic area represented a Pancreatic Intraductal Papillary Mucinous Neoplasm (IPMN) of mixed gastric-type and pancreatobiliary-type, involving the main pancreatic duct and secondary ducts with low-grade and high-grade dysplasia. In the periphery of this IPMN, a 14 mm of long-axis associated invasive carcinoma was observed. This associated carcinoma was characterized by focal gland formation and by poorly differentiated cells with a syncytial appearance, associated with a dense lymphoplasmocytic and neutrophilic infiltrate. The immunohistochemical profile was: CK7, EMA, CK19 positive, MUC5 and MUC6 focally positive, CK20, CDX2, CEH, MUC2, p53, PanTRK, chromogranin and synaptophysin negative. A focal loss of SMAD4 was observed. Moreover, there was a loss of MSH2 and MSH6 expression, suggesting microsatellite instability. This was confirmed by PCR (Idylla assay). The tumor was staged as: pT1cN0 according to UICC 2017. Molecular analysis was performed both on the invasive carcinoma and on the high-grade dysplasia IPMN revealing the same mutation profile: KRAS G12D and TP53 S90Pfs*33 mutations. EBV Chomogenic In Situ

Hybridization was performed but was negative. The proposed diagnosis was mixed IPMN associated with invasive medullary carcinoma that presented loss of MSH2 and MSH6 expression. Pancreatic medullary carcinoma is a rare pancreatic tumor. The histological and molecular profile of this tumor is characterized by significant tumor infiltrating lymphocytes, poorly differentiated epithelial cells with nest-like architecture, syncytial growth and pushing borders, presence of microsatellite instability, usually MLH1 silencing, and a wild-type KRAS mutation status. Moreover, some poorly differentiated adenocarcinoma with EBV infection may histologically mimic medullary carcinoma. Despite poor differentiation, patients with medullary carcinoma seem to have a better prognosis than patients with conventional ductal adenocarcinoma. The present case reports for the first time, at the best of our knowledge, the coexistence of IPMN lesions and pancreatic medullary carcinoma, both having the same molecular alterations. It also describes the second case of pancreatic medullary carcinoma with microsatellite instability MSH2 and MSH6 silenced, the first having been described by Banville et al in 2006.

R04

Primary tumor budding and histological growth patterns of liver metastases in colorectal cancer

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Introduction: Histological growth patterns (HGPs) of colorectal liver metastases (CRLM) have a strong prognostic value. Patients undergoing surgery for CRLM with desmoplastic-type HGP (DHGP), characterized by a peritumoral fibrous rim with numerous immune cells, have improved outcome when compared with patients with CRLM of the replacement-type HGP (RHGP), characterized by cancer cells growing into the liver parenchyma, with minimal inflammation, no angiogenesis and no desmoplastic rim. The biology behind the distinct HGPs remains largely unknown.

Aim: We hypothesized that the migratory capacities of cancer cells of the primary tumor could determine the HGP of the liver metastases. To address this question, we compared primary tumor budding (PTB) with the HGPs of the CRLM.

Methods: In a retrospective series of 263 patients operated for CRLM, we identified 50 patients with DHGP and 25 with RHGP, defined by the presence of the respective HGPs in ≥95% of the tumor-liver interface. The PTB and the HGP have been scored on hematoxylin-eosin (HE) sections according to international guidelines, blinded for outcome.

Results: Primary tumor and CRLM clinico-pathological characteristics were similar in DHGP and RHGP patient groups. Significantly more patients in the DHGP group received chemotherapy before primary tumor and CRLM resection. Five-years DFS after resection

of CRLM was significantly better in the DHGP group (44.5% versus 17.6% in RHGP group, p=0.02). Median PTB score was significantly higher in the RHGP group (6.9 versus 4.3, p=0.02), whereas all RHGP patients had some degree of PTB, as compared with 18% of the DHGP patients with zero PTB (p=0.03).
Conclusions: Our results indicate that PTB in colorectal cancer is associated with RHGP-type CRLM, suggesting that the migratory capacity of cancer cells at the primary tumor level may favor the development of liver metastases with an infiltrative pattern and accelerated growth.

R05
An unusual hepatic vascular tumor in a 3-year old child.
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Case Report: A 3-year old female infant presented to our hospital with abdominal pain, vomiting, fever and diarrhea. Clinical and radiological work up revealed a hypervascular tumor of the liver without metastatic disease. The patient underwent partial hepatectomy. The resection specimen showed a large, partly cystic tumor mass, which had a rather soft appearance on section. Microscopic examination revealed a vascular tumor with a biphasic architecture. On one hand there was a diffuse infiltration by thin-walled branching vessels without endothelial atypia, compatible with infantile hemangioma. On the other hand, the tumor presented with hobnailed rounded epithelioid and, less common, spindle shaped endothelial cells with large, atypical vesicular nuclei and amphophilic cytoplasm. These cells formed sheets, papillae and canon-like balls within vascular channels. There were numerous mitoses. Immunohistochemistry showed a strong positivity for CD31 and ERG in the atypical cells. The diagnosis of an angiosarcoma arising in association with infantile hemangioendothelioma/hemangioma of the liver was established. Infantile hepatic angiosarcoma is a very rare, highly malignant tumor with a poor overall outcome with mean survival time ranging from 10 month to 2 years. To our knowledge only 19 cases IHA arising in association with infantile hemangioma have been described from 1971 until now in the English literature. In the literature there is ambiguity about the nomenclature of infantile hepatic hemangiomatous lesions. Consensus exists about type I infantile hepatic hemangioendothelioma (IHHE), which is considered as a benign lesion. Type II infantile IHHE is according to some pathologists categorized as a precursor lesions or as a low grade angiosarcoma, while others consider it as synonym of angiosarcoma. In the differential diagnosis a retiform haemangioendothelioma and epithelioid haemangioendothelioma is included. There is no treatment consensus for this uncommon tumor. Complete surgical resection with or without adjuvant therapy is proposed in literature. Liver transplantation is discouraged due to high recurrence rate and poor posttransplant survival. Neoadjuvant therapy is also described in cases that

are not amenable to surgical resection. In our case PET/CT showed postoperatively metastatic disease in the lungs. Hence the patient received 6 cycles of chemotherapy with paclitaxel and gemcitabine after the hepatectomy. Hereafter weekly maintenance therapy with vinblastine and methotrexate was administered. The therapy was well tolerated. The last abdominal and thoracic CT scan, 5 months after diagnosis, showed no evidence for local recurrence, nor evolution of the lung lesions.

R06

Grayish macule found in the middle and the lower parts of the esophageal mucosae : a fortuitous discovery

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Case Report: - Background and objective A 57-year-old woman known for antral gastritis and bulbar ulcer underwent an upper endoscopy control. During the later, a fine, grayish, flat and poorly delimited macule was noted in her middle and lower third esophagus. Little is known about this entity and the aim here is to highlight is existence by description of its clinical and histopathological features. - Material and methods Following upper endoscopy control, biopsies were taken. Histological examination with realization of stainings and immunochemistries were undertaken. - Results H&E stain showed the presence of non atypical cells containing dark granules along the basal membrane of the squamous epithelium. Masson-Fontana staining and immunochemistries (CD68, PS100, HMB-45, Melan-A, MART1) allowed confirmation of the melanocytic nature of the cells. - Conclusion « Melanocytosis » or « melanosis » of the esophagus is a rare lesion occurring more frequently in Asia and in male and, is commonly found in the middle and/or the lower third part. From a histological point of view, it is characterized by presence of a proliferation of non atypical melanocytes containing an increased amount of melanin pigment within the esophageal mucosae. Melanocytic markers (as PS100, HMB-45, Melan-A and MART1) allow confirmation of the cellular origin. Errors of neural crest cells migration during embryogenesis or secondary inflammatory reaction are usually suggested as the main cause of melanosis. Differential diagnosis includes « pseudomelanosis » such as hemosiderosis, lipofuscin pigment accumulation, exogenous deposition (anthracosis, dye,…) or melanocytic lesions as (blue) naevus and primary melanoma. Other entity such as black oesophagus, has to be excluded. Malignant transformation in melanoma has been frequently proposed. However, the exact etiology and natural course are not known yet. The knowledge of the existence of this entity and subsequent follow up after diagnosis are the keys for patient's care by the gastroenterologist in order to avoid a potential malignant transformation. Authors and affiliations Angélique Dubail1, Anne Jouret-Mourin1, Patrick Collins2, Nicolas de Suray 3, Hélène Dano1 1. Department of Pathology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain,

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R07

Intratumoral and peritumoral expression of CCR2 in pancreatic adenocarcinoma and its impact on prognosis.

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Introduction: Pancreatic ductal adenocarcinomas (PDACs) are tumors that remain associated with a poor prognosis which is largely explained by the presence of a globally immunosuppressive tumor microenvironment. In particular, PDACs have been recognized as using the CCL2 / CCR2 (C-C chemokine receptor type 2) chemokine pathway. Overexpression of CCL2 in PDACs results in recruitment of inflammatory CCR2 + monocytes from the bone marrow to the primary tumor.

Aim: The aim of our study is to investigate the expression of CCR2 in PDACs in the tumor and peritumoral tissues as well as its clinical significance.

Methods: An analysis of the immunohistochemical expression of CCR2 on sections of paraffin-embedded tissue was performed on a cohort of 55 PDAC patients operated from 2007 to 2018 without neoadjuvant treatment previously received. After verification by an experienced pathologist, a quantitative analysis of the membrane and cytoplasmic labeling of CCR2 was carried out using the Visiopharm™ software both on the tumor (tumor glands and directly adjacent stroma) and peritumoral areas (any tissue located at ≤ 1mm around the tumor area with the exception of the lymph nodes, duodenal mucosa and tertiary lymphoid structures associated with the duodenal mucosa) (Figure 1). The risk of early mortality (<24 months) associated with the expression of CCR2 in the intra- and peritumoral areas was then investigated by logistic regression.

Results: Compared to the long survivors (≥24 months, n = 22), the short survivors (<24 months, n = 33) had significantly less membrane and cytoplasmic expression of CCR2 in the peritumoral area [median (P25-P75): 0.0005968 (0.0003142 - 0.0007888 / µm2) vs 0.0003492 (0.0001719 - 0.0004625 / µm2), p-value = 0.024]. In addition, the expression of CCR2 in the peritumoral area was positively correlated with overall survival (Spearman's correlation coefficient = 0.325, p-value <0.05). Finally, after adjusting for the main confounding clinical factors, multivariate analysis by logistic regression demonstrated that the presence of high expression of CCR2 in the peritumoral area (> 0.0005250) was a protective factor against early mortality [OR :

0.10 (95% CI: 0.02—0.65), p-value = 0.038]. In contrast, the expression of CCR2 in the tumor area was not associated with survival at 24 months in our PDAC cohort.
Conclusions: High expression of CCR2 in the peritumoral tissues is associated with long survival (≥24 months). These results can be explained by the fact that the CCR2 + monocytes recruited by the primary pancreatic tumor do not initially exhibit an immunosuppressive profile. This suggests that the phenotypic transformation of inflammatory monocytes into tumor associated macrophages (TAMs) with an immunosuppressive profile occurs within the tumor, in direct contact with the tumor microenvironment of PDACs.

R08

Clinical course and histopathological findings in DGAT1 mutation linked congenital diarrhea. Case report of a 17-year-old patient.

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Case Report: We report a case of a 17-year-old patient who suffered since early childhood from severe congenital diarrhea, protein-losing enteropathy and failure to thrive, requiring total parenteral nutrition. Work-up and referral to a specialized intestinal failure center could not identify the underlying cause. As a toddler, it became clear she was able to tolerate carbohydrates and proteins, but that her gastrointestinal complaints were linked with the intake of fat. With a fat-free diet it was possible to switch to enteral nutrition, first via a gastrostomy tube, later per os. This clinical picture is consistent with DGAT1 deficiency caused by biallelic mutation in the DGAT1 gene, which encodes acyl CoA:diacylglycerol acyltransferase 1, described in 2012. DGAT1 is crucial for triglyceride synthesis and highly expressed in the gut. Diarrhea may result from intestinal barrier dysfunction due to cytotoxicity caused by the dysregulated fatty acid metabolism. Duodenal biopsies revealed villus blunting, severe acute inflammation, presence of aggregates of macrophages and multinucleated giant-cells, including Touton-like giant cells, a type of multinucleated giant cells seen in lesions with high lipid content, most probably linked to the inability to digest fat. At the age of 10 she developed in addition a clinical picture of gluten intolerance with duodenal biopsy showing villus atrophy and increase in intra-epithelial lymphocytes compatible with celiac disease. Moreover, 5 years later she developed ulcerative colitis symptoms with focally enhanced gastritis, focal active ileitis and chronic active IBD-like colitis in colorectal biopsies. Gut barriers dysfunction may also play a role in these more recent developments. DGAT1 mutation associated diarrhea is an autosomal recessive disorder. Genetic analysis, revealed only one heterozygous likely pathogenic variant in DGAT1 (NM_012079.5): c.629_631del, p.(Ser210del) VUS), paternally inherited. Immunohistochemistry, however, showed complete loss of DGAT1 expression in the

intestinal epithelial cells, consistent with biallelic DGAT1 inactivation. Hence, a non-coding pathogenic variant may have been missed. A high index of suspicion is warranted in older children and young adults suffering from congenital diarrhea and protein-losing enteropathy, as this disorder most probably is underdiagnosed. Reporting the histopathological findings and clinical evolution of this rare disorder is important. As shown in our case weaning of parenteral nutrition was possible and lifelong parenteral nutrition or intestinal transplantation and its associated complications could be avoided. Despite this serious illness, the patient has grown into a sporty young lady who is doing very well at school.

R09

Histological growth patterns of non-colorectal non-breast non-neuroendocrine liver metastases

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Introduction: There is no reliable factor to predict the benefit of surgery in patients with liver oligometastases (LM) from non-colorectal non-breast non-neuroendocrine origin (NCRNBNNELM). In colorectal cancer, the histological growth pattern (HGP) of LM is a strong prognostic factor, as the postoperative outcome is significantly better in patients operated for desmoplastic HGP (DHGP) LM, characterized by a peritumoral fibrous rim with inflammation and angiogenesis, as compared with replacement HGP (RHGP) LM, with cancer cells growing into the liver parenchyma, with minimal inflammation and vessel co-option. Currently, the HGPs of NCRNBNNELM have not been systematically explored.

Aim: We aimed to evaluate the HGPs and their potential prognostic value in patients undergoing resection of NCRNBNNELM.

Methods: A retrospective series of 30 patients undergoing R0-resection for oligo-NCRNBNNELM was analyzed. Demographic and clinico-pathologic parameters were collected. HGP were assessed on hematoxylin-eosin stained tissue sections of all resected LM, according to international guidelines and blinded for outcome. LM were categorized as DHGP or RHGP when >50% of the tumor-liver interface presented the characteristics of these respective patterns. The prognostic values of clinico-pathologic parameters and HGPs were analyzed.

Results: Among the 30 patients, 16 presented with DHGP LM and 12 with RHGP LM. In 1 case the LM had a pushing-type HGP and 1 LM (GIST origin) had an unclassifiable HGP. Neither the primary tumor or LM characteristics, nor the systemic and surgical treatments were different between DHGP and RHGP groups. Postoperative recurrence-free survival was significantly better in the DHGP group, reaching 37.5% at 5-years, as compared with 0% in the RHGP group ($p=0.03$). No other clinico-pathological variables were found to be prognostic in multivariate analysis.

Conclusions: Similar to colorectal LM, NCRNBNNELM have distinct HGPs that can be scored as DHGP or RHGP. As in colorectal LM, DHGP in patients with NCRNBNNELM appears to be an independent prognostic factor for improved postoperative survival in patients undergoing surgical resection. This observation has to be confirmed in a larger cohort.

R10

Acinar cystic transformation of the pancreas: a case report

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Case Report: A 70 year old man presented with an incidental small nodular lesion in the pancreatic tail, detected by CT-scan and further investigated by MRI which suggested the possibility of a small neuro-endocrine tumor. On fine needle aspiration cytology (FNAC), a few atypical cell groups were seen with focally weak positivity for synaptophysin, which led to the tentative diagnosis of a well differentiated neuro-endocrine tumor. The differential diagnosis included normal pancreatic parenchyma and solid pseudo-papillary tumor. The surgical resection specimen of the pancreatic tail was fixed in 4% buffered neutral formalin for about 34 hours. Gross sectioning (performed according to the protocol of Verbeke et al) revealed a red-brownish solid nodule with an adjacent smaller, multilocular mass on the posterocaudal margin of the pancreas. Both lesions were entirely paraffine embedded and microscopically analyzed. Morphological examination revealed two distinct lesions. The solid red-brownish nodule was identified as an intrapancreatic accessory spleen, known to be a radiological mimicker of well vascularized neuro-endocrine tumors. The cystic mass posed a more challenging diagnostic problem. It was composed of several cystic spaces separated by stroma containing a few acini. The cystic spaces varied in diameter and some had incomplete septa with club-like pseudopapillary projections. The cystic lumen contained thickened eosinophilic material and the lining epithelium varied in thickness and appearance. On the one hand cuboidal epithelial cells with densely granular cytoplasm were seen. On the other hand flattened epithelium was noticed. The nuclei were small. There was no increased mitotic activity. Immunohistochemistry was performed to identify the different cell types. Synaptophysin and chromogranin A showed strong positivity in a few lining epithelial cells and in the intercystic Langerhans islets. Chymotrypsine showed patchy cytoplasmic positivity in the lining granular epithelium, while Bcl-10 and trypsine were negative and p53 immunohistochemistry showed a wild type staining pattern. CK7 was strongly expressed in a majority of the lining epithelial cells. Ki-67 confirmed a low proliferation activity of 1-2%. Based on the morphological and immunohistochemical findings the diagnosis of acinar cystic transformation (ACT) of the pancreas was made. ACT, also referred to as acinar cell cystadenoma, is a rare non-neoplastic cystic lesion, with 75 cases described to date. All reported cases are benign, without evidence of recurrence, malignant transformation or association with acinar

carcinoma. This rare cystic lesion can occur throughout the pancreas and can be a diagnostic challenge with main differential diagnosis being other pancreatic cystic lesions or tumors (e.g. acinar cystadenocarcinoma, post-obstruction dilatation of the pancreatic duct). The etiology is still unknown but at least in some cases, it is considered a metaplastic phenomenon of the pancreatic ductal system in response to inflammation and dilatation. This hypothesis is supported by the patchy immunohistochemical reactivity for both ductal epithelial marker CK7 and acinar markers trypsin and chymotrypsin. ACT has been reported in cases of post-obstructive dilatation due to pancreatic neuro-endocrine tumors (PanNET) and pancreatic ductal adenocarcinomas. Zhang et al recommend to systematically perform careful macroscopic examination for distal obstruction causing masses. In our case the obstruction was probably caused by the intrapancreatic accessory spleen and to our knowledge, this is the first report of ACT in the context of obstruction by an accessory spleen. We would also like to emphasize the challenging preoperative diagnostic work-up in this case. An intrapancreatic accessory spleen is a known radiological mimicker of a neuro-endocrine tumor and the cytological aspiration revealed a few synaptophysin positive cells with low mitotic activity also pointing towards the possibility of PanNET.

R11

Diagnosis of metastatic cancer in an uncommon location: Importance of clinical-pathological correlation

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Case Report: - Background and objective A 65-year-old woman suffered from pain and tumefaction in the distal phalanx of the right middle finger. The patient was previously operated for a pancreatic head adenocarcinoma (4 years before) with metastases in the right lung and in a mediastinal lymph node. Clinically, an uncommon metastatic location in the finger was suspected. In this case report, we sought to describe a clinical-pathological finding of an acrometastasis and to review literature of this rare and atypical entity. - Material and methods The patient underwent surgery with amputation of the right middle finger. Then, the specimen was grossly and microscopically examined to confirm the hypothesis of a metastatic localization of the pancreatic adenocarcinoma. - Results The gross examination objectified a tumefaction of the finger's soft tissue associated with focal hemorrhagic spots. The skin and the nail were both intact. Histopathological analysis showed a glandular proliferation composed of cribriform structures lined by a pseudostratified, atypical columnar epithelium admixed with nests of tumoral cells floating in large mucus lakes. Lymphovascular invasion, perineural invasion and tumoral osteolysis were noted. Tumor cells exhibited a strong cytoplasmic expression for cytokeratins 7, 19 and 20. - Conclusion Acrometastasis is a rare and atypical metastatic location. Carcinomas that metastasize

in this site mostly come from the lung, breast or kidney, pancreatic origin is therefore uncommon. The amputation is performed when other therapeutic options fail (e.g. radiotherapy). Main differential diagnosis include arthritis and infection. The pathobiological mechanism is unclear but many hypothesis have been proposed. Acrometastasis occurs late in the course of the disease and is usually associated with advanced stages. In addition, literature shows that, after diagnosis, life expectancy of the patient is very short (around 6 months) and surgery is only performed for palliative reasons. Even if the occurrence of acrometastasis is rare, it is important to bear in mind this option. Authors and affiliations Angélique Dubail1, Pamela Baldin1, Ivan Borbath2, Olivier Barbier3, Christine Galant 1 1. Department of Pathology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium. 2. Department of Hepatology and gastroenterology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium. 3. Department of Orthopaedic surgery, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

R12

Curious condylomatous lesions of the anal area in a young male patient : not all condylomatous-like lesions are related to HPV infection !

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Case Report: Anal lesions with a « tumoral » presentation in young patients are most often related to an underlying HPV infection and span from simple condyloma to epidermoid carcinoma. However, some of them do not correspond to condyloma. In this regard, we would like to draw attention on the importance of a precise diagnosis to provide an adequate treatment. We have recently experienced the case of a 25-year- old man with a medical history of gastric by-pass. He was admitted in the gastroenterology department for pain and discomfort in the anal area. Physical examination showed exophytic lesions localized on perianal skin and anal mucosa. The clinical appearance was that of classical condylomas at first. A surgical biopsy was therefore performed for diagnostic purposes and to rule out a possible carcinomatous process. Microscopic examination revealed psoriasiform inflammatory changes with epidermal pseudoepitheliomatous hyperplasia but no dyplasia or condylomatous features. By contrast, there were numerous plasma cells infiltrating the dermis, with neutrophils in the epidermis and focal necrotic keratinocytes. What is your diagnosis ?

R13

Difficulties and pitfalls in the differential diagnosis of IBD: a case report.

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Case Report: The definite diagnosis of Crohn disease (CD) or ulcerative colitis (UC) based on the evaluation of biopsies or resection specimens in suspected inflammatory bowel disease (IBD) can be challenging. The difficulty most often results from overlapping features between the two pathological entities and/or insufficient clinical, radiological and endoscopic data. Another pitfall may rely on previous diagnoses without questioning them. To illustrate these problems, we present the case of a 47-year-old man in whom an IBD was clinically suspected one year ago. The patient underwent biopsies which confirmed the diagnosis of chronic inflammatory disease and directed towards UC. During this endoscopic investigation, tumor lesions were detected, justifying partial colectomy. The histological examination of the resected specimen showed two adenocarcinomas and multiple foci of low- and high-grade dysplasia in the inflammatory mucosa. Histological examination of the surgical specimen confirmed the IBD. The presence of granulomas through the colonic wall led to a diagnosis of CD. The patient benefited from a follow-up recto-sigmoid resection that revealed features more suggestive of UC. The definite diagnosis was finally made after a thorough study of the medical history which revealed that the patient had suffered from an unrelated disease more than 27 years ago. This case is representative of (i) the need for optimal communication between clinicians and pathologists, (ii) the importance of knowing the patient's medical history, and (iii) not blindly rely on the previously mentioned diagnosis to establish an accurate diagnosis.