ABSTRACTS

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ABSTRACTS

BELGIAN ASSOCIATION FOR THE STUDY OF THE LIVER (BASL) /
BELGIAN LIVER INTESTINE COMMITTEE (BLIC)

- A01 –

SAFETY AND PRELIMINARY EFFICACY OF HUMAN ADULT LIVER PROGENITOR CELLS (HEPASTEM™) IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) OR ACUTE DECOMPENSATION (AD) AT RISK OF DEVELOPING ACLF : A EUROPEAN PHASE /IIA OPEN-LABELLED STUDY. F. Nevens (1), T. Gustot (2), P. Laterre (3), L. Lasser (4), L. Haralampiev (5), V. Vargas (6), D. Lyubomirova (7), A. Albillos (8), V. Barthel (9), N. Clerget-Chossat (9), E. Sokal (9) / [1] KU Leuven, Belgium, Hepatology and Liver Transplantation, [2] Erasme Hospital, Brussels, Belgium, Gastroenterology/HepatoPancreatology/Digestive Oncology, [3] Saint-Luc University Hospital, Brussel, Belgium, Intensive Care, [4] CHU Brugmann, Brussels, Belgium, Gastroenterology, [5] Hospital Medica Ruse, Ruse, Bulgaria, Internal Diseases, [6] Hospital Vall d'Hebron, Barcelona, Spain, Hepatology, [7] University Multiprofile Hospital for Active Treatment "Dr. Georgi Stranski", Pleven, Bulgaria, Clinical Gastroenterology with Hepatology, [8] Hospital Universitario Ramón y Cajal Catedrático de Medicina, Universidad de Alcalá, Madrid, Spain, Gastroenterology and Hepatology, [9] Promethera Biosciences, Mont-Saint-Guibert, Belgium, Product Development

Introduction : Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation (AD) of cirrhosis associated with failure of one or more organs. HepaStem™ is a suspension of Human Allogenic Liver Progenitor Cells derived and expanded from the parenchymal fraction of collagenase-digested adult human liver. The immunomodulatory properties of HepaStem™ are expected to restore immune balance and liver function in patients with ACLF or AD.
Aim : The primary objective is the safety of 1 or 2 infusions of various doses of cells up to Day (D)28 post treatment. Secondary objectives include preliminary efficacy up to month (M)3.
Methods : Twenty-four patients were enrolled. The first patient (ACLF) received no cells due to technical issue. The second patient (ACLF) received 2 infusions of 4.2 x 10^6 cells/kg, the third patient (ACLF) received 1 infusion of 5.3 x 10^6 cells/kg, 6 patients (2 ACLF and 4 AD) 1 infusion of 0.6-0.8 x 10^6 cells/kg, 3 patients (2 ACLF and 1 AD) 2 infusions of 0.6 x 10^6cells/kg, and 12 patients (9 ACLF and 3 AD) 1 or 2 infusion of 1.2 x 10^6 cells/kg.
Results : The second patient had severe epistaxis and the third one bled at the puncture site of the transjugular biopsy. They recovered; one had liver transplantation and the other one was well at 1 year. After dose adjustment in the subsequent dose-cohorts, no serious events causally related to HepaStem™ were reported. No other bleedings occurred, or any drop of platelets, fibrinogen, or coagulation factors. Adverse events were in line with those expected regarding the underlying diseases and comorbidities. In patients without liver transplantation (N=18), bilirubin and MELD score decreased, and albumin slightly increased as compared to pre-infusion values. Also, elevated baseline levels of C-Reactive Protein and neutrophil counts returned to normal in most patients.
Conclusions : At high cell doses (250 x 10^6 cells), 2 patients with initial severe coagulation disturbances experienced bleeding possibly related to HepaStem™. This could be linked to tissue factor expressed by HepaStem™, which activate the coagulation cascade and lead to consumption of coagulation factors, as shown in preclinical studies. No bleedings related to HepaStem occurred at 0.6 to 1.2 x 10^6 cells/kg doses, or changes in coagulation parameters; these dosages were safe in this AD/ACLF patient population. Preliminary data showed improvement of liver function and systemic inflammation post infusion. The clinically significant MELD and bilirubin improvement is considered as an encouraging sign of efficacy.

- A02 –

VIRAL HEPATITIS IN BELGIAN PRISONS : A FIRST-TIME MULTICENTER PREVALENCE STUDY. D. Busschots (1), R. Bielen (1), Ö. Köc (1), E. Dercon (2), C. Brixko (3), P. Laukens (4), P. Bilaey (4), F. De Smet (4), G. Hellemans (4), G. Muyldermans (5), L. Van Baelen (5), H. Van Vlierberghe (6), G. Robaeys (1) / [1] Hasselt University, Hasselt, Belgium, Health and Life Sciences, [2] zorGGroep Zin, Hasselt, Belgium, Addiction Care, [3] CHR La Citadelle, Belgium, Department of Gastroenterology and Hepatology, [4] Federale Overheidsdienst Justitie, Brussel, Belgium, Coördinatie Medische Zorg, [5] Sciensano, Brussels, Belgium, Epidemiology and Public Health, [6] UZGent, Gent, Belgium, Department of Gastroenterology and Hepatology.

Introduction : Prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection among prisoners is many times higher than in the general population. The high rates of viral hepatitis infection in prisoners, and the substantial risks associated with an untreated infection underline the need for screening and access to treatment in prisons. To date, there is no targeted screening in Belgian prisons and currently there are no data on the prevalence of HCV or HBV infections in prison.
Aim : Through targeted screening, we want to map the prevalence of HCV and HBV in prisons in Belgium.
Methods : The study started on 1 April 2019 in several prisons for both prisoners in pre-trial detention and long-term convicts throughout Belgium. The eligible candidates (>18y and signed informed consent form) were tested by finger

prick for HCV antibodies (Ab) using the Oraquick® test and hepatitis B surface antigen (HBsAg) using the HBsAg Rapid Test Device®. While waiting for the results (20 minutes), an encoded questionnaire was filled out.
Results : From 1 April 2019 till 7 November 2019 a total of 456 prisoners were screened. Of these, 21 (4.6%) tested positive for HCV Ab and 5 (1.1%) tested positive for HBsAg. The prevalence of HCV Ab did not differ in prisoners in pre-trial detention compared to long-convicts, respectively 10/160 (6.3%) and 11/285 (3.9%, p=0.159). All participants who tested positive on one of the tests was referred to the physician in prison for a vene puncture to determine HCV RNA. To date, HCV RNA was determined in 12/21 and was present in 8 (66.7%).
Conclusions : These preliminary results show an increased prevalence for HCV Ab in prisons in Belgium. This is markedly lower than mentioned in previous European studies.

- A03 -

HYPOXIA-INDUCED ANGIOGENESIS PROTECTS THE LIVER FROM SMALL FOR SIZE SYNDROME. A. Dili (1), M. De Rudder (2), B. Pirlot (2), L. Dewachter (3), C. Bertrand (4), C. Bouzin (5), I. Leclercq (2) / [1] CHU UCL Namur, Yvoir, Belgium, Surgery and Laboratory of Hepato- Gastroenterology; UClouvain - IREC - GAEN department, [2] Laboratory of Gastroenterology and Hepatology, Institut de Recherche Expérimentale et Clinique, UCLouvain, Brussels, Belgium, Laboratory of Gastroenterology and Hepatology, IREC, UCL, Brussels, [3] ULB, Brussels, Belgium, Laboratory of Physiology and Pharmacology, [4] CHU-UCL-Namur site Godinne, Yvoir, Belgium, Surgery, [5] Institut de Recherche Expérimentale et Clinique (IREC), Catholic University of Louvain (UCL), Belgium, IREC Imaging Platform.

Introduction : Liver regeneration is a highly regulated process which requires an equilibrium between the hepatocyte proliferation and angiogenesis in order to maintain liver function. After partial hepatectomy, hepatocyte proliferation (organogenesis) proceeds sinusoidal remodelling (angiogenesis) causing a transient perturbation of the lobular architecture, with proliferating hepatocytes forming avascular clusters. As the magnitude of hepatocyte proliferation correlates with the extent of hepatectomy (and portal hyperperfusion), an extended hepatic resection triggers a vast regenerative response of hepatocytes, with formation of large avascular, and thus non-functional, hepatocyte islands. Such lobular temporospatial disorganization, resulting from a tremendous parenchymal cell proliferation and a slow sinusoidal endothelial cell (SEC) proliferation, causes transient hypoxia in the regenerating liver. Small for size syndrome (SFSS), a clinical entity characterized by hyperbilirubinemia, ascites, coagulopathy and hepatocellular failure, develops after major hepatectomy leaving a very small liver remnant or after liver transplantation with a small graft. Portal hyperperfusion is at the origin of a compensatory constriction of the hepatic artery (hepatic arterial buffer response), desarterialisation of future liver remnant (FLR) and hypoxia. Simultaneously, portal hyperperfusion also enhances hepatocyte proliferation in the early phase of liver regeneration, with the formation of avascular hepatocyte clusters. Hypoxia is, thus, considered at the origin of liver dysfunction in SFSS-setting hepatectomy.
Aim : Recently, based on a rat model of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), with a small, insufficient for survival FLR, we showed that hypoxia activated an early angiogenic response, resulting in a preserved sinusoidal morphology during the first phase of liver regeneration. When we experimentally induced hypoxia in an upfront SFSS-setting hepatectomy, survival rates significantly improved. Hypoxia had no impact on hepatocyte proliferation. Activation of hypoxia sensors surged an early angiogenic switch and preserved the sinusoidal architecture with a favorable impact on survival, suggesting an improved functional organization of the regenerating hepatocytes.This study aims to decipher the role hypoxia-induced angiogenesis in the setting of a SFSS hepatectomy.
Methods : The first part of the study focused on developing a mouse model of extended, SFSS-setting, partial hepatectomy (PHx-80%). We used a 70% PHx (PHx-70%) model as control animals. To test the impact of hypoxia, SFSS-hepatectomy mice were submitted to normoxia (inspired oxygen fraction-FiO2 : 21%), local hypoxia by hepatic artery ligation, and systemic hypoxia by placing the animals in hypoxic chambers (FiO2 : 11%) immediately after the operation and for 3 consecutive days. We assessed mortality, FLR hypertrophy, hepatocyte and liver SEC proliferation at different timepoints.
Results : Compared to 70% partial hepatectomy, resection of 80% of the total liver masse (PHx-80%) showed high mortality rates up to 68% at 7 days (p=0,002), confirming that PHx-80% was a SFSS-setting hepatectomy. After PHx-80% most deaths occurred the first 72hours after the operation (56%), suggesting that liver dysfunction occurred during the early phase of liver regeneration (organogenesis). Hepatocyte proliferation 3 days after the operation was significantly enhanced in PHx-80% compared to PHx-70% (p=0,03), while sinusoidal endothelial cell proliferation did not differ, suggesting an amplified disequilibrium of hepatocyte and SEC proliferation in the regenerating lobule in the SFSS-setting PHx-80%. Hepatic artery ligation, combined to PHx-80%, tended to have a favorable, although not significant, impact on survival (75% on postoperative day (POD) 3, 56% on day 7) compared the normoxic SFSS-setting PHx-80% (46% on POD3). When animals subjected to SFSS-setting hepatectomy were placed into hypoxic chambers (FiO2 11%), survival significantly improved (95% at 7 days) compared to PHx-80% (p=0,0007). FLR mass recovery and hepatocyte proliferation was similar between the hypoxic and normoxic SFSS-liver remnants. However, local and systemic hypoxia significantly triggered early angiogenesis as attested by the sinusoidal endothelial cell proliferation on postoperative day 1.

Conclusions : The current study supports our previously published data and confirms that hypoxia rescues survival from SFSS. While the improved survival cannot be attributed to an increased FLR mass recovery (reflection of hepatocyte proliferation), our data support that a surge of hypoxia during the early phase of liver regeneration triggers early sinusoidal endothelial cell proliferation. By balancing angiogenesis with hepatocyte proliferation, hypoxia improves the cellular "crosstalk" and restores the lobular liver architecture allowing an efficient liver regeneration after major hepatectomy.

- A04 -

18F-FLUOROCHOLINE AND 18F-FLUORODESOXYGLUCOSE PET/CT FOR CLINICAL STAGING OF PATIENTS WITH HEPATOCELLULAR CARCINOMA. H. Couvert (1), R. Marechal (2), R. Moreno-Reyes (3), O. Vierasu (3), M. Pezzullo (4), A. Bucalau (5), G. Verset (5) / [1] ULB Faculty of Medicine, Anderlecht, Belgium, Medical student, [2] CHU Tivoli, La Louvière, Belgium, Gastroenterology, [3] Erasme Hospital, Brussels, Belgium, Nuclear medicine, [4] Erasme Hospital, Brussels, Belgium, Radiology, [5] Erasme Hospital, Brussels, Belgium, Gastroenterology.

Introduction : 18F-Fluorocholine positron emission tomography/computed tomography (18F-FCH PET/CT) is an emerging metabolic imaging technique for the diagnosis and management of hepatocellular carcinoma (HCC). 18F-Fluorodeoxyglucose PET/CT (18F-FDG PET/CT) is not recommended for routine detection of intrahepatic HCC due to its low sensitivity. Nevertheless, recent studies have shown promising results for the detection of extrahepatic spread and predicting prognosis.
Aim : The aim of this study is to assess the percentage of positivity of 18F-FCH PET/CT, 18F-FDG PET/CT and the combination of the two radiotracers in HCC patients.
Methods : Sixty- two HCC patients that underwent 18F-FCH PET/CT for staging were included in this single centre retrospective study and tumor metabolism was assessed qualitatively. For 51 of them 18F-FDG PET/CT was also performed.
Results : A total of 62 patients (median age 63 years, range 34-83) with radiologically or histopathologycally confirmed HCC were included. Patients were mostly men (85.5%) with cirrhosis (88, 7%). The majority presented a well-compensated cirrhosis (Child A 64.2%) related to alcohol consumption (54.9%). Multifocal disease was observed in 69,4% of patients, with intermediate stage in 33.9% and advanced stage in 14.5%. Forty-two patients were treatment-naïve and 20 had received previous treatments (resection or RFA and/or transarterial therapies). In the global population (n=62), 18F-FCH PET/CT was positive for 45 patients (72.6%). Regarding the 51 patients who benefited of both radiotracers (18F-FCH and 18F-FDG), 47.1% had a positive 18F-FDG PET/CT, 98% were positive for at least one radiotracer and 27.5% were positive for the two. 73.8% of the treatment-naïve patients had a positive 18F-FCH PET/CT. Of the 37 patients evaluated with both radiotracers, 48.6% were 18F-FDG positive, 29.7% were 18F-FDG+18F-FCH positive and 97.3% were 18F-FCH or 18F-FDG positive. Furthermore, in 6 patients, lesions not described by standard radiology (computed tomography scanner and/or magnetic resonance) were detected by PET/CT.
Conclusions : The combination of 18F-FCH and 18F-FDG PET/CT seems to be useful for the HCC staging, with a combined positivity rate reaching 100%. Prospective trials with quantification of radiotracer uptake are mandatory to confirm this observation.

- A05 -

ARE LIVER INCLUSIVE INTESTINAL GRAFTS PROTECTED AGAINST REJECTION? M. Clarysse (1), E. Canovai (1), L. Ceulemans (1), T. Vanuytsel (2), G. De Hertogh (3), D. Monbaliu (1), J. Pirenne (1) / [1] University Hospitals Leuven, Belgium, Abdominal Transplant Surgery, [2] University Hospitals Leuven, Belgium, Gastro-enterology, [3] University Hospitals Leuven, Belgium, Pathology.

Introduction : Experimental/clinical data suggest that inclusion of a liver (Liv-In) protects against humoral/cellular acute and chronic rejection of simultaneously transplanted organs. This is due to liver clearance of preformed (or prevention of formation of de novo) donor-specific antibodies (DSA) and activation of regulatory/deletional tolerogenic mechanisms. However, data on the liver protective effect in Intestinal Transplantation (ITx) are scarce.
Aim : A thorough review of the effect of Liv-In versus no liver-inclusive graft on the outcome of ITx in University Hospitals Leuven.
Methods : Observational retrospective. In 2000-2019, 22 ITx were performed in 21 patients (1 reTx). Rejection, preformed / de novo DSA, graft loss and survival data were extracted from patient files and analysed according to presence (Liv-In) or absence (NoLiv-In) of liver. Induction immunosuppression (IS) was IL-2 receptor AB (20 patients) or anti-thymocyte globulin (2 patients). Maintenance IS are tacrolimus, azathioprine and steroids. Tacrolimus was more rapidly tapered & lower in Liv-In (<5µg/L) vs NoLiv-In (6-8µg/L) at 1 year postTx.
Results : There were 11 Liv-In (6 combined Liver-ITx (cLi-ITx); 5 Multivisceral Tx) and 11 NoLiv-In ITx. Follow-up : 3 months – 17 years. One patient had preTx class 1 DSA which disappeared after cLi-ITx. Three patients developed de novo DSA, of whom 2 were treated conservatively, as they were clinically well (Liv-In) and there was a low MFI (< 4.500). In the latter patient (NoLiv-In), de novo DSA were successfully treated with azathioprine. The incidence of early

(< 3 months) and late acute rejection (AR) (> 3 months) was 64% and 55% in NoLiv-In vs Liv-In, respectively (p=0.5). Overall incidence of grade 3 (severe) AR was 55% versus 9% in NoLiv-In vs Liv-In, respectively (p=.0317). Chronic rejection was seen in the NoLiv-In group only (18%). Overall graft loss was 5 in NoLiv-In {3 to rejection (at 2, 7, 176 months), 1 to AR/CMV 11 months; 1 to ischemia after endoscopy 3,5 years} vs 1 (partial) in Liv-In {acute rejection at 2 months} (p=.155 for graft loss due to rejection). Overall patient death was 3 in NoLiv-In {1 Aspergillus after AR treatment 8 months; 1 sepsis 58 months (51 months post-Txectomy); 1 multi-organ failure 86 months} vs 2 in Liv-In {1 death to Aspergillus after AR treatment 4 months; 1 death to NSAID-induced transplant bowel necrosis 12 years} (p=0.5). One-/5-year death-uncensored graft survival was 91%/91% in Liv-In vs 64%/48% in NoLiv-In (p=.09). 1-/5-year patient survival was 90%/90% in Liv-In vs 88%/71% in NoLiv-In (p=.47).
Conclusions : Liver inclusion protects intestinal grafts against severe acute rejection, despite receiving less immunosuppression. More effective immunosuppression is needed for isolated ITx. Liver inclusive ITx shows a trend for better graft and patient survival, despite being medically/surgically more challenging.

- A06 -

PREVALENCE AND CHARACTERISTICS OF CYSTIC FIBROSIS-ASSOCIATED LIVER DISEASE IN A COHORT OF ADULT CYSTIC FIBROSIS PATIENTS. Z. Issa (1), S. Gohy (2), B. Delire (1), G. Dahlqvist (1) / [1] Saint-Luc University Hospital, Brussel, Belgium, Hepato-gastroenterology, [2] Saint-Luc University Hospital, Brussel, Belgium, Pulmonology.

Introduction : Cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasians and is caused by CF transmembrane conductance regulator (CFTR) gene mutation. CF-associated liver disease (CFLD) is the 3rd leading cause of death in CF patients. Its prevalence is controversial since the term CFLD is used to describe a wide range of manifestations. Therefore, it is important to distinguish CF-associated from CF-related liver disease. CFLD is thought to be a paediatric disorder although adult-onset CFLD (ad-CFLD) is being increasingly reported together with the arrival of new definition criteria using non-invasive liver fibrosis tests.
Aim : We aim to determine the prevalence and characteristics of CFLD in a cohort of adult CF patients.
Methods : We retrospectively studied a cohort of CF patients followed at our CF clinic. Inclusion criteria were age >18 years, a typical form of CF and at least 1 year of follow-up. We excluded pulmonary transplant patients. Data on baseline and CF characteristics were collected. CFLD was defined as having 2 out of 3 criteria : persistent elevation of transaminases and/or gamma-glutamyltransferase, abnormal ultrasound findings and/or abnormal transient elastography (cut-off >6.8 kPa). Non-invasive fibrosis markers were calculated in all CFLD patients. Ad-CFLD was defined as CFLD diagnosed >18 years. Severe CFLD (s-CFLD) was defined as CFLD with cirrhosis and/or portal hypertension.
Results : A total of 113 patients were included, median age was 29 years and 58 (51%) were male. Median age at CF diagnosis was 6 months, 17% had meconial ileus, 54% had deltaF508 homozygous mutation, and 83% had pancreatic exocrine insufficiency. Sixteen patients (14%) had isolated hepatic steatosis. Forty patients (35%) had CFLD including 28 (70%) male patients. Median age at CFLD diagnosis was 10 years. Twenty-one patients (19%) had s-CFLD with a median age of 13 years and median delay to s-CFLD diagnosis was 2 years. Two s-CFLD patients had nodular regenerative hyperplasia, 1 had hepatocellular carcinoma and 4 others underwent liver transplantation. Six patients (5.3%) had ad-CFLD with a median age of 42 years including 1 patient with s-CFLD.
Conclusions : Thirty-five percent of adult CF patients had CFLD in our cohort and 19% had s-CFLD. We used new definition criteria for CFLD and identified ad-CFLD in 6 patients. Better characterization of liver involvement in CF is crucial in order to better target medical care in this population.

- A07 -

PLASMA PROTEIN GLYCOMICS COMBINED WITH CIRCULATING FRAGMENTS OF CYTOKERATIN-18 ARE RELIABLE BIOMARKERS TO DIAGNOSE ALCOHOLIC HEPATITIS.
X. Verhelst (1), A. Geerts (2), L. Meuris (3), H. Degroote (2), M. Tanguy (4), H. Davy (4), T. Issoufaly (4), F. Durand (5), N. Callewaert (3), H. Van Vlierberghe (2), P. Rautou (5) / [1] Ghent University Hospital, Ghent, Belgium, Department of Gastroenteroly and Hepatology, [2] Ghent University Hospital, Ghent, Belgium, Gastroenterology and Hepatology, [3] VIB, Gent, Belgium, VIB-UGent Center for Medical Biotechnology, [4] Université de Paris, France, Centre de recherche sur l'inflammation, Inserm, U1149, CNRS, [5] Hôpital Beaujon – Hôpitaux Universitaires Paris Nord Val de Seine, Clichy, France, Service d'Hépatologie, DHU Unity, DMU Digest.

Introduction : Alcoholic hepatitis (AH) is a severe liver disease with high mortality if left untreated. The hallmark of AH diagnosis remains histologic examination of a liver biopsy specimen. Transjugular liver biopsy being not available in all centers, there is a need for non-invasive biomarkers of AH. We recently showed that circulating fragments of cytokeratin-18, called M65, are higher in patients with HA and identified cut-off values.
Aim : The goal of this study was to assess the plasma N-glycomic profile of patients with HA and determine whether this glycomic profile could allow non-invasive diagnosis of HA in patients with clinical suspicion of this disease.

Methods : Plasma N-glycomic profiles were analysed using DNA sequencer assisted fluorophore assisted carbohydrate electrophoresis (DSA-FACE). This analysis was performed on plasma samples from a prospective cohort of patients with a clinical suspicion of AH (n=87) who underwent a transjugular liver biopsy. An optimal glycomic profile related to the diagnosis of AH was defined using logistic regression analysis.
Results : Out of the 87 patients included (82% male, median age 53), 44 patients had biopsy proven AH. Patients with AH had a different plasma protein glycosylation profile from patients without AH, characterized by increase in branch fucosylated triantennary glycan (NA3Fb), known to be related to acute phase response, and decrease of undergalactosylated glycans (NG1A2FB). A combination of these glycans (log NA3Fb/NG1A2F) was higher in patients with AH than in those without (OR 3.9 (p=0.001; 95% CI 1.8-8.8)). Using -1.0 and - 0.4 as thresholds for this combination of glycans to exclude and diagnose HA respectively, liver biopsy could be avoided in 69% of the patients and 75 % were correctly classified. When restricting the analyses to the 63 patients with a suspicion of severe AH (age, bilirubin, INR, and creatinine (ABIC) score B or C), using the same cut-offs, liver biopsy could be avoided in 65% of patients with a diagnostic accuracy of 81%. Combining the glycomic marker with plasma M65 levels further increased diagnostic accuracy for AH to 97% and could avoid liver biopsy in 55% of patients with ABIC score B or C.
Conclusions : A specific plasma glycomic signature (log NA3Fb/NG1A2F) is strongly associated with the presence of biopsy proven AH in patients with a clinical suspicion of this disease. Combining this glycomic signature with plasma M65 concentration in patients with a suspicion of severe AH can avoid liver biopsy in 55% of the patients, with a high diagnostic accuracy of 97%. These markers can be analysed using routine equipment, facilitating clinical implementation.

- A08 -

LONG-TERM OUTCOME OF SYMPTOMATIC ALCOHOLIC HEPATITIS WITH A MADDREY DISCRIMINANT FUNCTION < 32. D. Degré (1), R. Stauber (2), G. Englebert (3), F. Sarocchi (4), L. Verset (5), F. Rainer (2), W. Spindelboeck (2), H. Njimi (6), E. Trépo (3), T. Gustot (3), C. Lackner (4), P. Deltenre (3), C. Moreno (3) / [1] CUB Hôpital Erasme, Belgium, Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, [2] Medical University of Graz, Austria, Division of Gastroenterology and Hepatology, Department of Internal Medicine, [3] CUB Hôpital Erasme, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, [4] Medical University of Graz, Austria, Institute of Pathology, [5] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Department of Pathology, [6] Université Libre de Bruxelles, Belgium, Biomedical Statistics.

Introduction : Patients with alcoholic hepatitis and a modified Maddrey's discriminant function (mDF) <32 have a low risk of short-term mortality. However, few data exist concerning long-term outcomes.
Aim : The aims of this study were to evaluate 5-year survival rates and to identify predictive factors for long-term prognosis in this patient population.
Methods : We studied patients from 2 centres who were admitted for hepatic decompensation (ascites, hepatic encephalopathy, or jaundice) and who had histological findings of steatohepatitis and an mDF <32. Clinical and biological parameters were recorded at the time of liver biopsy and alcohol consumption was recorded during follow-up. We performed Cox proportional hazard survival analysis to identify factors associated with 5-year survival.
Results : One hundred and twenty-one patients were included (male : 64%, mean age : 51.5±10.3 years, presence of cirrhosis : 84%). The median MELD and mDF scores were 14 [25th-75th percentile : 11.7-16.1] and 19 [25th-75th percentile : 11.1-24], respectively. During follow-up, 30% of the patients remained abstinent. Survival rates at 1, 6, 12, 24, and 60 months were 96.7±1.6%, 90.1±2.7%, 80.8±3.6%, 69.9±4.3%, and 50.7±4.9%, respectively. The majority of deaths (80%) were liver-related. In multivariable analysis, encephalopathy at baseline and alcohol abstinence were predictive of 5-year survival. The 5-year survival rates of patients without and with encephalopathy at baseline were 60.5±5.8% and 29.7±8%, respectively, and the 5-year survival rates of abstinent and non-abstinent patients were 74.8± 8% and 40.9±.8%, respectively.
Conclusions : Mortality of patients with alcoholic hepatitis and an mDF <32 presenting with an acute decompensation is around 50% at 5 years. Hepatic encephalopathy at baseline and lack of alcohol abstinence impair long-term prognosis. New treatment strategies, including measures to ensure abstinence, are required.

- A09 -

THE LINK BETWEEN THE GUT AND THE LIVER DURING EARLY ALCOHOLIC LIVER DISEASE. L. Maccioni (1), B. Pirlot (1), I. Leclercq (1), Y. Horsmans (2), B. Schnabl (3), P. Starkel (2) / [1] Institut de Recherche Expérimentale et Clinique (IREC), Catholic University of Louvain (UCL), Belgium, Laboratory of Hepato-gastroenterology (GAEN), [2] Clin Universitaires St-Luc, UCL, Brussels, Belgium, Department of Hepato-gastroenterology, [3] University of California San Diego (UCSD), San Diego, United States (the), Department of Medicine - Division of Gastroenterology.

Introduction : A minority of patients with alcohol use disorder (AUD) develop progressive alcoholic liver disease (ALD). Animal data suggest that alcohol-induced intestinal barrier dysfunction, dysbiosis and microbial translocation could all contribute to ALD. However, data to support these mechanisms in humans are lacking.

Aim : We assessed the links between ALD severity, intestinal permeability (IP), microbial translocation and the gut immune system in AUD patients.
Methods : Actively drinking AUD patients (n=86) admitted to a rehabilitation program were included. Fasting blood and liver stiffness (kPa)/controlled attenuation parameter (CAP) measurements were obtained at admission and distal duodenal biopsies on the next day. ALD severity was clinically defined as : no liver disease (normal AST, ALT, CAP<250 dB/m, no fibrosis (kPa <6)), steatosis (normal AST, ALT, CAP>250 dB/m, no fibrosis), steato-hepatitis, SH (elevated AST, ALT, CAP>250 dB/m, no fibrosis) and steato-fibrosis, SF (SH and significant fibrosis (kPa >7.6)). IP was assessed using urinary excretion of the radioactive probe 51Cr-EDTA, fecal albumin content and tight junctions' integrity by immunofluorescence in duodenal biopsies. Serum markers for microbial translocation, liver cell damage (cytokeratin18 (CK18-M65)), and intestinal fatty acid binding protein (iFABP) were assessed by ELISA, intestinal gene expression by qPCR and duodenal immune cells by immunohistochemistry/flow cytometry.
Results : Two populations of AUD patients were identified : 60% with normal and 40% with high IP (high urinary 51Cr-EDTA and fecal albumin, disrupted tight junctions). Serum iFABP was normal suggesting no significant enterocyte damage in high IP. Among pro-inflammatory cytokines, only mucosal IL1β mRNA raised in AUD patients compared to controls. Serum microbial gram- (LBP, sCD14) and gram+ (Peptidoglycan-recognition proteins) translocation markers increased in AUD patients but did not correlate with IP or IL1β. LBP and sCD14 rose with progressive ALD confirmed by high CK18-M65 distinguishing simple steatosis from SH/SF (AUROC 0.9221). Elevated mucosal TGFβ mRNA, a potential inducer of immune tolerance, and reduced numbers of gut macrophages and CD8+ T cells, involved in adaptive responses point to an impaired gut immune response in patients with progressive ALD.
Conclusions : In AUD patients, ALD severity is associated with higher microbial translocation independent of increased IP or mucosal inflammation. Impaired gut microbial immune surveillance could play a role.

- A10 -

ROLE OF THE GUT MICROBIOTA IN THE MODULATION OF THE GUT-LIVER-BRAIN AXIS IN ALCOHOL USE DISORDERS : PROOF OF CONCEPT WITH THE FECAL MICROBIOTA TRANSPLANTATION. S. Leclercq (1), T. Le Roy (2), S. Furgiuele (3), V. Coste (2), L. Bindels (2), A. Neyrinck (2), C. Quoilin (4), C. Amadieu (2), V. Tagliatti (3), P. Cani (2), K. Verbeke (5), J. Colet (3), P. Stärkel (6), P. De Timary (4), N. Delzenne (2) / [1] UCLouvain, Belgium, LDRI/MNUT and IoNS, [2] UCLouvain, Belgium, LDRI/MNUT, [3] UMons, Mons, Belgium, Laboratory of Human Biology & Toxicology, [4] UCLouvain, Belgium, IoNS, [5] KU Leuven, Belgium, Translational Research Center in Gastrointestinal Disorders, [6] UCLouvain, Belgium, IREC/GAEN.

Introduction : It is well established that alteration of the gut microbiota composition can disturb many aspects of host physiology, including metabolism, immunity and peripheral and central nervous system with consequences for brain functions and behavior. In a previous study, we showed that alterations of the gut microbiota composition of alcohol-dependent (AD) patients were associated with low scores of sociability, high scores of depression, anxiety and alcohol craving, suggesting the existence of a gut-brain axis in AD patients.
Aim : The aim of the study was to demonstrate the causal role of the gut microbiota in the development of liver and brain alterations associated with alcohol dependence, by using fecal microbiota transplantation.
Methods : The fecal microbiota of AD patients and healthy controls (CT) were transferred into two groups of mice which were subsequently tested for liver metabolism, brain functions and behavior. Metabolomics (H1-NMR) was used to pinpoint key metabolites involved in gut-liver-brain interactions.
Results : We found that mice transplanted with the gut microbiota of AD patients exhibited increased depression-like behavior and decreased social behavior compared to CT-recipient mice. Furthermore, AD-recipient mice showed alterations of brain myelination, neurotransmission and neuroinflammation. Metabolomics analysis revealed, in AD-recipient mice, elevated ethanol concentration in the portal vein and decreased plasma levels of a ketone body, the b-hydroxybutyrate (BHB), which was consistent with a reduced expression of the liver enzyme Hmgcs2, the main control point of ketogenesis. Exposition of mice to a ketogenic diet had beneficial effect on social behavior and brain functions, thereby supporting the hypothesis that BHB is a key metabolite in the gut-liver-brain axis. The involvement of these two metabolites, ethanol and BHB, and their links with the psychological symptoms were confirmed in a cohort of AD patients.
Conclusions : The results of this study confirm the production of ethanol by intestinal bacteria that consequently impacts liver and brain metabolism and reinforce the existence of a gut-liver-brain axis in alcohol use disorders. Modification of the gut microbiota composition, through nutritional approaches, might be helpful in the management of alcohol-dependent patients.

- A11 -

MYOSTEATOSIS IS ASSOCIATED WITH EARLY NASH IN THE CONTEXT OF OBESITY AND METABOLIC SYNDROME. M. Nachit (1), G. Vande Velde (2), W. Kwanten (3), O. Schakman (4), J. Thissen (5), M. De Rudder (1), C. Bouzin (6), B. Op De Beeck (7), Y. Horsmans (8), L. Van Gaal (9), S. Francque (3), I. Leclercq (1) / [1]

UCLouvain, Belgium, Institut De Recherche Expérimentale Et Clinique, Laboratory of Hepato-Gastroenterology, [2] KU Leuven, Belgium, Department of Imaging and Pathology, [3] Antwerp University Hospital, Belgium, Department of Gastroenterology and Hepatology, [4] UCLouvain, Belgium, Institute of Neuroscience, Laboratory of Cell Physiology, [5] UCLouvain, Belgium, Institut De Recherche Expérimentale et Clinique, Endocrinology, Diabetology, and Nutrition Department, [6] UCLouvain, Belgium, IREC Imaging Platform, [7] Antwerp University Hospital, Belgium, Department of Radiology, [8] Cliniques universitaires Saint-Luc, Brussels, Belgium, Service d'hépato-Gastro-Entérologie, [9] Antwerp University, Belgium, Laboratory of Experimental Medicine and Pediatrics - Division of Endocrinology.

Introduction : A substantial body of literature supports that a low muscle mass, low strength or a higher muscle fatty infiltration are associated with NAFLD presence and severity. However, whether these muscle alterations are mere consequences of NASH, whether changes in the muscle compartment might be a signature of hepatocellular damages and inflammation, and whether these changes might play a pathophysiological role in NAFL to NASH transition remain hypothetical.
Aim : To investigate muscle changes in correlation with liver disease progression in NAFLD rodent models and in a human cohort.
Methods : For over 34 weeks, we followed WT mice fed a standard chow as controls (Ctl), WT mice fed a high fat (HF) diet (60% fat) as a model of simple steatosis (WT HF) and foz/foz mice fed a HF diet as a model of progressive NASH (FOZ HF). We developed and validated a novel preclinical micro-Computed Tomography (micro-CT) based methodology to prospectively study skeletal muscle mass and fatty infiltration in muscle and liver in a high-throughput and non-invasive manner. We used grip strength test to evaluate muscle functionality and analyzed liver histology at monthly intervals. We used CT to measure skeletal muscle mass and fatty infiltration retrospectively in a large cohort of 197 morbidly obese patients with biopsy proven NASH (n=117, 62.4%), NAFL (n=35, 18.9%) or normal liver histology (n=33, 17.8%). All data are mean±SEM.
Results : WT ND mice had normal liver histology at all times; WT HF mice developed modest steatosis at late time points; all FOZ HF had NAS >5 as from W12, with minimal fibrosis at W20 and patent pericellular fibrosis at W34. In FOZ HF with NASH, muscle mass dissociated from body weight gain. The relative decrease in muscle mass was associated with severe loss of muscle strength from W12 on (Ctl : 244±4g; WT HF : 251.9±6g vs FOZ HF : 228.6±4g) which further worsened with time (165.2±5.2g at 34W in FOZ HF). This was not seen in the other groups. Myosteatosis was the earliest muscular change as reflected by a significantly lower muscle density in FOZ HF as early as 4 week (0.79±0.02) when compared to Ctl (0.91±0.02) and reached a minimum at 12W (0.37±0.05 in FOZ HF vs 0.85±0.02 and 0.75±0.02 in Ctl and WT HF) then plateaued. Myosteatosis severity in FOZ HF, unexplained by body weight gain, was strongly correlated with NAS score ($r=-0.87$, $n=67$, $p<0.001$), irrespectively of the time point studied. Importantly, myosteatosis powerfully discriminated NASH from isolated steatosis or normal liver (AUROC = 0.96, $p<0.001$) in this model. In a large population of 185 morbidly obese patients, the CT-based psoas density index (reflecting myosteatosis) was significantly lower ($p<0.01$) in patients with NASH F-0,1 (1.44±0.03) and NASH F2+ (1.41±0.08) than in those with isolated steatosis (1.69±0.05) or normal liver histology (1.74±0.04). PDI identified patients with biopsy proven NASH amongst those with uncomplicated steatosis and normal liver histology with a good diagnostic performance (AUROC = 0.74, $p<0.001$), outperforming classical biomarkers such as FIB4, NFS and CK18 (AUROC = 0.57, 0.52 and 0.55 respectively). Furthermore, PDI and ALT levels were the only independent factors predicting NASH in a multivariate statistical model with associated AUROC of 0.81 ($p<0.001$).
Conclusions : Our data support that in NAFLD, hepatocellular damage and inflammation that characterize progression to NASH associate with myosteatosis. This observation paves the way for the exploitation of myosteatosis as a non-invasive marker of NASH and suggesting a muscle-liver reciprocal crosstalk during liver disease progression.

- A12 -

HEPATITIS E VIRUS GENOTYPE 3 SUBTYPE DEPENDENT CLINICAL OUTCOMES IN BELGIUM 2010-2018.
T. De Somer (1), M. Peeters (2), S. Klamer (3), F. Nevens (4), J. Delwaide (5), P. Stärkel (6), P. Willems (7), S. De Maeght (8), C. Moreno (9), M. Van Hoof (10), I. Colle (11), F. Sermon (12), C. Van Steenkiste (13), F. Janssens (14), J. Van Acker (15), A. Marot (16), E. Bottieau (17), M. Reynders (18), C. De Galocsy (19), L. Lasser (20), M. Steverlynck (21), J. Maus (22), W. Verlinden (23), A. Geerts (24), M. Gallant (25), S. Van Outryve (26), H. Reynaert (27), J. Mulkay (28), J. Decaestecker (29), V. Suin (2), S. Negrin-Dastis (30), S. Van Gucht (2), T. Vanwolleghem (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology & Hepatology, [2] Sciensano, Brussels, Belgium, National Reference Centre of Hepatitis Viruses, Viral Diseases, Infectious Diseases in Humans, [3] Sciensano, Brussels, Belgium, Epidemiology of Infectious Diseases, [4] UZ Leuven, Leuven, Belgium, Gastroenterology & Hepatology, [5] CHU of Liège, Belgium, Gastroenterology & Hepatology, [6] Cliniques universitaires Saint-Luc, Brussels, Belgium, Gastroenterology & Hepatology, [7] Sint Augustinus Ziekenhuis GZA, Antwerp, Belgium, Clinical Biology, [8] Centres Hospitaliers Jolimont, Belgium, Gastroenterology & Hepatology, [9] Hopital Erasme, ULB, Belgium, Gastroenterology & Hepatology, [10] Clinique Saint-Luc Bouge, Namur, Belgium, Gastroenterology & Hepatology, [11] ASZ, Aalst, Belgium, Gastroenterology & Hepatology, [12] OLV Aalst, Aalst, Belgium, Gastroenterology & Hepatology, [13] AZ Maria Middelares, Ghent, Belgium, Gastroenterology & Hepatology, [14] Jessa Ziekenhuis, Hasselt, Belgium, Gastroenterology

& Hepatology, [15] AZ Sint-Lucas, Ghent, Belgium, Clinical Microbiology, [16] CHU UCL Namur, Yvoir, Belgium, Gastroenterology & Hepatology, [17] Institute of Tropical Medicine Antwerp, Antwerp, Belgium, Internal Medicine Infectious Diseases, [18] AZ Sint-Jan Brugge-Oostende, Brugge, Belgium, Medical Microbiology, [19] Hôpitaux Iris Sud, Brussels, Belgium, Gastroenterology & Hepatology, [20] CHU Brugmann, Brussels, Belgium, Gastroenterology & Hepatology, [21] CENTRE HOSPITALIER MOUSCRON, Mouscron, Belgium, Gastroenterology & Hepatology, [22] ZNA Middelheim, Antwerpen, Belgium, Gastroenterology & Hepatology, [23] AZ Nikolaas, Sint-Niklaas, Belgium, Gastroenterology & Hepatology, [24] UZGent, Gent, Belgium, Gastroenterology & Hepatology, [25] Jan Yperman Hospital, Ieper, Belgium, Gastroenterology & Hepatology, [26] GZA Sint-Vincentius ziekenhuis, Antwerpen, Belgium, Gastroenterology & Hepatology, [27] UZBrussel, Brussel, Belgium, Gastroenterology & Hepatology, [28] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology & Hepatology, [29] AZ Delta, Roeselare, Belgium, Gastroenterology & Hepatology, [30] Grand Hôpital de Charleroi, Charleroi, Belgium, Gastroenterology & Hepatology.

Introduction : Hepatis E Virus (HEV) infections are emerging in the Western civilization with a predominance of HEV genotype 3 (gt3). Except for immunosuppression, male gender, age older than 50 years and chronic liver disease, no correlators with clinical outcomes of a HEV gt3 infection have been identified. In Belgium, diagnosis of HEV is centralized at the National Reference Center (NRC) for Viral Hepatitis, Sciensano.
Aim : We analyzed virological factors and clinical outcomes in a nationwide cohort of HEV patients in Belgium with the aim of finding other correlators with clinical outcomes.
Methods : Demographic, clinical and biochemical parameters of HEV infections documented at the NRC Sciensano between 2010 and 2018 were collected. Serum HEV-IgM, -IgG and HEV RNA were determined by ELISA and RT qPCR. HEV was subtyped by Sanger sequencing of an ORF2 fragment. Odds ratios (OR), risk ratios (RR) and 95% confidence intervals (95% CI) were calculated using STATA.
Results : 402 cases were identified. Among 300 cases with clinical data, the median age was 57 years and 69% of patients were males. HEV viremia was detected in 211 patients with a genotype identified in 177 patients. HEV gt3 infections largely predominate (93% [165/177]) with subtypes 3c (38% [67/177]) and 3f (44% [78/177]) almost equally represented. The percentage of immunocompromised patients was higher for patients infected with a virus from the clade of gt3c (achi), compared to a virus from the clade of gt3f (efg) (30% vs 16%; OR3c=2.2 [1.0-4.7] p=0.045). A similar, however non-significant trend was observed for patients with pre-existing liver cirrhosis (9.9% vs 3.4%; OR3c=3.1 [0.8-12.5]). Biochemically, patients with a HEV gt3f infection had higher ALT peak values and higher peak bilirubin values compared to patients with a HEV gt3c infection (respectively mean of 2199 vs 1528 U/L; p=0.005 and mean of 8.6 vs 4.1 mg/dl; p=0.001). In addition, patients with a HEV gt3c infection were treated more frequently in ambulatory care settings compared to patients with a HEV gt3f infection. The percentage of patients admitted to the hospital was higher for patients with a HEV gt3f infection compared to patients with a HEV gt3c infection (61% vs 36%; RR3f=1.7 [1.2-2.4] p=0.003). There were no differences between the subtypes in intensive care unit admissions (5.7%), in hospitalization durations (median of 4.0 weeks), in chronicity (18% vs 14%, RR3f=0.8 [0.4-2.0]), nor in deaths (1.4% vs 4.8%; RR3f=3.4 [0.4-30]).
Conclusions : A similar number of HEV gt3c and gt3f infections have been diagnosed in Belgium. Despite more pre-existing comorbidity in patients infected with HEV gt3c, HEV gt3f infections are associated with a more severe disease course according to laboratory values and hospitalization rates. Our nationwide analysis is the first to identify a correlation between HEV gt3 subtype and clinical outcomes.

- A13 -

TRANSCRIPTOME PROFILING OF LIVER BIOPSIES BEFORE ANTIVIRAL TREATMENT START CAN PREDICT HCC DEVELOPMENT 8.3 YEARS BEFORE CLINICAL DIAGNOSIS IN CHRONIC HEPATITIS B AND C PATIENTS.

S. Van Hees (1), B. Cuypers (2), S. Bourgeois (3), K. Kreefft (4), D. Sprengers (5), G. Robaeys (6), P. Meysman (2), L. Vonghia (1), P. Michielsen (1), S. Francque (1), R. De Man (4), A. Driessen (7), A. Boonstra (4), K. Laukens (2), T. Vanwolleghem (1) / [1] Antwerp University Hospital, Belgium, Department of Gastroenterology and Hepatology, [2] Antwerp University, Belgium, Department of Mathematics and Computer Science, [3] ZNA Stuivenberg, Borgerhout, Belgium, Department of Gastroenterology and Hepatology, [4] Erasmus Medical Center, Rotterdam, Netherlands (the), Department of Gastroenterology and Hepatology, [5] GZA Antwerp, Belgium, Department of Gastroenterology and Hepatology, [6] Hospital East-Limburg, Belgium, Department of Gastroenterology and Hepatology, [7] Antwerp University Hospital, Belgium, Department of Pathology.

Introduction : An accurate prediction of Hepatocellular Carcinoma (HCC) development in Chronic Hepatitis B (CHB) and C (CHC) patients is currently impossible.
Aim : In this study we explored pre-antiviral treatment liver transcriptome profiles of CHB and CHC patients with and without HCC development during long-term follow-up and investigated their potential to predict future HCC development.
Methods : HCC developing cases (n = 34) were identified through retrospective chart review of all CHB and CHC patients with an available pre-antiviral treatment liver biopsy from 5 large Hepatology clinics. Cases were split in 4

subgroups based on infecting virus (HBV/HCV) and cirrhosis status (yes/no) at baseline liver biopsy. Each subgroup of cases was matched for different demographic (e.g. gender and age at biopsy) and clinical (e.g. cirrhosis at biopsy and infecting virus) factors to a group of controls without HCC development during an equal or longer follow-up time. RNA derived from baseline biopsies (total n = 72) was sequenced. Differentially Expressed Genes (DEG; FC > 1.5 and q < 0.2) were called in each subgroup and a random forest classifier was trained to predict HCC development.
Results : The total cohort consisted of 72 patients, of whom 34 developed a HCC at a median of 8.3 years after liver biopsy. Despite perfect matching for clinical and demographic characteristics, at least 452 DEG were found between cases and controls in each subgroup. Among the top 20 up- and down-regulated genes in each subgroup, 40-75 % has previously been linked to oncogenesis, underlining the biological relevance. Ingenuity Pathway Analysis showed an enrichment for the "Wnt-beta catenin signaling" pathway in the cirrhotic CHB group and the "molecular mechanisms of cancer" pathway in the non-cirrhotic CHC group. These results strongly suggest a genetic imprint for HCC development several years before clinical diagnosis. A random forest classifier tested with leave-one-out-cross-validation was able to predict HCC development with an accuracy of 84.7 %, a Negative Predictive Value of 92.1 % and a Positive Predictive Value of 75.8 % based on the subgroup and baseline expression levels of 20 genes, of whom several have previously been linked to hepatocarcinogenesis.
Conclusions : Pre-antiviral treatment liver biopsies of chronic hepatitis B and C patients show a genetic imprint for future HCC development that allows to accurately predict HCC development 8.3 years before clinical diagnosis.

- A14 -

UNLIKE HBA1C LEVEL AND THE AMOUNT OF VISCERAL ADIPOSE TISSUE, THE PRESENCE AND SEVERITY OF NAFLD DO NOT PREDICT THE OCCURRENCE OF MAJOR ADVERSE CARDIOVASCULAR EVENTS IN AN OBESE BELGIAN POPULATION. M. Van Herck (1), C. Conrad (2), S. Kleevens (2), C. De Block (3), E. Dirinck (3), L. Van Gaal (3), A. Verrijken (3), V. Segers (4), E. Van Craenenbroeck (4), A. Driessen (5), P. Michielsen (2), T. Steinhauser (6), T. Vanwolleghem (2), J. Weyler (2), L. Vonghia (2), S. Francque (2) / [1] University of Antwerp, Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology and Hepatology, [2] University of Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology and Hepatology, [3] University of Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Endocrinology, [4] Antwerp University Hospital, Belgium, Cardiology, [5] Antwerp University Hospital, Belgium, Pathology, [6] Antwerp University Hospital, Belgium, Gastroenterology and Hepatology.

Introduction : Cardiovascular disease is the most important cause of morbidity and mortality in non-alcoholic fatty liver disease (NAFLD) patients.
Aim : The present study aimed at determining the predictive value of NAFLD grade at baseline, as well as other clinical parameters, with respect to the occurrence of major adverse cardiovascular events (MACE) during follow-up.
Methods : Patients who consulted the metabolic unit of the Antwerp University Hospital between 2006-2012 and underwent a liver biopsy because of a clinical suspicion of NAFLD, were included consecutively with informed consent. The FLIP algorithm was used to define NAFLD grade : no NAFLD, non-alcoholic fatty liver (NAFL), non-fibrotic non-alcoholic steatohepatitis (NASH, less than F2) and fibrotic NASH (F2 or greater). MACE were defined as the occurrence of stroke, (non) ST elevation myocardial infarction [(N)STEMI)] or unstable angina. The occurrence of MACE was examined by reviewing the in-hospital and the nation-wide accessible electronic patient files. Statistical analysis was performed using Cox regression.
Results : 323 patients (M :F 99 :224) were included with a mean age of 44 ± 12 y and a mean BMI of 39.5 ± 6.4 kg/m². Liver biopsy demonstrated no NAFLD in 69, NAFL in 93, non-fibrotic NASH in 126 and fibrotic NASH in 35 patients. Glucose tolerance testing was normal in 187, impaired in 109 and showed a new diagnosis of type 2 diabetes in 27 patients. The mean blood pressure was 128 ± 14 / 76 ± 9 mmHg and 31 % of patients were being treated for arterial hypertension. Cholesterol, HDL and triglyceride levels were 204 ± 41, 49 ± 14 and 153 ± 80 mg/dL resp. and 10 % of patients were on statin treatment. 47 % of patients had an active smoking habit. Over a mean follow-up period of 4.6 ± 3.6 y, MACE were registered in 10 patients (2 no NAFLD, 2 NAFL, 4 non-fibrotic NASH and 2 fibrotic NASH). NAFLD grade did not show predictive value with respect to the occurrence of MACE (p=0.799). In contrast, baseline HbA1c level and the amount of visceral adipose tissue, as assessed by computed tomography, were found to be strong predictors [resp. HR 4.741 per % (95% CI 1.515-14.651), p=0.007 and HR 1.010 per cm2 (95% CI 1.003-1.017), p=0.003]. Conversely, no predictive value was shown for cholesterol, HDL or triglyceride levels, nor for sex or smoking habit. Concerning the systolic blood pressure, although no significant predictive value was demonstrated with respect to MACE, significance was reached with respect to the subgroup of acute coronary syndrome patients (n=7), comprising unstable angina and (N) STEMI [HR 1.058 per mmHg (95% CI 1.015-1.103), p=0.008].
Conclusions : In this population of obese patients, NAFLD grade was not shown to be a significant predictor of the occurrence of MACE during a mean follow-up period of 4.6 y. Conversely, the HbA1c level and the amount of visceral adipose tissue were strong predictors, underlining the importance of insulin resistance and central obesity in the development of cardiovascular disease.

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DO PATIENTS WITH NAFLD HAVE AN INCREASED INCIDENCE OF CARDIOVASCULAR COMPLICATIONS AFTER LIVER TRANSPLANTATION? J. Van Herck (1), L. Verbeke (2), J. Verbeek (3), C. Verslype (3), W. Laleman (3), H. Van Malenstein (3), D. Cassiman (3), S. Van Der Merwe (3), I. Jochmans (4), M. Sainz Barriga (4), D. Monbaliu (4), J. Pirenne (4), F. Nevens (3) / [1] KU Leuven, Belgium, Medicine, [2] AZ Sint-Maarten, Mechelen, Belgium, Gastroenterology, [3] UZ Leuven, Leuven, Belgium, Gastroenterology and Hepatology, [4] UZ Leuven, Leuven, Belgium, Abdominal Transplantation Surgery.

Introduction : Patients with non-alcoholic fatty liver disease (NAFLD) have several risk factors for cardiovascular morbidity. Post-LTX immunosuppression increases cardiovascular mortality.
Aim : We investigated the post-LTX morbidity and mortality in pts transplanted for NAFLD.
Methods : The study population consisted of 232 LTX pts : 112 NAFLD pts and a control group of 120 hepatitis C (HCV) pts. Data collection consisted of metabolic risk factors, recurrence of NAFLD, cardiovascular diseases (coronary artery disease, stroke, atrial fibrillation, heart failure) and death.
Results : At the moment of LTX there were no differences in age, gender and pack years of smoking. NAFLD patients were slightly older (63 vs 61 y), had a higher MELD (16 vs 13) and fewer HCC (46% vs 63%). NAFLD became only recently a frequent indication for LTX and the post-LTX follow-up was shorter (median 6 vs 13 y). NAFLD pts had pre-LTX higher BMI (30 vs 26), more diabetes (DM) (64% vs 28 %), arterial hypertension (70% vs 25%) and dyslipidemia (33% vs 6%). They had a higher pre-LTX total cardiovascular morbidity (24% vs 12%). There was no difference in the 6 wks postoperative mortality (1,7% vs 2,5%). Differences during post-LTX follow-up were : BMI (29,5 vs 25,5), DM (73% vs 42%) and dyslipidemia (57% vs 35%). The incidence of post-LTX NAFLD was significantly higher in NAFLD pts (43% vs 8%) ($p < 0,0001$). The cardiovascular morbidity was slightly higher in the NAFLD group (12.8 vs 9.3 % at 5 y, $p=0,03$), although there was no difference in the overall survival between the 2 groups, both in the total group nor in pts without HCC at baseline.
Conclusions : Cirrhosis due to NAFLD is a rapidly growing indication for LTX. These pts have a high pre- and postoperative cardiovascular risk profile. However, there is no difference in the immediate postoperative mortality. There is an important recurrence rate of NAFLD after LTX. At 5 y there is a slightly increased cardiovascular morbidity, but this did not result in a higher overall mortality.

- A16 -

ALCOHOLIC LIVER DISEASE AND LIVER TRANSPLANTATION IN PATIENTS WITH PRIOR BARIATRIC SURGERY. L. STROOBANT (1), A. VANLANDER (2), F. BERREVOET (2), X. VERHELST (1), Y. VAN NIEUWENHOVE (3), X. ROGIERS (2), H. VAN VLIERBERGHE (1), A. GEERTS (1), S. LEFERE (1) / [1] Ghent University, Ghent, Belgium, Gastroenterology and Hepatology, Hepatology Research Unit, [2] Ghent University, Ghent, Belgium, General and Hepatobiliary Surgery, [3] Ghent University, Ghent, Belgium, Gastrointestinal Surgery.

Introduction : Bariatric surgery (BS) is an effective therapeutic option for severe obesity, yet recent studies have indicated that patients with prior BS, mainly Roux-en-Y gastric bypass, are at increased risk for developing alcohol use disorder. However, whether these patients also develop alcoholic liver disease (ALD), with progression to end-stage liver disease and a need for liver transplantation (LT), has not been described.
Aim : Investigate the occurrence and severity of ALD following BS in a cohort of patients undergoing LT evaluation.
Methods : We performed a single-center retrospective cohort study on patients listed for LT due to ALD at the Ghent University Hospital between 2008 and 2018. We compared the clinical, demographic and biochemical characteristics as well as survival of patients with and without a history of BS. Patients with concurrent liver diseases, as well as patients who underwent weight loss surgery less than one year before diagnosis of liver disease were excluded.
Results : We included 11 patients with and 177 patients without a history of BS in this analysis. Liver cirrhosis was diagnosed after a median of 7.4 years following weight loss surgery. BS patients were younger (median 45 versus 60 years, $P<0.0001$) with a female predominance (72.7% versus 22.0%, $P<0.001$). Notably, the liver function was impaired to a greater degree in those having undergone BS, as evidenced by a higher MELD score (median 26 versus 17, $P = 0.0003$), INR (2.30 versus 1.51, $P = 0.001$) and serum bilirubin (4.90 versus 2.48, $P = 0.053$). The timeframe between diagnosis, listing and LT was significantly shorter in patients with prior BS. Conversely, hepatocellular carcinoma was less prevalent (9.1% versus 51.1%, $P=0.007$). After transplantation, the incidence of postoperative complications and 3-year survival rate (90% (95%CI 71.4%-100%) in BS patients versus 83.7% (95%CI 77.6%-89.8%) in the concurrent cohort, $P=0.274$) were similar. A sensitivity analysis showed that neither exclusion of patients with HCC nor matching by age and gender affected the main results. Similarly, the type of BS surgery (6 out of 11 patients had undergone a Roux-en-Y gastric bypass) had no impact on the main study variables.
Conclusions : Alcohol use disorder after BS can progress to end-stage liver disease. These patients were younger and developed more acutely decompensated disease than those without prior BS. Survival after LT is comparable to ALD patients without a history of BS. These results urge further study in this area.

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EFFICACY OF ENTEROSCOPY-ASSISTED ERCP IN LIVER TRANSPLANT PATIENTS WITH ROUX-EN-Y RECONSTRUCTION AND SUSPECTED BILE DUCT PATHOLOGY. T. Moreels (1), P. Deprez (1), G. Dahlqvist (1), B. Delire (1), L. Coubeau (2), O. Ciccarelli (2), E. Bonaccorsi Riani (2), P. Goffette (3), E. Sokal (4), H. Piessevaux (1) / [1] Cliniques universitaires Saint-Luc, Brussels, Belgium, Hépato-Gastroentérologie, [2] Cliniques universitaires Saint-Luc, Brussels, Belgium, Transplantation abdominale, [3] Cliniques universitaires Saint-Luc, Brussels, Belgium, Radiologie, [4] Cliniques universitaires Saint-Luc, Brussels, Belgium, Gastroentérologie & Hépatologie Pédiatrique.

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 enteroscopy-assisted ERCP to evaluate and treat biliary complications in liver transplant patients with Roux-en-Y reconstruction.
Methods : Between 2016 and 2019 all enteroscopy-assisted ERCP procedures in liver transplant patients were analysed for indications and ERCP technical success and complication rates. Clinical success was measured by the evolution of liver function tests (without other interventions). Enteroscopy-assisted ERCP was performed using different types of single-balloon enteroscopes (SBE).
Results : A total of 32 patients (25 males) with a mean age of 42±3 years (range 16-81) underwent 51 enteroscopy-assisted ERCP procedures. Indications were suspicion of anastomotic stricture (53%), cholangitis (31%), bile duct stones (10%), biliary leak (3%) and sepsis of unknown origin (3%). Technical ERCP success rate per patient was 81.25% (26/32). Failure was due to inability to reach the hepaticojejunal anastomosis. ERCP was normal in 10/26 (39%), confirmed the anastomotic stricture in 9/26 (35%), bile duct stones in 5/26 (19%) and biliary leak and an indwelling metallic stent both in 1/26 (4%). 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 with a median number of 1 procedure. Only minor adverse events (self-limiting cholangitis) were encountered in 4/32 patients (12,5%). Of all 51 ERCP procedures, 49% were considered easy, 27% were difficult or very difficult (8%) and 17% were impossible. Technical success rate was highest when the prototype XSIF-180JY SBE was used (100% for 14 procedures) and lowest with the commercially available SIF-Q180 SBE (50% for 6 procedures). Clinical success of therapeutic ERCP was measured by the evolution of biliary liver function tests before the start of the ERCP procedure, 1 day after and 30 days after the last 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 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. Enteroscopy-assisted ERCP may be considered as an alternative to PTC to evaluate and treat the biliary system in these patients.

- A18 -

MYELOID IRE1A DELETION ALTERS HEPATIC MACROPHAGE PHENOTYPE AND ATTENUATES EXPERIMENTAL NON-ALCOHOLIC STEATOHEPATITIS-RELATED HEPATOCELLULAR CARCINOMA. S. Van Campenhout (1), L. Tilleman (2), S. Lefere (1), A. Vandierendonck (1), A. Geerts (1), X. Verhelst (1), F. Van Nieuwerburgh (2), H. Van Vlierberghe (1), L. Devisscher (3) / [1] Ghent University, Ghent, Belgium, Internal Medicine and Pediatrics, [2] Ghent University, Ghent, Belgium, Pharmaceutics, [3] Ghent University, Ghent, Belgium, Basic and Applied Medical Sciences.

Introduction : Obesity, diabetes and associated non-alcoholic steatohepatitis (NASH) are characterized by adipose tissue and hepatic fat accumulation and inflammation and are rising causes of hepatocellular carcinoma (HCC). Macrophages are important immune cells involved in inflammation and tumour development. Inositol-requiring enzyme 1 alpha (IRE1a) has shown to be involved in macrophage cytokine production and myeloid-specific IRE1a knock-out (mKO) mice showed reduced weight gain during high fat diet feeding. However, the effect of myeloid-specific IRE1a deletion on NASH and subsequent HCC development has not been examined.
Aim : Here, we investigated the effect of myeloid-specific IRE1a deletion on experimental NASH-HCC development. Furthermore, the liver macrophage population was characterized during disease development.
Methods : Mice with non-functional myeloid IRE1a were created by crossing IRE1a floxed mice with LysM-Cre mice. Two-day old mKO and wild type (WT) mice were subcutaneously injected with streptozotocin (STZ) or PBS as control and male mice were fed a high-fat, -sucrose, -cholesterol diet (Western diet, WD) or control diet from the age of 4 weeks until 21 weeks. Mice were evaluated for obesity, diabetes, NASH and HCC. The macrophage population was evaluated by flow cytometry and RNA sequencing on FACS isolated cells.

Results : STZ+WD feeding resulted in impaired glucose tolerance, advanced NASH with fibrosis and HCC development. mKO STZ mice showed lower fasting glucose levels at the start of WD feeding, and an improved glucose tolerance and attenuated HCC development after 17 weeks of WD feeding despite a similar degree of liver steatosis and inflammation compared to WT mice. Transcriptomic analysis of liver Kupffer cells (KCs), macrophages and monocytes revealed phenotypical changes in NASH-HCC. Myeloid IRE1a deletion in healthy mice resulted in an altered transcriptomic profile with downregulation of pathways involved in immune system activation in KCs and macrophages, downregulation of metabolic pathways in KCs, whereas pathways involved in cell division and metabolism were upregulated in monocytes. Macrophages showed both up- and downregulated metabolic pathways. NASH-HCC attenuated the differential gene expression profile of mKO and WT liver isolated macrophages.
Conclusions : Our results show that myeloid-specific IRE1a deletion results in an altered transcriptional profile of hepatic macrophages and attenuates diabetes induction and NASH-related HCC development.

- A19 -

ACTIVE NON-ALCOHOLIC STEATOHEPATITIS AND SEVERE FIBROSIS ARE ASSOCIATED WITH DYSFUNCTIONAL ADIPOSE TISSUE AND WORSEN WITH MORE SEVERE ADIPOSE TISSUE INSULIN RESISTANCE INDEPENDENTLY OF BODY MASS INDEX. L. Vonghia (1), M. Gaggini (2), A. Verrijken (3), J. Weyler (1), F. Carli (2), B. Patricio (2), W. Kwanten (1), T. Vanwolleghem (1), E. Dirinck (3), A. Driessen (4), L. Van Gaal (3), S. Francque (1), A. Gastaldelli (2) / [1] Antwerp University Hospital, Belgium, Department of Gastroenterology and Hepatology, [2] Institute of Clinical Physiology, CNR, Pisa, Italy, Pisa, Italy, Cardiometabolic Risk Unit, [3] Antwerp University Hospital, Belgium, Department of Endocrinology, Diabetology and Metabolic Diseases, [4] Antwerp University Hospital, Belgium, Department of Pathology.

Introduction : Adipose tissue act as an endocrine organ that influences the metabolism by releasing adipokines, proinflammatory factors and free fatty acids (FFA), which contribute to insulin resistance (IR). Non-alcoholic fatty liver disease (NAFLD) occurs in the setting of IR due to increased delivery of free fatty acids (FFA) from peripheral lipolysis and de novo lipogenesis while clearance of hepatic FFA is through mitochondrial beta-oxidation, the dominant oxidative pathway, or by triglycerides (TG) secretion in plasma.
Aim : We explored whether adipose tissue insulin resistance (adipo-IR, which measures the impaired suppression of lipolysis in the presence of high insulin levels), plasma FFA, TG and beta-hydroxybutyrate (BOH) (that reflects liver FFA oxidation) concentrations were associated to the severity of Non-alcoholic steatohepatitis (NASH).
Methods : A large cohort of consecutively recruited patients with liver biopsy (n=211) were included in the study and characterised for presence of glucose intolerance (IGT) or diabetes (T2D) by oral glucose tolerance test. We measured plasma FFA, BOH, lipid profile, Adipo-IR (FFAxInsulin) and fat distribution by CT. Data were analysed by logistic multivariable analysis (LMA) adjusted for age, BMI, presence of IGT/T2D and odd ratios (OR) were calculated.
Results : Liver histology was as follows : 55 no NAFLD, 34 non-alcoholic fatty liver (NAFL) and 122 NASH. TG (128±5 vs 141±8 vs 176±7 mg/dL) and Adipo-IR (9.0±0.7 vs 10.6±1,1 vs 13.5 ±0.9 mmol/l*pmol/l) increased ($p<0.008$) from noNAFL, NAFL to NASH. Visceral fat was increased similarly in NAFL (218±15 cm2) and NASH (196±6 cm2) compared to noNAFL (139±8 cm2, $p<0.0001$), while Body mass index (BMI), subcutaneous fat, BOH and FFA were similar in the 3 groups. Presence of NASH was associated with increased Adipo-IR (OR=2.5, CI 1.5-4.5, p=0.0005) after adjusting for age, BMI, IGT/T2D. In case of increased necro-inflammation (ie “active NASH”, the sum of ballooning and lobular inflammation ≥3) the OR was 2.6 (CI 1.4-4.7, p=0.003). There was no independent association of FFA, BOH or TG. Moreover, NASH with severe fibrosis (F2-F4) had a much higher Adipo-IR (18.7±4.1 mmol/l*pmol/l) vs NASH F0-1 (12.2+0.7 mmol/l*pmol/l), NAFL (10.6±1.1 mmol/l*pmol/l) and noNAFL (8.6±0.8 mmol/l*pmol/l, $p<0.001$). In NASH with severe fibrosis (F2-4) the association with Adipo-IR had an OR=3.3 (CI 1.4-8.0, p=0.003) adjusted for age, BMI, IGT/T2D.
Conclusions : Increased adipo-IR was significantly associated to presence of active NASH and severe fibrosis independently of BMI, showing the importance of dysfunctional adipose tissue as a main target in this disease.

- A20 -

MUSCLE FAT INFILTRATION IN OBESE PATIENTS IS ASSOCIATED WITH NAFLD RELATED FIBROSIS SEVERITY – RESULTS FROM A PROSPECTIVE BODY COMPOSITION AND IMAGING STUDY. N. Lanthier (1), S. Hiel (2), M. Nachit (3), J. Rodriguez (4), J. Thissen (5), P. Trefois (6), N. Delzenne (4) / [1] Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium, Service d’Hépato-Gastroentérologie, [2] UCLouvain, Belgium, Metabolism and Nutrition Research Group, Louvain Drug Research Institute,, [3] UCLouvain, Belgium, Laboratory of Gastroenterology and Hepatology, Institut de Recherche Expérimentale et Clinique, [4] UCLouvain, Belgium, Metabolism and Nutrition Research Group, Louvain Drug Research Institute, [5] Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium, Service d’Endocrinologie, [6] Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium, Department of Radiology.

Introduction : The association between NAFLD and visceral adipose tissue or sarcopenia has been reported, although results are discordant.
Aim : The goal of this study is to analyze the spectrum of NAFLD among obese patients recruited prospectively and to detect clinical, biological and imaging data associated with steatosis or fibrosis.
Methods : Baseline data of obese patients (BMI ≥ 30) randomized in a single center (Food4Gut study) were included. Transient elastography (TE) was done to quantify both liver steatosis by controlled attenuation parameter (CAP) measurement and liver fibrosis by liver stiffness measurement (LSM). Body composition was evaluated using bioelectrical impedance analysis. Subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), muscle areas and muscle fat infiltration were measured on CT-scan images at the third lumbar level.
Results : Fifty-two Caucasian patients (mean age : 50 years, 50 % male, mean BMI 35.8) were included. TE was successful in 49 patients (94%). XL probe was used in 20 patients (38%). Mean LSM was low (6.5 kPa). Mean CAP result was high (324 dB/m) with the majority of the patients (73%) presenting severe steatosis (CAP ≥ 296 dB/m). 12 patients (24%) had advanced fibrosis defined by LSM ≥ 7.8 kPa (M probe) or ≥ 6.4 kPa (XL probe). Compared to patients with discrete or moderate steatosis, patients with severe steatosis had higher ALAT values (45.3 vs 28.1 UI/L, $p<0.01$) and fasting blood glucose levels (109.2 vs 95.1 mg/dL, $p<0.05$). Bioimpedance analysis did not evidence any difference between those two groups. However, CT-scan revealed a significant higher VAT area (275.4 vs 197.3 cm², $p<0.01$), similar SAT area and unexpected higher skeletal muscle index (61.9 vs 52.9 cm²/m², $p<0.05$) in patients with severe steatosis compared to others. Patients with severe fibrosis compared to patients with normal liver elasticity had a significant higher fat free mass at bioimpedance analysis (76.3 vs 63.9 kg, $p<0.01$) and higher whole muscle area (200.1 vs 166.4 cm², $p<0.01$). Interestingly, those patients had a significant lower muscle density index, compatible with muscle fat infiltration (MFI). In a multivariate logistic regression analysis, MFI was the strongest predictor of advanced liver fibrosis.
Conclusions : Among obese subjects, patients with severe steatosis have a high muscle and visceral adipose tissue mass. Muscle fat infiltration provides a robust, skeletal muscle-specific characteristic linked to advanced liver fibrosis, suggesting a muscle-liver axis in the pathogenesis of NAFLD complications.

- A21 -

THE MECHANISMS OF STEATOSIS PATHOGENESIS DURING NASH DEVELOPMENT. A. Lamotte (1), I. Leclercq (1), N. Lanthier (2) / [1] UCLouvain, Belgium, Laboratory of Gastroenterology and Hepatology, Institut de Recherche Expérimentale et Clinique, [2] Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium, Service d'Hépato-Gastroentérologie.

Introduction : In non-alcoholic fatty liver disease (NAFLD), imbalance between fatty acid uptake, synthesis and their combustion or secretion can lead to steatosis. In some patients, non-alcoholic fatty liver (NAFL) evolves in a more aggressive disease form called non-alcoholic steatohepatitis (NASH) which promotes the development of fibrosis. An unanswered question is whether mechanisms for steatosis are stable over time or whether a specific steatotic process occurs during NASH development and promotes disease progression.
Aim : Here, we wanted to define the mechanisms of liver fat accumulation at various stages of NAFLD progression in a well-established NASH mouse model.
Methods : Wildtype (WT) and FOZ -/- mice received either a normal diet or a high fat diet (HFD) for 0, 4, 12 or 32 weeks (n=4-8/group). Liver paraffin-embedded sections were used for NAFLD severity assessment, based on the NAFLD activity score (NAS) and the Sirius red staining (fibrosis). Total RNA was extracted from the liver and the visceral adipose tissue of WT and FOZ -/- mice for gene expression analysis of key pathways potentially involved in steatosis pathogenesis.
Results : FOZ -/- mice fed a HFD developed steatosis after 4 weeks, NASH after 12 weeks (NAS=8) and fibrotic NASH after 32 weeks (NAS=7 + presence of fibrosis). In comparison with baseline situation (FOZ -/- 0 week), the transporter for extracellular fatty acid uptake (liver fatty acid transporter cluster of differentiation 36) significantly increased over time ($p<0.01$). Acetyl CoA oxidase, an enzyme of the peroxysomal β-oxidation was induced at early time point (4 weeks, $p<0.01$) and decreased thereafter ($p<0,05$). However, expression of carnitine palmitoyltransferase 1-α, a gene signing activation of mitochondrial β-oxidation was upregulated from week 4 and up to 32 weeks ($p<0.05$). De novo lipogenesis (DNL) assessed by stearoyl CoA desaturase 1 expression was stable over time. Apolipoprotein B expression, key for fatty acid export was initially upregulated during steatosis and NASH stages ($p<0.01$ at 4 and 12 weeks) but not at the fibrotic stage of the disease. Lipolytic enzymes adipose triglycerides lipase and hormone sensitive lipase in the epididymal white adipose tissue were upregulated in FOZ -/- HFD fed mice ($p<0.01$ and $p<0.001$, respectively) consistent with adipose tissue lipolysis at the NAFL and NASH stages. In contrast, in WT mice fed a HFD and developing only discrete steatosis over time, liver DNL was downregulated and no adipose tissue lipolysis was observed.
Conclusions : FOZ -/- develop fibrosing NASH over time due to an increased fatty acid transport to the liver, enhanced adipose tissue lipolysis, preserved de novo lipogenesis and at later timepoints downregulation of fatty acid export and defect in fatty acid oxidation. Those results open the possibility to evaluate targeted steatosis therapies according to

NAFLD stage. Those pathways are currently investigated in HFD FOZ-/- mice supplemented in high fructose corn syrup as well as in human NAFLD with various disease severity.

- A22 -

NEUTRALIZING ANTI-CD8 ANTIBODIES EFFECTIVELY REDUCE VISCERAL ADIPOSE TISSUE CYTOTOXIC T CELLS AND ATTENUATE NAFLD IN A HIGH-FAT HIGH-FRUCTOSE DIET MOUSE MODEL. M. Van Herck (1), L. Vonghia (2), W. Kwanten (2), T. Vanwolleghem (2), D. Ebo (3), P. Michielsen (2), J. De Man (2), B. De Winter (2), S. Francque (2) / [1] University of Antwerp, Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology and Hepatology, [2] University of Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology and Hepatology, [3] University of Antwerp, Belgium, Immunology - Allergology - Rheumatology.

Introduction : Non-alcoholic fatty liver disease (NAFLD) is a multisystem condition in which the liver, adipose tissue and the immune system are involved. T cells form a part of the adaptive immune system and can be subdivided in several subsets with distinct functions. We previously demonstrated that mice with severe NAFLD exhibit elevated hepatic T helper 17 cells (Th17, CD4+ RORγt+) and an abundance of CD8+ cytotoxic T cells (Tc) in the visceral adipose tissue (VAT).
Aim : The present study aimed at correcting these T-cell alterations through treatment with neutralizing anti-CD8 or anti-IL-17A antibodies and investigating the effect on the metabolic profile and liver histology.
Methods : Male 8-week old C57BL/6J mice (n=8 per group) were fed a high-fat high-fructose diet (HFHFD) for 20 weeks. Subsequently, they were injected intraperitoneally once weekly with either anti-CD8 antibodies, anti-IL-17A antibodies or an isotype control for a total of 3 weeks with concomitant HFHFD feeding. ALT and cholesterol levels were analyzed in plasma. Liver tissue was assessed histologically and the NAFLD Activity Score (NAS) was calculated. Tc cells were characterized in liver and visceral tissue (VAT) via flow cytometry and expressed as a percentage of CD45+ CD3+ cells. Data are presented as [Median (Q1-Q3), p-value].
Results : Compared to control mice, treatment with the anti-CD8 antibodies effectively decreased the percentage of Tc cells in VAT [resp. 37.4 % (32.2-40.8) vs. 23.1 % (16.3-25.2), $p<0.001$] and liver [resp. 38.8 % (35.9-46.2) vs. 28.5 % (21.4-30.7), $p<0.001$]. This decrease was associated with a reduction in ALT levels [resp. 113 U/L (79-161) vs. 35 U/L (8-45 U/L), $p =0.007$], liver weight (resp. 3024 mg (2577-3409) vs. 2195 mg (2068-2645), $p=0.010$) and cholesterol levels [resp. 174 mg/dL (154-187) vs. 150 mg/dL (142-162), $p=0.049$], while not affecting total body weight or fasted glycemia. Furthermore, histological assessment showed a decrease in NAS [resp. 6 (5-7) vs. 4 (3-5), $p=0.007$], predominantly by reducing steatosis and – to a lesser extent – ballooning. In contrast, treatment with the neutralizing anti-IL-17A antibodies did not induce any phenotypical changes, nor a significant reduction in the NAS [resp. 6 (5-7) vs. 6 (6-6), $p=0.130$]. However, when looking at the individual components of the NAS, the treatment with anti-IL17A antibodies did induce a reduction in lobular inflammation [resp. 2.0 (1.6-2.4) vs. 1.5 (1.0-1.5), $p=0.028$], which was confirmed by CD45 immunohistochemistry.
Conclusions : Neutralizing anti-CD8 antibodies effectively reduced VAT Tc levels and attenuated the severity of HFHFD-induced NAFLD. In contrast, anti-IL17A antibodies did not induce a reduction in NAS, although they attenuated lobular inflammation in the liver. These findings underline the importance of adipose tissue inflammation in the pathogenesis of NAFLD and identify a possible treatment target for NAFLD.

- A23 -

CASE-FINDING OF NON-ALCOHOLIC FATTY LIVER DISEASE-INDUCED LIVER FIBROSIS : PREVALENCE AND USE OF NON-INVASIVE SCORING VS. TRANSIENT ELASTOGRAPHY IN PRIMARY CARE. J. Wellens (1), M. Devos (2), L. Present (3), E. Vanderstraeten (1), S. Francque (4), L. Heyens (5), G. Robaeys (5), C. Van Steenkiste (1) / [1] Maria Middelares Medical Centre, Ghent, Belgium, Gastroenterology and Hepatology, [2] General practice Rendekens, Destelbergen, Belgium, General practice medicine, [3] General practice Rendekens, Destelbergen, Belgium, General practice medicine, [4] University of Antwerp, Belgium, Gastroenterology, [5] Hasselt University, Hasselt, Belgium, Faculty of health and life sciences.

Introduction : Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder in Western countries, with increasing prevalence, paralleling the metabolic syndrome and its components. Since abnormal liver function tests (LFTs) in primary care are poorly correlated with the severity of NAFLD, more sensitive and specific methods are needed to identify significant liver fibrosis. Therefore, non-invasive risk scores and liver stiffness measurements (LSM), were developed, but validation in a primary care-based population is still lacking.
Aim : Our objective was to determine the prevalence of significant fibrosis in a primary care-based cohort at risk for NAFLD. Secondly, we aimed to determine the usefulness of non-invasive risk scores for steatosis and fibrosis in this population.

Methods : This cross-sectional study recruited 165 adult patients >=35 years from 1 primary care practice in Heusden (East Flanders). Inclusion criteria consisted of diabetes mellitus type 2, BMI >= 30 kg/m^2, metabolic syndrome or history of cardiovascular disease. Patients with an alcohol consumption >= 30 and >= 20 g/day in males and females, respectively, were excluded from the analysis. Each participant was subject to an interview, anthropometric measurements and LSM using vibration-controlled transient elastometry VCTE with Fibroscan® with continued attenuation parameter (CAP) to evaluate for liver fibrosis and steatosis, respectively. LSM >= 7.9 kPa (M-probe), and >=7.2 (XL-probe), was used as a cutoff for significant fibrosis (i.e. F2). The non-invasive risk tools Fibrosis-4 (FIB-4), NAFLD fibrosis score and Fatty Liver Index (FLI) were calculated for each subject.
Results : 40 out of 165 patients had an elevated LSM on VCTE, suggesting significant fibrosis. Using TE as our gold standard, FIB4 showed a specificity of 49.6% and a sensitivity of 72.5% resulting in a PPV of 31.5% and a NPV of 85%. Since albumin was only available in 53% of patients in our study population, the NAFLD fibrosis score was not reliable as a screening tool. Using CAP as the gold standard, the FLI was a sensitive screening tool (sens 92.3%, spec 68.8%, PPV 95.6, NPV 44) for steatosis. There was a trend towards a greater prevalence of fibrosis in subjects with an increased waist circumference, BMI>30kg/m^2 (RR 1.4), decreased platelet count (RR 1.2), elevated AST/ALT ratio (RR 1.2), dyslipidaemia (RR 1.6), diabetes mellitus (RR 1.7), metabolic syndrome (RR 1.3) and a protective effect of statin use (RR 0.7).
Conclusions : Our study showed, based on VCTE, a prevalence of significant fibrosis of 24.2% in a population at risk for NAFLD in a primary care-based cohort. Secondly, the accuracy of non-invasive risk scores is unsatisfactorily low, questioning their usefulness as a screening tool instrument in this setting. Lastly, the best predictive factors for presence of significant fibrosis included an increased waist circumference, diabetes type 2 and lack of statin use.

- A24 -

THE EFFECTS OF ORAL BOSENTAN TREATMENT ON THE INCREASED INTRAHEPATIC VASCULAR RESISTANCE AND DISEASE SEVERITY OF EARLY NAFLD IN RATS. D. Van Der Graaff (1), W. Kwanten (2), J. De Man (1), B. De Winter (1), P. Michielsen (2), S. Francque (2) / [1] University of Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics (LEMP), [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology and hepatology.

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), which could be blocked by ET-A receptor inhibition (Van der Graaff, Hepatol 2018;68(Suppl) :1011A).
Aim : The aim of this study was to analyse the potential benefit of bosentan (BOS, an ET-A and -B receptor blocker) on liver haemodynamics and concurrent severity of disease in early NAFLD.
Methods : The effects of ET-1 inhibition were studied in male Wistar rats (n=8/group) fed a methionine-choline-deficient (MCD) diet, which induces severe steatosis after 4 weeks, or a control diet. Rats were daily gavaged with 100 mg/kg BOS or placebo during the complete 4 weeks of diet as preventive treatment or during the second 2 weeks of diet as curative treatment. The IHVR was studied by measuring the transhepatic pressure gradient (THPG) in an in situ ex vivo perfusion model at different flows (10-45 mL/min). Blood samples were collected before liver perfusion to determine ALT levels and liver tissue was harvested for histology.
Results : The basal THPG in steatotic livers was significantly increased compared to controls, with respectively 5.4 ± 0.3 mmHg and 4.4 ± 0.2 mmHg at 30 mL/min ($p<0.001$), as previously described (Van der Graaff et al., Lab Invest 2018). Preventive BOS treatment significantly decreased the THPG in steatotic livers, without affecting the THPG in controls (controls + placebo 9.2 ± 0.6 mmHg vs. controls + BOS 9.5 ± 0.3 mmHg, $p = 0.27$; steatosis + placebo 11.5 ± 0.4 mmHg vs. steatosis + BOS 10.1 ± 0.2 mmHg at 40 mL/min, $p < 0.01$). Moreover, despite comparable weight evolution (steatosis + placebo 199.6 ± 3.5 g and steatosis + BOS 200.3 ± 3.3 g at week 4, $p = 0.898$), liver weight and liver-to-total-body-weight (TBW) ratio were lower in preventive BOS-treated (4.6 ± 0.1% liver/TBW) compared to placebo-treated rats (5.2 ± 0.3% liver/TBW, $p < 0.01$) with steatosis. The degree of steatosis, expressed as % fat of total liver surface, was significantly lower in preventive BOS-treated rats (from 52.2 ± 0.7% placebo to 47.1 ± 2.0% BOS, $p < 0.05$). ALT significantly increased in MCD fed rats (94.9 ± 14.0 U/L), whereas preventive BOS-treated rats showed ALT levels comparable to control rats (48.4 ± 3.0 U/L, $p < 0.05$). In curative BOS-treated rats, we observed a similar significant decrease in THPG, liver and liver/TBW ratio and ALT level. The degree of steatosis showed an insignificantly decreased trend. In controls, none of the parameters were affected by BOS treatment.
Conclusions : BOS treatment significantly decreased the elevated THPG observed in steatosis. This effect goes along with a decrease in steatosis, lower liver weight and liver/TBW-ratio and normalisation of ALT in the absence of any effect on body weight. These findings strongly support the role of ET-1-related vascular alterations in NASH pathogenesis and its potential as a therapeutic target.

- A25 -

IMPACT OF AMINO ACID SUPPLEMENTATION ON SARCOPENIA IN NASH. C. Pichon (1), M. Nachit (1), G. Vande Velde (2), Y. Horsmans (3), I. Leclercq (4) / [1] Université Catholique de Louvain, Brussels, Belgium, Laboratory of Hepato-Gastroenterology, [2] KU Leuven, Belgium, Department of Imaging & Pathology, [3] Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium, Gastroenterology Unit, [4] Université Catholique de Louvain, Brussels, Belgium, IREC / Laboratory of Hepato-Gastroenterology.

Introduction : NAFLD represents a spectrum of diseases ranging from benign steatosis (NAFL) to non-alcoholic steatohepatitis (NASH). Unlike simple steatosis, hepatocellular injury and inflammation in NASH promote fibrosis and evolution to end-stage liver disease. Cross-sectional studies clearly showed that decreased muscle functionality and myosteatosis, reflecting poor muscle quality, are strongly associated with NAFLD and linked to the severity of NASH. As previously demonstrated in the lab, NASH in high-fat diet fed foz/foz mice is associated with severe myosteatosis and loss of muscle strength. Yet, mechanisms linking the liver compartment to skeletal muscle are poorly known. Systemic hyperammonemia caused by ammonia detoxification impairment in liver could promote muscle alterations. L-Ornithine L-Aspartate (LOLA) is known as an effective ammonia-lowering agent, often used for treating hepatic encephalopathy.
Aim : To evaluate the impact of administration of LOLA, an ammonia lowering treatment, on muscle during NASH development.
Methods : We used foz/foz mice (FZ) fed a high fat diet (HFD, 60% fat) as a model of NASH. After 4 weeks, mice were randomized and continued on a HFD (Ctrl) or received a HFD with 2 g/kg/j L-Ornithine L-Aspartate supplementation in drinking water for 8 weeks (LOLA group). At 4 weeks intervals, we measured body weight, glycemia and systemic blood ammonia concentration, and performed micro-computed tomography (micro-CT) to monitor changes in body composition, dorsal muscle area, and skeletal muscle and liver fatty infiltration (expressed as muscle or liver density to spleen density ratio). Muscle strength was measured by grip strength test. At the end of the experiment (12 weeks HFD or 8 weeks LOLA treatment), mice were sacrificed to analyze white adipose tissue, liver and muscle histology.
Results : At sacrifice, although LOLA mice had larger epididymal adipose mass (1,78±0,10 g versus 1,45±0,03 g in Ctrl ; p=0,0002), we observed no significant difference between Ctrl and LOLA mice in body weight (56,31±5,73 g and 53,97±2,71 g, respectively), liver weight (5,64±0,35 g and 5,84±1,08 g), glycemia (222,3±50.5 mg/dl and 258,2±73,2 mg/dl) and muscle strenght (217,5±19,0 gr and 189,8±18,8 gr). Systemic ammonia concentration stayed stable and low over time in both groups with no difference between Ctrl and LOLA (108,75±20,1 µg/dl and 91,50±15,1 µg/dl, respectively). In Ctrl, muscle density gradually decreased with duration on HFD. LOLA supplementation prevented further changes in muscle density, such as at 12 weeks muscle density was 0,563±0,070 H.U. in Ctrl and 0,813±0,053 H.U. in LOLA (p<0,0001). This supports that LOLA alleviates NASH-associated myosteatosis. Dorsal muscle area was smaller in LOLA mice than in Ctrl (49,17±3,00 mm² versus 55,25±1,26 mm² ; p=0,0457). Liver density rapidly dropped with HF feeding, but was partially rescued by LOLA treatment such as liver density was significantly higher than in controls at the end of the experiment (-0.610±0,240 H.U. in Ctrl versus -0,105±0,112 H.U. in LOLA ; p<0,0001).
Conclusions : Amino acids supplementation prevents myosteatosis development in a context of NASH. Mechanisms and direction of the crosstalk between liver and muscle in NAFLD are being explored.

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ASSESSMENT OF LIVER FIBROSIS STAGE IN ACTIVE NASH BY VCTE. J. Weyler (1), L. Vonghia (1), W. Verlinden (2), A. Bagdadi (1), P. Michielsen (1), T. Vanwolleghem (1), A. Driessen (3), S. Francque (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology and hepatology, [2] AZ Nikolaas, Sint-Niklaas, Belgium, Gastroenterology and hepatology, [3] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Pathology.

Introduction : Non-Alcoholic Fatty Liver Disease (NAFLD) is a highly prevalent chronic liver disease and represents a spectrum from Non-Alcoholic Fatty Liver (NAFL) to Non-Alcoholic Steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma. Patients with NAFLD and significant fibrosis (≥F2) are at highest risk for development of complications. Several non-invasive methods have been developed to diagnose and stage fibrosis. Vibration Controlled Transient Elastography (VCTE) is currently the most validated non-invasive technique to determine liver fibrosis stage. Besides food intake, alcohol consumption, congestion, and cholestasis, disease activity (inflammation) is correlated with overestimation of liver stiffness.
Aim : We aimed at studying the accuracy to detect liver fibrosis assessed by the VCTE in patients with NASH compared to patients without NASH in a cohort with biopsy-proven NAFLD.
Methods : Patients who underwent both a liver biopsy and VCTE in our centre and diagnosed with NAFLD were prospectively included. The different pathological features of NAFLD were scored using the Fatty Liver Inhibition of Progression (FLIP) algorithm. The diagnosis of NAFL required the presence of steatosis, whereas the diagnosis of NASH required the combined presence of steatosis, ballooning and lobular inflammation. The discriminative power of VCTE for the different fibrosis stages was assessed using ROC analysis. The potential added value of ALT and AST on the

previously described indices was analysed using a binary regression model, ROC analysis was performed on the saved predicted values of these regressions.
Results : 131 NAFLD patients were included. 31 patients or 23.7% had NAFL, fibrosis classification in this group was as follows : 45.2 % F0, 25.8% F1, 6.4 % F2, 9.7 % F3 and 12.9 % F4. 100 patients (or 76.3%) were included with NASH with fibrosis classification : 21.0 % F0, 29.0% F1, 20.0 % F2, 26 % F3 and 4 % F4. AUROC for predicting ≥F1 by VCTE was 0.729 in NASH compared to 0.903 in NAFL; AUROC for predicting ≥F2 by VCTE was 0.784 in NASH compared to 0.854 in NAFL; AUROC for predicting ≥F3 by VCTE was 0.804 in NASH compared to 0.899 in NAFL and AUROC for predicting F4 by VCTE was 0.889 in NASH compared to 0.972 in NAFL. To improve the accuracy of predicting fibrosis stage a combination of ALT, AST and VCTE was used. This resulted In the following AUROCs when combining VCTE and ALT : 0.772 for predicting ≥F1, 0.773 for predicting ≥F2, 0.800 for predicting ≥F3 and 0.875 for predicting F4. AUROCS for the combination of VCTE and AST were as follows : 0.783 for predicting ≥F1, 0.787 for predicting ≥F2; 0.798 for predicting ≥F3 and 0.884 for predicting F4.
Conclusions : Although VCTE is able to predict liver fibrosis stage with high accuracy, there is an important negative impact of disease activity on the accuracy when assessing liver fibrosis. Furthermore, there is no significant improvement of accuracy when using a combination of liver stiffness and ALT or AST for the prediction of liver fibrosis stage

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CURATIVE LIVER TRANSPLANTATION FOR HEMIN-REFRACTORY ACUTE INTERMITTENT PORPHYRIA : A TERTIARY CENTER EXPERIENCE. M. Bronswijk (1), S. De Cock (2), P. Vermeersch (3), F. D'heygere (4), D. Monbaliu (5), J. Pirenne (6), W. Meersseman (7), D. Cassiman (8) / [1] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology, [2] AZ Sint-Lucas Brugge, Assebroek/ Brugge, Belgium, Department of Gastroenterology and Hepatology, [3] University Hospitals Leuven, Belgium, Department of Laboratory Medicine, [4] AZ Groeninge, Kortrijk, Belgium, Department of Gastroenterology and Hepatology, [5] University Hospitals Leuven, Leuven, Belgium, Department of Abdominal Transplant Surgery and Coordination, [6] University Hospitals Leuven, Belgium, Department of Abdominal Transplant Surgery and Coordination, [7] University Hospitals Leuven, Belgium, Department of General Internal Medicine - Metabolic Diseases, [8] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology.

Introduction : In patients with acute intermittent porphyria (AIP) and intractable neurovisceral symptoms, liver transplantation is considered a curative treatment, owing to the correction of the underlying porphobilinogen-deaminase deficiency. However, due to the rarity of the affliction, outcome data following transplantation remain scarce.
Aim : To describe the baseline characteristics and outcomes of liver transplantation for AIP.
Methods : Records of all patients who underwent liver transplantation for AIP at the University Hospitals Leuven, were evaluated anonymously and retrospectively. Baseline characteristics, post-transplant complications and events during follow up were recorded and compared.
Results : In total, three patients were identified (1 male/2 female, mean age 43 years). All three patients underwent transplantation for debilitating recurrent attacks of abdominal pain, despite repetitive hemin infusions and even prophylactic infusions in one patient. No porphyria related renal insufficiency or neuropathy were identified. Opioid abuse and attack-related psychiatric symptoms were present in two out of three patients. Following liver transplantation, two patients developed anastomotic strictures, for which successful endoscopic stenting was performed. Only patient 1 developed an episode of acute cellular rejection, which was treated successfully with high dose IV steroids. In comparison to earlier work, no episodes of arterial thrombosis occurred, presumably owing to the systematic thromboprophylaxis with low dose aspirin. Histopathological evaluation of the explant livers showed typical AIP related findings, with nodular regenerative hyperplasia in one patient and hemosiderosis in the two remaining patients. Following transplantation, urinary screening for porphobilinogen became negative and resolution of psychiatric symptoms and opioid abuse was seen in both affected patients. After a median follow up of 37 months, no new attacks have been detected in all three patients.
Conclusions : Besides the curative effect of liver transplantation on AIP-related visceral symptoms, our data suggest that liver transplantation also seems to have a curative effect on porphyrin-related neuropsychiatric symptoms and associated opioid-abuse.

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OUTCOME IN CAUCASIAN PATIENTS WITH HEPATITIS B E ANTIGEN NEGATIVE CHRONIC INFECTION : A LONG-TERM OBSERVATIONAL COHORT STUDY. Ö. Koc (1), G. Robaeys (2), H. Topal (3), R. Bielen (1), D. Busschots (1), J. Fevery (4), G. Koek (5), F. Nevens (4) / [1] Universiteit Hasselt, Belgium, Faculty of Medicine and Life Sciences, [2] Ziekenhuis Oost Limburg, Genk, Belgium, Department of Gastroenterology and Hepatology, [3] University Hospitals Leuven, Belgium, Department of Abdominal Surgery, [4] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology, [5] Maastricht University Medical Centre, Maastricht, Netherlands (the), Department of Internal Medicine, Division of Gastroenterology and Hepatology.

Introduction : The term 'inactive hepatitis B carriership' was not advised anymore since there was an evolution to advanced liver disease in some of these patients. Sensitive PCR assays to measure hepatitis B virus (HBV) DNA became only available the last decade.
Aim : Hence, the long-term outcome of Caucasian patients in Western Europe with hepatitis B e antigen (HBeAg)-negative chronic infection, especially with a baseline HBV DNA level > 2,000 IU/mL, is still unclear.
Methods : Out of a cohort of 1,936 patients with chronic HBV contamination, 413 Caucasian patients were identified with HBeAg-negative chronic infection, defined as persistently normal alanine aminotransferase (ALT) levels and HBV DNA levels < 20,000 IU/mL.
Results : During a mean follow-up of 12 years, 366 (88.6%) maintained with a HBeAg-negative chronic infection status, whereas 25 (6.1%) developed chronic active hepatitis (CAH). The cumulative incidence of hepatitis B surface antigen loss was 9.2%. Nine out of 25 CAH cases were related to immunosuppression. The remaining 22 (5.3%) individuals had ALT > 2 x ULN due to non-HBV related causes. The cumulative probability of spontaneous developing CAH after 10 years was almost exclusively seen in patients with baseline HBV DNA level > 2,000 IU/mL (11.7% vs 1.2%, $p < 0.001$). Also advanced liver disease developed significantly more in patients with baseline HBV DNA level > 2,000 IU/mL (5.2% vs 1.5%, $p = 0.018$) and occurred especially in patients with obesity (16.7% vs 4.2% $p = 0.049$). The incidence of hepatocellular carcinoma and liver-related mortality was 0.0% and 0.2%, respectively.
Conclusions : Caucasian patients in Western Europe with HBeAg-negative chronic infection and baseline HBV DNA level of < 2,000 IU/mL have an excellent long-term prognosis in the absence of immunosuppressive therapy. However, patients with baseline HBV DNA level > 2,000 IU/mL are at risk to develop advanced liver disease.

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DEFECTIVE GUT ADAPTIVE IMMUNITY DURING EARLY ALCOHOLIC LIVER DISEASE. L. Maccioni (1), B. Pirlot (1), I. Leclercq (1), Y. Horsmans (2), B. Schnabl (3), P. Starkel (2) / [1] Institut de Recherche Expérimentale et Clinique (IREC), Catholic University of Louvain (UCL), Belgium, Laboratory of Hepato-gastroenterology (GAEN), [2] Clin. Universitaires St-Luc, UCL, Brussels, Belgium, Department of Hepato-gastroenterology, [3] University of California San Diego (UCSD), San Diego, United States (the), Department of Medicine - Division of Gastroenterology.

Introduction : Alcoholic liver disease (ALD) severity is associated with increased microbial translocation (MT) and gut barrier dysfunction. Mucosal T cells, specialists of adaptive immunity, 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 adaptive immunity, microbial translocation and ALD progression in alcohol use disorder (AUD) patients.
Methods : Actively drinking AUD patients (n = 37) admitted to a rehabilitation program were included. Fasting blood and liver stiffness (kPa)/controlled attenuation parameter (CAP) measurements were obtained at admission and distal duodenal biopsies one day after. Serum markers for gram– and gram+ microbial translocation (soluble CD14 and peptidoglycan recognition proteins (PGRPs), respectively) and liver cell damage (cytokeratin18 (CK18-M65)) were assessed by ELISA, duodenal immune cells by immunohistochemistry/flow cytometry. ALD severity was clinically defined as : non-progressive ALD, i.e. no liver disease (normal AST, ALT, CAP < 250 dB/m, no fibrosis); simple steatosis (normal AST, ALT, CAP > 250 dB/m, no fibrosis) and progressive ALD, i.e. steato-hepatitis, SH (elevated AST, ALT, CAP > 250 dB/m, no fibrosis); steato-fibrosis (SH and significant fibrosis (kPa > 7.6)).
Results : The duodenal mucosa of AUD patients was characterized by a reduction of CD3+CD8+ T cells compared to healthy subjects (n = 15). Within the CD8+ T cell pool, tissue-resident memory CD8+ (TRM; KLRG1-, CD103+) were significantly ($p < 0.05$) reduced. In addition, TRM of AUD patients had low CD69, a regulator of TRM tissue residency. Both changes (low TRM, low CD69) occurred independently from ALD severity. TRM inversely associated with PGRPs levels, a marker of gram+ translocation, suggesting their role in immunosurveillance. By contrast, programmed cell death protein 1 (PD1), a master regulator of adaptive immunity, was down-regulated while the senescence marker CD57 was increased in CD8+ T cells of AUD patients with clinically progressive ALD and high CK18-M65, a marker of liver cell damage, compared to controls. This shift to the senescent phenotype (CD8+, PD1low, CD57+) was associated with high sCD14, signing gram- translocation and points to an impairment of gut adaptive immunity.
Conclusions : In AUD patients, progressive ALD is linked to impaired gut adaptive immune responses which likely contribute to defective gut microbial immunosurveillance.

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ADOPTIVE CELL TRANSFER OF REGULATORY T CELLS CAUSES AN EXACERBATION OF HEPATIC STEATOSIS IN HIGH-FAT HIGH-FRUCTOSE DIET-FED MICE. M. Van Herck (1), L. Vonghia (2), W. Kwanten (2), T. Vanwolleghem (2), D. Ebo (3), P. Michielsen (2), J. De Man (2), B. De Winter (2), S. Francque (2) / [1] University of Antwerp, Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology and Hepatology, [2] University of Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology and Hepatology, [3] University of Antwerp, Belgium, Immunology - Allergology - Rheumatology.

Introduction : Non-alcoholic steatohepatitis (NASH) is a multisystem condition, involving the liver, adipose tissue, and immune system. Regulatory T (Treg) cells are a subset of T cells that exert an immune-controlling effect. We previously demonstrated a reduction of Treg cells in the visceral adipose tissue (VAT) in high-fat high-fructose diet- (HFHFD) fed mice, which was associated with more severe liver disease.
Aim : To further investigate the role of VAT Treg cells in NASH, we aimed to correct this immune disruption through adoptive cell transfer (ACT) of Treg cells.
Methods : Male 8-week-old C57BL/6J mice were fed a HFHFD for 20 weeks. Subsequently, CD4+ CD25+ Treg cells were isolated from the spleens of healthy 8 to 10-week-old C57BL/6J mice and were adoptively transferred to the HFHFD-fed mice via intraperitoneal injection. HFHFD-fed mice injected with PBS served as controls. Mice were sacrificed three days after the injection. Plasma ALT and cholesterol levels were determined. Liver and adipose tissue was assessed histologically. Cytotoxic T (Tc) cells, Treg, T helper (Th) 1 cells and Th17 cells were characterized in liver, VAT, subcutaneous adipose tissue (SAT), blood, and spleen via flow cytometry. Treg and Th1 cells are expressed as % of CD4+ cells. Data are presented as [median (Q1-Q3), p-value].
Results : Compared to controls, ACT of Treg cells increased the proportion of Treg cells in SAT [5.8% (5.1-9.1) vs. 8.5% (7.5-10.7), p=0.021], but not in any of the other investigated tissues [VAT 10.3% (7.4-12.1) vs. 10.2% (8.0-14.1), p=0.779; liver 3.5% (3.5-6.7) vs. 3.6% (1.9-7.1), p=0.536]. Moreover, in ACT mice Th1 cells were decreased in SAT [4.5% (2.0-6.5) vs. 0.1% (0.7-1.1), p=0.021], liver [5.2% (2.6-9.0) vs. 0.3% (0.1-3.3), p=0.035], blood [5.4% (3.9-8.4) vs. 2.0% (1.7-2.3), p=0.021], and spleen [2.2% (1.9-7.2) vs. 0.5% (0.5-1.2), p=0.026], while Tc cells or Th17 cells were not affected. Furthermore, the ACT increased the ALT levels [12 U/L (6-69) vs. 77 U/L (35-111), p=0.049] and the histological degree of steatosis [36% (31-41) vs. 44% (42-49), p=0.019], while not significantly affecting bodyweight, cholesterol level, or liver inflammation.
Conclusions : Surprisingly, ACT of Treg cells in HFHFD-fed mice caused an exacerbation of hepatic steatosis. This was accompanied by an increase of Treg cells in the SAT and a general decrease in Th1 cells, while it did not correct the previously described HFHFD-induced reduction in VAT Treg cells.

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THE EFFECTS OF ORAL VALSARTAN TREATMENT ON THE INCREASED INTRAHEPATIC VASCULAR RESISTANCE AND DISEASE SEVERITY OF EARLY NAFLD IN RATS. D. Van Der Graaff (1), W. Kwanten (2), J. De Man (1), B. De Winter (1), P. Michielsen (3), S. Francque (2) / [1] University of Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics (LEMP), [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology and hepatology, [3] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroeneterology and hepatology.

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 observed that this increased IHVR is in part mediated by angiotensin (ATII), which could be blocked by ex vivo liver perfusion with the ATII receptor blocker valsartan (VAL).
Aim : The aim of this study was to analyze the potential benefit of in vivo oral VAL treatment on liver hemodynamics and severity of disease in early NAFLD.
Methods : The effects of VAL were studied in male Wistar rats (n=7-8/group) fed a methionine-choline-deficient (MCD) diet, which induces severe steatosis after 4 weeks, or a control diet. Rats were daily gavaged with 30 mg/kg VAL or placebo during the complete 4 weeks of diet as preventive treatment or during the second 2 weeks of diet as curative treatment. 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 ALT and AST levels and liver tissue was harvested for histology.
Results : The basal THPG in steatotic livers was significantly increased compared to controls, with respectively 5.4 ± 0.3 mmHg and 4.4 ± 0.2 mmHg at 30 mL/min ($p<0.001$), as previously described (Van der Graaff et al., Lab Invest 2018). Curative VAL treatment significantly decreased the THPG both in steatotic (steatosis + placebo 15.6 ± 0.6 mmHg vs. steatosis + VAL 13.5 ± 0.6 mmHg at 50 mL/min, $p <0.01$) and control livers (controls + placebo 13.4 ± 0.4 mmHg vs. controls + VAL 11.4 ± 0.6 mmHg at 50 mL/min, $p <0.001$). Despite comparable weight evolution, liver weight and liver-to-total-body-weight (TBW) ratio were lower in curative VAL-treated (9.9 ± 0.5 g liver weight) compared to placebo-treated steatotic rats (11.5 ± 0.4 mg liver weight, p=0.8). However, histologically VAL treatment did not affect the degree of steatosis. ALT and AST were increased in steatotic rats (ALT controls 37.6 ± 4.6 U/L, steatosis 111.7 ± 27.7 U/L, $p<0.001$; AST controls 61.1 ± 8.2 U/L, steatosis 86.7 ± 9.1 U/L, p=0.8). After curative VAL treatment, ALT and AST levels became comparable to control rats (ALT steatosis + VAL 54.8 ± 9.0 U/L, p=0.26; AST steatosis + VAL 52.4 ± 7.7 U/L, p=0.5). In preventive VAL-treated rats with steatosis, we did not observe a significant change in THPG, but the decreases in liver weight, liver/TBW ratio and ALT and AST levels were significant. In controls, none of the parameters were significantly affected by VAL treatment.
Conclusions : Curative but not preventive VAL treatment significantly decreased the elevated THPG observed in steatosis, possibly due to compensatory mechanisms working in the preventive setting which have to be explored. VAL

treatment also caused a normalization of ALT, AST and improvement of liver weight and liver/TBW-ratio in the absence of effects on total body weight. These findings strongly support the role of ATII-related vascular alterations in NASH pathogenesis and its potential as a curative target.

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ALTERATIONS IN BILE ACIDS AND TGR5 ACTIVATION IN NONALCOHOLIC STEATOHEPATITIS. J. Gillard (1), A. Tailleux (2), L. Clerbaux (3), B. Staels (2), Y. Horsmans (4), L. Bindels (5), I. Leclercq (1) / [1] UCLouvain, Belgium, Institut de Recherche Expérimentale et Clinique, Laboratory of Hepato-Gastroenterology, [2] University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, Lille, France, U1011 - EGID, [3] University (Hospital) of Zurich, Zurich, Switzerland, Institute of Molecular Cancer Research and Department of Molecular Pathology, [4] Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium, Gastroenterology Unit, [5] UCLouvain, Belgium, Louvain Drug Research Institut, Metabolism and Nutrition Research Group.

Introduction : Upon bile acids (BA) activation, G-protein coupled receptor (TGR5) regulates lipid and glucose homeostasis, energy expenditure, inflammatory tone and fibrosis, all processes dysregulated in nonalcoholic steatohepatitis (NASH). Thus, altered BA sensing via TGR5 might contribute to NASH pathogenesis. In humans, BA analysis is restricted to systemic blood and feces and reflects BA that escaped hepatic uptake and intestinal reabsorption, respectively, and thereby does not reflect the enterohepatic BA pool. Studying BA in mice enables the assessment of BA profile in bile and portal blood.
Aim : We aimed to determine whether BA profile is altered in a mouse model of NASH and which are the mechanisms involved.
Methods : We studied 12 weeks HFD-fed foz/foz mice (FOZ; n=8) as a model of NASH (NAS $\geq$ 6) and compared them with 12 weeks HFD-fed WT mice (n=6) as a model of simple steatosis (NAS $\leq$ 1). Portal blood, bile, feces and tissues were sampled after 12h fasting and 4h refeeding. BA profiling was established by LC-MS/MS. To test TGR5 activation, HEK293T cells overexpressing TGR5 and a CRE luciferase reporter were exposed to portal plasma of FOZ and WT mice. Gene expression was measured by qPCR. Bile flow was assessed by cannulation of the gallbladder. Data are presented as mean ± SEM.
Results : Total BA concentration in bile was similar in both steatosis and NASH groups (WT : 8.824*10e7 ± 0.578*10e7 nM vs FOZ : 11.634*10e7 ± 1.310*10e7 nM; p=0.14) but the proportion of primary BA was higher (WT : 5.559*10e7 ± 0.720*10e7 nM, 62% vs FOZ : 9.138*10e7 ± 1.155*10e7 nM, 83%; p<0.05) and the proportion of secondary BA was lower in FOZ than in WT mice (WT : 3.265*10e7 ± 0.354*10e7 nM, 38% vs FOZ : 1.823*10e7 ± 0.218*10e7 nM, 17%; p<0.01). To understand the causes of altered BA profile, we investigated BA synthesis and transport in liver and ileum. As supported by equal bile flow and BA concentration, the amount of BA secreted by the liver was similar in FOZ and WT mice. Increased expression of Cyp7a1 and Cyp8b1 in FOZ mice (1.7- and 1.8-fold respectively; p<0.001) supports increased primary BA synthesis through the main classical pathway. Total BA concentration (WT : 182869 ± 40705 nM vs FOZ : 78563 ± 13213 nM; p<0.05) as well as the absolute and the relative concentration of secondary BA (WT : 64255 ± 10818 nM, 37% vs FOZ : 19766 ± 3898 nM, 25%; p<0.001) was lower in the portal blood of FOZ than in WT mice. This could be explained by a defective transformation of primary to secondary BA by the gut microbiota or by reduced intestinal BA reabsorption. However, similar fecal BA amount does not support the later hypothesis. Overall, altered BA profile in FOZ corresponded to low TGR5 agonist species in portal blood (WT : 25983 ± 4812 nM vs FOZ : 3391 ± 574 nM; p<0.001) and in accordance, in a TGR5 reporter assay, the plasma of FOZ mice was 3.4-fold less effective in activating TGR5 than the plasma of WT mice (p<0.01).
Conclusions : Deep alteration in BA pool, likely due to reduced transformation of primary to secondary BA by the gut microbiota, results in reduction of TGR5 ligands in the portal blood that could contribute to NASH pathogenesis in this experimental model.

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SIMBA : A USER-FRIENDLY HIGH THROUGHPUT TOOL FOR SPHEROID INVASION ANALYSIS OF HEPATOCELLULAR CARCINOMA CELL LINES. E. Van De Vijver (1), A. Vandierendonck (2), C. Ampe (3), M. Van Troys (3), H. Van Vlierberghe (2) / [1] Ghent University, Ghent, Belgium, Department Biomolecular Medicine, Department of Internal Medicine, [2] Ghent University, Ghent, Belgium, Department of Internal Medicine, [3] Ghent University, Ghent, Belgium, Department of biomolecular medicine.

Introduction : Due to the complex pathology of hepatocellular carcinoma (HCC) and its asymptomatic early stages, intrahepatic invasion and extrahepatic metastasis to a.o. the lung and abdominal lymph nodes are often already present at diagnosis. The evaluation of treatment effects on HCC invasion in in vivo models is currently far from evidentA and not feasible for high-throughput drug screening. 3D in vitro assays such as the spheroid invasion assay (SIA) have already proven their physiological relevance in different cancer typesB and have been applied in experimental HCCC.

Aim : In order to use SIA in high-throughput screening of HCC drugs, methods for fast and in depth data analysis are required. Accordingly, we developed SImBA (Spheroid Image Batch Analysis), a FIJI-based software tool which allows to perform high-throughput image segmentation, visualization and quantification of invasive spheroids.
Methods : Spheroids of two HCC cell lines (HEP3B and SNU423) were embedded in a 3D collagen Type I matrix. Phase contrast microscopy images were recorded at different time points to evaluate the invasive process of control and treated spheroids. Since FIJI is commonly used free softwareD, SImBA has been written as an open-source FIJI macro which ensures high user-friendliness and easy customization by the user. SImBA allows batch image processing independent of data set size and is applicable on images of variable and low contrast.
Results : Since SImBA is able to visualize and quantify the invasion data in multiple ways (using total spheroid area, spheroid outlines, area overlaps, montages and a derived invasion index), it allows to robustly demonstrate the effects of various drugs compared to control treatment. Importantly, effects on invasion and cytotoxicity can be linked using SImBA when fluorescent images of cytotoxicity from e.g. Sytox green staining are recorded.
Conclusions : We created a highly functional, easy to use free software tool for the quantitative analysis of high-throughput spheroid invasion and visualization of the invasive capacity of hepatic cancer cell lines. This will contribute to future drug screening in HCC using either 3D SIA or related assays using organoids.

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LONGITUDINAL CHARACTERIZATION OF MUSCLE ALTERATIONS IN A RODENT MODEL OF NASH. H. Louvegny (1), M. Nachit (2), C. Bouzin (3), J. Thissen (4), Y. Horsmans (5), G. Vande Velde (6), I. Leclercq (1) / [1] UCLouvain, Belgium, Institut de Recherche Expérimentale et Clinique, Laboratory of Hepato-Gastroenterology, [2] UCLouvain, Belgium, Institut de Recherche Expérimental et Clinique, Laboratory of Hepato-Gastroenterology, [3] UCLouvain, Belgium, Institut de Recherche Expérimentale et Clinique, Imaging Platform, [4] UCLouvain, Belgium, Institut de Recherche Expérimentale et Clinique, Pôle Endocrinologie, Diabétologie et Nutrition, [5] Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium, Gastroenterology Unit, [6] KUL, Belgium, Department of Imaging & Pathology.

Introduction : Non-alcoholic fatty liver disease (NAFLD), the most common chronic liver disease, represents a spectrum of disease ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). Unlike simple steatosis, hepatocellular lesions and inflammation present in NASH promote fibrosis and the evolution to end-stage liver disease. A substantial body of literature supports that a low muscle mass, low strength or a higher muscle fatty infiltration are associated with NAFLD/NASH presence and severity.
Aim : To investigate metabolic parameters and muscle changes in a widely used NASH rodent model.
Methods : For 8 weeks, we followed C57BL/6J fed a high-fat diet with choline deficiency (CDAA-HFD, n=12) or supplemented in choline (CSAA-HFD, n=11). Dorsal muscle area and density (i.e surrogates for muscle mass and myosteatosis) were assessed non-invasively with micro-computed tomography (micro-CT) at weeks 0, 4, 6 and 8 (W0,4, 6 ,8). Muscle strength was evaluated every two weeks with a grip test. Quadriceps was harvested and weighted and liver examined by histology at W4 and W8. Results are expressed as mean ± SEM.
Results : At W8, CSAA-HFD developed glucose intolerance without steatosis. By contrast, CDAA-HFD had normal fasting glycemia (90.5±7mg/dl), normal glucose tolerance and severe steatohepatitis (panlobular steatosis and severe inflammation) with pericellular fibrosis at W4. However, due to the absence of ballooning, criteria for NASH diagnosis are not met. CDAA-HFD had a significant lower weight than CSAA-HFD from W4 on (21.41±1.07g vs 24.85±1.09g, respectively, $p<0.0001$). While constant in CSAA-HFD, liver density was strikingly lower in CDAA-HFD from W4 on (-0.18±0.11 vs 0.91±0.04 in CSAA-HFD, $p<0.0001$). Dorsal muscle area and quadriceps weight were lower in CDAA-HFD (48±2.83mm², $p<0.0001$ and 175.55±10.13mg, $p=0.05$, respectively) than in CSAA-HFD (58.22±2.24mm² and 196.18±11.79mg, respectively) from W4 on. Muscle density was high in both groups (muscle/spleen density ratio>0.8), albeit significantly lower in CSAA-HFD at W8 than in CDAA-HFD mice with steatohepatitis (0.80±0.03 vs 0.89±0.04, respectively, $p<0.05$). Muscle strength did not change over the study period in both groups.
Conclusions : In CDAA-HFD, loss of muscle mass occurs together with severe steatohepatitis, but with no myosteatosis or metabolic syndrome. Further studies are needed to decipher the respective contribution of dietary choline deficiency, metabolic alterations and liver disease to changes in muscle compartment.

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DISCOVERY OF THE GUT MICROBIAL SIGNATURE DRIVING THE EFFICACY OF PREBIOTIC INTERVENTION ON LIVER STEATOSIS.
J. Rodriguez (1), N. Lanthier (2), S. Hiel (1), AM. Neyrinck (1), T. Le Roy (3), SA. Potgens (1), Q. Leyrolle (1), BD. Pachikian (1), MA. Gianfrancesco (4), PD. Cani (3), N. Paquot (5), M. Cnop (6), JP. Thissen (7), LB. Bindels (1), NM. Delzenne (1) / [1] UCLouvain, Belgium, Louvain Drug Research Institute. Metabolism and Nutrition Research Group, [2] UCLouvain, Belgium, Institut de recherche expérimentale et clinique. Laboratory of Hepato-Gastroenterology, [3] UCLouvain, Belgium, Louvain Drug Research Institute. Metabolism and Nutrition Research Group. WELBIO-, Walloon

Excellence in Life Sciences and BIOtechnology, [4] Université de Liège, Liège, Belgium, Laboratory of Diabetology, Nutrition and Metabolic disease, [5] Université de Liège, Liège, Belgium, Laboratory of Diabetology, Nutrition and Metabolic disease, [6] Université Libre de Bruxelles, Belgium, Center for Diabetes Research, Université Libre de Bruxelles, and Division of Endocrinology, Erasmus Hospital, Brussels, Belgium, [7] UCLouvain, Belgium, Institut de Recherches Expérimentales et Cliniques IREC. Pole of Endocrinology, Diabetes and Nutrition.

Introduction : Dietary supplementation with inulin as a prebiotic has been shown to lessen obesity and related metabolic disorders in some individuals. Previous work highlighted the interest of prebiotic supplementation in the management of hepatic steatosis in preclinical models. However, the efficiency of such nutritional interventions in humans remains unclear.
Aim : Using a cohort of obese individuals treated with inulin versus placebo (FOOD4GUT cohort), and a model of mice transferred with the fecal microbiota from obese patients, we have addressed the following question : do the characteristics of the gut microbiota in obese individuals influence the effect of inulin on hepatic disorders?
Methods : The gut microbiota of four-week old mice was depleted using antibiotics. Four groups of mice were then colonized with stools from four human obese patients (hum-ob) selected for different gut microbiota composition, presence of hepatic steatosis and response to inulin in an interventional study. Conventional and hum-ob mice were then fed with a high-fat diet (HFD) during four additional weeks, supplemented or not with native inulin (Cosucra) (6-9 mice per group).
Results : We demonstrated a different response to inulin supplementation in the four groups of mice inoculated with different fecal material. Inulin significantly reduced the hepatic lipid content in mice inoculated with the faeces of two out of the four donors. The decrease in hepatic lipid accumulation in “responder” mice was associated with a reduced activation of nuclear expression of markers involved in lipids synthesis (SREBP1 and SREBP2 proteins).. Despite an increased cecal content – signing gut fermentation - observed in all humanized mice, the regulation of the gut microbiota by inulin also differed between donors. Interestingly, some bacterial genera were positively correlated with liver lipids and triglycerides (Barnesiella, Bilophila, Butyricimonas…) whereas some others ones are negatively associated with these parameters (such as Akkermansia or Clostridium XIVa). The different regulation of these bacteria by inulin may explain the observed difference on hepatic lipid metabolism in responder and non-responders in humans.
Conclusions : Our work using a model of gut microbiota transfer from patients into mice highlighted the differential response of humanized mice to dietary supplementation with inulin. We propose that the gut microbiota is an important component to take into account for personalized nutrition related to prebiotic dietary fibers in the future and the management of metabolic disorders including hepatic steatosis.

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CARBON NANOPARTICLE C60 FULLERENE AS A TREATMENT OF HEPATOCELLULAR CARCINOMA. H. Kuznietsova (1), N. Dziubenko (1), T. Herheliuk (2), O. Lynchak (1), Y. Prylutskyy (1), U. Ritter (3) / [1] Taras Shevchenko National University, Kyiv, Ukraine, Institute of Biology and Medicine, [2] Institute for Problems of Cryobiology and Cryomedicine, Kyiv, Ukraine, Department of Biotechnical Problems in Diagnostic, [3] Technische Universität Ilmenau, Ilmenau, Germany, Institute of Chemistry and Biotechnology.

Introduction : Hepatocellular carcinoma (HCC) accounts for 75–85% of primary liver cancers and occupies the 4th position in ranks of cancer death in the World in 2018. It is poorly diagnosed, has an extremely unfavorable prognosis and lack of effective medication therapy. HCC development is characterized by oxidative stress - the main cause and trigger of malignant degeneration, progression and metastasis. Carbon-based nanoparticle pristine C60 fullerene has the powerful antioxidant properties and demonstrates anti-inflammatory and antifibrotic activity under liver inflammation and fibrosis and antitumor activity under colon cancer.
Aim : To discover the impact of C60 fullerene on HCC development on rat model and the possible mechanisms of realization of that.
Methods : 64 male Wistar rats with initial body weight 120±10 g were used in experiment. HCC was initiated by single N-diethylnitrosamine (DEN, 200 mg/kg) intraperitoneal injection. After two weeks tumor promotion was achieved by subcutaneous injection of CCl4 (0.1 ml/100g) twice/week continuously for 20 weeks. In 15 weeks after HCC initiation cell malignant degeneration and well-developed cirrhosis were confirmed and applications of C60 and reference 5-fluorouracil (5FU) were started. Pristine C60 fullerene aqueous colloid solution (C60FAS; 0.15 mg/ml, size of aggregates 1.2-100 nm) was administered daily intraperitoneally at dose of 0.25 mg/kg. 5FU (15 mg/kg) was administered weekly intraperitoneally. At the 22nd week half of the animals were sacrificed, liver injury was evaluated visually (according to 13-point scale), by histological (HE staining) and biochemical (liver and plasma blood markers) methods. Another half was left for survival estimation (up to 53 weeks). Metastasis rates were assessed in autopsies at the 22nd and 53rd weeks. To disclose the mechanisms of C60 action we additionally used HepG2 cells (human HCC). C60 effects on cell proliferation (MTT-test), pan-cytokeratin, vimentin and p53 expression (immunohistochemistry), redox and metabolic state (biochemical markers) were assessed.

Results : C60FAS partially prevented tumor development (0-2 small tumor nodes per animal in liver compared to multiple well-developed tumors in non-treated rats), reduced liver damage score from 11.33 down to 9.25 and diminished its fibrotic alteration from 6.0 points according to Ishak score (established cirrhosis) down to 3.0 points (rare portal-portal linking septs). C60FAS also normalized elevated in 1.3-4.8 times compared to control direct (BD) and total bilirubin (BT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) and tended down alanine- (ALT) and aspartate-aminotransferase (AST). 5FU demonstrated the same or even less efficacy : rare but well-developed tumors were observed in liver, liver damage score was equal to 10.25, fibrosis score – 3.8 (marked portal-portal and portal-central septs), BD, BT, AST and GGT remained elevated. The median survivals of animals treated by C60FAS and 5FU corresponded to 32 and 31 weeks, respectively, compared to 18 weeks for non-treated rats. Moreover, analyzing the autopsies and slides of the pancreas we observed no atypical cells in pancreas at the 22nd and 53rd week in C60FAS group, but well-developed metastasis at the 53rd week in 5FU group, whereas non-treated animals demonstrated neoplastic cells aggregates and even well-developed tumors at the 22nd week and obviously massive metastasis at the 53rd one. We suggested C60 to realize its protective effects through antioxidant activity, as evidenced by normalization of elevated malonic dialdehyde (MDA), protein carbonyl groups (PCG), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GP), reduced glutathione (GSH) and depressed glutathione-S-transferase in HCC rats. C60 also decreased CAT, GP, GSH and PCG but increased SOD and MDA (by 23-151%) in HepG2 cells, demonstrating the controversial effect on their redox state. Furthermore, C60 almost completely inhibited glucose-6-phosphate dehydrogenase and enhanced p53 expression in HepG2 cells, which might contribute to its cytostatic activity against these cells (IC50=9 mmol/l). C60 inhibited pan-cytokeratin expression contributing to its antifibrotic activity, but enhanced vimentin one, which is typical for some cytostatics.
Conclusions : The ability of C60FAS to inhibit HCC development and metastasis diminishing liver fibrosis and maintaining its functional activity was concluded. These C60 effects could be realized through normalization of liver redox state, inhibition of pan-cytokeratin expression and cytostatic activity.

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HIGH ACCURACY OF CONTROLLED ATTENUATION PARAMETER AND VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY FOR DETECTION OF STEATOSIS AND FIBROSIS RESPECTIVELY IN NAFLD.
J. Weyler (1), L. Vonghia (1), W. Verlinden (1), A. Bagdadi (1), P. Michielsen (1), T. Vanwolleghem (1), A. Driessen (2), S. Francque (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology and hepatology, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Pathology.

Introduction : Non-Alcoholic Fatty Liver Disease (NAFLD) represents a spectrum ranging from Non-Alcoholic Fatty Liver (NAFL) to Non-Alcoholic Steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma. Patients with NASH and significant fibrosis are at highest risk for development of complications. Several non-invasive methods have been developed to diagnose and quantify hepatic steatosis and to predict presence of significant (≥F2) or advanced (≥F3) fibrosis. Vibration Controlled Transient Elastography (VCTE) is currently the most common technique used to determine liver fibrosis stage. Real-time 2D Shear Wave Elastography (RT-2D-SWE) has the advantage of estimating liver stiffness in real time guided by a B-mode image. Controlled attenuation parameter (CAP) estimates the amount of liver fat.
Aim : To study the accuracy to detect liver fibrosis assessed by the VCTE in NAFLD; to compare the accuracy of VCTE with biochemistry-derived indices (FIB-4, NAFLD Fibrosis score (NFS)); and to study the ability to detect steatosis by CAP.
Methods : Patients who underwent both a liver biopsy and VCTE in our center and were diagnosed with NAFLD were prospectively included in our study. To assess the discriminant power of VCTE with CAP to predict steatosis (>5% steatosis on histology), a control group was created out of patients who underwent a liver biopsy for another indication.
Results : 126 patients with NAFLD were included (28.6% NAFL, 71.4% NASH; 42.9% had ≥F2 and 27.8% ≥F3, therefore well balanced to discriminate between fibrosis grades). AUROC for predicting ≥F2 by VCTE was 0.801 and 0.843 for ≥F3. Compared to the XL-probe, the M-probe was superior in detecting ≥F2 (AUROC 0.695 to 0.859), and superior in detecting in ≥F3 (AUROC 0.705 to 0.909). Furthermore, the M-probe was superior in detecting ≥F3 compared to the FIB-4 (AUROC 0.779) and NFS (AUROC 0.745). In a subcohort of 84 patients, elasticity was also assessed by RT-2D-SWE. Compared to the RT-2D-SWE, VCTE using the M-probe is superior in detecting ≥F2 (AUROC 0.803 to 0.939) and ≥F3 (AUROC 0.756 to 0.911). The ability to detect ≥F3 using the XL-probe is greatly increased using a combination of elasticity and CAP (AUROC 0.705 to 0.858). CAP was assessed in a population of 157 patients who underwent a biopsy for suspected liver disease all aetiologies. CAP has a high accuracy in predicting steatosis with an AUROC of 0.921 and was highly significantly correlated with histological steatosis grade (Kendall's rho coefficient 0.52 with $p<0.001$).
Conclusions : VCTE is able to predict liver fibrosis stage with a high accuracy, and with a low failure rate. The M-probe is superior in detecting fibrosis compared to the XL-probe or RT-2D SWE, and to the biological indices NFS and FIB-4. Using a combination of VCTE and CAP improves detection of advanced fibrosis measured with the XL-probe. CAP is highly accurate in detecting steatosis and is significantly correlated to histological steatosis grade. VCTE with CAP therefore seems a very promising tool in non-invasive screening for NAFLD.

NUTRITIONAL MODULATION OF THE GUT-LIVER-BRAIN AXIS IN ALCOHOL-DEPENDENT PATIENTS : PRELIMINARY RESULTS OF THE GUT2BRAIN STUDY. C. Amadieu (1), S. Leclercq (1), A. Neyrinck (1), P. Stärkel (2), P. De Timary (3), N. Delzenne (1) / [1] UCLouvain, Belgium, Louvain Drug Research Institute, Metabolism and Nutrition Research Group, [2] Laboratory of Gastroenterology and Hepatology, Institut de Recherche Expérimentale et Clinique, UCLouvain, Brussels, Belgium, Department of Hepato-Gastroenterology, [3] UCLouvain, Belgium, Institute of Neuroscience.

Introduction : The gut microbiota regulates many important functions including metabolism, immunity and brain functions. Our previous studies have shown that chronic alcohol abuse induced a leaky gut and alterations of the gut microbiota composition, which are correlated with psychological symptoms suggesting the involvement of the gut-liver-brain axis in the development of alcohol use disorders (AUD).
Aim : The Gut2Brain study aims at modulating the gut-microbiota of AUD patients by prebiotics (inulin), and to evaluate the relevance for behavior and health.
Methods : A randomized, double-blind, placebo-controlled study included 50 AUD patients hospitalized for a 3-week detoxification program in the St Luc hospital (Brussels, Belgium). Patients were assigned to the prebiotic or placebo group (maltodextrin). Biological (microbiota composition, metabolites, cytokines and liver function), psychological measurements (depression, anxiety, sociability) and dietary anamnesis were performed at the beginning and the end of the detoxification program (17 days of supplementation).
Results : Prebiotic treatment is well tolerated by patients. The compliance was 97% and there were 6 dropouts. The cohort is composed of 36% of women and the average age is 49. They consume about 137 grams of ethanol per day. Psychological and first biological data will be presented at the Belgian Week of Gastroenterology for the first time.
Conclusions : The Gut2Brain study investigates for the first time the effects of prebiotics on gut microbiota composition and function, inflammation and psychological symptoms of AUD patients taking into account their nutritional habits. This study will help to design new therapeutic and/or preventive targets for AUD patients.

THE PREVALENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES MELLITUS PATIENTS. L. Heyens (1), Y. Kockaerts (2), D. Busschots (3), R. Bielen (3), J. Wellens (4), C. Van Steenkiste (4), S. Francque (5), G. Robaeys (3) / [1] Universiteit Hasselt, Belgium, Health and life sciences, [2] Ziekenhuis Oost Limbug (ZOL), Genk, Belgium, Endocrinology, [3] Universiteit Hasselt, Belgium, Health and life sciences, [4] AZ Maria Middelares, Ghent, Belgium, Gastro-enterology and Hepatology, [5] Antwerp University, Belgium, Health and life sciences.

Introduction : Non-Alcoholic Fatty Liver Disease (NAFLD) is globally becoming the most frequent cause of chronic liver disease and is one of the leading causes for hepatocellular carcinoma. In patients with type 2 diabetes mellitus (T2DM), NAFLD is reaching epidemic proportions. Insulin resistance is a key contributor to the development of both NAFLD and T2DM. Therefore, patients with T2DM have a higher chance of developing NAFLD. Nevertheless, little to no epidemiologic data is available about the presence of NALFD in T2DM patients.
Aim : Our aim was to determine the prevalence of NAFLD and fibrosis in a cohort of T2DM patients followed at Ziekenhuis Oost-Limburg (ZOL), Limburg.
Methods : This monocentric, Belgian cohort study determined the prevalence of NAFLD and fibrosis by two methods : retrospectively, we used non-invasive score calculations and prospectively, we performed non-invasive liver assessment. The non-invasive score calculations used were the Fibrosis-4 (FIB-4) score, and the Fatty Liver Index (FLI), used to determine liver fibrosis and fatty liver, respectively. In 2018, 2,910 T2DM patients were followed at ZOL. Of these, 1,000 patients were retrospectively analysed at random. In total, 73 patients were included in a prospective study and underwent a non-invasive liver assessment by FibroScan®. The Vibration Controlled Transient Elastography (VCTE) was used to determine liver fibrosis and the Controlled Attenuation Parameter (CAP) to determine the liver fat content. Cut-off values as determined by the Belgium Association for the Study of the Liver (BASL) were used (Francque 2018).
Results : In total 28 of the 1,000 analysed patients were excluded due to other reported liver disease and aged 35 or younger. In 218/963 (22.4%) T2DM patients, values for the FLI score were available. In relation to steatosis, little to no steatosis (S1) was found in 12/189 (6.4%) patients, a moderate amount of liver fat (S2) was found in 27/189 (14.3%) patients, and a serious amount of liver fat (S3) in 150/189 (79.4%) of the patients. In 525/972 (54.0%) values for the FIB-4 were available. In relation to fibrosis 63/525 (12.0%) patients had a fibrosis score corresponding to F4, 125/525 (23.8%) had significant fibrosis (F2-F3), and 337/525 (64.2%) had little to no fibrosis (F0-F1). Prospectively seven of the 73 patients were excluded due to alcohol abuse, failed FibroScan® measurements or for not being six hours sober. CAP measurements were available in 64 of the 66 (96.9%) patients. In relation to steatosis, S1 was found in 13/64 (20.3%) patients, S2 in 7/64 (10.9%) patients, and S3 in 44/64 (68.8%) of the T2DM patients. VCTE measurements were available in all patients. In relation to fibrosis, 34/66 (51.5%) patients had F0-F1, 5/66 (7.6%) patients had F2-F3, and 27/64 (40.9%) patients had F4. No significant difference was found between the group of patients with a low body

mass index (BMI)<25kg/m2 and haemoglobin A1c (HbA1c) <6.5, and the group with a high BMI and HbA1c for the retrospective data.

Conclusions : The study revealed a high prevalence of steatosis in the T2DM cohort at ZOL. In this cohort, one out of four patients had significant fibrosis and even twelve percent had liver cirrhosis according to the non-invasive scores. When the VCTE was used, one out of ten patients had significant fibrosis and two out of five had developed liver cirrhosis. The differences between the non-invasive scores and the non-invasive liver assessment for liver fibrosis are a subject for future research.

- B01 -

HUMAN AND BACTERIAL-DERIVED AMYLOIDS TRIGGER A DISTINCT TRANSCRIPTIONAL RESPONSE IN PRIMARY MYENTERIC NETWORKS. N. De Loose (1), P. Verstraelen (2), G. Garcia-Diaz Barriga (2), S. Van Remoortel (2), E. Bartholomeus (3), A. Braun (4), M. Gries (4), K. Schäfer (4), W. De Vos (2), J. Timmermans (2) / [1] University of Antwerp, Antwerp, Belgium, Laboratory of Cell Biology and Histology, [2] University of Antwerp, Belgium, Laboratory of Cell Biology and Histology, [3] University of Antwerp, Belgium, Center for Medical Genetics, [4] University of Applied Sciences Kaiserslautern, Zweibrücken, Germany, ENS Group.

Introduction : Recent fundamental and clinical research suggests that the gut and its enteric nervous system (ENS) play a long-underestimated role in amyloid-associated neurodegeneration. With pathological hallmarks being phenocopied in the ENS and with the resident microbiome acting as a major source of amyloid-like proteins, the gut may represent a putative entry route to amyloid-driven degeneration. However, the mechanisms underlying amyloid toxicity in the ENS are poorly characterized, nor is it known whether amyloids of host and bacterial origin alter the gene expression profiles of enteric neurons to a different extent.
Aim : To assess the transcriptional response to amyloid exposure in the ENS and to investigate whether host- and bacterial-derived amyloids differentially affect primary myenteric networks.
Methods : Myenteric neuronal networks of the colon of WT Black6 mice were isolated and exposed to bacterial-derived amyloid aggregates (Curli), human amyloid oligomers (Aβ1-42), or peptides with a scrambled sequence (Aβscr). After 24 hours of incubation, RNA sequencing was performed using a QuantSeq 3' mRNA library prep kit and an Illumina NextSeq 500 sequencer. Differentially expressed genes were identified with an analysis pipeline combining RsubRead and DESeq2. Dysregulated pathways were explored using bioinformatic tools such as GeneOntology, EnrichR, DAVID, GSEA, SPIA and Pathview. Validation of top hits and associated genes was done via qPCR.
Results : We found that exposure of myenteric neurons to Aβ1-42 give rise to specific transcriptomic alterations that were not observed after incubation with Aβscr. These changes mainly pertained to inhibition of the cell cycle (57 genes including mdm2, PCNA, Cdks and Orc6) and dysregulation of genes implicated in DNA repair (31 genes). Interestingly, exposure to Curli (as compared to control medium) induced a transcriptomic signature that points to activation rather than inhibition of the cell cycle (15 genes). Exposure to Curli additionally induced a signature of genes involved in an innate immune response pathway. Among those, five genes (Tirap, Ptges, Sod2, Cxcl2 and Cxcl5) were associated with TLR signaling. Since amyloids were shown to activate TLR1/2 signaling in cultured macrophages (Tükel et al., 2010), we further focused on this pathway with qPCR and found that many TLRs are expressed in colon and ileum (Tlr1-Tlr13) tissue, and in primary myenteric cultures (Tlr2-Tlr7), and that active inflammation (as induced by DSS or TNBS) significantly triggers their expression. A pro-inflammatory cytokine cocktail (TNFα, IL1β and IFNγ) gave rise to a similar upregulation in primary myenteric cultures, and also resulted in upregulation of the Nlrp3 gene, a critical factor in inflammasome formation.
Conclusions : We have shown that enteric neurons respond differently to host-derived and bacterial amyloids, but that both amyloids may induce gene expression changes that adversely affect cell physiology. We are currently investigating whether these pathways also become dysregulated/activated in vivo, and what the long-term consequences are in the context of pathology development.

- B02 -

SEX-DIFFERENCE IN THE GASTROINTESTINAL PHENOTYPE DEPENDS ON THE SUSCEPTIBILITY FOR CO-MORBID DISORDERS SUCH AS ANXIETY. S. Wellens (1), A. Accarie (2), J. Toth (1), L. Wauters (1), R. Farré (1), J. Tack (1), T. Vanuytsel (1) / [1] KU Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID), [2] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Clinical and Experimental Medicine.

Introduction : Functional gastro-intestinal disorders (FGID) are twice as prevalent in women than in men. Susceptibility to anxiety and stress, both more prevalent in women, are reported as predisposing factors to develop FGID. The Wistar Kyoto (WKY) rat is an anxiety-sensitive strain compared to the more resistant Sprague Dawley (SD).
Aim : We aimed to investigate the intestinal phenotype in male and female WKY and SD rats and evaluate the gender difference in both strains to further unravel the complex interplay between sex and anxiety in the onset of visceral hypersensitivity, hyperpermeability and local immune cell infiltration
Methods : Male and female WKY and SD (n=7/group) were tested for anxiety behavior by using the marble burying test and for colonic sensitivity at d90 by measuring the visceromotor response (VMR) to isobaric (from 15 to 60 mmHg) distensions. Intestinal and colonic permeability, mast cell and eosinophil infiltration were measured with Ussing chamber studies, Chromotrope2R staining and Mast Cell Protease type 2 immunostaining respectively.

Results : For both genders, WKY showed an increased visceromotor response to colorectal distension (Fig.1) compared to SD which was associated with an increased anxiety-like behavior in females (8.5±1.3 vs 13.11±0.9 marbles buried, $p<0.03$) and males (9±1 vs 12.44±0.9, $p<0.05$). Female WKY displayed an increased paracellular permeability in the jejunum (197.9±55.64 vs 379±48.14 pmol/cm², $p<0.05$) associated with a trend to increased eosinophil infiltration (577.9±51.54 vs 732.7±57.58/mm², $p=0.09$) while male WKY tended to have increased transcellular (0.10±0.019 vs 0.18±0.03 µg/ml, $p=0.07$) and paracellular (170.3±23.34 vs 319±69.35pmol/cm², $p=0.09$) permeability. In both strains, females displayed an increased visceromotor response to colorectal distension (Fig.1) compared to males while the anxiety behavior was similar. For the WKY, females presented an increased immune cell infiltration characterized by eosinophils in both the colon (132.9±19.34 vs 407±44.10/mm², $p<0.05$) and jejunum (375.9±30.4 vs 732.7±57.58, $p<0.05$/mm²) while for the female SD, an increased transcellular permeability to horseradish peroxidase was found (0.1±0.019 vs 0.2±0.04 µg/ml $p<0.05$).
Conclusions : Our results highlight that the genetic background and the sensibility to disorders such as anxiety, modify the sex-difference in the gastrointestinal phenotype. These observations further confirm the necessity to consider not only gender, but also the genetic background of the animals in the study of FGID pathophysiology.

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EXAMINING THE PROCESSING OF LUMINAL INFORMATION BY THE ENTERIC NERVOUS SYSTEM USING CA2+ IMAGING. C. Fung (1), M. Hao (2), J. Tack (3), W. Boesmans (4), P. Vanden Berghe (3) / [1] KU Leuven, Leuven, Belgium, TARGID, [2] University of Melbourne, Parkville, Australia, Anatomy and Neuroscience, [3] KU Leuven, Belgium, TARGID, [4] Hasselt University, Hasselt, Belgium, Biomedical Research Institute (BIOMED).

Introduction : Monitoring of ingested nutrients by an organism is essential for balancing energy input. The gastrointestinal tract plays an important role in this homeostasis. Nutrient signals sensed by specialized enteroendocrine cells in the epithelium are conveyed to the enteric nervous system (ENS) to initiate intestinal reflexes facilitating digestion and absorption. However, the extent to which the ENS is 'aware' of the luminal composition remains elusive.
Aim : We aimed to address whether there are specific enteric pathways dedicated to detecting different luminal stimuli and to characterise the neuronal pathways subsequently activated following EEC stimulation.
Methods : Calcium imaging was performed on intact jejunal preparations from Wnt1-cre;R26R-GCaMP3 mice, which express the fluorescent calcium indicator GCaMP3 in their ENS. Glucose (300 mM), acetate (100 mM), and L-phenylalanine (100 mM), as a model sugar, short chain fatty acid, and amino acid respectively, were perfused onto the mucosa whilst imaging the underlying enteric neurons. The mucosal perfusion of high-K+ (75 mM) Krebs was used to broadly depolarize electrically excitable EECs. Nutrient transport or diffusion across the mucosa was mimicked by pressure ejecting nutrients from a micropipette impaled through the epithelium of a villus to target the containing nerve endings, or by applying nutrients onto ganglia in peeled preparations. Responders were further classified by their cell size, and neurochemistry using post-hoc immunolabeling of calbindin and neuronal nitric oxide synthase (nNOS) in the myenteric plexus, and choline acetyltransferase (ChAT) and vasoactive intestinal peptide (VIP) in the submucosal plexus.
Results : Mucosal depolarization, glucose, acetate, and L-phenylalanine each evoked Ca2+ transients in distinct subsets of myenteric (22 ± 3%, 17 ± 6%, 12 ± 2%, and 9 ± 2%) and submucosal neurons (24 ± 6%; 21 ± 4%; 24 ± 7%, and 23 ± 3% of total neurons within the field of view, respectively). The cell size ($P < 0.0001$; One-way ANOVA) and proportions of calbindin and neuronal nitric oxide synthase (nNOS)-immunoreactive myenteric neurons that responded differed significantly between the stimuli ($P < 0.0001$; $\chi 2$ test), while submucosal responders to all stimuli were predominantly cholinergic (ChAT+) and of similar size. Nutrients applied into villi or onto ganglia did not elicit neuronal responses, indicating that nutrients are first sensed at the epithelium. Myenteric responses to mucosal depolarization were abolished after severing the connections between the myenteric plexus and mucosa, demonstrating that the luminal signal is transmitted via nerve projections running between these layers. The 5-HT3 receptor antagonist ondansetron (10 µM) also significantly reduced the proportion of myenteric neurons responding to mucosal depolarization (ondansetron : 8 ± 1% vs. time control : 37 ± 2%; $P = 0.0003$, Two-way ANOVA, Sidak's multiple comparisons test). This suggests that the response to mucosal stimulation is partly mediated via 5-HT acting on 5-HT3 receptors.
Conclusions : Different nutrients applied to the epithelium triggered distinct patterns of myenteric neuronal activation, suggesting that the ENS is able to discriminate between different compositions of luminal content such that it can respond accordingly. Further, our data demonstrate that enteric nerves are not directly sensitive to nutrients, but respond to the release of EEC signalling mediators such as 5-HT.

- B04 -

BENEFICIAL EFFECTS OF THE LOCALLY ADMINISTERED TRPV4-ANTAGONIST HC-067047 IN A POST-INFLAMMATORY RAT MODEL FOR VISCERAL HYPERSENSITIVITY. N. Hanning (1), H. Ceuleers (1), S. Van Remoortel (2), H. De Schepper (3), A. Smet (1), J. Timmermans (2), J. De Man (1), B. De Winter (1) / [1] University of Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, [2] University of Antwerp, Belgium, Laboratory of Cell Biology and Histology, [3] Antwerp University Hospital, Belgium, Gastroenterology and Hepatology.

Introduction : Transient receptor potential (TRP) channels have been implicated in visceral pain signalling. TRPV4 is expressed in the human colon and is involved in the sensation of chemical, thermal and mechanical stimuli. Sensitization of TRPV4 is one of the potential mechanisms contributing to the development of visceral hypersensitivity in irritable bowel syndrome (IBS) (Beckers et al., APT 2017). However, its role in mechanosensation and the therapeutic potential of TRPV4 antagonism in IBS has been mainly studied in vitro.
Aim : The aim of this study was to investigate the effect of the intrarectal administration of HC-067047, a TRPV4 antagonist, on visceral hypersensitivity in a 2,4,6-trinitrobenzenesulfonic acid (TNBS)-colitis post-inflammatory rat model for IBS.
Methods : At day 0, acute colitis was induced in adult male Sprague-Dawley rats with a TNBS enema (4 mg, in 50% ethanol). Control animals received an enema with 0.9% NaCl. Three days later, the presence of colitis was confirmed by colonoscopic scoring. From day 10 onwards, colonoscopy was repeated every 4 days until full endoscopic healing was observed. Then, electromyographic (EMG) electrodes were sutured into the abdominal musculature and exteriorized at the scapular region. Three days later, the TRPV4 antagonist HC-067047 (0.01-1-10 mg/kg) or its vehicle (25% 2-hydroxypropyl-β-cyclodextrin) was administered in the colorectum under isoflurane anaesthesia (5% induction, 2% maintenance). After 30 min, visceral sensitivity was assessed by quantifying the visceromotor response (VMR) to increasing colorectal distension pressures (10–60 mmHg, 20s, 4min interval). The VMR was expressed as an integral of the EMG response (area under the curve (AUC); μV/20s) and corrected by subtracting the baseline activity. Afterwards, we investigated the effect of HC-067047 on the viscoelastic properties of the colonic wall by measuring the colonic compliance. A pressure-controlled ramp distension protocol was initiated directly after the VMR measurements (0-60 mmHg in steps of 5 mmHg, 30s interval). The corresponding volume of air in the balloon was recorded and volume-pressure curves were used to represent the colonic compliance. Finally, the inflammatory parameters (colonoscopy, macroscopy and myeloperoxidase activity) were scored to confirm the post-inflammatory status at the day of the VMR and compliance measurements.
Results : Rats that received a TNBS enema showed signs of a mild colitis at day 3 of the experiment, as demonstrated by the significantly increased colonoscopic scores compared to control animals (7.39 ± 0.32, n=28 vs. 0.00 ± 0.00, n=16, $p<0.001$). The post-inflammatory status of the animals at the day of the VMR measurements (days 13-17) was confirmed by colonoscopic and macroscopic scoring, as well as by measuring the myeloperoxidase activity. In the sensitivity experiments, both control animals and vehicle-treated post-colitis rats showed gradually increasing VMRs, but VMRs were significantly higher in post-colitis rats, indicating the presence of visceral hypersensitivity in these animals. VMRs were increased in post-colitis vs control animals at both low distension pressures (20 mmHg : AUC 270.00 ± 62.27, n=8 vs. 51.13 ± 16.84, n=8, p=0.01) and high distension pressures (40 mmHg : AUC 544.88 ± 94.61, n = 8 vs. 147.88 ± 49.96, n=8, p=0.04). Intrarectal treatment with HC-06707 (0.01-1-10 mg/kg) resulted in a dose-dependent decrease of the VMRs compared to vehicle-treated post-colitis animals, with the highest dose completely reversing the visceral hypersensitivity. This effect was present in HC-067047-treated (10 mg/kg) vs. vehicle-treated post-colitis rats at both low distension pressures (20 mmHg : 72.39 ± 28.95, n=7 vs. 270.00 ± 62.27, n=8, p=0.04) and high distension pressures (40 mmHg : 175.29 ± 42.57, n=7 vs. 544.88 ± 96.61, n=8, $p<0.001$). Administration of a high dose HC-067047 (10 mg/kg) had no effect on visceral sensitivity in control animals. Post-colitis animals displayed a colonic compliance similar to control animals and treatment with HC-067047 increased colonic compliance only in the lowest dose (0.01 mg/kg) in post-colitis rats. Treatment with HC-067047 had no effect on the post-mortem inflammatory parameters.
Conclusions : This study shows that local administration of the TRPV4 antagonist HC-067047 decreased visceral hypersensitivity in a post-inflammatory rat model for IBS. The effects of HC-067-47 in a high dose (10 mg/kg) on visceral pain cannot be attributed to changes in the colonic compliance. Our results confirm that TRPV4 is a potential target for the treatment of visceral pain in IBS.

- B05 -

DUODENAL BILE SALTS AND MUCOSAL CHANGES ARE LINKED WITH GASTRIC EMPTYING AND SYMPTOMS IN FUNCTIONAL DYSPEPSIA PATIENTS . L. Wauters (1), M. Ceulemans (1), M. Lambaerts (1), A. Accarie (1), J. Toth (1), R. Mols (2), R. Farré (1), P. Augustijns (2), J. Tack (1), T. Vanuytsel (1) / [1] KU Leuven, Belgium, TARGID, [2] KU Leuven, Belgium, Drug delivery and disposition.

Introduction : Despite increasing evidence for duodenal epithelial hyperpermeability and low-grade inflammation in functional dyspepsia (FD) patients (Vanheel et al. Gut 2014), the role of luminal changes has scarcely been studied.
Aim : We aimed to study duodenal bile salt concentrations and pH in relation to duodenal mucosal changes, gastric emptying and symptoms in FD.
Methods : FD patients (Rome IV) were recruited with aspiration of duodenal fluids via a naso-duodenal tube after endoscopic collection of duodenal biopsies. Bile salt concentrations were measured in fasting and every 15min during 1h in fed state (Fortimel®, 300 kCal) using LC-MS/MS after pH-measurement. Paracellular dextran-passage (4 kDa) was studied in Ussing chambers and eosinophils counted on H&E-stained sections per high-power field (HPF; 0.24 mm2). Gastric emptying for solids (14C-octanoic acid breath test T1/2) and PAGI-SYM scores were determined. Multilevel (mixed) models were constructed with pH and bile salt concentrations (total, primary and secondary) as dependent and

time as within-subject independent variable of interest. Next, the effect of individual bile salt concentrations on T1/2 and symptoms was assessed before and after adding mucosal dextran-passage and eosinophils in the model to test for potential mediation.
Results : In total, 22 FD patients (19 female, mean ± SEM age 31 ± 2 years) were included. A significant effect of time was found for the increase in pH ($F=5.38$, $p=0.004$) and total bile salt concentrations ($F=17.93$, $p<0.0001$) with a similar evolution for primary and secondary bile salts. Mean paracellular dextran- passage was 28.8 ± 2.6 pmol with 12.9 ± 5.4 duodenal eosinophils /HPF. T1/2 was 72.4 ± 8.3 min, which correlated with dextran-passage ($r=.73$, $p=0.002$). PAGI-SYM score was 2.4 ± 0.1 and correlated with duodenal eosinophils ($r=0.54$, $p=0.026$) but not T1/2 ($r=-0.18$, $p=0.48$). A significant effect of the secondary bile salt taurodeoxycholic acid was found on paracellular dextran-passage ($F=7.19$, $p=0.016$) and T1/2 ($F=7.82$, $p=0.014$), but the effect on gastric emptying was not mediated by dextran-passage ($F=0.19$, $p=0.67$). A significant effect of the primary bile salt taurocholic acid was found on duodenal eosinophils ($F=6.15$, $p=0.028$) and PAGI-SYM ($F=6.26$, $p=0.022$), but the effect on symptoms was not mediated by eosinophils ($F=0.93$, $p=0.35$).
Conclusions : In FD patients, gastric emptying rate is associated with duodenal mucosal permeability but not symptoms, indicating that gastric dysmotility may be secondary to duodenal pathology. Indeed, symptoms are associated with duodenal eosinophils in FD patients. Although duodenal bile salts have significant associations with both gastric emptying and symptoms, the mechanisms do not seem to involve duodenal barrier or immune function and require further study in FD.

- B06 -

INHIBITION OF ADHESIOGENESIS WITH PROTEASE INHIBITORS NAFAMOSTAT MESYLATE, UAMC-00050, AND ENOXAPARIN IN A MURINE MODEL FOR SEPSIS AND PERITONITIS. P. Plaeke (1), J. De Man (1), A. Smet (1), I. De Meester (2), K. Augustyns (3), P. Jorens (4), G. Hubens (5), B. De Winter (1) / [1] University of Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, [2] University of Antwerp, Belgium, Department of Medical Biochemistry, [3] University of Antwerp, Belgium, Department of Medicinal Chemistry, [4] Universiteit Antwerpen / Antwerp University Hospital, WILRIJK (Antwerpen), Belgium, Laboratory of Experimental Medicine and Pediatrics / Department of Intensive Care Medicine, [5] Universiteit Antwerpen / Antwerp University Hospital, WILRIJK (Antwerpen), Belgium, Antwerp Surgical Training, Anatomy and Research Centre (ASTARC) / Department of Abdominal Surgery.

Introduction : Intraperitoneal adhesions following surgery or peritonitis are responsible for a wide range of complications, including bowel obstruction, abdominal pain, and even infertility. Additionally, these adhesions tend to make subsequent abdominal procedures more challenging. Proteases, involved in the coagulation and fibrinolysis, are essential in the etiopathogenesis of adhesions as they assist in the development of fibrin scaffolding. This scaffolding is the first stage of adhesions development and is required for the transition to mature, fibrous adhesions.
Aim : To modulate intraperitoneal adhesiogenesis by administering the serine protease inhibitors nafamostat mesylate (NFM), UAMC-00050 and enoxaparin in a murine sepsis and peritonitis model.
Methods : Intraperitoneal adhesions were induced in OF1 mice (Charles River, France) by caecal ligation and puncture (CLP) under ketamine-xylazine anesthesia. For this, the abdomen was opened by midline incision and the caecum was ligated at 50% of its length. Subsequently, the ligated caecum was punctured once with a 21 G needle. Sham mice underwent the same midline laparotomy without ligating or puncturing the caecum. Analgesia (buprenorphine) and fluid resuscitation were provided throughout the experiments. Wellbeing was monitored using a clinical disease score. Mice were euthanized 48 hours later and adhesions were scored based on the number of abdominal tissues involved (extent), the tenacity of the adhesions, and the time required to gain access to the ileum. This acted as an objective marker for the surgical accessibility of the abdomen. Three treatment schedules were used. In the preventive set-up (NFM, UAMC-00050), the drug was administered once during the CLP procedure. In the curative set-up (NFM), the drug was administered 3 times, starting 12 hours after the CLP procedure. Finally, in the combined preventive and curative setup (NFM, UAMC-00050, enoxaparin), the drug was administered during the CLP procedure and repeated 3 times afterwards. Statistical analysis was performed with SPSS v26 (IBM, USA), using one way ANOVA with Dunnett's post-hoc test.
Results : The CLP procedure resulted in significantly elevated clinical disease scores (0.22 vs. 4.51, $p<0.001$) and significant weight loss compared to the sham procedure (-2.40% vs. -9.51%, $p<0.001$). No significant differences in clinical disease scores or weight loss were observed between any of the different groups that received any kind of treatment. Only one adhesion was encountered in the sham group (n=23), while the CLP procedure resulted in intraperitoneal adhesions in all vehicle-treated mice (n=43). Preventive treatment with NFM at a dose of 10 and 20 mg/kg, significantly reduced the extent of the adhesions with 36.1% and 45.8% respectively and reduced tenacity of the adhesions and the surgical access time with up to 33.9% (10 mg/kg, $p<0.001$) and 26.4% (20 mg/kg, $p<0.001$). Similar results were seen when NFM was administered in a combined preventive and curative set-up at a dose of 10 mg/kg. In contrast, the curative treatment schedule, in which NFM was administered 12 hours after the onset of CLP-induced sepsis, failed to make any difference. This indicated the first 12 hours to be crucial for the prevention of adhesions and thus a preventive dose is required to notice a beneficial effect. The protease inhibitor UAMC-00050, which has less factor Xa inhibitory activity compared to

NFM, failed to reduce adhesions at any dose (1 to 5 mg/kg) and in any treatment set-up. Enoxaparin (10 mg/kg), which specific inhibits factor Xa, significantly and firmly reduced the extent and tenacity of the adhesions with 58.0% ($p<0.001$) and 42.5% ($p<0.001$) and completely normalized the time to gain access and ligate the ileum to control values.
Conclusions : Protease inhibitors significantly reduced the extent and severity of intraperitoneal adhesions under the condition that they were administered preventively and specifically targeted coagulation pathways, as demonstrated by our experiments with enoxaparin and NFM. Since these protease inhibitors should target the coagulation system, accurate titration and specification of the proteases involved are required in future studies.

- B07 -

CROSSTALK BETWEEN MONOCYTE-DERIVED MACROPHAGES AND ENTERIC GLIAL CELL IS ESSENTIAL FOR TISSUE REPAIR AND RECOVERY OF GASTROINTESTINAL TRANSIT AFTER INTESTINAL INFLAMMATION. S. Ibiza (1), M. Stakenborg (2), S. Abdu Rahiman (1), V. De Simone (2), B. Ke (2), Q. Wu (2), D. Pirottin (3), T. Marichal (4), G. Matteoli (2) / [1] KUL, Belgium, Targid, Department of Chronic Diseases, Metabolism and Ageing, [2] KU Leuven, Belgium, Targid, Department of Chronic Diseases, Metabolism and Ageing, [3] University of Liege, Liège, Belgium, Department of Functional Sciences(DSF), [4] University of Liege, GIGA-R, Liège, Belgium, GIGA-R.

Introduction : Patients undergoing open abdominal surgery often suffer from a transient episode of intestinal dysmotility referred to as postoperative Ileus (POI). Intestinal manipulation (IM) during the surgery evokes tissue damage and consequently an inflammatory response leading to impaired gastrointestinal motility. Recently our lab revealed a critical role for monocyte-derived macrophages (Mφs) in supporting neuromuscular function and restoring intestinal homeostasis after surgical trauma. Blocking monocytes recruitment to the muscularis externa (ME) after IM increased neutrophil-mediated immunopathology and prolong the clinical outcome of IM. However, it is yet not clear how monocytes sense environmental cues and differentiate into pro-resolving Mφs with neurotrophic functions.
Aim : The main goal of our project is to clarify how muscularis externa specific cues promote differentiation of monocytes sense and respond to the environmental cues during Intestinal Manipulation. To answer these questions, we have employed state of the art single cell RNA sequencing (sc-RNA seq) of different subset of intestinal myeloid cells at the steady state, during the acute and resolution phase of IM. In addition, interaction between enteric glial cells (EGCs) and monocytes was studied both in vitro and in vivo.
Methods : Wild-type female mice (WT; C57BL/6J) were subjected to IM. The severity of IM was evaluated by assessing gastro-intestinal transit and recruited of immune cells in ME by flow cytometry analysis. Immune cells infiltrating in the ME of day 0, 1 and 3 after IM were isolated by cell sorting analyzed and was performed Sc-RNA seq on the Chromium Single Cell Gene Expression Solution (10x Genomics). The 'Seurat' R package was used for graph-based clustering and visualizations.'SingleR' package was used for immune cell type annotations. Trajectory analysis was performed with 'Monocle2'. Gene set enrichment analysis (GSEA) was done on the average expression of the cell clusters using java GSEA Desktop Application. To study the possible anti-inflammatory effect of EGC-released factors, primary murine embryonic EGCs were co-cultured with bone marrow or monocytes.
Results : SSc-RNAseq of immune cells from the naive, inflamed and resolving muscularis revealed a complex immune cell landscape during different phases of POI. In steady state, muscularis resident Mφs were the main important cells present. However, at day 1 post IM we found mainly recruitment of monocytes and neutrophils, and interestingly at day 3 post IM most of the infiltrated myeloid cells were cleared as the inflammation resolves and only resident Mφs-like were present. Trajectory analysis revealed possible differentiation trajectory of classical monocytes to give rise to mature Mφs via multiple intermediate phenotypes. During this differentiation, the monocyte derived Ly6C low and MHCII low Mφs express the major pro-resolving Mφ factor Arginase 1, and are enriched by several potent neurotrophic factors. Interestingly, IM induced the production of the monocyte chemoattractant CCL2 by EGC, suggesting crosstalk between this cells and monocytes. In vivo imaging revealed recruitment of monocytes in close proximity to EGCs. In vitro, EGCs were able to promote differentiation of bone marrow and intestinal monocytes into pro-resolving Mφs as proven by induction of Arginase1, MRC-1, MSR1 and IL10. In parallel, EGC-secreted factors reduced the expression of pro-inflammatory cytokines such as IL-12 and IL-6 in monocytes stimulated with LPS.
Conclusions : Our study reveals a critical role for monocyte-derived Mφs in restoring intestinal homeostasis after surgical trauma. EGC seems to exert a critical function in attracting and modulating monocytes both in vivo and in vitro. In particular, enteric glial secreted factors promote monocyte differentiation into arginase 1-expressing Mφs with essential tissue repair capability essential in restoring intestinal homeostasis and supporting neuromuscular function after surgical trauma.

- B08 -

ROLE OF BITTER TASTE RECEPTORS ON INNATE IMMUNITY IN JEJUNAL CRYPTS FROM LEAN AND OBESE SUBJECTS. K. Liszt (1), Q. Wang (1), A. Segers (1), L. Ceulemans (2), B. Van Der Schueren (3), M. Lannoo (4), D. Inge (1) / [1] KU Leuven, Belgium, Gut Peptide Research Lab, Targid, [2] University Hospitals Leuven, Belgium,

Department of Abdominal Surgery and Transplant Coordination, [3] University Hospitals Leuven, Belgium, Clinical and Experimental Endocrinology, [4] University Hospitals Leuven, Belgium, Department of Abdominal Surgery.

Introduction : Bitter is an aversive taste perceived on the tongue, which acts as the first defense mechanism to protect our body against the ingestion of potentially poisonous compounds. Bitter taste is detected by around 25 subtypes of the taste receptor type 2 family (TAS2Rs) in humans. These receptors are expressed at several extra-oral sites of the human body including the gastrointestinal tract. Activation of TAS2Rs in human sinonasal cells induces the secretion of antimicrobial peptides. Since, in a knock-in mouse strain the expression of a TAS2R in Paneth cells and goblet cells has been demonstrated, we hypothesized that activation of TAS2Rs in the gut epithelium may trigger similar effects. In addition, since obesity affects Paneth cell function and TAS2R expression we wanted to investigate whether these mechanisms are altered in obesity.
Aim : This study aimed to investigate the effect of bitter compounds on innate immune factors in jejunal crypts from lean and obese subjects and their potency to induce the killing of intestinal bacteria as E. coli.
Methods : Isolated crypts from the jejunum of lean multi-organ donors (BMI : 23.9 ± 1.1 kg/m2, n=9) and obese patients (BMI : 39.8 ± 0.7 kg/m2, n=25) undergoing Roux-en-Y gastric bypass surgery were treated with aloin and denatonium benzoate (DB) and their effect on the mRNA expression of mucins (MUC2, MUC13), α-defensins (DEFA5, DEFA6) and β-defensins (DEFB1, DEFB4A) was measured by RT-qPCR. To quantify the release of anti-microbial peptides, immunofluorescence staining against α-defensin 5 and 6, and lysozyme were performed after DB treatment. The effect of the cell culture supernatants of crypts stimulated with bitter agonists (synthetic, natural, and quorum signaling molecules) on E.coli growth was investigated by counting the number of colony forming units (CFU).
Results : Obesity did not alter basal mRNA expression of the measured innate immune markers. DB treatment for 4h decreased in a concentration-dependent manner DEFA5 ($P<0.05$) and DEFA6 ($P<0.05$) mRNA expression in crypts of lean and obese subjects. In addition, DB treatment decreased ($P<0.05$) MUC13 and DEFB1, but increased ($P<0.05$) MUC2 mRNA expression in crypts of obese subjects only. One TAS2R that is targeted by DB and aloin, TAS2R43, is not present in 33% of the world population due to a deletion polymorphism. DB (1 mM) and aloin (30 μM) reduced ($P<0.05$) DEFA6 mRNA expression by 43±18% and 34±15%, respectively, in obese patients with but not in those without TAS2R43. The effect of DB (-36±13%) on DEFA5 expression was independent of TAS2R43. DB caused an acute release of α-defensin 5 ($P<0.05$) and lysozyme ($P<0.05$) in obese but not in lean subjects. The supernatant of DB (0.5 mM) stimulated crypts did not affect E. coli growth. However, the bacterial quorum sensing molecule, C12 acyl homoserine lactone (25 μM), induced an inhibition of E.coli growth by 67±26% ($P<0.001$) in jejunal crypts, while the natural bitter compounds aloin and quinine (0.1 mM) enhanced ($P<0.05$) E.coli growth.
Conclusions : Bitter agonists regulate the expression of some innate immune factors in the human jejunum with a higher sensitivity in obese than in lean subjects. Bitter agonists have opposite effects on E.coli growth indicating that they do not only induce the release of antimicrobial peptides but also affect the release of molecules (e.g. mucins) that stimulate bacterial growth. Funded by FWO postdoc fellowship

- B09 -

ANTI-INFLAMMATORY EFFECTS ON DUODENAL EOSINOPHILIA RATHER THAN ACID-SUPPRESSIVE EFFECTS EXPLAIN THERAPEUTIC EFFICACY OF PROTON PUMP INHIBITORS IN FUNCTIONAL DYSPEPSIA PATIENTS.

M. Ceulemans (1), L. Wauters (1), D. Frings (1), A. Accarie (1), R. Farre (1), G. De Hertogh (2), J. Tack (1), T. Vanuytsel (1) / [1] KU Leuven, Belgium, TARGID, [2] KU Leuven, Belgium, Pathology.

Introduction : Proton pump inhibitors (PPI) are the first line treatment in functional dyspepsia (FD), a common gastrointestinal (GI) disorder characterized by duodenal mucosal hyperpermeability and eosinophilia (Vanheel et al Gut 2014). PPI lower gastric acid secretion and increase gastric pH, but their effect on duodenal pH, mucosal integrity and eosinophilia remains unclear.
Aim : We aimed to confirm duodenal hyperpermeability and eosinophilia in FD patients vs. healthy volunteers (HV) and to investigate the effect of PPI on duodenal pH, permeability, eosinophils and symptoms in FD patients. Next, we assessed the possible role of intraluminal pH on duodenal barrier and immune function as well as symptoms. Finally, we hypothesized that duodenal eosinophils mediate changes in symptoms in FD patients after PPI-therapy.
Methods : FD patients fulfilling Rome IV criteria and matched HV were recruited to undergo upper endoscopy with duodenal biopsies, followed by aspiration of duodenal fluids via a naso-duodenal catheter. Paracellular passage of a fluorescein-labeled dextran (4 kDa) was recorded in Ussing chambers as a measure for mucosal integrity. Eosinophils were counted on H&E-stained sections per high-power field (HPF; 0.24 mm^2). Fasted and fed (1 h after Fortimel®, 300 kCal) pH of duodenal fluids was measured and symptoms were scored using the Patient Assessment of GI Disorders Symptom Severity Index (PAGI-SYM). Procedures were repeated in FD patients after pantoprazole 40 mg OD for 4 weeks (on-PPI). Multilevel (mixed) models were constructed in SAS for each dependent variable (pH, passage, eosinophils and symptoms) with treatment (off- or on-PPI) as within-subject independent variable of interest. Next, duodenal pH and eosinophils were separately added as a between-subject independent variable in the model to test potential mediation.

Results : In total, 22 FD patients (19 females, mean ± SEM age 31 ± 2 years) and 25 HV (16 female, age 30 ± 2 years) were included. Duodenal fasted (6.75 ± 0.2 vs. 5.98 ± 0.27; p=0.03) but not fed pH (6.1 ± 0.2 vs. 5.7 ± 0.2, p=0.21) was higher in FD vs. HV off-PPI. Paracellular dextran-passage (28.77 ± 2.63 vs. 17.94 ± 1.78 pmol; p=0.002), eosinophils (12.88 ± 1.32 vs. 3.65 ± 0.55 /HPF; p<0.0001) and symptoms (2.41 ± 0.12 vs. 0.25 ± 0.08; p=<0.0001) were also higher in FD vs. HV off-PPI. Fasted duodenal pH (delta=0.54; p=0.16) was similar while fed duodenal pH (delta=0.51; p=0.01) increased significantly in FD on- vs. off-PPI. During PPI treatment, a significant decrease was found for dextran-passage (delta=-12.22 pmol; p<0.001), eosinophils (delta=-8/HPF; p<0.0001) and PAGI-SYM scores (delta=-0.72; p<0.001) in FD patients. No mediating effect was found for duodenal pH on paracellular dextran-passage, eosinophils or symptoms on vs. off PPI (all p>0.05). When including duodenal eosinophils in the model, a significant mediating effect of duodenal eosinophilia was found for the PPI-induced decrease in PAGI-SYM (F=5.16, p=0.04).
Conclusions : In FD patients, duodenal hyperpermeability, eosinophilia and GI-symptoms improved significantly on-PPI. The PPI-induced increase in duodenal pH did not mediate the reduction in paracellular dextran-passage, eosinophils and symptoms, suggesting alternative, acid-independent effects of PPI-therapy. Indeed, the PPI-induced decrease in symptoms was mediated by a reduction in duodenal eosinophilia, indicating that anti-inflammatory effects of PPI may also play a role in the duodenum of FD patients.

- B10 -

INNATE IMMUNE CELL POPULATIONS CHARACTERISE THE DISRUPTED GUT-LIVER AXIS IN EXPERIMENTAL PSC-UC. K. De Muynck (1), B. Vanderborght (2), S. Van Campenhout (2), L. Devisscher (1) / [1] Ghent University, Ghent, Belgium, Department of Basic and Applied Medical Sciences (Gut-Liver Immunopharmacology Unit), [2] Ghent University, Ghent, Belgium, Department of Internal Medicine & Pediatrics (Hepatology Research Unit).

Introduction : Primary sclerosing cholangitis (PSC) is a rare, idiopathic disease characterised by sclerosing 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 axis is increasingly recognized as key mediator in PSC and PSC-UC pathology, but a comprehensive understanding of innate myeloid immune cell dynamics in both the liver and the gut in context of cholestasis and related UC remains elusive.
Aim : Characterise the dynamics of hepatic and intestinal innate immune cell populations in a mouse model for cholestasis and ulcerative colitis.
Methods : Common bile duct ligated (CBDL) or sham operated male SV129 mice were sacrificed 2,4- and 6-weeks post-surgery to evaluate liver cholestasis, inflammation and fibrosis, and colitis. Dextran sodium sulfate (DSS) was administered to male SV129 mice for seven days to induce colitis and mice were sacrificed after 10 days to evaluate colonic and hepatic inflammation. Serum, liver and colon were sampled from each mouse and analysed via histology, qRT-PCR, multiplex and flow cytometry of neutrophils and monocyte/macrophage populations.
Results : CBDL resulted in a gradual increase in total and direct serum bilirubin levels and hepatic expression of inflammatory markers and fibrosis over time. Flow cytometric analysis showed that Kupffer cells (KCs) were depleted while neutrophils, monocytes and monocyte-derived macrophages were enriched in the livers of CBDL mice compared to livers of sham-operated mice. CBDL also resulted in a significant increase of neutrophils and monocytes in the colon while this was not observed in sham-operated mice. DSS effectively induced colitis as evidenced by weight loss, colon shortening, marked mucosal erosions and cell infiltration on histology, and significant increased expression of colonic inflammatory markers. Flow cytometric analysis showed an increase in neutrophils, monocytes and monocyte-derived macrophages in both the colon and the liver, an increase in CX3CR1lo macrophages in the colon and a depletion of KCs in the liver during DSS-induced colitis.
Conclusions : In mice, cholestasis and associated liver inflammation, and fibrosis, results in colonic infiltration of neutrophils and monocytes while colitis is marked by hepatic infiltration of these innate immune cell populations and a depletion of resident liver Kupffer cells, indicating liver injury. These results show the liver-gut interconnection with respect to innate immune cell populations in the context of experimental cholestasis and colitis.

- B11 -

ECONOMIC BURDEN IN PRIMARY CARE IRRITABLE BOWEL SYNDROME PATIENTS WITH DIFFERENT STOOL PATTERN SUBTYPES. K. VAN DEN HOUTE (1), C. TACK (2), J. BIESIEKIERSKI (3), L. BESARD (4), J. SCHOL (2), E. COLOMIER (2), F. CARBONE (2), J. TACK (2) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Chronische ziekten, metabolisme en veroudering, [2] KULeuven, Leuven, Belgium, TARGID, [3] La Trobe University, Victoria, Australia, Department of Dietetics, [4] UZ Leuven, Leuven, Belgium, maag-, darm-, en leverziekten.

Introduction : Irritable bowel syndrome (IBS), characterized by abdominal pain related to the stool pattern in the absence of an underlying organic disease, is highly prevalent in primary care. However, the health economic impact of

IBS symptoms in patients with different stool patterns remains to be further investigated. Our aim was to evaluate this economic impact of different stool types in a large primary care IBS cohort.
Aim : Our aim was to evaluate this economic impact of different stool types in a large primary care IBS cohort.
Methods : Newly diagnosed IBS patients, recruited by 67 primary care physicians, completed questionnaires regarding demographics, Rome IV criteria and stool pattern subtypes. In addition, the economic impact of symptoms over the last 3 months was collected using a Health Resource Utilisation (HRU) and Work Productivity and Activity Impairment (WPAI) questionnaire, assessing medical consultations, diagnostic tests, therapies, hospitalizations, and absence from work. Results are shown as mean±SEM and compared by non-parametric statistical tests, Mann-Whitney test, and Chi square test.
Results : Seventy percent of the 438 primary care IBS patients (41.1±0.7 years, 75% females) fulfilled the Rome IV criteria. The stool subtype distribution was : 21% constipation (IBS-C), 28% diarrhea (IBS-D), 39% mixed (IBS-M), and 12% unclassified; the latter group was not included in stool pattern subtype analysis. Significantly more patients in the group with diarrhea (75%) fulfilled Rome IV criteria compared to constipation (67%) or mixed (60%) ($p=0.002$). Of the patients with constipation and diarrhea, respectively 65% and 59%, visited their physician in the previous 6 months, which was significantly more compared to 33% with a mixed stool type (both $p<0.0001$). In addition, a significantly higher percentage of IBS-D (22%) patients underwent additional tests compared to IBS-C (9%, $p=0.008$) and IBS-M (9%, $p=0.001$), with higher prevalence of analyses of blood count ($p=0.007$), CRP ($p=0.04$), and analysis of stool samples ($p=0.05$), as well as a trend towards more thyroid function test ($p=0.06$). Sixteen percent of IBS-M patients had taken prescribed medication, which was significantly less than IBS-C (32%, $p=0.003$) and IBS-D (37%, $p<0.0001$). A similar result was found for medication without prescription (23% IBS-M vs. 30% IBS-C ($p=0.03$) and 28% IBS-D ($p=0.05$)). The proportion of patients with impaired functioning during working hours was also significantly higher in IBS-D (37%, $p=0.003$) and IBS-C (41%, $p=0.0009$) patients compared to IBS-M (22%).
Conclusions : In a large primary care IBS cohort, a higher percentage of IBS-D patients fulfilled Rome IV criteria compared to the group with constipation and a mixed stool type. In addition, they underwent more diagnostic tests in comparison to both other groups. The economic burden of patients with diarrhea and constipation was higher compared to mixed through physician consultations, medication use and work impairment.

- B12 -

EXPLORING THE MOLECULAR SIGNALLING PATHWAYS OF MUC1 AND MUC13 IN INTESTINAL EPITHELIAL CELLS DURING INFLAMMATION IN VITRO : IMPORTANT MEDIATORS OF INTESTINAL BARRIER INTEGRITY? T. Breugelmans (1), B. Cuypers (2), J. De Man (1), K. Laukens (2), B. De Winter (1), A. Smet (1) / [1] Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium, Faculty of Medicine and Health Sciences, [2] AdReM Data Lab, University of Antwerp, Antwerp, Belgium, Department of Mathematics and Computer Science.

Introduction : The intestinal mucosal barrier consists of a thick mucus layer, a single epithelial cell layer and the lamina propria interacting with innate and adaptive immune cells. Secreted and transmembrane mucins are major components of the mucus barrier. Besides providing protection to the underlying epithelium, transmembrane mucins also participate in the cell signal transduction in response to inflammation. Of particular interest are MUC1 and MUC13, which are increasingly expressed in the inflamed colonic mucosa of patients with inflammatory bowel diseases (IBD). Aberrant expression of mucins could disrupt barrier integrity resulting in chronic inflammation and subsequent progressing to cancer. Nevertheless, the molecular signalling pathways related to aberrant MUC1 and MUC13 expression in response to inflammation remain poorly understood.
Aim : This study aimed to explore and identify potential upstream regulators and downstream effectors of epithelial MUC1 and MUC13 expression during inflammation focusing on intestinal barrier-related genes.
Methods : LS513 intestinal epithelial cells were transfected with silencing RNA (siRNA) targeting MUC1 and MUC13, after which they were stimulated with 20 ng/mL TNF-α or IL-22 for 24h. Untreated cells and cells transfected with negative control siRNA were included as controls. siRNA transfection and cytokine stimulation were validated by qPCR. Subsequently, Illumina mRNA sequencing was performed to investigate differentially expressed genes (DEGs) and the corresponding canonical pathways involved. After data processing (using Trimmomatic v0.38, STAR 2.6.1a and DESeq2 tools), pathway analysis was performed using Ingenuity Pathway Analysis software (fold change > [1.5], $p < 0.05$, $q < 0.1$). Additionally, DEGs were further explored individually for their potential role in directly modulating intestinal barrier integrity.
Results : Transcriptome analysis of untreated LS513 cells silenced for MUC1 or MUC13 (vs unsilenced controls) revealed respectively 2006 and 3232 candidate downstream effectors. During the stimulation with TNF-α or IL-22, knockdown of MUC1 resulted in 39 and 857 and of MUC13 in 103 and 88 DEGs respectively. In the latter sets of genes, several molecular pathways were significantly enriched, including those involved in inflammation (e.g. IL-6 signalling, IL-17 signalling pathway), cell invasiveness (e.g. regulation of the epithelial-mesenchymal transition pathway) and cell-cell interactions (e.g. epithelial adherens junction signalling, tight junction signalling). A targeted search on intestinal barrier-related genes showed the differential expression of several claudins (CLDN1, 2, 3, 4, 7), cadherins (CDH3,

PCDH1) and tubulins (TUBA1A, TUBA1C, TUBA4A, TUBB, TUBB3) due to silencing of MUC1 or MUC13 during cytokine stimulation. Furthermore, the NFkB complex, ERK, EHF and STAT1/3 were identified as potential upstream regulators of MUC1 and MUC13 expression during TNF-α and IL-22 stimulation.
Conclusions : Silencing of MUC1 and MUC13 in intestinal epithelial cells resulted in cytokine-dependent and -independent changes in gene expression, including genes involved in the modulation of intestinal barrier integrity. These results highlight their importance in co-regulating intestinal barrier homeostasis.

- B13 -

POSTINFECTIOUS ONSET IN FUNCTIONAL DYSPEPSIA IS A RISK FACTOR FOR WEIGHT LOSS. J. Schol (1), F. Carbone (1), K. Van Den Houte (1), E. Colomier (1), J. Tack (1) / [1] KU Leuven, Belgium, TARGID.

Introduction : Functional dyspepsia is a prevalent disease and presents with symptoms located at the epigastric region. The Rome IV criteria differentiates the subgroups postprandial distress syndrome (PDS), characterized by early satiation and postprandial fullness, and the epigastric pain syndrome (EPS) characterized by epigastric pain or burning. Acute gastroenteritis and H. Pylori infection have been identified as risk factors for functional dyspepsia, in the former case referred to as postinfectious functional dyspepsia (PI-FD). It is unclear how these risk factors relate to functional dyspepsia.
Aim : Our aim was to study the association of PI-FD and H. pylori status with clinical profiles, including PDS or EPS, and the amount of weight loss.
Methods : Consecutive functional dyspepsia patients filled out questionnaires to assess symptom frequency and severity. Patients were identified as PDS, EPS or overlap subgroup according to Rome III criteria. Additionally, the post-infectious history and H. Pylori status were determined. Analyses were performed using Chi-square test. Results were considered significant if $p<.05$. Data are described as mean ± standard error of the mean.
Results : In a cohort of 620 patients with functional dyspepsia (68.4% females, 41±0.6 years old, 22.2±0.2 kg/m^2), 34.7% were characterized as PDS (n=215, 65.6% females, 41±1 years old, 22.1±0.3 kg/m^2), 19.4% as EPS (n=120, 67.5% females, 41±1 years old, 22.5±0.48 kg/m^2) and 46% showed overlap (n=285, 70.9% females, 41±1 years old, 22.1±0.3 kg/m^2). Postinfectious onset of symptoms was reported by 26% of patients, respectively 24%, 24% and 22% in the PDS, EPS and overlap subgroups. H. Pylori status was positive in 17% of patients, with 16%, 21% and 22% in respectively PDS, EPS and overlap groups (NS). Hence, PI onset was no risk factor for any of the subgroups (OR 0.80 (PDS); OR 0.82 (EPS), OR 1.37 (overlap)). Likewise, H. Pylori infection was no risk factor for subgroups (OR 0.70 (PDS), OR 1.06 (EPS), OR 1.3 (overlap)). Weight loss (5.3±0.3 kg) was reported by 59% of patients, distributed as 70% in PDS (5.4±0.5 kg), 47% (3.6±0.5 kg) in EPS and 55% (6.0±0.5 kg) in the overlap group. PI-FD patients were more likely to experience weight loss in the total patient group (OR 2.44, $p<.0001$), the EPS (OR 2.90, $p=.02$) and overlap group (OR 3.72, $p<.0001$) but not in PDS (OR 1.22, $p=.58$).
Conclusions : In this large cohort study, postinfectious onset of symptoms of functional dyspepsia is a risk factor for weight loss but is not associated with the symptom pattern of PDS, EPS or overlap subgroups.

- B14 -

VOLATILE ORGANIC COMPOUND PROFILING OF BREATH SAMPLES AS A BIOMARKER TO DISCRIMINATE BETWEEN PATIENTS WITH IRRITABLE BOWEL SYNDROME AND HEALTHY CONTROLS : A FEASIBILITY STUDY. K. Van Malderen (1), E. Janssens (1), J. De Man (1), B. De Winter (1), H. De Schepper (2), K. Lamote (1) / [1] Antwerp University, Belgium, LEMP, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology.

Introduction : There is a huge unmet need for non-invasive biomarkers for a better diagnosis and a more personalised treatment of irritable bowel syndrome (IBS) patients. An emerging research field to be explored for this purpose is volatomics, enclosing volatile organic compounds (VOCs). VOCs are detected in exhaled breath and faeces, reflect the human metabolism, and are induced by inflammation and gut microbiota, thereby serving as a potential biomarker source.
Aim : To assess whether VOC profiling of breath samples is feasible to distinguish IBS patients from healthy controls.
Methods : Breath and background samples of 9 IBS patients and 9 matched healthy controls were collected and analysed by multicapillary column/ion mobility spectrometry (MCC/IMS). Participants were requested to refrain from eating, drinking or brushing their teeth at least 2 hours prior to analysis. Participants were asked to put on a nose-clip and breathe tidally through a Spiroscout sampler for 3 minutes, after which 10ml alveolar air is collected and immediately analysed. After breath sampling, 10 ml of background air is collected by the internal MCC/IMS pump and analysed. In order to correct for potential background contamination, the alveolar gradient of VOCs was calculated. These VOC gradients were then used as independent variables in a lasso regression analysis followed by leave-one-out cross-validation, to discriminate IBS patients from healthy controls. Furthermore, principal component analysis was used to cluster IBS patients and healthy controls.
Results : IBS patients and controls were matched and had a mean (SD) age of 33.1 (8.2) years for healthy controls and 33.1 (8.5) years for IBS patients. Both groups included 2 males and 7 females. Considering the low sample size, IBS

subtypes were pooled (7 IBS-D and 2 IBS-M). IBS patients were differentiated from healthy controls, with a sensitivity of 100% (71.7%-100%), a specificity of 88.9% (56.2%-99.4%), a positive predictive value of 90% (59.7%-99.5%), a negative predictive value of 100% (68.8%-100%), an accuracy of 94.4% (75.6%-99.7%) and an area under the curve of 0.951 (0.815-1.000). Principal component analysis showed separate clusters of patients and controls.
Conclusions : VOC analysis in exhaled breath from IBS patients and healthy controls shows to be feasible and promising as a diagnostic tool (94.4% accuracy). However, in order to confirm its clinical utility in diagnosing IBS, further research in larger populations is needed, taking the IBS subtypes and confounders (such as medication and diet) into account.

- B15 -

PREDICTORS OF TREATMENT RESPONSE TO THE TRADITIONAL AND THE LOW FODMAP DIET FOR PATIENTS WITH IRRITABLE BOWEL SYNDROME. E. Colomier (1), L. Van Oudenhove (2), J. Tack (1), L. Böhn (3), S. Bennet (3), S. Störsrud (3), L. Öhman (3), H. Törnblom (3), M. Simrén (3) / [1] KU Leuven, Belgium, GI Motility and Sensitivity Research Group, Translational Research Center for GI Disorders, [2] KU Leuven, Belgium, Laboratory for Brain-Gut Axis Studies, Translational Research Center for GI Disorders, [3] University of Gothenburg, Göteborg, Sweden, Institute of Medicine, Department of Internal Medicine & Clinical Nutrition, Sahlgrenska Academy.

Introduction : The NICE traditional diet for irritable bowel syndrome (IBS) patients and the low fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) diet have shown efficacy in IBS patients. Predictors of diet response remain to be identified.
Aim : Therefore, we aimed to investigate psychological, nutritional, and microbial factors as diet response predictors for 4 IBS symptoms.
Methods : Seventy-five IBS patients were randomized to the low FODMAP (n=38) or NICE diet (n=37) for 4 weeks. Baseline measures included stool samples evaluated by the GA-map™ Dysbiosis Test, generating a Dysbiosis Index, 4-day food diaries for calculation of average daily energy and FODMAP intake (DIETIST XP V.3.1, Kostdata.se, Sweden), Patient Health Questionnaire, Hospital Anxiety & Depression Scale and Visceral Sensitivity Index to measure somatic symptoms, psychological distress, and gastrointestinal (GI) anxiety, respectively. Outcome measures were 4 subscales (bloating, constipation, diarrhea, and pain) of the GI symptom rating scale treated as continuous variables in linear mixed models. Models included the main effect of baseline predictors on subscale scores, the main effect of time as a linear slope, and the interaction effect testing if baseline variables predict response slope. Lastly, a diet variable (including its main effect and all interactions) was added to test if baseline variables differentially predict response to the low FODMAP and NICE diet.
Results : We included 65 patients; 32 on low FODMAP and 33 on NICE diet. In models without covariates, both diets were shown to be effective and reduced the severity of bloating, diarrhea, pain (all $p<0.0001$), and constipation ($p<0.05$). Adding the diet variable to the model without covariates indicated absence of differences in response between the diets for any of the symptoms, thereby confirming an earlier analysis of Böhn et al. For pain, a lower dysbiosis index ($p=0.02$) and higher energy intake ($p=0.003$) predicted better response to both diets (table 1). For constipation, lower dysbiosis index predicted better response to both diets ($p=0.009$). For diarrhea, FODMAP intake tended to be associated with response to both diets ($p=0.057$), driven by a significant association between higher baseline FODMAP intake and better response to the NICE diet. For bloating, higher levels of psychological distress predicted worse response to both diets ($p=0.03$). FODMAP intake emerged as a differential predictor for treatment response (interaction effect : $p=0.04$), with higher baseline intake associated with worse response to the low FODMAP diet, and better response to the NICE diet.
Conclusions : Patterns of psychological, nutritional, and microbial factors predict treatment response to the low FODMAP and NICE diet for specific symptoms. These findings may inform individual tailoring of dietary treatment advice in IBS patients.

- B16 -

SOMATIZATION, ANXIETY, DEPRESSION AND FEAR OF PAIN LEVELS ARE NOT SIGNIFICANTLY DIFFERENT ACROSS THE GASTROESOPHAGEAL REFLUX DISEASE SPECTRUM. A. Geeraerts (1), L. Van Oudenhove (2), H. Geysen (1), T. Vanuytsel (1), J. Tack (1), A. Pauwels (1) / [1] KU Leuven, Belgium, TARGID, [2] KULeuven, Leuven, Belgium, TARGID.

Introduction : Co-morbid somatization, (symptom-specific) anxiety and depression symptoms are prevalent in functional gastrointestinal disorders, such as functional dyspepsia. Based on previous research, it has been hypothesized that patients with functional heartburn (FH) display higher levels of anxiety and depression compared to the other phenotypes in the gastroesophageal reflux disease (GERD) spectrum. Furthermore, some studies suggest that psychological aspects play an important role in the pathophysiology of reflux hypersensitivity (RHS). However, it has recently been shown that esophageal hypervigilance and symptom-specific anxiety are consistent among the GERD spectrum, regardless of the acid exposure time (AET).

Aim : To investigate levels of somatization, anxiety, depression, and fear of pain among the different GERD phenotypes in a large cohort of patients seen at a tertiary care center.

Methods : Patients with typical GERD symptoms ('on' or 'off' proton pump inhibitors (PPIs), undergoing 24-hour impedance-pH monitoring (MII-pH) were asked to fill out several questionnaires. Patients were classified in 4 categories based on the MII-pH recordings (Lyon consensus) : true GERD, borderline GERD, RHS and FH. Depression and somatization were measured using the Patient Health Questionnaire (PHQ-9, PHQ-12, PHQ-15), anxiety was measured using the generalized anxiety module of the PHQ(7) and fear of pain was assessed with the Pain Anxiety Symptom Scale (PASS). Data were analyzed using SAS 9.5 (SAS Institute, Cary, NC, USA). General linear models were used to compare the averages between the 4 groups.

Results : Three hundred fifty-four patients were included, which were classified as follows : 115 true GERD, 68 borderline GERD, 57 RHS and 114 FH. Patients with RHS were significantly younger compared to patients with true GERD, borderline GERD and FH. Although the percentage of females was slightly higher in RHS and FH, this did not reach statistical significance. Patients with true GERD had a significantly higher BMI compared to patients with RHS and FH. Most importantly, we could not find any significant differences between groups in PHQ and PASS scores. The prevalence of depression (PHQ9 sum score $\geq$10) was 41% in our cohort, which is markedly higher compared to only 5.6% in the general population. 26.5% of our patients displayed a high level of somatization (PHQ15 sum score $\geq$15), compared to 3.1% in the general population.

Conclusions : This study shows that somatization, anxiety, depression and fear of pain was not higher in FH and RHS compared to patients with true and borderline GERD. Overall, our cohort shows a higher prevalence rate for depression and somatization compared to the general population. Therefore, screening for psychological and extraintestinal symptoms should be routinely performed in all different GERD phenotypes.

CASE REPORTS

- C01 -

A CURIOUS CASE OF COLLAGENOUS COLITIS. S. De Meulder (1), F. Van De Mierop (2) / [1] University Hospital, Gasthuisberg, Leuven, Belgium, Belgium, Gastro-enterology, [2] Sint Augustinus Ziekenhuis GZA, Antwerp, Belgium, Gastro-enterology.

A 77-year old woman presented with a two-month history of diarrhoea. She had a past medical history of infectious colitis dating from 2005, including duodenitis with partial villous atrophy on duodenal biopsy. Celiac serology was unremarkable at the time. She underwent a colonoscopy in 2007 after an episode of diverticulitis, which showed no abnormalities. Her medical history further included gastro-oesophageal reflux disease (GERD), hypertension, hyperlipidemia and hypothyroidism. She had also undergone a cholecystectomy and a hysterectomy. Her medication included pantoprazole, aspirin, loop diuretic, statin, levothyroxin, angiotensin-converting-enzyme inhibitor (ACE-inhibitor), benzodiazepine and diltiazem. Clinical examination was uneventful. Recent laboratory values were normal, including a normal thyroid function. Stool culture and screening for Giardia lamblia and Cryptosporidium were negative. She reported smoking a few cigarettes a day. A new colonoscopy was performed, which showed spontaneous mucosal tears with bleeding in the right colon. The pathology report confirmed the presence of microscopic colitis, more specifically collagenous colitis (CC). Given the impressive presentation, the patient was started on budesonide, with complete resolution of the symptoms a few weeks later. A follow-up gastroscopy was performed to attain new duodenal biopsies. These showed no signs of celiac disease. Pantoprazole was stopped, as the gastroscopy was normal, as were the statins. Budesonide was tapered over a 12-week period. She was also advised to quit smoking. Collagenous colitis (CC) is a condition characterized by chronic non-watery diarrhoea caused by inflammation in the colon. Typically, these patients have a normal looking bowel on endoscopy but inflammation on biopsy (1). In rare cases, there is superficial mucosal cracking. There is a known association with celiac disease. Smoking is a risk factor for the development of CC (2). Certain medication may also play a role in its pathogenesis (NSAIDs, PPIs, SSRIs and statins) (2-4). The first step in the treatment is to exclude provoking medication. In mild disease, antidiarrheal medication may suffice. There is an important role for the use of budesonide in the induction therapy, and if necessary also in the maintenance therapy (3). References : 1. Kafil T, Nguyen T, Patton P, Macdonald J, Chande N, McDonald J. Interventions for treating collagenous colitis (Review). Cochrane Database Syst Rev. 2017;(11). 2. Münch A, Aust D, Bohr J, Bonderup O, Bañares FF, Gastroenterology D, et al. Microscopic colitis : Current status, present and future challenges : Statements of the European Microscopic Colitis Group. J Crohn's Colitis [Internet]. 2012;6(9) :932–45. Available from : http ://dx.doi.org/10.1016/j.crohns.2012.05.014 3. Nguyen GC, Smalley WE, Vege SS, Carrasco-labra A. American Gastroenterological Association Institute Guideline on the Medical Management of Microscopic Colitis. Gastroenterology. 2016;150(1) :242–6. 4. Gentile N, Yen EF. Prevalence, Pathogenesis, Diagnosis, and Management of Microscopic Colitis. Gut Liver. 2018;12(3) :227–35.

- C02 -

INTESTINAL SPIROCHETOSIS : THINK ABOUT IT TO DIAGNOSE IT. F. Hamoir (1), N. De Suray (1), J. Dargent (2), P. Warzee (1) / [1] GHDC, Charleroi, Belgium, Gastroenterology, [2] IPG, Charleroi, Belgium, Pathology.

Background : Intestinal spirochetosis (IS) is a condition characterised by the attachment of spirochetal bacteries to the apical cell membrane of colorectal epithelium. The two main spirochetes species responsible of IS are Brachyspira pilosicoli and Brachyspira aalborgi. Even if IS pathologic significance remains uncertain, it's known as a cause of chronic diarrhea, rectal bleeding or abdominal pain. Prevalence of IS is significantly higher in developing countries than in areas with a high standard of living. In developed countries, the highest rates of colonization of stools with IS are found in homosexual males and in human immunodeficiency virus (HIV) infected individuals. Endoscopic biopsies must be performed to confirm the diagnosis of IS. Most of the time endoscopy is described to be macroscopically normal. Diagnosis is therefore based on histology. We report here five cases of IS recently diagnosed in our department.
Case Reports : Mean age of patients at diagnosis was 48.6 ± 13.2 years. All were males and it is worth noting that two patients had homosexual intercourse. Medical treatment included only pantoprazole for two patients, the other three were free of treatment. All five patients were symptomatic and had rectal bleeding. Two patients also complained of diarrhea and abdominal pain. Blood tests revealed CRP elevation (75 mg/L) with normal neutrophils in one and isolated hight level of neutrophils in another patient (9480/mm3). Lab results were unremarkable for the other three patients except for positive TPHA test in one. Lower intestinal tract endoscopy was performed in all patients. Macroscopic aspect of the colon mucosa was normal in three of them. Endoscopic examination showed local hyperhemia of the rectal mucosa in one and appearance of colitis and discontinuous low proctitis in last one. Histology revealed signs of IS in all five patients. Specific treatment (metronidazole 500mg three times a day for 10 days) was given to three patients with long-lasting complaints. Clinical remission was observed in two of them. The third received additional mesalazine treatment due to relapsing symptoms.

Conclusion : Intestinal spirochetosis is not frequent but certainly underdiagnosed. IS must be included in the differential diagnosis of chronic diarrhea, rectal bleeding and abdominal pain. Lower gastrointestinal endoscopy with biopsies is essential for its diagnosis.

- C03 -

AN ILEAL GIST AS A RARE CAUSE OF OVERT LOWER GASTRO-INTESTINAL BLEEDING IN A 25-YEAR OLD WOMAN : A CASE REPORT. E. Van Mieghem (1), S. Van Outryve (2), J. Wauters (2), P. Steger (2) / [1] GZA Sint-Vincentius ziekenhuis, Antwerpen, Belgium, Internal Medicine, [2] GZA Sint-Vincentius Ziekenhuis, Antwerpen, Belgium, Gastro-Enterology.

Gastro-intestinal stromal tumors (GISTs) are rare mesenchymal tumors of the digestive tract with a reported incidence in Europe of 10-15 per million people. Most frequently they occur in persons older than 40 with median age of 60 years. A small percentage of GISTs present themselves with overt gastro-intestinal bleeding. Case presentation A 25-year old woman presented herself at the Emergency department with profuse rectal bleeding and a syncope. On admission she suffered from normocytic anemia with a hemoglobin of 7,4g/dl. Gastroscopy, rectosigmoidoscopy and total colonoscopy were performed with no identification of an active source of bleeding. To exclude to possibility of a bleeding Meckel diverticulum, a radionuclide scan was performed, which was negative. During hospitalization hemoglobin fell to 5,6g/dl for which transfusion of 3 units packed cells was needed. A CT abdomen was performed on which a contrast-enhancing soft tissue mass was visualized in the left flank. For further work-up a MRI was performed which confirmed the presence of a mass localized next to the small intestine. Due to the possibility of a neuro-endocrine tumor (NET) a DOTANOC PET-CT scan was performed, which excluded the presence of a somatostatin-receptor expressing tumor. A laparoscopic resection was planned for further anatomopathological identification. During surgery a 4cm long-2.6cm wide tumor originating from the proximal ileum was visualized on the anti-mesenterial side of the bowel. Due to the size of the tumor laparoscopy was converted to mini-laparotomy during surgery. A single lymph node was also sampled during resection. Anatomopathological examination confirmed the diagnosis of a GIST with a low-risk profile according to the NIH-criteria due to only 1 mitotic count per 50 high-power fields (HPF) and tumor diameter <5cm. Tumor cells diffusely expressed CD117 and to a lesser extent CD34. 10 days after resection, the patient could be discharged from the hospital in good health. GISTs are the most common mesenchymal tumors of the gastro-intestinal tract, but they still only represent 1% of the digestive neoplasms. They are most commonly localized in the stomach (40-60%), followed by the small intestine (25-30%). Clinical presentation depends on size and location. In some cases they are found incidentally during endoscopy or laparoscopy for other indications, but they can also present with vague abdominal complaints. In more severe cases diagnosis is made following gastro-intestinal bleeding or bowel obstruction due to volvulus or intussusception. Gastro-intestinal bleeding due to a small bowel GIST can be a diagnostic challenge due to negative bidirectional endoscopy. Capsule endoscopy or CT angiography can be useful diagnostic tools to assess obscure gastro-intestinal bleeding. The gold standard for GIST is surgical excision with complete resection of the tumor. In high risk tumors referral to the oncologist for consequent adjuvant therapy with imatinib or other targeted therapies is recommended. Immunohistochemically GISTs are identified by expression of tyrosine kinase receptor CD 117 (c-KIT), platelet-derived growth factor receptor (PDGFR a-KIT) and CD34 expression. Lower gastro-intestinal bleeding is a frequent cause of hospitalization, but only in rare cases it is caused by a GIST. When other causes of digestive bleeding are excluded and following negative bidirectional endoscopy, the possibility of a small bowel GIST must certainly be kept in mind.

- C04 -

PSEUDO-ACHALASIA SECONDARY TO OESOPHAGEAL DEVIATION RESULTING FROM MEDIASTINAL SHIFT AND RIGHT ATRIAL ENLARGEMENT AFTER LEFT LOWER LOBECTOMY. M. Surmont (1), M. Aerts (1), R. Kunda (1), S. Kindt (1) / [1] UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium, Gastroenterology.

An 80-year-old man presented in May 2019 to the outpatient clinic for further investigation of longstanding dysphagia for solids. A left lower pulmonary lobectomy was performed in 1955 because of abcedation. He remains in follow-up for ischemic cardiomyopathy with enlargement of the left atrium. Repeated upper GI endoscopy since May 2017 provided no explanation for the dysphagia. Oesophageal biopsies excluded eosinophilic oesophagitis. Based on the presence of stasis of contrast in the middle third of the oesophagus associated with tertiary contractions during radiologic evaluation, but without evidence of achalasia, pneumatic dilatation up to 20 mm was performed twice. Because of persistent dysphagia, he was referred to our center for further analysis. Upper GI endoscopy showed slight signs of candidosis for which fluconazole was initiated without symptomatic improvement. Oesophageal manometry was compatible with type II achalasia. Additionally, deviation of the distal oesophagus attributed to an enlarged left atrium in the presence of a leftward mediastinal shift was demonstrated by contrast series and confirmed by CAT scan. Contrast retention was observed in the proximal oesophagus, but with normal evacuation at the oesophagogastric junction. No lung cancer was identified. Cardiac ultrasound confirmed the enlargement of the left atrium, with known reduced inferoseptal-inferior contractility.

In the absence of strictures, and because of the advanced age and associated comorbidities, a conservative treatment was advocated. Although a manometrical diagnosis of pseudo-achalasia has been described after fundoplication, gastric banding and lung cancer, this is the first time it is observed as a result of mediastinal shift and left atrial enlargement.

- C05 -

A PET-POSITIVE NODULE AFTER CHEMOTHERAPY. A. Van Oosterwyck (1), M. Cool (1), G. Deboever (1), L. Depypere (2), G. Van Parys (3), G. Lambrecht (1) / [1] AZ Damiaan, Oostende, Belgium, Gastroenterology and Digestive Oncology, [2] UZ Leuven, Leuven, Belgium, Thoracic Surgery, [3] AZ Damiaan, Oostende, Belgium, Pathology.

This report describes the case of a 76-year-old woman with complex oncological disease, who developed a rare complication. She has a history of non-small cell lung carcinoma in the right upper lobe (stadium cT3N2M0), for which she was treated with neo-adjuvant chemotherapy (cisplatin/gemcitabine) and superior bilobectomy, back in 2011. The same year the diagnosis of an intraductal breast carcinoma (stadium ypT2N1a) was made as well, for which she received radiotherapy and tamoxifen. In 2016 a distal subtotal pancreatectomy was performed for a ductal adenocarcinoma of the pancreas (pT3N1M0). First-line adjuvant chemotherapy was started with an oral fluoropyrimidine (S-1). After 18 months, tumor markers started to rise again, and two new lesions in the liver were found. Gemcitabine/paclitaxel was commenced. In the next years two metastasectomies were carried out. In the first metastasectomy, two lesions in the liver were removed, in the second one a muscle metastasis in the abdominal wall was resected - both histologically proven of pancreatic origin. Gemcitabine/paclitaxel was restarted after an initial pause. The next FDG-PET-scan in 2019 showed a FDG-positive lesion in the right lower lobe, concomitant with slight augmentation of CA 19.9. A VATS wedge resection was performed. Histology however showed no tumoral lesion but a granuloma. PCR examination showed no sign of Mycobacterium infection and further evaluation could also exclude sarcoidosis. Histological analysis of a lesion on the tongue two weeks later also revealed an ulcer with an underlying granuloma. After resection we saw no recurrence so far. Discussion : There was no clear cause for these granulomata. Therefore, we can probably assume that this was a drug induced reaction. Review of the literature showed some cases where taxanes such as paclitaxel and docetaxel (sometimes in combination with a monoclonal antibody) caused a granulomatous reaction. One article describes four cases of pyogenic granulomata. They were found on the left cheek, the right cheek, the left occipital region and the lower lip (1). Some other locations were intrahepatic (2), and mainly subungual and periungual (3, 4, 5). No reports of lung or tongue granulomas have been made so far. The granulomata in the other articles subsided after cessation of the chemotherapy. The pathogenesis is unclear. Conclusion : In this patient with three different tissue tumours, two granulomas were discovered, in the lung and on the tongue after therapy with paclitaxel. Given that there was no clear cause for the granulomas (no sarcoidosis, no infection, no Mycobacterium), we suspect there is a link with the chemotherapy she received. Paclitaxel is a taxane used in a wide array of neoplasms (such as breast, pancreatic and lung cancers). We found other reports -albeit few- of paclitaxel-induced granulomata.

- C06 -

NEOADJUVANT IMMUNOTHERAPY FOR A MSI-H LOCALLY ADVANCED RECTAL CANCER PATIENT : SHOULD WE DEFINE NEW STANDARD OF CARE FOR THESE PATIENTS? L. Mans (1), M. Pezzullo (2), A. Bucalau (3), N. D'haene (4), J. Van De Stadt (5), J. Van Laethem (3) / [1] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenterology, [2] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Radiology, [3] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenterology, [4] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Anatomopathology, [5] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Digestive Surgery.

A 27-year-old woman with history of rectal bleeding for 6 months was diagnosed with a tumor at the lower third of the rectum. The biopsy revealed a well differentiated adenocarcinoma with loss of MSH2. The microsatellite instability was confirmed as MSI-high by molecular biology. The CEA level was 1.4 microg/L (normal < 5.2 microg/L). There was no distant metastasis at the thoraco-abdominal CT scan. The FDG PETCT showed a lower rectal neoplasia with a right iliac lymphadenopathy. The rectal EUS showed an uT3N+ lesion without internal anal sphincter invasion and two adenopathies in the mesorectal fat. The pelvic MRI confirmed the neoplasia of the lower third of the rectum classified T3N2 MRF+. There was a history of colon cancer in father, paternal grandfather and paternal great-grandfather, confirming Lynch syndrome. An ovarian tissue preservation and an ovarian pexy were performed. Due to the microsatellite instability, we decided in multidisciplinary board, to perform an induction treatment by immunotherapy combining Ipilimumab (1 mg/kg) and Nivolumab (3 mg/kg). After one cycle, we performed a control rectoscopy showing a complete endoscopic response and the biopsies revealed the absence of tumor cells. The FDG PETCT confirmed a major response at the rectal lesion and stability of the iliac lymphadenopathy. A new rectoscopy was performed after 2 cycles confirming the complete endoscopic response. The treatment was continued with Nivolumab in monotherapy for one additional cycle. The pelvic MRI confirmed also the complete clinical response with the absence of thickening of the rectal mucosa. The FDG PETCT

showed a complete response both at the rectal and the lymphadenopathy levels after 3 cycles. A total mesorectal excision was performed on June 12th 2019. The pathological analysis revealed the complete absence of residual tumor cells. The resection margins were clear. There was no lympovascular or perineural invasion and no lymph node invasion (0/51 nodes). The lesion was classified ypT0N0. Due to initial clinical stage, we decided, in multidisciplinary board, to perform adjuvant immunotherapy by Nivolumab monotherapy for 4 months. The first evaluation, 6 months after resection, shows no relapse. Conclusions : this therapeutic approach is based on limited data but the phase II NICHE trial presented at ESMO 2018 showed a 100% (7/7 patients) of major pathological response in patients with dMMR colon cancer (MSI-H), including 4 complete responses. Due to the lack of data on the management of these patients with complete clinical response, we decided to perform surgery to confirm pathologically the complete response. This approach, still experimental, allowed in a young woman with child-bearing potential, to avoid chemoradiotherapy and therefore save her uterus and ovaries.

- C07 -

SPONTANEOUS PNEUMOBILIA. L. Janssens (1), D. Penrice (1), J. Brant (1), M. Halland (2) / [1] Mayo Clinic, Rochester, United States (the), Internal Medicine, [2] Mayo Clinic, Rochester, United States (the), Gastroenterology and Hepatology.

A 57-year-old woman presented to the clinic with a longstanding history of intermittent right upper quadrant discomfort. She had moved from Cameroon to the United States 2 years prior to presentation. Her medical history included a distant history of H. Pylori related gastric ulcer disease reportedly treated with proton pump inhibitors (PPI) and antibiotics. The patient endorsed mild right upper quadrant tenderness on physical exam. Laboratory work-up (normal value ranges in parenthesis) showed Alkaline Phosphatase 415 U/L (35-104 U/L), Alanine Aminotransferase 234 U/L (7-45 U/L), Aspartate Aminotransferase 75 U/L (8-43 U/L) and total Bilirubin 1.3 mg/dL (<1.2 mg/dL) without other abnormalities. Computed tomography of the abdomen revealed air in the intra- and extrahepatic bile ducts (Figure 1). The patient did not have hepatobiliary surgery or ERCP done previously and had no evidence of cholelithiasis on imaging. ERCP was performed and showed a stricture in the pyloric channel with fistulous communication to the biliary tree immediately upstream from this stricture (Figure 2), consistent with choledochoduodenal fistula. A therapeutic ERCP with sphincterotomy to prevent pooling of antral contents in the biliary tract was attempted using an infant side-viewing duodenoscope (due to inability to pass the adult duodenoscope through the pyloric stricture). Unfortunately, the abnormal duodenal anatomy with scarring of the highly dysmorphic pylorus and duodenal bulb as well as effacement of the major papilla prevented safe biliary access and sphincterotomy. The patient was consequently planned for surgery with truncal vagotomy, gastrojejunostomy and cholecystectomy for symptom relief. Choledochoduodenal fistula is a rare condition that can result in pneumobilia, abdominal pain and cholangitis. The most frequent etiology is bile duct inflammation secondary to choledocholithiasis. Other etiologies include iatrogenic injury, spontaneous fistula formation and nearby neoplasms. Longstanding peptic ulcer disease is a rare cause of choledochoduodenal fistula, in part due to the effectiveness of medical management of peptic ulcers. Our patient’s history of H. Pylori related peptic ulcer with uncertainty about completeness of eradication likely contributed to the development of the fistula. Management of the choledochoduodenal fistula is patient-specific but can include both medical (PPI +/- antibiotics) and surgical (vagotomy, gastrectomy or gastrojejunostomy) options.

- C08 -

NOT PROBIOTIC-RELATED SACCHAROMYCES CEREVISIAE FUNGEMIA IN AN INTENSIVE CARE PATIENT, A CASE REPORT. M. Moretti (1), E. Maillart (2), B. Mahadeb (3), P. Clevenbergh (2) / [1] UZ Brussel, Jette, Belgium, Department of internal medicine, [2] CHU Brugmann, Brussels, Belgium, Department of internal medicine and infectious disease, [3] CHU Brugmann, Brussels, Belgium, Department of microbiology.

Saccharomyces cerevisiae is a yeast commonly use in food industry and probiotics. It represents a rare, but rising cause of non-albicans Candida fungemia, predominantly in immunocompromised patient. The major source of infection is the use of probiotics and central venous catheter contamination. In the current article, a case of disseminate Saccharomyces cerevisiae infection in a not immunocompromised 68 years is presented. The patient was admitted to intensive care for surveillance after transverse colostomy, complicated by right hypochondria collection. The fungemia was not related to the consumption of probiotic, gut translocation was recognized as the definitive infection origin, as cultures of the abdominal collection and blood yielded Saccharomyces cerevisiae. The inflammatory immunosuppression state related to prolonged septicemia and broad-spectrum antibiotics promoted the selection of the yeast and the spreading through the gut barriers. The rarity of Saccharomyces cerevisiae infection and antimycotic resistances may delay the correct diagnosis, the appropriate treatment and pejorate the outcome.

- C09 -

A CASE OF MILIARY ABDOMINAL TUBERCULOSIS IN AN ANTI-TNF TREATED PATIENT WITH CROHN'S DISEASE. J. Jacobs (1), L. Pouillon (1), L. Peperstraete (2), J. Frans (3), T. Tollens (4), P. Bossuyt (1) / [1] Imelda Hospital, Bonheiden, Belgium, Gastroenterology, [2] Imelda Hospital, Bonheiden, Belgium, Pathology, [3] Imelda Hospital, Bonheiden, Belgium, Microbiology, [4] Imelda Hospital, Bonheiden, Belgium, Surgery.

We report a case of miliary abdominal tuberculosis in a Caucasian patient with Crohn's disease (CD) during treatment with anti-tumor necrosis factor (anti-TNF) therapy. This female patient was diagnosed with CD at age 19 in 1998. Initially, she was treated with 5-aminoacylic acid and azathioprine. Two years later (2000), anti-TNF therapy (infliximab) was associated due to a flare-up of the disease. In 2008, infliximab was cessated because of secondary loss of reponse, after which the patient received sequentially adalimumab, vedolizumab and ustekinumab. In April 2019, infliximab was re-initiated, in combination with methotrexate, under strict anti-allergic prophylaxis and after a negative tuberculosis screening. In September 2019, the patient presented at the outpatient clinic with mildly elevated body temperature in combination with generalised myalgia, since one month. Clinical examination did not reveal any abnormalities; laboratory analysis showed an abnormal C-reactive protein (CRP) level (66 mg/L). Since symptoms initially resembled a viral infection, a wait-and-see policy was chosen, and scheduled administration of infliximab was postponed with one week. Due to a lack of improvement of symptoms, the patient was re-admitted to the emergency department two weeks later. She reported severe abdominal cramps and melena, and had developed night sweats and fever up to 38.8°C. The abdomen was diffusely tender upon examination, but there were no palpable adenopathy's. CRP level was 48 mg/L, and blood cultures were taken. Chest X-ray was negative. CT-scan of the abdomen revealed necrotising adenopathies next to the terminal ileum and left hemicolon, signs of peritonitis, and hepatomegaly. Differential diagnosis included opportunistic infections, HIV, tuberculosis, atypical mycobacterial infection, flare up of Crohn's disease, lymphoma and a delayed hypersensitivity on infliximab. The patient was started empirically on broad-spectrum antibiotics. During the course of the subsequent hospitalisation, serial blood cultures remained negative. The patient continued to develop fever and CRP levels remained elevated. Given this fever of unknown origin, technical examinations were broadened. Transthoracic echocardiography was negative for endocarditis. Extensive serology including Brucella, Hantavirus, Q-fever and leptospirosis were negative. A PET-CT scan confirmed diffuse large mesenteric and retroperitoneal adenopathies, already shown before on routine imaging. Since thorough repeated anamnesis had revealed that the complaints of the patient started one month after she returned from a leisure trip to Hungary in July 2019, an opportunistic infection was suspected and a laparoscopy was performed. During this procedure, diffuse miliary spots on the peritoneum and necrotising adenopathies were found, clinically suggestive for miliary tuberculosis. Pathologic examination showed granulomatous adenitis, and the diagnosis of miliary tuberculosis was ultimately confirmed with positive Auramine stains and tuberculosis DNA testing. Quadruple therapy (ethambutol, isoniazide, rifampicine, pyrazinamide) was initiated with good clinical evolution. Since the patient had drunk unpasteurized goat milk during her trip in Hungary, a case of tuberculosis var. bovis from goat milk is suspected, final results of the Mycobacterial species typing is pending. Anti-TNF therapy is an effective treatment in patients with moderate to severe active CD. It is well established that anti-TNF treated patients have an increased risk for infections, including opportunistic infections. Tuberculosis is a common problem worldwide. Recent immigration waves made tuberculosis more prevalent in our region; there are yearly 9.3/100 000 reported cases of tuberculosis in the Belgian population, of which 0.5% were associated with anti-TNF treatment (Agentschap zorg en gezondheid, 2016). Most cases of tuberculosis during anti-TNF treatment are reactivations of latent tuberculosis. Therefore, screening for tuberculosis is important. It is usually performed by Tuberculin Skin Test (TST). When TST is positive or doubtful, interferon-gamma release assays (IGRAs) should be used. Routine use during screening of IGRA should however be avoided in patients with inflammatory bowel diseases, since concomitant use of immunosuppressants might hamper interpretation of the results. As shown by the case presented here, there remains a risk for de novo Mycobacterium tuberculosis infection during the course of immunosuppressive treatment. It should be considered in patients treated with anti-TNF therapy presenting with fever of unknown origin. Atypical forms such as abdominal miliary tuberculosis are difficult to diagnose since adenopathies shown on imaging can be misinterpreted as secondary to CD activity. In case of doubt, a laparascopy with prelevation of a lymph node for pathological, microbiological and molecular testing should be performed.

- C10 -

MANTLE CELL LYMPHOMA SIMULATING INFLAMMATORY BOWEL DISEASE. F. Lifrange (1), R. De Wind (1), C. Spilleboudt (2), A. Van Gossum (3), P. Demetter (4) / [1] Institut Jules Bordet, Belgium, Pathology, [2] Institut Jules Bordet, Belgium, Haematology, [3] Institut Jules Bordet, Belgium, Medical Oncology, [4] Institut Jules Bordet, Brussels, Belgium, Pathology.

A 73 years old man, followed since many years for a thrombopenia of unknown origin, consulted a gastroenterologist after a positive faecal occult blood test. Colonoscopy revealed an erythematous, friable, bleeding on contact mucosa in the rectum, the sigmoïd, the caecum, the ileocaecal valve and the terminal ileum. Initial biopsies suggested an indeterminate colitis or an ulcerative colitis. Entocort and Colitofalk treatment was started. At colonoscopy 6 weeks

later, mucosa was still friable and bleeding on contact. Another set of biopsies was taken. Histopathological examination revealed a diffuse monotonous lymphocytic infiltrate. Numerous small lymphocytes expressed CD20, Bcl-2 and cyclin D1 whereas immunohistochemical stainings for CD5, CD10, CD23 and Bcl-6 remained negative. Proliferation fraction was estimated 10-15% based on Ki-67 immunohistochemistry. A diagnosis of mantle cell lymphoma, classic variant was proposed. PET/CT 18F-FDG scan demonstrated multiple hypermetabolic supra- and infradiaphragmatic, cervical and mediastinal lymph nodes, splenomegaly, numerous hypermetabolic peritoneal foci and a diffuse radiotracer uptake throughout the colon wall. Mantle cell lymphoma is a mature B-cell lymphoma, usually very aggressive and incurable. It accounts for approximately 3-10% of non-Hodgkin lymphomas. Median age of onset is about 60 years . This tumour usually occurs in lymph nodes but extranodal involvement is frequent. Gastrointestinal tract is involved microscopically and macroscopically in more than 80% of cases. Most frequently colonic involvement is characterised by the presence of numerous polypoid lesions. Other possible features are superficial ulcers, large tumour masses or diffuse thickening of the mucosa. The t(11 ;14)(q13 ;q32) translocation, characteristic of mantle cell lymphoma, juxtaposes the immunoglobulin heavy chain (IgH) gene with the cyclin D1 gene (CCND1), causing cyclin D1 mRNA upregulation, subsequent cyclin D1 protein overexpression and eventual cell cycle dysregulation. This case illustrates the possible atypical presentation of mantle cell lymphoma and the importance of thorough histopathological examination in case of so-called inflammatory bowel disease that does not respond to treatment – be aware of mimickers...

- C11 -

BILIARY COMPLICATIONS IN HUMAN ALVEOLAR ECHINOCOCCOSIS : A CASE REPORT. M. Abdessalami (1), G. Rasschaert (1), L. Duez (1), C. Salem (1), P. Eisendrath (1), T. Serste (2) / [1] CHU Saint-Pierre, Brussels, Belgium, Hepato Gastroenterology, [2] CHU Saint-Pierre, Brussels, Belgium, Hépato-Gastroenterologie.

Introduction : Alveolar echinococcosis (AE) is caused by the larval stage of the fox tapeworm Echinococcus multilocularis. This rare parasitic infection can be associated with biliary complications (biliary strictures, dilations and fistulas) and may eventually lead to secondary biliary cirrhosis. Apart from partial hepatectomy, treatment options include long term antiparasitic chemotherapy. Biliary damage occurs in about 30% of cases and is potentially treated with therapeutic endoscopic procedures.
Case report : A 30-year-old Caucasian male, presented at our institution with ascites. He was treated 3 years ago in Russia for an undisclosed affection of the liver leading to a partial right hepatectomy. Exact information on his medical record was difficult to obtain. Numerous stellate angiomata and tensed ascites were observed during clinical examination. A chest X-ray suggested the presence of an organized pleural effusion. The blood panel demonstrated mild cholestasis (alkaline phosphatase 1.3 times the upper limit of the normal), mild hyperbilirubinemia (3.1mg/dL), thrombocytopenia (65.000 platelets per µL) and a prothrombin time of 66.9%. Viral serology showed the presence of HBs Ag without detectable DNA levels. Magnetic resonance cholangiopancreatography (MRCP) revealed a highly dysmorphic liver. The post-hepatectomy status of liver segments VI and VII was confirmed. Multiple cystic lesions (uncountable, about 5 to 10 mm) with thick walls, without bile duct communication, were found throughout the liver parenchyma. Multiple biliary duct stenosis and dilations, both intrahepatic and extrahepatic were described on MRCP. These abnormalities mimicked sclerosing cholangitis and were mainly located on right liver. A 2 cm long filiform subhilar bile duct stricture required insertion of 3 plastic biliary stents (12 and 15 cm, 8.5 French) via endoscopic retrograde cholangiopancreatography (ERCP). This endoscopic procedure confirmed the sclerosing cholangitis-like shape of the right intrahepatic bile tree and disclosed a biliary fistula communicating with the right pleural cavity. Three different parasite serology tests for AE performed on a blood sample were positive : a haemagglutination essay, a western blot and an ELISA EM18 (Kit Bordier®). Western blotting was used as confirmatory test. Moreover, the ELISA that was highly positive, is known to be the most specific for AE. Liver biopsy was performed and found to be compatible with the diagnosis of secondary biliary cirrhosis and microscopic cholangitis. The final diagnosis of AE and secondary biliary cirrhosis was retained. A long-term treatment with albendazole 800mg daily was initiated. Pleural effusion and ascites were controlled after biliary drainage and proper diuretic prescription. Median and long term clinico-biological evolution is currently under investigation and the hypothesis of a future liver transplant as a definitive cure is not ruled out.
Discussion : Echinococcus multilocularis is distributed throughout the Northern Hemisphere. It remains a rare disease in Western Europe, compared to endemic regions such as Russia where our patient was born. During the course of the disease, AE can mimic a neoplastic lesion with progressive growth and dissemination from the liver towards several organs. Treatment options include surgery, as the preferred first line therapy (including liver transplantation), and long-term chemotherapy with benzimidazoles. Despite treatment, biliary complications still occur in one third of the patients, significantly influencing the outcome. The bile ducts and the intrahepatic biliary tree can be compressed or even destroyed by the growing parasite. The clinical presentation of these biliary complications encompasses cholangitis lesions (defined as abnormal ERCP or MRCP findings that could evocate sclerosing cholangitis), common bile duct stenosis, biliary fistulas and secondary biliary cirrhosis. AE is a severe infectious disease with significant morbidity and mortality despite substantial increases in diagnostic and therapeutic improvements.
Conclusion : This case report of hepatic AE with biliary strictures and fistulas leading to secondary biliary cirrhosis, illustrates the whole spectrum of biliary complications that potentially characterize the natural course of this rare

infectious disease. References : 1. Torgerson PR, Schweiger A, Deplazes P,et al. Alveolar echinococcosis : from a deadly disease to a well-controlled infection. Relative survival and economic analysis in Switzerland over the last 35 years. J Hepatol 2008; 49 : 72-77 2. Kadry Z, Renner EC, Bachmann LM,et al. Evaluation of treatment and long-term follow-up in patients with hepatic alveolar echinococcosis. Br J Surg 2005; 92 : 1110-1116

- C12 -

JUST ANOTHER LIVER CYST (OR NOT!). L. Abreu De Carvalho (1), O. Uyttebroek (1), A. Vanlander (2), X. Rogiers (2), F. Berrevoet (2) / [1] Ghent University Hospital, Ghent, Belgium, HPB surgery and liver transplantation, [2] Ghent University Hospital, Ghent, Belgium, HPB surgery and Liver transplantation.

We report the case of a 34-year-old male who was referred to the emergency department after the recent onset of jaundice, weight loss and pain in the upper abdominal quadrants. CT-scan showed a cystic structure at the hepatic hilum of 14 cm diameter with intrahepatic bile duct dilation and a thrombus in the inferior vena cava (IVC). Total bilirubin was 12 mg/dl. Careful interpretation of the imaging led to the diagnosis of a type IV4a bile duct cystic dilation (multiple intra- and extrahepatic bile duct cysts - according to the modified Todani classification) with a thrombus in the IVC as a result of compression. Due to the risk of malignant transformation, an oncologic resection of the affected bile duct segments was planned, although no malignancy was suspected. Surgery was performed according to the planning with a combination of left hepatectomy, duodenopancreatectomy and thrombectomy of the IVC. There were no major complications and the patient was discharged after 20 days. Pathology report showed a pT3N2 cholangiocarcinoma with R0 resection. Cystic dilation of the common bile duct causes biliary obstruction resulting in proximal dilation of the intrahepatic bile ducts, but it is important to distinguish this finding from abnormal cystic dilation to be able to plan a correct and realistic surgical approach. Diffuse intrahepatic cystic dilations of the bile ducts (Todani type V – Caroli disease) can only be treated with a liver transplantation. In this case it meant being able to propose a left hepatectomy. Diagnostic work-up and treatment options for this challenging condition in adult patients shall be discussed.

- C13 -

PLEURAL EFFUSION AND ELEVATED LIVER TESTS : THINK VIRAL J. Meesters (1), J. Maus (2), S. Naegels (2) / [1] Universiteit Antwerpen / Antwerp University Hospital, WILRIJK (Antwerpen), Belgium, Gastroenterology, [2] ZNA Middelheim, Antwerpen, Belgium, Gastroenterology and hepatology.

We present a case of a 37-year-old man from Tibetan origin who presented at the emergency ward with diffuse abdominal tenderness, bloating and a dark discoloration of the urine. There were no complaints of fever, nausea or vomiting. There was no weight lost and the stools were normal. There was no significant prior history and he did not take any chronic medication. He had lived in Belgium for the past 15 years and had not gone abroad in that time. Clinical examination was normal, except for reduced breathing noises on the right side on lung auscultation. An x-ray of the thorax showed right-sided unilateral pleural effusion. Laboratory test showed a normal peripheral blood count, normal kidney function tests and normal electrolytes. The liver enzymes were elevated with a conjugated hyperbilirubinemia of 3,9 mg/dL and elevated transaminase liver tests with an ALAT of 1388 U/L and an ASAT of 961 U/L. A urgent CT scan confirmed unilateral pleural effusion and mild ascites, without any other structural problems. The liver parenchyma was homogenous and there were no signs of liver ischemia or vascular abnormalities. Further serological testing showed an acute hepatitis B infection with positive HBV surface antigen, positive HBV e-antigen, positive HBV IgM core antibodies and a viral load of 13600000 IU/L. Other causes of hepatitis were excluded (serology for hepatitis A, C, E, auto-immune causes and storage diseases). A diagnostic punction of the unilateral pleural effusion was performed which showed a exsudative fluid (protein count 34,6 g/L and protein to serum ratio of 0.59) and a lymphocytic predominance. Routine culture of the fluid was negative, TBC was excluded and cytology of the fluid came back negative for malignant cells. The diagnosis of acute hepatitis B infection was made with a secondary unilateral viral pleural effusion. No treatment was started, as there were no signs of acute liver failure. In the following weeks after diagnosis, there was a spontaneous normalization of the liver enzymes. After three weeks, the pleural effusion resolved completely. Unilateral pleural effusion complicating an acute hepatitis B infection is a rare. The first case was reported in 1971, with spontaneous resolution of the pleural effusion. (1) We found no more than ten cases described in Anglo-saxon literature, mostly in the pediatric population. (1-4, 5, 8) Unilateral pleural effusion as a result of viral hepatitis has been discussed in the literature, but mostly secondary to an acute hepatitis A infection. (6-8, 9). The underlying mechanism is not fully understood. It is thought to be immune-mediated secondary to immune circulating complexes. These immune complexes also cause polyarteritis nodosa and glomerulonephritis secondary to hepatitis. The underlying mechanism of immune complexes has been proven in glomerulonephritis but has not yet been proven as a cause of pleural effusion (4). References : 1. Gross PA. Pleural effusion associated with viral hepatitis. Gastroenterology. 1971;60(5) :898-902. 2. Cocchi P,. Letter : Pleural effusion in HBsAG-positive hepatitis. Journal of pediatrics. 1976;89(2) :329-30. 3. Flacks LM. A case of hepatitis B with pleural effusion. Australian and New Zealand journal of medicine. 1977;7(6) :636-7. 4. Lee HS. Pleural effusion coinciding with acute exacerbations in a patient with chronic hepatitis B. Gastroenterology. 1989;96(6) :1604-6. 5. Merrill WD. Hepatitis antigen in pleural fluid.

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- C14 -

BILE DUCT STONE EXTRACTION VIA PTC RENDEZVOUS ASSISTED SINGLE BALLOON ERCP. M. Somers (1), M. Niekel (2), S. Bouhadan (1), A. Jauregui (1), H. De Schepper (1), S. Francque (1), E. Macken (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Department of gastroenterology and hepatology, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Department of radiology.

Bile duct stone extraction via PTC rendezvous assisted single balloon ERCP. Therapeutic ERCP procedures in patients with surgically altered intestinal anatomy remain challenging. During the last years, several endoscopic techniques have been proposed to increase successful cannulation of the biliary tract (single balloon ERCP (SB-ERCP), surgically assisted ERCP, internal EUS-directed transgastric ERCP and transprosthetic endoscopic therapy). With the single balloon ERCP technique, some of the limitations of the duodenoscope in the setting of an altered intestinal anatomy can be overcome. Nonetheless, one of the major obstacles in SB-ERCP is obtaining biliary access in patients with a native papilla. This can be due to the limited length of the enteroscope, postoperative adhesions or sharp bends of the reconstructed intestine and a rather tangential view of the papilla with the forward viewing enteroscope compared with the side-viewing duodenoscope, without the possibilities made possible by the use of the elevator. We present a case of a 89-year-old patient with a history of gastric cancer and partial gastrectomy who presented with symptomatic choledocholithiasis, cholangitis and sepsis. Patient presented with fever and right upper quadrant pain since three days, despite antibiotic therapy (amoxicillin-clavulanic acid) started by the generalist. Lab results showed a high leukocyte count (19,2x10^9), elevated C-reactive protein (229 mg/l), elevated liver tests (GOT 212 U/l, GPT 200 U/l, gamma-GT 70 U/l) and elevated bilirubin (3.8 mg/dl). Abdominal ultrasound showed dilated intrahepatic bile ducts. Additional MRCP confirmed the presence of several large bile duct stones. Patient was referred to our hospital for a SB-ERCP, but, despite careful inspection, the papilla could not be seen. Therefore, a percutaneous transhepatic cholangiography (PTC) was done by the radiologist, leaving a drain into the duodenum. During a second SB-ERCP procedure a designated radio-opaque guidewire (0.035 inch, 550 cm) was advanced trough the biliodouodenal drain, then firmly grasped with a snare forceps and brought out of the patient, allowing the enteroscope to advance to the papilla. Cannulation and contrast injection of the bile duct confirmed the presence of several stones in the common bile duct (CBD). After sphincterotomy and balloon extraction of several concrements, a very large residual stone (+/- 20 mm) could not be removed and was impacted in the distal CBD. A 7 French, plastic stent was placed to maintain biliary drainage. An additional SB-ERCP is scheduled for additional stone removal. During the last decades, more patients with surgically altered bowel anatomy are being referred for ERCP, owing to a rise in prevalence of bariatric surgery, surgical interventions of pancreaticobiliary lesions and liver transplantation (1). One of the possible options to reach the biliary tract in these patients is single balloon assisted ERCP. In a meta-analysis of 15 trials (461 patients) the SB-ERCP procedural success rate, defined as the ability to provide successful intervention, was reported to be 61.7 % (1), meaning that in one third of the patients the procedure is unsuccessful. Although the rendezvous technique is well known in classic ERCP, we present this case to show that a rendezvous procedure combined with a SB-ERCP (using a long guidewire) can be helpful to accomplish biliary tract cannulation in difficult cases. Reference : 1. Inamdar S., Slattery E., Sejpal DV., Miller LS., Pleskow DK., Berzin TM., et al. Systematic review and meta-analysis of single-balloon enteroscopy–assisted ERCP in patients with surgically altered GI anatomy. Gastrointest Endosc 2015;82(1) :9–19.

- C15 -

ACUTE GRADE IV TOXIC HEPATITIS DUE TO THE E-SIGARETTE. G. Van Roey (1), C. Claessens (2), L. Van Tigchelt (2), J. Schouten (3), W. Verlinden (3), A. Hoorens (4) / [1] AZ TURNHOUT, Turnhout, Belgium, Gastroenterology, [2] AZ TURNHOUT, Turnhout, Belgium, gastroenterology, [3] AZ Nikolaas, Sint-Niklaas, Belgium, gastroenterology, [4] UZGent, Gent, Belgium, Pathology.

Introduction : In this abstract we present a case of Drug Induced Liver Injury (DILI) attributed to exposure of the electronic cigarette. The diagnosis is confirmed by complete recovery after cessation and recurrence of hepatitis following re-exposure to the e-cigarette (RUCAM score of 10).

Case report : Phase 1 : • Female patient,°1972 with a history of a gastric bypass in 2014 presented at the emergency department at April 23th 2018 because of progressive asthenia, diarrhea, epigastric tenderness and jaundice. She was on ethinylestradiol/levonorgestrel and pantoprazole. She did not report weight loss, alcohol consumption or viral symptoms. • Clinical examination revealed a patient with jaundice and hepatosplenomegaly. • Lab results : on admission, maximal values of AST and ALT were 917 and 1448 U/l resp, Bilirubin raised till 9,3 mg/dl. Highest ALP was 167 U/l, INR remained normal. Extensive viral, auto-immune and metabolic work-up was completely negative. • abdominal ultrasound : hepatoslenomegaly but no other abnormalities. • liver biopsy : interface hepatitis with periportal hepatitis; bilirubinostasis; eosinophilic infiltration : features of DILI, with a DD of auto-immune hepatitis. • Follow-up : all liver tests normalised completely within a few months without any therapy. Phase 2 : • November 13th 2019 : she presented at the emergency ward with symptoms of jaundice, dark urine, nausea and itching • exploration : AST and ALT of 846 and 1022 U/l resp., ALP 170 U/l, bilirubin 5,3 mg/dl, bile salts 411 micromol/l. Again, biochemical, serological and radiological work-up showed no causative abnormalities. • On extensive anamnesis, the only evident toxin she was exposed to was the use of the e-cigarette in 2018, which she stopped after hospitalisation in April 2018. She restarted "vaping" from October 2019 onwards till the last admission. After cessation of the e-cigarette, a slow recovery of the liver tests was noticed. • The RUCAM score for this toxin was 10, making the diagnosis of DILI highly probable. • Looking at the chemical composition of the e-cigarette the patient was using, she was exposed to propylene glycol, glycerine, nicotine and 5% of aroma's. The most hepatotoxic components are propably propylene glycol and the aroma's. **Conclusion** : This is the first report of DILI secondary to the use of e-cigarettes. The calculated RUCAM score was 10, making the diagnosis highly probable. In patients presenting with acute hepatitis vaping must be included in the differential diagnosis of DILI.

- C16 -

RESOLUTION OF A HEPATODUODENAL FISTULA AFTER NIVOLUMAB TREATMENT IN A PATIENT WITH ADVANCED HEPATOCELLULAR CARCINOMA : CHALLENGES IN IMMUNOTHERAPY. T. De Somer (1), E. Vanderstraeten (1), V. Bouderez (1), E. Monsaert (1), C. Van Steenkiste (1) / [1] AZ Maria Middelares, Ghent, Belgium, Gastroenterology & Hepatology.

We present the case of an 83-year-old male with a history of hemochromatosis for 13 years, presented with discomfort in the right upper quadrant of the abdomen. His medical history revealed arterial hypertension, a mild ischemic cerebrovascular accident and coronary artery disease. There was regular alcohol use (2-3 units daily), and on clinical examination central obesity (BMI 30.4 kg/m2) was noticed. At the first presentation, the patient had a WHO performance status of 1. Contrast-enhanced abdominal computed tomography (CT) showed multifocal liver lesions : 3 large nodules in the left liver lobe (largest diameter 10 cm) and 3 smaller lesions in the right liver lobe. Partial tumor thrombosis of the portal vein and hilar adenopathies were present, without lung or bone metastasis. Biochemically, the alpha-fetoprotein (AFP) at diagnosis was 1.685 µg/l. Biopsy of the largest lesion in the left liver lobe confirmed the presence of an HCC without underlying liver cirrhosis on the background of liver steatosis and hemochromatosis. The diagnosis of a Barcelona Clinic Liver Cancer (BCLC) HCC stage C was made. Systemic treatment with sorafenib was started. However, the tolerance of sorafenib was poor. The patient experienced excessive weight loss, pronounced anorexia and diarrhea, his WHO performance status diminished to 3-4. The AFP levels first declined to 848,4 µg/l after 1 month of treatment with sorafenib, but then gradually increased further on. Re-evaluation after 3 months treatment with sorafenib showed a stable disease on contrast-enhanced abdominal CT. However, the CT revealed the new finding of air inclusions caudally in the largest lesion in the left liver lobe, in continuity with the duodenum. Gastroscopy confirmed the presence of a large fistula in the duodenal bulb. A percutaneous endoscopic gastrostomy with jejunal extension was placed for support with enteral nutrition. Treatment with sorafenib was discontinued and the patient was evaluated for second line therapy with nivolumab in compassionate use, based on the data of the phase I/II trials mentioned above, available at that time. Treatment with nivolumab 3 mg/kg 2-weekly intravenously was started and was well tolerated. This resulted in clinical improvement and a return of his WHO performance score to 1. Re-evaluation after 3 months treatment with nivolumab showed a spectacular oncological response with normalization of the AFP, a dramatic reduction of the largest lesion in the left liver love and all other lesions, disappearance of the hilar adenopathies and a marked decrease of the tumor thrombus. The air inclusions in the largest left liver lobe disappeared and closure of the fistula was confirmed with endoscopy. Currently, this patient is treated for almost 1 year with nivolumab with further decrease of the liver lesions and tumor thrombus on consecutive radiological examination and a stable AFP. To our knowledge, no other cases are published describing fistula closure in HCC under treatment with immunotherapy. Also, the beneficial evolution in this patient shows that nivolumab may present a potential treatment option for a subpopulation of patients, despite the recent negative phase III trial.

- C17 -

A RARE COMPLICATION OF LEMMEL SYNDROME : BILIARY-DIVERTICULAR FISTULA FROM A DUODENAL DIVERTICULUM. S. Patel (1) / [1] Mayo Clinic, Rochester, United States (the), Department of Internal Medicine.

A 77-year-old female with no significant medical issues presented to primary care clinic with a seven day history of right upper quadrant abdominal pain radiating to the sternum and back. Examination demonstrated tenderness to midepigastric area and right upper quadrant. Laboratory work-up (normal value ranges in parenthesis) showed a leukocytosis to 12.0 (3.4 - 9.6 x10(9)/L), Alkaline Phosphatase 202 U/L (35-104 U/L), Alanine Aminotransferase 581 U/L (7-45 U/L), Aspartate Aminotransferase 540 U/L (8-43 U/L) and total Bilirubin 6.2 mg/dL (<1.2 mg/dL) without other abnormalities. Computed tomography of the abdomen revealed dilation of the extrahepatic and intrahepatic biliary tree as well as the gallbladder. Additionally, it demonstrated a large duodenal diverticulum (Figure 1). Right upper quadrant ultrasound showed cholelithiasis, no evidence of cholecystitis or choledocholithiasis. ERCP was performed which demonstrated duodenal diverticulitis with an obstructing stone and pus present in the diverticulum. Stone was extracted and a biliary-diverticular fistula was noted (Figure 2). Sphincterotomy was performed, with three stents placed. One temporary stent was placed in the ventral pancreatic duct, one in the common bile duct, and one stent was placed into the diverticulum to allow for ongoing drainage. Her abdominal pain was improved from where it had been prior to arrival. She was started on Zosyn and switched to levofloxacin for a planned 10-day course. At one month follow up, patient was feeling much improved and bilirubin was decreased to 1.2mg/dL. Lemmel syndrome is a rare condition in which patients present with obstructive jaundice caused by a periampullary duodenal diverticulum compressing the intrapancreatic common bile duct. Our case demonstrated a patient presenting with a rare complication of Lemmel syndrome, fistula formation between the biliary tract and GI tract through the duodenal diverticula. Treatment options for Lemmel syndrome is dependent on the underlying mechanism and complications that have arisen. While surgery is recommended in cases with extrinsic compression of the common bile duct, a cholecystectomy was deferred to the outpatient setting in our case given her periampullary inflammatory reaction related to a biliary diverticular fistula. This case highlights a rare but important etiology of obstructive jaundice in patients with no choledocholithiasis or tumour and possible complications that can arise. We must be vigilant in considering this diagnosis as misdiagnosis can lead to repeated episodes of jaundice and possible cholangitis.

- C18 -

DUBAI TOOK MY BREATH AWAY. C. Schoonjans (1), A. Geerts (2), H. Degroote (2), H. Van Vlierberghe (2), E. Van Braeckel (3), X. Verhelst (2) / [1] UZ Gent, Gent, Belgium, gastroenterology, [2] UZGent, Gent, Belgium, gastroenterology, [3] UZGent, Gent, Belgium, Pulmonology.

A 68-year old patient was admitted to the hospital because of shortness of breath and a dry cough, starting right after a trip to Dubai. Six years ago, he underwent an orthotopic liver transplantation because of alcoholic liver cirrhosis with a small HCC (2 cm), taking immunosuppressive medication (everolimus and mycophenolic acid). Three years ago, he had a coronary artery bypass graft. Blood examination showed minimal inflammation, with no signs of cardiac ischemia. Arterial blood gas showed hypoxia. Chest radiograph showed an interstitial lung pattern, with reticulonodular opacities. CT scan confirmed this with the image of a fibrotic end stage of an interstitial pneumonia. Echocardiography showed minimal decrease in systolic function, inferior akinesia and slightly elevated pulmonal pressure (36 mmHg + CVP). Pulmonary function test was restrictive (being normal pre-transplantation), with TLC of 57% and DLCO of 37%. Everolimus drug level was subtherapeutic (1.3 ng/ml). Infectious serology (including chlamydia/mycoplasma pneumoniae), Mantoux test, autoimmune serology and bronchoscopy with bronchoalveolar lavage (with PCR for Pneumocystis Jirovecii Pneumoniae) was negative. No anamnestic arguments for hypersensitivity pneumonitis. Based on exclusion of other causes, an everolimus-induced interstitial lung disease was suspected. For that matter, everolimus was replaced by tacrolimus. Gradually the oxygen dependence of our patient decreased, as did the symptoms. Five months later chest CT showed decrease of the interstitial/fibrotic findings, lung function tests improved (TLC 63% and DLCO 46%) and our patient did not need oxygen therapy anymore. During the course the persisting normal liver enzymes proved no arguments for liver rejection. In the literature case reports of interstitial lung disease (ILD) under treatment with mTOR (mammalian target of rapamycin) inhibitors were published in solid organ transplant patients (mainly renal), breast and neuro-endocrine tumours. Most of the data come from sirolimus, with better toleration for everolimus. Typically, there is no correlation to the everolimus concentration (as in our case with subtherapeutic levels). Immediate withdrawal of the drug is indicated, and there is no clear benefit from the addition of steroids in terms of improvement of symptoms. To our knowledge this is only the second case of everolimus induced ILD reported in a liver transplant patient, and the first one in which the outcome is not fatal. [1,2] Therefore, clinical suspicion needs to be high in every patient treated with a mTOR inhibitor (sirolimus as well as everolimus) presenting with new onset of pulmonary symptoms. Representative lung CT images can be shown during case presentation. References : 1. Lopez et al. Interstitial lung disease associated with mTOR inhibitors in solid organ transplant recipients : results from a large phase III clinical trial program of everolimus and review of the literature. J Transplant, 2014 (2014), p. 305931. 2. J. Schrader et al. Everolimus-induced pneumonitis : report of the first case in a liver transplant recipient and review of treatment options, Transplant International, vol. 23, no. 1, pp. 110–113, 2010.

- C19 -

REOPENING OF THE NATIVE PORTOMESENTERIC AXIS AFTER CAVOPORTAL HEMITRANSPOSITION IN A LIVER TRANSPLANT PATIENT. M. Clarysse (1), A. Wilmer (2), Y. Debaveye (3), W. Laleman (2), F. Nevens (2), S. Van Der Merwe (2), H. Van Malenstein (2), M. Sainz-Barriga (1), D. Monbaliu (1), J. Pirenne (1) / [1] University Hospitals Leuven, Belgium, Abdominal Transplant Surgery, [2] University Hospitals Leuven, Belgium, Gastroenterology and Hepatology, [3] University Hospitals Leuven, Belgium, Intensive Care Medicine.

Introduction : A 19-year-old woman presented with recent onset Budd-Chiari and extensive/refractory supra-hepatic and portomesenteric thrombosis (PVT) leading to acute liver failure. Urgent liver transplantation (LTx) was performed. Due to recurrent PVT immediately postTx, urgent reTx was performed.
Methods : At reTx sufficient flow from the native portomesenteric axis could not be obtained and therefore a partial cavoportal shunt (30% tapering of the inferior vena cava (IVC) just above the shunt) was created allowing acceptable portal inflow. An acute decline in portal inflow, one day later, rendered full ligation of the IVC necessary to again reach acceptable portal inflow, therefore creating a cavoportal hemitransposition (CPHT). However, an anatomical portoportal anastomosis/connection (despite absent/extremely low native portal flow at that time) was maintained.
Results : Postoperative period was uncomplicated. Interestingly, the native portomesenteric axis reopened several days later allowing physiological portal inflow - in addition to flow via the CPHT - . The patient was discharged 27 days later with normal liver function and adequate portal inflow. After 16 months, patient is well with normal liver function and adequate portal inflow through both the CPHT and the reopened native portomesenteric axis.
Conclusion : CPHT with maintenance of an anatomical portoportal connection should be considered in patients with extensive PVT in whom physiological portal inflow cannot be restored at the time of LTx, but in whom the native portomesenteric axis may reopen later.

- C20 -

THE USE OF RIBAVIRIN IN A SEVERE CASE OF HEPATITIS E INFECTION NECESSITATING RENAL REPLACEMENT THERAPY. M. Staessens (1), T. Vanwolleghem (2), L. Vonghia (2), S. Francque (2), T. Steinhauser (2), B. Bracke (3), L. Roossens (4), E. Philipse (5), M. Couttenye (5), K. Dams (1) / [1] Antwerp University Hospital, Belgium, Intensive Care Unit, [2] Antwerp University Hospital, Belgium, Gastroenterology and Hepatology, [3] Antwerp University Hospital, Belgium, Hepatobiliary, Transplantation and Endocrine Surgery, [4] Antwerp University Hospital, Belgium, Clinical Biochemistry, [5] Antwerp University Hospital, Belgium, Nephrology.

A 59-year-old male of Cambodian descent was admitted to a hospital in the Netherlands due to right upper quadrant pain, diarrhea and vomiting. He had recently travelled and had been staying in Cambodia for about three weeks. There was supposedly no contact with open waters. He had not been drinking tap water. There was no use of over-the-counter drugs, medicinal herbs. He had been taking verapamil, pantoprazole and atorvastatin during several years, and there had been no recent change to his drug dosing or scheme. On clinical examination at presentation there was a prominent icterus with dark discoloration of the urine. Cardiac and respiratory examination were unremarkable. The abdomen was non tender with pain on deep palpation in the epigastric and left hemi-abdomen. There was no apparent hepatosplenomegaly. The vital signs were within normal range. Abdominal ultrasound excluded biliary dilatation and acute cholecystitis. Initial lab results revealed significantly elevated liver enzymes, predominantly of the canalicular type, with total bilirubin above 30 mg/dL, conjugated bilirubin above 10 mg/dL, ALT 1792 U/L, AST 584 U/L, GGT 105 U/L and AP 138 U/L. Liver synthetic function tests were abnormal, with an INR of 1.4 and decreased albumin of 27 g/L. Platelet count was normal. Serology for viral hepatitis (including hepatitis A, B, C, E, EBV and CMV) came back positive for an acute hepatitis E infection (HEV IgM+; HEV IgG+). Due to further deterioration of the liver function tests, a significant acute kidney injury with a creatinine of 4,0 mg/dL, oliguria and respiratory deterioration, the patient was referred to the department of gastroenterology of the University Hospital of Antwerp. Consequently, a PCR for hepatitis E performed at the admitting hospital revealed a genotype 4b. Liver biopsy confirmed the diagnosis of a cholestatic hepatitis, compatible with an acute viral hepatitis. Shortly thereafter, increasing respiratory distress necessitated admission to the intensive care unit. Renal replacement therapy was commenced due to fluid overload, presenting as pulmonary edema, and inadequate urinary output. The diagnosis of acute tubular necrosis due to hyperbilirubinemia was made based on aforementioned findings and the presence of bilirubin crystals in the urine. Ribavirin was started 2 days after presentation. Therapeutic drug monitoring was regularly performed, and the dosage was adapted accordingly. About 3 weeks later, the PCR for hepatitis E became negative, but ribavirin was continued until a second HEV RNA PCR was negative in blood and stool. Unfortunately, the patient developed acute intestinal ischemia due to low flow phenomena and succumbed one day later as a result of severe therapy unresponsive septic shock. Hepatitis E is an acute viral hepatitis transmitted through the fecal-oral route and is most common in developing countries. Genotype 4b, as presented in our case, is mostly seen in southern Asian countries such as Cambodia. Classically, acute infection is asymptomatic, requires no pathogen guided treatment and is mostly supportive. Liver failure ultimately leading to liver transplantation or death is very rare. In severe cases however, ribavirin can be associated to the therapy, although there is little experience regarding the dosing, duration

and effectiveness of the therapy, with additional difficulty in patients needing renal replacement therapy. In this case, therapeutic drug monitoring aided in preventing drug overdose and side effects. Finally, hepatitis E was cleared. We will discuss differences in clinical presentation of HEV genotypes and the benefit of RBV drug monitoring in severe acute HEV.

BELGIAN SOCIETY FOR GASTROINTESTINAL ENDOSCOPY (BSGIE)

- G01 -

WIDE AREA TRANSEPITHELIAL SAMPLE ESOPHAGEAL BIOPSY COMBINED WITH COMPUTER ASSISTED 3-DIMENSIONAL TISSUE ANALYSIS (WATS3D) FOR THE DETECTION OF HIGH-GRADE DYSPLASIA AND ADENOCARCINOMA IN BARRETT : EUROPEAN MULTI-CENTER, PROSPECTIVE, RANDOMIZED, TANDEM STUDY. R. Bisschops (1), R. Haidry (2), H. Messmann (3), K. Ragunath (4), P. Bhandari (5), A. Repici (6), M. Munoz-Navas (7), S. Seewald (8), A. Lemmers (9), A. Castells (10), O. Pech (11), E. Schoon (12), R. Kariv (13), H. Neuhaus (14), B. Weusten (15), P. Siersema (16), L. Correale (17), F. Fromowitz (18), G. De Hertogh (19), J. Bergman (20), C. Hassan (17) / [1] University Hospitals Leuven, Leuven, Belgium, Gastroenterology and Hepatology, [2] University College London Hospitals, London, United Kingdom (the), Gastroenterology, [3] Clinic Augsburg III, Augsburg, Germany, Gastroenterology, [4] Nottingham University Hospital, Nottingham, United Kingdom (the), Gastroenterology, [5] Queen Alexandra Hospital Solent Centre for Digestive Diseases, Portsmouth, United Kingdom (the), Gastroenterology, [6] Humanitas Research Hospital & Humanitas University, Milan, Italy, Gastroenterology, [7] Universidad de Navarra, Navarra, Spain, Gastroenterology, [8] Clinic Hirslanden GastroZentrumHirslanden, Zurich, Switzerland, Gastroenterology, [9] Erasme Hospital, Brussels, Belgium, Gastroenterology, [10] Hospital Clinic of Barcelona, Barcelona, Spain, Gastroenterology, [11] Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany, Gastroenterology, [12] Catherina Ziekenhuis Eindhoven, Eindhoven, Netherlands (the), Gastroenterology, [13] Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, Gastroenterology, [14] University of Düsseldorf EvangelischesKrankenhaus Düsseldorf, Düsseldorf, Germany, Gastroenterology, [15] Antonius ziekenhuis, Nieuwegein, Netherlands (the), Gastroenterology, [16] Radboud UMC, Nijmegen, Netherlands (the), Gastroenterology, [17] Nuovo Regina Margherita Hospital, Rome, Italy, Gastroenterology, [18] Cdx Diagnostics, Suffern, United States (the), Pathology, [19] University Hospitals Leuven, Belgium, Pathology, [20] Amsterdam UMC, Amsterdam, Netherlands (the), Gastroenterology.

Introduction : The current Barrett's oesophagus surveillance strategy has an inherent risk of sampling error and missing non-visible high-risk pathology due to random sampling. Wide-Area Transepithelial Sampling (WATS) has the potential to increase detection of non-visible high-grade dysplasia and adenocarcinoma (HGD/AC).
Aim : In this randomized trial we aimed to compare the independent yield for HGD/EACs diagnosis resulting from WATS versus the 4 quadrant random forceps biopsy (RFB) in a multicenter setting and also evaluated the benefit of utilizing WATS as an adjunct to the 4 quadrant RFB.
Methods : Patients with known BE dysplasia following endoscopic resection of all visible lesions scheduled for ablation therapy at 15 European Barretts tertiary referral centers were assigned by 1 :1 randomization to receive either WATS followed by RFB (WATS, then RFB) or vice versa (RFB, then WATS). All WATs were examined with computer assistance by an experienced pathologist (FF) at the CDx Laboratory. Similarly, all RFBs were centralized and examined by a single expert pathologist (GD) (University Hospitals Leuven, Belgium). Both were blinded to clinical information. Primary endpoints were the detection rate of HGD/AC and the incremental detection attributable to WATS over RFB. Secondary endpoints were detection rate of HGD/AC for the two procedures in combination, detection rate of HGD/AC according to the order of WATS sample acquisition (i.e., before or after RFB acquisition) and procedural times. We compared paired binary data with McNemar's test.
Results : 147 patients (male/female : 123/24; mean age, 68.4 years) were included : 71/147 (48.3%) randomly assigned to the RFB then WATS group and 76/147 (51.7%) to the WATS then RFB group. Overall, we found 49 HGD/EAC cases. Of these, 25 were detected with both modalities, 14 were detected solely by WATS but missed by RFB and 10 solely by RFB but missed by WATS. The detection rate of HGD/EACs did not differ between WATS (39/147) and RFB (35/147) (26.5%, 95% CI :19.6-34.4% vs 23.8%, 95% CI :17.2-31.5%); p=0.541). Integrated WATS and RFB (49/147) significantly improved detection of HGD/EACs vs RFB alone (33.3%, 95% CI :25.8-41.6%; p<0.001), resulting in a number needed to treat of 10.5 to detect one additional HGD/EAC. The mean procedural time for RFB alone, WATS alone and integrated WATS and RFB were 6.4 (95% CI :5.8-7.2; median, 5.0; IQR,4-8) minutes, 4.8 (95% CI :4.1-5.5; median, 5.0; IQR, 3-6) minutes and 11.2 (95% CI :10.5-11.9; median, 10; IQR, 8-14) minutes, respectively.
Conclusions : In an enriched population with known dysplasia, WATS and RFB detected similar number of cases with HGD/EAC. However, the combination of the two techniques significantly improved detection of HGD/EAC compared to RFB alone, confirming the role of WATS as an adjunct to RFB.

- G02 -

A PROSPECTIVE, MULTI-CENTER VALIDATION STUDY FOR AUTOMATED POLYP DETECTION AS A SECOND OBSERVER. T. Eelbode (1), C. Hassan (2), H. Neumann (3), I. Demedts (4), P. Sinonquel (5), P. Roelandt (4), C. Camps (4), E. Coron (6), P. Bhandari (7), O. Pech (8), H. Willekens (4), F. Maes (9), R. Bisschops (4) / [1] KU Leuven, Belgium, Medical Imaging Research Center, [2] Nuovo Regina Margherita Hospital, Rome, Italy, Endoscopy, [3] University Medical Center Mainz, Mainz, Germany, First Medical Department, [4] KU Leuven, Belgium, Gastroenterology and hepatology, [5] KU Leuven, Belgium, TARGID, [6] CHU Nantes, France, Hepatogastroenterology,

[7] Portsmouth Hospital, Portsmouth, United Kingdom (the), Solent Centre for Digestive Diseases, [8] Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany, Gastroenterology and Interventional Endoscopy, [9] KU Leuven, Belgium, Medical Imaging Research Center, ESAT/PSI.

Introduction : Last year, we developed and presented a deep learning framework for automated polyp detection and localization. In contrast to classical CNN systems, our system uses temporal information or 'memory cells' enabling more accurate and confident predictions. Very little evidence is currently available on the performance of AI systems for polyp detection in real clinical practice. Additionally, studies have shown that 25% of all polyps are missed during colonoscopy, but it is unknown how many of these misses are due to failure of polyp recognition and how many due to suboptimal mucosal exposure.
Aim : The aim of this study is to prospectively validate our system in a multi-center clinical setting in order to obtain an estimate for power calculation for future non-inferiority or superiority trial design, to assess preliminary performance in comparison to experienced endoscopists and to assess miss rate due to polyp recognition failure.
Methods : Our AI system was trained with 131.619 semi-automatically annotated video frames from 825 unique polyps from 206 patients. This system was implemented in a module that can be placed bedside during the colonoscopy procedure. For this study, an experienced endoscopist (all with ADR>35%) does not see the output of the system while a second human observer looks at the AI-enhanced screen. We define four different situations that can occur during the procedure : (1) Obvious false positive - the system gives an obviously false detection (e.g. stool, forceps, air bubble, …). These are nuisances caused by the system but would never cause the endoscopist to take action and are not communicated to the endoscopist. (2) Other positives - a positive prediction that could indicate a missed polyp. When this location disappears from the image, the second observer asks the endoscopist to go back and inspect that location. If there is a polyp, this is an additional detection by the AI system. (3) False negative - a polyp was found by the endoscopist, but the AI system never indicated this location. (4) True positive – the system and endoscopist found the same polyp.
Results : Currently, 99/300 patients are included from three European centers (Leuven, Mainz and Rome). In total 199 polyps were found of which 181 were detected by both the endoscopist and the system. There were 13 polyps that were false negatives (all diminutive) and 5 additional detections made by the system. This corresponds to a 3% increase in polyps-per-colonoscopy for the combination of endoscopist with AI support. A very low average of 1 false positive per minute was recorded.
Conclusions : The interim analysis shows promising results for the clinical validation of a newly developed AI system that was developed in a unique way and different from most existing tools. These exploratory studies are of paramount importance to sufficiently power future trials and to estimate the optimal design of a trial (non-inferiority versus superiority). Our preliminary data suggest that the actual miss rate due to failure of polyp recognition is probably lower than expected and this might affect the design of future studies. We plan to have included 300 patients by the time of the BWGE 2020 and present the full results of this trial.

- G03 -

THE INCREMENTAL BENEFIT OF DYE-BASED CHROMOENDOSCOPY AS COMPARED TO HIGH-DEFINITION WHITE LIGHT AND VIRTUAL CHROMOENDOSCOPY FOR LESION ASSESSMENT AND PREDICTION OF SMI.

M. SIDHU (1), D. TATE (2), M. BOURKE (1) / [1] Westmead Hospital, Australia, Gastroenterology and Hepatology, [2] UZGent, Gent, Belgium, Gastroenterology.

Introduction : Analysis of the surface pit pattern (SPP), of large (>/=20mm) laterally spreading colonic lesions (LSL) can help predict the risk of submucosal invasion (SMI) and identify lesions not suitable for piecemeal endoscopic mucosal resection (EMR). Expert opinion mandates the use of dye-based chromoendoscopy for a reliable assessment of SPP. However, in the era of advanced optics the utility of high definition white light (HDWL) combined with virtual chromoendoscopy (VC) for lesion assessment remains unknown.
Aim : We sought to assess the incremental benefit of dye-based chromoendoscopy in addition to HDWL plus VC for the assessment of SPP and prediction of SMI in colonic LSL referred for EMR.
Methods : A prospective observational study of consecutive lesions referred for EMR at a single tertiary referral centre was performed (NCT03506321). Prior to resection all lesions were assessed for the following surface features; SPP as per the Kudo classification and an area of demarcation [where a regular neoplastic pit pattern (Kudo III/IV) became disordered (Kudo V)], initially performed using HDWL + VC [Narrow band imaging (NBI), Olympus, Tokyo, Japan)] by two trained independent blinded observers. The results were recorded by a third independent observer. Thereafter, indigo-carmine (0.2%) was sprayed directly onto the lesion surface and a repeat assessment performed by the same blinded observers. Overall inter-observer agreement was calculated, and significance reported using kappa co-efficient. Specific institutional review board approval was sought for this study.
Results : Over 22 months to September 2019, 205 consecutive LSL in 205 patients (50.7% – male) were enrolled. Median lesion size was 38mm (IQR : 30-50mm), 46.8% were situated in the right colon. The overall rate of SMI was 9.2% (19/205). Presence of a demarcated area on the lesion surface for all lesions had a negative predictive value (NPV) of [95.1%, 95%CI (90.5-97.6)] for predicting SMI at histology. There was no incremental benefit from the addition of

dye-based chromoendoscopy [NPV 94.6%, 95%CI (90.0-97.3)]. 23/205 (11.2%) LSL contained a demarcated area with HDWL plus VC and 20/205 with addition of dye-based chromoendoscopy. In addition, there was a high rate of inter-observer agreement as to the presence of a demarcated area between the two blinded observers, independent of whether dye-based chromoendoscopy was used; kappa co-efficient (k) 0.98 (SE – 0.03) with HDWL plus VC and k 0.96 (SE – 0.03) with the addition of dye-based chromoendoscopy.
Conclusions : The absence of a demarcated area (where a regular neoplastic pit- pattern becomes disordered) within LSL is strongly predictive for the absence of submucosal invasion histologically. It can be determined using high definition white light and virtual chromoendoscopy without the need for dye-based chromoendoscopy and has a high rate of interobserver agreement amongst experts.

- G04 -

MUCOSAL CAPILLARY PATTERN RECOGNITION BASED ON AUTOMATED IMAGE ANALYSIS DURING ENDOSCOPY ACCURATELY DETECTS HISTOLOGICAL REMISSION IN ULCERATIVE COLITIS. P. BOSSUYT (1), G. DE HERTOGH (2), T. EELBODE (3), S. VERMEIRE (4), R. BISSCHOPS (5) / [1] Imelda Hospital, Bonheiden, Belgium, Department of gastroenterology, [2] University Hospitals Leuven, Belgium, Department of Pathology, [3] University Hospitals Leuven, Belgium, Medical Imaging Research Center, [4] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology, [5] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology.

Introduction : A treat to target strategy in ulcerative colitis (UC) requires an objective evaluation tool to assess remission. The Mayo endoscopic subscore (MES) and the ulcerative colitis endoscopic index of severity (UCEIS) have important inter-rater variability mainly in evaluating remission. Histological remission is the best predictor for sustained clinical remission in UC. The infiltration of neutrophils is associated with morphological irregularities of the pericryptal capillaries.
Aim : The aim was to develop a new objective automated tool for a prototype colonoscopic system to assess histological remission based on the evaluation of the morphology of the pericryptal capillaries during endoscopy.
Methods : We used a prototype endoscopic system enabling activation of a short wave-length monochromatic light through adaptation of a LED system. This enables to evaluate in real time the mucosal architecture (crypts, pericryptal capillaries, bleeding) up to a depth of around 200µm. In initial observations histological non-remission was associated with bleeding (mucosal/luminal) and capillary congestion. For this, an image analysis algorithm was applied to provide a score that quantifies the specific morphology of the mucosal capillaries. The algorithm included two steps. First, bleeding (mucosal/luminal) was assessed by pattern recognition. Samples with bleedings were automatically classified as non-remission. In case of non-bleeding (mucosal/luminal), the degree of congestion of the capillaries was measured (maximal localized density estimation after morphological hessian based vessel recognition) to assess an ideal cut off value to identify histological remission (Geboes score (GBS) <2B.1; no neutrophils in the lamina propria). Consecutive UC patients at the University of Leuven were evaluated with the MES, UCEIS, visual capillary evaluation based on short wave-length monochromatic light and the automated image analysis algorithm. To test the reliability of the algorithm and scores, the results were correlated with the GBS. Biopsies were taken in the matching area of the endoscopic evaluation.
Results : Fifty eight patients with UC (53% male, median age 41y IQR 38-56, disease duration 7.1y IQR 2.4-16.4) with 113 evaluable segments (89% rectum or sigmoid) were included. The correlation between GBS and MES, UCEIS and visual short wave-length was good (r= 0.76, 0.75, 0.74, respectively). The automated image analysis algorithm detected histological remission with a high performance (sens 0.79, spec 0.90) compared to UCEIS (sens 0.95, spec 0.69) and MES (sens 0.98, spec 0.61), resulting in a positive predictive value of 0.83, 0.65 and 0.59 for the automated image analysis algorithm, UCEIS and MES respectively. The algorithm detects histological remission with high accuracy (86%).
Conclusions : Mucosal capillary pattern recognition based on image analysis with short wave-length monochromatic light detected histological remission with high accuracy in UC. This technique provides an objective and quantitative tool to assess histological remission and excludes inter-reader variability.

- G05 -

CONTINUOUS ADR50 MONITORING WITH INDIVIDUAL FEEDBACK IN LOWER GASTROINTESTINAL ENDOSCOPY, A QUALITY IMPROVEMENT INITIATIVE IN A BRUSSELS PUBLIC HOSPITAL. G. Rasschaert (1), L. Duez (1), C. Salem (1), C. Musala (1), M. Nkuize (1), P. Eisendrath (1) / [1] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology and Hepatology.

Introduction : Adenoma detection rate 50 (ADR50) reflects the percentage of colonoscopies in patients aged 50 years or older with at least one adenoma identified. Apart from being an indicator for adequate bowel mucosa inspection, ADR50 is inversely associated with the risk for interval colorectal cancer (CRC) and CRC mortality. ADR50, with a minimum standard of 25%, is considered by the European Society of Gastrointestinal Endoscopy (ESGE) as one of

the key performance measures for lower gastrointestinal endoscopy. Technical and human resources constraints limit implementation of recording of quality monitoring in endoscopy and linkage to the histopathology.
Aim : Deploy a ready able infrastructure for endoscopy quality monitoring with an automated linkage with histopathology to achieve a continuous monitoring of endoscopy quality indicators. Screen the global and individualized ADR50 at our centre. Can an augmentation of ADR50 be seen after individual feedback?
Methods : At first we adapted a company reporting system for colonoscopy by adding a dedicated tab for quality monitoring including : preparation, progression, indication and number of polyps resected. Second we automatically linked this endoscopy database with the histopathology database using the systematized nomenclature of medicine clinical terms® (SNOMED CT®). This results in a continuous monitoring of endoscopy quality indicators. It includes inter alia : rate of adequate bowel preparation, cecal intubation rate (CIR), polyp detection rate 50 (PDR50), ADR50 and percentage of adenoma among polyps resected (%ADR p). Participation was mandatory for all 9 endoscopists working at our centre. After the first 4 months of monitoring (January to April 2019) participants were confronted with their personal numbers and an anonymous ranking was communicated. This was done in a neutral way, without any consequences. After another 5 months of monitoring (May to September 2019) we compared the data of these two separate periods.
Results : A total of 1434 colonoscopies were performed during the first 9 months of monitoring, 682 during the first 4 months, 752 during the following 5 months. CIR was not subject to change (92%). An increase in ADR50 is observed in 7 out of 9 participants, resulting in a global increase of 4.6% (22.9% to 27.5%) ($P<0.05$). An increase in %ADR p is observed in 7 out of 9 participants, resulting in a global increase of 12.1% (53.4 to 65.5) ($P<0.05$). The reported ADR50 numbers meet the goals required by international guidelines. We assume these results underestimate reality because neither emergency - nor therapeutic colonoscopy procedures were excluded from our database.
Conclusions : An easy to use infrastructure for registration of quality monitoring in daily endoscopy practice in combination with an automated linkage with the histopathology database facilitates continuous monitoring of endoscopy quality indicators. This system allows giving feedback to individual endoscopists for personal performance assessment. An increase in personal ADR50 was observed in the majority of the endoscopists 5 months after personal feedback. This confirms the pedagogic value of feedback. In total an augmentation of the global ADR50 was observed. An increase in total %ADR p also reflects a better ability of the team for adenoma detection and consequently a more appropriate resection policy. This parameter can be helpful in pointing out individual needs. These results can be translated into a net quality improvement in the performance of lower gastrointestinal endoscopy at our centre.

- G06 -

THERMAL ABLATION OF THE MUCOSAL DEFECT MARGIN AFTER ENDOSCOPIC MUCOSAL RESECTION SIGNIFICANTLY REDUCES ADENOMA RECURRENCE – A PROSPECTIVE, INTERNATIONAL, MULTI-CENTRE TRIAL. M. Sidhu (1), N. Shahidi (1), L. Hourigan (2), S. Raftopoulos (3), A. Moss (4), S. Heitman (5), E. Lee (1), N. Burgess (1), S. Williams (1), D. Tate (6), M. Bourke (1) / [1] Westmead Hospital, Australia, Gastroenterology and Hepatology, [2] Greenslopes Private Hospital, Australia, Gastroenterology and Hepatology, [3] Sir Charles Gairdner, Australia, Gastroenterology and Hepatology, [4] Western Hospital, Australia, Gastroenterology and Hepatology, [5] University of Calgary, Canada, Departments of Medicine and Community Health Sciences, [6] UZGent, Gent, Belgium, Gastroenterology and Hepatology.

Introduction : Thermal ablation of the defect margin (TAM) after endoscopic mucosal resection (EMR) in the treatment of large (>/=20mm) laterally spreading lesions (LSL) has been shown to be efficacious in a clinical trial setting, with a fourfold reduction, in residual or recurrent adenoma (RRA) at 6 months first surveillance colonoscopy (SC1). The clinical effectiveness of this treatment is unknown.
Aim : We sought to evaluate the effectiveness of TAM on the rate of RRA post EMR in an international, multi-center prospective trial (NCT02957058).
Methods : We conducted a study of consecutive LSL, across five tertiary centers, referred for EMR. The primary endpoint was the rate of RRA at SC1. TAM was performed using soft coagulation (ERBE - Tübingen, Germany : 80W, Effect 4) via the snare-tip (STSC) to create a minimum 2-3mm rim of completely ablated tissue around the entire circumference of the resection defect. All endoscopists underwent an educational intervention prior, with two videos circulated at each centre and image review performed of treated LSL, critiqued to assess for uniform completeness of TAM. Detailed demographic, procedural and outcome data were recorded. Recurrence was defined endoscopically as the presence of a neoplastic pit pattern within an EMR scar and confirmed histologically. Exclusion criteria included LSL involving the ileo-caecal valve/appendiceal orifice and circumferential LSL.
Results : Over 40 months to September 2019, 866 LSL (54.7% - right colon, median size - 35mm) were enrolled and underwent EMR. TAM with uniform completeness was achieved in 795 LSL. 71 LSL (median size 40mm) had incomplete treatment with TAM (poor access – 26, patient related – 15, deep mural injury (>/=3) – 10, risk of significant stenosis – 8, other – 12). 424/494 (85.4%) of eligible LSL underwent SC1 at median 5.8 months (IQR :4.8-6.9). 9/424 (2.1%) cases had evidence of RRA (endoscopic or histologic). RRA was commonly unifocal (7/9), diminutive (6/9) and occurred at the edge of the scar (6/9). All recurrences were successfully treated endoscopically. For LSL with incomplete TAM, however, the rate of RRA was 28% (14/50), in those eligible for SC1.

Conclusions : In clinical practice routine thermal ablation of the defect margin after EMR is highly effective in reducing recurrence. This simple and inexpensive technique should be universally employed. Incomplete treatment, in difficult lesions, is associated with a higher rate of recurrence. Therefore, endoscopists should attempt complete margin ablation in all LSL undergoing EMR.

- G07 -

EUS-GUIDED INTRAHEPATIC ACCESS FOR RETROGRADE, ANTEGRADE OR TRANSGASTRIC BILIARY DRAINAGE : INDICATIONS, EFFICACY AND SAFETY FROM AN 8-YEAR TERTIARY CENTRE EXPERIENCE.
M. Bronswijk (1), G. Vanella (1), H. Van Malenstein (1), W. Laleman (1), S. Van Der Merwe (1) / [1] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology.
Introduction : Intrahepatic access for EUS-guided biliary drainage (IH-EBD) has demonstrated its feasibility, but still lacks convincing evidence on advantages and risks over comparators. Mainly retrospective series are burdened by small size, heterogeneous inclusion of patients and analysis of miscellaneous procedures, IH-EBD therefore struggles to find a role in clinical algorithms.
Aim : Our aim was to retrospectively analyse an 8-year tertiary centre experience with this technique and compare indications, efficacy and safety between different IH-EBD approaches.
Methods : All consecutive IH-EBD executed in one tertiary referral centre between 2012 and 2019 were retrospectively included. Indications, technical details, clinical/biochemical parameters and events during follow-up were extracted from individual patient files. Variables are expressed as proportions and median [interquartile range]. X-squared, Mann-Whitney U and Kruskal-Wallis test were used for comparisons as appropriate. Kaplan-Meier estimates were used for the stent dysfunction-free survival analysis.
Results : In this time interval, 104 IH-EBD were performed (malignancy : n=87 (83.7%); previously failed ERCP : n=81 (77.9%); altered surgical anatomy : n=23 (22.1%). Distal, hilar and anastomotic strictures represented 50%, 28.9% and 14.4% of indications. Sixteen transhepatic ERCP-rendez-vous procedures (RVs), 43 transhepatic antegrade biliary stentings (ASs) and 45 hepatico-gastrostomies (HGs) were identified. Seventeen [38%] HGs were executed with specifically designed half-covered stents. Overall technical success was 89.4%, whilst clinical success (lowering bilirubin or management of choledocholithiasis) was 94%. Using the ASGE lexicon, overall, severe and fatal complication rates were 16.7%, 3.0% and 0.9% respectively. Median hospital stay was 7 [2-10] days and in case of no complications, 4.5 [1-9] days. Stent dysfunction occurred in 17.1% after a median of 103.5 [42.5-168.0] days, resulting in a 72% probability of 6-months dysfunction-free survival. When comparing the three techniques, benign diseases were more prevalent among RVs (p=0.0004), while hilar/anastomotic strictures were mainly managed through HGs (p<0.0001). Technical failures were higher among RVs compared to ASs or HGs (25% vs. 4.4% and 11.6% respectively, p=0.036). Per-protocol clinical success was equivalently high. There was a trend toward a lesser extent of bilirubin decrease in the HG group (53.3% of cases experienced >50% decrease, compared to 66.7% and 96% in the RV and AS groups; p=0.007), which may be attributed to a significantly higher rate of disconnected ducts amongst HGs (53.5% vs. 6.2 and 2.2%, p<0.0001). No difference in severe adverse events was seen. Stent dysfunction was identified in 25%, 12.5% and 20.6% of RVs, ASs and HGs respectively (p=0.624), with a trend towards reduced stent dysfunction when HGs were created with purpose-specific stents vs. older stents (6.7% vs. 31.6%, p=0.0789).
Conclusions : The intrahepatic route for EUS-guided biliary drainage in failed ERCPs or surgically altered anatomy has a good clinical efficacy, relatively low dysfunction rate and an acceptable safety profile. While distal stenoses can also be managed through the extra-hepatic EUS-guided access, these results are particularly valuable for indications in which the only alternative would be percutaneous drainage. Increased technical expertise, specifically designed tools and high-quality comparisons are compelling for a standardized inclusion of this technique in the endoscopic armamentarium of tertiary referral centers.

- G08 -

ELECTROCAUTERY-ENHANCED LUMEN-APPOSING METAL STENTS FOR APPROVED AND NON-APPROVED INDICATIONS : A 2-YEAR SINGLE-CENTRE EXPERIENCE.
P. Hindryckx (1), D. Helena (2) / [1] Ghent University Hospital, Ghent, Belgium, gastroenterology, [2] Ghent University Hospital, Ghent, Belgium, Gastroenterology.

Introduction : Lumen-apposing stents are FDA-approved for the treatment of peripancreatic fluid collections (pancreatic pseudocysts, abscesses, and walled-off necroses). Over the last years, lumen-apposing metal stents (LAMS) have been used for a number of off-label indications : gastrojejunostomy, gastro-gastrostomy in patients with a gastric bypass, gallbladder drainage and bile duct drainage (choledochoduodenostomy).
Aim : To analyze indications and outcomes of electrocautery-enhanced LAMS placement over the last two years in a tertiary referral centre.
Methods : We performed a retrospective analysis of all electrocautery-enhanced LAMS placed over the last 2 years. We collected data on indications, technical and clinical success rates and early (<7d) or late (>7d) complications). Technical

success rate was defined as the successful deployment of the LAMS in the desired position. Clinical success rate was defined as follows : for pancreatic collections : complete resolution without the need for additional interventions; for choledochoduodenostomy : drop in baseline serum bilirubin with at least 50% within 2 weeks OR at least 75% within 4 weeks AND patient can receive chemotherapy if indicated; for gastrojejunostomy : complete resolution of gastric outlet symptoms; for gastro-gastrostomy : successful access to the excluded stomach; for gallbladder drainage : resolution of sepsis.
Results : From March 2018 until November 2019, 40 LAMS (Hot Axios, Boston Scientific) were placed in 38 patients, of which 32/40 (80%) in the last year. Indications were drainage of peripancreatic collections in 21 patients (55.2%), bulbocholedochostomy in 7 patients (18.4%), gastrojejunostomy in 4 patients (10.5%), gastro-gastrostomy in 5 patients (10.5%; 3/5 for biliary intervention and 2/5 to resolve gastric outlet obstruction of the excluded stomach), gallbladder drainage in 1 patient (2.7%) and drainage of a postsurgical abcess in 1 patient (2.7%). Overall technical success rate was high (38/40 LAMS; 95%). In the peripancreatic collection group, clinical success rate was 85.7% (18/21). One patient needed an additional LAMS (multigate approach), one patient needed additional double pigtail drainage (due to LAMS dislocation) and one patient needed surgical necrosectomy. Complications were a new infectious episode in 4 patients (19%), 1 massive bleeding needing urgent embolization in 1 patient (4.8%) and 3 minor bleedings upon LAMS removal (14.3%). Clinical success rate was 100% with zero complications in both the gastrojejunostomy and gastro-gastrostomy group, except for two patients (40%) in the gastro-gastrostomy group suffering from severe reflux that resolved upon removal of the LAMS and closure of the gastro-gastrostomy. Clinical success rate in the choledochoduodenostomy group was 71.4% (5/7). One serious complication occurred : malplacement of the stent with biliary leak and duodenal perforation needing interventional radiology and surgery.
Conclusions : LAMS are an important new tool in interventional endoscopy that may dramatically improve outcomes in adequately selected patient groups. Amongst all (approved and off-label) indications, choledochoduodenostomy is technically the most challenging and severe complications may occur. Hence, it should only be performed in centres with sufficient experience in LAMS placement.

- G09 -

COVERT CARCINOMA AMONG RECTAL ESD SPECIMEN IS HIGH : A EUROPEAN TERTIARY CENTER PROSPECTIVELY COLLECTED EXPERIENCE. M. Figueiredo Ferreira (1), A. Bucalau (1), V. Huberty (1), L. Verset (2), C. Maris (2), J. Van Laethem (1), I. El Nakadi (3), A. Lemmers (1) / [1] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenterology, [2] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Pathology, [3] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Digestive Surgery.

Introduction : Endoscopic resection (ER) represents the treatment of choice for superficial rectal lesions. Careful assessment of the lesions is crucial for decision making in order to optimize outcomes for the patient. Endoscopic submucosal dissection (ESD) is becoming increasingly common in Western countries and is currently proposed by the European Society of Gastrointestinal Endoscopy (ESGE) for the resection of large lesions due to the risk of harbouring a superficial invasive cancer. The rate of covert SMIC (unpredicted submucosal invasive cancer found on the specimen) has been described among endoscopic mucosal resection (EMR) specimen but is poorly known for rectal ESD in Europe.
Aim : In the current study, we aim to evaluate the rate of covert carcinoma among ESD specimen. Furthermore, we assess the efficacy and safety of this treatment approach in one European academic tertiary center.
Methods : Clinical and technical data from Erasme Hospital (Brussels) was systematically and prospectively collected from June 2015 to March 2019. Covert carcinoma is defined as no suspicion of cancer in the rectal lesion based on pit pattern analysis and pre-ESD biopsies if available. Complete resection (R0) is defined as no carcinoma and no adenoma on the margins. Curative resection is defined as en bloc R0 resection of a superficial lesion, well-differentiated adenocarcinoma (G1/G2), sm1 (≤1mm submucosal invasion, with no lymphovascular invasion, as defined by the ESGE). Procedure-associated complications and recurrence rate were also assessed.
Results : Sixty-four patients, mostly men (67.8%) with a mean age of 67 [30-85] years, underwent ESD for a superficial rectal lesion. Most of the lesions were laterally spreading tumors (61%) and were mainly located in the upper rectum (64% > 5 cm from the anal margin), with a mean size of 49 [10-130] mm. 80% of the lesions had a Paris O-Is component at endoscopic characterisation. The median duration of the procedure was 120 [IQR=120] minutes. En-bloc resection was achieved in 96.9% of patients and R0 resection in 59.4%. Histopathological examination displayed 31.3% (20/64) adenocarcinomas comprising 55% superficial tumors, 35% T1sm2/sm3 and 10% T2 lesions. Only 4 lesions were suspected to be carcinoma at the first evaluation, giving a covert carcinoma rate of 25% and a covert SMIC rate of 16.7%. Curative oncological resection was obtained in 40% of patients with carcinoma. Three out of five patients proposed for complementary surgery already underwent a surgical treatment and the histopathological examination showed no residual tumor on the specimen nor on lymphadenopathies. The other patients with a non-curative resection underwent a conservative follow-up strategy with no complementary treatment proposed, mostly due to the presence of significant comorbidities. Endoscopic follow-up was obtained in 32 benign lesion patients and 11 adenocarcinoma cases, disclosing a free-recurrence rate of 98% with only one case of recurrence (a patient with a non-curative resection of a T2 neoplasia).

These results are in favour of coagulation artefacts on the specimen seeing the 59.4% R0 rate. Altogether, 94% of the patients had no complication needing an intervention : 3 presented delayed bleeding managed endoscopically and one patient presented stenosis that was calibrated after one balloon dilation.
Conclusions : ESD for superficial rectal lesions is showing favorable results in terms of efficacy and safety. A 25% rate of covert carcinoma and 16.7% rate of covert SMIC among large rectal polyps underlines the added value of using ESD compared to piece-meal resections in selected cases. Careful assessment of the lesions is crucial, but still not optimal, for decision making in order to improve outcomes for the patient.

- G10 -

SUPERFICIAL ADENOCARCINOMA OF THE ESOPHAGOGASTRIC JUNCTION (AEGJ) : OUTCOMES OF ESD IN A WESTERN COHORT. M. Lefebvre (1) / [1] UCLouvain, Belgium, Gastro-enterology.

Introduction : The incidence of cardia carcinoma is increasing in western societies over the past few years and associated with poor prognosis. Although endoscopic resection is recognized as the first-line therapy for superficial cancer of the gastrointestinal tract, data on ESD for superficial AEGJ in western cohorts remain scarce.
Aim : The aim was to analyze the feasibility, outcomes and safety of ESD for the management of superficial AEGJ in a large cohort of patients.
Methods : This is an observational and retrospective study. All consecutive patients presenting with AEGJ tumours who underwent ESD between 2006 and 2019 were included. The following main outcomes were comparatively evaluated : en-bloc, complete (R0), and curative (depth less than sm2, G1-2, LV0) resection rates, and local recurrence. Secondary outcomes were perforation and delayed bleeding.
Results : Eighty-eight tumours in eighty-four patients were included and classified as HGD (7.9%), well or moderately differentiated carcinoma (60,2%), poorly or undifferentiated carcinoma (31.8%). En bloc resection and R0 rates were 96.6% and 68.2% respectively (R0 for vertical margins 77.9%). Curative resection rate was 48,9% due to LV invasion in 13pts and G3 foci in 9 pt. Local recurrence rates after curative resection was 4.5% at a mean follow-up of 23.7 months [IC 9-36]. Adverse events including perforation, delayed bleeding, and esophageal stricture were 1.7%, 0% and 27.9%, respectively. No perforation required surgery.
Conclusions : ESD for superficial AEGJ showed a high en bloc resection with an acceptable safety profile. The curative resection was however much lower due to unforeseen LV invasion and poorly differentiated areas even in mucosal and submucosal cancer. Recurrence rates remains low after curative resection. Safety profile was acceptable with no serious adverse events.

- G11 -

A MULTINATIONAL RETROSPECTIVE, COHORT STUDY OF PATIENTS WITH BURIED BUMPER SYNDROME TREATED ENDOSCOPICALLY WITH A NOVEL DEDICATED DEVICE. D. Costa (1), P. Hindryckx (2), E. Despott (1), A. Murino (1) / [1] The Royal Free Hospital and University College London (UCL) Institute for Liver and Digestive Health, United Kingdom (the), Gastroenterology, [2] Ghent University Hospital, Ghent, Belgium, gastroenterology.

Introduction : Buried bumper syndrome (BBS) is a rare complication of percutaneous endoscopic gastrostomy (PEG) placement in which the internal bumper migrates alongside the stoma and becomes sited into the gastric wall. Excessive tension between the internal and external bumpers, causing ischemic necrosis of the gastric wall, is the main etiological factor leading to BBS. Several techniques for endoscopic management of BBS have been described, including endoscopic knife- or papillotome-based techniques. However, these devices are used off-label and the procedures can be laborious. The first dedicated, specifically designed device (FlamingoR, Medwork) for endoscopic treatment of BBS has been recently producted. Inserted into the stomach through the external aspect of the PEG tube, this dedicated tool can be flexed by 180°, exposing a sphincterotome-like, cutting wire, which is used to incise the overgrown tissue until the PEG bumper is exposed.
Aim : To investigate the Flamingo device for the treatment of BBS
Methods : We conducted a retrospective, international multicentre, cohort study of patients with BBS treated with the Flamingo device between December 2016 and February 2019. Primary end point was the success rate of buried bumper endoscopic removal with the novel dedicated device. Secondary outcome was immediate and delayed complication rate, duration of the procedure and the success rate of replacement of a new PEG during the same procedure
Results : A total of 53 patients were included in the study (N=51 with complete buried bumper and N=2 with almost complete buried bumper). The buried bumper was successfully removed in 53 patients (96.4%). The median time for the endoscopic removal of the buried bumper was 22 minutes (range 5-60). Peri-procedural endoscopic complications occurred in 7 procedures (12.7 %) and were successfully managed endoscopically in all cases. In 44/53 patients (83%), a new PEG was successfully placed during the same procedure of removal of the buried bumper, through the same site of the gastric wall in 35 patients (80%), while a new gastrostomy was required in 9 patients (20%). A median follow-up of 96 days (range 1-593) was performed in 38 patients (69.1%), during which no significant complications occurred.

Conclusions : The data from this multinational cohort study show that the Flamingo device is a safe, quick and effective novel endoscopic tool for minimally invasive, endoscopic management of (complete) BBS.

- G12 -

AUTOMATED POLYP SIZE ESTIMATION WITH DEEP LEARNING REDUCES INTEROBSERVER VARIABILITY.
J. Suykens (1), T. Eelbode (2), J. Daenen (1), P. Suetens (1), F. Maes (1), R. Bisschops (3) / [1] KU Leuven, Belgium, Medical Imaging Research Center, ESAT/PSI, [2] KU Leuven, Belgium, Medical Imaging Research Center, [3] KU Leuven, Belgium, Gastroenterology and hepatology.

Introduction : In many countries, colonoscopy is part of the screening process for colorectal cancer (CRC). The recommended surveillance interval for patients depends on the findings during the procedure : the number of polyps found, the in-vivo estimated size of these polyps and their histology are all considered when determining surveillance interval. Studies have shown that polyp size is directly correlated with the risk of future CRC and larger polyps are also at greater risk for harbouring an invasive growth. Polyp size is thus an important factor in the clinical decision-making. Despite its big impact, there is no objective way of measuring polyp size in-vivo. Endoscopists typically provide a visual estimate of polyp size, but several studies have reported low accuracies and most of the times, the size is overestimated.
Aim : In this study, we aim to enable more accurate in-vivo polyp size measurements during endoscopy and ultimately reduce the number of clinical mis-sizing by endoscopists. To this end, we develop an AI system that can objectively infer polyp size based on a reference tool in an endoscopic image.
Methods : To enable accurate size estimation, we make use of a biopsy forceps as reference tool which is brought in the same plane as the polyp. For automated inference of polyp size, we developed two separate deep learning algorithms : the first one (1) automatically detects and delineates the polyp in an endoscopic image and retrieves the polyp size as the longest straight-line distance across the delineated polyp region; the second one (2) finds the two outer points of the open biopsy forceps and the distance between them. Since the exact dimensions of the forceps are known, we can compute the size of the polyp in the image by combining both measurements. Both algorithms were trained on separate datasets. For polyp delineation (1), we collected complete pull-through colonoscopy videos from 206 patients with a total of 825 polyps for training, validation and testing of the system (n= 561, 100, 164 respectively with no overlapping patients). For forceps detection (2), we collected complete pull-through colonoscopy videos from 41 patients with a total of 69 polyps, from which 289 image frames were extracted for training, validation and testing of the system (n = 195, 59, 35 respectively with no overlapping polyps) that each contain a polyp and an open biopsy forceps, both in the same plane. For evaluation of size estimation accuracy, we report the 10% trimmed average of the difference between the size as visually estimated by the endoscopist or automatically by the algorithm and the ground truth. The latter is obtained based on manual delineation of the polyp and the two landmarks on the forceps and was itself validated in a colon phantom with spherical objects of known size.
Results : In the test set, the forceps is recognized on 83% of the images and the polyp is detected on 89% of the images. Valid size estimates could be obtained for 71% of the images. In real practice, the endoscopist would be asked to take a new picture for the other cases. The trimmed average difference between the ground truth and the size estimated by the algorithm is 0,52 mm (SD 1,78 mm), while the difference between the ground truth and the endoscopist's estimation is 1,40 mm (SD 1,82 mm). Our algorithm thus leads to a decrease in overestimation bias by 63% (p-value < 0.1).
Conclusions : In this research, we show that the automated delineation of the polyp and detection of the forceps helps in estimating the polyp size and significantly reduces the endoscopists' estimation error. This can potentially lead to better decisions on the patient's surveillance interval, which we intend to evaluate in a larger patient cohort.

- G13 -

EUS-DIRECTED TRANSGASTRIC INTERVENTION (EDGI) IN PATIENTS WITH SURGICALLY ALTERED ANATOMY : MONOCENTRIC EXPERIENCE.
L. Monino (1), M. Tom (1), P. Hubert (2), D. Pierre (1) / [1] Université Catholique de Louvain, Brussels, Belgium, Gastroenterology, [2] Université Catholique de Louvain, Brussels, Belgium, Gastroenterology.

Introduction : The number of patients with surgically altered anatomy has increased steadily since the emergence of obesity surgery. In these patients with Roux-en-Y gastric bypass (RYGB), access to the duodenum, bile ducts, pancreas or excluded stomach is a real challenge. EUS-guided gastro-gastric or jejuno-gastric anastomosis using lumen apposing metal stent (LAMS) allows the creation of a new antegrade access to the excluded stomach. Transgastric access allows the performance of diagnostic and therapeutic endoscopy procedure via LAMS in patients with RYGB.
Aim : We evaluated efficacy and safety of EUS-directed transgastric intervention (EDGI) to create a gastro-gastric or jejuno-gastric anastomosis in RYGB patients using lumen apposing metal stent (LAMS).
Methods : A monocentric retrospective study of consecutive cases of patients with RYGB who had an EUS-directed trans-gastric intervention (EDGI) procedure using LAMS between January 2018 to October 2019.

Results : 9 patients (5 women; mean age 57±6 years) underwent 10 EDGI with LAMS. Technical and clinical success rates were 100%. The indications for performing the EDGI procedure were : treatment of chronic pancreatitis (n=3, multiple plastic stents), treatment of a biliary obstruction (n=4; stone extraction in 3 and 1 choledocobulbostomy) and diagnostic procedure (one occult hemorrhage evaluation and one targeted duodenal biopsy) . In one of these patients, a redo EDGI was performed due to a recurrence of lithiasis in pancreatic duct after ablation of LAMS (after one year of follow up). EDGI was performed in two steps (8/10; 70%) : first step EUS-guided anastomosis and second step transgastric intervention spaced on average 12±4 days. Two EDGI was performed in one step (2/10), one of them due to severe acute cholangitis. Average time of EUS-guided anastomosis was 53±11 min. Two adverse events were encountered : 1 intraperitoneal LAMS placement and 1 LAMS dislodgment during the second step procedure.
Conclusions : EDGI appears to be feasible and effective in RGYB patients to perform antegrade diagnostic and therapeutic endoscopic procedures through LAMS. Care should be taken to deal with possible adverse events.

- G14 -

THE REAL LIFE DIAGNOSTIC ACCURACY OF REGULAR ARRANGEMENT OF COLLECTING VENULES IN DETECTING H.PYLORI-NEGATIVE PATIENTS. C. De Bie (1), E. Dubois (1), M. Bronswijk (1), R. Bielen (1), R. Bisschops (1) / [1] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology.

Introduction : A great deal of patients undergo endoscopic biopsies for the direct histopathological detection of H.pylori. Over the years, several authors have suggested that the identification of regular arrangement of collecting venules (RAC) can be used as an accurate optical tool for detecting H. pylori-negative patients. However, as most of these studies use strict in- and exclusion criteria, data concerning the real life diagnostic performance of RAC-positivity (RAC+) are scarce and perhaps therefore use in daily practice has remained limited.
Aim : Our aim was to provide real life data on the diagnostic accuracy of RAC+ in identifying H. pylori-negative patients.
Methods : Data from all gastroduodenoscopies with biopsies for H. pylori-screening were collected prospectively from September 2019 onwards. Procedures were performed by CDB, EDB, RBI and MB, using high definition endoscopes with magnification mode. All patients undergoing a gastroduodenoscopy with biopsies for H. pylori were considered for inclusion. During the procedure, biopsies were taken at the discretion of the endoscopist alone. In comparison to previous work, no age or medication restrictions were used, nor were patients excluded with a history of malignancy, GI bleeding or portal hypertension. A history of (distal) gastrectomy or gastric bypass, and/or poor visibility were the sole exclusion criteria. As previously described, the presence of RAC+ was evaluated during endoscopic evaluation of the lower part of the lesser curvature, following adequate insufflation and mucosal cleaning by means of a water jet. Patients were identified as RAC+ when diffuse star-like venules were identified in a diffuse pattern. If these findings were absent or only patchy, patients were considered RAC-negative (RAC-). H. pylori-status was confirmed by 2 samples in the gastric body and 2 in the antrum. Pathologist were blinded to the RAC-status.
Results : In this preliminary analysis, the first 155 consecutive patients were included (54% female, mean age 58 years (IQR 44-73). Reasons for performing upper gastrointestinal endoscopy and the subsequent endoscopic findings were similar in both groups. Seventeen patients (11%) were H.pylori-positive, all of which were RAC-. Compared to the RAC+ patients (n=38, 24.5%), RAC- patients (n=117, 75.5%) were older (18.4% vs. 44.4% ≥65 years, p=0.004) and were treated more often with PPIs (47.4% vs. 67.5%, p=0.034) and anticoagulants (5.3% vs. 19.7%, p=0.042). Most importantly, all RAC+ patients were H.pylori-negative, resulting in a sensitivity and NPV of 100%, yet low specificity (27.5%) and PPV (14.5%). Furthermore, reduced rates of RAC+ were seen amongst patients receiving PPIs (Odds Ratio (OR) 0.43 [95% CI 0.21 - 0.09], p=0.028) and anticoagulants (OR 0.22, [95% CI 0.05 - 1.01], p=0.052).
Conclusions : Our real life data suggest that RAC+ has great sensitivity for the detection of H.pylori-negative patients, at the expense of a poor specificity and PPV. Compared to historical data, lower rates of RAC+ were seen in the current study, which could be attributed to a higher mean patient age and an increased percentage of patients treated with PPIs and/or anticoagulants.

- G15 -

WHAT MATTERS FOR YOUR PATIENT DURING UPPER GASTROINTESTINAL ENDOSCOPY : AN EXPLORATORY RESEARCH ON PATIENT EXPERIENCE AND SATISFACTION. M. Surmont (1), Z. Del Rio (2), L. Skenazi (2), C. Hellemans (2), P. Eisendrath (1) / [1] CHU Saint-Pierre, Brussels, Belgium, hepato-gastroenterology, [2] ULB, Brussels, Belgium, Faculté des Sciences psychologiques et de l'éducation.

Introduction : The recent guideline of the European Society of Gastrointestinal Endoscopy (ESGE) on performance measures for endoscopy services recommends an at least annually assessment of patient experience. In 2019, the British Society of Gastroenterology published a position statement with a framework on patient experience in gastrointestinal endoscopy. Despite the increased interest, there is a lack of data in the research area of patient experience and satisfaction. Currently, there is limited evidence on how patient experience should be measured. All available measures of patient

experience today contain clinician derived information on aspects of procedures rather than information directly from patients.
Aim : The aim of this study was to highlight the main elements affecting patient satisfaction and experience during upper gastrointestinal endoscopy by using a questionnaire for patients.
Methods : A review of the literature and qualitative data of exploratory interviews with patients on their satisfaction and experience were used as the basis for the development of a questionnaire. This questionnaire contained an interactive part with eleven variables about patient experience. These variables were to be classified by importance by the patient. It was administered by one interviewer to outpatients who underwent an upper endoscopy in an urban Belgian hospital in Brussels, Belgium from March 14th to April 14th, 2019. An informed consent validated by local ethics committee was presented before each interview. The statistical analyses were performed with IBM SPSS.
Results : Out of 54 consecutive interviewed patients, 52 patients responded to the full questionnaire, of which 35 women. 46 % of the sample was between the age of 26 and 45 years. The mean of the global satisfaction was 8.82 out of 10 (standard deviation of 0.989). Perceived « Kindness of the team », "Professionalism of the team" and "Explanation of the results after the examination" were considered by patients as the three most important factors influencing the global satisfaction, by respectively 85%, 58% and 50% of the sample. On the other hand, "Fasting on the day of the exam", "Waiting time before the exam" and "Pain" were considered as less important factors influencing patient satisfaction, ranked as the last three items by respectively 58 %, 58% and 37% of the sample. There is a statistically significant difference in ranking between the eleven variables ($p<0.001$).
Conclusions : Patient experience and satisfaction are a part of health care quality. Most studies tend to focus on clinical outcomes and are clinician driven. Patient derived data of this exploratory study show that kindness and communication stand out as the most important factors in patient experience and satisfaction during upper gastrointestinal endoscopy. Larger studies with validated tools should confirm these results. In anticipation of a tool for patient derived experience, validated for use in an endoscopy setting, these results raise awareness about the elements that matters for your patient in terms of patient experience.

- G16 -

ESD FOR OESOPHAGEAL SQUAMOUS CELL CARCINOMA : A EUROPEAN TERTIARY CENTRE PROSPECTIVELY COLLECTED EXPERIENCE. M. Figueiredo Ferreira (1), A. Bucalau (2), V. Huberty (1), L. Verset (3), C. Maris (3), J. Van Laethem (1), I. El Nakadi (4), J. Devière (1), A. Lemmers (1) / [1] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenterology, [2] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenteroloy, [3] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Pathology, [4] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Digestive Surgery.

Introduction : Endoscopic submucosal dissection (ESD) is widely recognized as one of the treatment options in cases of superficial esophageal squamous cell carcinoma (SCC). However, reports from European centers on this endoscopic technique remain scarce and most of the available data still originates from Japanese series.
Aim : Hence, our aim is to present the results and evaluate the efficacy and safety of this treatment approach in one European academic tertiary center.
Methods : We performed a single-center systematic prospectively collected registry, including all the patients with superficial esophageal SCC treated by ESD from mars 2016 to november 2018. Our main outcomes were R0 resection (defined as vertical and lateral margins clear from carcinoma or dysplasia), curative resection (an en-bloc R0 resection with histology no more advanced than pT1a m2 SCC, with no lymphovascular invasion and no poor differentiation, as defined by the European Society of Gastrointestinal Endoscopy), procedure-associated complications and, finally, locally or distant recurrence rate.
Results : We included twenty ESD independent procedures performed on nineteen patients (mean age 65 [41-83] year old, 55% men). Most of the lesions were located in the medium and distal oesophagus (45%, respectively), with only 2 lesions (10%) located in the proximal region. The mean lesion size was 39 [15-100] mm and the mean procedure duration was 115 [30–180] min. 65% occupied more than 50% of oesophageal circumference. En-bloc resection was achieved in 20 cases (100%) and R0 resection in 18 cases (90%), with 2 patients presenting focal positive horizontal margins. A 6 months follow-up available in both cases showed no endoscopic or pathologic signs of SCC suggesting a coagulation artefact on the specimen. Curative resection was accomplished in 9 cases (45%). The resection was non curative in 11 cases for the following reasons : 3 en-bloc R0 G1 pT1a m3 SCC, 6 deep submucosal (sm2) SCC with free vertical margins, and 2 due to positive lymphovascular infiltration. One patient benefited from complementary radio-chemotherapy and one was submitted to complementary oesophagectomy (pT0N0). Other patients were followed endoscopically knowing their age or comorbidities, after multidisciplinary discussion. The endoscopic follow-up (median 15 [1-29] months) was available for 13 of the 17 patients without adjuvant oncological therapy and disclosed that 12 (92.3%) patients had no signs of recurrence. The only case with lymphatic recurrence appeared in a patient with non-curative ESD and past history of lymph node metastatic pharyngeal SCC. In 80% of the cases, there were no complications needing any intervention. Despite steroid administration in 65% of cases for secondary strictures prevention (locally injected triamcinolone for

>50% circumference resection or oral steroid for circumferential resections), 3 patients developed symptomatic strictures requiring endoscopic treatment. One patient presented delayed post-ESD local haemorrhage, treated successfully by endoscopic haemostasis.
Conclusions : Our preliminary data confirm the safety and technical quality of esophageal ESD for SCC in a tertiary European center. The complexity to predict the oncological stage opens the room for staging ESD with the major limit being the risk of secondary stricture. Further work must be done by multicentric studies to better stratify the place of adjuvant oncologic treatment.

- G17 -

A NEW 12-FRENCH PLASTIC STENT MAY BE AN ALTERNATIVE IN UNRESECTABLE DISTAL MALIGNANT BILIARY OBSTRUCTION. P. Deprez (1), T. Moreels (2), T. Aouattah (2), H. Piessevaux (2), E. Pérez-Cuadrado-Robles (2) / [1] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Gastro-Entérologie, [2] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Hepato-gastroenterology.

Introduction : Self-expanding metal stents (SEMSs) are recommended in unresectable distal malignant biliary obstruction (DMBO). However, stent dysfunction and migration are non-negligible.
Aim : To address the effectiveness and safety of a new 12-French plastic stent (PS).
Methods : Observational, prospective, frequency matched study. All consecutive patients who underwent biliary stenting by a 12-French PS were considered (index). A historical cohort matched by sex, etiology and metastatic status included patients with 10-French PS and SEMSs (referents). The outcomes were the stent patency, recurrent biliary obstruction (RBO), technical success, 30-days mortality and adverse events. A post-procedure analysis in removed stents was performed.
Results : Seventy-two patients (median age : 66, range : 32-94 years, 50% male) were included (24 index, 48 referents). There was no statistically significant difference in the stent patency median time (p=0.684). The RBO was significantly lower (50%) in the 12-French compared to the 10-French profile (50% vs. 81.3%, p=0.04), but no difference was found compared to FCSEMSs (50% vs. 43.8%, p=0.698). Technical success was 100% in all subgroups, without differences in 30-days (p=0.105). Adverse events were 4.2%. Of 11 removed 12-French PSs suspected to be dysfunctional, 7 (64%) were still permeable.
Conclusions : This new 12-French PSs could be an effective and cheaper alternative to SEMS in distal biliary malignant obstruction.

- G18 -

OBSTRUCTIVE COMPLICATIONS RELATED TO THE USE OF SELF-EXPANDABLE METALLIC STENT FOR THE TREATMENT OF DISTAL BILIARY STRICTURE. W. Soub Defeu (1), J. Devière (2), A. Lemmers (2) / [1] C.U.B. Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium, Gastroenterology, Hepatopancreatology and Digestive Oncology. [2] C.U.B. Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium, Gastroenterology, Hepatopancreatology and Digestive Oncology.

Introduction : Self-expandable metallic stents (SEMS) are currently routinely used for the endoscopic treatment of distal biliary stricture. However, the placement of these stents is associated with complications such as acute cholecystitis and pancreatitis.
Aim : The aim of this study was to compare the occurrence of these obstructive complications between different types of SEMS in our endoscopy unit.
Methods : This is a retrospective study of patients who underwent ERCP with SEMS for distal biliary stricture (benign or malignant) between January 2008 and June 2018. The incidence and the comparative analysis according to the type of SEMS (uncovered (USEMS), partially covered (PcSEMS), fully covered (FcSEMS)), the rate of cholecystitis or acute pancreatitis post ERCP, the permeability of the stent, their level of dysfunction (migration and occlusion) and the need for reintervention were performed.
Results : 224 patients were included in the study (81 patients in the USEMS group, 42 in the PcSEMS group and 101 in the FcSEMS group). The incidence of acute cholecystitis (7.25% vs 0% vs 5.33% p : 0.275) and the incidence of acute pancreatitis post ERCP with SEMS (3,7% vs 4.76% vs 5.94% p : 0.785) was similar between the different groups. In addition, acute cholecystitis was only found in patients with malignant stenosis. The importance of opacification of the cystico-vesicular system is not associated with the occurrence of post-SEMS cholecystitis. The incidence of stent migration was higher in the FcSEMS group (6.17% vs 11.9% vs 22.77% p : 0.006). For the rest of the variables studied (median duration of permeability, reintervention rate, survival time) there was no difference between the different types of SEMS
Conclusions : The use of SEMS is associated with a significant risk of acute pancreatitis and acute cholecystitis (especially in the group of malignant stenosis) without there being an association with the type of SEMS. The stent

migration is more frequent in the fully covered SEMS group, however reintervention rates for stent dysfunction was similar between different groups.

- G19 -

WE CANNOT TEACH OUR ENDOSCOPISTS TO ACCURATELY SIZE POLYPS : A FOLLOW-UP ON THE OOSTENDE POLYP SIZING STUDY. S. Van Langendonck (1), A. Billiet (2), K. Hertveldt (3), M. Cool (4), G. Lambrecht (4), G. Deboever (4) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastro-enterologie, [2] UZ Leuven, Leuven, Belgium, Gastro-enterologie, [3] AZ Damiaan, Oostende, Belgium, Pathologie, [4] AZ Damiaan, Oostende, Belgium, Gastro-enterologie.

Introduction : Polyp size is one of the defining characteristics after polypectomy to decide upon the surveillance recommendations. In current practice, this is often based on endoscopic estimation. Last year we presented data showing inadequate polyp sizing, mostly due to overestimation, leading to inappropriate surveillance recommendations. These data were met with some opposition, mostly pertaining the sessile polyps included. It was noted that they might shrink due to electrocautery and as such falsely lead to a high number of polyps overestimated.
Aim : To see if the findings of our previous study persisted when only considering pedunculated, Paris 0-Ip, polyps and to see if endoscopists can improve their ability to accurately size polyps.
Methods : A monocentric, prospective study was performed between February and November 2019. Experienced endoscopists sized polyps by visual estimation without the support of devices. This was then compared to the gold standard ex-vivo prefixation and postfixation measurements, to which the endoscopists were blinded. To eliminate the risk of electrocautery induced polyps shrinkage, only pedunculated, Paris 0-Ip, polyps were included. Other factors that influence surveillance recommendations were collected. The estimation error between endoscopic sizing and prefixation measurement was compared between the current study and a subanalysis of the previous one, selecting only the pedunculated polyps. Normality was tested with a Shapiro-Wilk test and continuous variables were compared with a paired sample T-test or a Mann-Whitney U test.
Results : In total 52 polyps were included in the study. The endoscopic sizing (13.19±4.33mm) differed statistically from the prefixation (at 11.94±4.20mm; $p<0.005$) and postfixation (11.65±4.26mm; $p<0.005$) measurements. Overestimation (63.5%) was seen more often than underestimation (21.2%). There was no statistically significant difference between prefixation and postfixation measurements ($p=0.244$). An inappropriate surveillance recommendation was given in 26.9% of the cases, of which 100% were due to overestimation. After considering other factors that define the surveillance recommendation, still 15.4% were erroneous. No statistically significant improvement in estimation error between the current (1.25±2.81mm) and previous (1.60±2.89mm) study could be found ($p=0.654$).
Conclusions : The previously reported findings suggesting that endoscopic polyp sizing is prone to overestimation resulting in inappropriate surveillance recommendations are being confirmed when only including pedunculated polyps. The previous noted possible awareness effect, leading to better endoscopic sizing, could not be withheld. As such there only seems to be limited teachability towards endoscopic sizing without the use of devices. Until the advent of new measuring devices, we propose using ex-vivo measurements in pedunculated polyps to establish post-polypectomy surveillance recommendations. Additional research is warranted to select the optimal sizing modality in sessile polyps.

- G20 -

RISK STRATIFICATION OF PATIENTS IN ER PRESENTING WITH ACUTE UPPER GASTROINTESTINAL BLEED USING EXTENDED GLASGOW BLATCHFORD SCORE. D. Krishnan (1), G. Panchakapesan (2), S. Shanmughanathan (2) / [1] SREE RAMACHANDRA MEDICAL COLLEGE, India, MEDICAL GASTROENTEROLOGY, [2] SREE RAMACHANDRA MEDICAL COLLEGE, India, Medical Gastroenterology.

Introduction : Up to 60% of patients who present to the emergency department with an acute upper gastrointestinal bleed (AUGIB) are at low risk of requiring intervention or of dying within 30 days. UK National Institute for health and Care Excellence guidelines have recommended early discharge without endoscopy for patients with an AUGIB and a Glasgow-Blatchford Score (GBS) of 0. However, this low-risk cut-off has a limited sensitivity in that only 3%–22% of patients score 0. Extension of the cut-off to ≤1 or<2 has been proposed in recent international guidelines and observational studies, respectively, to increase this proportion, so there is controversy as to the optimal cut-off and little data on performance in routine clinical practice.
Aim : The objective of this study was to compare the outcomes of patients with GBS less than or equal to 1 and more than 1 to aid discharge of patients from emergency department. Secondary objective was to compare it with another risk stratification score (Pre-endoscopy Rockall)
Methods : Single -centre study with retrospective analysis of patients with AUGIB over 18 months and associated adverse outcome defined as in hospital combined endpoint of blood transfusion, intervention or death.
Results : 115 patients presented with AUGIB during 18 months of study. 16 (14%) had a GBS ≤1. Of these, none had an adverse outcome. GBS ≤1 had a negative predictive value=100% in predicting adverse outcomes. Of GBS >1, 99

patients (86%), 32 patients (32.3%) required endotherapy, 31 patients (32.14%) required blood transfusions and had in hospital mortality of 10 patients (8.%). Our group have shown that a pre-endoscopy Rockall score of 0 (26 patients) is associated with a need for blood transfusions and endotherapy in 5 patients (19%), limiting its utility for the discharge of patients from the emergency department.
Conclusions : GBS >1 is associated with need for intervention and adverse events than with score ≤1. GBS of ≤1 is the optimal cut-off for the discharge of patients with an AUGIB from the emergency department. Its use has the potential to significantly increase the number of patients with an AUGIB who could be discharged from the emergency department that would, in turn, free up inpatient beds and save costs.

- G21 -

SAME DAY PROPOFOL SEDATION DOES NOT IMPAIR THE COMPLETION RATE OF CAPSULE ENDOSCOPY.
O. De Ronde (1), T. De Ronde (1), F. Wuestenberghs (1) / [1] CHU UCL Namur, Site de Godinne, Yvoir, Belgium, Department of Gastroenterology and Hepatology.

Introduction : Videocapsule endoscopy (VCE) is mainly used to investigate the small bowel in patients with overt or occult gastrointestinal (GI) bleeding of unknown origin after upper and lower GI endoscopies. Investigation of the entire small bowel is important to obtain the best diagnostic yield from the technique. All conditions slowing down GI motility theoretically increase the risk of an incomplete capsule endoscopy.
Aim : Since sedation by propofol is known to alter small bowel motility, our aim was to assess if same day sedation by propofol influence completion rate (primary outcome) or diagnostic yield (secondary outcome) of VCE ingested in the hours following the sedation.
Methods : This is a retrospective monocentric study including all consecutive patients who underwent a small bowel capsule endoscopy (MiroCam®, IntroMedic, Seoul, Korea) between August 2012 and March 2018 at Mont-Godinne University Hospital. 171 patients were kept for statistical analysis over a total of 182 patients (2 patients in which the pylorus was not crossed and 9 with missing data were excluded). Completion rate was defined as the percentage of capsule endoscopies which reached the cecum. The diagnostic yield was defined as the percentage of positive or suspicious findings according to the Costamagna classification. Quantitative data were compared using an unpaired t-test, while qualitative variables were compared using Fisher's exact test, both with a 95% confidence interval. A bilateral p-value <0.05 was considered statistically significant. Data were analysed using GraphPad Prism® Version 5.03 for Windows. Ethical approval for the analysis of the data was obtained (CE number 01/2017).
Results : Out of the 171 patients analysed, 70 (40.9%) were women. Mean age was 67.4 years (range 16-90 years). Mean body mass index was 27.3 kg/m². The indication of the VCE was occult GI bleeding in 65.5% of the cases, overt GI bleeding in 26.3% of the cases, follow-up of celiac disease in 2.3% of the cases, suspicion of Crohn's disease in 1.2% of the cases, follow-up of Peutz-Jeghers syndrome in 1.2% of the cases, and other indications in 3.5% of the cases. 48 (28.1%) patients underwent sedation by propofol on the same day before the ingestion of the VCE and 123 (71.9%) did not. All demographic characteristics were similar between both groups, except the proportion of in-patients (85.4% in the sedation group compared to 43.1% in the non-sedation group, $p < 0.0001$). Complete VCE were 39 (90.7%) in the sedation group and 100 (81.3%) in the non-sedation group ($p > 0.99$). The diagnostic yield was similar in both groups (29.2 vs 43.9% respectively, $p = 0.085$), but positive findings were more frequent in the group without same day sedation (16.7 vs 35.0% respectively, $p = 0.025$). The total small bowel transit time was 308.9 ± 107,8 minutes and 275,0 ± 96,68 minutes in sedation and non-sedation groups respectively ($p = 0.17$).
Conclusions : The completion rate of VCE was similar irrespective of a prior sedation by propofol or not. Therefore, administering capsules on the same day of endoscopies performed under sedation by propofol should not be discouraged. However, even if the diagnostic yield was similar in both groups, positive findings were significantly more frequent in patients with no sedation on the same day as VCE. A prospective randomized study is needed to determine whether prior propofol sedation influences the diagnostic yield of VCE.

- G22 -

PARTIALLY COVERED METALLIC STENT FOR TREATMENT OF GASTRIC LEAK AFTER SLEEVE GASTRECTOMY : A RETROSPECTIVE MONOCENTRIC EXPERIENCE OF 760 CONSECUTIVES SURGICAL PROCEDURES.
B. Vos (1), J. Rigaux (1), S. Evrard (2) / [1] Chirec, Braine-l'Alleud, Belgium, Gastroenterology, [2] Chirec, Braine-l'Alleud, Belgium, Gastroenterology.

Introduction : Laparoscopic sleeve gastrectomy (LSG) is now a standard surgical bariatric procedure. The most feared complication after LSG is staple line leak. Use of partially covered metallic stent for the treatment of upper GI leaks after bariatric surgery is now well described.
Aim : We reported here our institutional experience with a partially covered metallic stent specifically designed for the treatment of leak and perforation occurring after LSG (Endo-Flex Esophagus metal stent -Eso-Cremer 20 cm length and a diameter of 20-25mm).

Methods : A retrospective analysis was performed by all the LSG cases performed in Braine l'Alleud-Waterloo hospital between January 2016 and October 2019. The data collected included patient demographics, operative and perioperative parameters. Statistics analysis are expressed in median (minimum-maximum).
Results : Among the 760 patients who underwent LSG, 11 (1.4%) with gastric leaks were identified. Of these 11 patients, 10 (91%) were women. The patients had a median (min-max) age of 37 (25-71) years. Leaks were diagnosed at a median of 6 days postoperatively : early (0-2 days) in 2 cases (18%), intermediately (3-14 days) in 8 cases (73%), and late (>14 days) in 1 cases (9%). Surgical drainage was performed in 9 patients (82%) and none in 2 patients (18%) corresponding to early leaks cases. All patients were initially treated by endoscopic placement of Endo-Flex Esophagus metal stent (Eso-Cremer 20 cm length) with a median (min-max) stenting duration time of 49 (15-76) days. All stents were placed successfully. The presence of the stent caused, in all patients, gastric reflux and distal Forrest III ulcer due to distal prosthesis part. One session removal stent was possible in 10 patients (91%) and one patient need a fully covered metal stent to remove initial stent. Primary success endoscopic stenting occurred in 8 patients (73%) and 3 patients need a rescue endoscopic pig-tails drainage (2 directly after removal stent and 1 late recurrence associate to complementary surgical drainage). One patient kept benign stenosis which need iterative endoscopic dilatation, stenting, endoscopic section and corticoid injection. Finally, all patients have success management of gastric leak.
Conclusions : Gastric leak rate after LSG is low and within surgical recommendation in our hospital. Primary success endoscopic with Endo-Flex Esophagus metal stent occurred in main part of patients with low rate of complications. Endoscopic pig tails drainage rescue is efficient to obtain complete gastric leak resolution.

- G23 -

RADIOFREQUENCY ABLATION OF BARRETT ESOPHAGUS : POST REIMBURSEMENT EXPERIENCE OF A TERTIARY BELGIAN HOSPITAL. S. Ouazzani (1), A. Lemmers (1), N. D'haene (2), L. Verset (3), J. Deviere (1), P. Eisendrath (4) / [1] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, [2] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Pathology, [3] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Pathology, [4] Saint-Pierre University Hospital, Brussels, Belgium, Gastroenterology.

Introduction : Barrett esophagus (BE) is a premalignant condition of esophageal adenocarcinoma, with an increasing incidence. Endoscopic treatment of BE with dysplasia and early neoplastic lesions is the standard of care and includes endoscopic resection (ER) of visible lesions containing early neoplasia, followed by endoscopic ablation. Among different ablation techniques, radiofrequency ablation (RFA) is the most used and effective with a safe profile. This technique is refunded by the Belgian Health system since April 2016.
Aim : We report our experience in treatment of BE by RFA from this date.
Methods : We reviewed prospectively recorded data of patients from a single tertiary care hospital, Erasme university hospital. Patients were referred for the ablation of a BE complicated by high grade dysplasia (HGD) and/or early cancer between April 2016 and October 2019. Prior to endoscopic ablation, all patients with visible lesions beneficiated of ER (by endoscopic mucosal resection (EMR) or endoscopic sub-mucosal dissection (ESD)). RFA was performed with different ablation devices, according to intestinal metaplasia (IM) length and configuration. Ablation devices included circumferential express balloon catheter (BARRX360) and focal catheters (BARRX90, UltraLong and 60). Ablation sessions were separated by three months and were performed up to IM clearing with maximum 5 sessions. During follow-up endoscopies, biopsies were performed according to Seattle protocol. Follow-up endoscopies were performed every 3 months during the first year, every 6 months during the second year, and annually thereafter. The rates of dysplasia and IM complete eradications (CE) were calculated, as well as the rate of dysplasia and IM recurrence and the rate of complications.
Results : A total of 41 patients were treated by RFA, with 19 of them being still on ablation program, and 2 being lost from follow-up. Thirty-five (85%) were men and the median age was 70 years (IQR :64-77). BE median circumferential and tongue lengths were 2 cm (range :0-16) and 5 cm (1-16) respectively. 31 patients (76%) had ER of visible abnormalities prior ablation, consisting in EMR for 22 patients (71%) and in ESD for 9 patients (29%). The other ten patients beneficiated of RFA as the treatment of HGD without visible lesion. The worst pre-RFA histology was HGD in 20 patients, intramucosal cancer in 19 patients and superficial submucosal adenocarcinoma in 2 patients. Among this group, 20 patients reached the end of the ablation program at the end of this study period. Patients underwent a median of 2 focal RFA sessions (IQR :1-3) and eight patients (40%) had at least one express balloon catheter RFA session. CE of dysplasia was achieved by RFA in 18 patients (90%). The two other patients having residual dysplastic BE after 5 RFA sessions, received complementary treatment by argon plasma coagulation with finally dysplasia eradication, giving a global CE of dysplasia of 100%. CE of IM was achieved in 15 patients (75%). Among the others, two are the aforementioned patients with remaining dysplasia, two had only focal IM at the neo-squamocolumnar junction (neoSCJ). The last one had a remaining C0M2 BE after one RFA session and was not treated by more session according to patient's preference but is still followed. Twelve patients with CE of dysplasia were followed during at least 12 months (median follow-up of 15 months). Nonexperienced dysplasia recurrence at one year of follow-up. Nine patients with CE of IM were followed during at least 12 months (median follow-up of 15 months). Among them, two (22%) experienced IM

recurrence at one year of follow-up. One of them was millimetric, located 5 cm above the neoSCJ and not found in the follow-up after biopsy sampling. The other presented only histologic IM at the neoSCJ, without endoscopically visible BE. Among the whole cohort, six patients (14%) presented symptomatic strictures after RFA, all successfully treated by endoscopic dilatation and stenting for one case. There were no other serious adverse events, including bleeding, perforation or procedure-related deaths.

Conclusions : Our results confirm the efficacy and safety of the multimodal endoscopic management of early Barrett's neoplasia. Clinical significance of residual junctional IM without visible BE after ablation is questionable. Long-term follow-up in multicentric studies would help choosing between an aggressive or permissive strategy.

GENERAL GASTROENTEROLOGY

- GE01 -

CLINICAL AUDIT ON EFFECTIVENESS OF HELICOBACTER PYLORI TREATMENT IN SINGAPORE - A MULTIRACIAL ASIAN COHORT. K. Lim (1), A. Tiing Leong (1), K. Andrew Boon Eu (1), A. Daphne (1), T. Eng Kiong (1) / [1] Changi general hospital, Singapore, Singapore, Gastroenterology and hepatology.

Introduction : H. pylori eradication reduces the risk of gastric malignancies and peptic ulcer disease. In Singapore, first-line therapies include 14-day PAC [proton pump inhibitors (PPI), amoxicillin, clarithromycin] and PBMT (PPI, bismuth, metronidazole, tetracycline). Globally the success of PAC has declined due to increasing clarithromycin resistance, although there are regions where it remains effective. A 15-year retrospective study from Singapore showed that while amoxicillin resistance rates remained low, there was a temporal increase in clarithromycin resistance rates, increasing from 7.9% during the period 2000-2002 to 17.1% during the period 2012-2014. A clarithromycin resistance rate of 15% to 20% in the population is generally regarded as indication of low treatment success rate with empiric PAC and should prompt reconsideration of the use of PAC as empiric first line therapy. In the context of failure of first line therapy, empiric second line therapies using 14-day PBMT and PAL (PPI, amoxicillin, levofloxacin) are commonly utilized.
Aim : This clinical audit examined the efficacy of current empiric first- and second-line H. pylori eradication therapies in Singapore, a multiracial Asian cohort.
Methods : Clinical data of H. pylori-positive patients who underwent first- and second-line eradication therapies from 1 January 2017 to 31 December 2018 were reviewed. Treatment success was determined by 13C urea breath test performed at least 4 weeks after treatment and 2 weeks after PPI cessation. The primary outcome measures of this study were the efficacies of current recommended empiric first and second line H.pylori eradication therapies in Singapore. The secondary outcome measures were adherence to current treatment guidelines in terms of choice of treatment regimen and treatment duration, the impact of variables including gender and nationality on success rate of treatment and the difference between different empiric H.pylori therapies. Statistical analysis was performed using SPSS software (version 20.0; SPSS, Chicago, IL). Continuous variables were analyzed using t-test and categorical variables were analyzed using Chi-square and Fisher's exact tests as appropriate. A p value< 0.05 was considered as statistically significant.
Results : A total of 963 [PAC : 862; PMC (PPI, metronidazole, clarithromycin) : 36; PBMT : 18; PBAC (PAC with bismuth) : 13; others : 34] and 98 patients (PMBT : 62; PAL : 15; others : 21) received first and second line therapies respectively. Fourteen-day first- and second-line therapies were prescribed in 65.2% and 81.6% respectively. The mean age was 54.4 years (+/-14.8), 56% were males and 83.2% Singaporeans. First line treatment success rates were PAC (7-day : 76.9%; 10-day : 88.3%; 14-day : 92.0%), PMC (7-day : 0; 10-day : 75.0%; 14-day : 69.8%), PBMT (10-day : 100%; 14-day : 87.5%) and PBAC 14-day 100%. First line fourteen-day treatment was superior to 7-day (90.8% vs 71.4%, $p = 0.028$). PAC was superior to PMC ($p < 0.001$) but similar to PBMT ($p = 0.518$) and PBAC ($p = 0.288$) in 14-day therapies. Gender and nationality did not show any impact on treatment outcome. Fourteen-day second line PAL and PBMT had similar efficacy (85.7% vs. 82.7%, $p = 0.788$).
Conclusions : The efficacy of empiric first line PAC, PBMT and PBAC for 14 days were similar and more than 90% eradication rate. The success rates for second line PBMT and PAL were similar and remained fair, greater than the minimum threshold of 80% but less than 90%.

- GE02 -

BISMUTH-BASED VS. STANDARD TRIPLE THERAPY FOR THE ERADICATION OF HELICOBACTER PYLORI IN BELGIUM : PRELIMINARY RESULTS. S. François (1), F. Mana (2), R. Saminou (3), V. Lamy (4), S. Cadranel (5), P. Bontems (5), V. Miendje Deyi (6), E. Macken (7), S. Kindt (8) / [1] UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium, Gastro-enterologie, [2] Clinique Saint-Jean, Brussels, Belgium, Gastroenterology, [3] Saint-Pierre University Hospital, Brussels, Belgium, Gastroenterology, [4] CHU, Charleroi, Belgium, Gastroenterology, [5] CHU Brugmann, Brussels, Belgium, Paediatrics, [6] CHU Saint-Pierre, Brussels, Belgium, Clinical Biology, [7] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology, [8] UZ Brussel, Jette, Belgium, Gastroenterology.

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. ER (confirmed by urea breath test at least 6 weeks following treatment) were compared 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, a sample size of 125 patients per group is required.

Results : Overall 142 patients were included (STT 70, BQT 72). 10 patients were lost to follow-up (7%). No significant difference in ER between BQT and STT was observed in ITT (82% vs 74%, p= 0.27) neither in PP analysis (88% vs 80%, p= 0.21).
Conclusions : Despite the numerical advantage of BQT, preliminary results demonstrate no statistical difference between both treatment arms. The currently achieved ER differ from the estimated ER used for sample size calculation. Based on the currently observed gain in ER for BQT over STT, a sample size of 328 patients per group would be required, questioning the cost-effectiveness of BQT.

- GE03 -

INULIN-ENRICHED DIET AS A SUSTAINABLE DIETARY APPROACH TO MODULATE PSYCHOLOGICAL HEALTH IN OBESE SUBJECTS : LINK WITH THE GUT MICROBIOTA AND METABOLIC DISORDERS. Q. Leyrolle (1), R. Cserjesi (2), S. Hiel (1), M. Gianfrancesco (3), J. Rodriguez (1), D. Portheault (4), L. Bindels (1), M. Mulders (5), G. Zamariola (6), C. Amadieu (1), A. Neyrinck (1), P. Cani (1), N. Lanthier (7), P. Trefois (8), O. Klein (9), O. Luminet (5), N. Paquot (3), M. Cnop (4), J. Thissen (10), N. Delzenne (1) / [1] UCLouvain, Belgium, Metabolism and Nutrition Research Group, Louvain Drug Research Institute, [2] Université Libre de Bruxelles, Belgium, Faculty of Psychological Science, and Education, [3] ULiège, Belgium, Laboratory of Diabetology, Nutrition and Metabolic disease, [4] Université Libre de Bruxelles, Belgium, ULB Center for Diabetes Research, Université Libre de Bruxelles, and Division of Endocrinology, Erasmus Hospital, [5] UCLouvain, Belgium, Research Institute for Psychological Sciences, [6] UCLouvain, Belgium, Faculty of Psychological Science, and Education, [7] UCLouvain, Belgium, Laboratory of Hepatogastroenterology, Institut de recherche expérimentale et Clinique, [8] Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium, Medical Imaging Department, [9] ULB, Brussels, Belgium, Faculty of Psychological Science, and Education, [10] UCLouvain, Belgium, Pole of Endocrinology, Diabetes and Nutrition; Institut de Recherche Expérimentale et Clinique IREC.

Introduction : Inulin-type fructans (ITF) can modulate the gut microbiota in favor of bacteria and metabolites prone to improve host physiology. Several vegetables are rich in inulin-type fructans.
Aim : This study aims to assess the impact of native inulin and of nutritional intervention with vegetables rich in ITF on anthropometry, metabolic and psychological symptoms in obese patients.
Methods : A randomized, simple-blinded, multicentric, placebo-controlled trial was conducted in 106 obese patients assigned to two groups : the prebiotic versus the placebo group, who received either 16 g/d of native inulin or maltodextrin, coupled to dietary advice to consume inulin-rich or -poor vegetables for 3 months. Anthropometric measurements, food intake, psychological questionnaires, serum biology, and fecal microbiome sequencing were performed before and after the intervention.
Results : Inulin supplementation improved weight loss, decreased diastolic blood pressure,level of aspartate transaminase, DPP-IV activity and insulinemia. Placebo led to minor changes in the gut microbiota, whereas inulin increased Bifidobacterium, Lactobacillus, Catenibacterium, and decreased Clostridium cluster XIVa, Butyricimonas, and Desulfovibrio. Inulin improved some psychological and cognitive symptoms especially emotional competence and flexibility. Exploratory analysis highlighted associations between gut microbiota composition, biological parameters and psychological outcomes. We observed that some factors such as metformin treatment modulated the anthropometric and metabolic response. Moreover, gut microbiota composition at baseline led to different evolution in term of metabolism and psychological symptoms (emotion and cognition).
Conclusions : The implementation of an inulin-rich diet is an efficient way to promote weight loss, metabolic and psychological health. Our data support the interest of modulating the composition of gut microbiota to improve both metabolic and psychological symptoms in obese subjects. Finally, we were able to show that some parameters (medications, gut microbiota composition) predicted the response to the inulin supplementation.

BELGIAN INFLAMMATORY BOWEL DISEASE RESEARCH AND DEVELOPMENT GROUP (BIRD)

- I01 -

INTEGRIN EXPRESSION CHANGES ON THE T CELL SUBSETS INFLUENCE THE RESPONSE TO VEDOLIZUMAB IN INFLAMMATORY BOWEL DISEASE PATIENTS. C. De Galan (1), S. Van Welden (1), S. Bos (1), S. Tavernier (2), T. Lobaton Ortega (3), G. Gonzales (1), W. Van Moerkercke (4), B. Strubbe (5), H. Peeters (5), E. Macken (6), M. De Vos (3), D. Laukens (1), P. Hindryckx (3) / [1] Ghent University, Ghent, Belgium, IBD research unit - Gastroenterology, Internal Medicine and Pediatrics, [2] University Hospital Ghent, Ghent, Belgium, Primary Immune Deficiency Research Lab, Department of Internal Medicine and Pediatrics, Centre for Primary Immunodeficiency Ghent, Jeffrey Model Diagnosis and Research Centre, [3] University Hospital Ghent, Ghent, Belgium, Department of Gastroenterology, [4] AZ Groeninge Hospital, Kortrijk, Belgium, Department of Gastroenterology, [5] AZ St Lucas, Ghent, Belgium, Department of Gastroenterology, [6] University Hospital Antwerp, Edegem, Belgium, Department of Gastroenterology.

Introduction : Vedolizumab is a gut-selective alpha4beta7 integrin inhibitor approved for the treatment of Ulcerative Colitis (UC) and Crohn's disease (CD). The exact mechanism of action remains to be unravelled and there is no consensus whether the response to vedolizumab is associated with integrin expression profiles of the innate, adaptive immunity or both. Response prediction to vedolizumab is particularly relevant since it is a rather slow-acting molecule.
Aim : We investigated whether baseline levels and/or early changes in the integrin-expressing T cell subsets during the induction phase can predict the response to vedolizumab in inflammatory bowel disease (IBD) patients.
Methods : In this prospective multi-centric study, 71 patients with CD (n=28) or UC (n=43) with moderate-to-severe disease were included at the start of vedolizumab treatment. The response to vedolizumab was determined on a clinical, biochemical and endoscopic level at the end of the induction phase (week (W)14). The clinical response was defined as a drop in the Harvey Bradshaw index (HBI) of at least 3 points for CD and a reduction in Mayo score of at least 3 points with no rectal bleeding for UC. The biochemical response was defined as a 50% reduction of CRP or when the CRP normalized (<10 mg/l) for CD and a 50% reduction or normalization (<250µg/g) of calprotectin for UC. The endoscopic response was evaluated positive when there was a drop of at least 1 point in the endoscopic Mayo score for UC. For CD, the endoscopic response was not investigated, because an endoscopy at W14 is not part of the standard of care. During the induction phase, peripheral blood mononuclear cells (PBMCs) were collected at W0, W2, W6, W10 (only CD) and W14, before vedolizumab administration. Variation between the different centers was reduced by isolating the cells 6h after blood collection. The PBMCs were analyzed by flow cytometry to evaluate the CD4+/CD8+ Alpha4Beta7+, Alpha4Beta1+ and AlphaEBeta7+ T cell populations. Based on the distribution of the data, statistics were performed by an independent sample t-test or a Mann-Whitney U test.
Results : The flow cytometry analyses revealed that only the CD4+ Alpha4Beta7+ T cell subset at baseline was significantly increased in UC patients with a favorable clinical (P= 0.042), biochemical (P=0.025) and endoscopic response (P= 0.054). This was not the case in CD. In CD, the baseline number of CD4+ Alpha4Beta1+ T cells was lower in clinical (P= 0.094) and biochemical responders (P= 0.004). No other significant baseline or delta change differences were identified between the responders and non-responders in the other investigated T cell subsets in both UC and CD.
Conclusions : This prospective cohort study showed that in UC patients, clinical, biochemical and endoscopic response to vedolizumab treatment is associated with a high number of CD4+ Alpha4Beta7+ T cells in circulation at baseline. In CD patients, the relationship is less clear and the response is rather linked to a low number of Beta1+ T cells. A second cohort is being recruited to confirm our findings. The final aim is to build a predictive model that is feasible for use in clinical practice.

- I02 -

THE INTERPLAY OF MICROBIOME DYSBIOSIS AND IMMUNE SYSTEM DEREGULATION IN PATIENTS WITH CROHN'S DISEASE. N. Seyed Tabib (1), C. Caenepeel (1), K. Machiels (2), S. Verstockt (1), B. Verstockt (3), N. Ardeshir Davani (1), J. Sabino (3), M. Ferrante (3), S. Vermeire (3) / [1] KU Leuven, Belgium, Department of chronic diseases, metabolism, ageing, [2] KU Leuven, Leuven, Belgium, Department of chronic diseases, metabolism, ageing, [3] University Hospitals Leuven, Belgium, Department of Gastroenterology.

Introduction : The perturbation of composition, function, and structure of the gut microbiota known as dysbiosis is a key factor in inflammatory bowel disease (IBD) pathogenesis. There is a crosstalk between the microbiota and the gut immunological niche.
Aim : To better understand this interaction, we characterized the degree of dysbiosis and dysregulation of the immune proteome in Crohn's disease (CD) patients to see if subtypes of patients could be identified.
Methods : We collected faecal and serum samples of 146 CD patients (60.3% female, median [IQR] age 39 [26-50], median [IQR] FC 678.0 [153.7-1800.0], median [IQR] C-reactive protein(CRP) 5.2 [1.9-14.7]) and 63 healthy controls

(HC) (50% female, median [IQR] age 36 [27-55], median [IQR] FC 30.0 [30.0-32.4], median [IQR] CRP 0.5 [0.4-1.2]). Microbiota phylogenetic profiling was conducted using 16S rRNA gene sequencing. Proteomic analysis was performed using a panel of 91 inflammatory proteins (OLINK Proseek). Microbial dysbiotic index (MDI), defined as the logarithm of the sum of [abundance in organisms increased in CD] over the [abundance of organisms decreased in CD] was calculated and patients were ranked from Q1 (the least dysbiotic state) to Q4 (the most dysbiotic state). For the proteomic score, 32 proteins that correlated (adj. $p < 0.01$) with faecal calprotectin (FC) were selected. A penalized logistic regression model was trained on these proteins, to distinguish HC from super active (defined as FC $\geq$ 1800 µg/g). We next developed an inflammatory proteomic score (IPS) defined as the weighted sum of serum level of inflammatory proteins, using the coefficient value of the regression model as the protein's weight. Using the IPS score, patients were clustered from Q1 (the least inflammatory state) to Q4 (the most inflammatory state). Statistical analyses were performed in R version 3.5.2.
Results : The MDI did not correlate with standard phenotypic subgroups based on the Montreal classification but did positively correlate CRP (spearman $r=0.27$, $p<0.001$) and FC level (spearman $r=0.3$, $p<0.001$). The regression model identified 14 proteins [including CCL20, CXCL1, IL-7, IL-17A, FGF-19] distinguishing super active CD patients from HC with accuracy, sensitivity, and specificity of 95.6%, 92.3%, 100%, respectively. IPS positively correlated with CRP (spearman $r=0.73$, $p<0.001$) and FC level (spearman $r=0.68$, $p<0.001$). Likewise, MDI and IPS-based clusters were significantly different in CRP and FC levels. Different components of the microbiome correlated with the proteome in a subset of samples. For example, fibroblast growth factor 19 (FGF-19) positively correlated with Faecalibacterium and negatively with Fusicatenibacterium. Of note, we observed a significant positive correlation between MDI and IPS (spearman $r=0.33$, $p<0.001$).
Conclusions : We were able to define clusters of patients based on molecular characterization of different players in IBD pathogenesis such as microbiota and proteome. This molecular clustering in a given patient could be considered as a novel therapeutic and personalized approach to IBD. Further validation in larger cohorts is required.

- I03 -

EXPOSURE TO AN INFLAMMATORY MIX RE-INDUCES INFLAMMATION IN ORGANOIDS OF ULCERATIVE COLITIS PATIENTS, INDEPENDENT OF THE INFLAMMATORY STATE OF THE TISSUE OF ORIGIN. K. Arnauts (1), B. Verstockt (1), J. Sabino (1), S. Vermeire (1), C. Verfaillie (2), M. Ferrante (1) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing, KU Leuven, Leuven, [2] Stem Cell Institute Leuven, Leuven, Belgium, Department of Development and Regeneration, KU Leuven, Leuven.
Introduction : Patient-derived intestinal organoids provide a powerful tool to unravel mechanisms underlying inflammatory bowel disease (IBD). Recently, we showed that organoids derived from inflamed regions in ulcerative colitis (UC) patients lose their inflammatory phenotype during ex vivo culture and were undistinguishable from organoids of non-inflamed regions in these patients [1].
Aim : To study UC in an ex vivo model, we hypothesized that inflammation should be re-induced towards levels corresponding to the in vivo situation. In addition, we aimed to elucidate if organoids derived from inflamed regions are more sensitive towards inflammatory stimulation, compared to organoids from non-inflamed regions of UC patients and non-IBD controls.
Methods : Biopsies were obtained from 8 patients with active UC (endoscopic Mayo score of $\geq$2), both in inflamed and non-inflamed regions, and in 8 non-IBD controls. Crypts were isolated and cultured as organoids for at least four weeks. Organoids were subjected to a predefined inflammatory mix (MIX : 100 ng/ml TNF-α, 20 ng/ml IL-1β, 1 µg/ml Flagellin) or medium only (CTRL) for 24 hours. RNA was extracted from organoids for RNA sequencing by Lexogen QuantSeq for Illumina. Differential gene expression and pathways were studied through DESeq2 and Ingenuity Pathway Analysis (False discovery rate <0.05).
Results : Prior to inflammatory stimulation, principal component analysis (PCA) demonstrated separate clustering between organoids derived from non-IBD controls and UC patients. Exposure to the inflammatory mix induced transcriptional activation of inflammatory genes (CXCL1, DUOXA2, IL1β, IL8, IL23α,.. all $p<0.001$) and pathways in all conditions. However, organoids of non-IBD controls clustered separate from organoids of UC patients. Within organoids of UC patients (inflamed vs non-inflamed origin), we observed no differentially expressed genes after inflammatory stimulation but organoids clustered per patient instead. Inflammatory markers in UC organoids reached transcriptional expression levels (CXCL1, CXCL2, IFNGR1, IL1β, DUOXA2,..) and activated pathways (antigen presentation, interferon signaling, granulocyte adhesion and diapedesis) similar to those observed in crypts derived from inflamed biopsies.
Conclusions : Inflammation can efficiently be (re-)induced in organoids from both UC and non-IBD origin. However, a different response was observed between organoids of non-IBD and UC origin. Of note, in UC organoids the state of inflammation in the source tissue was irrelevant. In conclusion, we showed that it is essential to re-induce inflammation in patient specific organoids, but there is no need to obtain biopsies from inflamed regions. [1] https ://doi.org/10.1093/ecco-jcc/jjy222.010

SERUM PROTEIN MARKERS FOR EARLY AND DIFFERENTIAL IBD DIAGNOSIS VALIDATED BY MACHINE LEARNING APPROACHES. S. Verstockt (1), N. Verplaetse (2), D. Raimondi (3), B. Verstockt (1), E. Glorieus (4), M. De Decker (5), L. Hannes (2), V. Ballet (6), E. Vandeput (1), Y. Moreau (3), M. Ferrante (1), D. Laukens (7), F. Mana (5), M. De Vos (8), S. Vermeire (1), I. Cleynen (2) / [1] University of Leuven, Leuven, Belgium, CHROMETA, [2] University of Leuven, Leuven, Belgium, Department of Human Genetics, [3] University of Leuven, Leuven, Belgium, ESAT, [4] University Hospital Ghent, Ghent, Belgium, Department of Gastroenterology, [5] University Hospitals Brussels, Belgium, Department of Gastroenterology, [6] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [7] University Hospital Gent, Belgium, Department of Gastroenterology, [8] University Hospital Gent, Gent, Belgium, Department of Gastroenterology.

Introduction : The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions with a polygenic and multifactorial pathogenesis. Intensified treatment early in the disease course of IBD results in better outcomes. This is however challenged by the diagnostic delay faced in IBD, and especially in CD. Therefore, markers supporting early and differential diagnosis are needed.
Aim : In this study, we aimed to discriminate IBD patients from non-IBD controls, and CD from UC patients, using serum protein profiles combined with an IBD polygenic risk score.
Methods : Patients naïve for immunosuppressives and biologicals, and without previous IBD-related surgery were prospectively included within 3 months after diagnosis, across three Belgian IBD referral centres (PANTHER study). We collected serum from 127 patients (88 CD, 39 UC) and 66 age- and gender-matched non-IBD controls. Relative serum levels of 576 unique proteins were quantified (OLINK). Proteins were ranked according to : (1) adjusted (adj.) p values obtained from differential expression analysis; (2) importance scores from machine-learning feature-selection algorithms (univariate feature selection, logistic regression with L2 penalty and Random Forest). For all individuals, a weighted IBD polygenic risk score (PRS) was calculated (PRSice 2.0) for the 242 known IBD risk loci. Receiver operating characteristics (ROC) and area under the curve (AUC) analysis were performed to measure the performance of top ranked proteins and the IBD PRS (R\ROCR).
Results : Following statistical analysis, 243 serum proteins were found to be differentially expressed (adj. $p < 0.05$) between IBD patients and controls. Three top ranked markers were also identified as top 10 ranked proteins by all feature-selection algorithms and resulted in a significant AUC of 93% (95% CI : 89-97%) to distinguish IBD from controls. While adding the IBD PRS did not further contribute (AUC 93% [95% CI : 89-97%]), the top ranked protein on its own had a strong discriminative power with an AUC of 87% (95% CI : 82-92%). When comparing UC and CD, we found 15 differentially expressed proteins. Two proteins ranked within the top 10 across all feature-selection algorithms. This two-marker panel could discriminate UC from CD with an accuracy of 88% (95% CI : 82-96%). Adding the IBD PRS did not further improve the prediction model (AUC=88% [95% CI : 81-96%]).
Conclusions : Machine learning approaches validated top differentially expressed serological proteins with diagnostic potential in IBD. We identified a three-marker panel classifying IBD patients and non-IBD controls, and a two-marker panel discriminating UC from CD.

A MUCOSAL MARKER PREDICTING TOFACITINIB INDUCED ENDOSCOPIC RESPONSE IN ULCERATIVE COLITIS. B. Verstockt (1), S. Verstockt (2), D. Alsoud (2), J. Sabino (3), M. Ferrante (4), S. Vermeire (4) / [1] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology, [2] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Chronic Diseases, Metabolism and Ageing, KU Leuven, [3] University Hospitals Leuven, Leuven, Belgium, Gastroenterology and Hepatology, [4] University Hospitals Leuven, Belgium, Gastroenterology and Hepatology.

Introduction : The pan-Janus kinase (JAK) inhibitor tofacitinib (TFC) has recently been approved for and added to the treatment armamentarium of patients with moderate-to-severe ulcerative colitis (UC). With increasing choices and absence of predictive biomarkers generated from pivotal trials, real world data are needed to stratify patients based on their molecular fingerprint in order to improve likelihood of response.
Aim : To identify molecular markers predicting response to tofacitinib therapy.
Methods : We obtained inflamed colonic biopsies from 52 consecutive patients initiating biological therapy (anti-TNF [n=16], vedolizumab [VDZ, n=20]) or TFC [n=16] for active UC (Mayo endoscopic sub-score ≥ 2). Treatment choices were made in agreement between patient and physician, but all included patients were naïve for the mode of action initiated. All patients were treated with standard dosage according to the label. Response was defined as a Mayo endoscopic sub-score ≤ 1 and assessed by week 8-14. RNA was extracted and single-end RNA sequencing performed using Illumina HiSeq4000. Sequencing data were analysed through differential gene expression (DESeq2) and an unbiased network biology approach (Weighted Gene Coexpression Network Analysis).

Results : Response was observed in 5 (31.2%) anti-TNF, 13 (65.0%) VDZ, and 5 (31.2%) TFC treated patients. Previously reported markers for anti-TNF response, including oncostatin M (p=0.62), TREM1 (p=0.70) and IL13RA2 (p=1.0) could not differentiate TFC responders from non-responders. Similarly, the 4-gene vedolizumab signature [MAATS1, PIWIL1, RGS13 and DCHS2] could not discriminate TFC responders from non-responders (p=0.13). No baseline differences in JAK/STAT-signalling could be identified either. Hence, we performed an unbiased network analysis of all TFC samples which identified 1 cluster of 65 genes, significantly correlating with response (p=0.006). The hub gene within this network turned out to be the most differentially expressed gene (p=1.5E-9, fold change [FC] 2.3), with a predictive accuracy for response of 100% (p<0.001). In contrast, this gene could not predict anti-TNF or vedolizumab induced response (p=0.13; p=0.10 respectively). Of interest, baseline expression of the identified marker did not correlate with C-reactive protein, faecal calprotectin, Mayo endoscopic sub-score and other inflammatory markers including IL-6, IL-1B or epithelial markers. In TFC responders, the identified biomarker was significantly reduced by week 8, as compared to baseline (fold change [FC] -3.1, p=0.0004), but not in non-responders (FC 1.2, p=0.2).
Conclusions : We identified a TFC-specific biomarker unrelated to disease severity, increasing the potency of a robust predictive marker based on its underlying mode-of-action. Validation in independent larger datasets is warranted.

- I06 -

SLC12A2 AS A POTENTIAL HISTOLOGICAL MARKER OF ULCERATIVE COLITIS ASSOCIATED COLORECTAL DYSPLASIA. A. Merli (1), S. Vieujean (2), C. Massot (2), N. Bletard (3), F. Quesada Calvo (2), D. Baiwir (4), G. Mazzucchelli (5), L. Servais (1), O. Wéra (6), C. Oury (1), L. De Leval (7), C. Sempoux (8), M. Roberto (9), M. Scharl (10), G. Rogler (11), E. De Pauw (5), C. Coimbra Marques (12), A. Colard (13), A. Vijverman (14), P. Delvenne (15), M. Meuwis (2), E. Louis (16) / [1] University of Liege, Liège, Belgium, GIGA Institute, [2] CHU of Liège, Belgium, Gastroentérologie, hépatologie, oncologie digestive, [3] CHU of Liège, Belgium, Anatomie et cytologie pathologiques, [4] University of Liege, Liège, Belgium, GIGA Plateforms, [5] University of Liege, Liège, Belgium, Chimie, [6] CHU of Liège, Belgium, Oncologie médicale, [7] Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, Service de pathologie clinique, [8] Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, Pathologie Clinique, [9] University Hospital of Liège Liège, Liège, Belgium, Gastroenterology and Hepatology, [10] University Hospital, Zurich, Switzerland, Gastroenterology, [11] University Hospital, Zurich, Switzerland, Gastroenterology and Hepatology, [12] CHU of Liège, Belgium, Sciences cliniques, [13] CHC, Liège, Belgium, Gastroenterology, [14] CHR La Citadelle, Belgium, Gastro-entérologie et Oncologie digestive, [15] CHU of Liège, Belgium, Sciences biomédicales et précliniques, [16] CHU of Liège, Belgium, Sciences cliniques - Hépato-gastroentérologie.

Introduction : Patients suffering from ulcerative colitis (UC) are at increased risk of developing dysplasia (DAI) and colorectal cancer (CAC). Differentiating DAI from inflammation remains difficult for both endoscopists and anatomopathologists due to macro and microscopic features shared by these lesions.
Aim : The aim of our work was to confirm, by histological evaluation, a potential proteomic biomarker discriminating early DAI lesions from chronic inflamed and normal tissues in UC.
Methods : We included 15 paired tissues from UC patients (n=5) presenting low-grade DAI. Epithelial cells were isolated by laser capture microdissection and analyzed by label-free proteomics. We selected one protein differentially distributed between DAI, inflamed (I) and normal (N) tissues for confirmation by immunochemistry (IHC). IHC characterization was performed using both the staining intensity score (0 to 4) and the staining pattern : “gradient” (staining intensity increasing from the epithelium lumen to the bottom of the crypts) or “no gradient” (homogenous staining). UC patients with DAI (n=28), dysplastic lesion in non-inflammatory colon (DSp) (n=9), CAC (n=14) and at high risk of CAC (>10 years of UC duration) but free of dysplasia or cancer (n=23) were included. We further studied this potential marker tissue distribution in the mouse model of CAC (AOM/DSS treated mice) to trace its presentation at different evolution stages and assessed low (n=51), high-grade DAI (n=35) and CAC (n=38), as well as relevant paired control tissues. This potential tissue marker was finally evaluated in sporadic precancerous colorectal lesions of UC-free patients with low (n=19) and high-grade (n=16) adenomas and cancerous lesions (CRC) : pT1 to pT4 (n=82) and compared to paired normal tissues when available.
Results : Proteomics identified 1070 proteins among which 19 showed a differential distribution between DAI and I or N. The sodium chloride co-transporter SLC12A2 was only identified in DAI. SLC12A2 IHC “no gradient” staining pattern was associated to DAI and DSp compared to I or N (with p <0.0001 and 0.0002 respectively). The IHC score was also higher for DAI, DSp and CAC compared to paired I and N (p<0.0001 and 0.0084 respectively). These results were confirmed from low-grade dysplasia to more advanced lesions in the AOM/DSS mice model. The “no gradient” pattern was also significantly associated to low and high-grade adenomas, and CRC of UC-free patients compared to normal control tissues. The sensitivity and specificity of SLC12A2 histological pattern reached 89% and 95% for DAI versus I; 90% and 93% for CAC and/or DAI versus I. In addition, the sensitivity and specificity reached 99% and 87% for all precancerous and cancerous lesions (DAI, DSp, CAC and CRC) versus N and I (including also non-progressing UC patients).
Conclusions : A specific histological pattern for SLC12A2 is associated to precancerous and cancerous colorectal lesions and is able to be discriminate these lesions from inflammation and normal tissue in UC. The continuous upregulation of

SLC12A2 in advanced colorectal lesions in the CAC mice model also suggests a role of this protein in the pathophysiology of inflammation-associated colon neoplasia.

- I07 -

THE GUT MICROBIOTA DURING BIOLOGICAL THERAPY FOR INFLAMMATORY BOWEL DISEASE. C. Caenepeel (1), S. Vieira-Silva (2), B. Verstockt (1), K. Machiels (1), N. Davani (1), J. Sabino (3), M. Ferrante (3), J. Raes (2), S. Vermeire (3) / [1] Catholic University of Leuven (KU Leuven), Belgium, Department of Chronic Diseases, Metabolism and Ageing, [2] Rega Institute for Medical Research, Leuven, Belgium, Department of Microbiology and Immunology, Laboratory of Molecular Bacteriology, [3] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology.

Introduction : The expansion of therapeutic options in IBD brought forward a need to personalize treatment maximizing both efficacy and safety. Gut inflammation in inflammatory bowel disease (IBD) patients has been associated with reduced microbial richness, reduced abundance of short-chain fatty acid producers and of gram-positive bacteria.
Aim : We aimed to explore the longitudinal impact of treatment on the inflammatory burden and fecal microbiota in patients with CD and UC, treated with anti-tumor necrosis factor (anti-TNF) therapy, vedolizumab (VDZ) or ustekinumab (UST).
Methods : We collected faecal samples from 349 IBD patients (112 UC, 237 CD) initiating biological therapy (anti-TNF, VDZ or UST), between 2010 and 2019 at a tertiary referral centre. Samples were collected at baseline, week 14 and week 24. Microbiota phylogenetic profiling was conducted by 16S rRNA gene sequencing and faecal microbial loads were determined using flow cytometry. Moisture levels, as marker for transit time, were measured using lyofilisation. Disease activity and response were assessed by faecal calprotectin (FCal). Statistical analyses were performed in R, version 3.5.1. Enterotyping was based on the Dirichlet multinomial mixtures approach [1]
Results : The faecal microbiota profiles of the cohort showed high diversity, with samples being classified into all four enterotypes (Bact1-, Bact2-, Rum- or Prev-enterotype), although Bact2 was 6-10-fold more prevalent in patients compared to controls. The variation in faecal microbiota composition was explained (multivariate dbRDA) by patient diagnosis (R2=1.2%, p= 1.00E-04), timepoint (pre- or post-treatment (R2=0.52, p=0.006), and followed significantly by age, gender and faecal moisture. The full model only explained 2.85% of the microbiota variation. During treatment, a numeric although non-significant decrease in the dysbiotic Bact2 enterotype prevalence was observed in the CD cohort, but not observed in the UC cohort. A significant decrease in FCal concentrations (UC w0 vs 14, p= 5.12E-08, CD w0 vs 14, p= 2.56E-08 and w0 vs 24, p= 4.86E-08) was observed with treatment, and accompanied by a significant increase in microbial loads (UC w0 vs 14, p= 0.023869, CD w0 vs 14, p= 0.002142 and w0 vs 24, p= 0.020071). Only treatment-associated variables - week of treatment (p=2.4E-18), diagnosis (0.00053) and timepoint (p=0.00733) – were significant predictors for response (FCal used as proxy for disease activity), while microbiota-associated variables (enterotype, microbial load and faecal moisture) were not. Pre-treatment samples were associated to higher FCal levels, together with UC diagnosis. This suggest that the response-time of the microbiota to treatment may be higher than host inflammatory response.
Conclusions : The prevalence of the inflammatory Bacteroides 2 enterotype was 5-10 fold higher in CD and UC patients as compared to controls. Although initiation of biological therapies lead to a decrease in inflammation levels as witnessed by faecal calprotectin, and increase in microbial richness, a shift in enterotypes did not occur.

- I08 -

DEVELOPMENT AND VALIDATION OF DRIED BLOOD SPOT SAMPLING AS A TOOL TO IDENTIFY THE BEST TIME POINT TO MEASURE PREDICTIVE USTEKINUMAB SERUM CONCENTRATIONS IN PATIENTS WITH CROHN'S DISEASE. N. Van Den Berghe (1), B. Verstockt (2), E. Vandeput (2), V. Ballet (2), A. Gils (1), M. Ferrante (2), S. Vermeire (2), D. Thomas (1) / [1] University of Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [2] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology.

Introduction : Therapeutic drug monitoring of ustekinumab (UST), a monoclonal antibody directed against the p40 subunit of interleukin 12/23, can serve as a tool to identify underexposed Crohn's disease (CD) patients, as UST concentrations have been linked to treatment response. Drug concentrations are most often measured when a patient is losing response. To reduce the risk of loss of response, drug concentrations could be measured upfront to predict the chance of achieving response later on and optimizing treatment if necessary. Identification of the optimal time point to measure UST levels that have a predictive value for long-term outcome requires studies with multiple sampling. Dried blood spot (DBS) sampling allows convenient and remote collection of a blood drop through a small finger prick.
Aim : The current study aimed to develop and validate the DBS method in order to identify the best time point to measure UST concentrations to predict long-term outcome in CD patients and explore the pharmacokinetic profile.
Methods : UST concentrations (0.2-80 µg/ml) were spiked in citrated whole blood and 40 µl was spotted onto protein saver cards. After punching a 6 mm disc, DBS were extracted and the UST concentration was measured with an in-

house developed MA-UST56A2D11/MA-UST56C1H12 ELISA. The extraction efficiency, accuracy, precision and the effect of anti-UST antibodies on UST detection were evaluated. Additionally, the effect of the spotted blood volume, the stability of the DBS card at room temperature (RT) and DBS extract at -20°C was examined. To evaluate the correlation between UST in DBS extracts and serum, DBS and serum were simultaneously collected from 8 UST-treated CD patients at two different time points.
Results : Spiking UST to citrated whole blood and subsequent spotting and extraction revealed an average extraction efficiency of 65 ± 9% (n = 11). The accuracy and imprecision of all concentrations tested was 92-109% and 11-18%, respectively. Addition of anti-UST antibodies to spiked UST samples caused a similar decrease in UST concentration in DBS extracts as in serum. Spotted blood volumes between 15 and 50 µl demonstrated similar recoveries. Storing the DBS card at RT for up to 2 weeks and DBS extract at -20°C for 2 months did not impair recovery. UST concentrations in DBS extracts (range : 0.55-12.1 µg/ml) from CD patients correlated strongly with those in serum (Pearson r = 0.982, p <0.0001).
Conclusions : DBS is a robust method that facilitates multiple sampling for the determination of UST concentrations in CD patients. To explore the pharmacokinetic profile of UST and identify the best time point during induction to predict long-term outcome, a prospective study in which multiple DBS are collected in active CD patients initiating UST is warranted.

- I09 -

SAFETY OF THE SEQUENTIAL USE OF BIOLOGICAL THERAPY IN INFLAMMATORY BOWEL DISEASE : RESULTS FROM A TERTIARY REFERRAL CENTRE. A. Moens (1), V. Ballet (1), J. Sabino (1), S. Vermeire (1), M. Ferrante (1) / [1] University Hospitals Leuven, Belgium, Gastroenterology and Hepatology.

Introduction : Switching between biological therapies is frequently observed in routine management of inflammatory bowel disease (IBD). Yet, it is unknown if sequential use of biologicals affects safety such as serious infections and malignancies.
Aim : We aimed to compare the occurrence of serious infections and malignancies in regard to the number and classes of biologicals to which patients were exposed.
Methods : This retrospective cohort study included all IBD patients exposed to commercially available biologicals from 1999 to 2019 in a tertiary referral centre. Follow-up started at initiation of first biological. Exclusion criteria included : patients <18 years, episodic administration of biologicals or administration for another indication than IBD and loss to follow-up <2 years after start of first biological. Via review of full electronic medical records, we studied the development of serious infections (defined as any infection leading to hospitalization or treatment change) and malignancies. Poisson and Cox regression models were used.
Results : In total 1374 patients [54% female, 75% Crohn's disease, 87% prior exposure to immunodoluators (IM), median age at last follow-up 44 (33-55) years, median time on biological 6.4 (3.6-10) years] were included. The majority of patients (n=878,64%) was exposed to only one class of biological, 28% (n=379) to two classes and 9% (n=117) to three classes. Almost half of the patients (n=575, 42%) was exposed to one biological therapy, whilst 33% (n=453), 17% (n=239) and 8% (n=107) of patients was exposed to two, three or more than three different biological therapies respectively. During a median (IQR) follow-up of 8 (4-13) years, 373 serious infections and 127 malignancies were reported in 245 (19%) and 92 (7%) patients, leading to an incidence rate of 2.2 and 0.8 per 100.000 patients per year, respectively. The number of serious infections was dependent on prior exposure to IM (p=0.001), the number of biologicals (p=0.042) and the number of biological classes to which the patients was exposed (p=0.004, overall test Poisson model p=0.0001). The risk of serious infections increased when a patient was exposed to three or more different biologicals or two or more different classes of biologicals. The number of malignancies was also affected by the number of biologicals (p=0.028) to which the patient was exposed, with a higher risk of developing a malignancy with exposure to an increasing number of biologicals. Cox regression for the time to develop a first or second malignancy was independent of exposure to IM, number of biologicals as well as number of different biological classes to which the patients was exposed. Median (IQR) time to develop a first or second malignancy after start of the first biological was 6 (3-9) and 6 (4-12) years.
Conclusions : In this large single centre cohort study spanning 20 years, the overall risk of serious infections and malignancies in patients exposed to biologicals remains low, yet the risk increased with more and sequential use of biologicals so close vigilance is needed.

- I10 -

NEOPLASTIC LESIONS OUTSIDE DISEASED AREA IN IBD PATIENTS : A NATIONAL COHORT STUDY. A. Cremer (1), P. Demetter (2), M. De Vos (3), J. Rahier (4), F. Baert (5), T. Moreels (6), E. Macken (6), E. Louis (7), S. Vermeire (8), D. Franchimont (1) / [1] Erasme Hospital, Brussels, Belgium, Department of Gastroenterology, [2] Institut Jules Bordet, Brussels, Belgium, Department of Pathology, [3] Ghent University Hospital, Ghent, Belgium, Department of Gastroenterology, [4] CHU UCL Namur, Yvoir, Belgium, Department of Gastroenterology, [5] AZ Delta, Belgium, Department of Gastroenterology, [6] Antwerp University Hospital, Edegem, Belgium, Department of Gastroenterology,

[7] CHU Sart Tilman, Liège, Belgium, Department of Gastroenterology, [8] University Hospitals Leuven, Belgium, Department of Gastroenterology.

Introduction : Patients with inflammatory bowel diseases (IBD) are at increased risk of dysplasia and colitis-associated cancer (CAC). The presentation of neoplastic lesions (low-grade dysplasia (LGD), high-grade dysplasia (HGD) or colorectal cancer (CRC)) is reported to vary depending if the lesions are located inside disease area (IDA) or outside diseased area (ODA).
Aim : The primary aim was to analyse the characteristics and prognostic of IDA compared to ODA neoplastic lesions in a large cohort of IBD patients.
Methods : We performed a multicenter retrospective pathological data collection from 7 tertiary referral regional or academic IBD centers in Belgium. Clinical, endoscopic and pathological data were retrieved through retrospective electronic chart review. From the IBD pathology databases, 1183 colorectal lesions were identified in 541 IBD patients : 415 developed dysplasia (77%) and 126 CRC (23%) during their follow-up. Biopsies and surgical specimen were centrally reviewed by an expert IBD pathologist to confirm the diagnosis of dysplasia and/or CRC.
Results : 410 patients had IDA lesions, while 131 patients had ODA lesions. There was more ulcerative colitis among patients with IDA lesions in comparison with patients with ODA lesions (60% vs 44%, $p<0.01$). More patients with IDA lesions had HGD (9%) or CAC (27%) during their follow-up compared to the group of patients with ODA lesions (3% of HGD and 11% of CRC) ($p<0.0001$). Median follow-up duration after IBD diagnosis was 19 (IQR 10-29) and 14 (IQR 5-24) years in patients with IDA and ODA lesions, respectively ($p<0.01$). Mortality was higher in patients with IDA than in those with ODA lesions (15% vs 5%, $p<0.05$). Associated primary sclerosing cholangitis was present in 10% of patients with IDA lesions, while in none with ODA lesions ($p<0.01$). When comparing IBD patients with IDA lesions and CAC (=111) to those with ODA lesions and sporadic CRC (n=15), median age at IBD diagnosis was lower (29 (IQR :22-49) vs 41(IQR :28-54) years; $p=0.0001$). IDA lesions were more frequently non-visible (8% vs 0%), non-polypoid (36% vs 15%), diagnosed during surgery (8% vs 2%), and $\geq$ 1 cm (37% vs 19%) than ODA lesions ($p<0.0001$). ODA sporadic CRC were more frequently located in the right colon compared to IDA CAC (5/16 (31%) vs 21/133 (16%), $p<0.01$).
Conclusions : Neoplastic lesions outside diseased area were more likely to be visible, polypoid, < 1cm, in the right colon and diagnosed at endoscopy than inside disease area lesions. A lower prevalence of HGD and cancer were reported with neoplastic lesions outside diseased area.

- I11 -

PROSPECTIVE STUDY OF PHARMACOKINETICS OF INFLIXIMAB DURING INDUCTION IN PATIENTS WITH CROHN'S DISEASE AND ULCERATIVE COLITIS (PACIFIC). C. Liefferinckx (1), P. Bossuyt (2), D. Thomas (3), J. Rahier (4), E. Louis (5), F. Baert (6), P. Dewint (7), L. Pouillon (2), G. Lambrecht (8), S. Vermeire (9), D. Franchimont (1) / [1] Hopital Erasme, ULB, Belgium, Department of Gastroenterology, [2] Imelda General Hospital, Belgium, Department of Gastroenterology, [3] KU Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [4] CHU-UCL-Namur site Godinne, Yvoir, Belgium, Department of Gastroenterology, [5] Centre Hospitalier Universitaire Sart-Tilman, Liège, Belgium, Department of Gastroenterology, [6] AZ Delta, Belgium, Department of Gastroenterology, [7] AZ Maria Middelares, Belgium, Department of Gastroenterology, [8] AZ Damian, Belgium, Department of Gastroenterology, [9] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology.

Introduction : Loss of response (LOR) to infliximab (IFX) remains a challenge in routine management of IBD patients. Previous studies have pinpointed the interest of early therapeutic drug monitoring (TDM) of infliximab at week 6 to predict LOR.
Aim : We evaluated IFX high resolution pharmacokinetics (PK) during induction with intermediate and peak PK levels.
Methods : This is a prospective, multicentre (n=9), interventional study approved by EC (P2017/484) and registered at EMA (Eudra CT 2015-004618-10). Fourteen blood samples were collected per patient from baseline to week 30. All patients were IFX naïve with active disease according to clinical, biological and endoscopy criteria. The primary outcome evaluated the inter-individual variability of IFX PK during induction and correlation with remission at week 30. In addition to trough levels, intermediate and peak levels were also measured and defined as drug level between two infusions and drug level early on after infusion (+2h), respectively. Remission was defined as having a Harvey Bradshaw Index (HBI) $\leq$4 and C-Reactive Protein (CRP) $\leq$5 for Crohn's disease (CD), and as a clinical Mayo score $\leq$2 and faecal calprotectin <250 µg/g for ulcerative colitis (UC). IFX samples were measured by ELISA (Apdia) while a drug-tolerant affinity capture elution anti-infliximab assay was used to measure anti-infliximab antibodies (ATI) at week 6, 22 and 30
Results : The study population included 55% (n=34) of CD patients and 45% (n=28) of UC patients. Fifty-three percent of CD patients had complicated phenotypes with 23.5% B2 (n=8) and 29.4% B3 (n=10) while 78.6% of UC patients (n=22) had an extensive disease (E3). A concomitant immunosuppressor was used in 59.6% of patients. At baseline, median HBI was 8 (IQR 6-10) for CD patients with median CRP of 14 (IQR 5.9-24) and median SES-CD of 11.8 (IQR 7.25-20) while median clinical mayo score was 7 (IQR 6-9) for UC patients with median faecal calprotectin of 1698 (IQR 226 - 1800) and subscore endoscopic Mayo of 3 (IQR 2-3). Among the 62 patients enrolled, 33.9% of patients

(n=21/62) were in remission at week 30. Eight patients dropped out due to disease worsening. Median trough levels at week 6 were higher among patients in clinical remission at week 30 (remission : 21.7 µg/ml, IQR (9.5-36) vs no remission 11.3 µg/ml, IQR (5.7-15.3), p=0.02) confirming previous observations. However, intermediate levels at day 3 (remission 82.4 µg/ml, IQR (58.4-99.5) vs no remission 58.8 µg/ml, IQR (46.9-76.9), p=0.02) as well as peak levels after third infusion (remission 141.1 µg/ml, IQR (117-171) vs no remission 122.8 µg/ml, IQR (98-136.5) p=0.04) were also significantly higher in patients in clinical remission at week 30. Of the 9 patients with detectable ATI (9/62, 14.5%), the great majority was treated with monotherapy (7 mono vs 2 combo, p=0.04). ATI were detected as soon as week 6. At week 2, infliximab levels were significantly lower among patients in which ATI developed at a later time point (p= 0.006) and this observation was confirmed when measuring intermediate levels at day 17 (p=0.002), trough levels at week 6 (p=0.002) and intermediate levels at week 10 (p=0.001).
Conclusions : This multicentre prospective study demonstrates that intermediate levels as early as day 3 predict remission at week 30 in IBD patients. Low IFX levels during induction were correlated to future ATI development. PK modelling may allow to better select patients early on for sustained remission with infliximab.

- I12 -

IMPACT OF GENETIC BURDEN ON FAMILIAL AGGREGATION OF INFLAMMATORY BOWEL DISEASE.
H. Lee (1), L. Hannes (1), M. Vancamelbeke (2), V. Ballet (3), M. Ferrante (4), S. Vermeire (4), I. Cleynen (1) / [1] KU Leuven, Leuven, Belgium, Laboratory for Complex Genetics, Department of Human Genetics, [2] KU Leuven, euven, Belgium, Department Chronic Diseases, Metabolism & Ageing (CHROMETA), Translational Research Center for Gastrointestinal Disorders (TARGID), [3] UZ Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [4] KU Leuven, Leuven, Belgium, Department Chronic Diseases, Metabolism & Ageing (CHROMETA), Translational Research Center for Gastrointestinal Disorders (TARGID).

Introduction : Family history of inflammatory bowel disease (IBD) is the strongest risk factor for IBD. There currently, however, is limited understanding of the contribution of genetic risk scores to familial aggregation of IBD.
Aim : We aimed to evaluate the association between the IBD polygenic risk score (PRS) and familial IBD and determine its contribution to familial IBD.
Methods : We included 54 multiple-affected families (≥ 3 first-degree relatives affected) of European ancestry, including 189 affected IBD patients (156 Crohn's disease; 33 ulcerative colitis), and 133 unaffected relatives. For all individuals, Immunochip genotypes were available. Weighted PRSs with estimates derived from literature were calculated using PRSice-2.0, including clumping and different p-value thresholds (pT) to select which variants to include in the score. Explained variance (Nagelkerke pseudo-R^2) was calculated across different pTs. To account for possible intra-familial correlations, the association between PRS and familial IBD was evaluated in age- and sex-adjusted generalized mixed regression models including family as random effects. Sporadic cases (n=1768) and non-IBD controls (n=868) with Immunochip genotypes were used for comparison.
Results : Using pT=0.05 for PRS calculation, we found that affected relatives had a higher PRS than unaffected relatives (P=1.00x10-02), sporadic cases (P=4.58x10-02), and non-IBD controls (P<2.20x10-16). The risk of disease in families increased by 1.23-fold (95% confidence interval (CI) 1.21–1.24) for every incremental standard deviation in PRS. Individuals in the highest quartile had a 3.45-times higher risk of IBD (95% CI 1.77–6.72) than those in the lowest quartile. However, the proportion of the explained variance between affected and unaffected family members was smaller than that of sporadic IBD and non-IBD controls; and the best pT was different for familial or sporadic IBD. In familial IBD, the best-fit PRS was at pT=6.90x10-03 and explained 5.3% (P=3.07x10-04) of variance, whereas in sporadic IBD, the best-fit PRS was at pT=0.08 and explained 16.7% (P=8.48x10-63). For sporadic IBD, a typical increase in the proportion of variance explained was seen with more liberal p-value thresholds and levelling off at ~pT=0.1. What was striking however, was that in familial IBD this additive genetic variance was only observed until pT=0.01, after which explained variance dropped dramatically.
Conclusions : Higher IBD polygenic risk increases the risk for familial IBD as it does for sporadic IBD. In sporadic IBD, the increased risk is defined by variants of all p-value levels (until ~pT=0.1). In familial IBD, the difference between those affected or not is in the higher-effect variants (p-value<0.01).

- I13 -

VEDOLIZUMAB CONCENTRATIONS IN COLONIC MUCOSAL TISSUE OF ULCERATIVE COLITIS PATIENTS INVERSELY CORRELATE WITH THE SEVERITY OF INFLAMMATION.
N. Van Den Berghe (1), B. Verstockt (2), A. Gils (1), M. Ferrante (2), S. Vermeire (2), D. Thomas (1) / [1] University of Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [2] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology.

Introduction : Multiple studies have reported the association between vedolizumab serum concentrations and endoscopic outcome in patients with ulcerative colitis (UC). However, little is known about drug consumption in tissue and the relationship with mucosal inflammation.
Aim : This study aimed to investigate vedolizumab concentrations in tissue of UC patients and the correlation with their inflammatory state and serum levels.
Methods : A paired serum sample and colonic mucosal biopsy was collected in 36 UC patients at week 14 of vedolizumab treatment. In non-responders, defined as a Mayo endoscopic subscore of ≥2, inflamed colonic biopsies were taken in the sigmoid around 20-30 cm from the anal verge. In responders, defined as a Mayo endoscopic subscore ≤ 1, a biopsy was taken in a macroscopically uninflamed area at the same location. Biopsies were lysed by addition of 10 µl lysis buffer (50 mM Tris, 0.1% Triton X-100 and 100 mM NaCl) per mg tissue and vortexed every 5 min during 1 hour. Total protein content was measured and normalized to 3 mg/ml before analysis of the vedolizumab concentration using an in-house developed ELISA. Results are expressed as µg vedolizumab/mg total protein content
Results : A positive correlation was observed between vedolizumab concentrations in tissue and serum (Spearman r = 0.8447, p <0.0001), both in inflamed (r = 0.8609, p <0.0001, n = 16) and uninflamed tissue (r = 0.7925, p <0.0001, n = 20). The median tissue vedolizumab concentration in patients with Mayo endoscopic subscore 0, 1, 2 and 3 were 0.120, 0.074, 0.062 and 0.064 µg/mg, respectively (p <0.01 for trend), indicating that tissue drug levels inversely correlate with the severity of inflammation. Vedolizumab tissue concentrations were significantly lower in non-responders compared to responders (0.064 vs 0.112 µg/mg, p <0.05). Moreover, patients achieving Mayo endoscopic subscore 0 had significantly higher vedolizumab levels in colonic tissue compared to patients not achieving this outcome (0.120 vs 0.065 µg/mg, p <0.02). Interestingly, a trend was observed towards higher serum-to-tissue ratios of vedolizumab in non-responders compared to responders (p = 0.0523). This finding suggests that if two patients have the same serum vedolizumab concentration, the patient with mucosal inflammation is more likely to have lower tissue levels than the patient with no or limited inflammation.
Conclusions : Vedolizumab concentrations in colonic mucosal tissue of UC patients inversely correlate with the severity of inflammation. As the serum-to-tissue ratio of vedolizumab is numerically higher in non-responders compared to responders, the relative distribution of vedolizumab in serum and tissue might be more important than the drug concentration alone.

- I14 -

SAFETY AND EFFICACY OF COMBINING BIOLOGICAL THERAPIES TOGETHER OR WITH SMALL MOLECULES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE : A RETROSPECTIVE MULTICENTER NATIONAL OBSERVATIONAL CASE SERIES STUDY. L. Goessens (1), J. Colombel (2), A. Outtier (3), M. Ferrante (3), M. Truyens (4), T. Lobaton (4), F. Baert (5), P. Bossuyt (6), A. Cremer (7), E. Macken (8), B. Strubbe (9), J. Rahier (1) / [1] CHU UCL Namur, Site de Godinne, Yvoir, Belgium, Gastroenterology, [2] Mount Sinai School of Medicine, New York, United States (the), Gastroenterology, [3] University Hospitals Leuven, Belgium, Gastroenterology and Hepatology, [4] Universitair ziekenhuis Gent, Belgium, Gastroenterology, [5] AZ Delta, Roeselare, Belgium, Gastroenterology, [6] Imelda Hospital, Bonheiden, Belgium, Gastroenterology, [7] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenterology, [8] University Hospital Antwerp, Edegem, Belgium, Gastroenterology, [9] AZ Sint-Lucas, Ghent, Belgium, Gastroenterology.

Introduction : Few data is available regarding the combination of biological therapies (anti-TNF, anti-integrin, anti-interleukins (IL4, 12/23, 17A, 23)) or with a small molecule in patients with IBD.
Aim : We here report the safety and efficacy of combining these drugs through a national retrospective multicenter case series.
Methods : Cases were extracted from local databases within the last 3 years. Combined therapy was defined as the concomitant use for a minimum of 1 day of 2 biologics or 1 biologic with a small molecule. Patients' demographics, disease' characteristics and types of combined therapies were recorded. Safety was defined as the occurrence of any serious adverse event (SAE) : serious infection, opportunistic infection, any hospitalization, cancer and death, whereas the efficacy of combination was clinically appreciated by physicians.
Results : From 8 centers, 23 combined therapies were observed in 19 IBD patients (74% Crohn's disease, 21% ulcerative colitis and 5% IBD type unclassified). Median age at combination was 43.0 years ([IQR] : 31.5-59.0). Seventeen patients presented with a minimum of 1 concomitant IMID (ankylosing spondylitis (n=11), psoriasis or psoriatic arthritis (n=5) and other conditions (n=5)). Reasons for starting a combination were active IBD (57%), another active IMID (30%) or both (13%). Anti-TNF and anti-integrin were combined in 11 cases, anti-TNF and anti-ILs in 5, anti-integrin and anti-ILs in 4 and other combinations in 3 (anti-TNF+rituximab+methotrexate; anti-IL4+anti-IL12/23; anti-IL12/23+methotrexate+leflunomide). Median duration of combined therapies was 5 months ([IQR] : 2-9). During 15.8 patients/years of combined therapy, 11 adverse events (AE) including 9 SAE were recorded in 8 patients. Eight infections were reported with various combinations : anti-TNF and anti-IL in 4 cases, anti-TNF and anti-integrin in 3 and anti-TNF+rituximab+methotrexate in 1. Two infections (both anti-TNF+ anti-integrin) were graded severe leading to hospitalization, 6 were graded mild or moderate. Cancer and death were not observed. After combined therapy, IBD

disease activity was clinically improved in 44% and remained stable in 50% of patients, whereas clinical improvement of IMID was observed in 25% of patients. Overall, combination of treatments was withdrawn due to ineffectiveness or serious adverse events in 39% and 4 % respectively.
Conclusions : In our experience, combination of biologics in patients with IBD +/- another IMID was associated with short term increased efficacy in almost half of patients but also with a risk of infections in one third. No new safety signals were observed in this difficult to treat patients but extensive data are urgently needed.

- I15 -

TOFACITINIB INDUCES CLINICAL AND ENDOSCOPIC REMISSION IN BIOLOGIC REFRACTORY ULCERATIVE COLITIS PATIENTS : A REAL-WORLD BELGIAN COHORT STUDY. A. Cremer (1), T. Lobaton (2), S. Vieujean (3), P. Bossuyt (4), J. Rahier (5), F. Baert (6), O. Dewit (7), E. Macken (8), M. Somers (8), A. Vijverman (9), P. Van Hootegem (10), F. Mana (11), B. Willandt (12), P. Caenepeel (13), E. Humblet (13), F. D'heygere (14), A. Verreth (15), A. El Nawar (16), J. Coenegrachts (17), S. Dewit (18), S. De Coninck (19), N. Schoofs (20), S. Delen (21), J. Dutre (22), C. Thienpont (23), S. Vanden Branden (24), D. Staessen (25), D. Franchimont (1) / [1] Erasme Hospital, Brussels, Belgium, Department of Gastroenterology, [2] Ghent University Hospital, Ghent, Belgium, Department of Gastroenterology, [3] CHU Sart Tilman, Liège, Belgium, Department of Gastroenterology, [4] Imelda Hospital, Bonheiden, Belgium, Department of Gastroenterology, [5] CHU UCL Namur, Yvoir, Belgium, Department of Gastroenterology, [6] AZ Delta, Roeselare, Belgium, Department of Gastroenterology, [7] Cliniques universitaires Saint-Luc, Brussels, Belgium, Department of Gastroenterology, [8] Antwerp University Hospital, Edegem, Belgium, Department of Gastroenterology, [9] CHR Citadelle, Liège, Belgium, Department of Gastroenterology, [10] Algemeen Ziekenhuis Sint-Lucas, Belgium, Department of Gastroenterology, [11] Clinique Saint-Jean, Brussels, Belgium, Department of Gastroenterology, [12] AZ Sint-Jan Brugge-Oostende, Brugge, Belgium, Department of Gastroenterology, [13] Ziekenhuis Oost Limbug (ZOL), Genk, Belgium, Department of Gastroenterology, [14] AZ Groeninge, Kortrijk, Belgium, Department of Gastroenterology, [15] AZ Sint-Jozef, Belgium, Department of Gastroenterology, [16] CENTRE HOSPITALIER MOUSCRON, Mouscron, Belgium, Department of Gastroenterology, [17] Jessa Ziekenhuis, Hasselt, Belgium, Department of Gastroenterology, [18] Mariaziekenhuis Noord-Limburg, Overpelt, Belgium, Department of Gastroenterology, [19] Sint Andries ziekenhuis Tielt, Tielt, Belgium, Department of Gastroenterology, [20] Sint-Trudo ziekenhuis, Sint-Truiden, Sint-Truiden, Belgium, Department of Gastroenterology, [21] ZH Maas en Kempen, Belgium, Department of Gastroenterology, [22] ZNA Jan Palfijn, Merksem, Belgium, Department of Gastroenterology, [23] ZNA Antwerpen, Antwerpen, Belgium, Department of Gastroenterology, [24] Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium, Department of Gastroenterology, [25] GZA Sint-Vincentius ziekenhuis, Antwerpen, Belgium, Department of Gastroenterology.

Introduction : Tofacitinib, an oral small molecule Janus kinase inhibitor, has been approved in 2018 for the treatment of moderate to severe ulcerative colitis (UC) in Europe. We report on real-world short-term efficacy and safety data from a multicenter Belgium refractory cohort of UC patients with prior exposure to both anti-TNF and vedolizumab.
Aim : The aim of the study was to evaluate clinical and endoscopic response and remission rates at weeks 8 and 16.
Methods : This is an observational, national, retrospective multicenter study including all UC active patients started on tofacitinib (10 mg BID) from 25 centers in Belgium between November 2018 to August 2019. Prospectively collected data were retrospectively analyzed according intention-to-treat. Clinical response was defined as a decrease from baseline in Modified Clinical Mayo score (rectal bleeding, stool frequency) by ≥2 points, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. Clinical remission was defined as a Modified Clinical Mayo score ≤1. Endoscopic response was defined as a decrease from baseline in Endoscopic Mayo score by ≥1. Endoscopic remission was defined as an Endoscopic Mayo score ≤1. Complete endoscopic remission was defined as an Endoscopic Mayo score of 0. Descriptive statistics and Wilcoxon signed rank test were calculated using Medcal 19.1.
Results : Median disease duration at baseline of the 70 included patients was 13 years (IQR 8-16). Nearly all patients were refractory to at least one anti-TNF and vedolizumab. 3 patients did not receive anti-TNF, and 2 did not receive vedolizumab. Modified Clinical Mayo score at baseline was 5 (IQR 3-5), and Endoscopic Mayo score was 3 (IQR 2-3). Fifty-four percent (38/70) of patients required prolonged induction at 10mg BID. Median follow-up was 16 weeks (IQR 13-26). Clinical evaluation was available in all patients at week 8 and 49 patients at week 16, while endoscopic data were available in 52 patients and 42 at weeks 8 and 16, respectively. Clinical response and remission were 63% and 41% at week 8 and 76% and 53% at week 16. Endoscopic response and remission were 44% and 23% at week 8 and 69% and 50% at week 16. Complete endoscopic remission was 13% at week 8 and 19% at week 16. Fifty percent (21/42) of the patients under steroids at baseline could have stopped steroids at week 16. Median baseline Modified Mayo score (rectal bleeding, stool frequency and endoscopy) decreased from 7 (IQR 5- 8) to 4 (IQR 2-7) after 8 weeks (n=49) ($p<0.0001$), and down to 2 (IQR 1-5) at week 16 (n=40) ($p<0.0001$). Median CRP significantly decreased from baseline (5.3 mg/l, IQR [1.9–16.8]) to 1 mg/l at week 8 (IQR 0.5-6.2) (n=49) ($p=0.003$). Tofacitinib was well tolerated with only 1 reported case of single dermatome herpes zoster and no case of venous thromboembolism.

Conclusions : Tofacitinib very effectively induced short-term clinical and endoscopic response and remission even in a refractory cohort of patients with UC in a real-world clinical setting. During this short-term follow-up, tofacitinib was well tolerated with respect to adverse events.

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INTESTINAL FIBROSIS IN CROHN'S DISEASE PATIENTS IS MARKED BY AN UPREGULATION OF INNATE IMMUNE CELLS AND MUCOSAL B CELLS. B. Creyns (1), G. Dragoni (2), J. Cremer (2), G. Bislenghi (3), B. Verstockt (2), M. Ferrante (2), S. Vermeire (2), G. Van Assche (2), A. D'hoore (4), G. De Hertogh (5), C. Breynaert (6) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Departement of Clinical and Experimental Medicine, [2] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing, [3] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology, Leuven, Belgium, [4] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology, Leuven, Belgium., [5] KU Leuven, Belgium, Department of Imaging and Pathology, Translational Cell & Tissue Research, Leuven, Belgium. [6] University Hospitals Leuven, Belgium, Department of General Internal Medicine, Leuven, Belgium.

Introduction : Intestinal fibrosis represents a significant complication of Inflammatory Bowel Disease (IBD). An urgent need is present for the identification of pathways and markers involved in fibrogenesis to prevent and intervene with intestinal fibrosis. As intestinal fibrosis mainly occurs in the intestinal deeper layers, mucosal biopsies for studies in intestinal fibrosis are of limited information.
Aim : We aimed to characterize of the relative contribution of innate and adaptive immune cells in the mucosa and deeper layers in fibrotic distal ileum of Crohn's disease (CD) patients was performed.
Methods : Seventeen CD patients undergoing right hemicolectomy (RHC) for stricturing disease and 6 colorectal cancer (CRC) patients undergoing RHC were recruited. The resected ileum was divided in macroscopically inflamed and fibrotic tissue and single cell suspensions were made from mucosal and deeper intestinal layers for immune cell characterisation with flow cytometry. For comparison, proximal unaffected CD tissue and control ileum from CRC patients was included. Fibrosis and inflammation were confirmed on HE stained histological sections. Wilcoxon matched-pairs signed rank test between CD samples and Dunn's multiple comparisons test compared to CRC ileum were performed.
Results : From 12 CD patients, an additional macroscopically inflamed region could be identified next to the fibrotic area, with a decreased fibrosis score as compared to the fibrotic area (4.00 vs 6.00, $p=0.016$). Both fibrotic and inflamed regions had increased inflammation as compared to proximal unaffected CD and control non-IBD ileum (score : 4.00 and 4.50 vs 1.00 and 0.00, $p<0.001$ for all). In the inflamed ileum, no differences in immune populations were observed between mucosa and deeper layers, reflecting the transmural nature of CD. In contrast, CD19+ B cells were specifically enriched in the mucosa of fibrotic ileum, as compared to proximal CD mucosa (32.20 vs 20.40% of CD45+ cells, $p=0.008$). In the deeper layers of fibrostenotic CD ileum FcεR+ Siglec 8+ eosinophils (1.13 vs 1.17 % of CD45+ cells, $p=0.027$), mature CD11c+ dendritic cells (3.95 vs 2.96 % of CD45+ cells, $p=0.042$) and M2 CD206+ macrophages (0.35 vs 0.18% of CD45+ cells, $p<0.001$) were enriched as compared to the mucosa overlying the fibrotic tissue.
Conclusions : These results argue that inflammation in the deeper intestinal layers is different from the inflammatory signature seen in mucosal inflamed regions. We here report alternative innate immune cells expanded specifically in the deeper intestinal layers of fibrostenotic CD ileum that could identify targets for new anti-fibrotic therapies.

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FIBROGENESIS IN CHRONIC DSS COLITIS IS DRIVEN BY AN INNATE LYMPHOID CELL-INDEPENDENT INNATE IMMUNE RESPONSE. B. Creyns (1), J. Cremer (2), L. Boon (3), G. De Hertogh (4), M. Ferrante (5), S. Vermeire (5), G. Van Assche (5), J. Ceuppens (6), C. Breynaert (6) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Departement of Clinical and Experimental Medicine, [2] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing, [3] Bioceros, Utrecht, Netherlands (the), Bioceros, Utrecht, [4] University Hospitals Leuven, Leuven, Belgium, Department of Imaging and Pathology, Translational Cell & Tissue Research, Leuven, Belgium, [5] University Hospitals Leuven, Belgium, Department of Gastroenterology and Hepatology, Leuven, Belgium, [6] Allergy and Clinical Immunology Research Group, Leuven, Belgium, Leuven, Belgium, KU Leuven, Department of Microbiology, Immunology and Transplantation.

Introduction : Obtaining insights in the pathogenesis of intestinal fibrosis is a priority for improving outcomes in Inflammatory Bowel Diseases (IBD). Studies in murine models and human organ fibrosis indicate a role for innate immunity pathways in fibrosis.
Aim : The aim of this study was to dissect the role of innate lymphoid cells (ILC) in chronic intestinal inflammation and fibrosis.

Methods : A chronic 3-cycles dextran sulphate sodium (DSS) model was induced in wild type (WT), recombinant activating gene (RAG)-deficient (lacking adaptive immunity), RAG-/- common gamma chain (ɣc)-/- (lacking ILC) and anti-CD90.2 treated (ILC depleted) C57Bl/6 RAG-/- mice. One cycle of DSS comprised 1 week of DSS administration followed by 2 weeks of recovery with normal drinking water. Colonic lamina propria cells were isolated and CD45+Lineage-CD127+CD90.2+ ILC, Ly6C+ monocytes and Ly6G+ neutrophils were identified after staining by flow cytometry. Inflammation and fibrosis were scored by macroscopic and HE and Martius Scarlet Blue staining and fibrosis was evaluated by hydroxyproline quantification. For analysis Kruskal-Wallis testing with multiple Dunn's comparison was performed.
Results : In RAG-1-/- mice chronic inflammation and fibrosis developed similarly as in WT mice, with elevated KLRG-1+ ILC2 (68.90 vs 48.00 % of ILC, p=0.012) after repeated DSS exposure as compared to control mice. Chronic colitis could also be induced in RAG-/-ɣc-/- or ILC depleted RAG-/- mice (ILC : 0.99 vs 25.70% of CD45+ cells, p=0.029), with no attenuation of fibrosis (p>0.99) as compared to chronic DSS exposed RAG-1-/- mice despite the absence of ILC. Colon length decrease was more pronounced in RAG-/-yc-/- as compared to RAG-1-/- mice after chronic DSS colitis (7.15 vs 8.30 cm, p=0.046), while hydroxyproline levels and thickness of mucosa and muscularis propria were not different in RAG-/-yc-/- as compared to RAG-1-/- mice after chronic DSS. Moreover, after the second cycle of DSS a slower recovery of weight was seen in RAG-/-yc-/- mice as compared to RAG-1-/- mice (d31 : 88.64 vs 111.0% of initial weight, p<0.001; d35 p=0.001; d39 p=0.006 and d42 p=0.002). In absence of ILC, RAG-/-yc-/- mice increased lamina propria neutrophils (19.10 vs 5.91% of CD45+ cells, p=0.004) and monocytes (11.80 vs 3.25% of CD45+ cells, p=0.004) may represent an alternative source of inflammation.
Conclusions : These data argue against a pro-fibrotic role of ILC in the induction of fibrosis in chronic DSS colitis and suggest a protective and recovery-enhancing role of ILC after repeated intestinal injury.

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PROTEINS CITRULLINATION AND CROHN'S DISEASE : PAD4 BUT NOT PAD2 IS A STRONG MARKER OF ILEAL INFLAMMATION. G. Dragoni (1), B. Creyns (2), G. De Hertogh (3), B. Verstockt (1), W. Wollants (1), B. Ke (1), L. Marcellis (3), G. Matteoli (1), A. D'hoore (4), A. Galli (5), M. Ferrante (1), S. Vermeire (1) / [1] KU Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing, Translational Research Center for Gastrointestinal Disorders (TARGID), [2] KU Leuven, Belgium, Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, [3] KU Leuven, Belgium, Department of Imaging and Pathology, Translational Cell & Tissue Research, [4] University Hospital Gasthuisberg, Leuven, Belgium, Department of Abdominal Surgical Oncology, [5] University of Florence, Firenze, Italy, Clinical Gastroenterology Unit, Department of Biomedical Clinical and Experimental Sciences "Mario Serio".

Introduction : Citrullination is a post-translational modification of proteins, mediated by enzymes called PAD (peptidylarginine deiminases). The immune system can attack citrullinated proteins, leading to autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and ulcerative colitis, and the activity of PAD2 and PAD4 in innate immune cells has been demonstrated for these disorders. Recently, high levels of PAD2 have been described in activated fibroblasts in the context of liver fibrosis.
Aim : The aim of the study was to investigate the role of PAD2 and PAD4, both in inflammatory and fibrotic contexts of ileal Crohn's disease (CD).
Methods : We obtained ileal transmural samples from patients operated for stricturing ileal CD. Three different macroscopic areas within each resection specimen (i.e. proximal normal ileum, inflamed ileum & fibrotic ileum) were selected and histologically confirmed by an expert pathologist. Patients undergoing ileocolic resection for other conditions (e.g. right colon cancer) and with healthy terminal ileum were used as controls. For each region (normal CD, inflamed CD, fibrotic CD and control), immunohistochemistry (IHC), RNA and protein evaluations for PAD2 and PAD4 were performed. Multiplex immunofluorescence (IF) for PAD2, PAD4, myeloperoxidase, neutrophil elastase, CD68, vimentin and alpha-smooth muscle actin were carried out to investigate the enzymes-expressing cells. Additional IF was performed to study citrullinated histone 3 (H3cit) expression, the product of PAD4 activity in neutrophils and component of neutrophil extracellular traps (NETs). Statistical analysis was carried out with Kruskal-Wallis Test and post hoc Mann-Whitney Test.
Results : Resection specimens from 13 CD and 11 controls were included. IHC and IF showed an increased expression of both PAD2 and PAD4 in the neutrophils of inflamed areas, in cytoplasm and nucleus, respectively. Activated fibroblasts (vimentin+ and alpha-smooth muscle actin+) were negative for both enzymes. PAD4 mRNA expression was increased in inflamed tissue (p=0.001, p=0.008 and p=0.028 versus normal CD, fibrotic CD and controls, respectively), and confirmed using Western Blot. H3cit was increased in the ileal inflammatory infiltrates too, confirming high PAD4 expression. For PAD2, no significant changes were observed at RNA and protein level, mainly due to its reduced expression in epithelial cells from normal to diseased tissue.
Conclusions : Both PAD2 and PAD4 are strongly expressed in neutrophils of CD ileal resection specimens, but only PAD4 shows a significantly higher expression in the inflammatory context which translates in the formation of NETs. No direct relation was observed between PAD enzymes and intestinal fibroblasts.

VEDOLIZUMAB DOSE OPTIMIZATION : FINDINGS FROM A BELGIAN REGISTRY. E. Louis (1), V. Muls (2), P. Bossuyt (3), A. Colard (4), A. Nakad (5), D. Baert (6), F. Mana (7), P. Caenepeel (8), S. Vanden Branden (9), S. Vermeire (10), F. D'heygere (11), B. Strubbe (12), A. Cremer (13), J. Coche (14), V. Setakhr (15), F. Baert (16), A. Vijverman (17), J. Coenegrachts (18), F. Flamme (19), A. Hantson (20), K. Wijnen (20), E. Piters (20), P. Dolin (21) / [1] CHU Liege, Liège, Belgium, Gastroenterology, [2] Saint-Pierre University Hospital, Brussels, Belgium, Gastroenterology, [3] Imeldaziekenhuis, Bonheiden, Belgium, Gastroenterology, [4] Hopital CHC Liège, Belgium, Gastroenterology, [5] CHwapi Notre Dame, Tournai, Belgium, Gastroenterology, [6] Maria Middelares Medical Centre, Ghent, Belgium, Gastroenterology, [7] UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium, Gastroenterology, [8] Ziekenhuis Oost Limbug (ZOL), Genk, Belgium, Gastroenterology, [9] Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium, Gastroenterology, [10] UZ Leuven, Leuven, Belgium, Gastroenterology, [11] AZ Groeninge, Kortrijk, Belgium, Gastroenterology, [12] AZ Sint-Lucas, Ghent, Belgium, Gastroenterology, [13] Hopital Universitaire Erasme, Brussels, Belgium, Gastroenterology, [14] Clinique Saint-Pierre, Ottignies, Belgium, Gastroenterology, [15] CHU UCL Namur site Sainte Elisabeth, Brussels, Belgium, Gastroenterology, [16] AZ Delta, Roeselare, Belgium, Gastroenterology, [17] Hospital CHR de la Citadelle, Liège, Belgium, Gastroenterology, [18] Jessa Ziekenhuis, Hasselt, Belgium, Gastroenterology, [19] CHU Ambroise Paré, Mons, Belgium, Gastroenterology, [20] Takeda Belgium, Brussels, Belgium, Medical Affairs, [21] Takeda Pharmaceuticals, Epidemiology, London, United Kingdom, United States (the), Epidemiology.

Introduction : Vedolizumab (VDZ) dose optimization (DO), by interval shortening from 8-weekly (Q8W) to 4-weekly (Q4W) dosing, is used for patients with secondary loss of response. This report presents outcome data on patients receiving DO in real world clinical practice in Belgium.
Aim : The aim of this study was to assess the dose-optimization outcome data of vedolizumab therapy in Belgium.
Methods : The Belgian VDZ Registry (ENcePP EUPAS6469) enrolled 202 VDZ-treated Ulcerative Colitis (UC) or Crohn's Disease (CD) adult patients (26% with no prior use of anti TNF therapy) from 19 centres. Median length of VDZ therapy prior to enrolment was 11 months. Patients were followed-up every 6 months with assessment of IBD features, use of biologics, and disease activity. Clinical remission was defined as Harvey-Bradshaw Index (HBI) <5 or partial Mayo Score (pMS) <2, and clinical response as a 2+ point improvement in pMS or a 3+ improvement in HBI.
Results : During a median follow up of 19 months from enrolment, 57 (28%) patients (41 CD and 16 UC) received VDZ Q4W due to secondary loss of response. Q4W was mostly used in patients with CD or with prior anti-TNF therapy failure. The median starting point for Q4W dosing was 16 months after start of VDZ (interquartile range (IQR) 8-27 months) and median duration of Q4W dosing was 4 months (IQR 2-8 months). After changing to Q4W dosing 44% achieved clinical remission, 3% clinical response, and 53% showed no improvement. CD - UC - Total N=41 - N=16 - N=57 Clinical Remission 12/27 (44.4.%) - 4/9 (44.4%) - 16/36 (44.4%) Clinical Response 0 (0%) - 1/9 (11.2%) - 1/36 (2.8%) No Improvement 15/27 (55.6%) - 4/9 (44.4%) - 19/36 (52.8%) Missing disease activity scores 14 - 7 - 21 Among the 17 patients with clinical remission/response on Q4W dosing, 53% de-escalated back to Q8W, and continued with Q8W for a median duration of 12 months, 23.5% remained on Q4W with clinical remission, and 23.5% eventually stopped VDZ due to loss of response. A limitation of this study is that it did not systematically collect data on DO prior to recruitment, hence the proportion of patients receiving DO may be higher than reported here.
Conclusions : These real-world data show DO plays an important role in management of UC and CD. In this study, 28% of patients received DO following secondary loss of response to Q8W therapy. Forty-seven percent of patients receiving Q4W subsequently returned to clinical remission or had a clinical response, and half of these patients successfully returned to Q8W VDZ therapy. Controlled studies are warranted, ideally blinded, using more objective endpoint to reveal true success rate of dose-optimization.

SINGLE CENTER EXPERIENCE OF USTEKINUMAB : THERAPEUTIC DRUG MONITORING IN CROHN'S DISEASE PATIENTS. C. Liefferinckx (1), M. Fassin (2), D. Thomas (3), C. Minsart (2), A. Cremer (1), L. Amininejad (4), V. Tafciu (2), V. Wambacq (4), A. Van Gossum (4), D. Franchimont (1) / [1] Hopital Erasme, ULB, Belgium, Department of Gastroenterology, [2] ULB, Brussels, Belgium, Laboratory of experimental gastroenterology, [3] KU Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [4] Hôpital Erasme, ULB, Belgium, Department of Gastroenterology.

Introduction : Therapeutic drug monitoring (TDM) is a diagnostic tool in the monitoring of anti-TNF therapies. Yet, the benefit for TDM of new biologics such as ustekinumab (USK) is still controversial in real world experiences.
Aim : This monocentric retrospective study aims to correlate USK trough levels (TLs) with clinical and endoscopic data.
Methods : All patients have given written consent to the Biobank (B2011/005). Endoscopic disease was defined as quiescent in absence of endoscopic lesions, mild disease in presence of few superficial ulcerations, moderate in presence of several ulcers and severe in presence of numerous deep ulcers and/or inflammatory stenosis. 313 serum USK samples from 67 Crohn's disease patients were used to measure USK TL (USK ELISA, apDia) while 88 samples (at week 16,

and before and after optimization) were used to measure anti-drug antibody (ADA), using a drug-tolerant affinity capture elution anti-ustekinumab assay.
Results : Among the 67 CD patients included, 61.2% (n=41) were females. Sixty-five percent of patients had complicated phenotypes with 43.3% of B2 and 22.4% of B3. Also, 50% of patients had a history of previous CD surgery. Eighty percent and 22.4% of patients were previously exposed to anti-TNFα and vedolizumab, respectively. At USK baseline, the endoscopy was evaluated as quiescent, mild, moderate and severe in 3% (n=2), 4.5% (n=3), 38.8% (n=26) and 14.9% (n=10) of cases, respectively. The endoscopic evaluation at baseline was not available for 26 patients. The median follow-up was 73 weeks (IQR 39-92). An optimization due to loss of response was required in 44.8% of patients (n=30) after a median time of 38 weeks (IQR 24-55). To evaluate the drug efficacy, an endoscopy was performed in 61% of cases at a median time of 35 weeks (IQR 27-47). TLs were 5.2 µg/ml (IQR 2.1-8.8), 1.7 µg/ml (IQR 0.3-4.3) and 2.6 µg/ml (IQR 0.6-4.1) at week 8, 16 and 24, respectively. TLs at week 8 were correlated to the induction IV dose administrated (ρ spearman=0.3, p=0.03). At week 16, low TLs were associated with higher endoscopic activity in the follow-up (p=0.02) with TLs distributed as following : 2.47 µg/ml for quiescent endoscopic activity (IQR 0.9-4.6, n=10), 3.3 µg/ml for mild endoscopic activity (IQR 0.9-5.3, n=12), 2.1 µg/ml for moderate endoscopic activity (IQR 1-5.7, n=10), 0.11 µg/ml for severe endoscopic activity (IQR 0-0.4 n=6). This correlation TLs-endoscopic activity was not found at week 8 (p=0.5) with TLs distributed as following : 5.2µg/ml for quiescent endoscopic activity (IQR 3.3-7.7, n=10), 5 µg/ml for mild endoscopic activity (IQR 1.6-8.9, n=10), 4.1 µg/ml for moderate endoscopic activity (IQR 3-8, n=10), 0.3 µg/ml for severe endoscopic activity (IQR 0.2-3.2 n=6). Patients not requiring an optimization had higher TLs in maintenance than patients requiring optimization (2.45 µg/ml (IQR 1.3-4.4) vs 1.15 µg/ml (IQR 0.1-2.24), p=0.008). Obviously, optimization significantly increased TL (1.15 µg/ml (IQR 0.1-2.24) vs 6.6 µg/ml (IQR 2.3-11.3), p<0.001). ADA were undetectable in all the measured samples in maintenance
Conclusions : This real-world experience confirms a drug exposure-endoscopic response relationship. Week 16 seems to be an appropriate timepoint to monitor drug exposure. Earlier USK TLs, at week 8, appear less valuable to be monitored due to the influence of initial IV dose. The absence of immunogenicity suggests that it is not a key driver in the loss of response.

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PREVALENCE OF FATIGUE IN A SEVERE IBD COHORT HIGHLY EXPOSED TO BIOLOGICS. C. Liefferinckx (1), M. El Hamdi (2), M. Fassin (3), A. Cremer (2), C. Minsart (2), L. Amininejad (2), V. Wambacq (2), A. Van Gossum (2), D. Franchimont (2) / [1] Hôpital Erasme, ULB, Belgium, Gastro-enterology, [2] Hopital Erasme, ULB, Belgium, Department of Gastroenterology, [3] ULB, Brussels, Belgium, Laboratory of experimental gastroenterology.

Introduction : In addition to physical and psychological factors, systemic inflammation, anemia and/or malnutrition contribute to fatigue in Crohn's disease (CD) and ulcerative colitis (UC). Despite recent advances in the management of the disease, fatigue is a major disabling symptom for IBD patients.
Aim : The aim of this prospective study is to evaluate the prevalence of IBD patients suffering from fatigue in a tertiary IBD referral center and delineate its contributing factors
Methods : The aim of this prospective study is to evaluate the prevalence of IBD patients suffering from fatigue in a tertiary IBD referral center and delineate its contributing factors. All patients with a confirmed IBD diagnosis were eligible. A given written consent has been obtained for each patient (P2019/053). Fatigue evaluation was assessed by FACIT-F. Self-report questionnaires were used to assess different factors related to fatigue : disease activity was assessed by patient-reported outcomes (PRO), anxiety by State and Trait Spielberger scores, depression by Beck score (BDI-II), sleep quality by Insomnia severity index (ISI) and Epworth scale, and quality of life by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ). Biological values including haemoglobin, C-reactive protein (CRP), thyroid stimulating hormone (TSH), folic acid and B12 vitamin were collected when available. Baseline data are here presented.
Results : Among the 128 patients included, 72.7% (n=93) and 27.3% (n= 35) of patients had Crohn's disease (CD) and ulcerative colitis (UC), respectively. This cohort was characterized by a high prevalence of CD complicated behaviors and UC pancolitis. Eighty-four percent of patients (n=108) were exposed to biologics at the time of completion of the questionnaire distributed as following : 62.5% (n=80) exposed to infliximab, 7% (n=9) exposed to adalimumab, 10.9% (n=14) exposed to vedolizumab, 3.9% (n=5) exposed to ustekinumab, 15.6% (n=20) not exposed to any biologics. Finally, 46 percent of patients (n= 59) reported an inactive working status. The prevalence of fatigue was 65.6% stratified as severe (FACIT-F <20) and moderate (FACIT-F 20-40) in 21.1% and 44.5%, respectively. Fatigue was clearly associated with active disease in CD (p<0.001) but not with active disease in UC (p=0.15). Higher Trait Spielberger scores reflecting anxiety were found related to fatigue in both females (p=0.009) and males (p=0.01). Higher Beck score reflecting depression was associated with fatigue (p<0.0001). Higher Insomnia severity index (ISI) and Epworth scale reflecting quality of sleep were found related to fatigue (p<0.0001). Finally, SIBDQ reflecting quality of life was significantly higher in IBD patients who did not suffer of fatigue (p<0.0001). All biological values were within normal ranges and did not influence fatigue. Older age at diagnosis was associated with lower FACIT-F score (p=0.001) while disease duration was not (p=0.32). No correlation was found between fatigue and any specific biologics (p= 0.08).

Conclusions : This prospective study reported a fatigue prevalence of 65.6% in a severe IBD cohort highly exposed to biologics. Beyond disease activity in CD, psychological factors (whether they are causes or consequences) such as anxiety, depression, poor quality of life and insomnia were associated to fatigue.

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REAL-WORLD EXPERIENCE OF PERI-OPERATIVE TREATMENTS ON SURGICAL COMPLICATIONS AFTER ILEO-CAECAL RESECTION IN CROHN'S DISEASE. S. Di Stefano (1), C. Liefferinckx (2), A. Cremer (2), L. Amininejad (2), A. Van Gossum (2), J. Deviere (2), J. Van De Stadt (3), D. Franchimont (2), A. Buggenhout (3) / [1] University of Verona. G.B. Rossi University Hospital, Italy, Gastroenterology and Digestive Endoscopy Unit. The Pancreas Institute, [2] Hopital Erasme, ULB, Belgium, Department of Gastroenterology, [3] Hopital Erasme, ULB, Belgium, Clinic of Colorectal Surgery – Department of Digestive Surgery.

Introduction : The current recommendations remain vague as to whether biologics are safe or deleterious when surgery is contemplated in patients with Crohn's disease (CD). Conflicting data do not enable to adopt a definitive position on the time to surgery.
Aim : The aims of this study were to evaluate the impact of perioperative treatments on the rate of surgical complications and to report surgical recurrence rate of CD after ileo-caecal (IC) resection.
Methods : This was a retrospective monocentric cohort study of consecutive CD patients who underwent IC resection between 1996 and 2018. An ethic committee approval has been obtained (P2019/376). The overall rate of surgical complications was evaluated within 30 days after surgery. The effect of pre- and post -operative treatments were assessed on overall morbidity, general and infectious complications, anastomotic leakage and risk factors. The preoperative period extended to the 12 weeks before the time of surgery. Statistical analyses were performed using SPSS.
Results : The study population included data of the 165 CD patients who underwent a primary IC resection. Ninety percent of the population had complicated behaviour at time of surgery with 52.7% B2 (n=87) and 37.6% B3 (n=62). One quarter of the overall population had an associated peri-anal disease (n=44). The prevalence of smoking in our population was 24% (n=40). In preoperative period, 52% of patients (n= 86) were treated with an immunosuppressor and 29.7% were treated with an anti-TNFa. To note that 4 patients received ustekinumab (n=2) and vedolizumab (n=2). Finally, a use of steroids was found in 77% of cases (n=127) during this preoperative period. The median age at time of the first IC resection was 35 years (IQR 24-44) while the median follow-up was 6.1 years (IQR 1-11). The overall rate of complications was 18% including 8.7% and 3.3% patients with infectious complications and anastomotic leakage, respectively. No risk factors have been found to be associated with surgical complications. In particular, immunosuppressants and biologics did not increase the risk of surgical complications. Twenty-four percent of patients (n=39/160) needed a second IC resection due to stenosis at the anastomosis site in 69.2% of cases (n=27/39). Surgical recurrence was found to increase linearly over time with a second surgery after a median follow-up of 8 years (IQR 2-12). In univariable regression, anti-TNFa, immunosuppressor as well as antibiotic had a significantly protective role on surgical recurrence with odd ration (OR) of 0.18, 0.2 and 0.34, respectively. In multivariable regression, anti-TNFa used as post-operative treatment remained protective on surgical recurrence in multivariable regression with OR of 0.15, p=0.001.
Conclusions : Prevalence of complications after an IC resection in CD patients was of 18% in this retrospective monocentric cohort. No risk factors were found to be associated with surgical complications. Anti-TNFa seem to have a protective role on surgical recurrence.

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PERSISTENCE OF VEDOLIZUMAB MAINTENANCE THERAPY : FINDINGS FROM A BELGIAN REGISTRY. E. Louis (1), V. Muls (2), P. Bossuyt (3), A. Colard (4), A. Nakad (5), D. Baert (6), F. Mana (7), P. Caenepeel (8), S. Vanden Branden (9), S. Vermeire (10), F. D'heygere (11), B. Strubbe (12), A. Cremer (13), J. Coche (14), V. Setakhr (15), F. Baert (16), A. Vijverman (17), J. Coenegrachts (18), F. Flamme (19), A. Hantson (20), K. Wijnen (20), E. Piters (20), G. Hantsbarger (21), P. Dolin (22) / [1] CHU de Liège, Liège, Belgium, Gatroenterology, [2] Saint-Pierre University Hospital, Brussels, Belgium, Gastroenterology, [3] Imeldaziekenhuis, Bonheiden, Belgium, Gastroenterology, [4] Hopital CHC Liège, Belgium, Gastroenterology, [5] CHwapi Notre Dame, Tournai, Belgium, Gastroenterology, [6] Maria Middelares Ziekenhuis, Gent, Belgium, Gastroenterology, [7] UZ Brussel, Jette, Belgium, Gastroenterology, [8] Ziekenhuis Oost Limbug (ZOL), Genk, Belgium, Gastroenterology, [9] Onze-Lieve-Vrouw Ziekenhuis, Aalst, Belgium, Gastroenterology, [10] UZ Leuven, Leuven, Belgium, Gastroenterology, [11] AZ Groeninge, Kortrijk, Belgium, Gastroenterology, [12] AZ St Lucas, Ghent, Belgium, Gastroenterology, [13] Hopital Universitaire Erasme, Brussels, Belgium, Gastroenterology, [14] Clinique Saint-Pierre, Ottignies, Belgium, Gastroenterology, [15] CHU UCL Namur site Sainte Elisabeth, Brussels, Belgium, Gastroenterology, [16] AZ Delta, Roeselare, Belgium, Gastroenterology, [17] Hospital CHR de la Citadelle, Liège, Belgium, Gastroenterology, [18] Jessa Ziekenhuis, Hasselt, Belgium, Gastroenterology, [19] CHU Ambroise Paré, Mons, Belgium, Gastroenterology, [20] Takeda Belgium, Brussels, Belgium, Medical Affairs, [21] Takeda Pharmaceuticals Company, Statistics, Boston, United States (the), Statistics, [22] Takeda Pharmaceuticals, Epidemiology, London, United Kingdom, United States (the), Epidemiology.

Introduction : Clinical trials and observational studies have demonstrated clinical efficacy of vedolizumab (VDZ) as maintenance therapy for Crohn's Disease (CD) and Ulcerative Colitis (UC). This report presents long term data on persistence of VDZ maintenance therapy in real world clinical practice in Belgium.
Aim : The aim of this study was to assess the real-world persistence of vedolizumab maintenance therapy in Belgium.
Methods : The Belgian VDZ Registry (ENCePP EUPAS6469) enrolled 202 VDZ-treated Ulcerative Colitis (UC) or Crohn's Disease (CD) adult patients (26% with no prior use of anti TNF therapy) from 19 centers across Belgium. Median length of VDZ therapy prior to enrolment was 11 months. Patients were followed-up every 6 months after enrolment with assessment of IBD features, use of biologics, and disease activity. Clinical remission was defined as Harvey-Bradshaw Index (HBI) <5 or partial Mayo Score (pMS) <2. Missing value imputation (last observation carried forward) was used to partially account for missing disease activity scores. If a 6-monthly disease activity score was missing, the disease activity score from the previous 6-monthly assessment was used.
Results : The mean duration of VDZ therapy, including use prior to enrolment, was 31 months, with 68% of CD patients and 75% of UC patients using VDZ therapy for 48 months. Clinical remission rate after 42 months of VDZ therapy was higher in UC (84%) than CD (67%), and higher for patients without prior anti-TNF therapy (87%) than those with prior anti-TNF therapy (70%). CD : Duration of VDZ therapy (Months) - Persisting with VDZ % - Clinical Remission1 % 6 - 98% (124/126) - 64% (21/33) 12 - 92% (116/126) - 71% (39/55) 18 - 83% (105/126) - 67% (55/82) 24 - 79% (99/126) - 57% (46/81) 30 - 73% (92/126) - 54% (37/69) 36 - 72% (91/126) - 67% (36/54) 42 - 69% (87/126) - 67% (24/36) 48 - 68% (86/126) UC : Duration of VDZ therapy (Months) - Persisting with VDZ % - Clinical Remission1 % 6 - 99% (67/68) - 58% (7/12) 12 - 96% (65/68) - 68% (19/28) 18 - 91% (62/68) - 76% (31/41) 24 - 88% (60/68) - 80% (35/44) 30 - 79% (54/68) - 82% (31/38) 36 - 76% (52/68) - 86% (24/28) 42 - 75% (51/68) - 84% (16/19) 48 - 75% (51/68) 1Clinical remission denominators at each time point do not include patients enrolled after the time point, whose follow-up had yet to reach the time point, or with HBI/pMS score missing. Fifty-seven (29.4%) patients discontinued VDZ during follow-up, due to loss of response (n=40), adverse event (n=7), clinical remission (n=4), pregnancy planning (n=3), and patient choice (n=3).
Conclusions : These real world long-term Belgian data demonstrate a high persistence of VDZ maintenance therapy among both CD and UC patients, with highest clinical remission rates seen in patients with UC and those with no prior anti-TNF therapy.

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USTEKINUMAB IN CROHN'S DISEASE : « REAL-LIFE » DATA FROM A MONOCENTRIC PATIENT'S COHORT. L. Monin (1), S. Dubois (1), S. Vieujean (2), C. Reenaers (1), C. Van Kemseke (1), P. Latour (1), D. Van Daele (1), E. Louis (2) / [1] CHU Liege, Liège, Belgium, Gastroentérologie, [2] CHU de Liège, Liège, Belgium, Gastroentérologie.

Introduction : The pivotal clinical trials have largely demonstrated the efficacy and safety of ustekinumab in both bio-naïve and bio-failure Crohn's disease. As trial patients substantially differ from real life patients and as most real-life cohort published so far only include very few bio-naïve patients it is important to gather real life data in both bio-naïve and bio-failure patients.
Aim : Assess efficacy and safety of ustekinumab in bio-naïve and bio-failure patients treated with utekinumab in routine practice and look for predictors of response.
Methods : We performed a retrospective monocentric study. All patients who started a treatment with ustekinumab in our department between 2016 and July 2019 were included. A primary non-response was defined by the absence of maintenance therapy beyond week 16. A secondary non-response was defined by the cessation of therapy for another reason than side effects or stopping in sustained remission. Treatment persistence was assessed by Kaplan Meier curves and predictors of initial response and treatment persistence were studied by univariate and multivariate Cox model.
Results : 143 CD patients were analyzed, including 25 bio-naïve. Thirty-seven patients were still in their induction phase at the time of analysis and 6 patients were lost to follow-up. Therefore, analyses on efficacy were performed on 100 patients, including 20 bio-naïve. There were 23/100 primary non responders. This primary non-response was lower in younger patients (OR 0.96, CI95% 0.93-0.99, p=0.017). Probability of being still treated with ustekinumab was 71.3% and 53.4% at one and two years respectively. Treatment cessation was higher at older age at diagnosis (HR 1.04, CI95% 1.01-1.06,p=0.003), lower with longer disease duration (HR 0.95, CI95% 0.92-0.99,p=0.014) and lower with steroid weaning (HR 0.22, CI95% 0.05-1.03,p=0.05). There was no influence of being bio-failure or not of the CRP and fecal calprotectin level on primary response or treatment persistence. 16.5% of the patients needed a hospitalization related to their Crohn's disease and 16.7% had infection requiring antibiotics.
Conclusions : Around 80% of CD patients initially respond to ustekinumab and around 70% continue this treatment over one year. Bio-failure patients seem to respond as well as bio-naïve patients. There was no new safety signal.

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CHRONIC FATIGUE IN ASSOCIATED WITH INCREASED DISEASE-SPECIFIC AVOIDANCE IN INFLAMMATORY BOWEL DISEASE PATIENTS. L. Fierens (1), I. Van De Pavert (2), M. Walentynowicz (2), S.

Coenen (3), P. Geens (3), E. Weyts (3), L. Van Oudenhove (1), J. Vlaeyen (2), A. Von Leupoldt (2), G. Van Assche (3), S. Vermeire (3), M. Ferrante (3), I. Van Diest (2) / [1] KU Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Chronic Diseases, Metabolism, and Ageing, [2] KU Leuven, Belgium, Health Psychology Research Group, [3] UZ Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology.

Introduction : A substantial group of patients with inflammatory bowel disease (IBD) experience fatigue, even while in clinical remission (1). At present, disease-specific behaviours that maintain or worsen symptom burden including fatigue have not been explored.
Aim : We developed a questionnaire evaluating IBD-specific avoidance behaviour and investigated how this relates to self-reported fatigue.
Methods : This study was a close collaboration between the psychology and gastroenterology department of our tertiary referral center. A 72-item IBD-specific avoidance behaviour questionnaire (IBD-B) was generated based on literature review and input from clinicians and a patient focus group (N=10). Between July 2018 and March 2019, 500 consecutive IBD patients were included at our infusion unit (wave 1) (participation rate 79%, 48% male, 66% Crohn's disease (CD), median age 40). Patients completed the 72-item IBD-B, a demographic questionnaire, patient-reported outcome assessing disease activity (PRO2) and a Visual Analogue Scale (VAS) for fatigue. Test-retest reliability was assessed in 89 patients (54% male, 70% CD, median age of 40) who completed the IBD-B, PRO2 and VAS fatigue scale a second time after 4-12 weeks (wave 2). Clinical remission was defined as an abdominal pain score ≤1 and a liquid to very soft stool frequency ≤1.5 in CD patients and as no rectal bleeding and a stool frequency ≤1 in patients with ulcerative colitis. A principal component analysis (PCA) was then used to reduce the number of items and investigate the underlying factor structure of the IBD-B. The predictive value of IBD-specific behaviours for fatigue was finally investigated both cross-sectionally and prospectively.
Results : At wave 1, 46% and 69% of CD and UC patients, respectively, were in clinical remission. For use in clinical practice, PCA suggested a reduction of the 72-item to a final 25-item IBD-B and a seven-factor solution which could be interpreted as behaviours related to : (1) avoidance of certain food and activities, (2) ensuring toilet access, (3) reduced sexual activity, (4) cognitive avoidance, (5) not sharing with others, (6) alternative treatments and (7) active disease management (loading factors >0.5 and respectively α = 0.84, 0.89, 0.91, 0.81, 0.85, 0.85 and 0.63). The final 25 item IBD-B showed good psychometric properties. The median (IQR) total IBD-B and fatigue scores were, respectively, 29 (40-20) and 52 (77-25) for patients in clinical remission compared to 38 (48-28) and 74 (87-50) for patients not in clinical remission (both $p<0.01$). Significant Pearson correlations were found between fatigue and IBD-B factors 1, 2, 3, 5, 6 and 7 in patients without clinical remission (N=225 and respectively r = 0.484, 0.241, 0.279, 0.287, 0.159 and 0.134) compared to IBD-B factors 1, 2, 3 and 5 in patients in clinical remission (N=253 and respectively r = 0.370, 0.242, 0.136 and 0.144). Prospective analysis indicated significant correlations between IBD-B factors 1, 2 and 3 (wave 1) and fatigue (wave 2), controlled for CRP (wave1) (N=87 and respectively r = 0.438, 0.334 and 0.226).
Conclusions : The IBD-B is a valuable tool to accurately measure IBD-specific avoidance behaviour in IBD patients. IBD patients without clinical remission report higher IBD-B values and show a higher correlation between avoidance behaviour and fatigue. Further research should now focus on identifying predictors for fatigue in IBD patients in clinical remission. (1) Jelsness-Jørgensen L-P, Bernklev T, Henriksen M, et al. Chronic fatigue is associated with increased disease-related worries and concerns in inflammatory bowel disease. World J Gastroenterol 2012;18(5) :445–52.

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INCREASED ENDOPLASMIC RETICULUM STRESS SPECIFIC CHAPERONES CHARACTERISE CD FIBROSIS EPITHELIUM TISSUES AND PARTICIPATE TO IN VITRO INDUCTION OF INTESTINAL FIBROBASTS DIFFERENTIATION.

S. Vieujean (1), S. Hu (1), E. Bequet (1), C. Salee (1), C. Massot (1), N. Bletard (2), N. Pierre (1), F. Quesada Calvo (1), D. Baiwir (3), G. Mazzucchelli (4), E. De Pauw (4), P. Delvenne (2), M. Meuwis (1), E. Louis (1) / [1] CHU of Liège and Laboratory of translational gastroenterology, GIGA-R, ULiège, Belgium, Hepato-gastroenterology and digestive oncology, [2] CHU of Liège, Belgium, Anatomy and Pathology, [3] ULiège, Belgium, Proteomics facility of GIGA, [4] ULiège, Belgium, Laboratory of mass spectrometry, CART.

Introduction : Intestinal fibrosis is a complication of Crohn's disease (CD) characterized by myofibroblasts and extracellular matrix accumulation within the submucosa and smooth muscles, leading to bowel strictures. No medical treatment exists to treat or reverse intestinal fibrosis leading often to surgical resection. The potential role of intestinal epithelium in the fibrotic process remains poorly defined.
Aim : The aim of our work was to assess the involvement of intestinal epithelium in fibrosis initiation and worsening in CD.
Methods : We performed a pilot study on ileal fibrostricturing CD surgical samples (n=5), comparing the proteome of surface epithelium isolated by laser capture microdissection in normal and fibrotic zones. Confirmation of the specific protein increases was obtained by immunohistochemistry in colonic and ileal samples of CD (n=44) compared to healthy subjects (n=40), as well as in intestinal epithelial cell line under induced Endoplasmic Reticulum (ER) stress. A model

of fibroblast to myofibroblast differentiation induction was also challenged using preconditioned media of intestinal epithelial cells after a pulsed ER stress.
Results : Label free proteomics revealed high ER stress in the epithelium surrounding fibrotic bowel wall, involving Anterior gradient protein 2 homolog (AGR2) and 78kDA glucose regulated protein (BiP). Confirmation of both proteins increase was obtained by immunohistochemistry. ER stress induction in intestinal epithelial cells was associated with an intracellular increase of AGR2, BiP and ER stress markers as sXPB1 and CHOP. AGR2 was also detected in the culture medium of these epithelial cells and myofibroblast differentiation was obtained using this culture medium.
Conclusions : The increase of ER stress proteins observed in fibrostenosing tissues together with these preliminary evidences of fibroblast to myofibrobast differentiation obtained by paracrine action of intestinal epithelial cell preconditioned to ER stress induction, suggest a role of epithelial ER stress in Crohn's disease intestinal fibrosis

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AN EASY AND RAPID TARGETED NEXT GENERATION SEQUENCING-BASED GENOTYPING ASSAY FOR THE VALIDATED IBD RISK LOCI. S. Verstockt (1), L. Hannes (2), S. Deman (2), W. Wollants (1), E. Souche (2), B. Verstockt (1), I. Van Der Werf (3), A. Hoischen (4), M. Ferrante (1), S. Vermeire (1), I. Cleynen (2) / [1] University of Leuven, Leuven, Belgium, CHROMETA, [2] University of Leuven, Leuven, Belgium, Department of Human Genetics, [3] University of Antwerp, Belgium, Department of Biomedical sciences, [4] Radboud University Medical Center, Netherlands (the), Department of Human Genetics.

Introduction : Inflammatory bowel diseases (IBD) are complex genetic diseases for which 242 susceptibility loci have been identified thus far. For translational or functional follow-up studies it can be of interest to know the genotype of specific variants. For other studies a composite genetic risk score – the polygenic risk score – is of value. There currently is a gap in technology to genotype a few hundred variants in a flexible and cost-effective way.
Aim : We therefore developed a genotyping assay for the 242 validated IBD susceptibility loci.
Methods : Using MIPgen v.1.1, we designed molecular inversion probes (MIPs) covering 269 independent variants from the 242 IBD loci. MIP libraries were prepared according to Neveling et al. (Clin Chem. 2017), followed by paired-end sequencing using a MiSeq® System (Illumina). In the pilot studies, 16 IBD patients were genotyped, and results were compared with available immunochip (ichip) data. Genotypes for the covered variants were obtained using an in-house developed pipeline, and performance metrics were assessed (incl. genotyping call rate, percentage off-target reads and concordance with ichip-based genotypes). After optimization, we genotyped 279 individuals (168 IBD patients and 111 non-IBD controls). We also calculated a weighted IBD polygenic risk score (PRSice 2.0) for these.
Results : Despite a genotyping call rate of 94.3%, the first pilot run suffered from a high rate of off-target reads (52.5%). After redesigning poorly performing MIPs, off-target reads dropped to 9.4%, and the genotyping call rate increased to 97.5%. Concordance with genotypes previously obtained from ichip was 99.3%. When applying the optimized design on a larger scale (ie. on the 279 individuals), we obtained similar performance metrics, with 8.0% off-target reads and a genotyping call rate of 97.3%. Moreover, upscaling resulted in a turnaround time of 2.5 working days/96 samples and a cost of €14/sample. The calculated IBD polygenic risk scores showed higher scores in patients as compared to controls (5.5E-03 versus 4.0E-03, p=8.80E-10; R^2 IBD polygenic risk score=0.15, p=1.28E-07), however with a large overlap between both groups. Quartile analysis showed that individuals within the highest quartile had an 8.1-fold (95% CI : 3.7-17.5) increase in risk towards IBD compared to individuals in the first quartile.
Conclusions : We developed a cost-effective genotyping assay for currently known IBD risk loci, with an integrated bioinformatics pipeline from raw sequencing data to individual genotypes and calculation of a polygenic risk score. Furthermore, this assay enables genotyping of individuals on a large scale while remaining flexible to implement newly identified genetic variants.

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VOLATOMICS IN INFLAMMATORY BOWEL DISEASE AND IRRITABLE BOWEL SYNDROME : A SYSTEMATIC REVIEW. K. Van Malderen (1), J. De Man (1), B. De Winter (1), H. De Schepper (2), K. Lamote (1) / [1] Antwerp University, Belgium, LEMP, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology.

Introduction : There is a need for non-invasive, specific biomarkers to aid in the diagnosis, treatment and follow-up of patients with inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). A new development in this area is the research on volatile organic compounds (VOCs), which are induced by the human metabolism, inflammation and gut microbiota. VOCs are secreted in breath, faeces and urine and, serve as potential non-invasive biomarkers.
Aim : Systematic review regarding volatomics in IBS and IBD.
Methods : PubMed and Scopus were screened for literature on VOCs in IBS and IBD. Quality of the articles was assessed with the AXIS tool. Data about study population, study design, volatomic characteristics and results was catalogued.
Results : Of the 24 articles selected (1 randomised controlled trial, 2 cohort studies and 21 cross-sectional studies), 11 reported significant changes in individual VOCs between patient groups and healthy volunteers. On quality assessment,

most studies scored 13 or 14 (respectively 21 and 46%) on 20, indicating an average study quality. Sixteen articles described a total of seventeen VOC models, discriminating between IBS, IBD and healthy volunteers with acceptable accuracies in breath (70%-100%) and faecal (58%-85%) samples. Promising compounds in breath and faeces are propan-1-ol for diagnosis and monitoring of IBD patients, and 1-methyl-4-propan-2-ylcyclohexa-1,4-diene (γ-terpinene) as biomarker for IBS. Furthermore, three interventional studies underlined the potential of VOCs in predicting treatment outcome and follow-up of patients in IBS and IBD. However, a major limitation in current VOC research is the lack of standardisation in both study population and research methods. Interesting VOCs frequently originated from short-chain fatty acids, closely related to inflammatory pathways. All studies stressed the influence of the microbiota on VOC composition, but only one study specifically looked into this interaction.
Conclusions : Our review shows great promise for future use of VOCs as non-invasive breath and faecal biomarkers in personalised medicine. Hence, well designed studies that correlate VOCs to IBD/IBS pathogenesis, while taking microbial influences into account, are still key before clinical implementation can be expected. Currently identified VOCs of interest are propan-1-ol in IBD and 1-methyl-4-propan-2-ylcyclohexa-1,4-diene in IBS.

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PROGNOSTIC AND THERAPEUTIC LONG-TERM OUTCOME OF PATIENTS WITH ULCERATIVE PROCTITIS : ANALYSIS FROM A LARGE REFERRAL CENTER COHORT STUDY. E. Dubois (1), A. Moens (1), J. Sabino (1), M. Ferrante (1), S. Vermeire (1) / [1] UZ Leuven, Leuven, Belgium, Gastroenterology & Hepatology.

Introduction : Data about long term prognostic and therapeutic outcome of patients with ulcerative proctitis (UP) are scarce. Real world data are very important as these patients are usually excluded from participation in randomized controlled clinical trials.
Aim : The aim of our study was to assess the prognostic and therapeutic outcome of patients with UP followed at a single referral center over time.
Methods : All patients diagnosed with ulcerative colitis limited to the rectum (further defined as UP) and followed at our referral center between 1998 and 2018, were identified via an automated search of electronic medical records and were reviewed for long-term therapeutic outcome. Treatment success was defined as clinical remission (complete disappearance of UP-related symptoms as judged by the treating physician) and endoscopic inactive disease (mayo endoscopic sub-score of 0 or 1 on sigmoidoscopy) if available at last follow-up.
Results : From a total of 1561 patients with ulcerative colitis (UC), 168 patients with UP were identified (54% female, mean age at diagnosis 36 years). While the majority (118 patients or 70%) had proctitis since diagnosis, another 50/168 (30%) were diagnosed with left-sided colitis or extensive colitis but had a predominant disease course of proctitis afterwards. Nearly all patients received treatment with 5-ASA but 71 patients (42%) were refractory to rectal ± oral therapy with 5-ASA and corticosteroids necessitating azathioprine in 41 patients (24%) and/or biological therapies in 59 patients (35%). Azathioprine was started as monotherapy in 34 patients. Anti-TNF was the first line biological in 45 and vedolizumab in 14 patients. After a median follow-up of 76.5 months (IQR 34.3-143.8) clinical remission was observed in 143 patients (85%) and in 52/71 patients with 5-ASA refractory proctitis (73%). In this last group clinical remission rates were significantly higher for patients treated with biologicals (44/59 or 75%) as compared to patients treated with azathioprine (8/34 or 24%; $p < 0.0001$).
Conclusions : 10% of patients with ulcerative colitis from our referral center cohort had disease confined to the rectum. With a median follow-up of more than 6 years, good clinical outcomes were recorded with 85% of patients achieving clinical remission. Nevertheless, more than one third needed escalation to biologicals to control the proctitis. Long term outcome in patients on biologicals was superior to azathioprine. Our data do not suggest inferior outcomes for patients with proctitis compared with left-sided or extensive colitis.

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EFFECTIVENESS OF USTEKINUMAB IN REFRACTORY CROHN'S DISEASE : A REAL-LIFE EXPERIENCE IN A TERTIARY REFERRAL CENTER. M. Truyens (1), J. Geldof (1), G. Dewitte (1), E. Glorieus (1), A. Peeters (1), P. Hindryckx (1), T. Lobaton Ortega (1) / [1] UZ Gent, Gent, Belgium, Gastroenterology.

Introduction : Ustekinumab (UST) is increasingly being used in Belgium for moderate to severe Crohn's disease (CD).
Aim : The aim of the current study was to describe the real-life experience with UST in our tertiary center.
Methods : A retrospective study was performed in patients with CD who were started on UST between December 2017 and August 2019. All patients received an intravenous (IV) induction dose of 6 mg/kg body weight, followed by 8-weekly 90 mg subcutaneous UST. The clinical and endoscopic response were assessed by the physician after induction and during the maintenance phase.
Results : In total, 67 patients were included of which 42 patients (62.7%) were refractory to 2 or more biologicals (TNF inhibitors and/or vedolizumab). UST was started in association with an immunosuppressant or corticosteroid in 14 (20.9%) and 29 (43.3%) patients respectively. The clinical response was assessed in 52 patients after the induction

dose (week 4-8) : 14 patients (26.9%) had no response, 34 (65.4%) had a clinical response and 4 (7.7%) were in clinical remission. During the maintenance phase, patients were assessed after a median treatment duration of 26 weeks (IQR 21.8-30). A clinical response was seen in 32/54 patients (59.3%). An additional 11/54 patients (20.4%) reached remission. Endoscopy was performed in 16 patients and an endoscopic response was confirmed in 6/16 patients (37.5%), remission in 1 patient (6.3%). After 1 year of treatment with UST, 33 patients could be evaluated : clinical response and remission were seen in 14/33 (42.4%) and 14/33 (42.4%) respectively. Endoscopy was performed in 16 patients : 7/16 patients (43.8%) showed a response, 2/16 (12.5%) were in endoscopic remission. The median duration of treatment at the moment of inquiry was 15 months (IQR 7-25). UST was discontinued in 16 patients (23.9%) after a median of 27.5 weeks (IQR 12.3-52.8). Reasons for discontinuation were loss of response (LOR), including 5 patients needing surgery (n=10), primary non-response (n=3), malignancy (n=1), adverse event (n=1) and patients' wish (n=1). In 29 patients (43.3%) optimization of UST was necessary due to partial response (n=13) or due to LOR (n=16). The optimization consisted of an IV re-induction in 2 patients, shortening of the dosage interval in 16 patients and a combination of both in 11 patients. The effect of optimization could be assessed in 22 patients : 10 patients regained a good clinical response and 5 patients attained clinical remission after optimization. In 7 patients UST was stopped despite optimization, most often due to persistent LOR.
Conclusions : In this tertiary population of refractory CD patients, treatment with UST resulted in a good clinical response in more than 70% of patients. Of note, 43.3% needed dose optimization, with a good clinical response in almost half of the cases. The endoscopic response in this preliminary analysis was modest.

- I31 -

THE IMPACT OF VEDOLIZUMAB ON EXTRA-INTESTINAL MANIFESTATIONS IN IBD PATIENTS : A REAL-LIFE EXPERIENCE OF A SINGLE CENTER COHORT. M. Truyens (1), J. Geldof (1), G. Dewitte (1), E. Glorieus (1), A. Peeters (1), D. Elewaut (2), G. Varkas (2), T. Lobaton Ortega (1) / [1] UZ Gent, Gent, Belgium, Gastroenterology, [2] Universiteit Gent, Gent, Belgium, Department of Rheumatology, Faculty of Medicine and Health Sciences, Host-Microbiota Interaction Lab (HMI) and Laboratory for Molecular Immunology and Inflammation.

Introduction : Vedolizumab (VDZ), a gut-specific anti-integrin, is approved as a treatment for moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). Extra-intestinal manifestations (EIM) are frequently associated with inflammatory bowel disease (IBD). However, the effect of VDZ on these EIM remains unknown.
Aim : The aim of this study was to describe the prevalence of EIM in IBD patients at the start of VDZ treatment, their evolution and the occurrence of new EIM during continued treatment.
Methods : A single center study was performed in IBD patients who were started on VDZ between May 2010 and February 2019. Retrospectively, the physician-reported EIM and intestinal disease activity (clinical and endoscopic data) were assessed at baseline, 6 weeks, 6 months and after 1 year of VDZ treatment.
Results : The cohort consisted of 134 patients, including 77 CD patients, 56 UC patients and 1 patient with unclassified IBD. At VDZ initiation EIM were assessed in 127 patients of whom 17.3% had at least 1 EIM : 9 hepatic EIM (2 patients with toxic hepatitis, 2 with autoimmune hepatitis and 5 with PSC), 7 arthropathies (6 patients with axial spondyloarthropathy and 1 with peripheral arthritis), 3 non-specified axial or peripheral arthralgias and 3 cutaneous EIM (urticaria, psoriasis and erythema nodosum). At 6 weeks after treatment initiation 26/121 patients (21.5%) had ≥ 1 EIM. In 13 patients a new EIM was seen : in 2 patients an arthropathy, in 6 arthralgia, 2 patients with myalgia and 3 cutaneous EIM. At 6 months 113 patients were assessed of which 26 (23%) had ≥ 1 EIM. Nine new EIM developed : 1 arthropathy, 4 arthralgias, 2 cutaneous EIM, 1 hepatic EIM and 1 myalgia. At 1 year 17/105 patients (16.2%) had ≥ 1 EIM. In total, 18 out of all 19 preexisting EIM remained stable. Of the 9 patients with arthralgia at 6 months, the arthralgia had resolved in 5 patients at 1 year of follow-up, whereas in 4 patients the arthralgia remained stable. One new non-specified rash was observed at 1 year and 1 patient reported deterioration of myalgia. The intestinal disease activity was assessed at 6 months and 1 year after VDZ initiation. At 6 months, a clinical response was seen in 34 of the 109 evaluated patients (31.2%), an additional 62/109 patients (56.9%) reached clinical remission. In 81 patients endoscopy reports at 6 months showed endoscopic response in 35/81 patients (43.2%) and endoscopic remission in 22 patients (27.2%). At 1 year of treatment with VDZ, the intestinal disease activity was assessed in 106 patients. Clinical response and remission were seen in 24/106 (22.6%) and 72/106 (67.9%) respectively. Endoscopy was performed in 44 patients : 7 (15.9%) showed response, 25 (56.8%) were in endoscopic remission. VDZ was stopped in 39/130 (30%) patients. Reasons were : active intestinal disease (32 patients), patients' choice (1 patient) or because of deep disease remission (1 patient). In 5 patients VDZ was stopped because of insufficient control of EIM.
Conclusions : Overall, in patients treated with VDZ a good clinical and endoscopic intestinal response was observed. However, the evolution of the EIM appears unaffected by the use of VDZ in our cohort. Prospective data are needed to confirm these results.

BELGIAN SOCIETY FOR PAEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION (BESPGHAN)

- K01 -

HOW SWITCHING TO BIOSIMILAR INFLIXIMAB LED TO STOPPING TREATMENT IN 3 PEDIATRIC CROHN PATIENTS. S. Vande Velde (1), R. De Bruyne (1), M. Van Winckel (1), V. Stephanie (1) / [1] Ghent University Hospital, Ghent, Belgium, pediatric gastroenterology.

Objective : Great uncertainty remains about risks and benefits of stopping treatment in patients with inflammatory bowel disease (IBD). Confronted with 3 patients with antibodies for infliximab in stable remission, cessation of treatment was discussed with patients and parents. We present the clinical, and biochemical data of 3 paediatric Crohn patients before and after stopping treatment.
Methods : In 2017 all paediatric IBD patients treated with originator infliximab at the Department of paediatric Gastroenterology, Ghent University Hospital, were switched to biosimilar Remsima®. Faecal calprotectin, infliximab through levels and antibodies, white cell count (WBC), haemoglobin (Hb) and C-reactive protein (CRP) were measured before and after switching to biosimilar.
Results : In total 21 IBD patients (3 UC-19 CD) between 7 and 15 years old were switched. In 3 (14%) patients on monotherapy antibodies for infliximab were detected, after 22 to 82 months of use. None of the patients had previous surgery. All 3 were in clinical and biochemical remission (see Table 1). Colonoscopy was performed with normal macroscopic view (Crohn's Disease Endoscopic Index of Severity score of 0) and confirmed histological remission in all. Switching to another treatment or cessation of treatment was discussed with patients and parents, and all 3 decided to stop treatment. Evaluation after 2 years shows that all 3 are still in clinical remission. Six- monthly clinical and biochemical (Hb, WBC, CRP and calprotectin) follow up is foreseen.
Conclusions : We present 3 paediatric Crohn patients with a 2-year medication-free survival after stopping infliximab. These cases may lead an open window to further research in treatment discontinuation in paediatric IBD. Factors predicting relapse, optimal monitoring strategy following withdrawal have to be further elucidated, specifically for children and not converted from adult care.

- K02 -

POST-INDUCTION INFLIXIMAB TROUGH LEVELS PREDICT LONG-TERM ENDOSCOPIC REMISSION IN PAEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE. K. Van Hoeve (1), E. Dreesen (2), I. Hoffman (3), M. Ferrante (4), S. Vermeire (4) / [1] University Hospitals Leuven, Leuven, Belgium, Department of Paediatric gastroenterology & Hepatology & Nutrition, [2] Katholieke Universiteit Leuven, Leuven, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies, Department of Pharmaceutical and Pharmacological Sciences, [3] University Hospitals Leuven, Belgium, Department of Paediatric gastroenterology & Hepatology & Nutrition, [4] University Hospitals Leuven, Belgium, Department of Gastroenterology & Hepatology.

Introduction : Although higher infliximab (IFX) trough levels (TL) have been associated with better outcomes, the ideal predictive sampling time and cut-points to achieve endoscopic remission remains unclear in children with inflammatory bowel disease (IBD).
Aim : Therefore, we evaluated the pharmacokinetics of IFX during induction to predict long-term outcome of IFX.
Methods : All children age <18 years with Crohn's disease (CD) or ulcerative colitis (UC) starting IFX therapy for active luminal disease from May 2017 till May 2019 were enrolled. Only IFX naïve patients were consecutive included and followed-up prospectively six months after initiation of IFX therapy. Exclusion criteria were IFX exposed patients, absence of endoscopic activity or a patient's refusal to participate. Patients were treated with standard intravenous IFX 5 mg/kg (2h infusion) at weeks 0, 2 and 6 followed by a maintenance therapy starting at week 12. IFX serum levels were measured by Ridascreen IFX Monitoring ELISA (TL at week 2-6-12, peak at week 0-2-6 and intermediate at week 1-4). IFX serum levels and cumulative drug exposure (area under the curve (AUC) till week 12) were correlated with outcome at month six. Clinical remission was defined as PUCAI/PCDAI <10, biochemical remission as CRP ≤5 mg/L + ESR ≤20 mm/h, endoscopic remission as SES-CD <3 or Mayo endoscopic sub-score =0 and deep remission if both clinical + endoscopic remission. Results were analysed using Mann-Whitney U-test (presented as median [interquartile range]).
Results : A total of 252 serum induction levels were included from 32 patients (20 CD and 12 UC; 38% male; median age at start of IFX 13.8 years [11.3-14.9]; 84% on concomitant thiopurines). Clinical remission was achieved in 24 (75%) patients and 18 (56%) were in endoscopic remission (all in deep remission) at month six. Endoscopic remission at month six was associated with significantly higher median IFX serum levels at week 4 (38.8 µg/mL [24.3–46.0] vs 23.5 µg/mL [10.5–36.6], p=0.017), at week 6 (19.9 µg/mL [10.1-26.3] vs 11.1 µg/mL [3.7–19.9], p=0.031), at week 12 (9.6 µg/mL [5.5–11.9] vs 3.5 µg/mL [2.7–7.2], p=0.004) and higher cumulative drug exposure during induction (AUC week 0-12 : 4574.7 µg*day/mL [3783.0–5160.8] vs 3722.9 µg*day/mL [3102.2–3991.9], p=0.008). Median IFX TL at week 12 were significantly higher in children with clinical remission (8.6 µg/mL [5.1–12.0] vs 4.3 µg/mL [3.1–5.9], p=0.033), but

not for biological remission (6.7 µg/mL [4.0-12.0] vs 4.3 µg/mL [1.2–7.2], p=0.250) at month six. Biological remission was only evaluated in patients with elevated biomarkers at baseline (n= 23/32; 71.9%). However, early and persistent normalization of baseline biomarkers (time between IFX initiation and moment of persistent CRP and ESR normalisation) correlated well with the week 12 TL (rs= -0.522; p= 0.011). ROC analysis identified an IFX TL at week 12 ≥ 5.0 µg/mL and an AUC week 0-12 ≥ 4056.0 µg*day/mL as minimal target to achieve endoscopic remission at month six (AUROC : 0.796 [95%CI : 0.62-0.97] and AUROC : 0.778 [95%CI : 0.61-0.94] respectively). Height, haemoglobin and PCDAI score at start of IFX therapy, significantly correlated with week 12 IFX TL.
Conclusions : Adequate IFX exposure during induction in paediatric IBD patients is associated with significantly better clinical, endoscopic and deep remission rates at month six. Model-informed precision dosing can assist physicians to achieve optimal exposure during induction more precisely (and rapidly) what is essential for an optimal outcome.

- K03 -

DETECTION OF HELICOBACTER PYLORI IN CHILDREN AND ADOLESCENTS : DIAGNOSIS AND TREATMENT IN JESSA HOSPITAL BETWEEN 2016 AND 2019. P. Hilkens (1), K. Magerman (1), E. Janssens (2), L. Waumans (1), R. Cartuyvels (1), P. Alliet (2) / [1] Jessa Hospital, Hasselt, Belgium, Clinical laboratory, [2] Jessa Hospital, Hasselt, Belgium, Dept of Paediatrics.

Introduction : Recent studies regarding the epidemiology of Helicobacter pylori indicate a significant variation in its worldwide prevalence, which is often associated with socioeconomic status and hygiene standards. The increasing resistance of H. pylori against current antimicrobial therapies and the subsequent failure of infection eradication are major challenges in the management of H. pylori infections in children and adolescents. Current ESPGHAN/NASPGHAN guidelines state that invasive diagnostic testing, i.e. bacterial cultures or histopathology combined with additional (molecular) assays on tissue biopsies, is only recommended when effective treatment can be offered. Furthermore, strain-specific antimicrobial sensitivity needs to be determined in order to provide a tailor-made therapy that will increase the likelihood of successful infection eradication.
Aim : The goal of this study was to obtain more insight into patient demographics of children and adolescents diagnosed with H. pylori infection according to the most recent ESPGHAN/NASPGHAN guidelines. Furthermore, the success of antimicrobial therapy will also be evaluated.
Methods : A retrospective analysis of patient data of children and adolescents diagnosed with and treated for H. pylori infection in Jessa Hospital between 2016 and 2019 was performed.
Results : Between 2016 and 2019, 508 gastric biopsies from paediatric patients (ages 1 to 16 years old) were taken in order to determine the presence of H. pylori by means of bacterial culture combined with a rapid urease test. Bacterial cultures were positive for H. pylori in 5% of these patients. Further analysis indicated that 77% of these positively diagnosed patients had a foreign background and 15% of them had a family history of peptic ulcers. All of the patients complained of abdominal pain and nausea. Nodular gastritis was present in 65% of the cases, as shown by endoscopy. Antimicrobial susceptibility testing pointed out resistance against metronidazole in 20% of these patients, while 8% showed resistance against either amoxicillin or levofloxacin. Given the susceptibility of all tested strains for clarithromycin, all of the culture-positive children and adolescents were treated with a clarithromycin-containing regimen, in accordance with the current ESPGHAN/NASPGHAN guidelines. More specifically, these patients were treated with triple therapy, i.e. 4 weeks of omeprazole and 2 weeks of amoxicillin/clarithromycin. Treatment success was evaluated in 82% of the cases, either with an urea breath test or endoscopy when an urea breath test was difficult to perform. In 17% of these patients, the infection was not successfully eradicated and an additional treatment regimen was started. 18% of the culture-positive and treated patients did not respond to any of the recommended follow-up appointments.
Conclusions : Retrospective analysis pointed out a relatively low prevalence of H. pylori infection in Jessa Hospital between 2016 and 2019. Diagnosis was based on a positive bacterial culture combined with a rapid urease test. The determination of antimicrobial susceptibility allowed clinicians to start a tailor-made treatment regimen which led to successful infection eradication in 83% of the evaluated patients. These data underline the importance of patient-specific therapy and follow-up, as recommended by the most recent ESPGHAN/NASPGHAN guidelines.

- K04 -

ACHALASIA OR PSEUDO-ACHALASIA IN A 2-YEAR-OLD BOY. P. De Bruyne (1), S. Theuns-Valks (2), A. Mubarak (3), L. De Ridder (1), B. De Koning (1), J. Escher (1) / [1] Sophia Children's Hospital - Erasmus MC Rotterdam, Rotterdam, Netherlands (the), Paediatric Gastroenterology, [2] Albert Schweitzer Hospital, Dordrecht, Netherlands (the), Paediatrics, [3] Sophia Children's Hospital - Erasmus MC Rotterdam, Rotterdam, Netherlands (the), Paediatrics.

We present the case of a 2,5-year-old boy. At the age of 20 months, he presented with feeding problems. Barium swallowing radiographic study showed signs of achalasia, which was confirmed by esophageal manometry. Treatment with endoscopic balloon dilatation of the lower esophageal sphincter was unsuccessful and was followed by a peroral endoscopic myotomy (POEM). After this procedure, feedings problems unfortunately did not approve and while

waiting for a Heller myotomy, he continued to be fed through a nasogastric tube. Four months after the POEM, the boy presented with sudden icterus and itch. Further investigations showed cholestasis caused by obstruction of bile ducts by a surrounding tumour. The tumour turned out to be an inflammatory myofibroblastic tumour (IMT) and the patient is currently treated with immunotherapy. In retrospect, the question is raised whether the feeding problems of this boy are caused by achalasia or by a pseudo-achalasia associated to the tumour.

- K05 -

USE OF USTEKINUMAB IN AN INFANT WITH VERY EARLY ONSET INFLAMMATORY BOWEL DISEASE : 18 MONTHS FOLLOW-UP. B. Hauser (1), K. Huysentruyt (2), E. De Greef (2), G. Veereman (2), Y. Vandenplas (2) / [1] UZ Brussel, Jette, Belgium, Pediatrics, [2] UZ Brussel, Jette, Belgium, Paediatrics.

Treatment in very early onset inflammatory bowel disease (VEOIBD) is challenging when no genetic defect is found. We describe the succesful use of ustekinumab in an infant with VEOIBD. The healthy born infant developed bloody diarrhea at the age of 5 months. Since both parents were allergic, a cow's milk protein allergy was suspected. An extensive protein hydrolysate was started with temporary improvement. At relapse, a left colonoscopy showed follicular hyperplasia with histologic signs of allergic colitis at 8 months of age. A diet without cow's milk, eggs and soy but with an elemental formula resulted in a temporary improvement. At 12 months of age, an upper endoscopy and ileocolonoscopy were performed because of recurrence of symptoms. They showed a mild antritis and duodenitis as well as some colonic aphteous lesions, one ulcer in the caecum and a normal terminal ileum. Histology showed a mild ileitis and local cryptitis not directly suggestive for an IBD. Blood analysis showed mild anemia, inflammation and hypoalbuminemia. Coprocultures were negative. VEOIBD was suspected, even though immunologic and genetic work-up remained negative. She was started on azathioprine, mesalazine and prednisolone with temporary improvement. A stool culture at 14 and 15 months of age was positive for a toxin-producing Clostridium difficile. She received metronidazole and vancomycine consecutively with temporary improvement. An ileocolonoscopy performed at the age of 16 months showed diffuse aphteous lesions, deep and superficial ulcers and a normal terminal ileum. Cryptitis, cryptabcesses and cryptdestruction confirmed the VEOIBD diagnosis. Clostridium difficile was eradicated. Azathioprine, mesalazine and prednisolone were stopped. Infliximab was started at the age of 16 months (10 mg/kg week 0, 10 mg/kg week 2 and 15 mg/kg week 6) but failed to improve symptoms. Levels remained low and anti-TNF antibodies developed. Methotrexate was tried at 18 months without effect. Transfusion dependent anemia and severe failure to thrive remained with unchanged lesions on an ileocolonoscopy performed at the age of 19 months. Ustekinumab in compassionate use was requested to Janssen and this new treatment could be started. An induction dose of 65 mg ustekinumab IV at the age of 19 months was administered followed by a maintenance dose of 45 mg SC/8 weeks up to now. Methotrexate was continued. Stool consistency and blood loss improved progressively after the third maintenance dose. Growth resumed. A colonoscopy after 14 months of treatment with Ustekinumab showed no macroscopic inflammation and inactive chronic colitis on biopsies and no inflammation biochemically. Through levels after the third, fourth, six and seventh maintenance doses were respectively < 0.3, 0.7, 6.5 and 6.1 µg/ml. Infantile onset IBD is a challenging disease within the group of VEO-IBD. While ustekinumab is an effective therapy approved for adult Crohn's disease, off-label use in the paediatric population is increasing. The first results suggest that ustekinumab is efficacious and safe in paediatric patients with IBD. We report to the best of our knowledge the first patient with a VEO-IBD successfully treated with ustekinumab without side-effects and in complete remission after 18 months of treatment.

BELGIAN WORKING GROUP ON PROCTOLOGY

- M01 -

INJECTION OF BOTULINUM TOXIN SIGNIFICANTLY INCREASES EFFICIENCY OF FISSURECTOMY IN THE TREATMENT OF CHRONIC ANAL FISSURES. J. Wyndaele (1), G. Coremans (1), P. Roelandt (1) / [1] UZ Leuven, Leuven, Belgium, Gastroenterology & Hepatology.

Introduction : While acute anal fissures can be treated with topical therapy to reduce sphincter hypertonia (e.g. isosorbide dinitrate, diltiazem), chronic fissures frequently require more invasive instrumental therapy. Currently the golden standard remains lateral internal sphincterotomy, however this is complicated by a long-term risk of faecal incontinence. Fissurectomy can be a valuable alternative but is less efficient because of absence of correction of underlying hypertonia.
Aim : In this study we aim to evaluate the additional effect of injection of botulinum toxin during fissurectomy in the treatment of chronic anal fissures.
Methods : A single-centre retrospective analysis of 298 fissurectomies with or without injection of botulinum toxin was performed.
Results : The majority of patients undergoing fissurectomy were women (65%, mean age 45.0 years vs. 35% men, mean age 48.3 years), often because of ventral fissures (30% in women vs. 8% in men). Fissurectomy resulted in resolution of complaints in 81.1%, while additional injection of botulinum toxin resulted in resolution in 90.1% ($p<0.05$). Complication rate was identical between the two groups, mainly (flatus) incontinence (4.5% vs 4.9% with botulinum toxin) and post-operative bleeding (1.8% vs 2.5% with botulinum toxin).
Conclusions : Injection of botulinum toxin significantly increases the efficiency of fissurectomy in the treatment of chronic anal fissures without additional complications.

- M02 -

ANAL DYSPLASIA IN HIV-SEROPOSITIVE MEN. PREVALENCE IN THE GHENT POPULATION. E. Gökce (1), J. Van Dorpe (2), A. Hoorens (2), J. Pelgrom (3), F. Van Wanzeele (3), L. Vandekerckhove (3), S. Callens (3), D. De Looze (4) / [1] Ghent University, Ghent, Belgium, Faculty of Medicine and Health Sciences, [2] Ghent University Hospital, Ghent, Belgium, Pathology, [3] Ghent University Hospital, Ghent, Belgium, Internal Medicine, [4] Ghent University Hospital, Ghent, Belgium, Gastroenterology.

Introduction : Although anal cancer is rare in the overall population, its incidence is increasing in the last decades. Especially HIV-positive men are at increased risk for developing anal squamous cell carcinoma (SCC), mainly because of the high prevalence of high-grade anal intraepithelial neoplasia (HGAIN; AIN2/3) among those patients. No studies have examined the prevalence and the natural history of anal intraepithelial neoplasia (AIN) in HIV-positive men in Belgium.
Aim : Our study aims to identify the prevalence of AIN in HIV-patients, who underwent anal screening in the Ghent University Hospital. Furthermore, we tried to determine the natural history of HGAIN. In addition, we compared the results of the cytology to those obtained from high-resolution anoscopy (HRA).
Methods : Forty-eight HIV-positive men [95,8% men who have sex with men (MSM)], who underwent ≥2 screening procedures for anal dysplasia, were enrolled in this study. All patients received digital rectal examination, anal cytology and HRA at each visit. Biopsies were taken if suspicious lesions were revealed by HRA. All follow-up visits were included, giving a total of 166 cytology samples and HRA procedures performed between 18/08/2010-15/10/2019. The swab samples have been grouped in 'HSIL' [high-grade squamous intra-epithelial lesions (HSIL) or atypical squamous cells-cannot exclude HSIL (ASC-H)] and 'non HSIL' [Negative for Intraepithelial Lesion or Malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intra-epithelial lesions (LSIL)].
Results : During a median follow-up period of 44 months the median number of screening procedures was 3 per patient (median age 51 years). 160 of 166 cytology samples were suitable for analysis, 47 (29.4%) of which showed 'HSIL' while the remaining 113 (70.6%) swabs showed 'non HSIL'. Among the participants : the prevalence of HSIL was 50% on the first visit, 23.3% on the second and 16.7% on the third. We identified a regression of 30.2% from 'HSIL' to 'non HSIL' between the first and second visit ($p= 0.001$); a regression of 36.7% between the first and third visit ($p < 0,001$); and a regression of 24.0% between the second and third visit ($p = 0,388$). Only two patients received coagulation therapy for intra-anal warts; the other patients regressed spontaneously. Throughout the entire follow-up duration, we found one patient, who progressed to carcinoma in situ. Furthermore, a statistically significant association is found between detecting clinically suspicious lesions on HRA and having an anal swab that shows 'HSIL'. Anoscopic findings suggestive of dysplasia were found during 50 of 160 (31.1%) HRA procedures. If a diagnosis of 'HSIL' was detected on cytology, the prevalence of visualizing a suspicious lesion on concurrent HRA was 53.2% (24 of 47), while this percentage was 22.1% (25 of 113) when 'non HSIL' was found on anal cytology.
Conclusions : We found a high percentage of spontaneous regression from 'HSIL' to 'non HSIL' among HIV-positive participants. Further studies with a larger study population and longer median follow-up duration are required to determine

the sustainability of these regressions and to generalize our findings to the entire HIV-population. Despite the high regression grade, one patient progressed to carcinoma in situ. This shows the importance of regular screening to prevent invasive SCC. Based on the findings of new studies that are trying to determine biomarkers and risk factors that predict whether HSIL will regress or progress, it may be possible in the future to create a screening program wherein patients with an increased risk of progression can be monitored closely, while patients with a high probability of regression can be screened at larger intervals.

BELGIAN GROUP FOR DIGESTIVE ONCOLOGY (BGDO)

- O01 -

REAL WORLD INCIDENCE OF MICROSATELLITE INSTABILITY OR EBV POSITIVITY IN A BELGIAN COHORT OF PATIENTS WITH ADENOCARCINOMA OF THE ESOPHAGUS, GASTROESOPHAGEAL JUNCTION AND STOMACH. S. De Meulder (1), X. Sagaert (2), P. Nafteux (3), B. Topal (4), C. Verslype (5), S. Tejpar (5), E. Van Cutsem (5), J. Dekervel (5) / [1] University Hospital, Gasthuisberg, Leuven, Belgium, Gastro-enterology, [2] University Hospital, Gasthuisberg, Leuven, Belgium, Pathology, [3] University Hospital, Gasthuisberg, Leuven, Belgium, Thoracic Surgery, [4] University Hospital, Gasthuisberg, Leuven, Belgium, Abdominal Surgery, [5] University Hospital, Gasthuisberg, Leuven, Belgium, Gastroenterology and Hepatology.

Introduction : Patients with adenocarcinomas of the esophagus, gastroesophageal junction (GEJ) or stomach with microsatellite instability (MSI) or Epstein Bar Virus positivity (EBV+) might be good candidates for immunotherapy. Incidences of about 10% have been reported for both features but are dependent on geographical region and disease stage (1).
Aim : The aim is to study the occurrence of MSI and EBV + in a single center cohort of patients with adenocarcinoma of the esophagus and stomach.
Methods : We retrospectively assessed the files of all patients with a newly diagnosed adenocarcinoma of the esophagus, GEJ or stomach between 1/8/2018 and 31/10/2019. MSI status was determined using immunohistochemistry (IHC) and polymerase chain reaction (PCR). EBV + was assessed using in situ hybridization.
Results : Between 1/8/2018 and 31/10/2019 there were 226 newly diagnosed adenocarcinomas of the esophagus, GEJ and stomach. 55 (66,0% stage IV) of them were tested for EBV, but only 1 turned out to be EBV positive (1,8%). 97 patients (54,3% stage IV) were tested for MSI using IHC, of which 8 were MSI-high (8,2%). All MSI-high cases were confirmed by PCR. The EBV positive patient had stage IV disease at presentation. Of the MSI-high patients, 2 had stage Ib cancer, 1 stage III and 2 stage IV. The disease stage of 3 patients was unknown. Half of the MSI-high tumors identified were located at the GEJ.
Conclusions : The incidence of EBV+ in our cohort is clearly lower than would be expected after reviewing the literature (2,3). Due to the presence of therapeutic implications, testing was mostly performed in stage IV disease which might entail a selection bias. The lower incidence of EBV+ may also be due to geographical and racial factors (4). Finally, we found a remarkably high incidence of MSI-high tumors in the GEJ. The reflex to test for MSI should therefore not be based on the location of the tumor. References : 1. Nishikawa J, Iizasa H, Yoshiyama H, Shimokuri K, Kobayashi Y, Nakamura M, et al. Clinical Importance of Epstein–Barr Virus-Associated Gastric Cancer. :1–13. 2. Kim ST, Cristescu R, Bass AJ, Kim K, Odegaard JI, Kim K, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. Nat Med [Internet]. 2018;24(September). Available from : http ://dx.doi.org/10.1038/s41591-018-0101-z 3. Gu L, Chen M, Guo D, Zhu H, Zhang W, Pan J, et al. PD-L1 and gastric cancer prognosis : A systematic review and meta-analysis. 2017;1–14. 4. Bass AJ, Thorsson V, Shmulevich I, Reynolds SM, Miller M, Bernard B, et al. Comprehensive molecular characterization of gastric adenocarcinoma. Nature [Internet]. 2014;513(7517) :202–9. Available from : http ://dx.doi.org/10.1038/nature13480

- O02 -

INDUCTION BY MFOLFIRINOX FOLLOWED BY STEREOTAXIC BODY RADIOTHERAPY WITH SIMULTANEOUS INTEGRATED BOOST (SIB-SBRT) AT THE TUMOR-VESSEL INTERFACES (TVI) FOR THE NEOADJUVANT TREATMENT OF LOCALIZED PANCREATIC CANCERS. C. Bouchart (1), J. Engelholm (2), M. Bali (2), J. Closset (3), J. Navez (3), P. Loi (3), Y. Gökburun (4), T. De Grez (4), A. Hendlisz (5), L. Mans (6), P. Eisendrath (7), D. Van Gestel (1), L. Moretti (1), J. Van Laethem (6) / [1] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Radiotherapy-Oncology, [2] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Radiology, [3] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastrointestinal Surgery, [4] CHR, Namur, Belgium, Gastroenterology and digestive oncology, [5] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Digestive Oncology, [6] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenterology-Hepatology and Digestive Oncology, [7] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology.

Introduction : The optimal treatment sequence for localized pancreatic ductal adenocarcinoma (PDAC) remains controversial. The stereotactic body radiotherapy (SBRT) technique has the advantages of limiting interruption of systemic treatments and increasing the biological equivalent dose delivered potentially leading to improved local control, resection rates and overall survival (OS).
Aim : We report here the preliminary results of our neoadjuvant treatment strategy including mFOLFIRINOX followed by SBRT with simultaneous integrated boost (SIB) at the tumor-vessels interfaces (TVI).

Methods : From August 2017, all patients diagnosed with high-risk resectable (HR-R), borderline (BR), or locally advanced (LA) PDAC - according to the criteria defined by the National Comprehensive Cancer Network (NCCN) - were prospectively included. Induction by mFOLFIRINOX alone or followed by gemcitabine/nab-paclitaxel (G/NabP) if no response or intolerance was delivered for an average of 7 cycles. After a radiological assessment showing no progression, SBRT was delivered (35Gy in 5 sessions) with a TVI-SIB up to 50Gy. Patients with partial, complete response (CR) or stable disease were explored for oncologic resection 4 to 6 weeks after SBRT. Acute toxicities (≤ 6 months) were graded according to CTCAE v.4.
Results : Twenty-seven patients with localized PDAC - 1 HR-R, 9 BR, 17 LA - received either mFOLFIRINOX only (85%) or followed by G/NabP (15%). The median age at diagnosis was 60.5 years (P25 52 - P75 70) and the median follow-up is currently 11.5 months (P25 7 - P75 14.5). After radiological assessment, 3 patients developed metastases, 1 presented a CR and surgery was directly performed, 2 were not candidates for SBRT due to the failure of fiducials insertion and 21 received SIB-SBRT (78%). Of these 21 patients, 4 became metastatic at the pre-surgical assessment (19%), 4 were inoperable due to portal cavernoma or initial contraindication to general anesthesia (19%) and 13 patients (62%; 1HR-R, 5 BR, 7 LA) were explored. Resection was not performed in 4 patients due to per-operative discovery of liver metastases (n=2/13) or non-reconstructible vascular invasion (n=2/13). The R0 resection rates >0.1mm and ≥1mm are respectively 78% (n=7/9) and 44% (n= 4/9). The 6 months OS and progression free survival rates are respectively 100% and 70% for the entire cohort. To date, the 1-year OS for patients with sufficient follow-up who received the complete neoadjuvant sequence with SBRT is 91% (n=10/11) versus 81% for the entire cohort (n=13/16). Acute toxicity is minimal, with most patients experiencing fatigue (grade≤2 : 90%) and flare-up epigastric pain (grade 1 : 52%). No acute grade ≥3 gastrointestinal toxicity has been reported.
Conclusions : These preliminary results indicate that the integration of SIB-SBRT following multi-agent induction chemotherapy is feasible for the neoadjuvant treatment of localized PDAC. Our first analyses show favorable R0 resection rate, acute toxicity profile and 1-year OS in selected patients.

- O03 -

FEASIBILITY AND CLINICAL IMPACT OF ROUTINE MOLECULAR TESTING OF GASTROINTESTINAL (GI) CANCERS AT A TERTIARY CENTRE WITH A MULTI-GENE, NEXT GENERATION SEQUENCING (NGS) PANEL. G. Bregni (1), T. Sticca (2), T. Akin Telli (1), S. Camera (1), L. Craciun (3), L. Shaza (1), A. Deleruelle (1), M. Anciaux (1), G. Machiels (1), A. Deleporte (1), C. Vandeputte (1), P. Demetter (3), D. Larsimont (3), A. Hendlisz (1), F. Sclafani (1) / [1] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Medical Oncology, [2] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Molecular Pathology, [3] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Pathology.

Introduction : High-throughput sequencing technologies have been increasingly used in research, but limited data are available on the feasibility and clinical value of these when adopted as part of standard care. Since 2014, a multi-gene NGS panel has been used in routine clinical practice in our Cancer Network, with a central laboratory being accredited to carry out molecular profiling at the request of the treating physician.
Aim : Five years after the implementation of this NGS panel in our Cancer Network, we have analysed feasibility and clinical implications of routine multi-gene NGS testing in gastrointestinal cancer patients.
Methods : All consecutive gastrointestinal cancer patients for whom tumour genomic testing by a multi-gene NGS panel was requested from April 2014 to Jun 2019 as part of routine practice in the IRIS Network were retrospectively identified from a prospectively maintained database. The Truseq Amplicon Cancer Panel (Illumina) was regularly used as NGS assay over the study period. This is a multiplexed targeted resequencing assay that allows the detection of mutations (at a frequency below 5%) in hotspots regions of 48 cancer-related genes including ABL, AKT, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R1, CTNNB1, EGFR, HER-2, HER-4, FBXW7, FGFR-1, FGFR-2, FGFR-3, FLT-3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH-1, JAK-2, JAK-3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH-1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB-1, RET, SMAD-4, SMARCB1, SMO, SRC, STK11, TP53, and VHL. The primary objective of the study was feasibility, assessed by analysing the test success rate and the median turnaround time in the IRIS Network population. Secondary objectives included NGS results and the impact that these had on the management decisions for patients treated at the Institut Jules Bordet. Associations were tested with Fisher's test or Chi-square test, as appropriate. P values <0.05 were considered as statistically significant.
Results : From April 2014 to June 2019, 447 NGS tests were requested for patients with gastrointestinal cancers within the IRIS Network. Sequencing was successful in 421 cases (93.8%), 279 of which were managed at the Institut Jules Bordet (224 colorectal (CRC), 21 oesophago-gastric, 17 bilio-pancreatic, 9 GIST, 4 appendix, 3 small intestine, 2 hepatocellular). In successful and failed cases, respectively, analyses were attempted on core biopsy (37.0% vs 66.7%), surgery (62.6% vs 16.7%), and fine needle aspiration (0.4% vs 12.4%) samples ($p<0.001$). Median turnaround time was 12.5 days, reducing from 17 days in 2014 to 10 days in 2019 ($p<0.0001$). The majority of successfully tested patients (85.6%) had metastatic disease. Across all tumour types, TP53 was the most frequently mutated gene (45.9%), followed by APC (42.1%), KRAS (39.7%), PIK3CA (12.1%), SMAD4 (7.6%), BRAF (6.2%), and NRAS (5.5%). All other mutated genes were detected in less than 5% of samples. Excluding RAS/BRAF and KIT/PDGFR mutations, sequencing

results impacted on the management of 4 (1.4%) patients. Using the publicly available OncoKB Database and excluding well known actionable or clinically relevant mutations such as KRAS, NRAS, BRAF, KIT and PDGFRA, 57 out of the 279 successfully tested patients (20.4%) had tumours harbouring at least one altered actionable gene. When taking into account the tumour type in which the altered gene is known to be actionable, only 10 (3.6%) of the study patients could be candidate for targeted treatment. To further evaluate the clinical impact of the additional mutations detected by NGS, we searched through the Clinical Trials Transformation Initiative trials registry for available clinical trials for which patients could have been screened if they all had been tested in October 2019. This analysis revealed that a genomically-matched clinical trial could be offered to up to 65 patients (23.3%).
Conclusions : Our findings confirm that multiple NGS testing is feasible in the clinical setting with acceptably low failure rates and rapid turnaround time. Nevertheless, genomic data that were additional to those routinely provided by standard targeted sequencing had virtually no influence on the management of patients during the study period. The clinical impact of the NGS technology could substantially increase with the identification of new biologically relevant genetic alterations, the increased availability of novel therapeutics and genomically-matched clinical trials, and the routine implementation of institutional/network Molecular Tumour Boards.

- O04 -

DNA METHYLATION ANALYSIS OF THE PDX1 GENE CAN BE USED FOR PNET SUBTYPING AND HAS A POSSIBLE PROGNOSTIC VALUE. G. Boons (1), T. Vandamme (2), J. Ibrahim (3), A. Schepers (3), G. Roeyen (4), A. Driessen (4), C. Blenkiron (5), K. Parker (6), M. Peeters (4), G. Van Camp (3), K. Op De Beek (1) / [1] University of Antwerp, Belgium, CORE / Human Molecular Genetics, [2] Universiteit Antwerpen / Antwerp University Hospital, WILRIJK (Antwerpen), Belgium, NETwerk, [3] University of Antwerp, Belgium, Human Molecular Genetics, [4] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, NETwerk, [5] University of Auckland, New Zealand, Maurice Wilkins Centre & Department of Molecular Medicine and Pathology, School of Medical Sciences, Faculty of Medicine and Health Sciences, [6] University of Auckland, New Zealand, Discipline of Oncology, Faculty of Medicine and Health Sciences.

Introduction : Estimating prognosis of non-functional pancreatic neuroendocrine tumour (PNET) patients remains challenging. Mutation status of DAXX/ATRX/MEN1, histone modification patterns and immunohistochemistry for relevant transcription factors, including PDX1, have recently been used to perform subtyping and distinguished two main subtypes, A and B. These subtypes are linked to cell-of-origin and associated with clinical outcome.
Aim : In this study, we assessed whether DNA methylation of PDX1 can be used to identify the A and B subtypes, linked to cell-of-origin, and tested the prognostic value of these subtypes.
Methods : DNA methylation analysis using Infinium Methylation EPIC and 450K arrays (Illumina) was performed on DNA from fresh-frozen tissue of 41 PNETs. Additional DNA methylation data of 42 PNETs and healthy alpha and beta cells were collected through public databases. Methylation values of CpGs in the PDX1 region were extracted and used to perform clustering to identify subtypes for survival analysis. Available clinicopathological and sequencing data were included in the analyses.
Results : Clustering analysis identified two separate clusters. One cluster contained the alpha cells and 97% of the mutated PNET samples, suggestive of the A subtype. The other cluster consisted of beta cells and mostly wild type PNETs, suggestive of the B subtype. A significant association was found between mutation status and subtype (Chi-square, $p<0.001$). Furthermore, Kaplan-Meier analysis showed a trend towards longer overall survival (OS) for patients with subtype B ($p=0.058$). Median OS for type A was 11.9 years (95% CI 9.9 years – not reached) and has not been reached for type B.
Conclusions : DNA methylation analysis can be used to perform subtyping and links subtype with cell-of-origin by including DNA methylation patterns of alpha and beta cells. This subgrouping might have prognostic properties.

- O05 -

FIGHT-202 : A PHASE 2 STUDY OF PEMIGATINIB IN PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC CHOLANGIOCARCINOMA. E. Van Cutsem (1), A. Vogel (2), V. Sahai (3), A. Hollebecque (4), G. Vaccaro (5), D. Melisi (6), R. Al-Rajabi (7), A. Paulson (8), M. Borad (9), D. Gallinson (10), A. Murphy (11), D. Oh (12), D. Efrat (13), D. Catenacci (14), C. Lihou (15), H. Zhen (16), L. Féliz (15), G. Abou-Alfa (17) / [1] University Hospitals Gasthuisberg and KU Leuven, Belgium, Department of Digestive Oncology, [2] Hannover Medical School, Germany, Department of Gastroenterology, Hepatology and Endocrinology, [3] University of Michigan, Ann Arbor, United States (the), Rogel Cancer Center, [4] Gustave Roussy, France, Department of Adult Medicine, [5] Providence Cancer Center Oncology and Hematology Care Clinic, United States (the), Hematology Oncology, [6] Università degli studi di Verona, Italy, Digestive Molecular Clinical Oncology Research Unit, Department of Medicine, [7] University of Kansas Cancer Center, United States (the), Department of Internal Medicine, Division of Hematology/ Oncology, [8] Baylor University Medical Center, United States (the), Baylor Charles A. Sammons Cancer Center, [9] Mayo Clinic Cancer Center, United States (the), Department of Internal Medicine, [10] Morristown Memorial Hospital,

Carol Cancer Center, United States (the), Department of Hematology/Oncology, [11] Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, United States (the), Department of Oncology, [12] Seoul National University Hospital, Seoul National University College of Medicine, Korea (the Republic of), Department of Internal Medicine, [13] Fox Chase Cancer Center, United States (the), Department of Hematology/Oncology, [14] University of Chicago Medicine, United States (the), Department of Medicine, [15] Incyte Corporation, United States (the), Clinical Development, [16] Incyte Corporation, United States (the), Biostatistics, [17] Memorial Sloan Kettering Cancer Center, United States (the), Department of Medicine.

Introduction : Fibroblast growth factor receptor (FGFR) 2 alterations are implicated in cholangiocarcinoma. Pemigatinib is a selective, potent, oral FGFR1, 2, and 3 inhibitor.
Aim : We present data from a phase 2, open label, single arm study of pemigatinib in patients with previously treated locally advanced or metastatic cholangiocarcinoma (NCT02924376).
Methods : Eligible adults had documented FGF/FGFR gene status and evident disease progression after ≥1 prior treatment. Patients were assigned to cohorts A (FGFR2 gene rearrangements/fusions), B (other FGF/FGFR gene alterations), or C (no FGF/FGFR gene alterations), and received oral pemigatinib 13.5 mg QD (21-day cycle; 2 weeks on, 1 week off) until disease progression/unacceptable toxicity. Primary endpoint was centrally confirmed objective response rate (ORR; cohort A); secondary endpoints were ORR (cohorts B, A+B, and C); duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.
Results : As of data cutoff (Mar 22, 2019), 146 patients were enrolled (cohort A, n=107; B, n=20; C, n=18; 1 patient undetermined). Median (range) age was 59 (26–78) years; 61% and 39% had 1 and ≥2 prior therapies, respectively. Fewer patients discontinued therapy in cohort A (71%) vs B and C (each 100%), mainly for progressive disease (53%, 75%, and 67%, respectively). ORR in cohort A was 35.5% (95% CI, 26.5%–45.4%), with 3 complete responses; median DOR was 7.5 (95% CI, 5.7–14.5) months; DCR was 82% (95% CI, 74%–89%); median PFS and median OS were 6.9 (95% CI, 6.2–9.6) and 21.1 (14.8–not reached) months (OS not mature at cutoff), respectively. In cohorts B and C, there were no responses. Overall, most common adverse events (AEs) were hyperphosphataemia (60%; grade ≥3, 0%), alopecia (49%; 0%), diarrhoea (47%; 3%), fatigue (42%; 5%), nail toxicities (42%; 2%), and dysgeusia (40%; 0%). Hyperphosphataemia was managed with diet modifications, phosphate binders, if needed; diuretics or dose reductions/ interruptions. Discontinuation, dose reduction and interruption due to AEs occurred in 9%, 14% and 42% of patients, respectively.
Conclusions : These data support pemigatinib as a potential treatment option for previously treated patients with cholangiocarcinoma harbouring FGFR2 gene rearrangements/fusions.

- O06 -

"NEOPAC" : A MULTI-CENTRIC PROSPECTIVE OBSERVATIONAL REGISTRY ON THE NEOADJUVANT THERAPEUTIC APPROACH TO THE LOCALISED PANCREATIC ADENOCARCIMONA, A COLLABORATIVE MULTICENTRIC PROJECT (CHU LIÈGE – FLCD - CUSL – ULB ERASME).

J. Siplet (1), L. Mans (2), M. Figueiredo (3), R. Marechal (3), A. Frere (4), C. Rinken (4), B. Delhougne (4), G. Houbiers (5), C. Hubert (6), J. Closset (7), F. Kreutz (8), H. Kalantari (9), J. Van Laethem (3), D. Van Daele (5), I. Borbath (10) / [1] Clin Universitaires St-Luc, UCL, Brussels, Belgium, Gastroenterology, [2] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenterology, [3] Erasme Hospital, Brussels, Belgium, Gastroenterology, [4] CHR La Citadelle, Belgium, Gastroenterology, [5] CHC, Liège, Belgium, Gastroenterology, [6] Saint-Luc University Hospital, Brussel, Belgium, Digestive Ssurgery, [7] Erasme Hospital, Brussels, Belgium, Digestive Surgery, [8] CHR Verviers, Verviers, Belgium, Oncology, [9] CHR Verviers, Verviers, Belgium, Gastroenterology, [10] Saint-Luc University Hospital, Brussel, Belgium, Gastroenterology.

Introduction : Therapeutic management of localized pancreatic adenocarcimona (L-PDAC) is currently based on the evaluation of the tumor resectability using radiological criteria and review by expert MD board. These criteria lead to the following three situations : 1. Resectable tumors, 2. Unresectable tumors, that will receive induction chemotherapy eventually followed by radiotherapy. 3. Borderline resectable lesions that rely on specific vascular involvement criteria, for which neoadjuvant therapy is advised, although still proven efficient. These recommendations remain however based on observational retrospective studies. It is therefore important that, in our practice, we either conduct these approaches as part of controlled studies, or that we record these data on prospective registries.
Aim : To implement a multicentric registry of patients with L-PDAC, prospectively enrolled in a common database in order to 1/evaluate the clinical practice of academic and large general hospitals regarding the multimodal management of L-PDAC and 2/ assess the relevant prognostic factors allowing a surgical R0 resection and its prediction to patient's outcome.
Methods : The NEOPAC project includes patients with L-PDAC and being treated in one of the following centres : Cliniques Saint-Luc (CUSL), ULB Erasme, CHU Liège, CHR Citadelle, CHC Saint Joseph and CHR Verviers. The recorded data were clinical (gender, age, weight, size, ECOG PS,...), biological (CA 19.9 level, bilirubin level,...), radiological (tumor location, size, vascular involvement, cTNM, metabolic activity) and pathological (R status, N

stage,..). Patients were characterized by a single investigator, as resectable, borderline resectable or locally advanced, according to vascular involvement description, based on NCCN guidelines. For each patient, administered treatments (neoadjuvant chemotherapy, radiotherapy, adjuvant chemotherapy, type of surgery), tumor response and feasibility/ tolerability of the whole therapeutic sequence were recorded. Follow-up at different time points is planned and ongoing.
Results : From March 2017 to November 2019, 84 patients have been enrolled. Baseline characteristics showed a 1 :1 gender ratio, a mean age of 65 years (39-91); ECOG at baseline was 0 (43%), 1 (53%) or 2 (4%). Mean tumor size was 36 (+/-18) mm and mean CA 19.9 level was 1445 (+/-7264) UI/mL. Tumor localization was head in 65%, body and tail in 35%. Among currently evaluated patients, 9 had resectable tumors, 34 had borderline tumor and 33 had unresectable locally advanced diseases. Neoadjuvant chemotherapy was administered to 70/76 (93.4%) patients; mainly FOLFIRINOX (78.7%) or gemcitabine/nab-paclitaxel (14,7%). Forty-seven patients currently achieved complete neoadjuvant chemotherapy sequence. At the end of neoadjuvant treatment, we observed 3 complete response (CR), 23 partial response (PR), 12 stable disease (SD) and 4 progressive disease (5 patients were not evaluable). Grade 3 or 4 toxicity was observed in less than 25% of cases and discontinuation of chemotherapy was necessary because of toxicity in 13% of cases. 17 patients received neoadjuvant chemo-radiotherapy after chemotherapy. Concerning patients who completed full neoadjuvant sequence : among readily resectable patients, 4/5 were resected without any neoadjuvant therapy (3 R0 : alive without recurrence, 1 Rx : alive with recurrence) and 1 was given chemotherapy (not resected because unfit for surgery). Among borderline patients, 12/22 were operated (9 R0 : 1 recurrence, 2 R1 : 1 recurrence, 1 undefined : recurrence). Among locally advanced tumors, 4/19 were resected (3 R0 : 1 with recurrence, 1 R2). Preferred adjuvant regimen was gemcitabine (N= 8/20, 42%) followed by FOLFIRINOX (N= 7/20, 37%). Amongst all resected patients, 9 are alive without recurrence, 4 had a relapse (all of them metastatic), and 1 was lost to follow-up. No death in resected patients has been reported so far.
Conclusions : Currently available data among NEOPAC show FOLFIRINOX to be the main neo-adjuvant treatment for borderline resectable and locally advanced L-PDAC. Full neoadjuvant sequence is feasible in most of our patients before attempt of surgery. Its efficacy allowed R0 resection for many borderline tumors and for several initially unresectable diseases. Enrolment of patients is ongoing. Data on more patients, with longer follow-up and OS results will be shown at the meeting.

- O07 -

NTRK GENE FUSIONS IN BILIARY TRACT CANCERS. A. Demols (1), L. Rocq (2), M. Charry (2), N. De Nève (2), A. Verrellen (2), A. Ramadhan (2), C. Van Campenhout (2), S. De Clercq (2), J. Closset (3), V. Lucidi (3), J. Van Laethem (1), I. Salmon (2), N. D'haene (2) / [1] CUB Hôpital Erasme, Belgium, Gastroenterology and GI Oncology, [2] CUB Hôpital Erasme, Belgium, Pathology, [3] CUB Hôpital Erasme, Belgium, Digestive Surgery.

Introduction : Gene fusions involving one of the 3 neurotrophic tyrosine receptor kinases (NTRK) have been identified in approximately 1% of solid tumors. TRK inhibitors (e.g. larotrectinib) have been shown to have anti-tumor activity, in such cases, regardless of tumor type. While NTRK gene fusions have been previously reported in bilio-pancreatic cancers, the incidence and molecular characteristics of NTRK gene fusions in patients with bilio-pancreatic cancers have not been well-characterized.
Aim : Aim is to evaluate and to characterize retrospectively the incidence and molecular characteristics of NTRK gene fusions in patients with biliary tract cancers.
Methods : Formalin-fixed paraffin-embedded archival blocks from surgical resections, biopsies or cytological samples of biliary tract tumors including intra-hepatic cholangiocarcinoma (IH), extra-hepatic cholangiocarcinoma (EH), perihilar cholangiocarcinoma (PH) and gallbladder tumors (G) were selected/retrieved from the tumor bank of the CUB Hôpital Erasme between January 2010 and July 2019. A two-step diagnostic method incorporating immunohistochemistry (IHC) screening followed by NGS analysis was used. Pan–TRK IHC (monoclonal antibody clone EPR17341 [AbCam, Cambridge, MA]) was used for the screening method. Staining intensity (negative, weak, moderate or strong), pattern (negative, focal or diffuse) and localization (cytoplasmic or nuclear) were evaluated. The presence of at least weak staining tumor cells led to testing by a RNA-based NGS panel (Oncomine Focus Assay, ThermoFisher scientific).
Results : 162 archival tumors samples (88 surgical resections, 56 biopsies and 18 cytology) have been selected, including 66 IH, 36 PH, 33 EH and 27 G (72 female and 90 male). 149 samples were suitable to perform IHC. 17 samples were IHC positive. Intensity of staining was weak in 16 samples and moderate in one. Staining location was cytoplasmic (14/17), nuclear (2/17), and nuclear+cytoplasmic (1/17). NGS testing of the 17 IHC positive samples revealed a single NTRK 3 gene fusion (ETV6(4)-NTRK3(14)). In this case (female patient with a poorly differentiated PH, deceased), IHC had a weak focal cytoplasmic and nuclear staining. Overall in the patients screened by IHC and confirmed by NGS, the percentage of NTRK fusions was 0.67 %.
Conclusions : NTRK gene fusions are rare in biliary cancers but testing is of high interest due to the emergence of possible treatment with specific TRK inhibitors. These results support the use of NGS to confirm positive IHC results during diagnostic screening.

- O08 -

RESULTS OF A FIRST PAN-TRK IHC RINGTRIAL. K. De Winne (1), L. Sorber (2), S. Lambin (1), L. Keulen (1), G. Broeckx (1), P. Pauwels (1), K. Zwaenepoel (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Pathology, [2] University of Antwerp, Belgium, CORE.

Introduction : Neurotrophic tyrosine kinase receptor (NTRK) is a family of 3 proto-oncogenes including NTRK1, NTRK2 and NTRK3 which encode TRK A, TRK B and TRK C proteins respectively. Oncogenic fusions involving the kinase domain of these genes have been identified frequently in some less common cancers and rarely in some more common cancers. Identification of NTRK fusions is important for therapeutic management, and in some tumor types for diagnosis. NTRK fusions can be detected on a molecular level by a variety of techniques like next-generation-sequencing (NGS), RNA-based assays or fluorescence in situ hybridisation (FISH). Compared to these molecular assays, the use of immunohistochemistry (IHC) provides several benefits like a quick turnaround time, use of less tissue, lower cost and wide availability.
Aim : Because of the limited experience with tyrosine kinase receptor (TRK) gene fusion, a Belgian ring trial for TRK immunohistochemistry (IHC) staining was organised by the pathology department of Antwerp University Hospital. The trial was conducted between January and July 2019 with a total of 9 participating laboratories and aimed to harmonize pan-TRK IHC staining protocols and pan-TRK IHC interpretation.
Methods : The first and last slides of six selected cases were stained for TRK using the VENTANA pan-TRK Assay (clone EPR17341) on the Benchmark Ultra platform. Each participating laboratory received two unstained slides and was asked to return one TRK–stained slide per case and to report the protocol used and their interpretation. One site participated with two different protocols. The stained slides were evaluated by two designated pathologists. The results of a comparative study evaluating the IHC interpretations from the in-house pathologists of the different laboratories and those obtained from the trial-designated pathologists were communicated to the participating laboratories.
Results : Two different clones were used during the ring trial : A7H6R (Cell Signaling) and EPR17341 (Abcam/Ventana). The VENTANA pan-TRK Assay (clone EPR17341) on the Benchmark Ultra platform was most popular and used by 40% of the labs. The remaining in-house protocols used EPR17341 in its concentrated form (abcam) or A7H6R (Cell Signaling). Overall, 7 protocols achieved a sufficient performance mark and 3 labs were advised to further optimise the protocol. Interpretation of panTRK IHC proofed to be challenging in cases with physiological TRK expression. In addition, depending on the NTRK fusion partner, the staining can vary strongly in both intensity and staining pattern.
Conclusions : To our knowledge, this is the first panTRK IHC ring trial. According to our results, the EPR17341 and A7H6R clones are both highly recommendable antibodies for panTRK IHC. Labs using the Ventana ready-to-use system based on the EPR17341 clone and using the recommended protocol settings scored best. However, given some small optimisation, all labs scored well on the technical staining and the succeeding evaluation.

- O09 -

THE ASSOCIATION BETWEEN PRIMARY TUMOUR LOCATION, BIOMARKERS AND SURVIVAL : A BELGIAN POPULATION-BASED STUDY. K. Janssens (1), G. Van Camp (1), E. Fransen (2), K. Op De Beeck (1), N. Van Damme (3), M. Peeters (4) / [1] Center of Medical Genetics, Edegemn, Belgium, Oncology, [2] University of Antwerp, Belgium, StatUa Center for Statistics, [3] Belgian Cancer Registry, Brussel, Belgium, Belgian Cancer Registry, [4] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Oncology.

Introduction : Nowadays, it is widely accepted that patients with left-sided colorectal cancer (CRC) have a significantly better prognosis than those with right-sided CRC, across all CRC stages. However, these conclusions are based on retrospective analysis of data of clinical trials. These findings need to be confirmed in population-based studies. Furthermore, the underlying mechanisms that cause this difference in survival have not been identified yet. It has been hypothesized that KRAS, NRAS or BRAF mutations and deficient mismatch repair status (MMR) can be (partially) responsible for the prognostic effect of primary tumour location (PTL).
Aim : The aim of this study is to evaluate the prognostic effect of PTL in the non-selected Belgian population and to determine the role of biomarker status (MMR status and BRAF and RAS mutational status) in this prognostic effect.
Methods : In Belgium, data on patient and tumour characteristics of all new diagnosed cancers is collected in the Belgian Cancer Registry. First, we studied the 5-year relative survival of all patients diagnosed with CRC (all stages) between 2004 and 2015. We obtained information on age, sex, stage, PTL and survival. Secondly, we investigated the effect of biomarkers on survival in a random sample of about 2,000 patients diagnosed with de novo metastatic CRC (mCRC) in 2014 and 2015. In this group, we obtained additional information on biomarker status (KRAS, NRAS and BRAF mutational status and MMR status). Cancers were classified as right-sided (RCRC) if they were located in the caecum, ascending colon, hepatic flexure and transverse colon. Left-sided colon cancer (LCRC) was defined as a lesion of the splenic flexure, descending colon, sigmoid and rectosigmoid colon. Rectal cancer was analysed as a third separate group. Patients with an overlapping lesion, a tumour with unknown localization or a tumour located at the appendix were excluded.

Results : First, we included 93,011 patients : 27,863 (30%) with RCRC, 35,815 (38.5%) with LCRC, 27,359 (29.4%) with rectal cancer and 1,974 (2.1%) with an overlapping lesion of the colon or unknown localization. Overall, the 5-year relative survival rate for patients with RCRC was 65.6% (95% CI : 64.7-66.4%) compared to 68.4% (95% CI : 67.7-69.1%) for patients with LCRC and 66.1% (95% CI : 65.4-66.9%) for patients with rectal cancer, in all stages combined. When stratified by age, sex and stage, in every subgroup, the prognosis of LCRC was better compared to RCRC, except for stage I >80-year old males, stage II >70-year old males and females, stage III >80-year old females and stage IV >80-year old males. Secondly, we studied 1,035 mCRC patients diagnosed in 2014 and 1,182 patients diagnosed in 2015. Our data showed that KRAS and NRAS mutational status did not have a significant prognostic value in our study population and did not modify the prognostic effect of PTL. BRAF mutational status had a significant impact on survival ($p = 0.00107$), but did not modify the prognostic effect of PTL. We found a strong association between location and MMR ($p=4.4E-6$), with the deficient MMR status being more frequent among the RCRC patients. Due to this multicollinearity, the main effect of MMR status is not significant in a Cox Proportional Hazard model that includes location as covariate. Across all models, mean survival time was shorter in the right-sided mCRC.
Conclusions : This population-based study confirms in a real-life setting that relative survival is significantly higher in patients with LCRC compared to RCRC, across all stages and ages combined. However, in certain subgroups RCRC has a significantly better prognosis. Therefore, we can conclude that the prognostic effect of PTL is age and stage dependent in Belgian CRC patients. Furthermore, based on the survival rates of patients diagnosed with mCRC in 2014 and 2015, we can conclude that in mCRC left-sided tumours are associated with a better survival than right-sided tumours, regardless of RAS and BRAF mutational status or microsatellite instability. This corresponds with findings of previous research. Further research should focus on identifying the underlying complex molecular mechanisms that cause this difference in survival between left-sided and right-sided CRC.

- O10 -

DEVELOPMENT AND EXTERNAL VALIDATION OF A PROGNOSTIC MODEL BASED ON 18F-FDG PET/CT METABOLICALLY ACTIVE TUMOR VOLUME AND EARLY METABOLIC RESPONSE FOR OUTCOME PREDICTION IN METASTATIC COLORECTAL CANCER UNDER FIRST OR LAST LINE TREATMENT. E. Woff (1), A. Hendlisz (2), L. Salvatore (3), F. Marmorino (4), D. Genovesi (5), G. Critchi (1), T. Guiot (1), L. Ameye (6), M. Paesmans (6), P. Flamen (1) / [1] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Nuclear Medicine Department, [2] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Medical Oncology Department, [3] Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, Medical Oncology Department, [4] Azienda Ospedaliera Universitaria Pisana, Pisa, Italy, Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, [5] Fondazione Toscana "Gabriele Monasterio", Pisa, Italy, Nuclear Medicine Department, [6] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Data centre.

Introduction : Metastatic colorectal cancer (mCRC) still holds a poor prognosis, with 5-y survival rates less than 15%, despite significant improvements over the last 15 years notably with the introduction of new targeted drugs and their combination with cytotoxic chemotherapies. Nevertheless, significant differences in terms of survival among patients are well-known. In that context, prognostic biomarkers are urgently needed to improve patient stratification and thus facilitates treatment decision making.
Aim : This study aimed to develop and validate a model integrating whole-body metabolically active tumor volume (WB-MATV) and early metabolic response (mR) among clinical prognostic factors in metastatic colorectal cancer patients.
Methods : The development cohort included chemorefractory mCRC patients enrolled in two prospective Belgian multicenter non-randomized trials evaluating multikinase inhibitors as last line of treatment. The validation cohort prospectively included mCRC patients from one Italian center treated with chemotherapy and bevacizumab as first line. Baseline WB-MATV was defined as the sum of metabolically active volumes of all target lesions identified on the baseline 18F-FDG PET/CT. Early metabolic non-responder (mNR) patients were identified when at least one target lesion showed no significant decrease of SUVmax (<15%). Univariate analyses for overall and progression-free survival (OS/PFS) were performed to assess the prognostic values of WB-MATV and early mR and multivariate analyses to assess their prognostic independency along with clinical factors (age, gender, BMI, ECOG PS, and KRAS status).
Results : WB-MATV, early mR, and clinical factors were evaluable respectively in 191 and 94 patients of the development and validation cohorts. In univariate analyses, baseline WB-MATV and early mR were strongly related to outcome (OS/PFS) in both cohorts. Multivariate analyses identified in the development cohort four independent negative predictors for OS (high WB-MATV, early mNR, BMI<25, poor PS) and two for PFS (high WB-MATV and early mNR), and in the validation cohort two for OS (high WB-MATV, early mNR) and PFS (high WB-MATV, early mNR). A model combining baseline WB-MATV and early mR allowed to identify three risk groups for OS and PFS respectively with different median OS/PFS in the development (12.1 vs 6.7 vs 3.8 months for the low, intermediate and high-risk groups; $p<0.001$ for OS and 4.9 vs 2.9 vs 1.3 months; $p<0.001$ for PFS) and validation cohorts (40 vs 25.3 vs 15.7 months; $p<0.001$ for OS and 15.3 vs 10.6 vs 7.7 months; $p<0.001$ for PFS).

Conclusions : This study demonstrates the effectiveness of combined baseline WB-MATV and early mR as prognostic biomarkers for OS/PFS in mCRC, independently of patients' treatment. As independent predictors of outcome, combining these biomarkers allowed to improve risk stratification for OS and PFS in both the development and validation cohorts.

- O11 -

SARCOPENIA AS A PROGNOSTIC FACTOR IN PANCREAS CANCER PATIENTS RECEIVING NAB-PACLITAXEL+ GEMCITABINE : PRELIMINARY RESULTS OF 31 FIRST PATIENTS. A. Ram (1), C. Vandeputte (2), A. Hendlisz (2), B. Vos (3) / [1] Chirec, Braine-l'Alleud, Belgium, Oncology, [2] Institut Jules Bordet, Belgium, Gastro Intestinal Oncology, [3] Chirec, Braine-l'Alleud, Belgium, Gastroenterology.

Introduction : Body composition is known to be an important prognostic factor in oncology. Sarcopenia is a depletion of skeletal muscle mass, leading to adverse outcomes. Therefore, CT scan-based body composition assessment is a promising research tool in oncology. For cancer patients, sarcopenia has been associated with shortened survival and chemotherapy toxicity.
Aim : The purpose of this study is to assess the effect of sarcopenia in patients with metastatic or locally advanced pancreas cancer receiving Nab-Paclitaxel + Gemcitabine.
Methods : A retrospective study was performed in monocentric hospital group. Pancreas cancer patients receiving Nab-Paclitaxel+ Gemcitabine treatment were included. Patients who meets criteria for this treatment were metastatic patients or locally advanced unresectable patients. Muscle index was measured by computerized tomography and sarcopenia was defined using a published cut-off point. Clinical data were collected from patient's files including sex, age, CA19-9 and albumin serum levels, height, weight and BMI. Patients were separated in two groups : patients who completed a cycle of treatment and patients who did not. A cycle of treatment was defined by 3 cures every 28 days. Causes of non-completion includes death, progression of the disease or drug toxicity.
Results : Thirty-one patients were included : 20 (64.5%) men and 11(35.5%) women. 23 patients (74.2%) had metastatic disease and 8 (25.8%) patients had locally advanced disease. Cut-off value of skeletal muscle index to define sarcopenia was 55 cm^2/m^2 (men) and 39 cm^2/m^2 (women). 82.2% of patients were classified as sarcopenic based on the CT scan analysis. Median value of muscle index was 43.93 (29.86-53.78). Only 1 % of sarcopenic patients had a BMI <18.5% and 47.8% of sarcopenic patients had an albumin serum level <35g/L. Pre-treatment Ca19-9 measurement was available for 100% of the patients with a median value of 1377 (2-10000) U/ml. Thirty-three percent of patients did not complete the first cycle of treatment. 62.5% of those patients were sarcopenic. 90% of them died with a median overall survival time of 3 months. No correlation between sarcopenia and treatment completion could be statically demonstrated because of the lack of patients in the non sarcopenic (5 patients) group.
Conclusions : This study showed a high prevalence of sarcopenia in metastatic/ locally advanced pancreas cancer patients. Because of the lack of patients in non sarcopenic group, no correlation between sarcopenic patients and treatment completion could be established. However, high prevalence of sarcopenia may play a role in poor prognosis in pancreatic cancer. CT scan-based body composition assessment is a promising research tool in oncology. BMI and albumin serum level measures seem to underestimate numbers of malnourished patients. Larger sample size studies are needed to evaluate the role of sarcopenia in pancreas cancer.

- O12 -

IMMUNOTHERAPY AS SECOND-LINE TREATMENT IN GRADE 3 NEUROENDOCRINE CARCINOMAS : A PROSPECTIVE CASE SERIES FROM AN ENETS CENTER OF EXCELLENCE. T. Vandamme (1), L. De Backer (2), J. Van Den Brande (2), B. Op De Beeck (2), A. Driessen (2), M. Simoens (3), W. Demey (4), H. Prenen (2), M. Peeters (2), W. Lybaert (5) / [1] Universiteit Antwerpen / Antwerp University Hospital, WILRIJK (Antwerpen), Belgium, NETwerk, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, NETwerk, [3] ZNA Jan Palfijn, Merksem, Belgium, NETwerk, [4] KLINA, Brasschaat, Belgium, NETwerk, [5] AZ Nikolaas, Sint-Niklaas, Belgium, NETwerk.

Introduction : Metastatic WHO grade 3 extra-pulmonary neuroendocrine carcinomas (EP-NEC) have a poor prognosis and optimal treatment after first-line platinum-etoposide chemotherapy remains unclear. A recent, small phase II study combining ipilimumab and nivolumab showed promising results.
Aim : Evaluation of immunotherapy in NETwerk, an ENETS Center of Excellence, as new treatment option in EP-NEC.
Methods : Patient characteristics of all EP-NEC, discussed at the NET specific MDT (NET MDT), were prospectively recorded between August 2018 and November 2019. Progression-free survival (PFS) of patients receiving immunotherapy was calculated.
Results : To 9 of the 76 EP-NEC patients discussed at the NET MDT within the inclusion period, immunotherapy was proposed after first-line platinum-etoposide treatment. Two patients died before start of therapy due to rapidly progressive disease. Primary tumor location in the 7 patients receiving immunotherapy was bladder (N=3), pancreas (N=2), esophagus (N=1) and unknown (N=1). All patients were metastatic at the start of treatment and had a mean age of 65 ± 17 years. The median Ki-67 was 90% with both small-cell (N=5) and large-cell (N=2) morphology. Administered drugs

were pembrolizumab (N=3), nivolumab (N=1), ipilimumab-nivolumab (N=1), atezolizumab (N=1), and atezolizumab-bevacizumab (N=1) without severe adverse events. Median PFS was 6.57 months (95% CI 4.34 months – NR) with objective response in 4 patients. In two patients, treatment is ongoing.
Conclusions : Immunotherapy in high grade NENs is an upcoming new treatment option to be considered after first-line platinum-etoposide chemotherapy. The treatment is well tolerated and partial responses can be seen. PFS showed promise in this hard-to-treat population. Prospective studies in a larger NEC population with focus on immune markers are needed.

- O13 -

AL18F-NOTA-OCTREOTIDE PET IMAGING OF THE SOMATOSTATIN RECEPTOR : BIODISTRIBUTION, DOSIMETRY AND FIRST COMPARISON WITH 68GA-DOTATATE IN NEUROENDOCRINE TUMOUR PATIENTS. E. Pauwels (1), F. Cleeren (2), T. Tshibangu (2), M. Koole (1), K. Serdons (1), J. Dekervel (3), E. Van Cutsem (3), C. Verslype (3), K. Van Laere (1), G. Bormans (2), C. Deroose (1) / [1] University Hospitals Leuven, Leuven, Belgium, Nuclear Medicine, [2] KU Leuven, Leuven, Belgium, Radiopharmaceutical Research, Department of Pharmacy and Pharmacology, [3] University Hospitals Leuven, Leuven, Belgium, Digestive Oncology.

Introduction : Implementation of 68Ga-labeled somatostatin analogue (SSA) PET, the current standard for somatostatin receptor imaging, is often hampered by practical, regulatory and economic challenges related to 68Ge/68Ga-generators. Recently, the 18F-labeled SSA, Al18F-NOTA-octreotide (Al18F-OC), has been introduced as a potential promising alternative. The use of fluorine-18 offers several logistic advantages, such as higher production yield and longer half-life, also allowing for centralised production and distribution to distant PET centres. Furthermore, the shorter positron range of fluorine-18 could improve spatial resolution on modern PET cameras.
Aim : To assess the dosimetry of Al18F-OC in healthy volunteers and perform a first comparison of the biodistribution, lesion targeting and tumour uptake of Al18F-OC and 68Ga-DOTATATE in neuroendocrine tumour (NET) patients.
Methods : Six healthy volunteers (2M/4F; age 20-57 years) and six NET patients (5M/1F; age 48-74 years) were included. Patients had a routine clinical 68Ga-DOTATATE PET prior to the study scan (interval : 14-71 days). All subjects were injected with an IV bolus of 4 MBq/kg Al18F-OC. For healthy volunteers, 11 serial whole-body PET scans were acquired, from moment of tracer injection up to 90 minutes post-injection (PI). At 150 minutes and 300 minutes PI a 12th and 13th PET/CT were acquired. Patients underwent a whole-body PET/CT scan at 60, 90 and 180 minutes PI. For dosimetric assessment, all source organs showing relevant activity were delineated on the PET images, with CT guidance. Time-integrated activity for each source organ was determined by integrating the time-activity curves. Absorbed organ doses and effective dose were calculated using OLINDA/EXM. Biodistribution and tumour uptake were determined by measuring mean standardized uptake values (SUVmean) in normal organs and SUVmax in tumour lesions, respectively. Tumour-to-background ratios (TBR) for liver, bone and lymph node lesions were calculated, using normal liver, bone and gluteal muscle as background, respectively. A lesion-by-lesion analysis was performed and the detection ratio (DR), defined as the fraction of lesions detected was determined for each tracer and compared.
Results : The highest dose was received by the spleen (0.159±0.062 mGy/MBq), followed by the urinary bladder wall (0.135±0.046 mGy/mBq) and kidneys (0.070±0.018 mGy/MBq), in accordance with known specific uptake in the spleen and renal excretion of the tracer. The effective dose was 22.4±4.4 μSv/MBq, which is comparable to 18F-FDG. Biodistribution of Al18F-OC compared to 68Ga-DOTATATE, showed that uptake was similar, but overall somewhat lower with Al18F-OC in most organs. Most strikingly, uptake of 68Ga-DOTATATE was 4 to 6-fold higher in the salivary glands, compared to Al18F-OC ($p<0.001$). Mean tumour SUVmax was significantly lower for Al18F-OC (e.g. 12.3±6.5 at 2h PI vs. 18.3±9.5; $p=0.03$) but increased as a function of time after injection. However, no significant differences were found in TBR (e.g. 9.8±6.7 at 2h PI for Al18F-OC vs. 13.6±11.8 for 68Ga-DOTATATE; $p=0.26$). Mean TBR with Al18F-OC at 2h PI vs. 68Ga-DOTATATE was 4.5±3.2 vs. 4.1±3.4 for liver metastases, 7.5±5.2 vs. 9.0±8.4 for bone metastases and 27.1±21.7 vs. 36.5±28.3 for lymph nodes (all non-significant). In total, 242 lesions were detected with an overall DR that was high and comparable for both tracers (86.0% for 68Ga-DOTATATE vs. 90.1% for Al18F-OC at 2h PI; $p=0.68$). With 68Ga-DOTATATE, only liver lesions were missed, whereas Al18F-NOTA-octreotide missed mainly bone lesions. The DR for Al18F-OC was significantly lower at 60 minutes PI, compared to 120 and 180 minutes PI ($p<0.001$). These data suggest that PET images should preferably be acquired at least 120 minutes PI.
Conclusions : Al18F-OC shows favourable characteristics, in terms of dosimetry, biodistribution and lesion targeting in NET patients. Further head-to-head comparison is warranted to validate Al18F-OC as a clinical alternative for 68Ga-labeled SSA PET.

- O14 -

TREATMENT MANAGEMENT OF RECTAL NEUROENDOCRINE NEOPLASMS IN BELGIUM. F. De Maeyer (1), M. De Man (2), S. Ribeiro (2), S. Carton (3), P. Cuyle (3), T. Vandamme (4), C. Verslype (5), P. Demetter (6), I. Borbath (7), N. Van Damme (8), L. Van Eycken (8), A. Hoorens (9), K. Geboes (2) / [1] AZ Sint-Elisabeth, Zottegem, Belgium, Gastro-enterology, [2] UZGent, Gent, Belgium, Gastro-enterology, [3] Imeldaziekenhuis, Bonheiden, Belgium, Gastro-

enterology, [4] Ziekenhuis Netwerk Antwerpen, Belgium, Gastro-enterology, [5] UZ Leuven, Leuven, Belgium, Gastro-enterology, [6] Institut Jules Bordet, Brussels, Belgium, Gastro-enterology, [7] UCLouvain, Belgium, Gastro-enterology, [8] Belgian Cancer Registry, Brussel, Belgium, Belgian Cancer Registry, [9] UZGent, Gent, Belgium, Pathology.

Introduction : Rectal neuroendocrine neoplasms (rNEN) are considered rare and are subdivided in well differentiated neuroendocrine tumors (NET), grade 1, 2 or 3 and poorly differentiated neuroendocrine carcinoma (NEC). A treatment algorithm is suggested by the European Neuroendocrine Tumor Society (ENETS), based on WHO grade (KI 67 index) and tumor size with a pivotal role for endoscopic ultrasound (EUS).
Aim : To investigate the management of rNEN in Belgium.
Methods : In Belgium, data on patient and tumor characteristics of all new diagnosed cancers is collected in a national and population-based cancer registry, the Belgian Cancer Registry (BCR). All rNEN diagnosed between 2004 and 2015 were reviewed, focusing on clinicopathological data including tumor size, Ki 67, grade of differentiation, lymphovascular or perineural invasion, muscularis propria invasion and margin status. Whenever possible, tumors were re-classified according to the latest update of the WHO 2019 classification. In order to have an idea about the treatment management (EUS, endoscopic and/or surgical resection performed within one year before to one year after the incidence date), the clinicopathologcial data were linked with the administrative healthcare database. The original reports of EUS and endoscopic or surgical acts were not available for review.
Results : 670 tumors in total were identified and further subclassified into 531 NET G1, 53 NET G2, 11 NET G3, 66 NEC and 9 MiNEN (mixed adenocarcinoma NEC/NET). Endoscopic ultrasound had been performed in 245 cases. Tumor size was inconsistently reported in the pathology records : 52% of NET G1 were smaller than 1cm, 14% were between 1-2cm and 1% was larger than 2cm. 30% of NET G2 were smaller than 1cm, 13% were between 1-2cm and 17% were larger than 2cm. Size was missing in most NET G3 and was > 2cm in 42% of NEC. We collected for 499 patients a total of 692 therapeutic acts : endoscopic resection, local/radical surgery. In 393 patients both the type of NEN and the size were reported. The majority (83%) were G1 NET and most of them (69%) were small (<1 cm). For the latter endoscopic resection is recommended in the absence of muscularis propria invasion. Information on therapeutic acts was collected in 226 cases. In 77% an endoscopic resection was performed, in 15% local surgery (± endoscopic resection) and 8% had advanced surgery. For NET with intermediate size (1-2 cm) local surgery is recommended. In 50% of cases, local or radical surgery was performed. Large (>2 cm) G1 and G2 NET are rather rare. Radical surgery is advocated in these cases, which was executed in 79% of cases. In NEC, surgery was performed in 59% of cases. The recommended treatment choice (endoscopic/surgical resection) was applied in the majority of the cases, according to grade and size of NET. In the group of NEC a rather high proportion of patients received an oncological resection. It is possible that a proportion of these patients received peri-operative (radio)chemotherapy, but we did not collect these data. Finally, survival rates were calculated with a minimum follow-up of 2,5 years and a maximum of 14 years. Survival rate for G1 NETs, G2 NETs, G3 NETs, NEC and MiNEN were estimated 84,9%, 56,7%, 9,1%, 9,1% and 22,2%, respectively.
Conclusions : Based on the cancer registry data, we can withhold an incidence in rNEN in Belgium of 0.7/100.000/y. The majority (79%) were well-differentiated G1 NET. Well-differentiated G2 NET and poorly differentiated NEC comprise 8 and 10% of the cases, respectively. Well-differentiated G3 NET (2%) and MiNEN (1%) are rare. Data on management could be coupled in 58% of patients. This method does not allow to distinguish between surgery for other reasons with incidental finding of a NET and treatment decisions specifically for NEN. We do not have precise data on EUS findings or endoscopic/surgical reports and lack longitudinal follow-up. Recording of treatment decisions and outcome in a register - such as the DNET registry - or through the MDT boards, with mandatary reporting to the cancer registry could provide more relevant information.

- O15 -

TREATMENT OF APPENDICEAL NEUROENDOCRINE NEOPLASMS IN BELGIUM. S. Ribeiro (1), F. De Maeyer (2), M. De Man (1), S. Carton (3), P. Cuyle (3), T. Vandamme (4), C. Verslype (5), I. Borbath (6), P. Demetter (7), N. Van Damme (8), L. Van Eycken (8), A. Hoorens (9), K. Geboes (1) / [1] UZ Gent, Gent, Belgium, Gastroenterology, [2] AZ Sint-Elisabeth, Zottegem, Belgium, Gastroenterology, [3] Imelda Hospital, Bonheiden, Belgium, Gastroenterology, [4] Netwerk, UZA, Edegem, Belgium, Gastroenterology, [5] KU Leuven, Belgium, Gastroenterology, [6] UCLouvain, Belgium, Gastroenterology, [7] Institut Jules Bordet, Belgium, Pathology, [8] Belgian Cancer Registry, Brussel, Belgium, Register, [9] UZ Gent, Gent, Belgium, Pathology.

Introduction : Appendiceal neuroendocrine neoplasms (aNEN) are rare tumors. Right hemicolectomy should be offered to all patients with appendiceal neuroendocrine tumors (aNET) larger than 2cm. It is suggested to advice right hemicolectomy in patients with grade (G) 2 NET. In patients with a tumor size between 1 and 2 cm, right hemicolectomy should be discussed based on certain risk factors. The evidence for some of these advices is weak, because historical epidemiological data tend to be incomplete and because classification systems have changed over the recent years.
Aim : We aimed to have correct and complete epidemiological data on the incidence and type of aNEN in Belgium, specifically regarding the indication for right hemicolectomy and the incidence of pathological lymph nodes in these tumors.

Methods : In Belgium, data on patient and tumor characteristics of all new diagnosed cancers is collected in a national and population-based cancer registry, the Belgian Cancer Registry (BCR). All aNEN diagnosed between 2010 and 2015 were thoroughly reviewed, focusing on clinicopathological data including size of tumor, WHO grade (Ki 67), grade of differentiation, lymphovascular invasion, specific risk factors such as location, infiltration of the mesoappendix and margin status, as well as nodal status. A significant part of pathologists in Belgium use the College of American Pathologists (CAP) guidelines. Whenever possible, tumors were re-classified according to the latest update of the WHO 2019 classification. In order to have an idea about the treatment management (right hemicolectomy performed within a one-year window of the incidence date), the clinicopathological data were linked with the administrative healthcare database. The surgical reports were not available
Results : We identified 584 NETs over a period of 6 years, corresponding to a steady incidence of 0.9/100.000/year. It was impossible to classify 185 cases correctly because of missing pathological data, and 51 patients had to be reclassified. We found 348 NET G1, 50 NET G2 and 1 NEC based on the original pathological report. We had no information on size in 18 out of 348 aNET G1 and in 3 out of 50 aNET G2 patients; 16 out of 21 NET G1 tumors with a size larger than 2cm underwent a right hemicolectomy and 6/16 (38%) had positive lymph nodes. 6 NET G2 tumors had a size larger than 2cm. They all had a right hemicolectomy and 4 (67%) of them had positive lymph nodes. Seventy-one patients had a G1 tumor between 1 and 2 cm. At least 1 of the 4 prognostic factors was missing for all these patients. Right hemicolectomy should have been discussed in at least 31 patients because of at least 1 risk factor; 21 did receive a right hemicolectomy but only 1 of them had positive lymph nodes. Fifteen patients had a G2 tumor between 1 and 2 cm. Only 1 of these patients had all the risk factors reported. 9 of them underwent right hemicolectomy, but none were reported to have positive lymph nodes. 1 patient (out of 26) with a NET G2 < 1cm received a right hemicolectomy and had positive lymph nodes as well as 1 G2 NET that could not be classified according to size. 5 out of 8 patients that could not be classified according to grade underwent right hemicolectomy and 2 of those had positive lymph nodes.
Conclusions : The incidence in aNEN in Belgium is 0.9/100.000/year. We have real life data on the evolution of reporting upon introduction of the new WHO grading system, with uptake in 80% of cases by 2015. 32 % of cases could not be verified for correct classification because of missing pathological data. Size is reported in the majority of cases. Most patients have NEN < 1cm. Right hemicolectomy was performed in 76% of G1 NEN >2cm and in all G2 NEN > 2cm and positive lymph nodes were found in 38% and 2/3 of cases, respectively. We do not have enough cases for a risk stratification in patients with aNEN in between 1 and 2cm : right hemicolectomy should have been discussed in at least 46 patients : 30 underwent surgery but only 1 of them had positive lymph nodes.

- O16 -

COMPARISON OF DIGESTIVE AND NON-DIGESTIVE NEUROENDOCRINE NEOPLASM PATIENT CHARACTERISTICS AND SURVIVAL IN AN ENETS CENTER OF EXCELLENCE. T. Vandamme (1), L. De Backer (2), I. Dero (3), D. Galdermans (4), P. Abrams (5), T. Rondou (6), M. Ulenaers (7), C. Mattelaer (8), M. Peeters (2), W. Lybaert (9) / [1] Universiteit Antwerpen / Antwerp University Hospital, WILRIJK (Antwerpen), Belgium, NETwerk, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, NETwerk, [3] Sint Augustinus Ziekenhuis GZA, Antwerp, Belgium, NETwerk, [4] ZNA Middelheim, Antwerpen, Belgium, NETwerk, [5] GZA Sint-Vincentius ziekenhuis, Antwerpen, Belgium, NETwerk, [6] AZ Rivierenland BORNEM, Bornem, Belgium, NETwerk, [7] AZ Rivierenland, Rumst, Belgium, NETwerk, [8] ZNA Antwerpen, Wilrijk, Belgium, NETwerk, [9] AZ Nikolaas, Sint-Niklaas, Belgium, NETwerk.

Introduction : Since 2016 both digestive neuroendocrine neoplasms (D-NENs) and non-digestive NENs (ND-NENs) cases are treated within NETwerk, an ENETS Center of Excellence.
Aim : To compare patient characteristics and overall survival (OS) data of D-NENs and ND-NENs.
Methods : Patient characteristics of all NEN discussed on the NET specific multidisciplinary tumor board (NET MDT) from April 2016 to November 2019 were prospectively recorded. Median overall survival (OS) was calculated by Kaplan-Meier statistics and compared using Cox Proportional Hazard models.
Results : Since 2016 602 unique patients are discussed at the NET-MDT, including 21% of patients with ND-NEN (N=129; M/V : 74/55) and 473 with D-NENs (M/V : 306/296). WHO neuroendocrine tumor (NET) grade 1 were found in 48% of D-NEN and 25% of ND-NEN, NET grade 2 in 23% and 12% respectively, and NET grade 3 in 2% and 1%, respectively. High-grade neuroendocrine carcinomas (NEC) were diagnosed in 16% of D-NEN and 35% of ND-NEN. Mixed neuroendocrine neoplasm (MiNEN) was seen in 3% and 1% of D-NEN and ND-NEN respectively, while 1% of D-NENs and 19% of ND-NENs were classified as “other”, mainly consisting of Merkel cell carcinomas. The treatment plan of the NET MDT was different from the local MDT in 36% of the cases of D-NEN and in 34% of the cases of ND-NEN. D-NEN had a significant longer OS when compared to ND-NEN [mOS not reached (NR, 95%CI 14,8 years – NR) vs. 14,3 years (95%CI 3,8 – NR), HR 1.55, p=0.02]. However, significance was lost when correcting for tumor grade.
Conclusions : Discussing ND-NENs and D-NENs at the NET MDT leads to treatment change, indicating an added value in both tumor categories. ND-NENs tend to be higher grade than D-NENs, reflected by a poorer OS.

- O17 -

EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL 120 MG (LAN 120 MG) IN THE TREATMENT OF CLINICAL SYMPTOMS ASSOCIATED WITH INOPERABLE MALIGNANT INTESTINAL OBSTRUCTION (IMIO). L. Duck (1), G. Demolin (2), L. D'hondt (3), C. Dopchie (4), K. Hendrickx (5), B. Lannoye (6), F. Bastin (7), D. Lossignol (8), O. Hamdan (9), V. Vandenhaute (10), W. Lybaert (11), V. De Ruyter (12), B. Regnault (13), K. Geboes (14) / [1] Clinique Saint-Pierre, Ottignies, Belgium, Oncology, [2] CHC, Liège, Belgium, Gastroenterology, [3] CHU-UCL-Namur site Godinne, Yvoir, Belgium, Oncology, [4] Centre Hospitalier de Wallonie Picarde (CHWAPI),Ttournai, Belgium, Oncology, [5] OLV Aalst, Aalst, Belgium, Gastroenterology, [6] Vivalia Libramont, Libramont, Belgium, Palliative Care, [7] CHR Verviers, Verviers, Belgium, Oncology, [8] Institut Jules Bordet, Belgium, Palliative Care, [9] CSF Chimay, Chimay, Belgium, Oncology, [10] Cliniques de l'Europe Site Sainte-Elisabeth, Uccle, Belgium, Palliative Care, [11] AZ Nikolaas, Sint-Niklaas, Belgium, Oncology, [12] IPSEN NV, Merelbeke, Belgium, Medical, [13] Ipsen, Boulogne-Billancourt, France, Medical, [14] UZ Gent, Gent, Belgium, Gastroenterology.

Introduction : Inoperable malignant intestinal obstruction (IMIO) is a severe complication in patients with gastrointestinal or gynaecological cancers. Common clinical symptoms include nausea, vomiting, and abdominal pain. Therapy for patients with IMIO aims to relieve symptoms, limit nasogastric tube (NGT) use, and improve quality of life.
Aim : Previous studies have suggested the efficacy of somatostatin in relieving obstruction-related symptoms such as nausea, vomiting and pain. However, the therapeutic use of somatostatin is limited by its short half-life. The Lanreotide Autogel (LAN) formulation is a slow-release somatostatin analogue capable of maintaining therapeutic levels up to 28 days making it more convenient for clinical use, especially in long-lasting diseases
Methods : This was a single arm, multicentre study during which patients with IMIO received one deep subcutaneous injection of LAN 120mg at day 0 (D0). Evaluations were performed on D7, D14 and D28. The primary endpoint was the proportion of responders before or at D7. Response was defined as ≤2 vomiting episodes per day (for patients without NGT at baseline) or no vomiting recurrence (after NGT removal), during at least 3 consecutive days at any time point between D0 and D7. A proportion of 30% responders was used as reference for defining statistical significance. Responders at D28 were offered a second LAN 120 mg injection and were followed up until D56.
Results : A total of 52 patients (mostly with advanced gastrointestinal or ovarian malignancies) were included at 15 Belgian sites. At baseline, 17 patients were without NGT and 35 patients had an NGT. On D7 the proportion of responders in the intention-to-treat population was 46.2%, significantly greater than the reference proportion of 30% ($p=0.0055$). Patients without NGT were solely responsible for this effect (response : 88.2% versus 25.7%). Important improvements were also seen in patients with NGT upon further follow-up : median time to response by Kaplan-Meier estimate was 9 days for the overall population, 3 days for patients without NGT and 14 days for patients with NGT ($p<0.0001$). Of the responders, 21 patients received a second injection of LAN 120 mg and all maintained responder status up through D56. Several quality of life assessments including the Edmonton Symptom Assessment System (ESAS), pain assessment using a Visual Analog Scale (VAS), and Karnofsky Performance Status (KPS) improved throughout the study. Episodes of nausea steadily decreased during both phases of the study. The safety profile of LAN 120 mg was similar to that reported in other indications. The most frequently reported adverse events were related to gastrointestinal disorders including diarrhoea and abdominal pain.
Conclusions : This study was the first using long acting LAN 120 mg in patients with IMIO and included patients with different types of cancers representing a "real life" clinical setting. Results suggest LAN 120 mg has an effect in controlling clinical symptoms in patients with and without NGT at baseline. Moreover, the maintained response throughout the longer follow-up coupled with steady improvements in quality of life assessments demonstrates LAN 120 mg could provide much needed relief to patients with IMIO due to advanced malignancies.

- O18 -

RAMUCIRUMAB FOR PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA AND ELEVATED ALPHA-FETOPROTEIN : OUTCOMES BY PRIOR LOCOREGIONAL AND PRIOR SORAFENIB TREATMENT FROM REACH AND REACH-2. I. Borbath (1), J. Llovet (2), E. Assenat (3), B. Daniele (4), C. Wang (5), R. Widau (6), K. Buelens (7), I. Nitu (8), A. Zhu (9) / [1] Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium, HepatoGastroenterology and Digestive Oncology, [2] Mount Sinai School of Medicine, New York, United States (the), Medicine, [3] St-Eloi University Hospital, Montpellier, France, Department of Medical Oncology, [4] Azienda Ospedaliera G. Rummo, Benevento, Italy, Medical Oncology Unit, [5] Eli Lilly and Company, Indianapolis, United States (the), Statistics, [6] Eli Lilly and Company, Indianapolis, United States (the), Clinical Research, [7] Eli Lilly Benelux, Brussels, Belgium, Medical Affairs, [8] Eli Lilly Romania, Bucharest, Romania, Medical Affairs, [9] Massachusetts General Hospital, Boston, United States (the), Department of Hematology/Oncology.

Introduction : Patients with localised hepatocellular carcinoma (HCC), preserved liver function, and good performance status commonly receive locoregional treatment with transarterial hemoembolization (TACE) but have high rates of recurrence and require systemic therapy. Oral multikinase inhibitors that have shown improvements in overall survival in

HCC are associated with clinically important toxicities that commonly require dose adjustment or discontinuation due to intolerance. Ramucirumab, a human IgG1 monoclonal antibody, inhibits activation of vascular endothelial growth factor receptor 2 (VEGFR2). REACH (NCT01140347) and REACH-2 (NCT02435433) studied ramucirumab in patients with HCC who progressed on or were intolerant to sorafenib, and REACH-2 only enrolled patients with baseline α-fetoprotein concentration of ≥400 ng/mL. In REACH-2 ramucirumab treatment improved OS compared to placebo (HR 0.71, [95% CI : 0.53–0.95], supporting findings in REACH patients with baseline AFP ≥400 ng/mL (HR 0.67, [95% CI : 0.51–0.90]).
Aim : Here we report outcomes by prior TACE treatment (yes vs no) as well as by reason for discontinuation of prior sorafenib (intolerance or progressive disease) in the pooled population of patients from REACH-2 and REACH (AFP ≥400 ng/mL).
Methods : Patients with advanced HCC, Child-Pugh A, Barcelona clinic liver cancer (BCLC) stage C or B disease refractory/not amenable to locoregional therapy, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1, with disease progression or intolerance to sorafenib, were randomised in REACH (1 :1) or REACH-2 (2 :1) to receive ramucirumab 8 mg/kg or placebo every two weeks. A pooled meta-analysis of patient-level data (stratified by study) from REACH-2 and REACH (AFP ≥400 mg/mL) was performed. Treatment effects are reported by prior TACE (yes vs no) and reason for sorafenib discontinuation (intolerance or progressive disease) by Cox proportional hazard model; median overall survival (OS) and progression free survival (PFS) were estimated by Kaplan-Meier method.
Results : Baseline characteristics were generally balanced between ramucirumab (n=316) and placebo (n=226) treatment arms. Overall, 179 (57%) patients in the ramucirumab arm and 123 (54%) in the placebo arm had received prior TACE, with a median of 1 treatment in both arms. Regional differences were noted, with increased prevalence and frequency of prior TACE treatment in Asia compared to Western countries (75% Japan, 70% Asia [except Japan], 39% Western countries). Efficacy was similar between TACE and non-TACE subgroups (OS interaction p-value = 0.948). In patients who received prior TACE, ramucirumab treatment improved OS compared to placebo (median 8.2 vs 5.2 months; HR 0.69, [95% CI : 0.53-0.90] and PFS (median 2.8 vs 1.5 months; HR 0.56, [95% CI : 0.43-0.72]). Similarly, in non-TACE patients, ramucirumab treatment also improved OS compared to placebo (median 7.7 vs 5.0 months; HR 0.71, [95% CI : 0.52-0.95]) and PFS (median 2.8 vs 1.6 months; HR 0.58, [95% CI : 0.43-0.79]). All patients received sorafenib as the only systemic therapeutic intervention for advanced HCC prior to study entry. Seventy patients (13%) discontinued sorafenib therapy due to intolerance and 472 (87%) patients discontinued sorafenib due to disease progression. Median durations of prior sorafenib treatment were 2.5 months for sorafenib intolerant and 4.0 months for sorafenib progressors. Efficacy was similar between intolerant and progressive patients (OS interaction p-value = 0.5801). In sorafenib-intolerant patients, ramucirumab treatment improved OS compared to placebo (median 10.2 vs 6.7 months; HR 0.59, [95% CI : 0.34-1.02]) and PFS (median 4.4 vs 1.4 months; HR 0.32, [95% CI : 0.19-0.55]). Similarly, in sorafenib-progressive patients, ramucirumab treatment also improved OS compared to placebo (median 8.0 vs 4.7 months; HR 0.71, [95% CI : 0.58-0.88]) and PFS (median 2.7 vs 1.6 months; HR 0.64, [95% CI : 0.52-0.79]). Hypertension was the most frequently reported Grade ≥3 treatment-emergent adverse event in all of the analysed subgroups and consistent with the data from each individual study.
Conclusions : Ramucirumab improved OS and PFS for patients with advanced HCC and a baseline AFP ≥400 ng/mL, irrespective of prior TACE treatment or reason for discontinuation of sorafenib. The safety profile was consistent across each subgroup compared to the intent to treat population.

BELGIAN PANCREATIC CLUB (BPC)

- P01 -

FEASIBILITY AND SAFETY OF EUS-GUIDED PLACEMENT OF FIDUCIAL MARKERS FOR STEREOTACTIC BODY RADIATION THERAPY IN PANCREATIC CANCER : A PROSPECTIVE EVALUATION. M. Figueiredo Ferreira (1), C. Bouchart (2), M. Luigi (2), L. Mans (1), Y. Gokburun (3), T. De Grez (3), M. Bali (4), J. Engelholm (5), J. Van Laethem (1), P. Eisendrath (6) / [1] Erasme University Hospital - Université Libre de Bruxelles (ULB), Bruxelles, Belgium, Gastroenterology, Hepatopancreatology and Digestive Oncology, [2] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Radiotherapy, [3] CHR, Namur, Belgium, Gastroenterology, [4] Institut Jules Bordet, Brussels, Belgium, Radiology, [5] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Radiology, [6] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology.

Introduction : In patients with high-risk/borderline resectable or locally advanced pancreatic ductal adenocarcinoma (PDAC), stereotactic body radiation therapy (SBRT) is a new potential neoadjuvant treatment option, aiming to improve curative resectability rates, local control and overall survival. The SBRT technique allows the delivery of higher equivalent biological dose to the tumor than conventional radiotherapy, particularly at the tumor/vessels interface, while reducing collateral damage to the adjacent organs. The insertion of inert radiopaque markers in or close to the tumor is a prerequisite for pancreatic SBRT, in order to precisely localize the target and track the tumor motion. Endoscopic ultrasound (EUS) placement of fiducial markers in PDAC is currently the preferred route of insertion.
Aim : The aim of this study was to assess the feasibility and safety of EUS-guided fiducial placement in our two academic centers. Moreover, we intended to co-evaluate both the technical and quality success of this technique, from the endoscopist's and radiotherapist's points of view, respectively.
Methods : We prospectively collected clinical and technical data concerning all the PDAC patients that were submitted to EUS-guided placement of fiducial markers and treated with SBRT. The procedures were performed by two experienced endoscopists, in two different academic hospitals. Patients were either under deep sedation or under general anesthesia and received antibiotic prophylaxis prior to insertion. Two types of radio-opaque markers were inserted : polymer markers (Polymark 0.8x3mm) back-loaded in a regular 19G FNA needle and gold markers delivered with a pre-loaded 22G dedicated needle (EchoTip® Ultra Fiducial Needle, Cook). Fluoroscopy was often used. "Technical success" was defined as at least one marker presumed to be inside the tumor at the end of the EUS procedure. After simulation computed tomography (CT), the number of visible markers and their location (in regards to the tumor and to each other) were assessed by the radiotherapist, who proposed a quality score including the following criteria : number of markers inside or < 1 cm from the tumor, number of markers located in the extremity of the tumor, their location in different planes, their distance from the biliary stent (if present) and the distance between the fiducials (if more than one visible marker). The score ranged from 0 to 12 points and "high quality success" was defined as a score equal or higher than 6.
Results : From February 2018 to November 2019, a total of 37 patients were enrolled. The majority were male patients (54.1%), with a median age of 60 year old (IQR 18). The mean tumor size was 25.9 mm (SD 7.7) and lesions were mostly located at the pancreatic head (70%). All the lesions were close or invading at least one vessel, except one (60% and 35% had venous and arterial vessels involvement, respectively). A total of 97 fiducials were implanted, with a median number of 3 fiducials placed per patient (range 0-4). The technical success rate was 92%, with failure of fiducials placement in 3 patients, mostly due to interposing vessels or difficulty to define the tumor limits (altered by induction chemotherapy). Adverse events were observed in three patients (8%), with 1 case of post-procedural fever, 1 case of mild acute pancreatitis and 1 case of biliary stent migration. All the patients that had fiducial markers placed could receive SBRT treatment. At pre-SBRT CT evaluation, however, there were 2 patients whose markers had migrated. From the other 32 patients, 76 % had at least 2 markers inside or less than 1 cm from the tumor and in 75% there was at least one marker located in the tumor's extremity. Nevertheless, markers placement in different spatial planes was achieved in only 56% of the cases and there were 72% with at least 2 markers were positioned too close from each other. As predefined, this resulted in a high quality success rate of 62.5%.
Conclusions : Our results contribute to demonstrate the good feasibility and security of EUS-guided fiducial markers placement, with encouraging results in terms of SBRT achievability. The radiotherapy quality score underlines factors that may improve treatment dose distribution through optimal fiducial position and highlights the way for improvement in marker delivery.

- P02 -

LONG-TERM SAFETY OF INDWELLING DOUBLE PIGTAIL STENTS FOR DRAINAGE OF PANCREATIC COLLECTIONS WITH DISCONNECTED PANCREATIC DUCT SYNDROME. P. Gkolfakis (1), A. Bourguignon (1), M. Arvanitakis (1), A. Baudewyns (1), P. Eisendrath (2), D. Blero (1), A. Lemmers (1), M. Delhaye (1), J. Devière (1) / [1] Erasme Hospital, Brussels, Belgium, Gastroenterology, [2] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology.

Introduction : Transmural indwelling double-pigtail stents (DPS) are recommended for patients with disconnected pancreatic duct syndrome (DPDS) and peripancreatic fluid collections (PFC).
Aim : To evaluate the long-term safety and efficacy of indwelling DPS.
Methods : Medical files of patients treated with transmural DPS for DPDS-associated PFC (walled-off necrosis or pseudocysts due to acute or chronic pancreatitis) and a minimum follow-up of 48 months were reviewed. Overall, early (<28 days) and late complication rates were calculated. Long-term outcomes (efficacy and collection recurrence) were assessed.
Results : From 2002 to 2014, 116 patients [86 (74.1%) men; age 48.1±15 years; 57 (49.1%) chronic pancreatitis] with complete pancreatic duct rupture confirmed by MRCP or ERCP were identified. They underwent 175 transmural drainages (150 (85.7%) transgastric access; 2 DPD deployed in 71 (40.5%) of the cases). Sixty-nine (59.4%) of the initial drained collections were pseudocysts (94.2±50mm) and the main indication was infection (55/116; 47.4%). Mean follow-up was 80.6±34.4 months. Per intervention complication rates were 20.5% (36/175); 11.4%(20/175) and 9.1% (16/178) for overall, early and late complications, respectively. Among early complications, 15/20 occurred peri-interventionally (bleeding and pneumoperitoneum) and 8 required further intervention or transfusion. Among late complications (stent-induced ulcer, bleeding, organ compression and abscess) only 2/16 required additional intervention other than stent removal. No death related to the procedure occurred. In per patient analysis, the complication rate was 1 per 21.6 patients-years of follow-up and 1 per 48.7 patients-years of follow-up regarding late complications. Migration (spontaneously or intended) of initial DPS occurred in 86/116 (74.1%) patients (42±36.7 months). Early migration (<6, <12 and <24 months) was related to an increased risk of collection recurrence ($p \leq 0.02$). At the end of follow-up endoscopic treatment was considered unsuccessful in 6/116 (0.05%) patients.
Conclusions : Indwelling DPS for DPDS are related to a low risk of long-term complications and lower risk of PFC recurrence.

- P03 -

ENDOSCOPIC ULTRASOUNDED-GUIDED RADIOFREQUENCY ABLATION FOR PANCREATIC LESION : BELGIAN EXPERIENCE. L. Monino (1), B. Ivan (1), P. Hubert (2), M. Tom (2), D. Pierre (2) / [1] Université Catholique de Louvain, Brussels, Belgium, Gastroenterology, [2] Université Catholique de Louvain, Brussels, Belgium, Gastroenterology.

Introduction : Radiofrequency ablation (RFA) allow to ablate dysplasic or neoplasic tissue thanks to thermal coagulative necrosis and immunomodulation. Recently, new devices have allowed the use of radiofrequencies guided by EUS. EUS-RFA quickly emerged as a simple technique for the treatment of benign pancreatic tumors.
Aim : We evaluated efficacy and safety of RFA to treat neuroendocrine tumor and metastatic renal cell carcinoma.
Methods : Retrospective study of consecutive case of pancreatic lesion with radiofrequency ablation between July 2018 and May 2019. EUS-RFA was performed with a 18G cooling needle.
Results : 11 patients (5 women, mean age 58+/-13 years) underwent EUS-RFA for pancreatic lesion. 13 lesions with an average size of 15.2+/-4.4 mm were treated with EUS-RFA. The indications for performing radiofrequency ablation were : nonfunctional neuroendocrine tumor (n=4), Insulinoma (n=3) and metastatic renal cell carcinoma localized to pancreas (n=4). Technical success rate for the procedure was 100%. Three adverse events were encountered (27%) : one gastric wall hematoma and two acute pancreatitis one of these complicated with a pancreatic pseudocyst managing endoscopically. At six month, among the patient with NET three had completed disappear and four a partial response (decrease size tumor>50%). At six months, among the patients with metastatic renal cell carcinoma, two had completed response, one partial response and one no response.
Conclusions : EUS-RFA appears to be an interesting treatment of neuroendocrine tumor and metastatic renal cell carcinoma localized to pancreas.

- P04 -

TREATMENT OF A LARGE WON WITH A NOVEL INSTRUMENT : THE ENDOROTOR DEN MICRODEBRIDER. E. Macken (1), M. Somers (1), H. De Schepper (1), A. Jauregui (1), S. Bouhadan (1), S. Francque (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology and Hepatology.

Walled off necrosis (WON) is a complication of an acute pancreatitis. Endoscopic treatment consists of drainage by placement of a stent, either a metal stent (lumen apposing metal stent (LAMS) or a self-expanding metal stent (SEMS)), or plastic stents (double pigtail stents). However, in case of the presence of a large amount of necrotic tissue in the cyst, the placement of stents is seldom sufficient and additional necrosectomy is necessary. Removal of the necrotic tissue can be cumbersome and time consuming because of the sticky and thick nature of the debris. Necrotic tissue is easily teared down in pieces using the grasping forceps or loop, and multiple passages with the endoscope are necessary. Moreover, solid debris will often block the stent(s). We tried the new microdebrider catheter (EndoRotor, Interscope Medical, Inc) for necrosectomy. This device can be used in a 3.2 mm endoscopic working channel to resect and remove solid debris.

We hereby present the case of a 64-year old man who presented with an acute necrotic pancreatitis with the development of a big necrotic collection with a diameter of 12 cm and compression of the stomach and duodenum. In September 2019, a Hot Axios stent (Boston Scientific, diameter 15 mm) was placed under endoscopic ultrasonography (EUS) guidance. Subsequent necrosectomies were difficult because of the adherence of the thick necrotic tissue to the wall of the cyst. A lot of debris was still present. In October 2019, two procedures with the EndoRotor were able to remove all of the necrotic tissue. Patient is doing well at the moment and CT confirmed the succesfull clearance of the necrosis and complete resolution of the cyst. The EndoRotor (Interscope Medical, Inc) is a dedicated instrument for transluminal endoscopic debridement of infected pancreatic tissue. It delivers cutting with simultaneous suction and irrigation through standard flexible endoscopes, in this way enabling debridement with the scope remaining in the cyst without the need for multiple passages as is the case with the use of a loop or grasping forceps. The debrided material is automatically collected. The cutter window can be rotated 360 ° to optimize access. The EndoRotor is used with a compact EndoRotor Console with a cutter speed between 1000 rpm and 1750 rpm and an irrigation flow rate of 5 ml/min. In 2018, two patients were treated with the EndoRotor in Rotterdam with complete removal of the necrotic tissue (1) and during the United European Gastroenterology (UEG) week Schlag presented a poster with the interim results of 12 patients who underwent microdebrider-assisted necrosectomy (2). No adverse events were reported, one patient died not attributed to microdebrider use. A 96 % reduction in size of the necroma on CT at 21 days post-initial proceure was reported. By our knowledge, this is the first use of the EndoRotor system in Belgium. We think this is a valuable technique in the case of severe WON when placement of a stent is not sufficient and additional necrosectomy is necessary. 1. van der Wiel S et al, The EndoRotor, a novel tool for the endoscopic management of pancreatic necrosis. Endoscopy 2018; 50 : E240-E241
2. Schlag C et al, Endoscopic microdebrider-assisted necrosectomy for walled-off pancreatic necrosis – a prospective international multicenter feasibility study. Poster UEG week 2019

- P05 -

AUTOIMMUNE PANCREATITIS : BEWARE OF MALIGNANCIES. C. Dumont (1), I. Borbath (1), C. Dragean (2), M. Komuta (3), P. Deprez (1) / [1] Cliniques universitaires Saint-Luc, Brussels, Belgium, Gastroenterology, [2] Cliniques universitaires Saint-Luc, Brussels, Belgium, Radiology, [3] Cliniques universitaires Saint-Luc, Brussels, Belgium, Pathology.

Background : Autoimmune pancreatidis (AIP) is a rare chronic inflammatory disease. AIP type 1 belongs to the spectrum of igG4-related diseases. Manifestations and presentation of the AIP type 1 can mimic adenocarcinoma with pancreatic mass and obstructive jaundice. Evolution in clinical, histological and radiological criteria (International Consensus Diagnostic Criteria for Autoimmune Pancreatitis) allows easier diagnostic. Few articles and studies try to show a correlation between AIP or other Ig4-related diseases and extra-pancreatic neoplasia like gastric, lung and prostate cancer.
Case-report : In September 2019, a 58-year-old man, from Romania, well-known from surgical department for a recent laparoscopic total gastrectomy because of diffuse high-grade carcinoma and adenocarcinoma in situ, was admitted in the Emergency department for asthenia and jaundice. Laboratory tests showed cholestasis and hyperbilirubinemia (6.5 mg/dl). Abdominal CT and RMN confirmed a pancreatic head tumor (24x20x17 mm) with biliary duct dilatation. EUS-guided biopsies were performed with an FNB needle. Histology did not describe malignant patterns but included inflammatory cells with diffuse lymphoplasmocytic infiltration, fibrosis and obliterative venulitis. After exclusion of other diseases, a diagnostic of AIP type 1 was retained based on a positive plasma-IgG4 serology and histology. Tumor markers (CEA and CA19.9) were negatives. 18F-FDG-PET did not reveal other organs involvements. The patient was treated with corticosteroids.
Conclusion : We report a rare case of concomitant presentation of gastric neoplasia and AIP. Few single-center studies, case-reports and reviews of literature begin to support a shared pathogenesis between both entities. These articles state that malignancy appears just before or within one year after AIP diagnostic. It could become an interesting concept to start considering AIP as a paraneoplasic syndrome.

- P06 -

GROOVE PANCREATITIS. J. Brant (1), S. Sweetser (2) / [1] Mayo Clinic, Rochester, United States (the), Internal medicine, [2] Mayo Clinic, Rochester, United States (the), Gastroenterology.

Case Report : A 65-year-old man presented to the hospital for worsening abdominal pain and postprandial nausea and vomiting. Medical history was notable for chronic alcohol abuse, a solitary kidney after childhood nephrectomy for a Wilm's tumor, and diabetes. His abdominal pain was described as diffuse occurring intermittently over the previous 2 months with radiation to the back. On physical exam the patient endorsed mild epigastric tenderness that did not significantly worsen with palpation. Laboratory work up demonstrated a mildly elevated lipase of 95 U/L (reference range 12–61 U/L) and otherwise normal liver biochemistries. Right upper quadrant ultrasound demonstrated mildly dilated intrahepatic ducts as well as a mildly dilated common bile duct measuring up to 8mm in diameter. Adjacent to the distal portion of the common bile duct was a heterogeneous mass-like area felt to represent a soft-tissue mass. Computed

tomography of the abdomen with intravenous contrast revealed cystic lesions within the uncinate process of the pancreas with multiple peripancreatic fluid collections and an underlying IPMN. Additionally identified was a diffusely fluid-filled dilated stomach with inflammatory changes surrounding the duodenum felt to likely be reactive inflammation from pancreatitis resulting in a functional gastric outlet obstruction (Figure 1). The patient subsequently underwent upper endoscopy for evaluation of gastric outlet obstruction with identification of acquired duodenal stenosis with two areas of intrinsic moderate stenosis observed in the first and second portions of the duodenum and an associated component of extrinsic compression in the first portion of the duodenum. A healed scar was observed in the second portion of the duodenum and edematous and inflamed mucosal changes in the first portion (Figure 2). Biopsy obtained showed histopathologic evidence of reactive inflammatory changes within the duodenal mucosa without evidence of malignancy. A nasojejunal tube and nasogastric tube were placed endoscopically for nutritional support and gastric decompression. To further exclude malignancy, an endoscopic ultrasound with pancreatic biopsy was considered however due to the degree of duodenal stenosis and lack of a discrete focus for biopsy the procedure was deferred. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were measured within normal limits at 2.6 ng/mL and 17 U/mL, respectively. Overall, the patient's clinical history, imaging and endoscopic findings were felt to be consistent with groove pancreatitis. The patient was discharged from the hospital with a planned trial of 4 weeks of conservative medical management (enteral feeding, analgesics, and proton-pump inhibitor) allowing for improvement of pancreaticoduodenal inflammatory changes. Follow up with gastroenterology and surgery was planned to determine further management with consideration for pancreaticoduodenectomy.

Groove pancreatitis is a rare entity of segmental pancreatitis first described in the 1970s characterized by inflammation and fibrosis of the pancreaticoduodenal groove containing the pancreatic head, duodenum and common bile duct. Groove pancreatitis most commonly occurs in males aged 40-60 with a history of chronic alcohol and/or tobacco abuse. Clinical features include an often chronic and relapsing course of symptoms characterized by abdominal pain, nausea and vomiting. In patients with associated duodenal stenosis postprandial vomiting is often a predominant feature. Similarly, patients with common bile duct stenosis may develop obstructive jaundice. Laboratory values are often nonspecific with only slight elevations in liver biochemistries or pancreatic enzymes. The pathophysiology of groove pancreatitis is complex and felt to be complex and related to physiologic and anatomic factors resulting in inflammatory exudate, cyst formation and deposition of fibrotic tissue. Given the overlapping features of pancreatic adenocarcinoma and groove pancreatitis including risk factors and clinical presentation it is imperative that pancreatic adenocarcinoma is excluded before establishing the diagnosis. In contrast to pancreatic adenocarcinoma, patients with groove pancreatitis do not have significant elevations in tumor markers such as CEA or CA 19-9. CT and MRI imaging along with EUS with biopsy can assist with differentiating to two entities, however it should be noted that the possibility of a sampling error may prevent a negative biopsy from excluding malignancy. Groove pancreatitis can be managed with conservative medical therapy; however, in patients with severe clinical symptoms or when malignancy cannot be excluded surgery is often required. Surgical treatment typically involves pancreaticoduodenectomy via Whipple procedure or pylorus-preserving pancreaticoduonectomy.

- P07 -

NIVOLUMAB-INDUCED PANCREATITIS. L. Janssens (1), S. Patel (1), N. Takahashi (2), S. Majumder (3) / [1] Mayo Clinic, Rochester, United States (the), Internal Medicine, [2] Mayo Clinic, Rochester, United States (the), Radiology, [3] Mayo Clinic, Rochester, United States (the), Gastroenterology and Hepatology.

Case Report : A 38-year-old woman with a history of metastatic malignant melanoma treated with nivolumab presented with waxing and waning epigastric pain over the past four months. She denied any symptoms of nausea, vomiting, diarrhea, constipation or weight loss. Laboratory studies (normal value ranges in parenthesis) revealed hemoglobin 12.5 g/dL (11.6-15), ALT 15 U/L (7-45), AST 20 U/L (8-43), AP 60 U/L (35-104), total bilirubin 0.3 mg/dL (<= 1.2), lipase 439 U/L (12-61), amylase 136 U/L (26-102) and creatinine 0.69 mg/dL (0.59-1.04). Calcium, triglyceride and IgG4 levels were normal. Computed tomography (CT) scan of the abdomen showed heterogeneous parenchymal enhancement in the pancreatic body that was PET-avid (Figure 1A). Endoscopic ultrasound (EUS) performed to rule out pancreatic metastasis demonstrated a bulky pancreatic body and tail with hypoechoic rind (Figure 1B) but otherwise unremarkable pancreatic duct and common bile duct. EUS-guided pancreatic biopsy showed focal mild inflammation characterized by a neutrophilic infiltrate and fibrosis with no IgG4-positive plasma cells (Figure 1C). Her symptoms persisted and serum lipase levels remained persistently elevated. Follow-up CT abdomen 2 months after index presentation demonstrated mildly decreased but persistent pancreatic enhancement diffusely in the pancreatic body, head and neck with mild inflammation of peripancreatic fat in these same areas (Figure 1D). The patient was diagnosed with nivolumab-induced pancreatitis. She was treated with prednisone 40 mg daily for 4 weeks followed by a slow taper by 5 mg every week over total treatment duration of three months. Her symptoms resolved within two weeks of steroid initiation and her lipase levels normalized to 26 U/L (12-61) at the first recheck 6 weeks after initiation of steroids.

Nivolumab is an anti-PD-1 antibody that is used for the treatment of metastatic melanoma and non-small cell lung cancer. Due to its mechanism of action that involves inhibition of effector T-cells, nivolumab can induce immune-related adverse events. Nivolumab-induced pancreatitis is a rare but recognized side effect of this medication. Similar to our

patient, previous reports have suggested that the radiographic appearance of nivolumab-induced pancreatitis resembles autoimmune pancreatitis (AIP). The appropriate treatment regimen for nivolumab-induced pancreatitis is currently unclear, with reports showing resolution after interventions ranging from discontinuation of nivolumab to requiring high doses of steroids (1-2 mg/kg) and even additional immunosuppressive treatment with mycophenolate mofetil. In our case, we initially stopped the offending drug and, due to continued clinical and biochemical derangements, treated with oral steroids following our standard protocol for AIP. In our patient initial imaging had demonstrated inflammatory changes (Figure 2A), follow-up imaging demonstrated resolution of inflammatory changes but significant pancreatic atrophy mimicking the radiologic response of treated AIP (Figure 2B). The long-term natural history of nivolumab-induced pancreatitis including the risk of pancreatic exocrine and endocrine insufficiency remains unknown and warrants further study.
We conclude that nivolumab-induced pancreatitis has radiologic similarities with AIP and in our patient was steroid-responsive at standard prednisone dosing used to treat AIP. Post-treatment pancreatic atrophy suggests that these patients should be monitored for future development of pancreatic exocrine and endocrine insufficiency.

- P08 -

OPIOD RELATED SPHINCTER OF ODDI DYSFUNCTION CAUSING DOUBLE DUCT SIGN IN A PATIENT WITH GASTRIC BYPASS. C. Salem (1), C. Musala (2), G. Rasschaert (2), L. Duez (2), T. Serste (2), P. Eisendrath (2) / [1] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology, [2] CHU Saint-Pierre, Brussels, Belgium, Hepato-Gastro-Enterologie.

Introduction : Chronic morphine abuse has been reported as a rare cause of concomitant dilation of both pancreatic (PD) and common bile duct (CBD), known as the double duct sign (1,2,3). Endoscopic ultrasound (EUS) findings of this rare entity have been occasionally reported (4). We report a 59-year-old man recently diagnosed with double duct sign, with a history of chronic opioid abuse evaluated for episodes of abdominal pain and general status alteration. The patient has a history of bypass surgery, that made the diagnosis more challenging. In order to rule out malignancy, EUS-directed trans gastric intervention (EDGI) was performed to enable pancreatic head EUS and potential ERCP.
Case report : This is a new report of a 59-year-old man admitted to the hospital for several episodes of abdominal pain and general status alteration in May 2019. The patient is a chronic morphine consumer with an average of 300mg per day in a context of fibromyalgia. He was operated of a gastric bypass for morbid obesity in 2017. The patient has no history of alcohol and tobacco consumption. An earlier Computed Tomography scan (CT scan) from two month ago, revealed biliary and pancreatic duct dilation (10mm and 9 mm respectively). The patient didn't come back for planified workup. During current hospitalization, new CT scan and Magnetic resonance cholangiography (MRCP) were performed and revealed worsening duct dilation (17mm and 19mm respectively) without evidence of an obstructive tumor or lithiasis. Lab analysis showed a new cholestasis onset : alkaline phosphatase 155 U/L, GGT 72 U/L, serum bilirubin of 0.2 mg/dL, aspartate aminotransferase of 20 U/L and alanine aminotransferase of 24 U/L. Endoscopic ultrasound (EUS) revealed simultaneous dilatation of the CBD and PD (double duct sign) with anechoic lumens of both the ducts. Pancreatic and periampullary region exploration was limited due to post bypass anatomy. After a multidisciplinary discussion and in the concern of excluding a periampullary tumor, it was decided to perform an EUS trough an artificial gastro-gastric anastomosis, eventually combined with a biliary sphincterotomy and stenting. At the first stage, using a therapeutic echo-endoscope, a lumen apposing metal stent (LAMS) of 20mm diameter with electrocautery delivery system was inserted between the proximal jejunum and the excluded stomach. The trans-anastomotic EUS was perform 28 days after the LAMS implantation. It revealed biliary and pancreatic duct dilation up to the papilla, in a context of pancreas divisum with some stigmas of chronic pancreatitis, absence of tumor or other cause of obstruction. Both procedures were concluded without any complications. ERCP wasn't finally realized given the favorable evolution of cholestasis. These results and spontaneous evolution led us to a suspicious diagnosis of chronic sphincter dysfunction. Patient was readmitted to our unit 35 days post procedure, for prosthesis removal. He had no symptoms and stable liver function test. He regained 6 kilos of weight since his last admission with an actual BMI of 23.5. The Axios prothesis was removed under general anesthesia and a double pigtail was inserted without particular difficulties.
Discussion : Several studies showed that chronic opiate use may responsible of common bile duct dilation by increasing sphincter of Oddi tonicity and resulting in secondary SOD (1,2,3,5). EUS is an important part the work-up in case of bile duct dilation to exclude small malignant lesion in the ampullary area (6). Beside the report of new case with suspected morphine abuse related double duct sign, this case illustrates also the problem of access to pancreatic head in a modified anatomy. EDGI is a recent technique to gain access to the excluded stomach in order to facilitate conventional pancreatic head EUS exploration and ERCP (6,7). Previous case series showed that EDGI is associated with high technical and clinical success, and with insignificant risk of short- and long-term adverse events (6,7). Opiate abuse is an uncommon cause of SOD and a prolonged history of opiate addiction must be sought in patients with unexplained biliary dilatation or dual duct after adequate workup to evaluate potential underlying pathologies (5,6).

BELGIAN WORKING GROUP ON DIGESTIVE PATHOLOGY

- R01 -

LOW-GRADE DYSPLASIA IN BARRETT'S ESOPHAGUS IS DOWNGRADED IN HALF OF THE CASES AFTER SYSTEMATIC EXPERT PATHOLOGY REVIEW BEFORE PATIENT REFERRAL FOR ENDOSCOPIC TREATMENT. P. Leclercq (1), G. De Hertogh (2), R. Bisschops (1) / [1] UZ Leuven, Leuven, Belgium, Gastroenterology, [2] UZ Leuven, Leuven, Belgium, Pathology.

Background : Barrett's esophagus (BE) is the only known precursor condition for esophageal adenocarcinoma (EAC). Progression is thought to occur in a stepwise fashion from non-dysplastic BE (NDBE) to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and finally to EAC. Therefore, regular endoscopic surveillance with biopsies is required for these patients. Dysplasia in BE biopsies is associated with low observer agreement among general pathologists. Expert pathology review of all diagnosis of dysplasia is advised by most BE guidelines. The majority of patients with community LGD will be downstaged after expert review and have a low progression risk. Confirmed LGD has an increased risk of malignant progression, reported up to 9% per patient-year. Since endoscopic management of BE patients depends on the dysplasia grade, expert pathology review leads to a significant impact on the management and outcome of patients.
Aim : The aim of this study was to document the discrepancy between expert and community pathologists in grading BE dysplasia before patient referral for endoscopic treatment.
Methods : Between January 2017 and August 2019, sets of biopsy specimen from 129 dysplastic BE patients were referred from community centers to our tertiary referral center for expert pathology review as a prerequisite for dysplastic BE endoscopic management. These slides and blocks were reassessed by two gastro-intestinal (GI) expert pathologists. Diagnosis were stratified according Vienna Classification supported by p53 immunostaining. In this study, we retrospectively documented the discrepancy between expert and communautary pathologists in grading dysplasia in this selected BE population.
Results : LGD was confirmed by expert pathologist in 33/68 patients (49%), 20 patients (29%) were downgraded to NDBE, 5 patients (7%) indefinite for dysplasia (IFD) and 10 patients (15%) were upgraded to HGD, no cancer was missed. HGD was confirmed by expert pathologist in 52/61 patients (85%), downgraded to NDBE in 1 patient (2%) or to LGD in 4 patients (7%) and upgraded to EAC in 4 patients (7%).
Conclusions : Discrepancy in BE dysplasia grading between community and tertiary referral centers is still high, especially for LGD. Community diagnosis of LGD is down-staged to NDBE in 49% of the cases after expert GI pathologist review. Therefore, skipping the expert pathology review step in LGD BE patients could lead to overtreat almost half of the patients.

- R02 -

SUBACUTE LIVER FAILURE IN A PREGNANT FEMALE. L. Keulen (1), N. Gestels (2), P. Jorens (2), S. Francque (3), A. Driessen (1) / [1] Antwerp University Hospital, Belgium, Dept. of Pathology, [2] Antwerp University Hospital, Belgium, Dept. of Intensive Care, [3] Antwerp University Hospital, Belgium, Dept. of Gastroenterology and Hepatology.

Introduction : Liver diseases during pregnancy may pose a clinical diagnostic challenge as it may affect mother as child. Pregnancy-related liver diseases occur in approximately 3% of the pregnancy and may be the cause of maternal death in approximately 6%.
Aim : The aim is to discuss the pregnancy-related liver diseases.
Methods : Macroscopic and microscopic examination.
Results : We present a case of a 29yr old pregnant female, who in the 25th week of gestation, was admitted to the hospital with abdominal pain, disturbed liver tests and progressive jaundice. In early pregnancy she underwent laparoscopic gastric bypass surgery. Previous pregnancies were uneventful. At admission no signs of chronic liver disease or hepatic encephalopathy were detected. Patient had significant disturbed liver enzymes with bilirubinemia, elevated INR, hypoalbuminemia. No proteinuria, nor hypertension was found. No bile duct abnormalities, nor ascites was observed during radiological examination, but a florid steatohepatitis was detected. From clinical point of view the cause of the clinical deterioration of the patient was not obvious. Hence a liver biopsy was performed. After the procedure the condition of the patient suddenly worsened with symptoms of hepatic encephalopathy. As the fetus showed signs of distress, an urgent caesarian section was performed. Postoperatively the liver functions of the mother normalized quickly and patient was discharged after a few days.
Conclusions : During pregnancy there occur several physiologic changes in the mother. Although the liver usually continues normal to function, the high metabolic demand may sometimes cause a mild alteration of the liver enzymes. Liver diseases during pregnancy may be related to pre-existing liver diseases, such as viral hepatitis, or may be unique to the pregnant state, e.g. the HELLP-syndrome. In this patient however there is an additional differential diagnostic problem, as the bariatric surgery was associated with a significant weight loss (27 kg) in a few months' time. This may

cause a severe liver dysfunction, certainly in this condition of high metabolic demand in this pregnant female. Early diagnosis is however necessary as mother's as well as child's lives are at risk.

- R03 -

ACTINOMYCOSIS OF THE PANCREAS : A CASE REPORT. E. Ameloot (1), F. Berrevoet (2), P. Hindryckx (3), J. Boelens (4), J. Van Dorpe (1), A. Hoorens (1) / [1] Ghent University Hospital, Ghent, Belgium, Dept. of Pathology, [2] Ghent University Hospital, Ghent, Belgium, Dept. of General, Hepatobiliary and Liver Transplantation Surgery, [3] Ghent University Hospital, Ghent, Belgium, Dept. of Gastroenterology and Hepatology, [4] Ghent University Hospital, Ghent, Belgium, Dept. of Laboratory Medicine and Dept. of Infection Control.

Case Report : A 65-year-old woman presented to the emergency department with a painful, subcutaneous swelling in the right flank. She had a history of liver cirrhosis due to chronic alcoholism, several episodes of acute pancreatitis and recurrent need of stenting of the common bile duct because of direct compression by an inflammatory mass lesion in the head of the pancreas. The subcutaneous abscess was incised and drained and the patient was admitted to the hospital for intravenous antibiotics. CT abdomen showed progression in size of the pancreatic mass lesion in comparison to previous imaging and was suspect of a pancreatic intraductal papillary mucinous neoplasm (IPMN) with malignant degeneration. The mass was considered operable and a Whipple procedure was performed. Upon gross examination of the pancreas, a distinct mass with a diameter of 1 cm was observed, next to the common bile duct. The mass had a yellow-greenish colour and felt soft. The stent in the common bile duct contained a similar solid, soft, yellow-greenish substance. In the duodenum there were defects in the wall, also containing the same substance. Microscopic examination of the duodenum and common bile duct showed several abscesses composed of a mixed inflammatory infiltrate and tangled long narrow filamentous structures forming rounded basophilic masses with eosinophilic borders, reminiscent of sulphur granules. Morphology and characteristics in HE, PAS, Grocott and gram staining confirmed Actinomyces infection. Besides abscess formation in the common bile duct and pancreatic duct, inflammation and necrosis with inoculation of bacteria in the surrounding pancreatic tissue was observed. There were no signs of malignancy. Despite appropriate antibiotic treatment, the patient died shortly afterwards. Pancreatic, with potentially subsequent abdominopelvic actinomycosis, is a rarely occurring condition, however important to be considered in the differential diagnosis, as it can lead to a progressive suppurative fistulising and fibrosing infection with sinus tracts characteristically burrowing across normal tissue boundaries and into adjacent organs. Eventually sinus tracts may reach external surfaces forming a draining sinus or even penetrating bone leading to osteomyelitis. Early diagnosis and treatment are imperative in preventing serious and potentially life-threatening complications.

- R04 -

AN UNUSUAL APPENDICEAL MASS RISES A DIAGNOSTIC CHALLENGE. A. Vandendriessche (1), S. Deprez (2), J.-B. Cornille (3), A. Driessen (1) / [1] Antwerp University Hospital, Belgium, Pathology, [2] AZ Nikolaas, Sint-Niklaas, Belgium, Pathology, [3] AZ Nikolaas, Sint-Niklaas, Belgium, Surgery.

Introduction : Acute appendicitis is one of the most common acute conditions of the abdomen, most commonly treated with acute emergency surgery. Although pathological examination of the resection specimen frequently shows an acute inflammation, in a limited number of cases unusual findings are found.
Aim : To discuss the diagnostic problem of appendiceal mucinous neoplasms.
Methods : Macroscopic and microscopic examination.
Results : We discuss a case of 54-year-old women, who presented with an acute appendicitis and a pericaecal abscess. This was at first instance conservatively treated with drainage, anti-inflammatory drugs and antibiotics. Although radiological examination showed a decrease of the size of the pericaecal collection, patient's complaints of pain and discomfort persisted. An explorative laparatomy with resection of the base of the caecum with appendix was performed. Pathological examination of the specimen (length 7,6 cm, size 5.6*3 cm) revealed a diverticulum of the appendix, covered with an intestinal epithelium that turns into a pseudostratified epithelium. In the depth it extends into mucous lakes, surrounded by inflammatory cells, situated up to the serosal surface. Intermingled with this process we observed several irregular glandular structures with a different appearance. These structures were delineated by a cylindric type of epithelium, surrounded by a cellular stroma. At some areas we observed a transition of the two different types of epithelium into each other. This hampered the evaluation of the growth process of the pseudostratified epithelium. Hence immunohistochemistry was performed to the determine the origin of these morphologically different glandular structures and to assess their extent in the wall of the appendix. This showed that the morphologically different glandular structures had a different immunohistochemical pattern. Hence a diagnosis of a low-grade appendiceal mucinous neoplasm, intermingled with endometriosis was made.
Conclusions : For pathologists it is a diagnostic challenge to determine the risk of peritoneal dissemination of low-grade appendiceal mucinous neoplasms (LAMN). LAMN (incidence 1/100 000/yr) are in situ tumours, if they are limited to the muscularis propia. Extension into the serosa, eventually with penetration of serosal surface increases however the risk for

peritoneal disease. In this case LAMN was associated with endometriosis, which is present in up to 35% of the intestine, but rare in this location. Endometriosis makes assessing the degree of invasion difficult, as in this case, the epithelium of endometrial glands is colonized by the mucinous epithelium of the LAMN. Moreover, endometrial epithelium may develop intestinal metaplasia. Therefore, pathological examination of the complete appendix, supplemented with immunohistochemistry, is required in order to assess the extent of LAMN and hence the risk for peritoneal dissemination.

- R05 -

GASTRITIS : DEMOGRAPHIC AND ENVIRONMENTAL FACTORS BASED ON A CROSS-SECTIONAL STUDY IN BELGIUM AND BUKAVU. M. Surmont (1), M. Van Gossum (1), A. Philippe (2), A. Nteranya (3), V. Muls (1), M. Nkuize (1), J. Mungwete (3), M. Abedi (3), M. Gomez (4), D. Larsimont (2), T. Serste (1), R. Ntounda (1), J. Mulkay (1), H. Njimi (5), E. Munguakonkwa (3), P. Demetter (6), P. Eisendrath (1), D. Mukwege (7) / [1] CHU Saint-Pierre, Brussels, Belgium, Department of Gastroenterology, [2] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, Pathology Department, [3] Panzi Hospital -UEA, Bukavu, Congo (the Democratic Republic of the), Department of Gastroenterology, [4] Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium, pathology department, [5] ULB, Brussels, Belgium, Institute of Statistics, [6] CHU Saint-Pierre, Brussels, Belgium, Pathology Department, [7] Panzi Hospital -UEA, Bukavu, Congo (the Democratic Republic of the), Department of Gynaecology.

Introduction : Gastric cancer is currently the fifth most common and the third most deadly cancer worldwide. Based on the gastric carcinogenesis and the Correa cascade, patients with chronic atrophic gastritis and intestinal metaplasia are at risk for gastric adenocarcinoma. Histological gastritis staging scores Operative Link for Gastritis Assessment (OLGA) and Operative Link for Gastritis Intestinal Metaplasia Assessment (OLGIM) allow the selection of patients at risk for gastric cancer. Up to 89% of all gastric cancers can be attributable to Helicobacter Pylori (HP) infection, known as a class I carcinogen for gastric neoplasia. More than 50% of the population worldwide is infected, with the highest prevalence in Africa, Latin America, the Caribbean and Asia. The outdated 'African Enigma' refers to the contrast between the high prevalence of HP infection and the low incidence of reported peptic ulcers and gastric cancers in Africa.
Aim : This cross-sectional study compares prevalence and histological findings of gastritis, based on OLGA and OLGIM scores in symptomatic patients in 2 different populations living in respectively Belgium and Congo. The study also evaluates environmental and demographic factors in gastritis.
Methods : In this study, 680 patients in an urban Belgian hospital in Brussels (group 1) and 250 patients in an urban hospital in Bukavu, Democratic Republic of Congo (group 2) with epigastric pain underwent upper endoscopy during the period September 2017 - January 2019. Gastric biopsy sampling was performed according to the Sydney protocol. Each biopsy was revised by a Belgian pathologist. Histopathology identified the presence of acute and chronic inflammation, atrophy, intestinal metaplasia with OLGA and OLGIM scores and dysplasia. Immunohistochemical stains were used for the detection of HP.
Results : 580 patients in the Belgian centre and 174 patients in the Congolese centre were included of which respectively 38% and 47% men with a mean age of 46 years. Hundred Belgian patients were excluded of the study because of HP eradication in the past and 76 Congolese patients because of poor quality of the paraffin embedded biopsies. The prevalence of HP infection in the Belgian group and the Congolese group was respectively 36% and 52%. There was significant more use of tobacco and proton pump inhibitors in the Belgian group, whereas the Bukavu population used more alcohol and anti-inflammatory drugs. The prevalence of HIV was not different in both groups. Severe acute and chronic gastric inflammation was in both HP positive subgroups more prevalent in the gastric antrum compared to the fundus. There were statistically significant more patients with OLGA stages 1 or 2 and OLGIM 1 or 2 in the African group than the European group, respectively 22% versus 13% and 18% versus 12%. Nevertheless, there was no significant difference for the presence of OLGA and OLGIM stages 3 and 4 between both groups nor was there a statistically significant difference in dysplasia. Focusing on age, the prevalence of OLGIM stages 1 and 2 was significant higher in the African group older than 60; 13.3% for patients younger than 60, 35.3 % for patients older than 60. There were significant endoscopic lesions such as erosions and ulcerations in 27% of the cases in both groups and there was no significant difference in HP infected patients.
Conclusions : This cross-sectional study shows interesting data on the African situation since there is a paucity of data for this area, related to limited access to endoscopy and health care in general and lack of national cancer registration in most of the African countries. In contrast to what the 'African Enigma' claimed, the data shows no significant difference in severity of gastritis in the African and European group nor in presence of significant endoscopic lesions. These data confirms the role of age and HP infection but there is no geographical difference.

- R06 -

DIAGNOSING STRONGYLOIDES IN BIOPSY SPECIMENS : A CASE REPORT. S. RUSU (1), C. Royer-Chardon (1), P. Rossignon (2), G. Verset (2), V. Huberty (2), D. Blero (2), L. Perez-Casanova Gomez (1), C. Maris (1), N. D'haene (1) / [1] Erasme Hospital, Brussels, Belgium, Pathology, [2] Erasme Hospital, Brussels, Belgium, Gastroenterology.

Case Report : We report a case of a 71-year-old male who presented bilateral lower limb oedema, diffuse pain, difficult prehension for the last 3 weeks, loss of appetite and weight, complicated by nausea and vomiting the last week prior to medical consult. The clinical examination revealed epigastric and umbilical region abdominal pain. The blood tests revealed an inflammatory syndrome, severe anaemia, hypereosinophilia and electrolyte imbalance (hypokalemia, hypoalbuminemia). Thoraco-abdominal ultrasonography and computed tomography showed multiple hilar and mediastinal adenopathy, bilateral pleural effusion, ground-glass opacity in the right anterior lung basal segment, suggesting an infectious etiology. Considering the patient's history of gastric ulcer and the epigastric pain, an endoscopy was performed. No peptic ulcer was objectived but a post-Bilroth I status. The mucosal aspect was normal and biopsies were performed. Histological examination of the duodenal biopsies showed blunted and atrophic villi, an increased number of plasma cells, lymphocytes and neutrophils in the lamina propria and in the lining epithelium resulting in cryptitis and crypt abscesses' images. Multiple coiled adult females, rhabditiform larvae and eggs of Strongyloides stercoralis were observed in the crypts. Although strongyloidiasis could not be confirmed based on microscopy alone, an infection with Strongyloides Stercoralis was confirmed in this particular case using ELISA technique and stool examination. Strongyloidiasis is distributed worldwide, but more common in wet and warm regions. It is transmitted through direct penetration of human skin by infective larvae when in contact with soil. Light infections in healthy subjects often are asymptomatic but in immune suppressed patient the outcome can be fatal. Three clinical phases are described in immunocompetent patient : cutaneous, pulmonary (due to migration of the larvae in the lungs and tracheobronchial pathways) and intestinal (usually three weeks after infection). Symptomatic patients present aspecific complaints such as hunger pains, cramping, intermittent diarrhea and constipation, as well as moderate anaemia, weight loss and leukocytosis with eosinophilia. Diagnosing Strongyloidiasis is challenging, especially in countries where its prevalence is low. It can be evocated on tissue biopsies when adult females and/or larvae and/or eggs are identified. However, confirmation by stool examination or serologic test is needed before initiating antiparasitic therapy.

- R07 -

81-YEAR-OLD MAN WITH ULCERATED MASS IN THE CAECUM. C. Royer-Chardon (1), S. Rusu (1), A. Brahimi (2), L. Mans (3), N. Bachir (4), A. Demols (3), I. Simon (2), L. Perez-Casanova Gomez (1), C. Maris (1), J. Nortier (2), N. D'haene (1) / [1] Erasme Hospital, Brussels, Belgium, Pathology, [2] Erasme Hospital, Brussels, Belgium, Nephrology, [3] Erasme Hospital, Brussels, Belgium, Gastroenterology, [4] Erasme Hospital, Brussels, Belgium, Digestive Surgery.

Case Report : A 81-year-old man with chronic renal failure treated with hemodialysis since 6 years presented with right flanc abdominal pain. His medical history consists of arterial hypertension, renal cysts, monoclonal gammopathy of undetermined significance, carbohydrate intolerance and aortic stenosis. The treatment of the patient consisted of sodium bicarbonate, calcium and magnesium acetate, sevelamer carbonate, acetylsalicylic acid, acenocoumarol and calcium polystyrene sulfonate. Abdominal computed tomography (CT) showed circumferential thickening of the caecum and the right colon up to 2.5 cm thick, over a length of 9.4 cm, which was worrisome for a neoplastic etiology. Colonoscopy showed an ulcerated caecal mass, with a large ulcer extending over 7 cm, and colonic diverticulosis. Differential diagnosis between neoplastic etiology or pseudotumoral mass of ischemic colitis origin was made. The biopsy revealed a largely ulcerated colonic mucosa with no sign of malignancy. Serum CA19-9 was slightly elevated, CEA was normal. Thoraco-abdominal CT did not reveal distant metastasis. Despite negative biopsies, given the high clinical suspicion of malignancy and the presence of lower gastrointestinal bleeding, a right colectomy with lymph node dissection was performed. Gross examination showed a serous adhesion between the caecum and the terminal ileum. At the opening, two ulcers in the caecum were observed. Microscopic examination revealed an ulcerated colon mucosa with acute inflammation of the colon wall associated with a subacute peritonitis. Crystal foreign material was observed in the ulcers but also in the colon mucosa at distance. Two types of crystal foreign material were observed : bright purple crystals consistent with calcium polystyrene sulfonate crystals (Kayexalate) and yellow/pink crystals with fish scale appearance consistent with sevelamer crystals. Beside calcium acetate/ carbonate supplements, sevelamer is a phosphate binder widely prescribed to patients with severe to end-stage chronic kidney disease. Sevelamer crystals deposition is a rare cause of gastrointestinal mucosal injury. The most common clinical manifestation is bleeding. Despite rarely reported, clinicians should be aware of such pseudotumor presentation named.

- R08 -

INCIDENCE OF APPENDICEAL NEN AND ADHERENCE TO PATHOLOGY CLASSIFICATION RULES IN BELGIUM. S. Ribeiro (1), F. De Maeyer (2), M. De Man (1), S. Carton (3), P. Cuyle (3), T. Vandamme (4), C. Verslype (5), I. Borbath (6), P. Demetter (7), N. Van Damme (8), L. Van Eycken (8), A. Hoorens (9), K. Geboes (1) / [1] UZ Gent, Gent, Belgium, Gastroenterology, [2] AZ Sint-Elisabeth, Zottegem, Belgium, Gastroenterology, [3] Imelda Hospital, Bonheiden, Belgium, Gastroenterology, [4] Netwerk, UZA, Edegem, Belgium, Gastroenterology, [5] KU Leuven, Belgium, Gastroenterology, [6] UCLouvain, Belgium, Gastroenterology, [7] Institut Jules Bordet, Belgium, Pathology, [8] Belgian Cancer Registry, Brussel, Belgium, Register, [9] UZ Gent, Gent, Belgium, Pathology.

Introduction : Appendiceal neuroendocrine neoplasms (aNEN) are rare tumors. Classification systems have changed significantly and repeatedly over the years, largely because of changes in terminology. There is a definite need for unbiased data on the epidemiology of NEN. Most existing data are incomplete because they are retrieved from registries kept by groups of (expert) centers, such as the DNET registry. In Belgium, data on patient and tumor characteristics of all newly diagnosed cancers is collected in a national and population-based registry, the Belgian Cancer Registry (BCR). The BCR also receives the pathology protocols describing results of (pre-)malignant specimens.
Aim : The aim of the present study is to have epidemiological data of aNEN in Belgium and to investigate the evolution of pathological reporting.
Methods : Pathology reports of all aNENs diagnosed between 2010 and 2015 were thoroughly reviewed. A significant part of pathologists in Belgium use the College of American Pathologists (CAP) guidelines, first introduced for NET in June 2012. All reports were checked for clinicopathological data including size of tumor, WHO grade (Ki 67), grade of differentiation, lymphovascular invasion, location, infiltration of the mesoappendix, nodal involvement and margin status, because treatment algorithms are based on these parameters. Right hemicolectomy should be offered to all patients with appendiceal neuroendocrine tumors (aNET) > 2cm. It is also suggested to advise right hemicolectomy in patients with grade (G)2 aNET. In patients with a tumor size between 1 and 2 cm, right hemicolectomy should be discussed based on certain risk factors. Classification was examined and adapted to the WHO 2019 classification, if necessary.
Results : We identified 584 aNENs over a period of 6 years, corresponding to a steady incidence of 0.9/100.000/year. It was impossible to verify classification in 185 cases because of missing pathological data. Fifty-one patients had to be reclassified according to the WHO 2019 guidelines. After reclassification, there were 348 NET G1, 50 NET G2 and 1 neuroendocrine carcinoma (NEC). Fifty-six% of patients were female, mean age 39y. The size of the tumor was mentioned in 94% of 584 cases. WHO grade and grade of differentiation were both retrievable in 44% of cases in 2010 and in 80% and 72% of cases respectively in 2015. Twenty-one NET G1 and 6 NET G2 tumors were larger than 2cm. We found no information on tumor size in 18 G1 and 3 G2 patients. 71 patients had a G1 tumor sized between 1 and 2 cm. At least 1 of the 4 commonly used prognostic factors was missing for all these patients; 2 prognostic factors were missing for 28 (39,4%) patients, and 3 or more were missing for 23 (32,3%) patients. 15 patients had a G2 tumor between 1 and 2 cm. Only 1 of these patients had all the risk factors reported while at least 1 of the 4 prognostic factors was missing for the majority of them (n= 14; 93,3%) and 2 or more prognostic factors were missing for 7 (46,7%) patients. Of note, depth of infiltration of the mesoappendix is not included in the CAP checklist.
Conclusions : Based on the Belgian cancer registry data, we can withhold an incidence for aNEN of 0.9/100.000/year. Tumor size was reported in the majority of cases. Most patients have NEN < 1cm. We have real life data on the evolution of reporting upon introduction of the new WHO grading system, with uptake in 80% of cases by 2015. 32% of cases could not be verified for correct classification because of missing pathological data. 9% of cases had to be reclassified, pointing out that previous reports based on retrospective datasets should be interpreted with caution and original pathological reports (or specimens) should be checked for specific parameters. Missing information in other parameters may be influenced by size, because these parameters only affect decisions in tumors between 1-2cm. However, in all but 1 of these cases at least 1 of the known risk factors were missing

- R09 -

INCIDENCE OF RECTAL NEN AND ADHERENCE TO PATHOLOGY CLASSIFICATION RULES IN BELGIUM.
F. De Maeyer (1), M. De Man (2), S. Ribeiro (2), S. Carton (3), P. Cuyle (3), T. Vandamme (4), C. Verslype (5), P. Demetter (6), I. Borbath (7), N. Van Damme (8), L. Van Eycken (8), A. Hoorens (9), K. Geboes (2) / [1] AZ Sint-Elisabeth, Zottegem, Belgium, Gastro-enterology, [2] UZGent, Gent, Belgium, Gastro-enterology, [3] Imeldaziekenhuis, Bonheiden, Belgium, Gastro-enterology, [4] Ziekenhuis Netwerk Antwerpen, Belgium, Gastro-enterology, [5] UZ Leuven, Leuven, Belgium, Gastro-enterology, [6] Institut Jules Bordet, Brussels, Belgium, Gastro-enterology, [7] UCLouvain, Belgium, Gastro-enterology, [8] Belgian Cancer Registry, Brussel, Belgium, Belgian Cancer Registry, [9] UZGent, Gent, Belgium, Pathology.

Introduction : Rectal neuroendocrine neoplasms (rNEN) and MiNEN (mixed adenocarcinoma and neuroendocrine carcinoma (NEC) or neuroendocrine tumor (NET)) are rare tumors. Their incidence is rising since the introduction of screening programs for colon cancer. Classification changed significantly and repeatedly over the years, because of changes in terminology. There is a need for unbiased data on the epidemiology of NEN. Most existing data are incomplete because they are retrieved from registries kept by groups of (expert) centres. In Belgium, data on patient and tumor characteristics of all new diagnosed cancers is collected in a national and population-based registry, the Belgian Cancer Registry (BCR). The BCR also receives the pathology protocols describing results of (pre-) malignant specimens.
Aim : The aim of the present study is to have epidemiological data of rNEN in Belgium and to investigate the evolution of pathological reporting.
Methods : Pathology reports of 686 rNEN diagnosed between 2004 and 2015 were thoroughly reviewed. A significant part of pathologists in Belgium use the College of American Pathologist (CAP) guidelines, first introduced for NET in 2013. All reports were searched for clinicopathological data including size of tumor, WHO grade (Ki 67), grade of differentiation, lymphovascular or perineural invasion, invasion of the muscularis propria and margin status, because

treatment algorithms are based on these parameters. Classification was judged on the basis of the WHO 2019 classification and adapted, if necessary.

Results : Sixteen out of 686 cases were not NEN. A total of 670 cases in 667 patients were withheld. A gradual increase in the number of cases was noted, rising to 70+ cases annually from 2011 onwards. The majority (79%) were well-differentiated G1 NET. Well-differentiated G2 NET and poorly differentiated NEC comprise 8 and 10% of the cases, respectively. Well-differentiated G3 NET (2%) and MiNEN (1%) are rare. Size of the tumor reporting rose from 33% of original reports to 68% in 2015. WHO grade and grade of differentiation were mentioned in 33 and 9% of cases in 2004, increasing to 85 and 55% of cases in 2015 respectively. Invasion of muscularis propria and lymphovascular or perineural invasion were less frequently reported. All diagnoses were verified or adapted according to the WHO 2019 classification. 57% of the 670 cases were classified correctly, 27% could not be verified due to missing data and 16% had to be reclassified. 369/531 (69%) cases were true NET G1, 23% were probably G1 and 4 patients had a Ki 67 < 5%. Ki 67 index and size were reported in 62% of these G1 NET. 25 patients were classified as NET G2 with certainty and another 28 were reclassified to this group, leading to 53 NET G2 patients with 100% reporting of Ki67 index. The number of G3 NET is possibly overestimated, due to missing data in the pathology reports : 8/11 cases had insufficient data to be reclassified. Only 2 patients could be regarded as G3 NET with certainty, because both differentiation and Ki67 index were reported. Sixty-six NEC were withheld. The diagnosis of a true NEC could not be verified in 7 cases, due to insufficient data. Twelve cases were coded as large cell carcinomas. Seventeen G3 NET were reclassified to a large cell NEC, resulting in a total of 29 large cell NECs. A total of 30 cases of small cell NEC were reported. Six G3 NET had to be reclassified to a small cell NEC, resulting in 36 small cell NECs in total. Ki67 index was reported in 71% of the cases.

Conclusions : Based on the cancer registry data we can withhold an incidence in rNEN in Belgium of 0.7/100.000/y from 2011 onwards. We see an increase in annual incidence, mainly due to better reporting and because of the introduction of screening programs for colorectal cancer. Despite changes in terminology and classification systems, only 27 % of cases (mainly G1 NET) could not be verified for correct classification because of missing data in the pathology reports. However, 16% of cases had to be reclassified, pointing out that previous reports based on retrospective datasets should be interpreted with caution and original pathology reports (or specimens) should be checked for specific parameters.