

# ABSTRACTS

## XXX<sup>th</sup> Belgian Week of Gastroenterology 2018

### ABSTRACTS

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- B01 — B16 Belgian Network on Gastrointestinal Mechanisms (GIREM)
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- G01 — G18 Belgian Society for Gastrointestinal Endoscopy (BSGIE)
- H01 — H02 Belgian Microbiota and Helicobacter Study Group
- I01 — I38 Belgian Inflammatory Bowel Disease Research and Development Group (BIRD)
- K01 — K05 Belgian Society for Pediatric Gastroenterology, Hepatology and Nutrition (BeSPGHAN)
- M01 — M05 Belgian Working Group on Proctology
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**BELGIAN ASSOCIATION FOR THE STUDY OF THE LIVER  
(BASL)**

- A01 -

SCREENING FOR HEPATITIS C AT THE EMERGENCY DEPARTMENT : BABY BOOMERS SHOULD ALSO BE SCREENED IN BELGIUM. R. Bielen (1), C. Kremer (2), Ö. Koc (1), D. Hendrickx (2), P. Vanelderden (3), N. Hens (4), F. Nevens (5), G. Robaey (6) / [1] Hasselt University, Hasselt, Belgium, Faculty of Medicine and Life Sciences, [2] Hasselt University, Diepenbeek, Belgium, Faculty of Science, Center for Statistics, [3] Ziekenhuis Oost-Limburg, Genk, Belgium, Department of Anaesthesiology, Intensive care medicine, Emergency care and Pain therapy, [4] Hasselt University, Diepenbeek, Belgium, Faculty of Science, Interuniversity Institute for Biostatistics and statistical Bioinformatics, [5] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [6] Ziekenhuis Oost-Limburg, Genk, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** The estimated prevalence of Hepatitis C viral infection (HCV) in Belgium is low (0.87%), and to date, there is no screening policy available. Several studies in Europe and in the United States have reported higher rates of HCV infection when screening is performed in emergency departments (ED) (2-3% and 10-18%, respectively) and the Centre for Disease Control recommends screening for patients born in the baby boom period (1945-1965) in the United States.

**Aim :** We aimed to study the prevalence of HCV in an ED population in Belgium (including the baby boom cohort) and to study the risk factors associated with HCV infection.

**Methods :** We performed a monocentric, cross-sectional seroprevalence study between January and November 2017 in a large non-university hospital in Belgium (Ziekenhuis Oost-Limburg, Belgium). Patients between 18 and 70 years old who presented at the ED were eligible. After informed consent, patients completed a risk assessment questionnaire and were screened for HCV Ab (Abbott HCV 3.0 ELISA) with reflex HCV RNA testing (qRT-PCR). A multiple logistic regression model with post-stratification analysis for the age and gender distribution of the population of Middle-Limburg was used to study the risk factors for HCV infection. A post-hoc power analysis was performed in order to determine the probability of detecting an effect of a given size with a given level of confidence, given the observed sample sizes.

**Results :** Of 2.913 patients, 2.330 agreed to participate. Of the HCV Ab positive patients, 10 (32.3%) were previously cured, and 9 (29.0%) spontaneously cleared the virus. None of the 12 patients with chronic HCV infection were in follow-up at a hepatology department. We obtained enough power ( $\geq 0.8$  ; 95% CI) for the analysis of the baby boom cohort, drug use, tattoos, and imprisonment. In the final weighted model, age (by gender) (OR : 28.7 ; 1.53-537.02), drug use (OR : 20.7 ; 5.12-83.94) intravenous drug use (OR 1069.7 ; 152.29-7514.68) and being born in a high endemic birth country (OR : 91.0 ; 14.86-557.32) were withheld as significant risk factors for HCV infection ( $p < 0.05$ ). In the final model, the specificity and sensitivity were 0.97 and 0.74, respectively, indicating good discriminative ability.

**Conclusions :** The prevalence of HCV Ab was higher than previously estimated for the general population in Belgium. However, HCV RNA prevalence was lower. None of the patients with chronic HCV infection were in follow-up at a hepatology department. Screening in drug users, immigrants from high-endemic countries and people born between 1948-1967 is recommended.

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- A02 -

THE THROMBOGENIC RISK INDUCED BY INTRAPORTAL INFUSION OF ADULT DERIVED HUMAN LIVER STEM/MESENCHYMAL CELLS IN WISTAR RATS CAN BE CONTROLLED WITH A COMBINATION OF ANTICOAGULANT DRUGS, HEPARIN AND BIVALIRUDIN. L. Coppin (1), M. Rozzi (2), M. Komuta (3), S. Horman (4), E. Sokal (1), X. Stéphenne (1) / [1] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Pediatric Hepatology and Gastroenterology, [2] Institut de Recherche Expérimentale et Clinique (IREC), Catholic University of Louvain (UCL), Belgium, PEDI lab, [3] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Pathology Laboratories, [4] Institut de Recherche Expérimentale et Clinique (IREC), Catholic University of Louvain (UCL), Belgium, CARD lab.

**Introduction :** Mesenchymal Stem cell (MSC) transplantation is a fast-emerging therapy for regenerative medicine. However, MSCs express a procoagulant activity (PCA) inducing a thrombogenic risk in recipient patients. This thrombogenic risk is due to activation of the coagulation cascade, triggered by Tissue Factor (TF) on MSCs, resulting in fibrin production and platelet consumption. In vitro the PCA of Adult Derived Human Liver Stem/Mesenchymal Cells (ADHLSCs) can be controlled by an anticoagulant cocktail, combining an antithrombin activator (Heparin) and a thrombin inhibitor (Bivalirudin).

**Aim :** The aim was to study in vivo, the effect of an anticoagulant cocktail on thrombogenic risk induced by intraportal ADHLSCs. First, we wanted to characterize the thrombogenic events induced by ADHLSCs infusion. Then we wanted to study the effect of the anticoagulant cocktail on these events. Finally, the effect of cell dosage on the thrombogenic risk was studied.

**Methods :** Wistar rats (n=3 per group) were infused with ADHLSCs through an intraportal catheter. Rats were infused with 3 different cell dosages (50, 12.5 and 5 million ADHLSCs/kg), with or without administration of anticoagulant therapy (Heparin and Bivalirudin). Control group was infused with PBS. Blood samples were collected before and 1 hour after cell infusion. Hemoglobin and platelet levels were analysed with an automated hematology analyser, Cell-Dynn Emerald (Abbott). Rats were sacrificed and liver tissue was collected 1 hour after cell infusion. Serial slides were performed to analyse the localisation of ADHLSCs (human Beta 1 integrin staining) and fibrin (P.T.A.H. coloration). Cell quantification and localisation was analysed with digital imaging system, Visiopharm. Fibrin was analysed in Portal Veins (PV) containing ADHLSCs by digital imaging system, TissueIA.

**Results :** ADHLSCs intraportal infusion induced after 1 hour a significant decrease ( $p < 0.05$ ) in platelet count with production of fibrin around the infused cells localized in PVs. No platelet consumption or fibrin production was observed in the control (PBS) group. In the anticoagulated group, platelets also decreased significantly ( $p < 0.05$ ) but fibrin production was significantly ( $p < 0.001$ ) reduced, from  $86.6\% \pm 6.4$  to  $26.4\% \pm 13.8$ . When different cell dosages were infused, we observed a correlation between the number of infused cells and the number of cells in the liver. The number of cells in liver tissue (cells/mm<sup>2</sup>) and the number of PVs containing cells (PVs containing cells/total PV) were significantly ( $p < 0.01$ ) lower when lower cell dosages were used, compared to the higher cell dosage group. Consumption of platelets was also correlated to cell dosage. No decrease in platelets was observed when  $5 \times 10^6$  cells/kg were infused without anticoagulation, and when  $12.5 \times 10^6$  cells/kg were infused with anticoagulation. Platelets tended to decrease less in the high cell dose group,  $50 \times 10^6$  cells/kg when anticoagulant therapy was administered. No significant difference has been observed in the production of fibrin in PVs between the different cell dosages. In all conditions, hemoglobin did not decrease significantly, meaning that blood sampling did not interfere with our results.

**Conclusions :** Intraportal infusion of ADHLSCs activated the coagulation cascade resulting in fibrin formation and platelet consumption 1 hour after cell infusion. The use of a combination of anticoagulant drugs, heparin and bivalirudin, could prevent the formation of fibrin, but a significant decrease in platelets was still observed. However, this decrease tends to be less and can even be controlled when lower cell dosages are used. The production of fibrin and thus the activation of the coagulation cascade was not dependent of cell dosage.

- A03 -

LIVER STIFFNESS AND STEATOSIS EVALUATION BY TRANSIENT ELASTOGRAPHY IN OBESE PATIENTS : BASELINE RESULTS ANALYSIS FROM A PROSPECTIVE BELGIAN STUDY. N. Lanthier (1), S. Hiel (2), J. Rodriguez (2), B. Delire (3), M. De Barcy (4), J. Thissen (4), N. Delzenne (2) / [1] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Service d'Hépatogastroentérologie, [2] Université catholique de Louvain, Brussels, Belgium, Metabolism and Nutrition Research Group, Louvain Drug Research Institute, [3] Cliniques universitaires Saint-Luc, Brussels, Belgium, Service d'Hépatogastroentérologie, [4] Cliniques universitaires Saint-Luc, Brussels, Belgium, Service d'Endocrinologie et de Nutrition.

**Introduction :** Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. The detection of this condition and the evaluation of disease severity are important considering possible hepatic and extra-hepatic complications. Liver stiffness measurement (LSM) using transient elastography (TE) by Fibroscan® (FS) has been extensively studied in order to quantify non-invasively liver fibrosis in hepatitis C patients and in a lower proportion in NAFLD patients. FS allows also the calculation of the controlled attenuation parameter (CAP) simultaneously with LSM providing an evaluation of liver steatosis. A high rate of technical failure related to obesity status has been suggested in previous trials.

**Aim :** The goals of this study are first to evaluate the feasibility of both CAP and LSM measurement in obese individuals, second to analyze the spectrum of NAFLD among those patients and third to detect clinico-biological data associated with steatosis or fibrosis.

**Methods :** Baseline data (clinical and biological) of patients randomized in a single center for the Food4Gut study were recorded. All patients had obesity (body mass index  $\geq 30$ ) with minimum one metabolic complication (high blood pressure, hyperglycemia or elevated liver enzymes). TE was done in a fasted condition for quantification of both LSM (fibrosis) and CAP (steatosis), using either M or XL probe based on automatical device probe selection. A minimum of 15 measurements were made to obtain the median valid liver stiffness measurements (in kPa) and interquartile range. Technical success was defined as 15 valid measurements with a success rate  $> 70\%$ .

**Results :** Forty-Six Caucasian patients (mean age : 51 years, 52 % male) were included. Fibroscan was successful in all patients except one due to the presence of multiple large liver cysts. M probe was used in 29 patients (63%) and XL probe in 17 patients. Mean LSM was low ( $6.7 \text{ kPa} \pm 1.3 \text{ kPa}$ ). 13 patients (28%) had advanced fibrosis defined by  $\text{LSM} \geq 7.8 \text{ kPa}$  (M probe) or  $\geq 6.4 \text{ kPa}$  (XL probe). No patient had no steatosis based on CAP values. Mean CAP result was 326 dB/m (mean IQR 30 dB/m) with the majority of the patients (76%) presenting severe steatosis ( $\text{CAP} \geq 296 \text{ dB/m}$ , n=35). LSM was significantly higher in male than in female patients ( $p=0.008$ ). Significant correlations were found for CAP ( $R=0.39$ ,  $p=0.005$ ), gGT values ( $R=0.38$ ,  $p=0.008$ ) and ALT ( $R=0.34$ ,  $p=0.01$ ). For CAP results, significant correlations were ALT values ( $R=0.31$ ,  $p=0.03$ ) and waist circumference ( $R=0.29$ ,  $p=0.04$ ).

**Conclusions :** FS provides excellent quality results and important information estimating the degree of fatty liver and assessing the disease severity in terms of fibrosis at the same time. Failure due to high BMI was not observed in our study population with the use of M and XL probes. Among obese patients, a high proportion of severe steatosis was diagnosed with such technique and advanced liver fibrosis was suspected in 28% of the patients. High steatosis scores correlated with higher liver stiffness measurement.

- A04 -

SMALL FOR SIZE SYNDROME AND HYPOXIA : LESSONS LEARNED FROM THE ASSOCIATED LIVER PARTITION AND PORTAL VEIN LIGATION FOR STAGED HEPATECTOMY (ALPPS) PROCEDURE IN RATS. A. Dili (1), V. Lebrun (2), C. Bertrand (3), I. Leclercq (4) / [1] CHU UCL Namur, Yvoir, Belgium, Surgery and Laboratory of Hepato- Gastroenterology, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium, [2] Université Catholique de Louvain, Brussels, Belgium, Laboratory of Hepato- Gastroenterology, Institut de Recherche Expérimentale et Clinique, [3] CHU UCL Namur, Yvoir, Belgium, Surgery, [4] Université catholique de Louvain, Brussels, Belgium, Laboratory of Hepato- Gastroenterology, Institut de Recherche Expérimentale et Clinique.

**Introduction :** Small for size syndrome (SFSS) is a clinical entity developing after major hepatectomy leaving a very small liver remnant or after liver transplantation with a small graft. Hypoxia of the future liver remnant (FLR) in SFSS is due to portal hypertension with a compensatory constriction of the common hepatic artery (hepatic arterial buffer response-HABR). It is believed that desarterialisation of FLR is the main cause of SFSS. Over the years, surgical interventions to decrease portal flow have been used to avoid postoperative liver failure (PLF). On the contrary, some studies suggest that an increase of the portal flow improves liver regeneration. ALPPS is a surgical technique that combines portal vein ligation and parenchymal transection to obtain rapid future liver remnant hypertrophy. This increases the number of patients eligible for a major, staged, hepatectomy. It has been developed for patients that could not be operated in an upfront hepatectomy because of a very small FLR with high risk of SFSS. When the ALPPS procedure is performed, portal ligation addresses the whole portal blood flow through a small liver remnant sinusoidal network, while parenchymal transection excludes all intrahepatic portal collaterals. This procedure sets the liver remnant in the same hemodynamic portal conditions as in SFSS, and yet, patients not only do not develop liver insufficiency, but they obtain increased FLR hypertrophy.

**Aim :** This study aims to understand the role of the hepatic hemodynamics in liver regeneration and the differences between SFSS and ALPPS.

**Methods :** The first part of the study focused on developing the ALPPS rodent model to mimic faithfully the human procedure. Survival was evaluated. Flow rate in portal trunk (PV) and common hepatic artery (HA) were measured by US-Doppler in the ALPPS and SFSS model. Damage associated molecular patterns (DAMPs), such as HMGB1, are released during hypoxia, as well as Hypoxia Inducible factors (HIF1a and HIF 2). ELISA analysis was performed on cardiac and portal blood at different time points for HMGB1, and on nuclear/cytoplasmic extract for HIF1a and 2a.

**Results :** ALPPS was associated with a low seven-day mortality rate (29.41%) compared to SFSS (77.78%) ( $p < 0.0001$ ). Portal flow in the FLR was increased in both ALPPS and SFSS by a factor 4 to 5 compared to flow in sham animals ( $p < 0.0001$ ), but without significant difference between the 2 groups. A decrease in HA flow occurred after ALPPS compared to sham ( $p < 0.0001$ ) and was further lowered after SFSS suggesting a HABR consecutive to portal hyperperfusion. HABR was more important in the SFSS group compared to ALPPS ( $p = 0.002$ ). While arterial blood was distributed in the entire liver in ALPPS, it only entered the 10% FLR in SFSS, in consequence, effective arterial, more oxygenated, flow into FLR was increased after SFSS compared to ALPPS ( $p = 0.0007$ ). Immunohistochemistry using pimonidazole (an ischemia marker associated to hypoxia) demonstrated a significantly higher ischemia at day 1 in ALPPS compared to sham and SFSS ( $p = 0.0002$ ). Based on these observations, systemic intravenous injection of dimethylloxalglycine (DMOG), a molecule inducing hypoxia, significantly decreased mortality in SFSS (DMOG-SFSS 16.6% vs 77.78% in SFSS ( $p < 0.0001$ )). ELISA analysis showed that HMGB1, HIF1a and HIF2a were significantly higher post ALPPS compared to SFSS at different early time points.

**Conclusions :** Our animal model is the first introducing ALPPS with minimal FLR, leading to high mortality due to SFSS if ALPPS is not performed. Hemodynamic study proves no difference in portal hyperperfusion between the 2 surgical procedures. However, in SFSS, significant increase in hepatic artery blood flow through the liver parenchyma was observed, suggesting that liver insufficiency is not related to parenchymal desarterialisation ; on the contrary, reduction of arterial liver perfusion, as observed in ALPPS, may protect the FLR from hepatocellular failure and stimulate regeneration. This has been proved by an improvement in survival on SFSS when systemic DMOG administration is used. DAMPs may contribute to protection against SFSS.

- A05 -

A NEW "TREATMENT-RESPONSE SCORE" FOR AUTO IMMUNE HEPATITIS IS PREDICTIVE OF LONG-TERM EVENT-FREE SURVIVAL AND OVERALL SURVIVAL. A MULTICENTER BELGIAN COHORT STUDY.

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**Introduction :** Autoimmune hepatitis (AIH) is a rare autoimmune liver disease. Without proper diagnosis and treatment AIH leads to the development of cirrhosis and end-stage liver disease. The diagnosis is based on an internationally recognized scoring system. Patients with early initiation of treatment have an excellent prognosis that is similar to a matched control population. However, data for Belgian patients with AIH are limited.

**Aim :** To (1) assess the prevalence and general characteristics of patients with AIH in the Ghent area (Belgium) and (2) to look for predictors of long-term outcome in patients with AIH.

**Methods :** In this retrospective study, data of 212 patients with AIH were reviewed in the hepatology department of Ghent University Hospital, AZ Nikolaas (Sint-Niklaas) and AZ Maria Middelaes (Ghent). Patients with follow-up time shorter than 1 year were excluded. Clinical, biochemical and outcome data, including development of cirrhosis, hepatocellular carcinoma (HCC), need for liver transplantation and death, were collected. Statistical analysis included Mann Whitney U test, Cox regression analysis and Kaplan-Meier survival analysis,

**Results :** Development of cirrhosis with decompensation occurred in 11 patients (6.7%). Ascites was the most common form of decompensation (n=8, 72.7%). Nine patients (5.1%) developed HCC during follow-up, 8 patients died (4.9%). Five-year and ten-year survival was respectively 96.9% and 83.1%. Changes in levels of bilirubin, AST, ALP and GGT after 6 months of first-line treatment for AIH were significantly related to a composite endpoint (adverse outcome), defined as decompensation, HCC development, liver transplantation or death. A “treatment response score” was developed based on these changes and was highly related to adverse outcome (p=0.003). ROC analysis showed an AUC for this score of 0.82 (p<0.001). Using a cut-off derived from the ROC-curve, this score showed a sensitivity of 72.7% and specificity of 82.6% for adverse outcome. Again based on this cut-off, the Kaplan-Meier survival analysis showed an excellent prognosis in “responders” after 6 months of therapy, compared to an adverse outcome in patients with an adverse outcome (Log Rank : p=0.002).

**Conclusions :** Response to treatment after 6 months in AIH using a newly developed scoring system is an excellent predictor of long-term event-free survival in AIH. A validation in two independent Belgian cohorts is ongoing.

- A06 -

GENERATION OF A UNIQUE LIVER PROGENITOR CELL GENE SIGNATURE TO IDENTIFY LPCS AND LPC ACTIVATION IN CHRONIC LIVER DISEASES. S. Verhulst (1), P. Sancho-Bru (2), A. Ceulemans (3), T. Roskams (4), L. Van Grunsven (1) / [1] Vrije Universiteit Brussel (VUB), Jette, Belgium, BMWE - LIVR, [2] d'Investigacions Biomèdiques August Pi i Sunner, Spain, Laboratory of Liver Fibrosis, [3] KUL, Belgium, Imaging and Pathology, Translational Cell and tissue Research, [4] University Hospital, Gasthuisberg, Leuven, Belgium, Imaging and Pathology, Translational Cell and Tissue Research.

**Introduction :** Chronic liver diseases are frequently associated with a ductular reaction. This includes the activation of liver progenitor cells (LPCs), especially in conditions in which hepatocytes are senescent. The extent to which LPCs contribute to liver regeneration is still a subject of debate. The different isolation methods and the use of diverse LPC markers to isolate, characterize and lineage-trace LPCs in healthy, damaged and regenerating livers is certainly one of the culprits.

**Aim :** In this study we want to compare the gene expression profiles of different LPC populations, i.e different species and isolation methods as well as LPC cell lines, and establish a gene signature that identifies LPCs and their activation.

**Methods :** In this study, we analyzed online available gene expression profiles of human (enriched in EPCAM, TROP2 or side population) and mouse (enriched in HNF1b, FOXL1 or MIC1C3) LPCs. We compared their transcriptomes and analysed co-expressed genes by using supraHex and AmiGO. A unique LPC signature was created by pooling enriched genes from each LPC population using venn diagrams. Gene set enrichment analysis using this LPC signature was performed on different iPS- and ESC-derived LPCs, differentiated HepaRGs and on data sets from livers of patients with cirrhosis, ASH, NAFLD or NASH.

**Results :** Comparison between human and mouse LPC populations showed high similarities in genes involved in proliferation and development. Overlap of genes enriched in all LPC population resulted in 45 genes and contains well-known LPC markers but also genes never described in LPCs. LPCs derived from human iPS- or ESC-derived LPCs and undifferentiated HepaRGs showed a higher enrichment of our signature compared to previously established LPC signatures. Gene set enrichment analysis with the LPC signature of liver expression profiles of ASH, NASH and cirrhosis suggests that only these diseases are accompanied by a strong LPC activation.

**Conclusions :** We compared and characterized for the first time human and mouse LPC gene profiles and created a unique LPC signature through an unbiased approach. This signature can be used to identify primary LPCs, LPC cell lines

or LPCs derived from iPS or hESCs and as a tool to evaluate LPC expansion in liver diseases. In the future, we would like to correlate the LPC signature with the outcome of the liver disease.

- A07 -

THE OUTCOME OF ACUTE-ON-CHRONIC LIVER FAILURE IN THE INTENSIVE CARE IS SIMILAR TO A PROPENSITY MATCHED ICU POPULATION WITHOUT LIVER DISEASE. S. Van Der Merwe (1), P. Meersseman (2), L. Langouche (3), M. Mekeirele (2), H. Korf (1), J. Du Plessis (1), D. Cassiman (1), W. Laleman (4), F. Nevens (5), A. Wilmer (2), G. Van Den Berghe (3) / [1] KU Leuven, Leuven, Belgium, Chronic Diseases, Metabolism and Ageing, [2] UZ Leuven, Leuven, Belgium, Internal Medicine, [3] KU Leuven, Leuven, Belgium, Cellular and Molecular Medicine, [4] UZ Leuven, Leuven, Belgium, Chronic Diseases, Metabolism and Ageing, [5] UZ Leuven, Leuven, Belgium, Gastroenterology and Hepatology.

**Introduction :** Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation of cirrhosis, development of organ failure and high short-term mortality. It is unclear whether the ICU outcome in ACLF is different from other ICU populations.

**Aim :** Here we compared the clinical course and host response in critically ill ICU patients with or without ACLF matched for baseline severity of illness scores.

**Methods :** A post-hoc analysis was performed of the large EPaNic ICU study (n=4640) : 133 patients were identified with cirrhosis of whom 71 patients fulfilled the Canonic criteria for ACLF. These patients were matched for type and severity of illness and demographics to 71 septic and 71 medical ICU patients without liver disease. The clinical, biochemical and outcome parameters were compared and, in a subset of 100 patients, day 1 serum cytokines were quantified.

**Results :** The outcome of ACLF when compared to septic or medical ICU patients, matched for baseline parameters of illness severity, was similar regarding length of ICU stay, development of new infections, organ failure and septic shock, ICU hospital and 90-day mortality. CRP and platelets levels were lower in ACLF patients throughout the first week in ICU. Baseline cytokines IL-10, IL-1 $\beta$ , IL-6, and IL-8 were similarly elevated in ACLF and septic ICU patients, whereas serum TNF- $\alpha$  was higher and CCL13 lower in ACLF.

**Conclusions :** ACLF patients admitted to the ICU showed comparable clinical and ICU outcomes compared to non-ACLF patients without liver disease with similar baseline severity of illness characteristics. This suggest that admission criteria to the ICU should not be different in ACLF compared to other populations. Furthermore, ACLF patients that are liver transplant candidates should be identified early in their ICU course.

- A08 -

TRANSCRIPTIONAL REPRESSORS ZEB1 AND ZEB2 REGULATE COLLAGEN PRODUCTION IN DRUG-INDUCED HEPATIC STELLATE CELL ACTIVATION IN MICE. I. Mannaerts (1), L. Stradiot (2), N. Eysackers (2), L. Van Grunsven (2) / [1] Vrije Universiteit Brussel (VUB), Jette, Belgium, LIVR VUB, [2] Vrije Universiteit Brussel (VUB), Jette, Belgium, Liver Cell Biology Laboratory.

**Introduction :** Upon liver injury, hepatic stellate cells become activated myofibroblast-like cells. They lose their vitamin A storing capacity and become collagen producing cells with migratory capacities. This transdifferentiation has been compared to an epithelial to mesenchymal differentiation. This is a strictly orchestrated process, in which a role for E-box repressors, including Snail family members and Zeb proteins, and a role for the miR-200 family has been established. Both the transcriptional repressors and microRNAs that regulate the epithelial to mesenchymal differentiation are transforming growth factor- $\beta$  sensitive regulators.

**Aim :** In this study we investigated the role of Zeb proteins ( $\delta$ ef1 and Sip1) and miR-200 family members during stellate cell activation, migration and fibrosis.

**Methods :** BalbC mice were used to isolate primary hepatic stellate cells, cells were activated by culture in fetal bovine serum containing medium. Repeated carbontetrachloride administration to mice induced liver fibrosis and liver cell types were isolated from these mice using the recently published UFACS3 flow cytometry protocol. The role of ZEB proteins was investigated by siRNA mediated silencing in vitro and in vivo. In vivo targeting of the siRNA to stellate cells was obtained by coupling vitamin A to liposome carriers. Effects of ZEB knock down were evaluated by real time polymerase chain reaction, immunohistochemistry, western blot and migration and proliferation assays.

**Results :** An siRNA mediated silencing of Zeb repressors induced a strong up-regulation of E-cadherin and resulted in a mild decrease of stellate cell activation marker Acta2. In addition, ectopic expression of miR-200c also induced E-cadherin mRNA and protein expression and reduced stellate cell migration in a transwell migration assay. Finally, we have used vitamin-A coupled liposomes to knock down Zeb1 and Zeb 2 in vivo in a chronic fibrosis model. Selective delivery was confirmed by lowered RNA levels of Zeb1 and Zeb2 in stellate cells, but not in other non-parenchymal cells. While the silencing Zeb1 and Zeb2 was modest, a significant reduction in collagen1a1 and collagen3a1 was observed.

**Conclusions :** E-box repressors Zeb1 and Zeb2 are important players in the regulation of stellate cell activation in vitro and in vivo.

- A09 -

INDIVIDUALIZED PREDICTION OF THE RISK OF LIVER-RELATED DEATH IN PATIENTS WITH ALCOHOLIC CIRRHOSIS. A. Marot (1), J. Henrion (2), J. Knebel (3), F. Signy (4), E. Trepo (5), C. Moreno (5), P. Deltenre (6) / [1] CHU UCL Namur, Yvoir, Belgium, Department of Gastroenterology and Hepatology, [2] Hôpital de Jolimont, Haine-Saint-Paul, Belgium, Department of Gastroenterology and Hepatology, [3] Université de Lausanne, Lausanne, Switzerland, Laboratory for Investigative Neurophysiology (The LINE), Department of Radiology and Department of Clinical Neurosciences, [4] Université de Lausanne, Lausanne, Switzerland, Ecole Polytechnique Fédérale de Lausanne, [5] Erasme Hospital, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, [6] Clinique Saint-luc Bouge, Namur, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** In patients with cirrhosis, prognostic models providing a precise estimate of the risk of death are essential for patient care.

**Aim :** To develop a model allowing an individualized prediction of the risk of liver-related death among patients with alcoholic cirrhosis, that takes into account the impact of abstinence.

**Methods :** Data related to death and causes of death were collected among patients with alcoholic cirrhosis consecutively seen in a single center during a 21-year period. Abstinence was defined as discontinuation of any alcohol intake within the first 12 months following inclusion. Multivariate Fine and Gray proportional hazards models were used to identify factors associated with liver-related death. We calculated Akaike information criterion values by adding variables using a forward step by step approach to build the best competing risk regression (CRR) model that predicts liver-related death. To validate the prediction of the model, a cross validation procedure was applied using a training set of 80% and a testing set of 20% of the data randomly chosen. The Brier score was used to estimate the quality of the prediction of the different models tested, the model with the lowest Brier score providing the best prediction.

**Results :** 489 patients (68% of male, median age 55 years [95% CI : 54-56], 45% Child-Pugh stages B or C, median MELD score 9.0 [95% CI : 8.5-9.7]) were included. During follow-up (median, 57 months), 247 patients died, 12 from hepatocellular carcinoma, 156 from liver failure and 76 from non-liver related causes. Three variables were independently associated with liver-related mortality : age (HR : 1.02, 95% CI : 1.01-1.04, p=0.01), Child-Pugh score (HR : 1.20, 95% CI : 1.11-1.29, p<0.001) and abstinence (HR : 0.42, 95% CI : 0.28-0.63, p<0.001). A CRR model using these 3 variables as covariates was built, providing a continuum risk of death at 5 years in abstainers and consumers. For any combination of age and Child-Pugh score, patients who did not abstain from alcohol had a greater risk of dying at 5 years than patients who abstained from alcohol. According to the Brier score, the prediction of liver-related death at 5 years was better using the CRR model than with the random model in 100% of the cases, with the Kaplan Meier model in 93%, and with the Cox model in 92%. The prediction of liver-related death was not better when the MELD score was used in the CRR model instead of the Child-Pugh score.

**Conclusions :** The CRR model combining age, Child-Pugh score and abstinence accurately predicts the risk of liver-related death on an individual basis among patients with alcoholic cirrhosis. Huge differences in 5-years prediction of death were observed in patients who abstained and who did not abstain from alcohol. This model may serve as a tool for prognosis assessment in a daily practice and may help to motivate patients to stop drinking.

- A10 -

IS IT TOO EARLY TO EXPAND BEYOND THE MILAN CRITERIA FOR LIVER TRANSPLANTATION? A RETROSPECTIVE, MULTICENTRIC STUDY IN BELGIUM. H. Degroote (1), E. Callebaut (1), J. De Kervel (2), J. Schreiber (3), J. Pirenne (4), C. Verslype (2), D. Ysebaert (5), P. Michielsen (6), V. Lucidi (7), C. Moreno (3), O. Detry (8), J. Delwaide (8), J. Lerut (9), G. Dahlqvist (10), R. Troisi (11), H. Van Vlierberghe (1) / [1] Ghent University Hospital, Ghent, Belgium, Hepatology and Gastro-Enterology, [2] University Hospital Gasthuisberg, Leuven, Belgium, Hepatology and Gastro-Enterology, [3] University Hospital Brussels, Vrije Universiteit Brussel, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, [4] University Hospital Gasthuisberg, Leuven, Belgium, Department of Hepato-Biliary and Pancreatic Surgery, [5] University Hospital Antwerp, Antwerp, Belgium, Hepato-Biliary and Pancreatic Surgery, [6] University Hospital Antwerp, Antwerp, Belgium, Hepatology and Gastro-Enterology, [7] University Hospital Brussels, Vrije Universiteit Brussel, Belgium, Hepato-Biliary and Pancreatic Surgery, [8] University Hospital CHU of Liège, Liège, Belgium, Liège, Belgium, Hepato-Biliary and Pancreatic Surgery, [9] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Hepato-Biliary and Pancreatic Surgery, [10] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Hepatology and Gastro-Enterology, [11] Ghent University Hospital, Ghent, Belgium, Hepato-Biliary and Pancreatic Surgery.



**Introduction :** Recent studies suggest that a subgroup of patients with liver cirrhosis receiving a liver transplantation (LT) for hepatocellular carcinoma (HCC) beyond the Milan Criteria (MC) can achieve a similar overall and tumor-free survival. Consequently, alternative allocation criteria extending beyond the size-and-number assigned within the MC are proposed. Until now there is no uniformity concerning the most valid alternative criteria. It is a fact however, that an increased percentage of patients with HCC undergoes transplantation beyond conventional indications. Recently, the use of (non-specified) expanded criteria has also been cited in international guidelines which leads to non-uniformed allocation protocols. Therefore, further validation of these new expanded criteria is an urgent need.

**Aim :** This retrospective, multicentric study has the objective to investigate the value of the up-to-7 criteria (with seven being the maximal allowed sum of the size of the largest tumor (in cm) and the number of tumors for any given HCC) compared to the MC as gold standard. For this purpose we evaluated if there was a difference in survival and risk of recurrence between patients within MC compared to patients beyond the MC, but within the up-to-7 criteria.

**Methods :** We analyzed 378 patients transplanted for non-metastatic HCC from 5 different transplant centers in Belgium (Ghent University Hospital, University Hospitals of Leuven, Erasme Hospital Free University of Brussels, University Hospital of Liège, University Hospital of Antwerp) between 1999 and 2015. Patient groups were determined according to radiological MC and up-to-7 criteria at listing. We did not consider microvascular invasion (MVI) for the up-to-7 criteria because this parameter is not available at listing in routine clinical practice. To validate this method, we compared the survival and recurrence between patients within the up-to-7 criteria in the presence or absence of MVI. We also assessed the correct estimation rate of pre-operative radiological staging compared to post-operative histological staging.

**Results :** In our cohort analysis based on pathological examination showed that 36,5% of patients were beyond MC and 25,1% beyond the up-to-7 criteria. Assessment of the accuracy of pre-operative radiological staging at listing resulted in a total discrepancy of 29,4% (22,0% understaged, 7,4% overstaged) for the MC and 20,1% (17,2% understaged, 2,9% overstaged) for the up-to-7 criteria. There was a statistical significant difference between the group of patients within MC compared to patients beyond MC in 5-year overall survival (75,1% vs. 53,2%,  $p=0.001$ ) and recurrence rate (10,9% vs. 30,0%,  $p<0,0001$ ). With similar results for the up-to-7 criteria (73,7% vs. 43,1%,  $p<0.001$  and 11,9% vs. 43,0%,  $p<0,0001$  respectively). We found no significant difference in 5-year overall survival rate between the subgroup of patients within MC vs. patients beyond MC but within the up-to-7-criteria (75,1% vs. 63,8%,  $p=0,259$ ). However, the latter subgroup had a tendency towards higher recurrence rate (10,9% vs. 19,0%,  $p=0,105$ ). Adjusting the up-to-7 criteria according to the presence of microvascular invasion on explant pathology resulted in a worse outcome. The 5-year overall survival and recurrence rate was 67,3% and 14,9% in the absence of microvascular invasion compared to 47,9% and 22,2% respectively in the subgroup of patients with microvascular invasion.

**Conclusions :** We found no significant difference in 5-year overall survival rate between patients within MC and beyond MC but within the extended up-to-7 criteria. The up-to-7 criteria have a higher pre-operative accuracy and discriminatory power for predicting survival and recurrence compared to the MC. Therefore the up-to-7 criteria could be considered as alternative selection criteria for liver transplantation in patients with HCC and liver cirrhosis. However, caution is warranted as expanding the criteria was associated with an increased 5-year recurrence in our cohort. This might be the price for extending beyond MC and reflects the Metroticket paradigm. The finding that inclusion of MVI resulted in worse outcome emphasizes the need to further prospectively validate models incorporating markers of tumor biology.

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TRANSCRIPTOMIC PROFILING OF INTRAHEPATIC B CELLS SUGGESTS A B-CELL IMPAIRMENT IN THE IMMUNE ACTIVE PHASE OF CHRONIC HEPATITIS B. S. Van Hees (1), J. Hou (2), A. Groothuisink (2), K. Kreeft (2), S. Bourgeois (3), L. Vonghia (1), S. Francque (1), P. Michielsen (1), A. Boonstra (2), T. Vanwolleghem (1) / [1] Antwerp University Hospital, Edegem, Belgium, Department of Gastroenterology and Hepatology, [2] Erasmus Medical Center, Rotterdam, Netherlands (the), Department of Gastroenterology and Hepatology, [3] ZNA Antwerpen, Antwerpen, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** Using a systems biology approach, we recently demonstrated a significant activity of B-cell related genes in whole blood and liver biopsies during sequential clinical phases of a chronic Hepatitis B Virus (HBV) infection.

**Aim :** We here investigated for the first time the transcriptome of paired sorted B cells from liver and blood across the different HBV clinical phases.

**Methods :** CD19+ B cells were purified by cell sorting (FACS Aria) from PBMC of healthy controls (HC ;  $n=13$ ) and untreated HBV patients in the 4 different HBV clinical phases : Immune Tolerant (IT ;  $n=3$ ), Immune Active (IA ;  $n=14$ ), Inactive Carrier (IC ;  $n=9$ ) and HBeAg negative phase (ENEG ;  $n=16$ ). In addition, paired CD19+ B cells were sorted from core needle liver biopsies of 6 IA, 5 IC and 3 ENEG patients. RNA-sequencing and data analysis was performed using Unique Molecular Identifiers. Two different bio-informatical analysis approaches were applied : 1. Analysis of Differentially Expressed Genes (DEG) with  $q<0.2$  and fold-change $>1.5$  ; 2. Gene pattern analysis on a literature based selected set of B-cell related genes ( $n=92$ ). FACS analysis was performed to assess CD10, CD21, CD27, CD38 and IgD expression on peripheral CD19+ B cells.

**Results :** FACS analysis of peripheral B-cell subsets did not show significant differences between different HBV phases. Analysis of DEG in peripheral B cells revealed only 5 common DEG across all HBV clinical phases vs. healthy controls. However, each individual HBV clinical phase showed a significant number of DEG (IA : n=912 ; ENEG : n=874 ; IC : n=785 and IT : n=562) when compared to the HC B cell transcriptome, with most overlapping DEG (n=348) in the IA and ENEG phase. This is highly suggestive for different roles of B cells during the distinct HBV clinical phases. Gene pattern analysis demonstrated lower expression of 4 genes, including PDL1 and IL2RA in peripheral B cells across all HBV clinical phases vs. healthy controls. Applying the gene set pattern analysis on intrahepatic B cells showed an upregulation of genes encoding B cell inhibitory proteins in the IA phase relative to the IC and ENEG phase. In addition, intrahepatic CXCR3 transcription was higher in both IA and ENEG phases. These patterns were absent in blood, suggesting a liver-specific HBV-associated B-cell impairment, but active recruitment during the IA phase. Detailed assessment and functional analysis of specific genes is ongoing in both liver and peripheral B cells.

**Conclusions :** This is the first assessment of gene expression profiles of B cells by RNASeq in blood and liver of chronic HBV patients. Bio-informatical analysis demonstrated a high number of DEG not only when comparing paired liver and blood B cells, but also -more importantly- when comparing the distinct phases of disease differing in levels of viral replication and liver damage.

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SHORT AND LONG-TERM SURVIVAL OF PATIENTS SUFFERING FROM NON-SEVERE ALCOHOLIC HEPATITIS. G. Englebort (1), D. Degré (2), T. Gustot (2), P. Demetter (3), A. Marot (4), P. Deltenre (4), E. Trepo (2), C. Moreno (2) / [1] Erasme Hospital, Brussels, Belgium, Department of Gastroenterology and Hepatopancreatology, [2] Erasme Hospital, Brussels, Belgium, Department of Gastroenterology and Hepatopancreatology, [3] Erasme Hospital, Brussels, Belgium, Department of Pathology, [4] Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, Division of Gastroenterology and Hepatology.

**Introduction :** Alcoholic hepatitis (AH) is a clinical syndrome characterized by the recent onset of jaundice in a context of heavy alcohol consumption. Typical histological lesions include steatosis, hepatocyte ballooning, and an inflammatory infiltrate with polymorphonuclear neutrophils. Although prognosis of severe forms of the disease, defined by a Maddrey discriminant function (mDF)  $\geq 32$ , has been well studied, survival of patient with non-severe AH, is currently unknown beyond 28 days.

**Aim :** The aim of our study was to define the short and long-term prognosis of these patients, and to determine prognostic factors of mortality.

**Methods :** This study included patients who had a histological diagnosis of alcoholic steatohepatitis with a mDF  $< 32$  between 1st of January 2003 and 31st of December 2014. We excluded patients with other causes of liver disease. The statistical analysis was performed on the overall population and then we defined two subpopulations of patients with or without signs of hepatic decompensation at admission.

**Results :** Our study cohort included 134 patients. 74 patients were admitted with liver decompensation and 60 for abnormal liver tests without any signs of liver decompensation. At baseline, patients' characteristics were : male gender : 66.4%, alcohol consumption  $> 80$ g : 82%, liver decompensation : 43% (ascites : 35%, encephalopathy : 22%, bilirubin  $> 3$ mg/dL : 26.1%), median age : 54.5 years (33-72), hepatic venous gradient : 12mmHg (1-33), prothrombin time : 75% (49-130), bilirubin : 1.7mg/dL (0.2-23), creatinine : 0.7mg/dL (0.3-2.9), albumin : 35.5 g/L (15-59), white blood cells : 7500/mm<sup>3</sup> (3100-24900), AST : 70IU/L (15-333), ALT : 44IU/L (8-403), GGT : 331IU/L (36-2882), MELD score : 11 (6.43-27.96) and mDF : 12 (0.3-31). 1- and 24-months survival were respectively 93.8% (+/-2.1%) and 74.8% (+/-4.0%) in the overall population. 24-months survival in patients with liver decompensation at admission was statistically lower compared to patients without liver decompensation : 66.5% (+/- 5.9%) versus 85% (+/-4.9%), respectively (p=0.025). Causes of death were related to liver decompensation in 73%. Low albumin and the absence of alcohol abstinence during the follow-up were associated with an increasing risk of mortality in the overall population.

**Conclusions :** In this large cohort of non-severe AH patients, short-term survival of these patients is satisfactory, but their long-term prognosis is severely impaired, particularly in patients with liver decompensation at the time of AH diagnosis. Identifying this group of patients and defining a specific therapeutic strategy including long term alcohol abstinence could be clinically relevant.

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ANGIOPOIETIN-2 AS THERAPEUTIC TARGET FOR PATHOLOGICAL ANGIOGENESIS AND INFLAMMATION IN NON-ALCOHOLIC STEATOHEPATITIS. S. Lefere (1), F. Van De Velde (2), S. Raevens (1), S. Van Campenhout (1), A. Vandierendonck (1), S. Neyt (3), C. Vanhove (4), C. Van Steenkiste (5), A. Hoorens (6), C. Casteleyn (7), X. Verhelst (1), H. Van Vlierberghe (1), B. Lapauw (2), A. Geerts (1), L. Devisscher (1) / [1] Ghent University, Ghent,

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**Introduction :** Angiogenesis and inflammation are interconnected mechanisms that influence the progression of non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH). Previous studies have shown that angiopoietin-2 (Ang-2) mediates both these processes, although this has not yet been investigated in NASH.

**Aim :** Our aim was to investigate the role of Ang-2 and its potential as therapeutic target in NASH by using human samples, an in vivo mouse model and in vitro assays.

**Methods :** Serum Ang-2 levels were determined in obese patients undergoing bariatric surgery (n=105) with concomitant liver biopsy, in healthy controls (n=30), and in mice fed the methionine choline deficient (MCD) diet. The Ang-2/Tie2 receptor inhibiting peptibody L1-10 (Amgen) was tested in vivo (4mg/kg intraperitoneally three times weekly) in the MCD diet model in a preventive and therapeutic setting (starting at week 0 and after 2 weeks, respectively), and in vitro on endothelial MS1 cells. Liver histology and chemokine expression were assessed. The hepatic vascular bed was visualized using corrosion casts. FACS-isolated liver endothelial cells and monocytes were analysed by qRT-PCR.

**Results :** Serum Ang-2 levels were increased in patients with NASH compared to lean controls, obese patients without steatosis and patients with NAFL (all  $p < 0.01$ ) and correlated with the severity of steatosis ( $p < 0.05$ ), inflammation and ballooning (both  $p < 0.001$ ), but not fibrosis. In line, serum, hepatic, and endothelial Ang-2 levels were increased in MCD diet fed mice ( $p < 0.001$ ), correlating with markers of endothelial dysfunction and inflammation. Efficient in vivo dosing was confirmed by increased Ang-2 serum levels in L1-10 treated mice. MCD fed mice treated with L1-10 showed less inflammatory foci and ballooning hepatocytes compared to control treated mice ( $p < 0.05$ ). Chemokine and endothelial dysfunction gene expression were similarly decreased following treatment. Fibrosis, assessed by sirius red area, was reduced. Liver endothelial cells and monocytes from L1-10-treated MCD fed mice expressed lower levels of dysfunction and inflammatory markers compared to cells from control treated mice. LPS-stimulated MS1 cells secreted pro-inflammatory cytokines and showed increased expression of endothelial dysfunction markers, which was significantly less pronounced in cells treated with LPS + L1-10.

**Conclusions :** Angiopoietin-2 mediates the cross-talk between angiogenesis and inflammation in NASH, and is upregulated in humans and MCD fed mice. Our findings provide evidence for Ang-2 inhibition as a therapeutic strategy in NASH.

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LONG-TERM OUTCOME IN PATIENTS WITH ACUTE LIVER FAILURE. A. Putignano (1), F. Figorilli (2), B. Agarwal (3), R. Jalan (4) / [1] Erasme Hospital, Brussels, Belgium, Hepatology and Gastroenterology, [2] Azienda Ospedaliero-Universitaria di Cagliari, Cagliari, Italy, Internal Medicine, [3] Royal Free Hospital, London, United Kingdom (the), Intensive Care Unit, [4] Royal Free Hospital, London, United Kingdom (the), ILDH, Division of Medicine.

**Introduction :** Acute liver failure (ALF) in patients requiring ICU admission is associated with high mortality. Emergency Liver transplantation (ELT) has emerged as the gold standard treatment for patients who are unlikely to survive with medical treatment alone. The determination of prognosis and listing for liver transplantation (LT) is assessed through prognostic tools of which the modified King's College Hospital (KCH) criteria is currently the most widely used. In light of the mounting evidence supporting the trend of improving spontaneous survival rates (without ELT) decade after decade, the actual role of ELT in ALF has been in the spotlight, rising questions about its benefit in some categories of patients. This is particularly relevant given the shortage of organs, the emergency nature of the surgery, which could compromise the short-term outcome, and the chronic complications associated with a LT, which could influence the long-term one, an observation which is predictable as potential spontaneous survivors (SS) would not be exposed to the late complications of a biliary surgery and a life-long immunosuppression therapy. However, a recent multicentre study has reported an exactly opposite finding, the one of poorer long-term outcomes for the SS, concluding that the treatment in ALF should preferably be surgical. Therefore, the long-term follow up data for many of the patients were missing.

**Aim :** To study the long-term (post ELT or spontaneous recovery) outcomes in a cohort of ALF patients admitted to a single large tertiary liver center equipped with transplantation facility and an established process of follow-up, in order to confirm or refute this observation.

**Methods :** Only patients who survived 90 days or longer following conservative or ELT intervention (Early survivors, ES), were retrospectively assessed for long-term outcomes ; they were stratified in 4 cohorts incorporating ALF aetiology (Acetaminophen overdose ; APAP, non-Acetaminophen ; nAPAP) and management strategy (SS and ELT) (APAP ELT, APAP SS, nAPAP ELT, nAPAP SS). Chi Squared or Fisher test (categorical variables) and ANOVA or Kruskal Wallis test (continuous variables) were used to compare baseline characteristics and outcomes among the cohorts ( $p < 0.05$ ) and Kaplan Meier curve (Log Rank test) to represent cumulative survival (Spss Inc., Chicago, IL).

**Results :** 200 consecutive ALF patients admitted to Royal Free Hospital ICU between 1990 and 2014 were included ; mean age 38.3 ( $\pm$  12.8), male 70, 35%. 76/87 deaths (87.4%) occurred within the first 90 days of ICU admission (Early Dead, ED), but less than 70% within 21 days. The causes of death in the ED group were related to the severity of the acute condition. The remaining 124/200 survived past 90 days, called ES :13/124 (10.5%) APAP ELT, 48/124 (38.7%) APAP SS, 36/124 (29.0%) nAPAP ELT and 27/124 (21.8%) nAPAP SS ( $p < 0.001$ ). 162/200 patients fulfilled the KCH criteria (81%), but only 70/162 (43.2%) were transplanted. More than 90% of the ED fulfilled the KCH criteria, but 55.7% ( $N = 39/70$ ) were not transplanted because they died waiting for LT or because delisted due to clinical deterioration. Among the ES, 92/124 patients (74.2%) fulfilled the KCH criteria, but 38/92 (41%), mainly APAP related, were not transplanted because of clinical improvement. The long-term deaths were 11/124 (8.9%, median survival 5.3y  $\pm$  IQR 9.1) ; three SS and 8 ELT ( $p = 0.025$ ) ; of the 8 ELTs, six died of transplant related complications and the other two committed suicide. The estimated overall survival was worse in ELT patients ( $p = 0.029$ ), in particular for APAP intoxication ( $p = 0.005$ ).

**Conclusions :** This study shows that ELT in ALF is associated to higher long-term mortality compared to SS, in particular for APAP aetiology, rising ethical and therapeutic considerations, given the need of a fair allocation of organs and the risks of unnecessary LT in patients that could avoid chronic complications and increased long-term mortality related to ELT. Also, it suggests that the KCH criteria have a low specificity and are inadequate at early recognising the candidates to ELT, as the short-term mortality (within 90-day from ICU admission) emerges to be a consequence of the selection of severely sick patients managed with ELT.

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THE EFFECTS OF METHOXAMINE AND ENDOTHELIN-1 ON THE INCREASED TRANSHEPATIC PRESSURE GRADIENT IN A RAT MODEL OF SEVERE STEATOSIS. D. Van Der Graaff (1), W. Kwanten (1), J. De Man (2), B. De Winter (2), P. Michielsen (1), S. Francque (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Department of Gastroenterology and Hepatology, [2] Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disease of the Western world. Prior to development of inflammation or fibrosis, the intrahepatic vascular resistance (IHVR) is increased both in animals and in patients, impairing hepatic blood flow and potentially causing disease progression. Similar to the mechanisms involved in portal hypertension during cirrhosis, hyperreactivity to vasoconstrictive agents is a potential mechanism of the increased IHVR in steatosis.

**Aim :** The present study seeks to elucidate the vasoconstrictive effects of alpha 1-adrenergic mediators and endothelin-1 (ET-1) on the IHVR in severe steatosis without inflammation or fibrosis.

**Methods :** The IHVR was studied by measuring the transhepatic pressure gradient (THPG) in an in situ ex vivo rat perfusion model, in which the liver is isolated, connected to a circuit with a pump and perfused by Krebs solution, with or without addition of drugs. The THPG was studied in Wistar rats ( $n = 6-8$ /group) on a methionine-choline-deficient diet, inducing severe steatosis after 4 weeks, and compared to rats on a control diet. The effects of the alpha 1-adrenergic agonist methoxamine (Mx,  $10^{-6} - 3 \times 10^{-4}$  M), the alpha 1-adrenergic antagonist prazosin (PRZ,  $10^{-7} - 10^{-4}$  M) and the vasoconstrictor ET-1 ( $10^{-12} - 3 \times 10^{-10}$  M) were studied in dose-response experiments, increasing the doses by 0.5 log M every 5 minutes at a constant flow of 30 mL/min. Subsequently, flow-pressure curves were constructed to investigate the effects of  $10^{-5}$  M Mx and  $10^{-10}$  M ET-1 by increasing the flow by 5 mL/min every 5 minutes (10-50 mL/min).

**Results :** The basal THPG in steatotic livers was significantly increased compared to controls at all flows (10-50 mL/min) ; at 30 mL/min  $5.4 \pm 0.3$  mmHg versus  $4.4 \pm 0.2$  mmHg [ $p < 0.001$ ] respectively. Dose-response curves showed a significantly increased vascular sensitivity and responsiveness of steatotic livers to Mx ( $EC_{50} = 10^{-5.0}$  M,  $T_{max} = 9.8$  mmHg) compared to controls ( $EC_{50} = 10^{-4.8}$  M,  $T_{max} = 8.2$  mmHg [ $p < 0.05$ ]). In flow-pressure experiments, the THPG of steatotic livers showed a significantly increased reactivity to Mx at all flows (10-50 mL/min). At 30 mL/min, Mx ( $10^{-5}$  M) significantly increased the THPG in control rats from  $4.4 \pm 0.2$  mmHg to  $7.5 \pm 0.4$  mmHg (70.5% increase ;  $p < 0.001$ ). In steatotic animals, Mx ( $10^{-5}$  M) increased the THPG after even more pronounced from  $5.4 \pm 0.3$  mmHg to  $10.5 \pm 0.6$  mmHg at 30 mL/min (94.4% increase ;  $p < 0.001$ ). PRZ did not alter the THPG in both controls and steatosis. ET-1 induced a dose-dependent increase of the THPG in both controls and steatosis, with significantly increased sensitivity and responsiveness to ET-1 in steatosis ( $20.3 \pm 1.3$  mmHg at  $3 \times 10^{-10}$  M) compared to controls ( $14.9 \pm 1.4$  mmHg at  $3 \times 10^{-10}$  M,  $p < 0.001$ ). Flow-pressure experiments confirmed the hyperreactivity to ET-1 in steatotic livers with a more rapid and higher increase in THPG and the maximum THPG was reached at significantly lower flows compared to controls (controls  $15.3 \pm 1.1$  mmHg at 30 mL/min, increase of 247.7% compared to Krebs ; steatosis  $23.8 \pm 0.6$  mmHg at 30 mL/min, increase of 340.7% compared to Krebs,  $p < 0.001$ ).

**Conclusions :** Steatotic rat livers demonstrate an increased reactivity to both Mx and ET-1 induced vasoconstriction, as compared to controls. The reactivity to the vasoconstrictor ET-1 was relatively larger compared to Mx. These results suggest that increased reactivity to vasoconstrictors, in particular to ET-1, can potentially be held responsible for the increased THPG as reported in NAFLD.

RISK OF HEPATOCELLULAR CANCER AND FIBROSIS EVOLUTION IN HCV PATIENTS TREATED WITH DIRECT ACTING ANTIVIRAL AGENTS. C. Hamoir (1), P. Starkel (1), G. Dahlqvist (1), Y. Horsmans (1), N. Lanthier (1) / [1] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Service d'Hépatogastro-entérologie.

**Introduction :** Chronic hepatitis C virus (HCV) is the leading risk factor for hepatocellular cancer (HCC) worldwide with an estimated annual incidence rate of 3.5%. The treatment of HCV has experienced a revolution since the emergence of new direct-acting antivirals (DAA). The emergence of DAA also allows the treatment of cirrhotic patients even decompensated. The expected outcome of DAA-induced SVR is also to reduce fibrosis and decrease complications of chronic hepatitis C, including HCC development. Alarming case series recently suggested a higher risk of HCC occurrence or recurrence following this new treatment strategy (Reig et al. and Conti et al. J Hepatol. 2016).

**Aim :** The goals of our study are first to evaluate the risk and determinants of HCC and second to assess the evolution of fibrosis in patients treated for HCV with advanced fibrosis stages (Metavir fibrosis stages F3 or F4) who achieved SVR after DAA treatment.

**Methods :** We conducted a prospective study of HCV patients with advanced liver fibrosis stages who were treated with DAA at Saint-Luc hospital between October 2014 and February 2017. We calculated the annual incidence rates for HCC. We used Cox regression models in order to identify factors associated with HCC. Transient elastography (TE) was performed 12 and 24 months after the end of DAA treatment and non-invasive liver fibrosis biomarkers (APRI, FIB-4 and Fibrotest) were performed twice a year during follow-up.

**Results :** Among the 143 patients who achieved DAA-SVR, 6 patients developed HCC. The median follow-up time was 13 months. The median occurrence time of HCC was 12 months. The annual incidence rate of HCC in our cohort was 2.7 per 100 patients. Risk factors associated with HCC after DAA in our multivariable model were genotype 2 and steatosis. We also found a significant increased incidence rate of HCC in non-Caucasian patients. Overall TE values significantly decreased after DAA treatment with a median value prior to treatment of 16,9 kPa (IQR : 11,7-27,4) to a median of 9,9 kPa (IQR : 6,8-21,3,  $p < 0,0001$ ) and 10,8 (IQR : 6,55-15,48,  $p = 0,006$ ) 12 and 24 months after the end of the treatment respectively. Biological fibrosis scores APRI, FIB-4 and Fibrotest also decreased significantly after DAA treatment.

**Conclusions :** We confirmed that DAA-induced SVR is associated with a reduction in the estimated fibrosis. DAA treatment does not seem to be associated with HCC promotion after HCV eradication in patients with advanced fibrosis stages. Nevertheless, as this HCC occurrence remains possible, imaging surveillance should be continued after SVR.

THE COMBINATION OF N-ACETYLCYSTEINE AND ANTI-MT ANTIBODIES AS NOVEL THERAPY FOR ACETAMINOPHEN-INDUCED LIVER INJURY. L. Devisscher (1), D. Laukens (2), H. Van Eeckhoutte (2), S. Raevens (2), S. Lefere (2), A. Hoorens (3), X. Verhelst (2), M. Lynes (4), A. Geerts (2), H. Van Vlierberghe (2) / [1] Ghent University, Ghent, Belgium, Gastro-enterology and hepatology, [2] Ghent University, Ghent, Belgium, Gastro-enterology and Hepatology, [3] Ghent University, Ghent, Belgium, Pathology, [4] University of Connecticut, Storrs, United States (the), Molecular and cell biology.

**Introduction :** Acetaminophen (APAP), known as paracetamol, is the most widely used antipyretic and analgesic over-the-counter drug and the foremost cause of acute liver failure in the U.S. and Europe. Currently, N-acetylcysteine (NAC) is the only pharmacological treatment option for patients suffering from APAP-induced liver injury (AILI) but NAC is only effective when given within the first 12-24 hours following APAP ingestion. Later, liver transplantation is the only curative and life-saving option, emphasizing the need for alternative treatment options. The underlying mechanism of AILI is hepatocyte death and the subsequent release of danger signals. These signals attract and/or activate immune cells including macrophages (Mf), which further contribute to inflammation and tissue damage. Thus, inhibition of Mf infiltration and activation represents an interesting therapeutic strategy for patients presenting with AILI. We and others have previously shown that metallothioneins 1 and 2 (MTs), acute phase proteins, have important danger signalling functions.

**Aim :** Therefore, we investigated the role of MTs and their potential as therapeutic target in AILI.

**Methods :** Metallothionein mRNA expression was determined in liver tissue of mice with AILI and in APAP treated BWTG3 cells. APAP hepatotoxicity was induced in fasted C57BL/6J mice by intraperitoneal (IP) injection of 300 mg/kg APAP, dissolved in heated PBS. Two hours after APAP intoxication, mice were treated IP with PBS, 200 mg/kg NAC, 15 mg/kg anti-MT antibodies (anti-MT, clone UC1MT), or the combination of NAC and anti-MT. Mice were sacrificed 24 hours after APAP injection, serum was collected for measurement of transaminase levels and livers were isolated and processed for further analyses including histology, qRT-PCR and flow cytometry. The Mf-polarizing effect of MTs was assessed on bone marrow-derived Mf.

**Results :** The expression of Mt1 and Mt2 was significantly increased in liver tissue of mice with AILI and in APAP treated hepatocytes. APAP intoxication resulted in increased levels of serum transaminases and extended necrotic

regions on liver histology. When comparing NAC to anti-MT treatment, both treatments resulted in a similar reduction in serum AST and ALT levels and the amount and extension of necrotic regions compared to untreated mice. Combining all treatment groups, only the combination of NAC+anti-MT showed significant lower serum transaminase levels and liver necrosis compared to untreated APAP-intoxicated mice. APAP-intoxicated mice exhibited increased hepatic expression of pro-inflammatory cytokines which were reduced in all treatment groups. Flow cytometric analyses showed a marked infiltration of CD45+Ly6G-F4/80+CD11b<sup>hi</sup>Ly6Chi monocytes and a reduction in the percentage of CD45+Ly6G-F4/80+CD11b<sup>int</sup>Ly6C-Tim4+ resident Kupffer cells in all APAP-intoxicated mice. Monocyte infiltration was reduced in both NAC and NAC+anti-MT treated mice whereas the reduction in Kupffer cells was partially rescued only in mice treated with the combination therapy. Anti-MT treatment of LPS-stimulated bone marrow-derived Mφ resulted in reduced expression of TNFA, Il1b, Arg1, iNos2 and the inflammasome-components NLRP3 and NLRP6.

**Conclusions :** Metallothioneins are upregulated during APAP-intoxication, and the neutralization of secreted MTs using a monoclonal antibody together with NAC exceeds the standard of care therapy in an experimental APAP model. In addition, we present evidence suggesting that secreted MTs are involved in inflammasome activation and Mφ polarization. Taken together, the combination of anti-MT and NAC might represent a novel therapeutic strategy for patients presenting with AILI.

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#### THE IMPACT OF PULMONARY ARTERIAL HYPERTENSION THERAPY IN PATIENTS WITH PORTOPULMONARY HYPERTENSION : A SINGLE TERTIARY CENTER COHORT ANALYSIS

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**Introduction :** Portopulmonary hypertension (PoPH) has an ominous prognosis. Pulmonary arterial hypertension (PAH) specific medical therapy aims to improve hemodynamics to a threshold at which liver transplantation could safely be performed. However, currently there is limited long-term outcome data available.

**Aim :** The aim of the present study was to evaluate efficacy of PAH therapy on cardiopulmonary hemodynamics, functional status, liver related complications and transplant outcome in patients with cirrhosis and PoPH in a single tertiary liver center with transplant facilities.

**Methods :** In patients treated for PoPH the evolution of New York Heart Association (NYHA) classification, the six-minute walk distance (6MWD), MELD score, complications of portal hypertension and final outcome were prospectively monitored. Hemodynamic parameters were re-evaluated by serial right heart catheterization.

**Results :** Between 1997 and 2016, 31 patients were diagnosed with PoPH of which 29 received medical treatment and had long-term follow-up. All patients with PoPH subjected to PAH therapy responded to therapy with a significant improvement of mPAP (-15%, p = 0.008), PVR (-42%, p = 0.012), CO (+36%, p = 0.01), CI (+40%, p = 0.011) and functional capacity (NYHA functional class (-0.9 points, p < 0.001) and 6MWD (+65 m, p < 0.001)) at 6 months. In addition, PAH treatment was associated with an improvement of MELD score (10 ± 3.7 to 8.8 ± 4.6, P = 0.025) and a significant decrease in portal hypertensive complications. Of the 10 patients with advanced liver disease (mean MELD >12) that evolved to mild PoPH, and thus became eligible for LTx, 7 showed hepatic recompensation. Overall, the 5 years mortality due to liver impairment in the absence of LTx was 8% and there was no difference in the 5-year survival in patients at baseline with or without advanced liver disease : 49% vs 42%. Mortality was primarily driven by cardiopulmonary complications.

**Conclusions :** These data confirm the benefit and safety of PAH therapy also in patients with PoPH. Moreover, a favorable response to PAH therapy not only affected prognosis but also seems to hold the potential to improve liver dysfunction and reduce portal hypertensive complications. This combined impact therefore questions the need for LTx in patients with compensated liver disease and PoPH.

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#### CYTOTOXIC CD8 T LYMPHOCYTES ARE ASSOCIATED WITH “ACTIVE” NASH : FROM THE BLOOD TO THE LIVER.

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**Introduction :** Non-alcoholic Fatty Liver Disease (NAFLD) is a major cause of liver disease, and it has been estimated to become the first indication for liver transplantation in the near future. Understanding the underlying mechanisms is, therefore, mandatory, also in order to facilitate drug discovery in this field. The liver is a frontline immunological organ containing numerous innate and adaptive immune cells playing a role in host defence. Increasing evidence suggests that an imbalance of pro- and anti-inflammatory responses involving both innate and adaptive mechanisms affects the induction and progression of Non-alcoholic Steatohepatitis (NASH). Liver myeloid and lymphoid immune populations are altered in animal models of NASH. However, the contribution of different immune cell populations in human NASH is unclear.

**Aim :** To identify a NASH-specific immuno-inflammatory signature in the blood and in the liver and to correlate with phenotype (liver histology, metabolic comorbidities) and genotype.

**Methods :** Flow cytometric analysis of 39 myeloid and lymphoid immune cell populations in blood was performed in patients without (n = 17) or with NASH (n = 21), stratified for type 2 diabetes mellitus (T2DM). Microarray analysis of liver biopsies was integrated with immunological data to discover gene signatures associated with active NASH (inflammation and ballooning). Specificity of the transcriptomic NASH signatures was tested at baseline and after one-year follow-up in an independent cohort of patients undergoing Roux-en-Y gastric bypass (n = 23) or dietary intervention (n = 11).

**Results :** Cytotoxic CD8 T lymphocytes were significantly increased in blood and in livers of NASH patients and correlated positively with liver inflammation and ballooning. T2DM affected levels of cytotoxic CD8 T lymphocytes in blood from subjects with no NASH, but had no additive effect on the NASH-associated increase of these cells. Protein expression of perforin and granzyme A in circulating CD8 T lymphocytes and expression of their genes (PRF1 and GZMA) in the liver were associated with lobular inflammation, ballooning, and a transcriptomic signature of apoptosis. Network integration of the transcriptomic data with clinical and immunological parameters revealed co-regulated gene modules, linked with NASH and CD8 T lymphocytes and enriched in genes involved in the control of inflammation and metabolism. These genes encoded nuclear receptors (RXRA, NR1D1, NR1D2), inflammatory transcription factors (JUN, STAT4) and inflammatory molecules (CRP, SAA1/2, IL18, CSF1, CXCL9/10). Genes involved in the regulation of glucose and lipid metabolism (FOXO1, IGF1, RORA) were negatively linked to both NASH and CD8 T lymphocytes in the liver and to glucose levels and HbA1c. Reduction of lobular inflammation and ballooning upon bariatric surgery or dietary intervention was correlated with a decrease of the hepatic expression of PRF1 and GZMA, and overall gene expression in the gene modules linked with NASH and CD8 T lymphocytes.

**Conclusions :** CD8 T lymphocytes are, independently from diabetes and obesity, associated with lobular inflammation and ballooning. The link between CD8 T lymphocyte hepatic accumulation and the specific alterations of transcription programs associated with NASH (including a pro-inflammatory gene signature) that is reversed upon disease activity reduction (by bariatric surgery or dietary intervention) indicates that CD8 T lymphocytes might constitute a new target for active NASH therapy. Moreover, the highly significant correlation between cytotoxic CD8 T lymphocytes and disease activity in NASH may also suggest that evaluation of these immune cell populations in blood might be used as part of non-invasive diagnostic analysis of NASH. In line, identifying patients for enrolling into the numerous on-going clinical trials without the need of a liver biopsy is a burning issue. The diagnostic accuracy of this approach needs, however, to be further studied in larger and appropriately designed studies.

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INSULIN RESISTANCE IN CIRRHOTIC PATIENTS : RESULTS FROM A LARGE PROSPECTIVE STUDY. F. Clarembeau (1), P. Starkel (1), G. Dahlqvist (1), I. Leclercq (2), N. Lanthier (1) / [1] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Service d'Hépatogastroentérologie, [2] Université Catholique de Louvain, Brussels, Belgium, Laboratory of Gastroenterology and Hepatology, Institut de Recherche Expérimentale et Clinique.

**Introduction :** Cirrhosis has a high morbidity and mortality. A lot of data suggest that cirrhosis could be associated with insulin resistance (IR) and diabetes mellitus (DM). The mechanisms underlying this process and the consequences of altered glucose homeostasis on morbi-mortality remain under debate.

**Aim :** We performed a prospective study to answer the following questions : is cirrhosis associated with IR and DM ; is IR, independently from DM, associated with cirrhosis severity ; are the different etiologies of cirrhosis associated with different levels of IR and does glucose homeostasis alterations correlate with higher morbidity and mortality?

**Methods :** From February 2016 to September 2017, patients seen at the hepatology clinic were prospectively enrolled in this study. At inclusion, fasting blood glucose and insulinemia were measured and used to calculate the homeostasis model assessment of insulin resistance (HOMA). Patients were separated in several cohorts, based on the presence or absence of cirrhosis (cirrhosis versus controls), absence or presence of DM (patients treated with glucose modulating agents) and IR (HOMA > 2.5). We recorded the cause of the underlying liver disease and the number of hospitalization due to cirrhosis complication and death during follow-up.

**Results :** 107 patients with cirrhosis and 20 (non-cirrhotic) controls accepted to participate in this study. Both groups were comparable in terms of age, body mass index, creatinine and triglyceride levels. Expectedly, cirrhotic patients

had however significant lower levels of albumin, platelets and cholesterol and significant higher levels of AST and INR. There were 43% of patients with DM within the cirrhotic group compared with 25% of patients within the control group, meaning that diabetes was more frequent in cirrhotic patients although it didn't reach statistical significance ( $p=0.13$ ). In cirrhotic patients without DM, IR was more pronounced than in control patients (mean HOMA-IR :  $5.93 \pm 4.68$  vs  $2.79 \pm 2.24$ ,  $p=0.004$ ). We also found that IR correlated with the severity of cirrhosis based on the MELD score ( $r=0.54$ ,  $p<0.001$ ). Different etiologies of cirrhosis were shown to exhibit different levels of IR ( $p=0.001$ ). DM was most prevalent in the NAFLD cirrhotic group with 75.6 % of the patients treated for diabetes within this group. IR and DM were also associated with an elevated morbidity and mortality ( $p=0.005$ ). A positive correlation between hepatovenous pressure gradient and HOMA ( $R=0.43$ ,  $p=0.02$ ) was observed, meaning that the reduction of liver clearance could play a role in insulin resistance.

**Conclusions :** IR is more frequent in cirrhotic than in non-cirrhotic patients. The level of IR is correlated with cirrhosis severity and is associated with a higher rate of complications and a lower survival rate within the cirrhotic group. Whether an early diagnosis of IR in this population and an appropriate treatment will reduce such complications remains to be defined.

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FIBROSCAN IS A USEFUL AND RELIABLE TOOL TO RULE OUT ADVANCED LIVER FIBROSIS AND SEVERE PORTAL HYPERTENSION IN ALCOHOLIC PATIENTS. M. Salavrakos (1), N. Lanthier (1), P. Starkel (2) / [1] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Hepato-gastroenterology, [2] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Hépatogastro-Entérologie.

**Introduction :** Transient elastography (TE) or Fibroscan® has been validated for the diagnosis and stadification of liver fibrosis in various liver diseases. Currently, there is no clear consensus on the optimal cut-off values and timing of TE in alcoholic liver disease (ALD).

**Aim :** The objectives of the study are : (a) to evaluate diagnostic accuracy of fibroscan for the diagnosis of fibrosis in alcoholic patients ; (b) to investigate the impact of two weeks of abstinence on TE results ; (c) to evaluate the diagnostic accuracy of TE for determining clinically significant portal hypertension ; (d) to study potential histological (steatosis, alcoholic hepatitis, perisinusoidal fibrosis) and biochemical (transaminases and cholestasis) confounding factors leading to misclassification by TE.

**Methods :** Patients admitted for alcohol withdrawal to a dedicated alcohol unit were evaluated by a first Fibroscan® on the day of admission. If the TE value was suggestive of significant fibrosis ( $\geq F2$ ), they were proposed a transjugular liver biopsy which was performed as close as possible to the admission date. A second Fibroscan® was proposed two weeks later to a subgroup of patients who had remained abstinent. A blood sample for routine biochemical data to calculate biological fibrosis scores was drawn at admission. Histological analysis was performed by an experienced liver pathologist.

**Results :** 118 patients were included in the study, among which 57 underwent a second Fibroscan®. Fibroscan® correlated well with the histological score ( $\rho=0.680$ ,  $p<0.01$ ) and showed a very good NPV, with a value of 92% for ruling out severe fibrosis ( $\geq F3$ ) and 93% for cirrhosis (F4). Our optimal cut-offs were found at  $\geq 11.7$  kPa for F2,  $\geq 15.2$  for F3 and  $\geq 21.2$  for F4. After two weeks of abstinence, there was a mean decrease of TE values of 2.7 kPa ( $\pm 0.9$ ) associated with a significantly better concordance between Fibroscan® and histology. Fibroscan® also correlated well with the hepatic venous pressure gradient (HVPG) ( $\rho=0.753$ ,  $p<0.01$ ) ; a TE value of 30.6 kPa for predicting an HVPG greater than 10mmHg yielded a 94% specificity. Fibroscan® performed better than all non-invasive blood tests. We could not find any impact of the confounding factors (steatosis, sub-clinical alcoholic hepatitis, cholestasis, sinusoidal fibrosis) on misclassification.

**Conclusions :** Fibroscan® is currently the most accurate non-invasive method for the diagnosis of fibrosis in patients with ALD. We can safely say that TE values below 11.7 kPa can rule out significant fibrosis and below 30.6 kPa varices. We did not find any factors which could explain the tendency of Fibroscan® to overestimate histological fibrosis, but a period of abstinence reduces this effect.

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THE EFFECTS OF NO MODULATORS ON THE INCREASED TRANSHEPATIC PRESSURE GRADIENT IN A RAT MODEL OF SEVERE STEATOSIS. D. Van Der Graaff (1), W. Kwanten (2), J. De Man (3), B. De Winter (4), P. Michielsen (2), S. Francque (2) / [1] Antwerp University Hospital, Edegem, Belgium, Gastroenterology and Hepatology, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Department of Gastroenterology and Hepatology, [3] Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium, Department of Gastroenterology and Hepatology, [4] Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology, University of Antwerp, Antwerp, Belgium, Department of Gastroenterology and Hepatology.



**Introduction :** Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disease of the Western world. Prior to development of inflammation or fibrosis, the intrahepatic vascular resistance (IHVR) is increased both in animals and in patients, impairing hepatic blood flow and potentially causing disease progression. Altered reactivity to or decreased production of nitric oxide (NO) are potential mechanisms, although previous data have shown conflicting results.

**Aim :** The present study seeks to elucidate the role of NO-mediated mechanisms on the IHVR in severe steatosis without inflammation or fibrosis.

**Methods :** The IHVR was studied by measuring the transhepatic pressure gradient (THPG) in an in situ ex vivo rat perfusion model, in which the liver is isolated, connected to a circuit with a pump and perfused by Krebs solution, with or without addition of drugs. The THPG was studied in Wistar rats (n=5-7/group) on a methionine-choline-deficient diet, inducing severe steatosis after 4 weeks, and compared to rats on a control diet. First, pre-constriction was induced by adding Methoxamine (alpha 1-adrenergic agonist, 10<sup>-5</sup> M) to the perfusion fluid. Subsequently, after 10 minutes the effects of acetylcholine (ACh, stimulator of endothelial NO production, 10<sup>-6</sup> - 3x10<sup>-4</sup>M) and sodium nitroprusside (SNP, NO donor, 10<sup>-5</sup> - 3x10<sup>-3</sup> M) in presence of Mx were studied in dose-response experiments, in which the dose was increased by 0.5 log M every 5 minutes at a constant flow of 30 mL/min.

**Results :** The basal THPG in steatotic livers was significantly increased compared to controls at all flows (10-50 mL/min), with respectively 5.4 ± 0.3 mmHg and 4.4 ± 0.2 mmHg at 30 mL/min [p<0.001]. Mx induced an increase of the THPG in both controls and steatosis, which was, as expected, more pronounced in steatosis. ACh did not alter THPG significantly in control rats nor in steatotic rats. Adding SNP to the perfusion fluid decreased the THPG in both groups. The decrease of the THPG appeared to be delayed in steatosis, but at higher doses of SNP (10<sup>-4</sup>-3x10<sup>-3</sup> M) the magnitude of the decrease was equal, as shown after correction for the more pronounced increase in THPG by Mx in steatotic livers (controls + saline -3.05 ± 0.67 mmHg vs. controls + SNP -6.57 ± 1.59 mmHg [p<0.001] ; steatosis + saline -2.95 ± 1.68 mmHg vs. steatosis + SNP -6.24 ± 1.20 mmHg [p<0.05]).

**Conclusions :** These experiments reconfirm an increased IHVR and hyperreactivity to Mx in steatosis compared to controls, as observed previously by our group. ACh did not significantly decrease the THPG in steatosis nor controls, which is conflicting with results of other research groups. The sensitivity to NO-mediated relaxation was unaltered, as shown by the equal reactivity to SNP in both controls and steatosis.

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ESTIMATION OF THE FUTURE LIVER REMNANT FUNCTION IS A BETTER TOOL TO PREDICT POST-HEPATECTOMY LIVER FAILURE THAN PLATELET-BASED LIVER SCORES. T. Chapelle (1), B. Op De Beeck (2), A. Driessen (3), G. Roeyen (4), B. Bracke (4), V. Hartman (4), I. Huyghe (5), M. Peeters (6), S. Francque (7), D. Ysebaert (4) / [1] Universiteit ziekenhuis Antwerpen, , Belgium, Hepatobiliary, Transplantation and Endocrine surgery, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Radiology, [3] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Pathology, [4] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Hepatobiliary, Transplantation and Endocrine surgery, [5] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Nuclear Medicine, [6] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Oncology, [7] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology & Hepatology.

**Introduction :** Recently, there has been increasing interest in the preoperative prediction and prevention of post-hepatectomy liver failure (PHLF). This is a particular concern in colorectal liver metastases (CRLM), when surgery follows potentially hepatotoxic chemotherapy. Platelet-based liver scores (PBLs) such as APRI and FIB-4 are predictive of chemotherapy-associated liver injury (CALI) and PHLF. Estimation of the future liver remnant function (eFLRF) by combining <sup>99m</sup>Tc-Mebrofenin Hepatobiliary Scintigraphy (HBSBSA) with future liver remnant volume ratio (FLRV%), is predictive of PHLF and related mortality.

**Aim :** We hypothesized that a HBSBSA based formula was a better predictor for PHLF than PBLs in chemotherapy-pretreated CRLM.

**Methods :** Between 2012 and 2016, 140 patients underwent liver resection for CRLM following systemic therapy. HBSBSA, FLRV%, eFLRF and PBLs were calculated and compared for their value in predicting PHLF

**Results :** eFLRF and FLRV% had a better predictive value for PHLF than HBSBSA alone and APRI and FIB-4 (AUC = 0.800, 0.843 versus 0.652, 0.635 and 0.658 respectively). In a subgroup analysis (Oxaliplatin all, Oxaliplatin = 6 cycles, Irinotecan all and Irinotecan = 6 cycles), eFLRF was the only factor predictive for PHLF in all subgroups (all : p = 0.05). Prediction of HBSBSA for chemotherapy associated steato-hepatitis (CASH) reached almost significance (p = 0.06). FIB-4 was predictive for sinusoidal obstruction syndrome (SOS) (p = 0.011). Only weak correlation was found between HBSBSA and PBLs.

**Conclusions :** eFLRF is a better predictor of PHLF than PBLs or HBSBSA alone. PBLs seem to measure other aspects of liver function or damage than HBSBSA.

MORPHOLOGICAL FEATURES OF SPONTANEOUS BACTERIAL PERITONITIS IN CIRRHOTIC PATIENTS. D. Haurylenka (1), T. Haurylenka (2) / [1] Republican Research Center for Radiation Medicine and Human Ecology, Gomel, Belarus, Internal Medicine, [2] Republican Research Center for Radiation Medicine and Human Ecology, Gomel, Belarus, Preventive Gastroenterology.

**Introduction :** The spontaneous bacterial peritonitis (SBP) is diagnosed only by the examination of ascitic fluid (AF). Therefore, data about morphological changes of peritoneum in cirrhotic patients with SBP rarely occur in publications. In 1963 H.O. Conn was the first who used the term «spontaneous peritonitis» and described acute jejunitis at 1 of 5 cirrhotic patients with neutrocytosis in AF.

**Aim :** To confirm the morphological features of SBP in cirrhotic patients.

**Methods :** There was a retrospective study that enrolled 308 hospitalized patients with cirrhosis (City Hospital's medical records) and 70 outpatients with cirrhosis (Department of Forensic Medicine's autopsy database). A total of 378 patients with decompensation cirrhosis died from 2000 to 2010. The SBP was diagnosed according to standard criteria.

**Results :** There are signs of peritoneal inflammation at autopsy among 378 patients (M/F : 240/138, mean age : 52 years) were found in 9 patients without a detectable intra-abdominal, surgically treatable source of infection. There were 8 cases among the hospitalized patients (2.6% ; 95%CI : 1.1-5.1) and one outpatient (1.4%). Etiologies of cirrhosis were : alcohol/cryptogenic : 8/1. During examination of abdominal cavity following gross findings was made : turbid AF, fibrin deposition on the small intestine's serosa. Histological changes were the following : serofibrinous peritonitis with massive polymorphonuclear cell infiltration of the omentum and small intestine serosa. The term "ascites-peritonitis" has been used by pathologists for the described features in their conclusions. According to medical records SBP has been diagnosed in 12 hospitalized patients after paracentesis (clinical symptoms were is abdominal pain, tenderness, fever, neutrophilic leukocytosis). However, the gross and histological findings, without an evident intra-abdominal, surgically treatable source of infection have been found in 3 patients.

**Conclusions :** In cirrhotic patients the frequency of peritonitis, in the absence of an evident intra-abdominal, surgically treatable source of infection, was low (2.4% ; 95%CI : 1.1-4.5). But the present study confirms that in SBP can develop features of classical peritonitis.

SCREENING FOR HEPATITIS C VIRAL INFECTION IN A NON-URBAN PRIMARY CARE FACILITY IN FLANDERS. G. Devolder (1), M. De Wilde (1), L. Goderis (1), D. Ann (1), E. Spillebeen (1), A. Geerts (2), A. Derese (3), H. Van Vlierberghe (2), X. Verhelst (4) / [1] Artsenpraktijk Vierschaar, Lendeledede, Belgium, Primary Care Facility, [2] Ghent University Hospital, Ghent, Belgium, Gastroenterology and Hepatology, [3] Ghent University, Ghent, Belgium, Primary Care Medicine, [4] Ghent University Hospital, Ghent, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** Chronic Hepatitis C virus (HCV) infection is a major cause of liver cirrhosis and hepatocellular carcinoma. Since the introduction of direct acting antiviral drugs, the majority of HCV infected patients can be treated successfully without major side effects. Today, the major challenge in HCV care is screening for patients unaware of their HCV status. Risk groups in need of prioritizing for screening have been defined, but it is not clear how valid these are in the Belgian population.

**Aim :** The aim of this study was to analyze the prevalence of chronic HCV infection in a non-urban primary care facility and analyze risk factors for HCV infection in this cohort.

**Methods :** All patients who went to their primary care physician in "Artsenpraktijk Vierschaar" in Lendeledede (Belgium) and in whom a blood examination for whatever indication was performed, were offered screening for HCV antibodies. Patients were included between 1 November 2016 and 1 October 2017. Every patient answered a questionnaire for the presence of risk factors for HCV (KCE report 173A 2011). If HCV antibodies turned out positive, HCV RNA was tested and if positive the patient was referred to a local hepatologist.

**Results :** A total number of 539 patients were tested for HCV antibodies. Five patients (0.93%) were positive for HCV antibodies. The first patient was a 27-year-old HIV positive patient with male to male sex (MSM) as a risk factor. The second patient was a 78-year-old male with spinal surgery in 1957. Blood transfusion is not probable but cannot be excluded. The third patient was a 59-year-old woman with meningococcal sepsis in 1984 with multiple blood transfusions. The fourth patient was a 29-year-old woman without any known risk factor for HCV infection. The last patient was an 89-year-old woman with multiple blood transfusions in the late fifties due to duodenal ulcers. One of these patients is part of the so-called babyboom generation (born between 1945 and 1965).

**Conclusions :** In this rural primary care facility HCV prevalence in patients who required a blood examination was 0.93%. Three out of five patients showed a risk factor for HCV infection (blood transfusion (n=2) and MSM (n=1)). The

data of this study do not support specific screening in the babyboom generation. On the other hand, these data support a universal once-in-a lifetime screening strategy for HCV in Belgium. The contribution of primary care physicians in this strategy is crucial.

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LIVER TRANSPLANTATION FOR ALCOHOLIC HEPATITIS : A SYSTEMATIC REVIEW WITH META-ANALYSIS. A. Marot (1), M. Dubois (2), E. Trepo (3), C. Moreno (3), P. Deltenre (4) / [1] CHU UCL Namur, Yvoir, Belgium, Department of Gastroenterology and Hepatology, [2] Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, Division of Gastroenterology and Hepatology, [3] Erasme Hospital, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, [4] Clinique Saint-luc Bouge, Namur, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** The rate of alcohol relapse among patients who underwent liver transplantation for alcoholic hepatitis (AH) is not precisely known.

**Aim :** To synthesize the available evidence on liver transplantation for AH to assess alcohol relapse and 6-month survival.

**Methods :** Meta-analysis of trials evaluating liver transplantation for AH, either clinically severe or diagnosed on the explant.

**Results :** Eleven studies were included. The pooled estimate rate for alcohol relapse was 0.22 (95% CI=0.12-0.36) in overall analysis with high heterogeneity between studies (I<sup>2</sup>=76%), 0.20 (95% CI=0.07-0.43) in the subgroup analysis including patients with clinically severe AH (I<sup>2</sup>=84%), 0.14 (95% CI=0.08-0.23) among patients with clinically severe AH in sensitivity analysis excluding the discrepant studies that did not use stringent selection criteria for liver transplantation (I<sup>2</sup>=0%), and 0.15 (95% CI=0.07-0.27) for recurrent harmful alcohol consumption among patients with clinically severe AH (I<sup>2</sup>=3%). The risk of alcohol relapse was not different between AH transplanted patients and patients with alcoholic cirrhosis who underwent elective liver transplantation in sensitivity analysis excluding the discrepant studies (OR=1.68, 95%CI=0.79-3.58, p=0.2, I<sup>2</sup>=16%). The pooled estimate rate for 6-month survival was 0.85 (95% CI=0.77-0.91, I<sup>2</sup>=49%), and 0.80 among patients transplanted for clinically severe AH (95% CI=0.69-0.88, I<sup>2</sup>=30%). AH transplanted patients had as good 6-month survival as patients who underwent elective liver transplantation (OR=2.00, 95% CI=0.95-4.23, p=0.07, I<sup>2</sup>=0%).

**Conclusions :** Using stringent selection criteria, 14% of patients with clinically severe AH have alcohol relapse after liver transplantation. The percentage of alcohol relapse of AH transplanted patients is similar than that of patients who underwent elective liver transplantation.

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EFFECTS OF GLP-1 RECEPTOR POLYMORPHISMS ON ADOLESCENT OBESITY. M. Maralani (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Phase-1 trials, Department of oncology.

**Introduction :** Obesity is one of the most common problems of the modern age. The effects of genetic and environmental factors on obesity has been evaluated in several studies. Non-alcoholic fatty liver disease (NAFLD) has become a frequently encountered problem. Hypertriglyceridemia and NAFLD have a strong relationship with hepatocyte and adipocyte's insulin resistance and obesity as well. It has been shown that following food intake, Glucagon-like peptide 1 (GLP-1) induces glucose-dependent insulin release from pancreatic  $\beta$ -cells. The effects of GLP-1 and the associated receptor (GLP-1R) upon the insulin release have been proved. The fact that these metabolisms act using GLP-1R pathway, indicates the possible role of this receptor in development of diabetes, glucose metabolism disorder and/or obesity. Implementation of GLP-1 as a pharmacological treatment for obesity is a stage which is not in routine use yet. GLP-1R polymorphisms can modify pharmacological effects of GLP-1 related substances and these polymorphisms may be a factor in pathogenesis. We therefore construct our hypothesis that GLP-1R gene polymorphisms/mutations can influence the development of disease associated with metabolic syndrome including obesity.

**Aim :** The aim of our study was to investigate genetic variations (mutation/polymorphism) of GLP-1R gene in children diagnosed with obesity and to identify their possible connections with NAFLD and insulin resistance.

**Methods :** DNA was isolated from taken blood samples using High Pure PZR Template Preparation Kit. Concentration and purity of the obtained DNA was measured. Polymerase chain reaction (PCR) was performed for the extracted DNA samples in order to replicate GLP-1R gene's exon 2, 4 and 5. Sanger sequencing was performed for these PCR products. later the results were analyzed according to "NC\_000006 reference sequence". Target variation in GLP-1R gene (exon 2, 4 and 5) was examined with SPSS 15 statistical program and mean  $\pm$  standard deviation was calculated.

**Results :** Three polymorphisms and one mutation were detected in fourth and fifth exons of GLP-1R gene. There were no significant differences in allele frequencies of these polymorphisms between groups with NAFLD (non-alcoholic

fatty liver disease) or insulin resistance, and also there were no significant differences in BMI, weight, height and other obesity related factors among the wild type, heterozygote and homozygote of these variants in patients ( $p > 0,05$ ). R131Q variation was detected in three cases from which 1/3 had fatty liver but none showed insulin resistance. There were also statistically meaningful results for 'Odds Ratio' among different genotypes and allele frequencies in groups with fatty liver and/or insulin resistance. One of our polymorphisms was rs6918287 for which in heterozygote group we detect double risk of insulin resistance. Patients with A allele also show approximately doubled risk for fatty liver occurrence. However, for rs3765468 we got tripled risk for insulin resistance in homozygous individuals and around double probability for fatty liver disease in heterozygous ones. The other SNP was rs6923761. In heterozygous individuals there is an increase in risk for fatty liver and a decrease in risk for insulin resistance. In homozygous group also, the prospect of insulin resistance is double declined. Patients with A allele of this polymorphism show a drop-in risk for insulin resistance as well.

**Conclusions :** Individuals with homozygous and heterozygous genotypes for polymorphisms/mutation were compared in terms of NAFLD and insulin resistance. According to statistical analysis it was observed that existence of polymorphisms and mutation may increase risk of fatty liver and insulin resistance. For the variable of obesity however, no significant difference was obtained. Moreover, our study indicated that R131Q is more probable to be a polymorphism rather than a mutation. GLP-1R's gene consists of 13 exons and due to its expression in a lot of organs ; it is a logical approach to sequence its whole gene. Therefore, in contribution of our work, we plan to sequence intronic regions and the entire exons. Besides, comparison of these data with GLP-1's blood values may be informative. The polymorphism and mutation found in this article can be investigated in different ethnic groups and larger populations. Further consideration of metabolic disease other than obesity, NAFLD and T2DM and their connections with GLP-1R is expected to provide great benefits.

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UNDER CONSTANT INJURY DUCTULAR-DERIVED HEPATOCYTES CLONALLY GROW AS ROBUST CARCINOGENESIS-RESISTANT POPULATION. R. Manco (1), L. Clerbaux (1), M. Bou Nader (2), C. Sempoux (3), C. Desdouets (2), Y. Horsmans (4), I. Leclercq (1) / [1] Université Catholique de Louvain, Brussels, Belgium, GAEN department, [2] Université Paris-René Descartes, France, Inserm, U1016, Institut Cochin, [3] Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, Institute of Pathology, [4] Cliniques universitaires Saint-Luc, Brussels, Belgium, Hepato-gastroenterology Unit.

**Introduction :** Cirrhosis and hepatocellular carcinoma, the end-stage manifestations of chronic liver disease, are associated with a ductular reaction (DR) characterized by the expansion of cholangiocytes. It has been demonstrated that cells in DR differentiate in hepatocytes in a subset of acute liver failure. In contrast, data supporting their function in chronic liver diseases remain little and conflicting.

**Aim :** Therefore, this study aimed to address the patho-physiological role of DR cells in a liver suffering from a long-lasting damage.

**Methods :** We used Osteopontin-iCreERT2 mice to trace the fate of DR cells and AAV8-TBG-Cre in Rosa26R-YFP mice to trace that of hepatocytes upon treatment with carbon tetrachloride (CCl<sub>4</sub>) for up to 24 weeks, a model mimicking in duration and severity the course of a human chronic liver disease. Rosa26R-confetti reporter mice were used for studying clonality.

**Results :** Upon CCl<sub>4</sub>, DR was transient but nevertheless yielded differentiated functional hepatocytes. As injury progresses, DR-derived hepatocytes clonally expanded to significantly regenerate the hepatocytes pool, and acquired functions of mature hepatocytes including zonal enzyme expression. Conversely to exhausted pre-existing hepatocytes, these newly formed and younger hepatocytes have untapped proliferative potential and are less vulnerable to further (and more dangerous) stimuli.

**Conclusions :** These findings suggest an explanation for sometimes extensive parenchymal reconstitution in livers suffering from years to decades of chronic hepatitis in advanced stage chronic hepatitis in humans that has not been convincingly demonstrated. Ductular-driven regeneration represents a safe regenerative process amenable to therapeutic manipulation in the chronically ill liver.

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POINT-OF-CARE DIAGNOSTIC TESTS FOR HBV AND HCV ARE ASSOCIATED WITH A HIGHER LINKAGE TO CARE IN AN ASIAN MIGRANT POPULATION. E. Ho (1), P. Michielsens (1), P. Van Damme (2), I. Veldhuijzen (3), T. Vanwolleghem (1) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology and Hepatology, [2] University of Antwerp, Antwerp, Belgium, VAXINFECTIO, Vaccine and Infectious Diseases Institute, [3] Municipal Public Health Service Rotterdam-Rijnmond, Netherlands (the), Division of Infectious Disease Control.

**Introduction :** Linkage to care for patients diagnosed with chronic hepatitis B (HBV) and C virus (HCV) infection remains a pressing issue - especially in high-seroprevalence populations.

**Aim :** This study compares the impact of point-of-care tests on the linkage to care, cost and turnaround time in a prospective comparison of two screening protocols in the Chinese population in three major cities in Belgium.

**Methods :** Two screening protocols were compared between 10/2014 and 5/2017. The first is a community outreach (CO) protocol in which serum was obtained through venipuncture and tested for HBsAg and anti-HCV (Elecsys, Roche Diagnostics). Screened persons were notified of results by letter and phone. The second protocol was a community partnership (CP) method, in which point-of-care tests (Biomérieux Vikia HBsAg and OraSure OraQuick HCV) were used to obtain HBsAg and anti-HCV results respectively through fingerstick blood and saliva. Positive results were confirmed during outpatient visits with serologic testing (Elecsys, Roche Diagnostics). Linkage to care was defined as having received specialist care follow-up before/on 10/2017 with HBsAg, ALT and HBV DNA test results for HBV and HCV RNA for HCV, and at least 1 abdominal ultrasound.

**Results :** Overall, 563 persons participated, four failed/declined venipuncture : for 559 individuals, valid results were obtained (456 in the CO protocol and 103 in the CP protocol). Thirty-seven (6.6%) tested positive for HBsAg. One person tested positive for anti-HCV (0.2%). Eleven of the 32 HBsAg positives diagnosed in the CO protocol (34%) are in specialist care follow-up, compared to 5 of the 6 positive patients (4/5 HBsAg and 1/1 anti-HCV) in the CP protocol (83%) (Mid-P exact  $p=0.041$ ). Two patients from the CO protocol are treated with antiviral therapy and one from the CP protocol is due to be treated. The cost of the CO protocol was €24,819 or €54.0 per person screened. The cost of the CP protocol was €2,750 or €26.7 per person screened, thus the CP protocol was more economically attractive. The turnaround time from venipuncture until postage of results ranged between 20 and 45 days in the CO protocol. For the CP protocol, the turnaround time was 15-20 minutes-results and an appointment for specialist care follow-up were given on-site.

**Conclusions :** In a population with a high HBV prevalence we found that screening based on point-of-care tests results in lower costs per person screened, and higher linkage to care.

- A30 -

LIVER TRANSPLANTATION IN JEHOVAH'S WITNESSES. M. Vandermeulen (1), N. Meurisse (1), P. Damas (2), A. Kaba (2), A. Lamproye (3), J. Delwaide (3), J. Joris (2), P. Honoré (1), O. Detry (4) / [1] CHU Liege, Liège, Belgium, Dpt of Abdominal Surgery and Transplantation, [2] CHU Liege, Liège, Belgium, Dpt of Anesthesiology and Intensive Care, [3] CHU Liege, Liège, Belgium, Dpt of Hepato- Gastroenterology, [4] Centre Hospitalier Universitaire de Liège, Liège, Belgium, Dpt of Abdominal Surgery and Transplantation.

**Introduction :** Liver transplantation (LT) is a major surgical procedure with large dissections and sutures of large vessels in patients with high portal hypertension and low levels of platelets and coagulation factors. In consequence, LT often requires large amounts of blood products. For religious reasons, most Jehovah's witnesses (JW) refuse infusions of any blood product, including autologous or homologous pre-donated blood, platelets, fresh frozen plasma, coagulation factor concentrates, or human albumin. However, they may accept solid organ transplantation, including LT.

**Aim :** The authors developed experience in abdominal and oncological surgery in JW and present here their results with LT in JW patients.

**Methods :** Over a 20-year period, 22 LT (16 DBD, 2DCD, and 4 LRLT with JW living donors) were performed in 21 JW patients and were analysed retrospectively. All patients received perioperative iron supplementation and erythropoietin. Two patients had percutaneous spleen embolization to increase platelet level. Anti-fibrinolytic (aprotinin or tranexamic acid) was administered during LT and meticulous surgical hemostasis was achieved, helped by argon beam coagulation. Continuous circuit cell salvage and reinfusion whereby scavenged blood was maintained in continuity with the patient's circulation, was used in all patients. Venovenous bypass was avoided during LT to minimize the coagulation disorders.

**Results :** There were 10 male and 11 female patients whose mean age was 48 years (ranges : 6-70). Indications for LT were HCV with (3) or without (1) HCC, PBC (2), PSC (1), HBV (2), autoimmune hepatitis (1), antitrypsin deficiency (1), sarcoidosis (2), amyloidosis (3), polycystic liver disease (1), alcoholic cirrhosis with HCC (1), cryptogenic (3), hepatic artery thrombosis (1). At transplant, mean pre-operative hematocrit was 41% (ranges : 22-50), mean platelet level was  $140 \times 10^3/\text{mm}^3$  (ranges : 33-355), and mean INR was 1.25 (ranges : 0.84-2.18). One LRLT recipient died at day 11 from aspergillosis and anaemia, and another DBD recipient at day 28 due to complications after hepatic artery thrombosis. One patient finally accepted to be transfused for severe anaemia. The mean hospital stay was 31 days (10-137). Kaplan-Meier patient survival was 85%, 72%, 72% at 5, 10 and 15 years, respectively.

**Conclusions :** According to the authors' experience, LT may be successful in selected and prepared JW patients who should not be a priori excluded from this life saving procedure. The indications for LT in JW were quite different from the common indications for LT, with a low rate of alcoholic cirrhosis. The experience with this particular group of patients helped the team to reduce transfusion needs in the non-JW patients.

ALVEOLAR ECHINOCOCCOSIS IS NOW ENDEMIC IN SOUTHERN BELGIUM. A. Cambier (1), P. Leonard (1), B. Losson (2), M. Hayette (3), J. Giot (1), N. Blétard (4), P. Meunier (5), R. Hustinx (6), N. Meurisse (7), J. Delwaide (8), P. Honoré (7), O. Detry (9) / [1] CHU Liege, Liège, Belgium, Dpt of Infectiology, [2] University of Liège, , Belgium, Dpt of Veterinary Medicine, [3] CHU de Liège, Liège, Belgium, Dpt of Microbiology, [4] CHU de Liège, Liège, Belgium, Dpt of Pathology, [5] CHU Liege, Liège, Belgium, Dpt of Radiology, [6] CHU Liege, Liège, Belgium, Dpt of Nuclear Medicine, [7] CHU Liege, Liège, Belgium, Dpt of Abdominal Surgery and Transplantation, [8] CHU Liege, Liège, Belgium, Dpt of Hepato- Gastroenterology, [9] Centre Hospitalier Universitaire de Liège, Liège, Belgium, Dpt of Abdominal Surgery and Transplantation, ECHINO-LIEGE.

**Introduction :** Until now, Belgium has been considered as a low-risk country for alveolar echinococcosis (AE). However, it was recently demonstrated by necropsy series that up to 51% of the red foxes (*Vulpes vulpes*) may be infected by *E. multilocaris* in some parts of Southern Belgium. The first local Belgian human AE cases were described in the early 2000's.

**Aim :** The aim of this study was to report the experience of a tertiary university hospital of Southern Belgium with AE management.

**Methods :** The authors retrospectively collected data from the parasitology laboratory (serologies), the hospital pharmacy in charge of supplying albendazole, and by searching through patient's files with medico-economic information service of a tertiary university hospital. The medical files were retrospectively reviewed.

**Results :** Twenty-one cases (66% male) of local AE have been recorded from 1999 to 2016. All patients were Belgian citizens with more than 30 years of life in Southern Belgium (Liege province : 10 cases (47.4%), Luxembourg province : 8 cases (36.8%), Namur Province : 3 cases (15.8 %)). Mean age of diagnosis was 66 years (ranges : (35-85y). Eighteen patients had hepatic involvement : 14 underwent surgical resection and 5 had unresectable liver lesions and underwent albendazole palliative therapy until death. During the same period, the faculty of veterinary medicine observed an increased rate of lethal hepatic AE in dogs, another indication of high AE incidence.

**Conclusions :** AE appears to be spreading in Belgium and has actually an uneven geographical distribution with endemicity in areas of Southern and Eastern Belgium. However, it is probable that local AE cases will be diagnosed in the whole country, considering that there is no reason that infected foxes remain in Southern Belgium and also the fact that some people from Northern Belgium might spend long period in Southern Belgium, with or without their dogs. The liver is the most frequently involved organ and the only cure can be achieved by complete R0 resection of all AE lesions. In reaction to this experience, the authors created a multidisciplinary group for AE diagnosis and management, including hepatologists, infectiologists, microbiologists, pathologists, radiologists, nuclear medicine specialists, surgeons and veterinarians. The authorities should be aware of this medical issue and should facilitate the access to Albendazole for AE patients. A complete national survey should be encouraged, and BASL might have an important role in this study.

DESCRIPTIVE EPIDEMIOLOGIC DATA ON LIVER CANCER IN BELGIUM, 2004-2025. F. Calay (1), K. Henau (1), J. Francart (2), N. Van Damme (2), C. Verslype (3), L. Van Eycken (2) / [1] Belgian Cancer Registry, Brussel, Belgium, Registration, [2] Belgian Cancer Registry, Brussel, Belgium, Direction, [3] UZ Leuven, Leuven, Belgium, Digestive Oncology.

**Introduction :** Liver cancer, characterized by a poor prognosis, is the sixth most common cancer worldwide with the highest incidence rates in Eastern Asia. It is the second most common cause of death due to cancer. Alcohol abuse and chronic viral hepatitis result in a long-term risk of liver cancer.

**Aim :** The study aims to present an epidemiological description of liver cancer incidence, trends, survival and prevalence in Belgium.

**Methods :** The Belgian Cancer Registry is a national and population based cancer registry, collecting data on patient and tumour characteristics since 2004. The registration is compulsory for the oncological care programs and for the laboratories for pathological anatomy. Vital status was retrieved from the Crossroads Bank of Social Security. The age-standardised incidence and mortality rates (WSR, n/100,000), relative survival, and prevalence were calculated. The trends 2004-2015 were estimated using the Average Annual Percentage Change (AAPC) method. The cancer incidence projections result from mathematical extrapolations of past trends in incidence and population growth. The extrapolation methods are based on regression models and assume that these trends will continue in the projection period.

**Results :** In 2015, 921 new liver cancers were diagnosed in Belgium, 658 in males (WSR : 6.4/100,000) and 263 in females (WSR : 2.1/100,000) with a male :female ratio of 3. Three quarters of the liver cancers are hepatocellular carcinomas (HCC), 21% are cholangiocarcinomas, and all others like (angio)sarcomas, hepatoblastomas and unspecified carcinomas account for 5%. Liver cancer incidence is strongly related to age, with the highest incidence rates in the age

group 70-75 years. More than half of all liver cancers with a known stage are diagnosed in advanced stages (stage III or IV). This is more pronounced for the cholangiocarcinomas where almost 70% are diagnosed as stage IV. The incidence rates (WSR) for liver cancer between 2004 and 2015 are annually increasing in males and females, AAPC = 6.8% and 6.0%, respectively. This increasing trend is observed for both sexes, for HCC (AAPC in males : 6.8%, females : 6.3%) and for cholangiocarcinoma (AAPC in males : 7.2%, in females : 7.6%). Liver cancer incidence rates for 2011-2015 are higher in the Walloon Region (WSR : 5.1/100,000) and in the Brussels-Capital Region (WSR : 4.9/100,000) than in the Flemish Region (WSR : 3.2/100,000). This pattern is only observed for HCC and not for cholangiocarcinomas. Cancer incidence maps for the years 2004-2011 have shown that the rates for HCC increase from the northeast, parallel to the border with the Netherlands, towards the border with France in the southwest of Belgium. In 2014, 889 persons died of liver cancer in Belgium, 547 males (WSR : 4.8/100,000) and 342 females (WSR : 2.1/100,000). The mortality rates (WSR) are increasing between 2004 and 2014 but less pronounced than the incidence rates (AAPC = 1.7% in males and females). The 5-years relative survival of liver cancer is low and comparable between males and females (22% for the years 2011-2015). Survival rates for HCC (26%) are higher than for cholangiocarcinoma (12%). A total of 1,999 individuals 1,393 males, and 606 females, diagnosed with liver cancer between 2006 and 2015, were still alive on the 31st of december 2015 (10 year prevalence). HCC accounts for 80% of these cases. The projected number of new invasive liver cancers is expected to double till 1,192 in males and 438 in females in 2025, an increase of 63%.

**Conclusions :** Liver cancer accounts for 1.4% of new cancer cases in Belgium and 3% of cancer deaths. The increased incidence rates of liver cancer can be mainly attributed to a strongly increasing cancer risk combined with ageing and growing population. The poor prognosis and the diagnoses in advanced stages confirm the importance of focussing primary prevention on risk factors such as alcohol consumption, non-alcoholic fatty liver disease (NAFLD), HBV and HCV infections.

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**MULTIVISCERAL TRANSPLANTATION FOR DIFFUSE PORTOMESENERIC THROMBOSIS : A CASE SERIES.** E. Canovai (1), L. Ceulemans (1), G. De Hertogh (2), M. Hiele (3), M. Sainz-Bariga (1), I. Jochmans (1), T. Vanuytsel (3), D. Monbaliu (1), J. Pirenne (1) / [1] UZ Leuven, Leuven, Belgium, Abdominal Transplantation, [2] UZ Leuven, Leuven, Belgium, Pathology, [3] UZ Leuven, Leuven, Belgium, Gastroenterology.

**Introduction :** Multivisceral transplantation (MVTx) entails the en-bloc transplantation of almost the entire abdominal contents including stomach, duodenum, pancreas, liver and small bowel. For adults, indications for MVTx include slow growing abdominal tumors involving the mesenteric vessels, massive abdominal losses due to trauma or ischemic disease and diffuse portomesenteric thrombosis (DPMT). In the latter, DPMT will often lead to life-threatening upper GI bleeding. Furthermore, these patients often have an underlying liver cirrhosis requiring a liver transplantation. In these cases, portal revascularization is technically impossible without simultaneous replacement of the entire portal system.

**Aim :** To study the results of multivisceral transplantation for diffuse portomesenteric thrombosis.

**Methods :** A retrospective analysis from prospectively maintained database ITx patients transplanted from 2000-2017 was performed and the MVTx patients were identified. Demographics, indication, donor characteristics, rejection episodes and survival were recorded.

**Results :** 4 male patients underwent MVTx in this period out of a total of 17 ITx performed at our center (24%). Median age at time of transplantation was 45 (range : 23-47). The indication for MVTx was DMPT with recurrent life treating bleeding from gastric and/or duodenal bleeding. Underlying causes were antiphospholipid syndrome, alcoholic cirrhosis, pancreatic neuro-endocrine tumor and unknown in one patient. Concomitant intestinal failure was present in one patient that required parenteral nutrition while awaiting transplantation. One patient had underlying liver failure and was hospitalized at time of transplantation. Median MELD score at time of transplantation was 13 (10-32). All patients received grafts from haplo-identical or compatible brain-dead donors (median age : 24.5 years). In order to reduce massive bleeding during exenteration of the native organs, embolization of the superior mesenteric artery and the celiac trunk was performed to reduce perioperative bleeding, followed by en-bloc resection of native stomach, duodenum, pancreas, liver and bowel, and finally en-bloc transplantation of the corresponding organs. GI continuity was restored by gastro-gastrostomy or esophago-gastrostomy proximally and colo-colostomy/ileo-colostomy distally. All patients received a protective double loop ileostomy for endoscopic surveillance. Patients received standard immunosuppressive regimens with basiliximab induction followed by triple maintenance therapy tacrolimus, azathioprine and corticosteroids. One patient also underwent a kidney transplantation in the left iliac fossa for pre-terminal kidney failure. There were 4 rejection episodes in 3 patients, 3 of which were treatable by increasing standard immunosuppression. One patient died 254 days after surgery due to invasive aspergillosis after a severe rejection. The 3 remaining patients are alive and are nutritionally independent (median follow-up 2.14 years).

**Conclusions :** Multivisceral transplantation should be considered in all patients with extensive intra-abdominal pathology that is otherwise untreatable. In case of diffuse portomesenteric thrombosis, MVTx allows for complete treatment of the underlying disease with good quality of life in patients who would otherwise die from severe bleeding. Coordination

amongst the donor, embolization and implantation teams is crucial to keep blood loss and cold ischemia times as short as possible.

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CU ISOTOPE RATIO SHIFTS IN COMMON BILE DUCT LIGATED MICE AND CORRELATES WITH THE DEGREE OF CHOLESTATIC-INDUCED LIVER DISEASE. S. Van Campenhout (1), M. Costas-Rodríguez (2), A. Hastuti (2), S. Raevens (1), A. Geerts (1), X. Verhelst (1), F. Vanhaecke (2), H. Van Vlierberghe (1), L. Devisscher (1) / [1] Ghent University, Ghent, Belgium, Gastroenterology and Hepatology, [2] Ghent University, Ghent, Belgium, Chemistry.

**Introduction :** Chronic liver disease covers a range of hepatic disorders which have resulted in liver cirrhosis. Identifying mechanisms which drive disease progression and non-invasive markers that can identify patients at risk are important challenges. We have previously shown that the serum Cu isotope ratio shifts in female cirrhotic patients in favour of the lighter isotope  $^{63}\text{Cu}$  compared to  $^{65}\text{Cu}$ , and that the magnitude of this shift correlates with disease severity.

**Aim :** To date, it is unclear which mechanisms underlie the Cu isotope ratio shift in chronic liver disease. Here, we used the common bile duct ligation (CBDL) model to investigate the different stages of cholestatic-induced liver disease and its correlation to Cu isotope ratios.

**Methods :** Eight-week-old SV129 mice underwent CBDL or sham surgery and were analysed 2, 4, 6 and 8 weeks post-surgery. Liver disease was assessed by serum bilirubin levels, Metavir fibrosis score and hepatic pro-inflammatory cytokine and chemokine levels. Multi-collector inductively coupled plasma-mass spectrometry was applied to determine Cu isotope ratios in serum and tissues. Duodenal explants from CBDL and sham operated mice were used to evaluate the contribution of two metal receptors CTR1 and DMT1 to Cu isotope uptake specificity.

**Results :** CBDL operated mice gradually developed cholestasis as demonstrated by higher total and direct bilirubin levels 2, 4, 6 and 8 weeks post-surgery (both  $p < 0.05$ ). This was associated with increased liver and spleen weights (both  $p < 0.0001$ ) and decreased body weights ( $p < 0.001$ ). Hepatic inflammatory chemokines CXCL1 and CCL2 were increased in CBDL mice compared to sham operated mice, independent of gender or time post-surgery (both  $p < 0.0001$ ). Mice developed F2 and F3 fibrosis after 6 and 8 weeks of CBDL respectively. Determination of Cu isotope ratios in various organs and serum revealed an overall shift in favour of the lighter isotope  $^{63}\text{Cu}$  (ranged from -0.2 to -1.4 per mille), which correlated with the levels of total and direct serum bilirubin, the hepatic inflammatory chemokines CXCL1 and CCL2 and the Metavir fibrosis score (all  $p < 0.003$ ). Spearman correlation coefficients were -0.885, -0.825, -0.677, -0.737 and -0.895 respectively. Duodenal explants from CBDL mice incubated with Fe, Zn and Cu showed a lower  $^{65}\text{Cu}/^{63}\text{Cu}$  isotope ratio compared to tissue from sham mice ( $p < 0.05$ ) whereas this was not observed when co-incubated with a DMT1 inhibitor.

**Conclusions :** Cholestasis is associated with a Cu isotope ratio shift in favour of the lighter isotopes in mouse serum and tissue, which might be mediated by a changed preference of DMT1 for Cu isotope uptake in the duodenum.

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CD4<sup>+</sup> ROR $\gamma$ T<sup>+</sup> T CELLS, CD4<sup>+</sup> T-BET<sup>+</sup>, CD4<sup>+</sup> CD25<sup>+</sup> FOXP3<sup>+</sup> T CELLS AND CD8<sup>+</sup> T CELLS ARE DIFFERENTIALLY ALTERED IN LIVER AND ADIPOSE TISSUE OF MICE FED A HIGH-FAT HIGH-FRUCTOSE DIET IN A TIME-DEPENDENT MANNER. M. Van Herck (1), L. Vonghia (2), P. Michielsen (2), C. Bridts (3), D. Ebo (3), J. De Man (1), B. De Winter (1), S. Francque (2) / [1] University of Antwerp, Antwerpen, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology and Hepatology, [2] Antwerp University Hospital, Edegem, Belgium, Gastroenterology and Hepatology, [3] University of Antwerp, Antwerpen, Belgium, Translational Pathophysiological Research, Division of Immunology and Allergology.

**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 differential functions.

**Aim :** We investigated the involvement of CD8<sup>+</sup> cytotoxic T cells, T helper 1 cells (Th1, CD4<sup>+</sup> T bet<sup>+</sup> ROR $\gamma$ T<sup>-</sup>), T helper 17 cells (Th17, CD4<sup>+</sup> T bet<sup>-</sup> ROR $\gamma$ T<sup>+</sup>) and regulatory T cells (Treg, CD4<sup>+</sup> CD25<sup>+</sup> Foxp3<sup>+</sup>) in the pathogenesis of NAFLD.

**Methods :** Male 8-week old C57BL/6J mice were fed control diet (CD) or high-fat high-fructose diet (HFHFD) for 10, 15, 20 or 25 weeks (n = 6-8 per group). Liver tissue was assessed histologically and the NAFLD Activity Score (NAS) was calculated. T cell subsets were characterized in liver, abdominal and subcutaneous adipose tissue (AAT, SAT) via flow cytometry. CD8<sup>+</sup> cells were expressed as a percentage of CD45<sup>+</sup> CD3<sup>+</sup> cells. T bet<sup>+</sup> ROR $\gamma$ T<sup>-</sup>, T bet<sup>-</sup> ROR $\gamma$ T<sup>+</sup> and CD25<sup>+</sup> Foxp3<sup>+</sup> cells were expressed as a percentage of CD3<sup>+</sup> CD4<sup>+</sup> cells. For statistical analysis, mice were grouped into two time points (10-15 weeks and 20-25 weeks). Data are presented as [median (interquartile range), p-value].



**Results :** Compared to CD mice, HFHFD mice became obese [body weight 44.2g (9.3) vs. 32.2g (4.1),  $p<0.001$ ] and developed NAFLD [NAS 4.0 (2.5) vs. 0.0 (1.0),  $p<0.001$ ]. Comparing HFHFD mice to CD mice, T-bet- ROR $\gamma$ t+ cells were present in larger numbers in liver tissue as of 10-15 weeks [0.6 (2.1) vs. 3.0 (1.8),  $p<0.05$ ]. Conversely, T-bet+ ROR $\gamma$ t- cells were less numerous in liver tissue as of 10-15 weeks [3.2 (7.1) vs. 0.7 (0.6),  $p<0.001$ ]. This effect dissipated, however, as of 20-25 weeks [1.9 (1.2) vs. 1.0 (3.2), not significant]. In AAT of HFHFD mice, CD25+ Foxp3+ cells were more numerous as of 10-15 weeks [2.0 (2.8) vs. 17.2 (25.7),  $p<0.01$ ]. In both AAT and SAT of HFHFD mice, CD8+ cells were more abundant, but only as of 20-25 weeks [AAT : 22.6 (10.7) vs. 36.4 (7.1),  $p<0.001$  ; SAT : 29.0 (18.6) vs. 38.0 (9.7),  $p<0.01$ ]. Interestingly, in AAT of HFHFD mice, a correlation existed between NAS and CD8+ cells ( $r=0.575$ ,  $p<0.01$ ).

**Conclusions :** Differential T cell subsets seem to be implicated in the various tissues involved in NAFLD in a time-dependent manner. In an early stage, CD4+ T bet- ROR $\gamma$ t+ Th17 cells were more abundant and CD4+ T bet+ ROR $\gamma$ t- Th1 cells less abundant in liver tissue of HFHFD mice, whereas CD4+ CD25+ Foxp3+ Treg cells were more numerous in AAT of HFHFD mice. In a later stage, CD8+ T cells became more abundant in both AAT and SAT of HFHFD mice. Additionally, CD8+ T cells in AAT seemed to be associated with progression to a more severe disease state.

- A36 -

WHO TO SCREEN FOR HEPATITIS C IN BELGIUM? COST-EFFECTIVENESS STUDY OF COMPREHENSIVE HEPATITIS C SCREENING IN FOUR TARGET GROUPS. L. Opstaele (1), S. Bourgeois (2), C. Moreno (3), F. Nevens (4), H. Van Vlierberghe (5) / [1] ANZ Medical Writing, Oostende, Belgium, [2] Ziekenhuis Netwerk Antwerpen, Belgium, [3] Hopital Erasme, ULB, Belgium, [4] University Hospital Gasthuisberg, Leuven, Belgium, [5] Universitair ziekenhuis Gent, Belgium.

**Introduction :** Chronic HCV infection is a serious disease, often asymptomatic and undiagnosed until serious liver damage has developed. Therefore, an important number of patients remain undetected or are diagnosed at a later stage of the disease. Oral direct acting antivirals (DAAs) are successful in treating HCV with very high sustained virologic response (SVR) and excellent tolerability, which can provide cure for almost all HCV patients. Therefore, increased HCV screening to diagnose and treat infected patients is a plausible health strategy.

**Aim :** Evaluate cost-effectiveness of comprehensive HCV screening compared to the current situation in four Belgian target groups : men who have sex with men (MSM), people who inject drugs (PWID), emergency (ED) attendees and the general adult population.

**Methods :** A screening model has been developed and combined with a treatment model (early treatment vs waiting model) to determine overall cost-effectiveness of both diagnosis and treatment of HCV. The screening model is a decision tree model simulating the screening process and covering the process from initial antibody test to diagnosis. The treatment model is a Markov state transition model, simulating treatment with oral DAAs versus natural disease progression. The models have been populated with Belgian data. Time horizon of the screening model was 5 years with one screening round per year. The treatment model had a time horizon of 60 years to account for disease burden. A deterministic sensitivity analysis (DSA), where all variables were varied by 20% was conducted to identify key drivers of the model results. Perspective of the analysis is the Belgian health care payer (RIZIV/INAMI). Indirect costs such as productivity loss are excluded from this analysis.

**Results :** The model calculated the number of HCV positive patients detected with comprehensive screening versus the number of HCV positive patients detected in the current situation. In the first screening year the number of patients detected : in the general population 1.826 versus 867 patients, in the ED population 878 vs 68 patients, in the MSM population 508 versus 254 patients and in the PWID population 714 versus 516 patients. After 5 years of screening the cumulative number of HCV positive patients detected with comprehensive screening compared to the cumulative number of HCV positive patients detected in the current situation : in the general population 8.310 versus 4.231 patients, in the ED population 2.056 vs 335 patients, in the MSM population 2.273 versus 1.364 patients and in the PWID population 1.629 versus 1.492 patients. The incremental cost per incremental QALY gained in comprehensive screening versus the current situation for the combined screening and treatment model in the first year of screening indicated that comprehensive screening was cost-effective compared to the current situation. The ICERs calculated by the model were : in the general population 5.139€/QALY, in ED 5.991€/QALY, in MSM 4.292€/QALY and in PWIDs 3.504€/QALY. Similar ICERs were found for the 5 screening rounds : in the general population 5.200€/QALY, in ED 7.346€/QALY, in MSM 4.302€/QALY and in PWIDs 3.524€/QALY. Results of the deterministic sensitivity analysis indicated that the HCV prevalence, awareness of HCV positivity, treatment initiation and the acceptance of initial antibody test were among the 10 variables leading to the greatest variation of the ICER. When these variables were varied by 20%, all ICERs remained below 10.000€/QALY. If the cost per DAA treatment was estimated at 30.000€ per treatment (40.000€ in base case), calculated ICER in the general population for the first screening year was 3.987€/QALY. In the general population a scenario analysis was undertaken with conservative estimates for HCV prevalence : 0,4% (0,6% in base case) and awareness of HCV positivity : 70% (50% in base case). In the first screening year 731 patients were detected with comprehensive screening and the calculated ICER was 6.584€/QALY.

**Conclusions :** The results of this cost-effectiveness analysis suggest that broadening screening in the general population or in the ED population is very likely to be a cost-effective investment to identify HCV infected individuals in order to treat them and to decrease the HCV prevalent and incident population. Public health efforts to implement HCV screening in high risk populations, PWID and MSM, is also cost-effective and efforts should continue. (Gilead funded the development of the used models.)

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RETROSPECTIVE ANALYSIS OF HCV INFECTED INDIVIDUALS IN A BELGIAN REGIONAL HOSPITAL. L. Bruwier (1), G. Bastens (1), N. Cielniaszek (2), D. Graas (2), B. Bastens (1) / [1] CHC Clinique Saint-Joseph, Liège, Belgium, Gastroenterology, [2] CHC Clinique Saint-Joseph, Liège, Belgium, Clinical Biology.

**Introduction :** Hepatitis C is a major public health problem ; chronic infection occurs in 75-80% of cases. It is estimated that about half of the chronically infected patients are not aware of their status. There is a need to a better knowledge of the epidemiology and natural history in Belgium.

**Aim :** This retrospective analysis aims to provide epidemiologic data in our institution and to improve patients' and physicians' awareness about Chronic Hepatitis C. Other aims are to improve screening for Hepatitis C, to improve care and access to treatment for infected patients

**Methods :** The global data base and the laboratory data from our institution were used from January 2014 to December 2016 to identify HCV positive individuals. The following keywords were tracked in both data base : HCV, Hepatitis virus, anti-HCV antibodies positive, HCV-RNA. The following parameters were analyzed : anti-HCV antibodies positive HCV-RNA, genotype, morbidity, complications, mortality, percentage of lost of follow-up, type of management, outcome of treatment. General practitioners were contacted in order to collect missing information about HCV positive individuals.

**Results :** -23063 sera were tested for anti HCV antibodies. 485 anti-HCV antibodies were positives. 76 patients had more than one assay. Finally, 383 patients were positive for HCV (1.66 % of tested patients). 155 patients (40.5%) were not checked for PCR. 13 of them died of undetermined causes and 142 were lost of follow-up. These 142 patients had no referral practitioner. 228 patients (59.5%) had a PCR assay. -96 had negative PCR and were cured : 34 after treatment and 62 presented a self-limited disease. Among these cured patients 2 were transplanted (1 for decompensated cirrhosis despite HCV eradication, 1 for hepatocellular carcinoma). -132 (34.5%) patients had a positive PCR. Mean age was 51.5 (22-89). 54 were females (41%) and 78 were males (59%). 18 of these 132 died during the examined period (2 of hepatocellular carcinoma, 3 of hepatorenal syndrome, 13 of undetermined causes or unrelated to HCV). Among these chronic infected patients, 8 were post-transfusional, 62 PWID, and 62 of unknown cause. Genotyping was realized in 79 patients. 27 patients had HCV genotype 1a, 13 had HCV genotype 1b, 3 had HCV genotype 1 (undetermined), 20 had HCV genotype 3, 14 had HCV genotype 4, 2 had HCV genotype 5. Of the 132 active patients, 13 were HIV coinfectd (9.8%)

**Conclusions :** Testing for Ac HCV is not well targeted and physician repeat the dosage too many times in the same patient - Among patients with positive anti-HCV antibody, 40.5% were not evaluated by PCR assay, and were lost of follow-up. The majority of these patients only came at the emergency department, and had no referral practitioner. - The prevalence of genotype 1b seems to decrease in our region, and genotype 3 is the second common type - 34.5% of HCV positive patients were confirmed by a PCR test. These chronically infected patients received no treatment for different reasons. These patients would benefit from the availability of the new potent drugs - There is an urgent need to improve physicians' knowledge about HCV, and to develop new strategies to deliver appropriate clinical care to the HCV infected population

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THE IMPACT OF INTRA-PATIENT VARIABILITY IN TACROLIMUS PRE-DOSE CONCENTRATIONS ON PATIENT OUTCOMES IN PEDIATRIC LIVER TRANSPLANTATION RECIPIENTS. C. Defrancq (1), N. De Wilde (1), A. Raes (2), M. Van Winckel (3), S. Van Biervliet (3), S. Vande Velde (3), X. Rogiers (4), A. Prytula (2), R. De Bruyne (3) / [1] Ghent University, Ghent, Belgium, [2] Ghent University Hospital, Ghent, Belgium, Department of paediatric nephrology, [3] Ghent University Hospital, Ghent, Belgium, Department of paediatric gastroenterology and hepatology, [4] Ghent University Hospital, Ghent, Belgium, Department of hepatobiliary surgery.

**Introduction :** The impact of the intra-patient variability in tacrolimus exposure (TAC IPV) on patient outcome in paediatric liver transplantation has been poorly studied.

**Aim :** The present study aims to investigate whether liver transplantation outcomes in paediatric patients are associated with TAC IPV of the first year of follow-up.

**Methods :** A single centre retrospective study was performed including forty living paediatric (median age 11 years ; range 1-18 years ; 22 male) patients transplanted between 2003 and 2016 at Ghent University Hospital. Median age at

liver transplantation was 1.5 years (range 0-17 years) with a median 8 years (range 1-13 years) follow-up. The intra-patient variability of the dose and weight adjusted tacrolimus pre-dose concentrations (TAC IPV) was calculated for the period 3 months to 12 months after liver transplantation and expressed as the coefficient of variation (CV). The association between the CV and following liver transplantation outcomes was tested : need for biopsy, hypertension, renal function, acute rejection, CMV/EBV viremia, presence of donor-specific antibodies and development of food allergy.

**Results :** Univariate analyses showed an association between the TAC CV and the need for biopsy during the first year post-transplantation ( $P = 0.02$ ) and the occurrence of one or more episodes of acute allograft rejection during the first year post-transplantation ( $P = 0.04$ ). The simple logistic regression models predicting the need for biopsy during the first year, indicated the TAC CV as a significant predictor with an odds ratio of 1.04 (per 1-unit increase ; 95%CI 1.0-1.1 ;  $P = 0.03$ ). The simple logistic regression models predicting the occurrence of acute rejection during the first year, indicated CMV viremia during the first year, occurrence of acute rejection during the first three months and the TAC CV as significant predictors with odds ratios of respectively, 18 (95%CI 1.8-177 ;  $P = 0.01$ ), 10 (95%CI 1.9-54 ;  $P = 0.01$ ) and 1.04 (per 1-unit increase ; 95%CI 1.0-1.1 ;  $P = 0.05$ ).

**Conclusions :** A high TAC-IPV is associated with the need for liver biopsy and acute rejection during the first year after transplantation. Our results highlight the importance of the variability of the tacrolimus trough levels as it provides a possible opportunity for monitoring, prevention and intervention. We speculate that future programs to reduce the intra-patient variability could improve the transplantation outcome.

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LOSS-TO-FOLLOW-UP IS AN IMPORTANT PROBLEM IN THE DIAGNOSIS AND FOLLOW-UP OF HEPATITIS C. W. Verlinden (1), S. Francque (2), T. Holvoet (3), S. Van Hees (4), C. Cottignie (4), V. Wijtvliet (4), L. Vonghia (2), P. Michiels (2), T. Vanwolleghem (2) / [1] Antwerp University Hospital, Edegem, Belgium, Gastroenterology and hepatology, [2] Antwerp University Hospital, Edegem, Belgium, Gastroenterology and Hepatology, [3] AZ Nikolaas, Sint-Niklaas, Belgium, Gastroenterology and Hepatology, [4] University of Antwerp, Antwerp, Belgium, Laboratory of experimental medicine and paediatrics.

**Introduction :** Many hepatitis C (HCV) projects focus on screening but little is known about the drop-out during follow-up (FU).

**Aim :** The aims of this study were to evaluate the loss-to-follow-up (LTFU) between the moment of positive HCV serology and hepatological assessment ; and to evaluate the drop-out rate during hepatological FU.

**Methods :** In the first part, a retrospective analysis was performed on patients with positive HCV antibodies (Ab) in a blood test requested by a non-hepatologist in a university and a non-university hospital. In the second part, a retrospective analysis was performed on patients with positive HCV RNA that were followed at the hepatology department of a university hospital to discover patients LTFU (untreated or unsuccessfully treated patients that never showed up at suggested FU date).

**Results :** In the first part of the study, 70 patients with positive Ab were included from the university hospital ( $49 \pm 13$  years, 54% male) from 19 different departments with a majority from the haematology (23%) and nephrology (19%) clinic. Blood tests were mostly performed as a routine test (63%). Of all patients, 16% had already been successfully treated in the past, 33% had a past infection with spontaneous clearance, 33% had an active chronic infection and 18% is unknown. Of patients in need for further testing, 33% was not referred for hepatological assessment nor was the result mentioned in the consultation or discharge report. In the non-university hospital, 97 patients with positive Ab were included ( $47 \pm 16$  years, 52% male) from 19 different departments with a majority from the psychiatry (20%) and gynaecology (17%) clinic. Blood tests were mostly performed as a routine test (95%). Of all patients, 5% had already been successfully treated in the past, 18% had a past infection with spontaneous clearance, 48% had an active chronic infection and 29% is unknown. Of patients in need for further testing, 38% was not referred for hepatological assessment nor was the result mentioned in the consultation or discharge report. In the second part of the study, 300 patients were included (66% male, 19% HIV positive) of which 131 (44%) patients were waiting for (new) treatment at the last consultation. Of these 131 patients, 98 (75%) were LTFU with 32% of them not showing up for a planned consultation while 68% never made/received a new appointment. Thirty-seven percent could not be contacted (changed phone number, no longer in FU at GP), 37% was treated/followed at another hospital, 6% was deceased and 2% was in a weak physical condition that did not permit FU. Eighteen percent could be contacted and were not in FU at our or another centre. Of these last patients, 22% didn't realize FU was necessary, 67% realized the necessity but hadn't come to organizing it and 11% was waiting for the hospital to contact them.

**Conclusions :** Many patients are lost between diagnosis and treatment, both in university and non-university hospitals. These results show the importance to implement strategies to optimize FU of HCV patients such as sending all positive HCV Ab results to the hepatologist, automatically planning new FU appointments and routinely revising patient databases to discover patients LTFU.

THE ASSOCIATION BETWEEN CHRONIC HEPATITIS C INFECTION AND COLON CANCER : A NATIONWIDE CASE-CONTROL STUDY. N. Le (1) / [1] Taipei Medical University, Taipei, Taiwan (Province of China), College of Medicine.

**Introduction :** Hepatitis C virus (HCV) is the common cause of hepatocellular carcinoma (HCC), a leading cause of cancer-related deaths worldwide. Besides, chronic hepatitis C (CHC) was revealed to be associated with various extra-hepatic malignancies, albeit inconclusive. One previous epidemiological study with 233 HCV carriers and 446 controls was demonstrated the higher rate of colorectal adenoma in individuals with CHC than the controls. Taiwan, in which colon cancer colorectal cancer rate led the third highest cancer, has reported as among the highest in prevalence of HCV infection in Northeast Asia region.

**Aim :** we conducted a nationwide case-control study to evaluate the association between CHC and colon cancer

**Methods :** Applying the exclusion criteria of participants having HIV positive, missing age and gender-related information, we identified 71,103 colon cancer subjects, and 71,103 non-colon cancer controls matched for sex, age randomly selected from the Taiwan National Health Insurance claims data between 2000 and 2011. The socio-demographic characteristics, HCV and colon cancer status were collected based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Pearson's chi-square test was used to compare the distributions of socio-demographic factors. The multivariate logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) to explore the association between CHC and colon cancer. Stratification by age and sex to evaluate sex- and age-specific risks of colon cancer.

**Results :** The proportion of colon cancer was higher in male than female (55.2% & 44.8%), increased in ages over 50 years old. Overall, patients with CHC had higher risk of colon cancer than non-CHC carriers (OR 1.11, 95% CI 1.02-1.20). Stratification by age and sex, it was revealed that middle aged male subjects (55-64 years old) infected with CHC had more risk of presenting with colon cancer (OR 1.13, 95% CI 1.01-1.70) than their controls. However, in females, the risk of colon cancer was increased in the older group (65-74 years old) (OR 1.24, 95% CI 1.01-1.53)

**Conclusions :** Chronic hepatitis C infection was significantly associated with colon cancer. Women with CHC were likely having the colon cancer later than males.

## BELGIAN NETWORK ON GASTROINTESTINAL REGULATORY MECHANISMS (GIREM)

- B01 -

PREDICTORS FOR COLONIC MANOMETRY OUTCOME RELATED TO HIGH-AMPLITUDE PROPAGATING SEQUENCES. J. Pannemans (1), I. Demedts (2), A. D'hoore (3), H. De Schepper (4), I. Hoffman (5), T. Vanuytsel (1), J. Tack (1) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium, TARGID, [2] UZ Leuven, Leuven, Belgium, Gastroenterology, [3] UZ Leuven, Leuven, Belgium, Abdominal surgery, [4] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology, [5] UZ Leuven, Leuven, Belgium, Pediatrics.

**Introduction :** Colonic manometry is advocated in the diagnostic work-up of refractory chronic constipation to identify patients with colonic inertia, who might benefit from surgery.

**Aim :** Since colonic manometry is only available in a few centers worldwide, there is a need for clinical predictors of colonic inertia.

**Methods :** Patients with treatment refractory constipation were referred to our center for colonic manometry. Prior to that, assessment of colonic transit with radio-opaque markers and anorectal manometry (ARM) was performed. Using ARM, sphincter pressures, first sensation, urge, increased rectal pressure and paired sphincter state were evaluated. For colonic manometry, bowel preparation was performed with 2L polyethylene glycol and water enemas. In all patients, a 40-sensor high-resolution colonic manometry catheter with 2.5 cm spacing, was advanced and clipped as proximal as possible during colonoscopy. Colonic motility was evaluated while the patient was still sleeping after the sedation, in an awake fasted state, during a standardized meal, postprandially, and after intra-colonic administration of 10 mg of Bisacodyl. Anterograde contractions were sub-classified as high-amplitude propagating contractions (HAPCs), according to the criteria used by Corsetti et al. (2017). Colonic inertia was defined as absence of HAPCs after intraluminal infusion of Bisacodyl. Mann Whitney U tests (2-tailed) were applied to compare transit and different anorectal and colonic manometric findings in patients with or without colonic inertia : colonic transit time, rectal sensory abnormality for first balloon sensation ( $\geq 30$  mL) or urge ( $\geq 90$  mL), and the possibility to expel a 50 mL balloon. Data are presented as median (interquartile ranges).

**Results :** Thirty-three patients (41.7 $\pm$ 17.8 years, 3 males) were studied. Standardized ARM was available for 26 patients. The number of HAPCs post-bisacodyl administration was greater in case of a sensation problem on ARM [7 (5-10) vs. 2 (1-6) ;  $p=0.034$ ]. A standardized pellet transit test was available for 26 patients with a median transit time of 118 (29-144) hrs. Colonic transit time was significantly longer in case of colonic inertia [141.5 (137.5-144) vs 113 (59-127.8) ;  $p=0.005$ ]. All patients with colonic inertia had a colonic transit time of  $\geq 137.2$  hours. Receiver operation characteristic curve analysis determined the optimum cut-off for predicting colonic inertia at 138 min, with a sensitivity and specificity of respectively 75 and 96%. Other parameters such as abnormal rectal sensitivity, urge or inability to expel a balloon were not linked to a prolonged transit time or to the presence of colonic inertia.

**Conclusions :** These data indicate the potential of a severely delayed colonic transit time to act as a marker for colonic inertia. Confirmation in a multi-center setting is needed before this can be implemented in clinical practice.

- B02 -

FECAL MICROBIOTA TRANSPLANTATION IN IRRITABLE BOWEL SYNDROME WITH PREDOMINANT ABDOMINAL BLOATING : RESULTS FROM A DOUBLE BLIND, PLACEBO-CONTROLLED, RANDOMIZED CONTROLLED TRIAL. T. Holvoet (1), M. Joossens (2), J. Boelens (3), E. Christiaens (1), L. Heyerick (1), B. Verhasselt (3), M. De Vos (1), P. Hindryckx (1), J. Raes (2), D. De Looze (1) / [1] Ghent University Hospital, Ghent, Belgium, Gastroenterology, [2] KUL, Belgium, Microbiology, [3] Ghent University Hospital, Ghent, Belgium, Microbiology.

**Introduction :** Intestinal microbiota dysbiosis is thought to play an important role in the pathophysiology of irritable bowel syndrome (IBS), especially in those patients with severe abdominal bloating. Faecal microbiota transplantation (FMT) is effective in correcting this gut microbiota imbalance, is a recommended treatment in recurrent *Clostridium difficile* infections and has shown promise in treating IBS patients.

**Aim :** In this placebo-controlled, randomized trial effects of FMT in IBS patients with severe abdominal bloating were examined.

**Methods :** Patients with refractory IBS symptoms and predominant abdominal bloating (defined by the ROME III criteria), aged 18-75 years and without constipation were included in this double-blind, placebo-controlled, single-centre clinical trial. Patients were randomly assigned (2 :1) to transplantation with fresh donor stool or with placebo (patient's own frozen stool). Donors (N=2) were selected based on both having a high microbial richness and yielding good clinical results in a preliminary pilot trial. They were screened for infectious diseases on a regular base (HAV, HBV, HCV, HIV, Treponema in blood, enteropathogens, *Clostridium difficile* toxin and parasites in stools). Transplants were prepared as previously described and administered through a nasojejunal tube which was placed electromagnetically

guided (Cortrak). Primary endpoint was self-reported improvement of overall IBS symptoms and abdominal bloating in particular, 12 weeks after transplantation. Secondary endpoints were changes in IBS related symptoms scores and IBS-related quality of life. Stool samples were collected before and at different timepoints following transplantation. 16S rRNA amplicon sequencing was performed to follow the dynamics of the gut microbiota. This study is registered on ClinicalTrials.gov (NCT02299973).

**Results :** Between December 2015 and September 2017 a total of 64 IBS patients was randomized to active donor treatment (N= 42) or placebo (N=22). One patient in the placebo group committed suicide in the month following FMT, no drop-outs were seen in the donor group. At week 12, 49% in the active treatment group reported adequate relief of both general IBS symptoms and abdominal bloating in particular, compared to 29% in the placebo group (P=0.004). A statistically significant reduction was seen in discomfort (mean reduction of 19% p=0.001), the number of stools (-13%, p=0.02), urgency (-38%, p=0.01), abdominal pain -26%, p=0.001) and flatulence (-10%, p=0.04) in the donor group but not in the placebo group, while IBS-related quality of life improved as well in the donor group (+16%, p=0.03). There were no significant differences in the efficacy of individual donors. Microbiota analysis are currently ongoing.

**Conclusions :** In this double-blind, placebo-controlled clinical trial, FMT with healthy donor stools significantly improved symptoms of IBS patients with predominant abdominal bloating.

- B03 -

EFFECTS OF NAFAMOSTAT MESYLATE ON INTESTINAL PERMEABILITY AND BACTERIAL TRANSLOCATION IN AN EXPERIMENTAL MODEL OF SEPSIS. P. Plaeké (1), J. De Man (1), C. Dua (2), S. Hens (2), S. Nullens (1), A. Smet (1), S. Malhotra (3), P. Jorens (4), G. Hubens (5), B. De Winter (1) / [1] University of Antwerp, Antwerp, Belgium, Laboratory of Experimental Medicine and Paediatrics, [2] University of Antwerp, Antwerp, Belgium, Faculty of Medicine, [3] University of Antwerp, Antwerp, Belgium, Department of Medical Microbiology, [4] Antwerp University Hospital, Edegem, Belgium, Department of Intensive Care Medicine / University of Antwerp, Laboratory of Experimental Medicine and Paediatrics, [5] Antwerp University Hospital, Edegem, Belgium, Department of Abdominal Surgery / University of Antwerp, Antwerp Surgical Training, Anatomy and Research Centre.

**Introduction :** Sepsis is a complex clinical entity, associated with high morbidity and mortality. For many years, the gastrointestinal tract has been associated with the pathophysiology of sepsis. While gastrointestinal inflammation can evolve to a systemic inflammatory response, systemic inflammation can also spread to the gastrointestinal tract. Here, disturbed intestinal permeability and bacterial translocation appear to be the common mechanism for the induction and maintenance of the septic state and many proteases are hypothesized to be involved.

**Aim :** The aim of this study was to determine the effect of Nafamostat-Mesylate (NFM), a broad-spectrum protease inhibitor on the intestinal permeability and bacterial translocation in a murine model for sepsis.

**Methods :** OF-1 mice (Charles River, 10 weeks of age) were randomized into 4 groups : 2 sham groups and 2 septic groups (n=15/group). Sepsis was induced by means of a Caecal Ligation and Puncture procedure (=CLP, Single puncture 21G, 50% ligation). Mice belonging to the sham group received a laparotomy without ligation or puncture of the caecum. Either Nafamostat-Mesylate (NFM, Selleckchem, 10 mg/kg) or the vehicle (Aqua) was administered intraperitoneally 5 min prior to the procedure and subsequently twice a day. All mice were housed identically, received similar postoperative fluid resuscitation and analgesia, and were clinically monitored for 2 days following the procedure. The disease severity was assessed with a validated clinical disease score (Heylen, 2013) and by measuring the weight loss. On the second day, the abdomen was reopened and the severity of the intra-abdominal sepsis was determined based on the presence of adhesions, reactions of surrounding tissues and encapsulation of the caecum by visceral adipose tissue. Next, the ileum was ligated distally and 4 kDa FITC-Dextran was injected directly into the lumen. One hour later, mice were euthanized, and FITC was measured spectrophotometrically. Intestinal inflammation was measured with RT-PCR. Blood and mesenteric lymph nodes were cultured and analyzed with MALDI-TOF after enrichment. Data was analyzed with ANOVA and LSD post-hoc testing.

**Results :** In comparison to the corresponding sham groups, mice with a CLP-induced sepsis had significantly worse clinical disease scores [ $0.08 \pm 0.08$  vs.  $4.60 \pm 0.16$ ,  $p < 0.001$ ], lost more weight [ $4.60\% \pm 0.54$  vs.  $10.86\% \pm 0.70$ ,  $p < 0.001$ ] and had increased gene expression of several pro- and anti-inflammatory cytokines [IL6 :  $1.37 \pm 0.30$  vs.  $4.71 \pm 0.81$ ,  $p < 0.001$  ; IL18 :  $1.17 \pm 0.13$  vs.  $3.06 \pm 0.34$ ,  $p < 0.001$ ]. Similarly, CLP-induced sepsis was associated with increased intestinal permeability for FITC-Dextran [ $1.27 \pm 0.14$  vs.  $2.36 \pm 0.35$ ,  $p = 0.05$ ] and increased bacterial translocation to the mesenteric lymph nodes [cultures positive  $6.67\%$  vs  $80.00\%$ ,  $p < 0.001$ ] and to the blood [Cultures positive  $0.00\%$  vs.  $26.67\%$ ,  $p = 0.03$ ]. Treatment with NFM had no significant effect on the clinical disease score, nor did it influence % weight loss resulting from the CLP-procedure. However, the formation of intra-abdominal adhesions and caecal fat encapsulation were highly reduced in the CLP + NFM group compared to the vehicle treated CLP-group. Remarkably, NFM increased small bowel permeability [ $3.47 \pm 0.62$  vs.  $2.36 \pm 0.35$ ,  $p = 0.043$ ] and the prevalence of positive hemocultures [ $53.33\%$  vs.  $26.67\%$ , NS] and cultures of the mesenteric lymph nodes [ $93.33\%$  vs.  $80.00\%$ , NS] even further, however the latter effect was not statistically significant. However, these nafamostat-induced changes were not associated with significant upregulated gene expression of several measured pro- and anti-inflammatory cytokines.

**Conclusions :** CLP-induced sepsis is associated with increased intestinal permeability and bacterial translocation. NFM 10 mg/kg reduced the intra-abdominal manifestations of sepsis, but in the meantime increased the intestinal permeability and bacterial translocation. Gene expression of several cytokines did not demonstrate any significant difference between the NFM-treated and untreated sepsis group. As NFM is a broad-spectrum protease inhibitor, NFM is hypothesized to mediate both protective and harmful proteases during the pathophysiology of sepsis. Further research on the mechanisms in which NFM modulates the gastrointestinal permeability remain necessary.

- B04 -

MRGPRC11 IS EXPRESSED IN MURINE VISCEROSENSORY SPINAL NEURONS : AN IMMUNOHISTOCHEMICAL AND RETROGRADE TRACING STUDY. S. Van Remoortel (1), J. De Man (2), B. De Winter (2), R. Buckinx (1), J. Timmermans (1) / [1] Laboratory of Cell Biology and Histology, Department of Veterinary Sciences, University of Antwerp, Antwerp, Belgium, [2] Laboratory of Experimental Medicine and Paediatrics, Division of Gastroenterology, University of Antwerp, Antwerp, Belgium.

**Introduction :** Mas-related G protein-coupled receptors (Mrgprs) belong to a large family of GPCR's that are expressed in dorsal root ganglion (DRG) neurons and are assumed to play a role in somatic pain. A well-characterized member, namely the murine Mrgprc11, has been linked to opioid signaling and reveals a marked functional orthology to the human MrgprX1. Both receptors have been shown to mediate histamine-independent itch upon peripheral stimulation and are thought to be involved in the central modulation of inflammatory and/or neuropathic pain by altering synaptic transmission from the DRG to the spinal dorsal horn. Though presence of Mrgprc11 has been demonstrated in CGRP-positive DRG neurons, to date no information is available on the presence of Mrgprc11 in viscerosensory spinal pathways.

**Aim :** This study aims : 1) to validate the specificity of a commercial and non-commercial antibody raised against Mrgprc11 and 2) to evaluate the distribution pattern of Mrgprc11 in viscerosensory pathways under normal and inflammatory conditions in mice.

**Methods :** DRG's were isolated from spinal levels that innervate the terminal ileum (T8-T13) and distal colon (T9-L2 and L6-S2). In order to identify viscerosensory DRG neurons that express Mrgprc11, we combined immunohistochemistry with retrograde DRG tracings from the terminal ileum (n=4) and distal colon (n=3), performed by intramural injections with Fast Blue. By means of qPCR, we examined Mrgprc11 expression in DRG's from spinal levels T8-T13 in two validated intestinal inflammation mouse models (a *Schistosoma mansoni* model and an acute TNBS-ileitis model, n=6 each).

**Results :** In contrast to the commercial antibody which turned out to be non-specific, the non-commercial Mrgprc11 antibody showed specific staining in DRG's from wild-type mice, whereas no staining was found in DRG neurons from knockout animals that lack Mrgprc11 expression. Moreover, an indirect comparison of the antibody with in situ hybridisation for Mrgprc11 showed a similar proportion of labelled DRG neurons. The immunohistochemistry on DRG's that were retrogradely traced from terminal ileum and distal colon revealed Mrgprc11 expression in up to 17.5±3.9% and 18.1±1.1% of these neurons, respectively. During intestinal inflammation caused by a parasitic infection with *S. Mansoni*, we found a significant upregulation in the mRNA expression of Mrgprc11 in DRG's that innervate the terminal ileum (T8-T13) whereas no expression difference was found in DRG's of acute TNBS ileitis mice.

**Conclusions :** At this point, our results provide first proof that Mrgprc11 is expressed in viscerosensory DRG neurons and that a Th2-mediated immune response to *S. mansoni* infection can alter its expression in these neurons. These results hint towards a role of Mrgprc11 in visceral sensitivity, albeit further studies on its functional role (as potential new opioid-like modulator of visceral sensitivity) are necessary.

- B05 -

LIVE CALCIUM IMAGING REVEALS NEURONAL CIRCUITRY DIFFERENCES IN THE MOUSE COLON. Z. Li (1) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Clinical and Experimental Medicine.

**Introduction :** Different regions of the gut exhibit specific motility patterns regulated by the enteric nervous system (ENS). Currently, little is known about how ENS circuits are differentially organized to generate these regionally distinct motility patterns.

**Aim :** To explore whether calcium imaging of the ENS can uncover differences in neuronal circuits between the proximal and distal colon.

**Methods :** Live Ca<sup>2+</sup> imaging was performed on myenteric plexus preparations from adult Wnt1-Cre ; R26-GCaMP3 mice, where all enteric neurons express the genetically-encoded Ca<sup>2+</sup> indicator, GCaMP3. Focal electrical stimulation was applied (300µsec, 20Hz, 2sec) and responses in individual neurons were analyzed. Immunohistochemistry was

performed to compare differences in the neuronal density and phenotype. Furthermore, we transduced the mouse ENS using AAV9-CMV-GFP which made it possible to trace the projections of individual myenteric neurons.

**Results :** Using a low magnification (5X) lens, we were able to simultaneously record the intracellular Ca<sup>2+</sup> changes from a large population of neurons in many ganglia (up to 1.3 mm x 1.7 mm field of view). Analysis of the number of myenteric neurons and the intraganglionic fibers showed that both these parameters were significantly higher in the proximal colon, which reflects the higher density of the myenteric neurons and higher packing of intraganglionic fibers at the stimulation site. Live Ca<sup>2+</sup> imaging showed that application of the nicotinic receptor antagonist, hexamethonium (200 μM), significantly decreased the electrically-evoked Ca<sup>2+</sup> transients in the majority of neurons in both regions. Moreover, fraction of neurons in which Ca<sup>2+</sup> responses were completely abolished by hexamethonium was significantly larger in the distal colon. Quantification of the proportion of ChAT<sup>+</sup> and nNOS<sup>+</sup> myenteric neurons indicated that the ratio of nitrergic neurons was higher in the distal colon. Additionally, AAV9 based transduction of the ENS revealed a larger percentage of descending interneurons in the distal colon.

**Conclusions :** Our live Ca<sup>2+</sup> imaging approach reveals differences in neuronal connectivity in the ENS. Although there is no difference in the proportions of ChAT<sup>+</sup> neurons, excitatory cholinergic transmission is more pronounced in the distal colon versus proximal colon. Furthermore, mapping projections of individual enteric neurons suggests that a larger fraction of nitrergic neurons is involved in the functional regulation of the distal colon.

- B06 -

UPREGULATION OF MAST CELL RELATED GENES IN IRRITABLE BOWEL SYNDROME. J. Aguilera-Lizarraga (1), D. Balemans (2), M. Florens (2), E. Perna (2), L. Decraecker (2), S. Theofanous (2), P. Jain (2), A. Denadai-Souza (2), D. Lambrechts (3), M. Wouters (2), G. Boeckxstaens (2) / [1] Katholieke Universiteit Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders, [2] KU Leuven, Leuven, Belgium, Chronic Diseases, Metabolism and Ageing, [3] VIB, Leuven, Belgium, Laboratory of Translational Genetics.

**Introduction :** Microscopic inflammation and mast cells are proposed to play an important role in the pathogenesis of irritable bowel syndrome (IBS). However, conflicting data with respect to the number of mast cells have been reported, suggesting that increased activation or increased release of mediators are more likely to underlie the involvement of mast cells in IBS. Moreover, several studies fail to confirm upregulation of pro-inflammatory cytokines in colorectal biopsies of IBS compared to healthy volunteers (HV).

**Aim :** In this study, we performed a detailed analysis of the expression of pro-inflammatory genes and genes involved in the synthesis and/or release of mast cell mediators in rectal and colonic biopsies of IBS patients.

**Methods :** Patients meeting the ROME III criteria for IBS were recruited and biopsies from colon descendens and rectum were collected. Colon descendens biopsies were collected from 50 HV and 90 IBS (IBS-alternating, 31 IBS-constipated, and 51 IBS-diarrhea) patients, rectal biopsies were collected from 70 HV and 77 IBS (11 IBS-alternating, 11 IBS-constipated, 34 IBS-diarrhea, 4 IBS-mixed and 17 IBS-unsubtyped) patients. RNA was extracted and real-time PCR was performed using OpenArray technology. Inflammatory genes (il1b, il4, il6, cxcl8, il10, il12a, tnf, ccl2, tgfb, il17a, il17rb, il13, il25, il33) and mast cell-related (mrgprx2, cpa3, kit, fcer1la, fcgr2b, fcgr3b) and histamine-related (hdc) genes were amplified. Relative gene expression was calculated as 2<sup>-ddCt</sup> (housekeeping gene : hprt1). Differences in gene expression was analyzed by Mann Whitney test, and differences in proportion of gene amplification between groups was analyzed by Fisher's exact test.

**Results :** With respect to pro-inflammatory cytokines, only il1b and ccl2 were significantly upregulated in IBS compared with HV (HV 0.55 IQR [0.2-0.9] vs. IBS 1.03 IQR [0.5-1.9], p<0.0001 ; and HV 0.8 IQR [0.4-1.8] vs. IBS 0.96 IQR [0.6-1.5], p<0.01 ; respectively). Of interest, Cpa3, known to be solely expressed in mast cells, and fcgr2b, involved in inhibition of mast cell degranulation, were significantly upregulated (HV 0.9 IQR [0.6-1.4] vs. IBS 1.05 IQR [0.7-1.5] ; p=0.056) and downregulated (HV 1.1 IQR [0.6-1.9] vs. IBS 0.87 IQR [0.5-1.4] ; p<0.05) respectively in IBS patients. Moreover, hdc, encoding histamine decarboxylase (synthesis of histamine) was amplified in 86% of IBS patients compared with 66% of HV (p<0.0001). Differences between IBS subtypes and the relationship of mast cell gene up/downregulation to symptoms are currently evaluated.

**Conclusions :** The mast cell-related genes cpa3, hdc and fcgr2b are differentially expressed in IBS compared to HV, supporting a pivotal role for mast cells and in particular for increased activation in the pathogenesis of IBS. These data further confirm mast cells and mast cell mediators as important targets for treatment of IBS.

- B07 -

FOOD ANTIGEN-SPECIFIC SENSITIZATION OF NOCICEPTIVE NERVES AS AN UNDERLYING MECHANISM OF VISCERAL PAIN IN IBS. J. Aguilera-Lizarraga (1), D. Balemans (2), C. Lopez-Lopez (3), J. Jaramillo-Polanco (3),



E. Perna (2), S. Theofanous (2), M. Florens (2), L. Decraecker (2), P. Jain (2), A. Denadai-Souza (2), C. Breynaert (4), S. Vanner (3), D. Reed (3), M. Wouters (2), G. Boeckxstaens (2) / [1] Katholieke Universiteit Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders [2] KU Leuven, Leuven, Belgium, CHRONIC DISEASES, METABOLISM AND AGEING, [3] Queen's University Kingston, Kingston, Canada, GI Diseases Research Unit, [4] UZ Leuven, Leuven, Belgium, Departement Microbiologie en Immunologie.

**Introduction :** Exposure of a food antigen during stress, abdominal infection or ingestion of bacterial superantigens triggers in mice an aberrant immune response against this antigen leading to mast cell activation and visceral hypersensitivity upon re-exposure. As we previously reported histamine 1 receptor (H1R)-induced sensitization of TRPV1 in patients with irritable bowel syndrome (IBS), we hypothesized that a similar mechanism would be involved. Moreover, given that ingestion of food is a major trigger of abdominal symptoms in IBS, we further hypothesized that IBS patients may exhibit a similar response upon exposure to food antigens.

**Aim :** 1. To evaluate if increased visceral hypersensitivity in mice infected or stressed in the presence of a food antigen and re-exposed to it leads to sensitization of TRPV1 of sensory neurons via H1R activation. 2. To investigate if, similar to our murine models, IBS patients exhibit an immune response upon exposure to food antigens.

**Methods :** Balb/c mice were infected with *Citrobacter rodentium* or stressed (water avoidance stress) in the presence of ovalbumin. After recovery of the infection or stress, mice were re-exposed to ovalbumin (+ovalbumin) or saline (control). Next, colons were incubated in RPMI medium and supernatant was collected. The ability of the supernatants to sensitize TRPV1 was evaluated in dorsal root ganglia (DRG) neurons using live Ca<sup>2+</sup> imaging. Neuronal excitability was evaluated using patch clamp recording of these neurons. The involvement of H1R was tested using pyrilamine and/or H1R KO mice. In humans, wheat, gluten and milk were injected in the rectal mucosa of 5 IBS patients and compared to 3 healthy volunteers. Skin testing was negative in all participants. Mucosal edema-diameter was measured and biopsies of the injection site were collected.

**Results :** Supernatants of infected + ovalbumin or the stressed + ovalbumin, but not of control mice, reduced rheobase ( $p < 0.05$ ) and increased the number of action potentials at 2x rheobase indicating neuronal hyperexcitability ( $p < 0.05$ ). This effect was inhibited by the H1R antagonist pyrilamine ( $p < 0.01$ ). Similarly, incubation of DRGs with supernatants of infected + ovalbumin mice, but not of control mice, significantly increased the Ca<sup>2+</sup> response to capsaicin of DRG neurons ( $p < 0.05$ ). This effect was also inhibited by pyrilamine and absent in H1R KO mice ( $p < 0.001$  and  $p < 0.01$ , respectively). Injection of histamine, but not saline, induced mucosal swelling (mean diameter) : HV : 13±6 mm ; IBS : 20±6 mm (NS). 5/5 IBS patients showed mucosal swelling : 2 patients reacted to all 3 antigens, 2 responded to 2 and 1 to 1 antigen. In contrast, none of the healthy volunteers showed a response.

**Conclusions :** Our data further support the concept that prior infection and/or stress can promote loss of oral tolerance to food antigens and that subsequent ingestion of that antigen can trigger visceral hypersensitivity. This involves mast cell activation, sensitization of TRPV1 and increased action potential discharge mediated by H1R activation. IBS patients demonstrate an immediate mucosal response to food antigens suggesting the involvement of a similar food antigen-specific mechanism leading to abdominal pain.

- B08 -

DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED TRIAL OF A PROBIOTIC COMBINATION PROBIOTER IN IRRITABLE BOWEL SYNDROME. F. Mokaddem (1), F. Fonteyn (2), I. Diedderen (2), B. Bastens (3), J. Deflandre (4), P. Thonart (2), E. Louis (5) / [1] Cliniques Sud Luxembourg, Arlon, Belgium, Gastroenterology, [2] LactoResearch SPRL, Belgium, R&D, [3] Centre Hospitalier Chrétien, Liège, Belgium, Gastroenterology, [4] CHR Citadelle, Liège, Belgium, Gastroenterology, [5] CHU Liege, Liège, Belgium, Gastroenterology.

**Introduction :** The pathophysiology of irritable bowel syndrome (IBS) is still incompletely understood but altered brain-gut interaction, visceral hypersensitivity, dysbiosis and altered immune interaction with a subclinical abnormal immuno-inflammatory response have been proposed. Particularly, some studies have shown a lower level of IL-10 among patients with IBS in comparison to controls with an inverse relationship between symptoms, intestinal permeability and IL-10. These observations give some evidences to increase IL-10 at the intestine level to reduce symptoms and improve QoL. Many studies have been published with one or many strains of probiotics most of them from the lactobacillus or/ and Bifidobacterium genu with conflicting results. After in vitro and ex vivo tests, strains of Lactobacillus Rhamnosus THT030903, Lactobacillus Plantarum THT030709 and Lactobacillus Casei THT030401 were selected for their ability to withstand stomach acid, bile salts and their capacity to stimulate interleukin-10 by human blood mononuclear cells. Based on the current hypothesis we conducted a multicenter RCT to assess the effect of this probiotic mixture (ProbioTer) on an IBS population.

**Aim :** To assess the efficacy of a probiotic mixture on symptoms improvement, transit satisfaction and quality of life.

**Methods :** Thirty-nine patients with IBS according to Rome III criteria were randomized in a double-blind placebo or ProbioTer trial. The patients were treated for 8 weeks and then followed up for 4 more weeks. The primary end-point

was the comparison of the magnitude of change in a validated global IBS assessment symptom score (IBS-SSS) based on frequency and intensity of abdominal pain, bloating, dissatisfaction of the intestinal transit and Quality of Life, using a 100-mm visual analogue scale between week 0 and week 8 in the treatment and the placebo group. Magnitude of change of IBS-SSS as well as different subscores, Global Assessment Improvement (IBS-GAI), Adequate Relief of the symptoms and IBS Quality of Life was also assessed as secondary end-points at week 4, 8 and 12.

**Results :** Of the 39 patients, 21 were randomly assigned to ProbioTer and 18 to placebo. Demographic factors were similar between the two groups. Globally, the IBS-SSS significantly improved between week 0 and 8, both in the treatment group and in the placebo group. We found no significant impact of treatment on improvement in IBS-SSS when using a global linear model at week 8, but in the treatment group, this effect was already noticed at week 2 and 4 whereas this effect was noticed only at week 8 in the placebo group. The improvement disappeared in the 2 groups at week 12. When analyzing the different component of the IBS-SSS, the frequency of pain decreased significantly only in the treatment group and not with placebo at week 2, 4 and 8 and this effect disappeared at week 12. There was no significant difference between placebo and treatment groups in of IBS Quality of Life score, IBS-Global Improvement, and proportion of patients reaching an Adequate Relief of their symptoms.

**Conclusions :** These results suggest that ProbioTer improves the IBS-SSS sooner and improves significantly the frequency of pain in comparison to the placebo group. These results support further studies with this probiotic combination in IBS.

- B09 -

PROSPECTIVE STUDY EVALUATING PREDISPOSING FACTORS AND IMMUNE-MEDIATED MECHANISMS UNDERLYING POST-INFECTIOUS IBS. M. Florens (1), S. Van Wanrooy (1), W. Peetermans (2), M. Wouters (1), W. Vanbrabant (3), J. Dooley (4), A. Liston (5), G. Boeckxstaens (1) / [1] KU Leuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing, [2] UZ Leuven, Leuven, Belgium, algemene interne geneeskunde, [3] UZ Leuven, Leuven, Belgium, Clinical Trial Center, [4] KU Leuven, Leuven, Belgium, Laboratory of Genetics of Autoimmunity (VIB-KU Leuven Center for Brain & Disease Research), [5] KU Leuven, Leuven, Belgium, Center for Brain & Disease Research.

**Introduction :** Psychological distress, the severity of infectious gastroenteritis (IGE) and the use of antibiotics during IGE are risk factors to develop post-infectious irritable bowel syndrome (PI-IBS). As most studies are retrospective in nature, data collected to assess risk factors may however not be accurate. Moreover, the role of immune activation in PI-IBS remains unclear mainly because tissue or blood samples collected prior to the infection are not available.

**Aim :** To identify predisposing clinical and psychological factors for the development of PI-IBS and immune changes evoked by an IGE episode and associated with persistent IBS symptoms.

**Methods :** 101 subjects traveling to high risk areas of IGE were asked to participate in a prospective study consisting of 4 visits : before travel, 2 weeks, 6 months and 1 year after travel. At each visit, subjects completed questionnaires on psychological profile (HADS, PHQ-12), bowel habits (Bristol Stool Scale, stool frequency) and gastrointestinal symptoms (GSRS and Rome III). Blood samples were collected for peripheral blood mononuclear cell isolation and rectal biopsies were taken. The IGE episode was self-assessed with respect to severity, duration and bowel habits. PI-IBS was diagnosed using the Rome III criteria and subjects with persistent post-infectious abdominal complaints (PI-AC, score >5) were identified using a composite score of loose stools (0-6), urgency (0-6) and abdominal pain (0-4).

**Results :** 47 of the 101 subjects reported IGE during travel. After 1 year, 2 subjects (4%) were diagnosed with PI-IBS and 8 (17%) subjects presented with PI-AC. The mean pre-travel somatization (PI-AC :  $5.6 \pm 2.8$  vs non-PI-AC :  $2.9 \pm 2.5$ ,  $p=0.01$ ) and anxiety score (PI-AC :  $6.3 \pm 3.0$  vs non-PI-AC :  $4.2 \pm 3.4$ ,  $p=0.04$ ) were significantly higher in PI-AC versus non-PI-AC. Of note, anxiety and depression scores of the total population were significantly lower compared to those reported in previous studies (anxiety :  $3.5 \pm 2.8$ , depression :  $1.6 \pm 2.2$  vs  $4.4 \pm 3.6$  and  $3.3 \pm 3.4$  in Wouters et al. 2015,  $p<0.01$ ). Binary logistic regression analysis identified basal stool consistency score, IGE severity and anxiety score as risk factors for PI-AC. Peripheral blood mononuclear cells analysis showed no differences in Th1, Th2, Th17, regulatory T cells or B cell populations in subjects with PI-AC versus non-PI-AC. Additionally, no differences in inflammatory gene expression were observed in the acute phase (2 weeks) or after 1 year of follow-up.

**Conclusions :** The incidence of PI-IBS in healthy subjects who developed IGE was only 4%, while 17% of infected individuals continued to report PI-AC. The low incidence in our study may be due to the low anxiety scores of the study population, suggesting a selection bias of subjects that are not concerned to provide repetitive rectal biopsies. Risk factors to develop PI-AC are pre-travel stool consistency score, IGE severity and anxiety score, while no role for persistent immune activation could be detected.

- B10 -

LONG TERM ADHERENCE AND EFFECTS OF LOW FODMAP DIET IN PATIENTS WITH IBS. L. Goossens\* (1), A. Weynants\* (2), M. Genetello (3), D. De Looze (4), M. Van Winckel (5) / [1] Ghent University, Ghent, Belgium, master

student in medicine, [2] Ghent University, Ghent, Belgium, master student in medicine, \* shared first authors, [3] Ghent University Hospital, Ghent, Belgium, Dietetics, [4] Ghent University Hospital, Ghent, Belgium, Gastroenterology, [5] Ghent University Hospital, Ghent, Belgium, Paediatric Gastroenterology.

**Introduction :** Short-term trials with low FODMAP diet (LFD) have shown promising results in the symptomatic management of Irritable bowel syndrome (IBS). The LFD is an intensive diet consisting of three phases. In the first phase, all food that contains fermentable oligosaccharides, disaccharides, monosaccharides and/or polyols (FODMAPs) are eliminated in the diet. This restriction phase is followed by a reintroduction phase and stabilisation phase. Data on long-term effects of the diet on IBS and long-term adherence are lacking.

**Aim :** To investigate the adherence and satisfaction with the diet and the long-term quality of life and symptom control in patients with IBS referred to a dietician in a tertiary care centre.

**Methods :** All patients, diagnosed with IBS by a gastroenterologist and referred between January 2014 and March 2016 for dietary advice and education concerning the LFD by an experienced dietician in the UZ Gent, are invited to participate in the study. Informed consent is acquired from all study participants, or their legal guardians, before participating in the study. The questionnaires are sent by email or regular mail and include the IBS-QOL questionnaire developed by Drossman et al. and a self-made questionnaire examining long-term adherence and satisfaction to the LFD, difficulties in application of the diet, disease course and IBS symptoms. Electronic data files of the participants are consulted following informed consent. Gender, age, IBS-subtype, number of dietary consultations and presence of abdominal bloating and flatulence at the moment of referring of the patient to the dietician for LFD are included in the data file. Statistical analysis is done using SPSS statistics 24 (SPSS Inc. Chicago IL, USA). The study was approved by the Ethical Committee of the UZ Gent.

**Results :** Of the 234 eligible patients, 90 filled in the questionnaires (38,5%). The median time span between the first dietary consultation and the day of completing the questionnaires is 99,5 weeks or nearly 2 years (min 49 w, max 168 w). 80 % report still following a diet in which certain FODMAP-rich food types are avoided. Only 15.3 % never deviate from the diet. One of the main reasons for not following the diet strictly is the lack of symptoms (50%). 55.6% of the participants deviate from the LFD when they are on holidays and when they eat in a restaurant. Eating with other people and feeling social pressure as well as eating at a friends' or family's place are also possible reasons to deviate (52.1% and 50%, respectively). 62.2 % indicate difficulties in applying the diet in real life. However, 88.9 % is satisfied that they follow or have followed the diet. The mean quality of life of the study participants is 72.3 scored on 100. The IBS-QOL does not significantly differ between patients following the diet very strictly, and patients deviating often from the diet ( $p=0.669$ ). The predominant disease course in the participants of this study is mild IBS with indolent course (43.0%). Abdominal distention is rated the most severe IBS symptom (mean score=5.5) by the participants, followed by flatulence (mean score=5.0) and abdominal pain (mean score=4.5). Patients who are still following the LFD, experience significantly less severe abdominal pain than patients who stopped following the diet or patients who have never started the LFD ( $p=0.044$ ).

**Conclusions :** The long-term IBS related quality of life seems to be similar to or even slightly better than the results found in short term studies. The long-term adherence and satisfaction to a low FODMAP diet is high in patients with IBS responding a questionnaire. Nevertheless, patients indicate that it is difficult to follow the LFD in the daily routine. Practical issues, social factors and the absence of symptoms were indicated as the main reasons for a drop-in adherence.

- B11 -

EFNB2 LIGAND AS KEY PLAYER IN VISCERAL HYPERSENSITIVITY. S. Theofanous (1), M. Florens (1), J. Aguilera-Lizarraga (1), E. Perna (1), L. Decraecker (1), M. Wouters (1), G. Boeckxstaens (1) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing.

**Introduction :** Interactions of the receptor tyrosine kinase Ephrin B2 (EphB2) with its ligand EfrinB2 (EfnB2) contribute to persistent pain states like post-inflammatory, somatic and neuropathic pain via modulation of NMDA receptors in the spinal cord. Visceral hypersensitivity (VHS) is a major mechanism in irritable bowel (IBS) syndrome and inflammatory bowel disease (IBD) in remission but the mechanisms involved are not fully understood.

**Aim :** In the present study, we studied the possible involvement of the EphB2/EfnB2/NMDA pathway at the level of the spinal cord in VHS in 2 well established murine models of VHS, maternal separation (MS) and post-TNBS colitis.

**Methods :** Wild type (WT) and mice lacking Efnb2 in Nav1.8 nociceptive neurons (cKO) were studied. VHS was induced by intracolonic instillation of TNBS (130 $\mu$ g/ml ; compared to 30% ethanol) or by water avoidance stress (1 hr ; WAS) in mice that underwent maternal separation (compared to non-handled control mice). VHS was assessed by quantifying the visceromotor response (VMRs) during colorectal distention prior to and at different time points after induction of VHS. At the end of the experiment, mice were sacrificed and colon tissue, spinal cord and dorsal root ganglia (DRG) were collected for H&E staining and gene expression using qPCR.

**Results :** In WT mice, TNBS induced VHS at 14 days after instillation returning to baseline perception at day 56. In contrast, cKO mice failed to significantly increase visceral pain perception following TNBS instillation (Fig 1). The development of VHS at t=14 days in WT mice was associated with significant upregulation of EfnB2 mRNA expression in the spinal cord. As expected, no changes in EfnB2 expression were observed in cKO mice. In MS WT mice, but not in non-handled WT mice, WAS induced VHS lasting up to 4 weeks. In MS cKO group, WAS induced VHS in all mice one week after WAS, but colorectal sensitivity returned to basal level at week 4. Five weeks after the WAS, the NMDA 2B subunit was significantly upregulated in the spinal cord of MS WT compared to MS cKO mice. No differences in tissue morphology (crypt height, distance between crypts) was detected between WT and cKO mice in either treatment group. Of note, cKO mice revealed significantly higher mRNA expression levels of inflammatory markers (Il1b, Il17, IFN $\gamma$ , TNF $\alpha$ , IL10,) while the muscularis externa was significantly thicker compared to that of WT mice in both models.

**Conclusions :** Mice lacking Efnb2 in Nav1.8 nociceptive neurons (cKO) fail to develop VHS in a post-inflammatory model (TNBS colitis) and only transiently become visceral hypersensitive in a model of stress-induced VHS. Moreover, the development of VHS is associated with upregulation of efnB2 and NMDA 2B receptor subunit in the spinal cord. Taken together, our data suggest that the EphB2/EfnB2/NMDA pathway at the level of the spinal cord is involved in VHS and may represent a novel therapeutic target.

- B12 -

THE CIRCADIAN CLOCK REGULATES DIURNAL RHYTHMICITY OF MICROBIAL SHORT-CHAIN FATTY ACID PRODUCTION AND THEIR RHYTHMIC EFFECTS ON COLON CONTRACTILITY. A. Segers (1), L. Desmet (1), T. Thijs (1), K. Verbeke (1), J. Tack (1), I. Depoortere (1) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing (CHROMETA).

**Introduction :** The gastrointestinal tract contains a powerful circadian clock that can be uncoupled from the master clock by altering feeding time or diet. At the molecular level, the circadian rhythm is regulated by the core clock genes, Clock and Bmal1. Desynchronization caused by e.g. rotating shift work likely favours the development of metabolic and gastrointestinal diseases. Intestinal microbiota, which are at the interface between ingested nutrients and the gut epithelium, undergo diurnal oscillations that are influenced by feeding rhythms.

**Aim :** This study aimed to investigate whether microbial production of short-chain fatty acids (SCFAs) shows a diurnal rhythm of 24 hours that is in phase with the rhythm of SCFA receptor expression (FFAR2, FFAR3, OLF78, HCAR2) and SCFA-regulated colonic motility. The role of BMAL1 in these 24-hour fluctuations was investigated as well.

**Methods :** C57Bl/6 mice were sacrificed over the course of 24 hours at 4-hour intervals (zeitgeber (ZT) 0 lights-on). Bmal1<sup>-/-</sup> mice and their wild type (WT) littermates were sacrificed at ZT 4 and ZT 16. Faecal SCFA concentrations were analysed by gas chromatograph-flame ionization detector and expression of SCFA receptors was determined by qPCR. The effect of increasing concentrations of a SCFA mix (1-100mM, molar ratio 3 acetate : 1 propionate : 1 butyrate) on electrical field (EFS)-induced excitatory neural responses in colon strips was measured.

**Results :** In the distal colon of WT mice, faecal acetate, propionate and butyrate concentrations showed diurnal fluctuations (P<0.05), peaking at ZT 6h04, 7h28 and 5h19, respectively. Ffar2, Ffar3 and Olfr78 but not Hcar2 were expressed in the smooth muscle layer. The expression of Olfr78 was not diurnal, while Ffar3 and Ffar2 expression showed diurnal rhythmicity (P<0.05, peaking at ZT 3h25 and 4h10, respectively) that was in phase with the rhythm of faecal SCFA concentrations. The SCFA mix concentration-dependently (EC50=61 mM) inhibited EFS-induced neural contractions. The inhibiting effect showed a diurnal rhythm (P<0.001) with a peak at ZT 3h45 and fluctuated in phase with fecal SCFA concentrations and Ffar3 expression. In contrast, neither excitatory neural responses nor acetylcholine-induced smooth muscle contractions showed a diurnal rhythm. In Bmal1<sup>-/-</sup> mice no fluctuations in faecal SCFA levels, Ffar3 mRNA expression and neural responses to SCFAs were observed between ZT 4 and ZT 16 which showed maximal changes in the WT littermates.

**Conclusions :** Diurnal production of SCFAs by the microbiota regulates the rhythm of Ffar3 expression in the myenteric plexus of the distal colon, which in turn might lead to diurnal fluctuations in SCFA-regulated colonic motility. Genetic deletion of the core clock gene Bmal1 abolishes rhythmicity of microbial SCFA production and their downstream effects.

- B13 -

INFLUENCE OF THE SLOW-RELEASE H<sub>2</sub>S DONOR GYY4137 AND THE H<sub>2</sub>S-RELEASING NAPROXEN DERIVATIVE ATB-346 ON POSTOPERATIVE ILEUS. J. Van Dingenen (1), R. Lefebvre (1) / [1] Ghent University, Ghent, Belgium, Department of Pharmacology - Heymans Institute.

**Introduction :** Postoperative ileus (POI), the impairment of gastrointestinal motility after abdominal surgery, is mainly due to intestinal muscular inflammation triggered by surgical handling. Hydrogen sulfide (H<sub>2</sub>S), known as a toxic gas,

has been recognized as an important mediator of many physiological processes, including inflammation and H<sub>2</sub>S is now exploited therapeutically for its anti-inflammatory effects. The slow-release H<sub>2</sub>S donor GYY4137 was shown to reduce gastrointestinal inflammation, but was not tested yet in POI. ATB-346 is a H<sub>2</sub>S-releasing derivative of the non-steroidal anti-inflammatory drug (NSAID) naproxen, developed to reduce gastrointestinal injury of naproxen when applied for rheumatic conditions. NSAIDs are commonly used to treat pain and inflammation in POI, because of their opioid-sparing effects.

**Aim :** The aim of this study was to investigate the effect of GYY4137, ATB-346 and naproxen on intestinal inflammation and gastrointestinal transit in POI.

**Methods :** C57Bl6J mice were fasted for 7 h, anesthetized (isoflurane) and after laparotomy, POI was induced by compressing the small intestine with cotton applicators (intestinal manipulation ; IM) for 5 min. GYY4137 (50 mg/kg, intraperitoneally), ATB-346 (16 mg/kg, intragastrically) or an equimolar dose of naproxen (10 mg/kg, intragastrically) were administered 1 h before IM. Gastrointestinal transit was assessed 24 h postoperatively using fluorescent imaging 90 min after fluorescein gavage (geometric centre [GC] of gastrointestinal fluorescein progression). The small intestine was divided in 6 equal parts ; mucosa-free muscularis segments were prepared and stored at -80° C for later analysis of myeloperoxidase (MPO) activity as an index of leukocyte infiltration, of the inflammatory cytokines interleukin (IL-)6, IL-1 $\beta$  and monocyte chemoattractant protein 1 (MCP-1), and of COX-2 and inducible NO synthase (iNOS) activity.

**Results :** IM profoundly delayed transit (GC : 3.6  $\pm$  0.5 versus 9.0  $\pm$  0.4 in non-operated controls ; mean  $\pm$  s.e.m. of n = 8 per group). Pre-treatment with GYY4137 (GC : 7.6  $\pm$  0.5) and ATB-346 (GC : 8.4  $\pm$  0.3) prevented the delayed transit seen after IM while naproxen only partially did (GC : 5.9  $\pm$  0.5). Administration of GYY4137 and ATB-346 significantly reduced the increase in MPO activity and in IL-6, IL-1 $\beta$  and MCP-1 levels in the intestinal muscularis caused by IM ; the reduction by naproxen was less pronounced and only reached significance for MPO activity and IL-6 levels. All treatments significantly reduced the increase in COX-2 activity caused by IM, naproxen not being less effective than GYY4137 and ATB-346 for this parameter. Preliminary data on part of the tissues of each group suggest that GYY4137 and ATB-346 but not naproxen are able to reduce the IM-induced elevation of iNOS activity.

**Conclusions :** The study shows that naproxen partially prevents POI, probably through its inhibitory effect on COX-2 activity in view of the previously established role of COX-2 in murine POI (Schwarz et al., Gastroenterology, 2001). However, both ATB-346 and GYY4137 were more effective, the result with GYY4137 showing that H<sub>2</sub>S per se can prevent POI. The mechanism of action of the H<sub>2</sub>S donors in POI will now be studied further.

- B14 -

EFFECT OF RESOLVIN D1, D2 AND E2 ON HISTAMINE-INDUCED SENSITIZATION OF TRPV1. E. Perna (1), M. Florens (1), J. Aguilera (1), S. Theofanous (1), L. Decraecker (1), M. Wouters (1), G. Boeckxstaens (1) / [1] KUL, Belgium, TARGID.

**Introduction :** Resolvins (RvD1, RvD2 and RvE1) are endogenous lipid mediators generated from  $\Omega$ -3 polyunsaturated fatty acids and display potent pro-resolving and anti-inflammatory properties. Of interest, recent studies have shown analgesic effects of resolvins in somatic pain models by modulating TRPV1/A1 activation and normalizing spinal cord synaptic plasticity (Xu et al., 2010). TRP channels, including TRPV1, also transmit visceral pain and are implicated in visceral hypersensitivity.

**Aim :** Previously, we showed that histamine-induced TRPV1 sensitization is a major mechanism involved in abdominal pain in patients with irritable bowel syndrome (IBS). Hence, we studied the effect of RvD1, RvD2 or RvE1 on TRPV1 sensitization to evaluate their potential to treat visceral pain in IBS.

**Methods :** Murine dorsal root ganglion (DRG) neurons (T10-L1 ; L6 ; S1) were isolated, cultured and loaded with Fura-2 (2mmol/L) as previously described (Wouters et al., 2016) to assess TRPV1 activation using Ca<sup>2+</sup> live imaging. First, the effect of RvD1, RvD2 and RvE1 (10-100nM-1 $\mu$ M) on TRPV1 channel activation was evaluated by incubating DRG neurons with RvE1, RvD1 and RvD2 prior to capsaicin application. Next, the effect of the resolvins was studied after sensitization of TRPV1 by pre-incubation with histamine, using resolvin concentrations devoid of an effect on TRPV1 activation (see first series). Data are expressed as mean  $\pm$  SEM ; Student's T-test or ANOVA (\*p<0.05).

**Results :** Results Pretreatment of DRGs with RvD1 (10-100nM-1 $\mu$ M) and low doses of RvD2 (1-10nM) did not affect activation of TRPV1 by capsaicin (10nM). RvE1 (100 nM-1 $\mu$ M) and high doses of RvD2 (100nM - 1 $\mu$ M) however reduced the Ca<sup>2+</sup> response to capsaicin. In a second series, TRPV1 was sensitized by 10 $\mu$ M histamine. Co-incubation of histamine with RvD1 (100nM), RvE1 (30nM) and RvD2 (10nM) significantly prevented histamine-induced sensitization of TRPV1 compared to vehicle. Next, to evaluate if resolvins could also reverse TRPV1 sensitization, DRGs were sensitized with histamine prior to treatment with RvD1 (100nM), RvD2 (10nM), RvE1 (30nM) or vehicle. RvD2 but not RvD1 or RvE1 was able to reverse histamine-mediated TRPV1 sensitization. Studies evaluating the effect on TRPV1 sensitization induced by supernatant from IBS rectal biopsies are ongoing.

**Conclusions :** Our findings demonstrate that RvD1, RvD2 and RvE1 dose-dependently interfere with TRPV1 activation, indicating that these mediators have analgesic properties. Of note low concentrations devoid of this analgesic effect

significantly prevent (RvD1, RvD2, RvE1) and even reverse (RvD2) histamine-induced sensitization of TRPV1. As we previously showed that TRPV1 sensitization is an important target for treatment of IBS patients, our data suggest that especially RvD2 may represent an interesting novel compound to further evaluate as treatment for IBS.

- B15 -

IN TOTO THREE-DIMENSIONAL MICROSCOPICAL IMAGING OF THE INTESTINAL WALL : COMPARISON OF EIGHT CLEARING PROTOCOLS. G. Bossolani (1), J. Detrez (2), J. Zanoni (1), W. De Vos (2), R. Buckinx (2), J. Timmermans (2) / [1] State University of Maringa, Maringa, Brazil, Department of Morphological Sciences, [2] University of Antwerp, Antwerp, Belgium, Veterinary Sciences, Laboratory of Cell Biology & Histology.

**Introduction :** The intestinal wall has a complex 3D architecture, consisting of epithelial, immune and vascular components, all of which are densely innervated by an extensive enteric nervous system (ENS). Traditional 2D histological techniques, based on thin cross sections or whole-mount preparations, are by definition destructive and therefore fail to provide a faithful 3D representation of this tissue. With an eye on visualizing intact intestinal tissue in toto, i.e. without the need for physical sectioning or topographical separation/removal of distinct layers of the intestinal wall, several optical clearing methods aimed at reducing optical scattering and absorption of photons, have been re-examined or newly developed. However, as yet, the applicability and performance of different clearing methods in intestinal segments has not been examined extensively.

**Aim :** In the present study, eight different clearing methods were directly compared and their validity for in toto imaging of the intestinal wall of mice was evaluated. Optical penetration depth, conservation of endogenous GFP fluorescence, compatibility with immunolabeling and nuclear staining, and degree of preservation of the topographical architecture and cellular morphology were used as evaluation criteria.

**Methods :** Four hydrophilic solvent-based clearing protocols (SeeDB2G/S, modified CUBIC, ScaleS and Ce3D) and four organic solvent-based clearing protocols (3DISCO, iDISCO, uDISCO and Visikol) were assessed in ileal segments (3 segments from 3 different animals per clearing protocol). Samples were collected from CX3CR1GFP/GFP and wild-type mice, fixed in 4% paraformaldehyde overnight and rinsed in PBS (3 x 10 min) prior to clearing. For immunostaining, the tissues were incubated up to 48 hrs with antibodies raised against neuronal, endothelial and/or fibroblast markers and combined with fluorescent nuclear stains such as DAPI and TO-PRO-3. All images were acquired using a Leica SP8/DLS confocal microscope, equipped with a light sheet module. The impact of the clearing on tissue morphology was assessed on hematoxylin-eosin stained paraffin sections at the light microscopical level and on SEM preparations.

**Results :** All clearing protocols demonstrated optimal compatibility with nuclear staining. Visikol- and ScaleS-treated intestinal samples displayed the lowest light penetration depth, while the CUBIC protocol yielded intermediate penetration depth as measured by an intensity z-profile in the confocal microscope. The five remaining clearing protocols (iDISCO, 3DISCO, uDISCO, SeeDB2G/S, Ce3D) allowed visualization of the full-thickness intestinal wall and did not have a significant negative impact on the antigen-antibody binding features. However, the organic solvent-based protocols iDISCO, 3DISCO and uDISCO showed a number of drawbacks, including substantial tissue shrinkage and distortion of normal ENS architecture, (in-)complete loss of GFP signal and mucosal epithelial damage. In addition, given their highly toxic nature and irritant effects on the airways, these clearing procedures required a more tedious handling. On the other hand, SeeDB2G/S- and Ce3D-based clearing retained the GFP signal, did not cause obvious tissue damage and were less harmful and thus less demanding in terms of sample handling. The Ce3D protocol (requiring < 12 hrs) was three times faster than the SeeDB2G/S protocol. Using these protocols, detailed 3D information could be obtained on CX3CR1-GFP expressing mononuclear phagocytes, PDGFR- $\alpha$ -immunoreactive fibroblasts, neuronal ( $\beta$ III-tubulin-Cy3 immunostaining) and vascular (CD31- $\alpha$ -Cy5-immunolabeling) networks across the intestinal wall.

**Conclusions :** Given the different composition of distinct organs/tissues (a.o. differences in lipid content), it is not guaranteed that a particular clearing protocol which has been successfully applied in for e.g. the brain, yields a similar qualitative outcome in other tissues. Therefore, it is indicated to have data available comparing distinct clearing protocols for a particular tissue. From all 8 clearing protocols tested, in our hands the Ce3D and, in second order, the SeeDB2G/S protocol gave the most optimal results for detailed in toto imaging of the mouse intestinal wall in terms of making the tissue transparent without having a negative impact on tissue morphology, antigenicity and immunofluorescence or preservation of GFP fluorescence.

- B16 -

THE TOUCHY BUSINESS OF GI MUCOSAL MECHANOSENSITIVITY. A. Beyder (1) / [1] Mayo Clinic, Rochester, United States (the), Gastroenterology & Hepatology.

**Introduction :** Mechanosensation is fundamental for normal GI function. Disruption of GI mechanosensitivity leads to the highly prevalent functional GI diseases such as irritable bowel syndrome (IBS) and visceral hypersensitivity. Given

the importance of mechanosensitivity for GI function, the GI tract has developed dedicated mechanosensory circuits that use specialized mechanosensory cells. One such important specialized mechanosensory cell is the enterochromaffin (EC) cell in the GI epithelium. In response to mechanical force, the EC cell secretes serotonin (5-hydroxytryptamine, 5-HT), which has important roles in GI motility, secretomotor and sensory functions. However, the molecular mechanisms of EC cell mechanotransduction are poorly understood.

**Aim :** The goal of the work in my laboratory is to determine the molecular mechanisms of EC cell mechanosensitivity.

**Methods :** We use transgenic animal models, primary and immortalized cell cultures, electrophysiology, calcium imaging, Ussing chambers and in vivo GI motility assays to determine the molecular mechanisms of EC cell mechanosensitivity.

**Results :** The EC cell has several developmental and functional similarities to the Merkel cell, which is a specialized mechanosensory cell in the skin that is important for somatosensory light touch. Both EC and Merkel cells employ some of the same genes to guide their development (e.g. *Atoh1*) and use 5-HT for downstream signaling. Recent studies have shown that the Merkel cell depends on mechanosensitive ion channel Piezo2 to convert force into physiologic response. We have recently discovered that both human and mouse EC cells specifically express Piezo2 channels. In an EC cell model, Piezo2 channels were important for mechanosensitivity by producing mechanosensitive ionic currents that were responsible for conversion of force into 5-HT release. We developed several novel mouse models to examine whether Piezo2 is involved in primary EC cell mechanotransduction. Using electrophysiology and calcium imaging, we found that EC cells are electrically excitable, and that Piezo2 channels are the primary sensors that generate receptor potentials in response to force, which in turn lead to transient intracellular calcium increase. We examined the role of Piezo2 in GI physiology using Ussing chambers, and found that EC cell Piezo2 channels are important for regulating mechanically stimulated epithelial secretion.

**Conclusions :** Our studies show that Piezo2 is the primary mechanosensor of the EC cell. Our current work is focused on understanding the mechanisms of EC cell mechanotransduction in GI physiology and pathophysiology.

## CASE REPORTS

- C01 -

AN UNUSUAL CAUSE OF BLEEDING IN A CIRRHOTIC PATIENT. M. Struyve (1), G. Robaeys (2) / [1] University Hospital, Gasthuisberg, Leuven, Belgium, Belgium, Gastroenterology, Hepatology and Endoscopy, [2] Ziekenhuis Oost Limburg (ZOL), Genk, Belgium, Gastroenterology/Hepatology/Endoscopy.

**Introduction :** Ectopic varices are common endoscopic findings in patients with portal hypertension. Ectopic variceal bleeding is rather rare and counts for only 1 to 5 % of all variceal bleedings. The rectum and the duodenum are the most common sites for ectopic varices, but they can be present along the whole intestinal tract and neighborhood. We report here an unusual case of an ectopic variceal bleeding, presented as an acute small intestine bleeding, due to a portosystemic shunt via dilated mesenteric veins and a varicose left ovarian vein in a patient with alcoholic cirrhosis. The involvement of an ovarian vein in ectopic variceal bleeding is rarely described.

**Aim :** The aim of this abstract is to illustrate a rare case of an ectopic variceal bleeding and its radiologic images.

**Methods :** We report the radiologic description of a patient presenting with an ectopic variceal bleeding due to a portosystemic shunt via dilated mesenteric veins and a varicose left ovarian vein. Results A 53-year-old woman was admitted at a psychiatric facility because of alcohol abuse. The patient was found at night lying unconsciously on the floor in a large pool of blood. She was urgently transferred to the hospital under medical assistance where she was stabilized and intubated and afterwards transported to the Intensive Care Unit. Her medical history consisted of an important addiction of alcohol with diagnosis of alcoholic cirrhosis in 2005 and schizophrenia. A physical examination at admission revealed an unconscious and hemodynamic instable patient. The abdomen was slightly tender. Rectal digital examination showed massive melena. Laboratory analyses demonstrated a deep anaemia (a serum hemoglobin of 5 g/dl [11.7-16.1]), a mild thrombopenia (blood platelets 141 x 1000/mm<sup>3</sup> [150-400]), a decreased prothrombin time (68%), a normal kidney function (serum creatinine level 0.93 mg/dl [0.5-0.9]), no signs of inflammation, normal liver enzymes and a hyperammonia (356 microgram% [11-51]). An urgent esophagogastroduodenoscopy was performed bedside at the ICU after stabilization of the patient. Neither an active bleeding nor potential bleeding source could be found. A left colonoscopy immediately followed showed a massive active lower intestinal bleeding, but again the site of bleeding could not be discovered. A contrast-enhanced computed tomography scan of the abdomen was performed shortly after. This examination demonstrated advanced cirrhosis with signs of portal hypertension, i.e. splenomegaly, edema in the mesenteric fat, some ascites and varices. Furthermore, a spontaneous portosystemic shunt was demonstrated, occurring by connections between mesenteric veins and a varicose left ovarian vein. These ectopic varices were in close contact with the submucosa of a dilated segment of the ileal part of the small intestine. In addition, CT demonstrated profound active intestinal bleeding caused by part of these ileal varices. During the short stay at the ICU, there was a hemodynamic stabilization of the patient with a spontaneous cessation of the intestinal bleeding, observed by meaning of stabilization of the serum hemoglobin value and spontaneous resolution of melena. In contrast, there was a progressively and rapid neurological deterioration due to post-hypoxic cerebral oedema with refractory epileptic insults. Therefore, we were not able to perform any endoscopic interventional treatment, interventional radiological procedures (transjugular intrahepatic portosystemic shunt (TIPS) e.g.) nor surgical treatment to manage the ectopic varices. The patient unfortunately died due to neurological complications.

**Conclusions :** Ectopic varices are dilated portosystemic venous collaterals located outside of the gastro-oesophageal region. Whereas they are common endoscopic findings in patients with portal hypertension, ectopic variceal bleeding is rather rare and counts for only 1 to 5 % of all variceal bleedings. The rectum and the duodenum are the most common sites for ectopic varices, but they can be present along the whole intestinal tract and neighbourhood. At present, there is no consensus well established on diagnostic workup for ectopic variceal bleeding and their therapeutic strategies. Further investigation of large series or randomized controlled trials is needed because nowadays most of the data available are based on case reports. We report here an unusual case of an ectopic variceal bleeding, presented as an acute small intestine bleeding, due to a portosystemic shunt via dilated mesenteric veins and a varicose left ovarian vein in a patient with alcoholic cirrhosis. The involvement of an ovarian vein in ectopic variceal bleeding is rarely described.

- C02 -

A CASE OF ACUTE HEPATITIS UNDER NIVOLUMAB TREATMENT. L. Wuyts (1), A. Janssens (2), L. Vonghia (3), P. Michiels (3), J. Van Meerbeeck (2), S. Francque (3), T. Vanwolleghem (3) / [1] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastro-Enterology, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Thoraxoncology, [3] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastro-Enterology.

**Introduction :** We present a case of a 54-year-old patient with an acute hepatitis caused by nivolumab, an anti-PD1 immunotherapy, and a subsequent 1-log decrease of HCV RNA load.



**Aim :** To describe the (antiviral) effects of Nivolumab on the liver.

**Methods :** A Pubmed search using searching Mesh terms “Nivolumab”, “PD1-inhibitor”, “immune checkpoint inhibitor” and “hepatitis C”

**Results :** We present a case of a 54-year-old patient with an acute hepatitis caused by nivolumab, an anti-PD1 immunotherapy marketed as ‘Opdivo’, which was used for treatment of a stage IV carcinoma of the lung. His social history was notable for a travel to the Philippines, including several episodes of unprotected sexual intercourse and a tattoo some years ago. Retrospective testing of HCV RNA documented exposure at least before 2017. Hepatitis C RNA load at that time was 6.41 log IU/ml, HCV genotype 1 b, a slight increase of GGT levels was seen and normal ALT and bilirubin levels. He was started with nivolumab at 2 mg/kg every three weeks. During treatment we encountered a severe ALT flare (peak values : AST 330 U/l ; ALT 663 U/l), along with an increase of GGT values (100 U/L), normal leukocyte count and no signs of coagulopathy. Symptoms only consisted of a feeling of exhaustion. The assumption of a nivolumab associated auto-immune hepatitis led to the interruption of the immune checkpoint inhibitor treatment. However, a subsequent 1-log decrease of HCV RNA load was noticed, which raised the possibility of an immunorestitution against the HCV- infected hepatocytes with cell lysis. Liver biopsy specimen demonstrated no evidence for auto-immune liver disease or fibrosis. Clinical evolution was well and serum transaminases declined to normal levels and HCV RNA load increased to baseline values. During the coming months nivolumab will be restarted and liver set combined with HCV RNA load will be carefully monitored. Chronic hepatotropic viruses and tumoural cells of hepatocellular carcinoma (HCC) develop mechanisms to induce exhaustion of the specific CD8+ T cells in order to escape immune destruction. Blockade of overexpressed negative co-stimulatory pathways, a process known as immune checkpoint modulation, is a promising novel therapy that could improve the treatment of liver diseases that feature T cell exhaustion (1- 2). Nivolumab (Opdivo, Bristol-Myers Squibb), a programmed death-1 (PD-1) immune checkpoint inhibitor and a fully human IgG4 monoclonal antibody (3), is FDA- approved for the treatment of certain patients with solid tumors and hematologic malignancies. The FDA previously granted orphan drug designation to nivolumab for the treatment of HCC (4). The dose-expansion phase of the CheckMate 040 study showed that the PD-1 immune checkpoint inhibitor nivolumab leads to durable responses in patients with advanced HCC previously treated with sorafenib, regardless of HBV or HCV infections. The kinetics of HCV RNA levels over time were assessed in patients infected with HCV with advanced HCC, and no patient achieved a sustained virological response for more than 24 weeks. Some patients infected with HCV had transient reductions in HCV RNA (1). Not a lot of clinical data is available on the antiviral effect of during repetitive nivolumab treatment. In a preclinical study, a short course of nivolumab treatment exhibited transient, but not persistent anti-HCV activity in one of 3 HCV infected chimpanzees (5). The PD-1/PD-L1 pathway is known to be upregulated in chronic viral (HBV, HCV, and HIV) infections where it may attenuate T-cell or NK-cell mediated antiviral host immune responses, thereby sustaining chronic infection (6). Only nivolumab and tremelimumab (a CTLA-4 checkpoint inhibitor) have completed clinical trials for viral hepatitis-related disease. A single dose of Nivolumab, a fully human anti-PD-1 monoclonal immunoglobulin-G4 that blocks ligand binding, was tested in 54 chronic HCV infected patients, many of whom had undergone IFN- $\alpha$  treatment. Five patients (9.2%) who received BMS-936558 (0.1 [n=1] or 10 mg/kg) and one placebo patient achieved the primary study endpoint of a reduction in HCV RNA  $\geq 0.5$ -log<sub>10</sub> IU/mL on at least 2 consecutive visits ; 3 (5.6%) (10 mg/kg) achieved a  $>4$ -log<sub>10</sub> reduction. Two patients (3.7%) (10 mg/kg) achieved HCV RNA below the lower limit of quantitation (25 IU/mL), one of whom (a prior null-responder) remained RNA-undetectable 1-year post-study (7-8). The anti-tumour and anti-HCV effect of tremelimumab was also tested in 21 chronic HCV patients with HCC. Tremelimumab also exhibited a good safety profile (6-7). A progressive course of decline in viral load was observed in most patients followed for at least 3 months. Three patients had a transient complete viral response during follow-up. In the only patient with available long post-treatment data, a positive viral load was observed 230 days after the last dose. A viral response (anytime  $>1$ -log drop in viral load) was observed in 9 of 12 patients (75%) that showed an immune response (anytime  $>5$ -fold increase at any time in the sum of IFN- $\gamma$ -producing cells against all antigen sources tested) and in 1 of 5 patients (20%) who did not (p = 0.036) (6). Activation of the immune system by immune checkpoint inhibitors may also lead to immune responses to normal tissue and consequently to autoimmune side effects. Autoimmune side effects most commonly affect the skin (rash, xerosis, pruritus), the gastrointestinal tract (colitis, diarrhea), the liver (hepatitis), and endocrine organs (hypophysitis, thyroiditis). Any organ may however be affected (9). During the Checkmate-40 study, a phase I/II study (1), the safety profile of nivolumab proved to be manageable and no new safety signals were observed.

**Conclusions :** In conclusion, in our patient the combination of high ALT levels with a transient 1-log drop in HCV RNA load can be ascribed to antiviral immune reconstitution during nivolumab. The further evolution of liver tests and HCV RNA load during nivolumab rechallenge will be presented.

- C03 -

ENDOSCOPIC SUBMUCOSAL DISSECTION OF A SUSPICIOUS ESOPHAGEAL LESION. L. Mans (1), P. Eisendrath (2), L. Verset (3), P. Demetter (3), V. Huberty (1), A. Demols (1), J. Deviere (1), A. Lemmers (1) / [1] Erasmus Hospital, Brussels, Belgium, Gastroenterology, Hepatopancreatology, Digestive Oncology Department, [2] CHU Saint-

Pierre, Brussels, Belgium, Gastroenterology and Hepatology Department, [3] Erasme Hospital, Brussels, Belgium, Department of Anatomopathology.

An 80-year-old woman, hospitalized for atrial fibrillation and cardiac decompensation, presented anemia and melena during her stay. An esogastroduodenoscopy revealed a 2x2cm Paris type 0-IIa+IIc neoplastic lesion at 30 to 32cm from the incisors. The IPCL pattern analysis with NBI and near focus revealed V-3 type suggesting the presence of submucosal infiltration. The biopsy revealed a poorly differentiated squamous cell carcinoma. Endoscopic ultrasound disclosed a 15mm mucosal lesion with extension in the submucosa (uT1N0Mx). There was no distant metastasis on work-up (thoracic and abdominal CT scan, bronchoscopy and PET CT). Due to the advanced age of the patient and her comorbidities, we decided in multidisciplinary oncologic meeting to perform a staging endoscopic submucosal dissection. The therapeutic alternative would be a major surgery in a patient with cardiac decompensation. An en-bloc endoscopic complete resection was performed using a Dual knife (Olympus, Japan) and glycerol solution. The procedure was well tolerated without any secondary symptoms nor stricture and patient was discharged on day 3. Surprisingly, the pathological analysis revealed a large-cell neuroendocrine carcinoma with no lympho-vascular involvement nor perineural invasion. Lateral margins were free but vertical resection margin revealed some tumoural cells. The Ki67 index was 95%. The pathological classification according to the TNM classification was pT1bNx. The multidisciplinary oncologic meeting had suggested an adjuvant treatment by radiochemotherapy which was refused by the patient. Therefore, surveillance was performed with esogastroduodenoscopy and thoracoabdominal CT scan. The 3-months follow-up showed no recurrence. Conclusion : ESD is the technique of choice for en-bloc resection of >15mm esophageal superficial carcinoma to obtain a good pathological analysis. Staging ESD is an option in aged and comorbid patients before choosing the right therapeutic approach. Esophagus large-cell neuroendocrine carcinomas are uncommon. Due to the lack of data, no treatment strategies have yet been established for esophageal neuroendocrine carcinomas.

- C04 -

TERMINAL ILEITIS AFTER KIDNEY TRANSPLANTATION : CROHN'S DISEASE OR OTHER CAUSE? E. Motté (1), L. Pipeleers (2), J. Sennesael (2), D. Urbain (1), F. Mana (1) / [1] UZ Brussel, Jette, Belgium, Gastroenterology, [2] UZ Brussel, Jette, Belgium, Nephrology.

The finding of a terminal ileitis after kidney transplantation can cause a diagnostic challenge. The development of de novo Crohn's disease during an immunosuppressive treatment is possible but rather rare. The exclusion of an infectious (CMV, TBC,...), drug-related (mycophenolate mofetyl (MMF), ...) or other cause in these immunodepressed patients with polypharmacy and polypathology is necessary, but often very difficult because of a shortage of specific diagnostic tests or their lack of sensitivity. We present 3 cases with each a different etiology, their diagnostic exploration with at the end an empiric diagnosis, and their evolution after treatment : 1 with diagnosis of Crohn's disease, 1 with CMV- and 1 with MMF-induced enterocolitis.

- C05 -

UNCOMMON CAUSE OF CHOLANGIOPATHY IN A CIRRHOTIC PATIENT : EUS FINDING. S. Mupingu (1), M. Fernandez Y Viesca (2), G. Verset (1), M. Palazzo (3), P. Eisendrath (1) / [1] Erasme Hospital, Brussels, Belgium, Gastroenterology, Hepatopancreatology and Digestive Oncology, [2] Hopital Erasme, ULB, Belgium, Gastroenterology, Hepatopancreatology and Digestive oncology, [3] Hôpital Beaujon, Clichy, France, Gastroenterology, Hepatopancreatology and Digestive oncology.

This is a case of 62-year-old epileptic man with mixed liver cirrhosis Child Pugh B7 (alcoholic and post viral hepatitis B). On February 2017, several investigations were performed in context of decompensated cirrhosis in another hospital. The initial work up included an abdominal CT scan and MRI which showed a 4-cm typical hepatocarcinoma in the seventh segment of the liver. Right intrahepatic bile ducts were also dilated with peri-portal distribution without common bile duct dilatation. The diagnosis of hepatocarcinoma with concomitant lesion of intrahepatic cholangiocarcinoma was upheld and the patient was sent in our institution for oncological management. Due to these atypical presentations, a new MRI and a Pet Ct were performed which showed no change in the lesions. Upon further, investigation with endoscopic ultrasound sonography (EUS) found multiple peribiliary cysts sized 2-4mm, with no communication with biliary tree, without any obstacle and no dilated common bile duct. The previously described nodule was precised but not punctured due to location (just behind the inferior vena cava). These EUS morphological findings suggest the diagnosis of peribiliary hepatic cysts developed in a patient with severe liver disease. The hepatocarcinoma was treated by hepatic transarterial chemoembolization. Peribiliary hepatic cysts are not so rare and mostly described in autopsy series of patients with end stage liver disease. No need for treatment in most of the cases. Differential diagnosis with cholangiocarcinoma is challenging. In our knowledge, this is the first case reported of peribiliary cysts diagnosed by EUS.

INFECTIOUS COMPLICATIONS IN A PATIENT WITH AUTOMATED LOW-FLOW ASCITES PUMP : A UNIQUE CASE REPORT. M. Saerens (1), T. Vanwolleghem (1), P. Michielsen (1), L. Vonghia (1), S. Francque (1) / [1] UZA, Antwerp, Belgium, Gastroenterology and hepatology.

**Introduction :** Recently, the three-year experience reports with automated low-flow ascites pump (Alfapump®) have been published. [1] Infectious complications after pump implantation have been described, rarely necessitating pump explantation in. However, there are no clear data on the optimal management in case of infectious complications in patients with an ascites pump device.

**Aim :** How to manage alfapump pocket infection.

**Methods :** We present a unique case of alfapump pocket infection with a review of literature.

**Results :** A 72-year old woman was referred to our university hospital in June 2016 because of refractory ascites. She was known with alcoholic liver disease since 2008, and was admitted with decompensated cirrhosis (CHILD C-12, MELD 22) with need of repeated paracentesis, usually with a two-week interval. She was intolerant to diuretics due to orthostatic hypotension and borderline kidney impairment. Because of advanced age and continued alcohol abuse, liver transplantation was not suitable. She was considered for transhepatic portocaval shunt (TIPS) implantation, but because of diastolic dysfunction, CHILD-C cirrhosis and borderline kidney function, advanced age with risk for hepatic encephalopathy, TIPS might harbor too many risks. Therefore, an automated low-flow ascites pump (Alfapump®) was considered and finally implanted on August 1 2016. She had one evacuating paracentesis after placement and was treated with norfloxacin as primary prevention of peritonitis. Upon follow-up, she developed a transient acute kidney impairment, which recovered after reducing the daily flow rate. She was readmitted on August 6 2017 because of decompensated cirrhosis, acute kidney failure and a E coli associated secondary peritonitis. Unsurprisingly, also urine culture was positive for E. coli. She was treated successfully with piperacillin-tazobactam for 10 days, after proven microbiological resistance to cephalosporins and ciprofloxacin. After intravenous rehydration and treatment with albumin, her kidney function returned to baseline. As the causative organism was resistant to ciprofloxacin, secondary prophylaxis with norfloxacin was discontinued. Repeated urine cultures and paracenteses were negative, and she was discharged home on August 18. She was readmitted two weeks later with a recurrent urinary tract infection and acute kidney impairment. There was no ascites. However, she also had a cellulitis around the pump implantation. She was treated with piperacillin-tazobactam. Because of suspected device pocket infection, the pump was explanted on Sep 8. Tip and device cultures remained negative. Few days later she developed ascites and a hepatic hydrothorax, with repeated need of paracenteses. Cultures remained sterile, and neutrophil count never exceeded 250/mm<sup>3</sup>. After nutritional support and physical rehabilitation, diuretics have been reintroduced successfully. She has been discharged in good condition on October 10 2017.

**Conclusions :** infectious complications after Alfapump implantation are far from uncommon, and device explantation may be necessary as source control.

ACUTE ESOPHAGEAL MUCOSAL DAMAGE AFTER LUGOL STAINING. Q. Van Thillo (1), A. Vanden Bulcke (2), C. Vandenbon (4), M. Cool (3), G. Lambrecht (3), G. Deboever (3) / [1] UZ Leuven, Leuven, Belgium, Internal medicine, [2] UZ Leuven, Leuven, Belgium, Gastroenterology, [3] AZ Damiaan, Oostende, Belgium, Gastroenterology, [4] AZ Damiaan, Oostende, Belgium, Geriatric Medicine.

A 79-year-old man presented with a superficial squamous cell carcinoma of the esophagus. A gastroscopy using chromoendoscopy with Lugol's iodine (Lugol) staining 5% (15 mL) was performed for more precise delineation of the superficial lesion. At the end of the procedure the patient experienced severe thoracic pain. An acute coronary syndrome was excluded by electrocardiogram and sequential measurement of troponin levels. A computed tomography scan ruled out a perforation of the esophagus. After one day, the pain ameliorated. A new gastroscopy was performed four days after the initial gastroscopy and showed intense inflammation with ulceration, edema and superficial desquamation of the whole esophagus. The diagnosis of chemical esophagitis as a result of Lugol application was made. The patient was treated with high dose proton pump inhibitors and liquid diet. A new esophagoscopy was performed four weeks later and total healing of the esophageal mucosa was documented, apart from the squamous cell carcinoma. A new application with a lower dose of Lugol (1% - 8 mL) was performed without any adverse reaction. Discussion Lugol's iodine is a combination of potassium iodide and iodine used for staining squamous cell carcinoma. Adverse reactions to Lugol staining have been described before. To the best of our knowledge this is the third endoscopic documented chemical esophagitis attributed to Lugol [1,2]. A questionnaire report after Lugol staining published in 1983 reported discomfort and chest pain in up to 30% of patients [3]. Anaphylactic reactions and changes of the gastric mucosa have also been described after Lugol staining [4]. We hypothesize that Lugol induced adverse reactions can be divided into a spectrum with at one end a direct toxic effect of Lugol on the mucosa which is dose-dependent and on the other

end a hypersensitivity reaction which is probably dose-independent. Sodium thiosulfate spray after Lugol's staining is proposed in one study to substantially reduce the adverse symptoms [5]. Sodium thiosulfate neutralizes free iodine and that way it can relieve the mucosal irritation, but it has no effect against allergic reactions. There is no consensus about the concentration of Lugol required for the staining effect. In studies, the concentration ranges from 0.5% to 5%. Higher concentrations are probably related with more adverse events [6]. Recently a Chinese research group started a randomized double-blind study to examine if image quality and adverse events are altered by different concentrations of Lugol ranging from 0.4% to 1.2% [7]. Conclusion Lugol staining of the esophagus can induce acute mucosal damage. The clinician should be aware of this adverse reaction and have knowledge of the Lugol concentration he is using. It would be reasonable to think that lower concentrations have less adverse effects, but this should be tested in clinical trials. At this moment we advise a low concentration (1-2%) and limited volume of Lugol with aspiration of the remaining Lugol in the stomach and esophagus at the end of the procedure. Sodium thiosulfate spray after the procedure is suggested to reduce the adverse events. References [1] Thuler FP, De Paulo GA, Ferrari AP. Chemical esophagitis after chromoendoscopy with Lugol's solution for esophageal cancer : case report. *Gastrointest Endosc.* 2004 Jun ;59(7) :925-926. [2] Park JM, Seok Lee I, Young Kang J et al. Acute esophageal and gastric injury : complication of Lugol's solution. *Scand J Gastroenterol.* 2007 Jan ;42(1) :135-137. [3] Aoyama N, Akaike S, Yoshizumi Y. Investigations of questionnaire about side effects of lugol staining. *Jpn J Gastroenterol Surg.* 1983 ;16 :939-944. [4] Tsurumaru D, Utsunomiya T, Matsuura S. Gastric mucosal changes caused by Lugol's iodine solution spray : endoscopic features of 64 cases on screening esophagogastroduodenoscopy. *Gastroenterology Research and Practice.* (2010), Article ID 494195. [5] Kondo H, Fukuda H, Ono H et al. Sodium thiosulfate solution spray for relief of irritation caused by Lugol's stain in chromoendoscopy. *Gastrointest Endosc.* 2001 Feb ;53(2) :199-202. [6] Sreedharan A, Rembacken BJ, Rotimi O. Acute toxic gastric mucosal damage induced by Lugol's iodine spray during chromoendoscopy. *Gut.* 2005 Jun ; 54(6) : 886-887. [7] ClinicalTrials.gov Identifier : NCT03180970 ; NCT03180944

- C08 -

A CASE OF PORTAL VEIN ANEURYSM. C. De Vloo (1), W. Meersseman (2), G. Maleux (3), S. Houthoofd (4), K. Op De Beeck (5), W. Laleman (1), F. Nevens (1), L. Verbeke (1), H. Van Malenstein (1), S. Van Der Merwe (1), C. Verslype (1) / [1] UZ Leuven, Leuven, Belgium, Department of Hepatology , [2] UZ Leuven, Leuven, Belgium, Internal Medicine, [3] UZ Leuven, Leuven, Belgium, Interventional Radiology, [4] UZ Leuven, Leuven, Belgium, Vascular surgery, [5] UZ Leuven, Leuven, Belgium, Radiology.

A 67-year-old man was admitted at the emergency with abdominal pain, located in the upper abdomen (mostly in the right upper quadrant), but not with features of a colic. There was no nausea, changes in stools, or fever. His medical history included only metabolic syndrome with diabetes mellitus, obesity and arterial hypertension. His abdomen was soft and not tender without organomegaly, ascites, abdominal masses. No stigmata from chronic liver disease, nor vascular abnormalities. Laboratory values showed only an elevated CRP (77 mg/L), with normal full blood count, kidney function and liver enzyme tests. Colour Doppler ultrasonography showed a portal vein thrombosis and a hyporeflexive mass of 5.2 cm next to the pancreas (no previous US to compare). Computed tomography (CT) scans confirmed an extension of the diameter of the portal vein up to 5.5 cm on the level of the splenic-portal confluence, complicated with total thrombosis of portal vein, expanding to the splenic vein and the superior mesenteric vein. Furthermore, a nodule in the corpus of the pancreas was seen. There were no signs of cirrhosis or chronic pancreatitis. Further diagnostic excluded all known thrombophilic factors (including JAK2-mutation) and a bone marrow aspirate revealed no signs of myeloproliferative diseases. Upper endoscopy was negative for varices. A liver biopsy showed a picture of regenerative nodular hyperplasia. EUS with FNA of the small pancreatic nodule showed a low grade neuroendocrine tumor with Ki 0.67%. After multidisciplinary discussion conservative management for this thrombosed portal vein aneurysm was adopted, and therapy with low molecular weight heparin was started. Portal vein aneurysm is an unusual vascular dilatation of the portal vein. Since first described by Barzilai and Kleckner in 1956, less than 200 cases have been reported, mainly as case reports or small surgical series. Portal vein aneurysm is defined as a portal vein diameter exceeding 1.9 cm in cirrhotic patients and 1.5 cm in normal livers. Most patients are asymptomatic, but approximately 50% have nonspecific abdominal pain as a major symptom. Etiology is still unclear, however congenital or acquired causes have been proposed. An incomplete regression of the right primitive distal vitelline vein can explain the congenital variant. Portal hypertension represents the main cause of the acquired version (others are necrotizing pancreatitis, abdominal trauma, surgery or malignancy). Most common locations for aneurysms of the portal venous system are splenomesenteric venous confluence, the main portal trunk or the intrahepatic portal vein branches at bifurcation sites (rarest locations are the splenic, mesenteric and umbilical vein). Complications of portal vein aneurysm are thrombosis, portal hypertension, rupture (rare because of the low portal venous pressure), gastrointestinal bleeding, duodenal compression, inferior vena cava obstruction or compression of common bile duct causing jaundice, cholestasis and cholelithiasis. The management remains somewhat controversial (no clear evidence or comparative studies). Conservative management with regular follow-up by ultrasound is the best option for the majority of patients. Surgical intervention (trombectomy, aneurysmectomy, or even liver transplantation) has been proposed, but remain controversial.

ENDOSCOPIC SUBMUCOSAL DISSECTION OF A GRANULAR CELL TUMOUR OF THE OESOPHAGUS. C. De Vloo (1), F. Marolleau (2), J. Dewyspelaere (2), L. Desomer (3), E. Steenkiste (4), D. De Wulf (2) / [1] UZ Leuven, Leuven, Belgium, Gastroenterologie, [2] AZ Delta, Roeselare, Belgium, Gastroenterology, [3] AZ Delta, Roeselare, Belgium, Gastroenterology, [4] AZ Delta, Roeselare, Belgium, Pathology.

We report two cases of an Abrikossoff tumour of the oesophagus, resected by endoscopic submucosal dissection (ESD). In the first case, a 25-year-old patient presented with epigastric pain. On upper gastrointestinal endoscopy a yellow, firm, sessile, submucosal lesion of 0.5 cm was seen. Endoscopic ultrasound (EUS) confirmed a submucosal mass in the distal oesophagus. We performed an endoscopic resection by endoscopic submucosal dissection (ESD) after marking the lesion, submucosal injection and circumferential incision with dual-knife. En bloc resection was performed and pathologic complete resection was achieved. Histologic features confirmed a benign granular cell tumour. No post procedural complications were observed. On endoscopic control 1 month after removal, a scar, but no residual tumour was seen. In the second case a submucosal mass was seen on the upper GI endoscopy of a 23-years old male, performed because of gastro-oesophageal reflux disease. EUS showed a submucosal mass of 1cm, nearby the muscularis propria, without invasion. Total resection by ESD en bloc has been done, without complications. Histological confirmation of an Abrikossoff tumour. No further resection or therapy was needed. Abrikossoff tumours or granular cell tumours (GCT) are infrequent lesions, initially described by Abrikossoff in 1926. These are usually benign neoplasms, which are predominantly found in head and neck region. The primary location in the oesophagus is uncommon (0.001 % of all tumours) and the lesions are generally restricted to the submucosal layer. Most oesophageal GCT have a benign clinical course, however 1-2% are malignant variants. Presentation is typically asymptomatic ; but sometimes with symptoms of dysphagia. The histogenesis and aetiology are still disputed but a neurogenic origin, arising from the Schwann cells, which in the oesophagus, form part of the submucosal neuronal plexus is generally favoured. The macroscopic appearance is typical (yellow, firm, well circumscribed submucosal neoplasm-like with reduced vascular patterns) but due to the rarity of this lesion, it can be mistaken with other similar lesions. Endoscopic treatment is increasingly used as an alternative to traditional surgical resection. Endoscopic resection by ESD appears to be a safe and effective treatment for GCTs in the gastrointestinal tract.

TWO RARE CONDITIONS AT THE SAME TIME AFTER GASTRIC BYPASS IN A YOUNG FEMALE. D. Dooremont (1) / [1] AZ Sint-Elisabeth, Zottegem, Belgium, Gastro-Enterologie

When two rare conditions happen at the same time, it can be difficult to determine any relationship and see the connection between the two. In this case report we will give an example. A young female of 19 years old was admitted in our emergency room with symptoms of anorexia and malaise, two months after undergoing a mini gastric bypass. There were also complaints of blurry vision. As medication she took Pantomed 40 mg/d together with a multivitamin. She noted to recently have taken nitrofurantoin for a urinary tract infection. There was no use of nicotine or alcohol. Clinical investigation showed a weight of 100 kg, slightly icteric sclerae and a mild painful right hypochonder during palpation. The blood showed markedly elevated liver enzymes with AST 248 U/L, ALT 508 U/L, gammaGT 133 U/L and total bilirubin of 3,85 mg/dL. The PT was 49% at admission. The thyroid hormones were normal. In the autoimmune serology only ANF was elevated, the other autoimmune tests were negative. The ferritin and ceruloplasmin were normal. Viral serology was negative, only positive IgG for EBV. An ultrasound of the liver showed slightly increased density of the liver, indicating a mild steatosis. The bile ducts weren't dilated. After given parenteral vitamin K the PT was normalized. A liver biopsy was performed after a couple of days because the liver enzymes didn't decrease. Anatomopathology revealed presence of microvesicular steatosis around the vene centerolobularis, some Mallory bodies, some loss of hepatocytes and mild bilirubinostasis, most likely caused by a toxic drug reaction. The treatment with nitrofurantoin was already stopped, because of the very slow decline in liver enzymes a treatment with oral budesonide 9 mg a day was given, although IgG and smooth muscle antibodies were negative. Under this treatment the liver enzymes gradually decreased. From admission the neurological signs progressively worsened with confusion, hearing loss and paraparesis. An urgent advice of the ophthalmologist and neurologist was asked. The ophthalmologist saw bilateral acute mild papilledema. As differential diagnoses were benign intracranial hypertension, an intracranial bleeding or tumour, meningitis, Addison, hypoparathyroidy or hypovitaminosis A proposed. A CT scan of the brain was performed immediately, without showing any lesions in the brain. An urgent NMR of the brain didn't show any pathological findings, although there were major artefacts caused by orthodontic material. Afterwards a lumbar puncture was performed which was normal. There were no arguments for benign intracranial hypertension or meningitis. The MMSE was 24/30 showing impaired cognition. The conclusion of our neurologists was that the neurological disease was caused by encephalopathy from the liver injury, even though the liver showed no progressive liver failure. The clinical state of the patient went progressively worse,

she slept a lot, had confusion and even paraparesis. In an epiphany I came up with the diagnosis of thiamine deficiency. Treatment with parenteral thiamine was started promptly. The day after there was already obvious neurological improvement. The vitamin B1 level at that time was 25 nmol/L, confirming the diagnosis. In the literature I could not find any case of nitrofurantoin induced liver failure and thiamine deficiency at the same time in the same patient. As a result of the toxic liver reaction she ate almost nothing, thereby she didn't take her vitamins. The combination of recent gastric bypass and anorexia led to malnutrition and vitamin B1 deficiency. In the first place it is very important to consider the diagnosis. Wernicke encephalopathy is a serious disorder and is classically described in chronic alcoholics, certainly here in the Western civilization. It has also been identified in malnutrition, prolonged fasting, gastrointestinal malignancies, dialysis, hyperemesis gravidarum, AIDS and bariatric surgery. If left untreated, it may lead to a state of chronic mental dysfunction known as Korsakoff's syndrome and even death. Nitrofurantoin is a commonly prescribed medication in primary care, side effects include diarrhea, neuropathy, pulmonary fibrosis, interstitial pneumonitis and hypersensitivity reactions. Hepatotoxicity accounts for 12% of reported adverse reactions and 25% of those resulting in death. Significant hepatotoxicity is rare following short courses, like in our case. Immune-mediated liver injury usually occurs in the setting of long-term use. The prognosis is variable.

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ACASE OF SEVERE ENTEROPATHY. P. Henry (1), H. Dano (2), H. Piessevaux (3), A. Jouret-Mourin (2) / [1] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Anatomie pathologique, [2] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Pathology, [3] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Gastroenterology.

**Introduction :** Sprue-like enteropathy associated with olmesartan was first described in 2012. Almost all reported cases presented with severe diarrhoea and weight loss. Variable degrees of duodenal villous atrophy were present in the majority of the patients, which may mimic celiac disease.

**Aim :** We report on a 63-year-old male patient referred to the gastroenterology department for severe diarrhoea, with significant dehydration and management in the intensive care unit. This patient had a history of type 2 diabetes, hypertension and diverticulitis. Systematic anamnesis revealed a daily consumption of more than a bottle of wine and ~30 cigarettes. His usual medication consisted of pantoprazole, fluoxetine, moxonidine, amlodipine, nebivolol and olmesartan.

**Methods :** The management of the patient included a GI endoscopy, with biopsies at different levels of the GI tract.

**Results :** Histology revealed an excess of intraepithelial lymphocytes in both the gastric and colonic regions, as well as celiac-like abnormalities in the duodenum (i.e. villous atrophy, intraepithelial lymphocytes and lamina propria inflammation). The diagnosis of olmesartan-associated enteropathy was considered. The clinical signs and histological alterations completely resolved after drug withdrawal.

**Conclusions :** In the literature, most patients with olmesartan-induced enteropathy present with sprue-like manifestations. Few patients have both gastritis and lymphocytic colitis. Here, we report on a patient with a panlymphocytic digestive disease (lymphocytic gastritis, colitis and duodenitis) inducing enteropathy caused by olmesartan. Olmesartan-induced enteropathy is a new clinical entity that must be included in the differential diagnosis of not only sprue-like pattern but also panlymphocytic digestive disease. Burbure N et al Hum Pathol 2016. 127\_134 Ianiro G et al Aliment Pharmacol Ther 2014, 401 : 16-23 Rubio-Tapia A et al Mayo Clinic Proc 2012 87 : 732-738

- C12 -

PROBIOTICS IN A CRITICALLY ILL MALNOURISHED PATIENT : TO DO OR NOT TO DO. M. Figueiredo (1), T. Sersté (1), M. Van Gossum (1) / [1] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology.

Probiotics are commonly prescribed as an adjuvant in the treatment of Clostridium difficile-associated diarrhoea. However, the exact beneficial role of these agents in the different clinical contexts has not yet been established and their safety profile is still a matter of debate in certain populations. We describe the case of a severely malnourished patient with a BMI of 8 kg/m<sup>2</sup> who managed to survive post-probiotic Saccharomyces fungemia and refeeding syndrome complications. A 21-year-old patient with anorexia nervosa and a BMI of 8 kg/m<sup>2</sup> presented to the emergency department for severe weakness and lipothymia. On examination, he was cachectic and in an extremely poor general condition. He had been bedridden for more than a month, as he did not have enough strength to stand. Upon physical examination, he presented with hypothermia (31.8°C), tachycardia (114/min), and hypotension (90/79 mmHg). Lower extremity oedema and sacral bedsores were also detected. Blood tests revealed a normocytic anaemia, hypokalaemia and hyponatraemia, severe hypoalbuminaemia and coagulopathy. C-reactive protein (CRP) was elevated. Extensive microbiological tests were also performed. The patient was then admitted to the intensive care unit for severe malnutrition and dehydration. Intravenous

fluid therapy and enteric feeding (500 kcal/day) were immediately implemented. On day two, the patient developed diarrhoea and stool analysis was positive for faecal leucocytes and Clostridium Difficile A and B toxins. Simultaneously, results came back positive for a urinary tract infection caused by Escherichia coli. Antibiotic treatment comprising levofloxacin and ornidazol was started. The severity and persistence of the diarrhoea, aggravating the dehydration and electrolytic problems, motivated the use of a probiotic containing Saccharomyces boulardii. Nutritional intake was also augmented to 1500 kcal/day to compensate for fluid losses. On day nine, there seemed to be no improvement. The probiotic treatment was then interrupted and antibiotics were changed to piperacillin-tazobactam and vancomycin. On day eleven, blood cultures came back positive for Saccharomyces cerevisiae and anti-fungal medication was administered (for a total of 14 days). Diarrhoea progressively stopped but then the patient started to develop confusion and mental state depression. Blood tests showed hepatic insufficiency and hyperammonemia, acute kidney failure, electrolytic imbalance, and metabolic acidosis. The patient also presented with respiratory failure requiring endotracheal intubation. Refeeding syndrome was then suspected and enteral nutrition interrupted and replaced by supplementary vitamins. Electrolytic balance was also carefully obtained. Nutrition was restarted four days later at a lower rate (15 kcal/kg). Still, the following weeks were marked by multiple consecutive episodes of bacteraemia and septic shock. A temporary tracheotomy was also performed after a long period (>3 weeks) of invasive mechanical ventilation. More than 3 months after admission, the patient was finally transferred to an internal medicine unit. He was discharged two weeks later with normal hepatic and kidney function and re-equilibrated electrolytes. His BMI was 11 kg/m<sup>2</sup> at this time. He was referred to a physical revalidation centre, as he still was not able to walk due to muscle wasting. We find this case interesting because it serves as a reminder of the risk of fungaemia associated with Saccharomyces boulardii probiotics administration, which has already been demonstrated in numerous studies in the past. These probiotics should then not be used in critically ill patients. Additionally, this case also illustrates the complexity inherent to the management of critically ill malnourished patients. The refeeding phase of these high-risk patients can trigger potentially fatal medical complications (such as refeeding syndrome, infection and severe arrhythmia). However, some studies have argued that these can be kept to a minimum if vitamin supplementation and strict progressive refeeding regimens are applied from the start. Still, most of the cases of surviving patients described in the literature concern patients with a BMI equal or superior to 10 kg/m<sup>2</sup> (which is two points higher than our patient).

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AN UNUSUAL CAUSE OF GASTROJEJUNAL ANASTOMOTIC STENOSIS AFTER ROUX-EN-Y GASTRIC BYPASS. Z. Issa (1), F. Corbisier (2), P. Delrée (3), P. Warzée (1) / [1] GHDC, Charleroi, Belgium, Hepato-gastroenterology, [2] GHDC, charleroi, Belgium, Abdominal and general surgery, [3] IPG, Charleroi, Belgium, Anatomopathology

Obesity is becoming a major health problem in Western countries with a prevalence rate reaching 22% in Belgium. Surgical treatment is often required to treat class III obesity (BMI > 40 kg/m<sup>2</sup>). Bariatric surgeries, such as Roux-en-Y gastric bypass (RYGB), can present a number of post-operative complications. Anastomotic stenosis is one of the most frequent complications of RYGB that usually develops at the gastrojejunal (GJ) anastomosis site. Suggested possible causes are ; the use of a circular stapler, local ischemia or an inflammatory response. We hereby present a case of an unusual cause of GJ anastomotic stenosis developing post-RYGB. A 45-year-old patient underwent RYGB for medically complicated morbid obesity (BMI at 50 kg/m<sup>2</sup>). He had metabolic syndrome (type 2 diabetes mellitus, resistant arterial hypertension and severe hypercholesterolemia), coronary heart disease, diabetic nephropathy and obstructive sleep apnea syndrome. The immediate post-operative period was uneventful and the postoperative oeso-gastrojejunal transit study was normal. The patient was discharged three days after the surgery. Six weeks later, the patient returned with severe dysphagia and dehydration. Gastroscopy showed total stenosis of the GJ anastomosis treated with endoscopic balloon dilation up to 12mm. Three weeks later, the patient had complete stenosis of the GJ anastomosis and a new session of endoscopic dilation was performed together with the placement of a covered metal stent. Unfortunately, the stent migrated two days later and a new one was placed and fixated by endoscopic clips. After two days, the new stent migrated again and was removed endoscopically. In the next three weeks, the patient's condition deteriorated and he had dysphagia again. Gastroscopy confirmed our clinical suspicion of complete stenosis of the GJ anastomosis. The patient was treated once again by balloon dilation up to 10mm and then by the placement of two overlapping covered stents fixated by endoscopic clips. Stents were removed endoscopically six weeks later and the passage of the endoscope within the stenosis was smooth. Ten days upon the removal of these stents, the patient relapsed and the complete stenosis of the GJ anastomosis recurred. In view of this recurrent and unexplained GJ anastomotic stenosis, the patient was addressed for surgical treatment. Echoendoscopy of the GJ anastomosis site prior to surgery revealed a couple of significant adjacent adenopathies. The patient underwent degastro-gastrectomy by laparoscopy about five months after the initial RYGB surgery. Anatomopathological examination of the surgical section showed important inflammation at the GJ anastomotic site with an eosinophilic infiltrate. One inflammatory nodule contained some structures compatible with parasites suggestive of Strongyloides stercoralis (image available). The patient had no history of intestinal complaints and his blood tests did not reveal eosinophilia nor signs of inflammation (normal C-reactive protein level). Further confirmation

and identification of the parasite by stool examination and/or serologic methods was impossible due to loss to follow-up. *Strongyloides stercoralis* is a soil-transmitted nematode (roundworm). Strongyloidiasis is endemic in tropical and subtropical areas where the prevalence can exceed 25%. In developed countries, it is more frequent in farmers, miners and in immigrant populations. Its life cycle can be entirely completed within the human host and includes infection of the small intestine. Infection is usually asymptomatic in immunocompetent individuals. Eosinophilia is not universally present. Main diagnostic tools include concentrated stool examination for rhabditiform larvae and serologic testing. First line treatment is Ivermectin with a high response rate. A couple of cases of roundworm infestation complicating surgical anastomoses were previously reported including one case of small bowel anastomotic breakdown following urinary diversion for cervical cancer due to *Ascaris lumbricoides* infestation, three cases of roundworm obstruction after Roux-en-Y hepaticojejunostomy in children (biliary ascariasis) and one case of anastomotic stenosis due to *Ascaris lumbricoides* infection after colonic resection for diverticulitis. One case of colonic anastomotic leakage due to *Taenia saginata* (tapeworm) was also described. To our best knowledge, this is the first case of GJ anastomotic stenosis after RYGB due to parasitic infection. Whether this finding should prompt preoperative evaluation for intestinal parasite infestation remains to be elucidated.

- C14 -

ADENOCARCINOMA OF THE GASTROESOPHAGEAL JUNCTION AFTER BARIATRIC SURGERY : TWO CASES REPORTS. M. Van Gossum (1), M. Figueiredo (1), E. Brauns (1), P. Eisendrath (1) / [1] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology.

**Introduction :** Barrett's esophagus (BE) is recognized as a premalignant lesion for oesophageal adenocarcinoma. BE appears as a consequence of gastroesophageal reflux disease (GERD), which is more common among the obese population. In morbidly obese patients who undergo laparoscopic Roux-en-Y gastric bypass (LRYGB), the incidence of GERD is 50% to 100% and BE occurs in up to 9% of patients. LRYGB is the best treatment option for obesity combined with GERD. It is an excellent antireflux procedure, because there is no acid production in the small gastric pouch and no duodenal reflux is present, due to the long Roux-en-Y limb. Also, induced weight may diminish systemic inflammation, which may contribute to metaplastic changes in the esophagus. Furthermore, improved compliance with proton-pump inhibitor therapy, as a consequence of enrolling in a bariatric program, further decreases acid production. Diagnosis of gastroesophageal disease as a consequence of preoperative gastroscopy has been the motivation for making changes in the therapeutic approach in over 50% of patients. Studies have demonstrated a regression rate of this premalignant disease in about one third of patient with no observed progression to dysplasia.

**Aim :** We described two cases of oesophageal carcinoma after LRYGB.

**Methods :** Between April 2013 and October 2017, 1575 patients underwent laparoscopic bariatric surgery at our institution. There were 1229 (78%) LRYGB, 299(19%) laparoscopic sleeve gastrectomies, and 47(3%) surgical revisions. Forty-two patients (2,6%) had BE preoperatively and underwent LRYGB.

**Case report 1 :** Routine preoperative upper endoscopy in a 67 years old male patient revealed a long-segment BE (C7M7) with intestinal metaplasia but no dysplasia in 2013. LRYGB was performed with no registered complications. A second endoscopy was performed two years later in another institution, in the context of upper GI haemorrhage. Marginal ulcer was observed, but no oesophageal lesion was described and a biopsy not performed. Maintenance therapy with proton pump inhibitors was proposed. In October 2017, the patient presented with retrosternal pain and weight gain. We performed a gastroscopy that showed a regression of the intestinal metaplasia (C5M5) but histological analysis revealed the presence of an adenocarcinoma of the distal portion of the oesophagus. An endoscopic mucosal resection was proposed.

**Case report 2 :** A routine preoperative upper endoscopy was performed in March 2015 in an asymptomatic 58-year-old patient. A long-segment BE (C5M5) was described and histological evaluation revealed a low-grade dysplasia. Postsurgical surveillance was proposed but not done. Melena and weight loss motivated the performance of a second upper endoscopy two years later. A large marginal ulcer and a suspicious lesion were identified. The diagnosis of oesophageal adenocarcinoma was confirmed by histological examination. Abdominal CT scan revealed multiple liver metastases. **Conclusions :** Our findings emphasize the importance of precise endoscopic evaluation before bariatric surgery in patients with GERD, and the necessity for continuing postsurgical surveillance in patients with known BE, and early evaluation in patients who develop new symptoms of GERD after bariatric surgery. Long-term follow-up for patients with BE according to standard surveillance protocols is still recommended in this particular patient'group.

- C15 -

ENDOLUMINAL VACUUM THERAPY FOR THE TREATMENT OF ESOPHAGEAL ANASTOMOTIC LEAKS. M. Struyve (1), H. Van Veer (2), L. Depypere (3), P. Naftoux (3), P. Roelandt (1) / [1] University Hospital, Gasthuisberg, Leuven, Belgium, Gastroenterology, Hepatology and Endoscopy, [2] University Hospital, Gasthuisberg, Leuven, Belgium, Thoracic surgery, [3] University Hospital, Gasthuisberg, Leuven, Belgium, Thoracic Surgery.



**Introduction :** Persisting suture dehiscence with esophageal anastomotic leaks after thoracic surgery is a difficult complication, especially when a surgical repair fails. We report a novel combined endoscopic and surgical therapy for the management of esophageal anastomotic leaks in a patient with a persisting suture dehiscence after a left thoraco-freno-laparotomy with partial esophagectomy and partial gastrectomy with an intrathoracic anastomosis because of an adenocarcinoma of the distal esophagus. **Aim :** The aim of this abstract is to illustrate a new combined endoscopic and surgical therapy for persisting suture dehiscence with esophageal anastomotic leaks.

**Methods :** We report a novel combined endoscopic and surgical therapy for the management of esophageal anastomotic leaks in a patient with a persisting suture dehiscence after a left thoraco-freno-laparotomy with partial esophagectomy and partial gastrectomy with an intrathoracic anastomosis because of an adenocarcinoma of the distal esophagus. We provide clear endoscopic figures and videos. **Case report :** A 65-year-old patient had undergone a left thoraco-freno-laparotomy with partial esophagectomy and partial gastrectomy with an intrathoracic anastomosis because of an adenocarcinoma of the distal esophagus. One month after the operation, the patient was admitted in the hospital complaining about shortness of breath with observed desaturation and an extreme cough. Blood analysis showed a highly elevated C-reactive protein of 153 mg/dl (normal < 5). Computed tomography (CT) scan of the chest and abdomen showed an esophageal anastomotic leak due to a suture dehiscence at the level of the esophagogastric anastomosis with leakage into the right posterior mediastinal space with extension to a collection into the right basal subpleural space (figure 1). X-ray esophagogram with Ultravist®, an iodine-based contrast agent, confirmed the presence of an important esophageal anastomotic leak with opacification of a supradiaphragmatic space (figure 2). These findings were confirmed on the esophagogastroduodenoscopy (EGD) (figure 3). The patient was treated with nothing by mouth, intravenous administration of antibiotics and intravenous rehydration. A surgical repair of the anastomosis was performed, but unfortunately it failed. We therefore treated the patient with an endoluminal vacuum therapy (Eso-SPONGE®, B. Braun Medical). Two polyurethane sponges of 13 mm and 15 mm were endoscopically positioned at the entrance of the wound cavity at the level of the suture dehiscence and continuous suction (- 75 mmHg) was applied by using drainage tubes fixed to the sponges (figures 3 and 4). An endoscopic replacement of the sponges was performed every 48 to 72 hours where we managed to reduce the amount and the volume of the polyurethane sponges. This endoluminal vacuum therapy was stopped at the moment we achieved a reduction of the wound cavity and a narrowing of the anastomotic leak where the anastomotic defect was too small for the further placement of a sponge. Closure of the anastomotic leak was achieved after 5 weeks and 15 replacement sessions in total.

**Conclusion :** Endoluminal vacuum therapy performed by a multidisciplinary endoscopic and surgical approach is a successful therapy for the management of persisting suture dehiscence with esophageal anastomotic leaks after thoracic surgery.

- C16 -

UNUSUAL YELLOW TO ORANGE COLONIC MUCOSAL APPEARANCE : WHAT COULD THAT BE? M. Struyve (1), M. Ferrante (2), W. Meersseman (3), L. Van Overbeke (4), D. Cassiman (3) / [1] University Hospital, Gasthuisberg, Leuven, Belgium, Belgium, Gastroenterology, Hepatology and Endoscopy, [2] University Hospital Gasthuisberg, Leuven, Belgium, Gastroenterology, Hepatology and Endoscopy, [3] University Hospital Gasthuisberg, Leuven, Belgium, Metabolic Center, [4] AZ Sint Maarten, Mechelen, Belgium, Gastroenterology, Hepatology and Endoscopy.

**Introduction :** We report here clear endoscopic and histopathological images of the involvement of the colon in Tangier disease, which is rarely described in literature due to its curiosity. **Aim :** The aim of this abstract is to illustrate a rare case of a yellow to orange appearance of the colonic mucosa as seen in Tangier disease illustrated with the aid of clear endoscopic and histopathological images.

**Case report :** A 51-year-old man was referred to the outpatient clinic for a routine colonoscopy because of abdominal discomfort in combination with loose stools suggestive for irritable bowel syndrome. His medical history consisted of pronounced atherosclerosis since young age and a tonsillectomy. Blood analysis revealed an abnormal lipid level with a low total cholesterol level of 80 mg/dl (normal < 190 mg/dl), an undetectable low (<3 mg/dl) HDL cholesterol level (normal > 40 mg/dl), a high triglycerides level of 807 mg/dl (normal < 150 mg/dl) and an undetectable low apolipoprotein A1 (< 0.20 g/L) (normal 1.04-2.02 g/L) and apolipoprotein A2. Colonoscopy revealed an irregular discoloration of the colonic mucosa with a yellow to orange appearance in combination with innumerable small yellow to brown dots with a scaly to cobblestone pattern and multiple polyps throughout the colon (figures 1 to 7). Histological analysis revealed colonic mucosa with focal aggregates of foam cells and foamy histiocytes in the lamina propria and submucosa (figure 8). Most polyps were hyperplastic deformed colonic mucosa with an excess of foamy histiocytes or so called xanthomateous lesions, other polyps were adenomatous lesions. Genetic testing showed a homozygous variant in the ABCA1-gene (c.5785G>T,p.(Val1929Phe)). The diagnosis of hypo-alpha lipoproteinemia due to Tangier disease was made.

**Conclusion :** Tangier disease is an inherent disorder of the lipid metabolism with an autosomal recessive transmission. It is a severe HDL deficiency syndrome leading to the accumulation of cholesterol in tissue macrophages and histiocytes. Due to mutations in the adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1-gene), which is a cell

membrane protein responsible for the depletion of cholesterol out of the cells by the secretion of an excess of cholesterol from cells into the HDL metabolism, there is an extremely low HDL cholesterol level and accumulation of cholesterol in macrophages. The clinical presentation is often characterized by pronounced and complicated atherosclerosis at young age, peripheral neuropathy and typical yellow-orange tonsils. Abdominal complaints comparable to the symptoms seen in irritable bowel syndrome (abdominal discomfort, loose stools ...) are described in patients with Tangier disease. Blood analysis shows a disturbed lipid profile with the absent of HDL cholesterol in combination with low total cholesterol, low LDL cholesterol, moderate elevated triglycerides levels and low apolipoprotein A1. We focused in this case report on the involvement of the colonic mucosa in Tangier disease that has a pathognomonic yellow to orange color in combination with small irregularities or dots. The presence of colonic polyps is often seen in Tangier disease and can histological either be hyperplastic colonic mucosa or even adenomatous lesions with aggregation of foam cells or foamy histiocytes. We report here clear endoscopic and histopathological images of the involvement of the colon in Tangier disease, which is rarely described in literature due to its curiosity.

## BELGIAN SOCIETY FOR GASTROINTESTINAL ENDOSCOPY (BSGIE)

- G01 -

AUTOMATED DIGITAL CALCULATION OF ENDOSCOPIC INFLAMMATION IN ULCERATIVE COLITIS : RESULTS OF THE RED DENSITY STUDY. P. Bossuyt (1), H. Nakase (2), S. Vermeire (3), H. Willekens (4), Y. Ikemoto (5), T. Makino (5), R. Bisschops (4) / [1] Imelda Hospital, Bonheiden, Belgium, Department of Gastroenterology, [2] Sapporo Medical University, Sapporo, Japan, Department of Gastroenterology, [3] University Hospital, Gasthuisberg, Leuven, Belgium, Department of Gastroenterology, [4] University Hospital, Gasthuisberg, Leuven, Belgium, Department of Gastroenterology, [5] Pentax Medical, Tokyo, Japan, Product development department.

**Introduction :** The evaluation of the endoscopic inflammation in ulcerative colitis (UC) using MAYO endoscopic subscore (MES) or ulcerative colitis endoscopic index of severity (UCEIS) is subjective leading to high inter- and intra-observer variability, mainly in the lower ranges of these scores. The grade of histological inflammation is predictive for relapse in UC even in patients with endoscopic remission. An objective operator-independent endoscopic tool that correlates with histological inflammation would greatly improve therapeutic decisions in UC.

**Aim :** To develop an objective real time digital endoscopic tool for the evaluation of endoscopic images in UC that correlates with histology.

**Methods :** The red density (RD) score is a calculation of the degree of redness based on a digital extraction of the intensity and distribution of red pixels in high definition white light (WL) endoscopic images. The RD algorithm was further refined by integrating computerized vessel pattern recognition and multiple regression analysis including the RD histogram and Robarts histological index (RHI). RD was used for the evaluation of endoscopic inflammation in UC, providing a continuous numeric scale from 0 to 255. To test the RD score, sequential patients with UC with planned endoscopy in two tertiary IBD centres (Belgium and Japan) were included. WL and RD images were collected according to a standardized protocol. All WL images were evaluated at random for MES and UCEIS by 2 blinded central readers. In case of discordance between the readers a consensus decision provided the final endoscopic scoring. Standardized biopsies were taken in the most inflamed area of the images. Biopsies were evaluated using the Geboes score and RHI.

**Results :** In total 46 patients providing 100 images were included. The RD score was stable and reproducible in the same patient. The distribution of the MES, UCEIS and RHI was skewed to the lower ranges of the different scores. There was an interobserver variability of  $\kappa=0.71$  and  $\kappa=0.65$  for the MES and UCEIS respectively after first central reading. Using the Spearman correlation test, RD showed a moderate correlation with the final consensus MES ( $r=0.58$ ) and UCEIS ( $r=0.56$ ). Using the Pearson correlation test, RD correlates strongly with the RHI ( $r=0.65$ ).

**Conclusions :** The evaluation of endoscopic inflammation using the RD score is feasible, reproducible and has a strong correlation with histology. This provides an independent objective tool for the evaluation of endoscopic inflammation in patients with UC. The strong correlation with histology provides also prognostic potential of RD.

- G02 -

ENDOBILIARY RADIOFREQUENCY ABLATION IN PATIENTS WITH INOPERABLE BILIOPANCREATIC TUMORS COMPLICATED WITH OBSTRUCTIVE JAUNDICE : THE IGNITE-1 TRIAL. W. Laleman (1), S. Van Der Merwe (1), L. Verbeke (1), H. Van Malenstein (1), R. Aerts (2), H. Prenen (1), E. Van Cutsem (1), C. Verslype (1) / [1] University Hospitals KULeuven, Leuven, Belgium, Gastroenterology & Hepatology, [2] University Hospitals KULeuven, Leuven, Belgium, Abdominal Surgery.

**Introduction :** Biliary stenting of unresectable malignant bile duct obstruction is generally accepted as the standard of care but is hampered by tumor ingrowth and stent dysfunction.

**Aim :** We aimed to test feasibility, efficacy and safety of a new endoscopically applied dedicated intraductal radiofrequency ablation (RFA) device and compare these findings to a historical matched control group

**Methods :** This project was designed as a prospective open-label phase 2 single center study aiming to include 18 patients with inoperable malignant biliary obstruction (9 proximal and 9 distal lesions). All were scheduled for biliary drainage with stenting via ERCP combined with intraductal RFA and compared to 18 matched historical control patients with stenting but without RFA. Main outcome measurements involved technical feasibility, adverse events within first 90 days, duration of stent patency and overall survival.

**Results :** Between December 2014 and November 2015, 18 patients were recruited and all underwent RFA to the intended region and without complications within 3 months post-procedure. Bilirubin levels post-RFA and stenting decreased significantly but did not differ to stenting alone. The average stent patency however proved to be longer after RFA ( $P<0.001$ ) with less stent dysfunction in the RFA group ( $P=0.08$ ). RFA-application delivered a survival benefit in comparison to the control group ( $P=0.0078$ ) with the best outcome for the subgroup treated with RFA combined with chemotherapy.

**Conclusions :** Intraductal RFA using a new device in patients with inoperable biliopancreatic complicated with jaundice appeared 100% feasible and safe. RFA resulted in a higher degree and longer maintenance of stent patency compared to a historical matched control group with only stenting. Moreover, a survival benefit was suggested when RFA was combined with palliative chemotherapy

- G03 -

SIMPLE ENDOSCOPIC TREATMENT OF ADENOMA RECURRENCE AFTER WIDE FIELD ENDOSCOPIC MUCOSAL RESECTION IS EFFECTIVE : A PROSPECTIVE STUDY OF 1558 LESIONS WITH LONG TERM FOLLOW UP. D. Tate (1), L. Desomer (2), H. Awadie (1), M. Sidhu (1), N. Burgess (1), K. Goodrick (1), M. Bourke (1) / [1] Westmead Hospital, Sydney, Australia, Gastroenterology and Hepatology, [2] AZ Delta, Roeselare, Belgium, Gastroenterology and Hepatology.

**Introduction :** Adenoma recurrence after wide field endoscopic mucosal resection (EMR) of laterally spreading colonic lesions  $\geq 20$ mm (LSLs) is a major limitation. Data on the optimal methods and outcomes of endoscopic treatment of recurrence (ETOR) is absent and no evidence based standard exists.

**Aim :** We examined the techniques and success of ETOR over time in a large prospective cohort.

**Methods :** Over 100 months to January 2017 prospective observational data on all recurrences after all EMR of LSL at the lead centre of the Australian Colonic Endoscopic Resection Study (ACE) was recorded. Recurrence was detected and described by endoscopic evaluation of the EMR scar using high definition white light and NBI. ETOR comprised coagulation current snare resection (ERBE Effect 2, 30W), cold avulsion forceps with adjuvant snare tip soft coagulation [CAST2] (ERBE Effect 4, 80W) or a combination of the two. The first and last 50-month time periods were analysed separately to compare the safety and efficacy of the primary techniques.

**Results :** 1558 patients with 1558 LSLs were included. 150 LSLs (9.6%) had evidence of recurrence at first surveillance colonoscopy (SC1). The mean age of patients with recurrence was 68 years and 55% were male. Recurrent LSLs were median 50mm in size (IQR 35-60mm) and located distal to the hepatic flexure in 52.7%. They were most commonly of Paris 0-IIa+Is morphology (46.7%) and displayed tubulovillous adenoma at histopathology (75.3%), with high grade dysplasia in 23.3%. 4 (2.7%) were resected en-bloc. Recurrence at the EMR scar was  $\leq 5$ mm in size (64%), uni-focal (75%) and within the scar (55%) or at the edge (45%). The commonest modality used to resect recurrence was hot snare with adjuvant STSC (35%). CAST was used in 30% and was also used in combination with hot snare (9%). CAST was more commonly used in the second half (62.5%) than the first half (10.6%,  $p < .001$ ) of the cohort. Injection prior to resection was performed in a minority (16%). In 124/143 (86.7%) cases where tissue was retrieved, there was histologic confirmation of recurrence. Endoscopic cure was achieved in 94.7% of cases at first surveillance colonoscopy post ETOR with 8 (5.3%) of cases referred for surgery primarily due to an inability to resect recurrence. For LSLs that underwent further surveillance, 89% (1 further surveillance), 86.5% (2 further surveillances) and 89.5% (3 further surveillances) of EMR scars respectively showed no evidence of recurrence.

**Conclusions :** Adenoma recurrence after EMR of LSLs is commonly diminutive and can be effectively treated using simple endoscopic techniques with rates of long-term remission approaching 90%. Based on this data, more technically complex, morbid and resource intensive endoscopic or surgical techniques are unnecessary to resect the majority of LSL recurrence after EMR.

- G04 -

SELF-SIZING RADIOFREQUENCY ABLATION BALLOON FOR ERADICATION OF BARRETT'S ESOPHAGUS : RESULTS OF AN INTERNATIONAL MULTICENTER RANDOMIZED TRIAL COMPARING THREE DIFFERENT TREATMENT REGIMENS. K. Belghazi (1), R. Pouw (1), A. Koch (2), B. Weusten (3), E. Schoon (4), W. Curvers (4), A. Gotink (2), R. Haidry (5), O. Pech (6), J. Bergman (1), R. Bisschops (7) / [1] Academic Medical Center, Amsterdam, Netherlands (the), Gastroenterology, [2] Erasmus Medical Center, Rotterdam, Netherlands (the), Gastroenterology, [3] St. Antonius Hospital, Nieuwegein, Netherlands (the), Gastroenterology, [4] Catharina Hospital, Eindhoven, Netherlands (the), Gastroenterology, [5] University College London Hospitals, London, United Kingdom (the), Gastroenterology, [6] St. John of God Hospital, Regensburg, Germany, Gastroenterology and Interventional Endoscopy, [7] University Hospital Gasthuisberg, Leuven, Belgium, Gastroenterology.

**Introduction :** The 360 Express RFA balloon catheter ("360 Express") for radiofrequency ablation (RFA) of Barrett's esophagus (BE) has the ability to self-adjust to the esophageal lumen ensuring optimal tissue contact during ablation.

**Aim :** Aim of this randomized clinical trial was to compare three different ablation regimens for treatment of BE using the 360 Express.

**Methods :** Patients with a 2-15 cm BE with low-grade dysplasia (LGD), high-grade dysplasia (HGD) or early cancer (EC) were included. Visible lesions were removed by endoscopic resection (ER) prior to RFA. Patients were randomly

assigned on a 1 : 1 : 1 ratio to the standard (1x10J/cm<sup>2</sup>-clean-1x10J/cm<sup>2</sup>), simple-double (2x10J/cm<sup>2</sup>-no clean), or simple-single ablation regimen (1x10J/cm<sup>2</sup>-no clean). Sample size calculation showed that 36 patients would be necessary in each arm. Primary outcome : percentage of endoscopically visual surface regression of BE at 3 months as scored by two independent blinded endoscopists. Secondary outcomes : adverse events and procedure time.

**Results :** Inclusion started September 2015 and was completed by October 2017. A total of 103 patients (81 male, median 66 yrs, median C4M7 BE) were included. Forty-three patients underwent ER prior to RFA (EC, n=22 ; HGD, n=13 ; LGD, n=6, non-dysplastic IM, n=2). Worst histology prior to RFA : HGD, n=42 ; LGD, n=51 ; non-dysplastic IM, n=10. In February 2017, after 28 patients were included in the simple-double arm, further inclusion in this arm was stopped because of an unexpected high risk of severe stenosis. Six patients developed a stenosis (21%, 95% CI : 10-39%) requiring a median of 6 dilations after simple-double ablation. The study was continued with the standard and simple-single arm. To date, a total of 90/103 patients have completed the study (standard, n=31/37 ; simple-single, n=31/38, simple-double, n=28/28). Median BE regression was higher in the standard arm compared to the simple-single regimen : 85% (IQR 75-94), 95% CI : 78-92% versus 73% (IQR 48-90), 95% CI : 59-85% (p0.009). A poor response (defined as ≤50% regression) was found in 3/31 and in 9/31 patients in respectively the standard and simple-single arm (p0.05). The standard ablation procedure was significantly longer : median 31mins (IQR 26-36) versus 17mins (IQR 13-20), p<0.001. Adverse events occurred in 5/37 patients in the standard arm (minor laceration n=4, unrelated death n=1) and in 5/38 patients in the simple-single arm (minor laceration n=3, minor bleeding n=1, pain and fever n=1).

**Conclusions :** Results of this randomized controlled trial suggest that c-RFA with the 360 Express using the standard regimen results in significant better regression after one treatment session compared with the simple-single regimen. However, the procedure is longer when using the standard regimen. The simple-double ablation regimen is not advised given the unacceptable risk of severe stenosis.

- G05 -

AN INTERNATIONAL SURVEY OF COLORECTAL POLYPECTOMY PRACTICE DEMONSTRATES ENCOURAGING ADHERENCE TO PUBLISHED GUIDANCE. D. Tate (1), L. Desomer (2), N. Burgess (1), H. Awadie (1), S. Heitman (3), N. Forbes (3), D. De Looze (4), J. Anderson (5), D. Rex (6), M. Bourke (1) / [1] Westmead Hospital, Sydney, Australia, Gastroenterology and Hepatology, [2] AZ Delta, Roeselare, Belgium, Gastroenterology and Hepatology, [3] Cumming School of Medicine, University of Calgary, Calgary, Canada, Gastroenterology and Hepatology, [4] Ghent University Hospital, Ghent, Belgium, Gastroenterology and Hepatology, [5] Cheltenham General Hospital, Cheltenham, United Kingdom (the), Gastroenterology and Hepatology, [6] Indiana University School of Medicine, Bloomington, United States (the), Gastroenterology and Hepatology.

**Introduction :** Multiple evidence-based guidelines have been produced recently to address the question of how best to perform colonoscopic polypectomy.

**Aim :** We aimed to assess the adherence to these guidelines in 7 countries using an online survey, comparing responses to the standards presented in the 2017 ESGE Colorectal polypectomy guideline.

**Methods :** An institutional review board approved online survey was distributed to the members the gastroenterological and surgical societies of 7 countries via email during July 2017. The survey presented images of colorectal polyps and their colonic location and asked for the polypectomy technique respondents would use in their daily practice. A reminder email was sent after two weeks and the survey closed after 4 weeks.

**Results :** 772 endoscopic practitioners responded to the survey. 707 (91.6%) fully completed the survey and their data was analysed. 162, 155, 131, 102, 60, 53 and 45 respondents were from Australia, USA, UK, Belgium, Canada, Israel and New Zealand respectively. 625/707 (88.8%) were physicians, 9.9% were surgeons and 1.3% were nurse endoscopists. Respondents had a median endoscopy practice duration of 18 years (IQR 10-27). Of two images of <10 mm right sided colonic polyps presented, 51.1% of respondents suggested they would perform cold snare polypectomy in line with guidance. 11.2%, however, suggested cold biopsy forceps and 37.7% suggested endoscopic mucosal resection (EMR) / hot snare polypectomy. Of two large 20 and 45mm transverse colon LSLs with no endoscopic evidence of SMIC, 80.9% suggested EMR, undertaken themselves (48.3%) or referred (32.6%) to another practitioner in line with guidance. 13% would have biopsied the 45mm lesion prior to referral. 9% suggested they would refer these lesions directly to a surgeon. Regarding an image of a large 80mm sigmoid lesion with an endoscopically visible demarcated area consistent with deep submucosal invasive cancer, 51.6% said they would refer to a surgeon in line with guidance whereas 27% suggested they would attempt EMR, 1.4% ESD and the remainder refer the case to another endoscopic practitioner. Comparing the adherence to guidelines throughout all questions, surgeons (50%) were less adherent than physicians (65%), P = <.001, consultants (63%) similar to trainees (67%), P = .122 and those who had undertaken an interventional endoscopy fellowship (63%) similar those who had not (64%), P = .450.

**Conclusions :** These data demonstrate encouraging adherence to international guidelines. The work of international endoscopy societies should focus on encouraging the use of and promoting training in cold snare polypectomy for diminutive polypectomy and techniques for endoscopic imaging of large colorectal polyps.

HIGHER MEAN BOSTON BOWEL PREPARATION SCALE SCORES WITH 1L PEG-BASED NER1006 VERSUS 2L PEG + ASCORBATE : POST HOC ANALYSIS OF A RANDOMISED PHASE 3 CLINICAL TRIAL. R. Bisschops (1), B. Bastens (2), A. Holvoet (3), R. Henrar (4), M. De Vos (5) / [1] University Hospitals KULeuven, Leuven, Belgium, Maag-, darm- en leverziekten, [2] CHC Clinique Saint-Joseph, Liège, Belgium, Service de Gastro-Entérologie, [3] AZ Sint-Lucas Brugge, Assebroek/ Brugge, Belgium, Gastro-Enterologie / Digestieve Oncologie, [4] Norgine NV, Leuven, Belgium, Medical Affairs, [5] UZ Gent, Gent, Belgium, Maag-, darm- en leverziekten.

**Introduction :** Effective colonoscopy requires effective colon cleansing. The cleansing efficacy and safety of NER1006 (PLENVU®), a novel 1L polyethylene glycol (PEG)-based bowel preparation, were assessed versus standard 2L PEG + Ascorbate in the randomised phase 3 clinical trial MORA.

**Aim :** In this post hoc analysis of MORA, cleansing efficacy was assessed using mean Boston Bowel Preparation Scale (BBPS) scores.

**Methods :** In MORA, 849 patients aged 18-85 years were randomised to split-dosing bowel preparation with either NER1006 evening/morning (NER1006 PM/AM), NER1006 morning only (NER1006 AM/AM), or standard 2L PEG + Ascorbate (2L PEG + Ascorbate PM/AM). Overall cleansing success and right colon high-quality cleansing success were the two primary endpoints. For this analysis, cleansing quality was assessed via colonoscopy videos by treatment-blinded central readers using the BBPS (scores 0-9 overall and 0-3 for the right colon segment). Mean scores were calculated.

**Results :** The analysis included 792 patients. Both NER1006 PM/AM and NER1006 AM/AM attained higher mean overall BBPS scores than 2L PEG + Ascorbate PM/AM (6.7 and 6.6 versus 6.3 ;  $P=0.0001$  and  $P=0.0058$ ). Similarly in the right colon, both NER1006 PM/AM and NER1006 AM/AM attained significantly higher mean segmental BBPS scores versus 2L PEG + Ascorbate PM/AM (2.2 and 2.2 versus 2.0 ;  $P=0.0003$  and  $P=0.0134$ ).

**Conclusions :** Both NER1006 dosing regimens, NER1006 PM/AM and NER1006 AM/AM, demonstrated superior mean overall and mean right colon cleansing efficacy versus 2L PEG + Ascorbate. NER1006 is therefore a more effective bowel preparation than 2L PEG + Ascorbate. To our knowledge, NER1006 is the first low volume bowel preparation to demonstrate higher cleansing efficacy than standard 2L PEG + Ascorbate.

LAUNCHING AN ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) PROGRAM IN A EUROPEAN ACADEMIC HOSPITAL : REVIEW OF THE FIRST 28 MONTHS OF EXPERIENCE. A. Lemmers (1), V. Huberty (1), C. Musala (1), A. Bucalau (1), P. Demetter (2), L. Verset (2), J. Van Laethem (1), A. Buggenhout (3), I. El Nakadi (3), J. Devière (1) / [1] Erasme Hospital, Brussels, Belgium, Gastroenterology, Hepatopancreatology and Digestive Oncology, [2] Erasme Hospital, Brussels, Belgium, Pathology, [3] Erasme Hospital, Brussels, Belgium, Abdominal Surgery.

**Introduction :** Launching a professional program of endoscopic submucosal dissection (ESD) for the treatment of early gastrointestinal neoplasia in Western countries is fastidious and debated.

**Aim :** After practicing few ESDs in selected indications, we sought to develop a structured ESD program by sending two advanced endoscopists (AL, VH) for 7 weeks to Japan (2015, Keio Cancer Center, Pr Yahagi) for lesion recognition and ESD learning, watching 95 ESD procedures, and performing 18 ESD on isolated pig stomach models. Further hands-on was performed on living pigs before treating patients. All ESDs were from then concentrated on these 2 operators, starting treating patients following European guidelines in June 2015. Here, we analyse the safety and efficacy of ESD from the beginning of our program.

**Methods :** Clinical and technical data were prospectively collected from June 18<sup>th</sup>, 2015 to October 10<sup>th</sup>, 2017, excluding ESD performed by foreign experts during live demonstrations. R0 resection rate was defined as clear margins (no dysplasia / no adenoma for lateral margins and clear vertical margin). Curative resection was defined following European ESD guidelines. All ESD were performed under general anaesthesia using a 20% glycerol submucosal injection solution and for 98% of them a Dual-knife (Olympus).

**Results :** 85 ESD were performed in 83 patients (41% female ; aged 69(27-98) years old) by two operators (AL, VH). Lesions were located for 28% in the oesophagus (10/24 squamous cell carcinoma), 21% in the stomach, 42% in the rectum and 9% in the colon. En-bloc resection rate was 99%, complete endoscopic resection rate was 98%. R0 resection rate was 68% globally (6% with positive vertical margin ; 2% with carcinoma in the lateral margin). In details, R0 resection rate was 83%, 88% and 57% for oesophageal, gastric and colorectal lesions respectively. Median specimen size was 40 (15-110) mm. Median procedure duration was 120 (IQR 90-180) min. In 91% of cases, there were none or conservatively managed complications. Two patients needed endoscopic hemostasis for delayed bleeding, 4 presented secondary stenosis needing dilations, one urgent surgery for sepsis after colonic perforation. Pathological analysis revealed a carcinoma in 79% of oesophageal lesions (14 pTis/pT1a ; 6 pT1b), in 16% of gastric lesions (2 pT1a ; 1 pT1b) and 30% of colorectal lesions (7 pTis/6 pT1). A neuroendocrine tumor was present in 1 oesophageal, 5 gastric and

2 rectal cases. Curative ESD was obtained in 75% of cases and 14 patients needed complementary oncological surgery with 50% of them having no residual tumor in the organ and negative lymph nodes. When endoscopic follow-up was recommended, data were obtained in 69% of cases with a median of 6 (range 1-24) months length and no recurrence of the lesion observed in 96% of cases. Pathological specimen processing was revised after the first 6 months implementing Japanese standards and increasing the rate of free lateral margins from 47 to 75%. For the rectum, despite a 31% positive (adenoma) lateral margin rate, 100% of patients were free of residual adenoma at the end of endoscopic follow-up, suggesting coagulation artefact effect on the specimen.

**Conclusions :** Nowadays, launching an ESD program in an academic European Center by experienced therapeutic endoscopists, after an observation period in an expert Japanese center, is possible, safe and quick with good results in terms of en-bloc resections and outcomes. Technical and pathological analysis efforts must be done to decrease positive lateral margins.

- G08 -

EUS TODAY AND TOMORROW : WHAT ARE WE DOING TODAY IN REAL PRACTICE IN DIFFERENT COUNTRIES AND WHERE ARE WE GOING? A BELGIAN SURVEY. L. Vandeputte (1), P. Deprez (2) / [1] AZ Sint-Jan Brugge-Oostende, Brugge, Belgium, Gastroenterology - Hepatology, [2] Clin. universitaires St-Luc, UCL, Brussels, Belgium, Gastroenterology – Hepatology.

**Introduction :** A round-table discussion was held at the last EGEUS-congress in Torino, on daily endoscopic ultrasound (EUS)-practice, comparing real-life EUS-practice in different member-societies of the EGEUS.

**Aim :** In order to provide the most recent and accurate data, we conducted a survey for the Belgian Group of Digestive Endosonography (BGDE), on the Belgian daily EUS-practice.

**Methods :** The EGEUS organising committee provided questions, on number of endosonographers per unit, type and numbers of instruments used, type and percentage of examinations, number of procedures per unit, years of experience of the operators, amount of procedures under sedation or anesthesia, availability of nurses dedicated to the EUS-room, presence of an EUS-suite shielded for RX rays, and EUS-training. From November 8 till 24, 2017, we conducted a survey on the Belgian daily EUS-practice. We contacted most of the known EUS-centres in Belgium, partly by phone-call, and mostly by e-mail. A second mail was sent, if an EUS-unit did not respond after 1 week.

**Results :** Thirty-nine of 57 invited units responded (68%), accounting for 71 individual endosonographers. All 7 university hospitals responded. Type of instruments per unit : 22/39 units have Olympus instruments, 14/39 have Pentax, 3/39 use a combination (Olympus+Pentax, Olympus+ Fuji, Olympus+Pentax+Fuji). All units have at least 1 linear probe, 4 units have 2 and 3 units have 3 linear probes. 18/39 units have both a linear and a radial probe. 26/39 units have a rigid rectal probe. 1/39 units has miniprobes. No unit performs only morphological diagnostics. 12/39 units do also fine-needle aspiration (EUS-FNA), while 27/39 do EUS-FNA as well as therapeutic procedures. 24/39 units do all procedures (except rectal procedures) under propofol-sedation (+/- intubation), while in 15 units, propofol-sedation is only in EUS-FNA (2/39 units) or in therapeutic procedures (13/39 units). Type of procedures, given as a mean of all responding units, expressed in percentage : Biliopancreatic procedures (48.6%) of all procedures, upper GI tract (20%), lower GI tract (17.3%), submucosal lesions (10.2%), lung cancer staging (3.5%) and evaluation of portal hypertension (0.4%). In 35.4% of all EUS-procedures, an FNA is performed. Number of units that perform a given number of procedures per year : <300 proc./year in 20 units, 300-500 proc./year in 11 units, 500-1000 proc./year in 6 units and >1000 proc./year in 2 units. Number of units performing therapeutic procedures, per group of procedure-volume : 10/20 units performing <300 proc./year do also therapeutic procedures, 2/11 units in the group of 300-500 proc./year, all (6/6) units in the group of 500-1000 proc./year, as well as all (2/2) units performing >1000 proc./year. Rapid on-site evaluation (ROSE) is available in only 1/39 units. 14/39 units have nurses, dedicated to the EUS-room. 9/39 units have an EUS-suite, shielded for X-rays. In 12/39 units education and/or training is provided. 53/71 Endosonographers have >5 years of experience, 14/71 have 1 to 5 years of experience, and 4/71 have <1 year of experience. Type of training/formation in EUS, received by the responding Belgian endosonographers : <3 months of formal training : 0/71 endosonographers ; 3 to 6 months of formal training : 5/71 ; >6 months of formal training 17/71 ; training during a fellowship 12/71 ; self-taught 3/71 ; training by observing experienced colleagues : 3/71 ; a combination of the above-mentioned : 31/71 endosonographers.

**Conclusions :** EUS is widespread throughout Belgium. Endosonographers are rather experienced, and well-equipped. Biliopancreatic procedures account for almost half of Belgian procedures. In about 35% of EUS-procedures an FNA is performed. There is a diversity in training/formation of Belgian endosonographers : about 50 % have had some formal training of whom 17% had their training during a fellowship, and about 40% had a combination of several types of training. Only a few endosonographers are self-taught. This raises the question to the need for a formal training programme (fellowship? certification?).

INTRADUCTAL CHOLANGIOSCOPY AND PANCREATOSCOPY INDICATIONS AND RESULTS. A. Taha (1), R. Garces Duran (1), T. Moreels (1), R. Yeung (1), T. Aouattah (1), M. Komuta (2), H. Piessevaux (1), P. Deprez (1) / [1] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Hepato-Gastroenterology Department, [2] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Pathology Department.

**Introduction :** Cholangiopancreatography allows direct endoscopic visualization of the biliary and pancreatic ductal systems. The SpyGlass Direct Visualization System is a single-operator intraductal device used in diagnostic procedures such as evaluation of indeterminate biliary stricture, intraductal papillary mucinous neoplasms of the pancreas, and therapeutic purposes such as intraductal lithotripsy for difficult biliary or pancreatic duct stones.

**Aim :** Retrospective review of indications, clinical utility and safety of intraductal cholangioscopy and pancreatoscopy,

**Methods :** A retrospective review of a prospective patients' database who underwent direct cholangiopancreatography in our tertiary referring center between 2007 and 2017

**Results :** A total of 78 consecutive patients were included with direct cholangioscopy in 71 patients, and pancreatoscopy in 7 patients. The major indications of cholangioscopy was the evaluation of indeterminate strictures (n = 35 (49.3%)), followed by difficult stones management (n = 24 (33.8%)), indeterminate filling defects (n=7 (9.8%)), selective cannulation of the right intrahepatic duct (n=1 (1.4%)), suspicion of papillomatosis (n=1(1.4%)), extension of papillomatosis before surgery (n=2 (2.8%)), intrahepatic migrated stent (n=1 (1.4%)), dilated intrahepatic ducts with no obvious cause (n=1 (1.4%)). The indication of pancreatoscopy was suspicion of IPMN (n=5 (71.4%)) and migrated intraductal stent (n=2 (28.6%)). Overall accuracy of visual findings for indeterminate stenosis in the cholangioscopy group was 88.56% with a sensitivity of 91.67% a specificity of 86.96% positive predictive value (PPV) of 78.57% and negative predictive value (NPV) of 95.23%. The sensitivity and specificity for indeterminate filling defects were 100%. The sensitivity and specificity of pancreatoscopy in detecting IPMN were 100%. 43 patients underwent SpyGlass-directed biopsy (39 biliary and 4 pancreatic), and the specimens procured from 42 patients (97.67%) were found adequate for histologic evaluation. Overall technical success rate of therapeutic procedures such as laser lithotripsy, selective guidewire insertion or migrated stent removal was 100% (26/26) in the cholangioscopy group however failure of extraction of the pancreatic stent was encountered in the pancreatoscopy group. Finally, adverse events were sepsis (10), pancreatitis (1), abdominal pain (1), cardiovascular event (1) and perforation with sub capsular abscess (1)

**Conclusions :** Intraductal procedures carry a great value in diagnostic as well as therapeutic procedures in pancreatobiliary diseases, as well as the tissue sampling is adequate for histologic diagnosis. It is a feasible and safe procedure now used in various indications.

ERCP IN PATIENTS WITH ROUX-EN-Y ALTERED ANATOMY AND INTACT VATER'S PAPILLA. E. Akpokavie (1), A. Slimani (2), P. Deprez (1), H. Piessevaux (1), T. Moreels (1) / [1] Cliniques universitaires Saint-Luc, Brussels, Belgium, Hépatogastroentérologie, [2] Cliniques universitaires Saint-Luc, Brussels, Belgium, Cardiologie.

**Introduction :** Endoscopic retrograde cholangiopancreatography (ERCP) in patients with Roux –en-Y surgically altered anatomy and intact Vater's papilla is a challenging procedure, even when using device-assisted enteroscopy (DAE).

**Aim :** To define factors influencing ERCP success in patients with short- and long-limb Roux-en-Y altered anatomy and intact Vater's papilla.

**Methods :** Retrospective analysis of patient records with Roux-en-Y altered anatomy and intact papilla who underwent DAE-ERCP at our centre from 2008 to 2017. The primary end points were defined as success by reaching the papilla, diagnostic success by opacification of the biliopancreatic ducts and therapeutic success by the treatment of the underlying biliopancreatic disease. The secondary endpoints were defined as the determination of factors playing a role in procedure's success, adverse events and patient's follow-up.

**Results :** A total of 65 patients with Roux-en-Y altered anatomy and intact papilla were identified. Patients were divided into two groups : gastric bypass group (long-limb Roux-en-Y) with 39 patients for a total of 44 procedures, and total gastrectomy group (short-limb Roux-en-Y) with 26 patients for a total of 36 procedures. ERCP procedures were performed under general anesthesia and CO2 insufflation, with 3 different, 200 cm long, single balloon enteroscopes (Olympus, Tokyo, Japan : XSIF-180JY, SIF-Q180 and SIF-Y0011) according to availability and operator's preference. The male/female ratio was 36%/64% for the gastric bypass group with a mean age of 50 ±10 years, and 58%/42% for the total gastrectomy group with a mean age of 70± 12 years. Vater's papilla was reached in 70% of the cases in the gastric bypass group and 83% of the cases for the total gastrectomy group (P>0.05 univariate analysis). Among those patients, diagnostic success was achieved in 90% and 83% respectively, while therapeutic success was reached 73% an 81% respectively (per protocol analysis). Type of endoscope (SIF-Y0011 with passive bending segment) and operator's experience were two factors influencing procedure's success (P<0.05 in uni- and multivariate analysis). Few



adverse events were encountered (11,2%), the main one being post-ERCP pancreatitis. No major procedure-related complications were observed.

**Conclusions :** ERCP in patients with Roux-en-Y altered anatomy with intact papilla remains a challenging procedure, even with the development of device-assisted enteroscopy. Short-limb Roux-en-Y, the SIF-Y0011 single-balloon enteroscope with a passive bending segment and the operator's experience are factors influencing procedure's success.

- G12 -

ENDOSCOPIC TREATMENT OF POSTOPERATIVE FISTULAS IN THE UPPER GASTROINTESTINAL TRACT. R. Tessa (1), B. Navez (2), M. Thoma (2), Y. Deswysen (2), P. Deprez (1), H. Piessevaux (1), T. Moreels (1) / [1] Cliniques universitaires Saint-Luc, Brussels, Belgium, Hépatogastroentérologie, [2] Cliniques universitaires Saint-Luc, Brussels, Belgium, Service de Chirurgie et Transplantation abdominale.

**Introduction :** Postoperative fistulas after upper gastrointestinal tract surgery occur in 2-6%. Fistula closure can be achieved by radiological, endoscopic or surgical intervention alone or in combination. However, there is no standardized treatment algorithm to deal with the problem.

**Aim :** The purpose of the study is to identify and evaluate the different therapeutic endoscopic options used throughout the years of the study period in correlation with the type of surgery and, their final clinical success and adverse event rate. The current study focusses upon the endoscopic treatment of postoperative fistulas in the upper gastrointestinal tract.

**Methods :** Single centre retrospective analysis of patients who underwent endoscopic treatment of postoperative upper gastrointestinal tract fistulas between 2006 and 2017.

**Results :** 27 patient files were studied : 12 (44%) men aged 63±4 years and 15 (56%) women aged 51±3 years. 63% of the patients were referred from another hospital. Surgical procedures were oncological (n=11 ; 41%) and bariatric (n=16 ; 59%). Fistulas occurred at the level of an anastomosis or at the level of a suture line. Fistula size was small (n=7 ; 26%) when the endoscope could not pass, medium size (n=8 ; 30%) when the endoscope could pass and large (n=12 ; 44%) in case of a large cavity. Overall endoscopic fistula closure rate was 67%. Endoscopy failed in 30%, needing redo surgery and 4% was lost to follow-up. In total 20 over-the-scope clips were used in 14 (52%) patients with a definitive fistula closure rate of 50%. In total, 23 fully covered self-expandable metal stents (SEMS) were used in 15 (56%) patients with a 53% closure rate. However, SEMS were complicated by stent migration (47%), stenosis (33%) and perforation (7%). Finally, internal fistula drainage with a total of 17 plastic double pigtail stents was used in 7 (26%) patients with a 71% closure rate, without adverse events. Hemostatic clips and fistula plugs never led to fistula closure. Total duration of endoscopic therapy was 72±9 days before complete fistula closure, with a mean of 3,3±0,4 endoscopic procedures per patient. Fistula closure rate was dependent on time delay between fistula diagnosis and endoscopic treatment (19±7 days for successful closure vs 99±40 days for failed closure, P<0.05), whereas it was not dependent of fistula size (71% closure rate of small fistulas vs 75% closure rate of medium size fistulas vs 64% closure rate of large fistulas, p>0.05).

**Conclusions :** Endoscopic treatment of postoperative upper gastrointestinal fistulas is effective in 2/3 of patients, often needing multiple endoscopic procedures. Internal fistula drainage using double pigtail stents seem more effective than over-the-scope clips or self-expandable metal stents. Closure rate depends on a shorter delay between fistula diagnosis and treatment, but not on the fistula size.

- G13 -

IS LUGOL NECESSARY FOR ENDOSCOPIC RESECTION OF SQUAMOUS CELL NEOPLASIA OF THE ESOPHAGUS? A. Ferreira (1), C. Mouradides (2), E. Robles (2), R. Yeung (2), R. Duran (2), C. Snauwaert (2), A. Jouret-Mourin (3), H. Piessevaux (2), P. Deprez (2) / [1] Hospital Beatriz Ângelo, Loures, Portugal, Gastroenterology, [2] Cliniques universitaires Saint-Luc, Brussels, Belgium, Service d'hépatogastroentérologie, [3] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Service d'Anatomie Pathologique.

**Introduction :** Mucosal chromoendoscopic enhancement with Lugol solution improves the sensitivity for squamous cell carcinoma (SCC) diagnosis. However, it is time-consuming and associated with increased esophageal motility which may difficult endoscopic resection. Narrow band imaging (NBI) is easier to use and has been shown to be useful for SCC diagnosis.

**Aim :** Our aim was to assess the effectiveness of Lugol when compared to NBI for lesion demarcation in esophageal SCC.

**Methods :** Retrospective observational cohort study of patients with esophageal SC neoplasia submitted to en-bloc EMR or ESD between 1999 and 2017 in an academic center. Patient demographic, lesion (size, morphology, histology and complete resection), procedural characteristics (endoscopist, scope model, lugol usage and resection technique) and follow-up data were collected from electronic records. Two groups were defined based on lugol usage. The primary outcome was complete lateral resection (CLR). Multivariate regression was used to adjust to potential confounders.

**Results :** A total of 101 patients had 132 lesions. Mean age was 65±9 years and 65.3% were male. The lesions were in the middle (60.8%) and lower (20.8%) esophageal thirds. Mean diameter was 29.6±16.8 mm with Paris morphology 0-IIb in 42.3% and 0-IIa in 29.3%. Lugol was used in 51.2%, submucosal dissection in 92.3% and 78% had invasive histology. CLR rate was complete for invasive carcinoma in 90.9% in Lugol group and 95.2% in NBI group (OR0.500 ; IC0.119-2.092 ; p=0.343) and 65.2% vs 66.7% (p=0.856) for dysplasia complete lateral resection. The effect remained non-significant even after adjusting for potential confounders. There were 2 relapses with lugol and 1 in NBI group. In an exploratory analysis for predictive factors of CLR (scope, previous local treatment, lesion morphology, diameter, location and EMR technique), the only significant association was with the scope model (p=0.005).

**Conclusions :** Mucosal inspection with lugol before EMR of esophageal SCC was not associated with increased CLR when compared to NBI.

- G14 -

MANAGEMENT OF LEAKS AFTER BARIATRIC SURGERY BY DOUBLE-PIGTAIL STENT INSERTION. A SINGLE-CENTER EXPERIENCE. G. Burnet (1), Y. Hoebeke (2), F. Corbisier (2), P. Warzée (1) / [1] Grand Hopital de Charleroi, Charleroi, Belgium, Service d'hépatogastro-entérologie, [2] Grand Hopital de Charleroi, Charleroi, Belgium, Service de chirurgie digestive.

**Introduction :** Bariatric surgery is a major treatment option for morbidly obese patient. In Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), most common complications, fistulae and leaks, occur in 0–8.3% and usually appear within the first week after surgery. Implantation of a partially or fully self-expandable metallic stent (SEMS) is a classical therapeutic option but is linked with complications such as migration or haemorrhage, perforation or stricture after removal and often badly tolerated. Other, more recent endoscopic options have been proposed for closing leaks such as internal drainage using pigtail loops placed inside the fistula and have since shown efficacy.

**Aim :** The aim of this retrospective analysis is to confirm the efficacy of double-pigtail stenting whether or not in combination with SEMS, in first-line or in second-line treatment as well as their overall tolerance and complication rate.

**Methods :** Between May 2014 and May 2017, we retrospectively analysed a total of 10 patients (8 male and 2 women) aged between 26-78 years, who presented leakage following RYGB (4/10) or SG (6/10) and who underwent endoscopic treatment by means of a double-pigtail stenting. Mean BMI before bariatric surgery was 40.9, ranged between 36 and 47. Three patients had already undergone primary bariatric surgery (Mason's gastropasty) before RYGB or SG. Endoscopy was performed using Olympus Endoscope GIF XTQ140. Drainage was achieved by placing two 3 to 5cm long 7Fr diameter double pigtails plastic stents (9/10) or a combination of 7Fr and 10Fr double pigtails (1/10) (Boston Medical).

**Results :** Fistula and collections occurred between 1 to 10 days after surgery with abdominal pain and/or fever as main symptoms for 9 patients. One asymptomatic patient underwent radiological investigations to confirm fistula because of abnormal amount of liquid in the percutaneous drain. Presence of leakage was confirmed radiologically (CT scan and/or upper GI swallow study) for 9 patients and by upper endoscopy in 1 patient. Surgical drainage of the collections had been performed in half of the patients before endoscopic intervention. Seven patients out of ten underwent trans-fistulary drainage as first-line treatment option, from which, two had a combination of both SEMS and double-pigtails. The other three patients had already been subjected to a treatment with SEMS before double-pigtail stenting. Endoscopy was performed, in average, 4.7 days after the leaks were diagnosed (range 1 to 8 days). Clinical and radiological success, defined as resolution of symptoms and of the leaks by either upper GI contrast swallow study or CT scan, was achieved in 9/10 patients after double-pigtail placement. Failure was observed in one patient who had first an endoscopy with double-pigtail placement followed by a second drainage attempt with another insertion of two double-pigtails. As the leakage remained, the stents were finally removed and replaced by a full covered SEMS which allowed symptom and leakage resolution. Pigtails were well tolerated and removed in most patients after 1-3 months (7/9). In two patients, stents migrated spontaneously. No complication was reported with double-pigtail placement. In one patient, subacute upper GI hemorrhage occurred due to oesophageal erosions secondary to SEMS placement. Oral nutrition could be resumed the day after endoscopy. Hospital stay after successful treatment with double pigtail was 12.1 days (N=2-32 days).

**Conclusions :** Double-pigtail stent use in first-line and second-line treatment for postoperative leaks after bariatric surgery is effective and safe. It is a well-tolerated procedure associated with an early resolution of symptoms and leaks.

- G15 -

ENDOSCOPIC MANAGEMENT OF BILIARY LEAKS : A SYSTEMATIC REVIEW. K. Vlaemynck (1), P. Hindryckx (1) / [1] University Hospital Gent, Belgium, Gastroenterology.

**Introduction :** Biliary leaks most commonly occur as a surgical complication, especially after laparoscopic cholecystectomy with a rate of up to 1%. The first-line treatment is endoscopy with retrograde cholangiopancreatography

(ERCP) to decrease the transpapillary pressure gradient, allowing preferential flow of bile into the duodenum rather than extravasation at the leak site. This can be achieved by a variety of endoscopic techniques including biliary sphincterotomy alone, biliary stenting with or without sphincterotomy and nasobiliary drainage with or without sphincterotomy. To date, no systematic review has been performed to determine the optimal endoscopic approach to biliary leaks.

**Aim :** The aim was to systematically review the benefits and harms of treating biliary leaks with different endoscopic techniques to inform clinical practice.

**Methods :** We searched MEDLINE/PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Scopus, Google Scholar and Web of Science. Selection criteria were article type (randomized clinical trials (RCT), case-control studies and prospective cohort studies) and topic (comparison of different endoscopic techniques for the management of biliary leaks). Studies were considered from journal articles and abstracts in any language and date of publication. Trials for inclusion were identified with title/abstract screening and subsequently, full-text screening. Risk of bias in the RCTs was assessed with the Cochrane Risk of Bias tool, whereas methodological evaluation of the prospective cohort studies was performed with the Newcastle-Ottawa scale. Data on study design, patient demographics, endoscopic treatment and outcomes were extracted. Odds ratios or mean differences were recalculated. 95% confidence intervals were calculated with the Wilson score method.

**Results :** The search strategy identified 5085 references of which eleven studies with a total of 660 participants fulfilled the inclusion criteria. Four randomized clinical trials (n=183) and seven prospective cohort studies (n=477) were included. Two RCTs compared sphincterotomy versus stenting. One RCT investigated the need for an additional sphincterotomy in the case of stenting. The last RCT was a comparative study of 7 French (Fr) versus 10 Fr stents. All RCTs had a high risk of bias. Four prospective cohort studies dealt with biliary leaks after cholecystectomy and one with different types of leaks. The other two studies included biliary leaks after hepatic resection and liver transplantation. The interventions performed were heterogeneous. Five of the seven prospective cohort studies were rated with high methodological quality and the other two with medium quality. Comparing sphincterotomy with stenting, there was a non-significantly lower risk of failure in the stenting group (ten studies ; n=284 ; success rate 94.4% versus 90.5% ; OR 0.56 ; 95% CI 0.22 to 1.42). Similarly, a non-significantly lower risk of failure was encountered in the combination group (stenting with sphincterotomy), compared to sphincterotomy alone (n=414 ; 94.5% versus 90.5% ; OR 0.55 ; 95% CI 0.26 to 1.18). Stenting with sphincterotomy was equally effective as stenting alone (n=382 ; 94.5% versus 94.4% ; OR 0.98 ; 95% CI 0.39 to 2.50). There were 0/20 complications in the sphincterotomy group compared with 9/110 (8.2%) and 2/88 (2.3%) in the stenting and combination groups, respectively (six studies). There was a significantly lower risk of failure in the leak bridging stent group compared with using short transpapillary stents (four studies ; n=164 ; 97.5% versus 82.6% ; OR 0.12 ; 95% CI 0.03 to 0.49). Comparing small-diameter (> 10 Fr) with large-diameter ( $\geq$  10 Fr) stents, there was a non-significantly lower risk of failure in the large-diameter stent group (eight studies ; n=331 ; 97.8% versus 95.4% ; OR 0.47 ; CI 0.12 to 1.75).

**Conclusions :** The reported clinical success in treating biliary leaks with sphincterotomy, stenting or the combination of both is high. There is no statistical difference between these interventions with respect to clinical success, although the bulk of evidence suggests a slightly reduced risk of failure when stenting is performed. Systematically combining stenting with sphincterotomy appeared to have no added value compared with stenting alone. Large-diameter stents that bridge the biliary leak (if possible) seem preferable.

- G16 -

EUS-GUIDED BILIARY DRAINAGE AND EUS-GUIDED RENDEZVOUS TECHNIQUE WHEN ERCP FAILS. A SINGLE CENTER COHORT DATABASE. D. De Wulf (1), L. Desomer (1), F. Baert (1) / [1] AZ Delta, Roeselare, Belgium, MDL.

**Introduction :** EUS-guided biliary drainage and EUS-guided rendezvous technique are increasingly used as an alternative therapeutic modality to percutaneous transhepatic biliary drainage in patients who fail ERCP.

**Aim :** To assess the efficacy, safety and results of EUS-guided biliary interventions.

**Methods :** Single operator retrospective cohort study of all patients who underwent an EUS-guided biliary intervention between January 2017 and November 2017.

**Results :** In 2017 a total of 13 patients (8 F, 5 M) with a median age of 75 years (range 57 - 94) underwent an EUS-guided biliary intervention in our institution. All patients had at least one failed or impossible (duodenal obstruction) ERCP attempt. 4 Cases were for a benign indication (stones), 9 cases for a malignant distal or mid bile duct obstruction. Successful endoscopic biliary drainage was achieved in all patients (13/13). All but one procedures were done from the bulbar access with a 19-gauche needle. When possible, a guide wire has placed transpapillary (successful in 10 out of 12 cases with access from the duodenal bulb). In 4 cases a biliary stent has placed in an antegrade way, in 6 cases we converted to a rendezvous ERCP. The guide wire could not pass the tumoral obstruction in two cases, so biliary drainage was achieved with a choledochoduodenostomy using a self-expanding metallic stent. One case needed drainage with hepaticogastrostomy because of tumoral invasion of the pyloric/duodenal bulb region. There was no procedure related

mortality. In the case of hepaticogastrostomy there was a pneumoperitoneum needing needle desufflation and a bile peritonitis needing a 3 days course of IV antibiotics. There were no complications in the 12 cases where the common bile duct was accessed via the duodenal bulb. There were no re-interventions needed. In 3 cases we performed a duodenal stenting at the same time.

**Conclusions :** EUS-guided biliary drainage and EUS-guided rendezvous technique in case of failed or impossible ERCP are safe and feasible techniques for biliary drainage. When possible an internal rendezvous or choledochoduodenostomy seems to be preferred above hepaticogastrostomy because of the lower complication ratio.

- G17 -

**PERSISTENT PAIN AFTER COLONIC ENDOSCOPIC MUCOSAL RESECTION : PREDICTORS, A MANAGEMENT ALGORITHM AND OUTCOMES.** L. Desomer (1), D. Tate (2), H. Awadie (2), L. Pillay (2), G. Ahlenstiel (2), M. Bourke (2) / [1] AZ Delta, Roeselare, Belgium, Gastroenterology and Hepatology, [2] Westmead Hospital, Sydney, Australia, Gastroenterology and Hepatology.

**Introduction :** Endoscopic mucosal resection (EMR) of large ( $\geq 20$  mm) laterally spreading colonic lesions (LSL) is safe, effective and superior to surgery. This advantage is based on a day stay model of care, however the most common adverse event is abdominal pain and this is a major impediment to its efficiency. No prospective data exist on the optimal selection of analgesics, the necessary recovery period or the triggers that should alert the practitioner to a more serious trajectory and the need for escalation of care.

**Aim :** We aimed to characterise potential predictors for PP and develop a simple and effective management algorithm for patients with PP based on the need for analgesics in recovery.

**Methods :** Data on consecutive patients with a LSL referred for EMR at a single, tertiary referral centre were included. Patient and lesion characteristics and peri-procedural data were prospectively collected. Standard post EMR care included 2 hours in first stage recovery followed by 1 hour in 2nd stage recovery where clear fluids were given and discharge after if the patients were well. Persistent post-procedural pain (PP) was graded from 0 to 10 using a Visual Analogue Scale (VAS). If PP occurred  $>5$  minutes, 1 gram of acetaminophen was administered parenterally and outcomes were monitored. If pain settled the patient was transferred to second stage recovery after medical review. PP  $>30$  minutes lead to clinical review and upgrade of analgesics to fentanyl, with a starting dose of 25 micrograms (mcg) up to a maximum of 100 mcg. Investigations, admission and interventions for PP were recorded.

**Results :** 166 patients with 166 lesions were included between February and April 2017. 34/166 (20.5%) of patients had PP requiring intervention (median VAS 5, IQR 3-6). 27/34 (79.4%) had resolution of pain with acetaminophen only and were ultimately discharged without sequelae. 7/34 patients (20.6%) required fentanyl (25 mcg of fentanyl in 3 patients, 50 mcg in 1, 75 mcg in 1 and 100 mcg in 2). A CT scan was performed in the 2 patients requiring 100 mcg of fentanyl, showing serositis in 1 patient and no abnormalities in the other. Both patients were admitted and managed conservatively (discharge day 6 and 2 respectively). The other 5 patients were discharged home on the same day after extended recovery. Predictors of PP were lesion size  $\geq 45$  mm ( $P=.003$ ), Paris classification ( $P=.022$ ) and intra-procedural bleeding requiring endoscopic control (IPB,  $P=.042$ ). Lesion size  $\geq 45$ mm and IPB were also independent variables on multivariate analysis with an odds ratio of 2.8 (95% confidence interval 1.3-6.3,  $p=.012$ ) and 2.3 (95% confidence interval 1.0-5.2,  $p=.042$  respectively).

**Conclusions :** Pain after EMR occurs in 20% of patients and is associated with larger lesion size and intraprocedural bleeding requiring endoscopic control in a multivariate analysis. If pain subsides after parenteral acetaminophen and does not recur the patient can be safely and confidently discharged to the step-down recovery area and after medical review allowed to leave hospital. PP despite parenteral acetaminophen heralds a more serious scenario and imaging should be considered when stronger analgesics do not relieve the pain.

- G18 -

**INTRADUCTAL ABLATION BY RADIOFREQUENCY PROBE OR CYSTOSTOME DURING ENDOSCOPIC AMPULLECTOMY MAY REDUCE THE LONG-TERM RECURRENCE RATE.** E. Perez-Cuadrado (1), H. Piessevaux (1), T. Moreels (1), A. Jouret-Mourin (2), P. Deprez (1) / [1] Saint-Luc University Hospital, Brussel, Belgium, Gastroenterology, [2] Saint-Luc University Hospital, Brussel, Belgium, Pathology.

**Introduction :** The feasibility and outcome of endoscopic resection in ampullary tumours with intraductal growth remains unclear.

**Aim :** To analyse the feasibility and outcomes of intraductal ablation in ampullary tumours.

**Methods :** All consecutive patients from 2000 to 2016 who underwent an endoscopic snare ampullectomy with a 6-month minimum follow-up were included. Factors related to recurrence were collected and analysed. Intraductal

ablation by wire guided radiofrequency or wire-guided 6, 8 or 10 Fr cystostome in cases of intraductal growth was evaluated in terms of safety and effectiveness.

**Results :** Seventy-three patients (58±14 y, 49.3% men, 34.2% FAP) presented with an indication for endoscopic ampullectomy. Median tumour size was 20mm (range : 8-80mm) and 79.5% of patients were symptomatic at diagnosis. EUS detected intraductal infra- (n=13) or supra-centimetric (n=3) ingrowth in 21.9% of cases (8 biliary and pancreatic, 3 pancreatic, 5 biliary). Ablation was performed by RFA in 2 patients and 6-10French cystostome in 14, followed by pancreatic and biliary stenting. There were no recurrences observed in these patients. In the full group, en-bloc resection was achieved in 34 lesions (46.6%, 28 R0-status) in a median of 1 (1-5) session. High-grade dysplasia was observed in 27 cases (37%) and adenocarcinoma in 6 (8.2%). Twelve patients experienced recurrence (16.4%) and 3 required surgery (median follow-up : 23 months). Familial adenomatous polyposis was not associated with recurrence (20% vs. 14.6%, p=0.553). By multivariate logistic regression analysis, ≥2 endoscopic sessions was the only factor associated with recurrence (OR :7.60 [95%CI :1.869–30.896],p=0.005). Complications (19.2%) were bleeding (n=6), pancreatitis (n=3), perforation (n=3) and biliopancreatic stenosis (n=2). There were no differences in the complication rate in patients with/without intraductal ablation (18.8% vs. 19.3%, p=0.961)

**Conclusions :** Intraductal biliary and pancreatic ablation is feasible, safe and may reduce the recurrence rate in ampullary tumours with intraductal ingrowth.

## BELGIAN MICROBIOTA AND HELICOBACTER STUDY GROUP

- H01 -

HELICOBACTER PYLORI ERADICATION : USE OF THE PDCA CYCLE TO ACHIEVE REAL WORLD DATA IN THE GHENT REGION AND TO IMPROVE ERADICATION OUTCOME. D. Baert (1), P. Burvenich (2), C. Van Steenkiste (1), E. Monsaert (3), E. Vanderstraeten (3), K. Rasquin (3), P. Dewint (3), N. Stoens (1) / [1] AZ Maria Middelaes, Ghent, Belgium, Gastro-enterology, [2] AZ Maria Middelaes, Ghent, Belgium, gastroenterology, [3] AZ Maria Middelaes, Ghent, Belgium, Gastro-enterology.

**Introduction :** The PDCA (Plan-Do-Check-Act) cycle is a validated quality management tool to improve processes and outcome in business and to facilitate change management. It can also be used in medicine for quality of care management, as is shown in the following. In 2014, we planned (Plan) to evaluate the actual performance of our department in Helicobacter Pylori (Hp) eradication according to the Maastricht IV/Florence Consensus Report 2012. Therefore, a monocentric retrospective data collection was conducted (Do). Data from 285 Hp positive patients, diagnosed by gastric biopsies or C13 breath testing in the period 2013-2014, were reviewed. The results (Check) demonstrated 3 major findings : 1/ Only 55% of the patients (158/285) completed their planned control breathing test after eradication therapy. 2/ First line therapy with PPI-Amoxi-Clarithro for 7 days resulted in 72% success rate (114/158 patients). 3/ The overall eradication rate after first, second and third line therapy was only 46 % (131/285) on an intention to treat analysis. Therefore, our group decided to adjust our Hp eradication regimen and our communication strategy to tackle the two major bottlenecks (Act).

**Aim :** To achieve real world data in the Ghent region and to improve eradication outcome of Hp. To emphasize the use of the PDCA cycle for quality management in medicine.

**Methods :** In the second cycle, we planned (Plan) to implement this new strategy throughout our department and to evaluate outcome. Hence, a prospective trial (period 2015) was started (Do). 120 consecutive Hp positive treatment naive patients were treated with sequential therapy in first line and a bismuth-containing quadruple therapy (Tryplera regimen) in second line. In addition, a communication strategy to the different stake holders was adopted, including (1) an additional questionnaire, information and visual storytelling to the patient, (2) a standardized report to the general practitioner and (3) a checklist for the participating gastro-enterologists.

**Results :** Results (Check) : Eighty percent (96/120) of the patients attended their planned control breathing test after eradication. The eradication rate after first line treatment was 82% (79/96 patients). Seventeen patients received second line therapy and 12 of these 17 patients underwent a second control breathing test. All 12 patients were eradicated. Sequential therapy was well tolerated and the uptake of the full 10 days regimen complete. The overall intention to treat eradication was 76 % (91/120). As a consequence, we validated the new Hp policy as standard of care throughout our department (Act).

**Conclusions :** Changing our Hp eradication policy led to a significant increase in the overall eradication rate (with negative control test) from 46 to 76 % on an intention to treat basis. Particularly, intensifying the communication towards the general practitioner (standardized protocol) and the patient (health literacy by visual story telling) had strong impact on outcome. This is an example of two consecutive PDCA cycles leading to a better outcome of care and emphasizes the benefit of quality improvement methods in daily clinical medicine.

- H02 -

FACTEURS ASSOCIES A LA SEROPREVALENCE DE L'HELICOBACTER PYLORI A BUKAVU, VILLE PROVINCIALE DE L'EST DE LA RD CONGO. P. Ngoma (1), B. Matungo (2), D. Lupande (3), C. Malu (4), P. Kengibe (1), A. Tshimpi (1), R. Fiasse (5), H. Dahma (6), E. Tshibangu (7), J. Kabinda (8), B. Longo-Mbenza (9), Y. Mienje (6) / [1] Cliniques Universitaires de Kinshasa (CUK), Kinshasa, Congo, Gastroentérologie, [2] Hôpital Provincial Général de Référence de Bukavu, Bukavu, Congo, Médecine, [3] Hôpital Provincial Général de Référence de Bukavu, Bukavu, Congo, Microbiologie, [4] Cliniques Universitaires de Kinshasa (CUK), Kinshasa, Congo, Médecine Interne, [5] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Gastroentérologie, [6] CHU Brugmann, Brussels, Belgium, Microbiologie, [7] Oita University, Yufu, Japan, Faculté de médecine, [8] Université Catholique de Bukavu, Bukavu, Congo, Faculté de médecine, [9] Cliniques Universitaires de Kinshasa (CUK), Kinshasa, Congo, Cardiologie.

**Introduction :** L'infection par Helicobacter pylori (H. pylori) est très répandue en Afrique sub-Saharienne. Cependant, il n'y a actuellement pas de données disponibles sur sa prévalence dans la ville de Bukavu à l'Est de la République Démocratique du Congo

**Aim :** L'objectif de cette étude était de déterminer la séroprévalence et les déterminants de l'infection par H. pylori à Bukavu

**Methods :** Il s'agissait d'une étude transversale réalisée dans la population les grappes des 3 communes de la ville de Bukavu. Le test ELISA «Anti H. pylori (IgG)», EUROIMMUN® a été utilisé pour le diagnostic. Les paramètres d'intérêt étaient les facteurs socio-démographiques, la consommation des boissons alcoolisées et du tabac et les symptômes gastro-intestinaux.

**Results :** Au total, 331 personnes âgées de 10 à 86 ans ont été incluses et 294 personnes, soit 89% (84,9-92,2) avaient une sérologie positive à H. pylori. La séroprévalence était de 86,2 % chez les hommes et de 83,2 % chez les femmes. La consommation d'alcool multiplie par plus 5 le risque de séropositivité (OR=5,73 (1,89-17,41) ; p=0,002) alors que le niveau d'étude nul le réduit de plus 50% (OR=0,41 (0,18-0,97) ; p=0,043) et la consommation de tabac de plus de 80% (OR=0,16 (0,04-0,65) ; p=0,010).

**Conclusions :** La séroprévalence de H. pylori est élevée à Bukavu. Elle est comparable à celle trouvée dans la plupart des pays en voie de développement. Des efforts doivent être entrepris pour mettre en œuvre les mesures de prévention contre cette bactérie par une éducation à la santé.

**ABERRANT MUC1 AND MUC13 EXPRESSION IN ASSOCIATION WITH PAR POLARITY COMPLEX AND VIP DYSFUNCTION IN A COLITIS T CELL TRANSFER MODEL.** T. Breugelmans (1), H. Van Spaendonk (1), M. Heylen (1), J. De Man (1), 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.

**Introduction :** There is emerging evidence that loss of the gastrointestinal mucosal barrier integrity is a significant contributor to the pathophysiology of inflammatory bowel disease (IBD). Mucins represent the major components of the mucus barrier and inappropriate overexpression of transmembrane mucins can affect the barrier integrity by disrupting cell polarity and cell-cell interactions resulting in tight junction dysfunction (Kufe, 2009). Aberrant expression of Muc1, Muc4 and Muc13 in particular is observed in colonic tissue samples of IBD patients (Sheng et al., 2011 ; Vancamelbeke et al., 2017). Nevertheless, the role of these mucins in mucosal barrier disruption in IBD still remains elusive.

**Aim :** In this study, we investigated the expression patterns of transmembrane mucins and the mediators involved in barrier homeostasis during the progression of colitis in mice.

**Methods :** Colitis was induced in immunocompromised SCID mice by the adoptive transfer of CD4+CD25-CD62L+ T cells from the spleens of BALB/c donor mice. At 2, 4 and 6 weeks post-transfer, animals were sacrificed and colonic tissue was collected for RNA and protein analysis of membrane-bound mucins (Muc1, Muc4 and Muc13), polarity proteins and the vasointestinal polypeptide (Vip). This latter protein is implicated in the regulation of tight junction and mucin expression (Hokari et al., 2005). Apoptotic cells in tissue sections were detected using a Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay.

**Results :** Our data showed that Muc1 was significantly increased after 4 weeks of colitis as compared to healthy control mice. Interestingly, a significant decrease of Muc13 expression was seen during acute colitis (2 weeks), whereas a remarkable turnover in expression was noted during chronic colitis (4-6 weeks). Normal intestinal MUC13 expression plays crucial roles in epithelial proliferation, differentiation and apoptosis but inappropriate overexpression of this mucin could lower the level of protection. Indeed, a higher number of apoptotic cells was observed in tissue of chronic colitis-induced mice. Furthermore, the polarity proteins Par3 and aPKC as well as Vip were significantly reduced in expression from week 2 onwards suggesting a disturbance in cell polarity.

**Conclusions :** The findings of this study highlight a potential role for Muc1 and Muc13 in mucosal barrier disruption in IBD and the underlying mechanisms involved necessitate further investigation. References Hokari et al., 2005. Vasoactive intestinal peptide upregulates MUC2 intestinal mucin via CREB/ATF1. *Am J Physiol Gastrointest Liver Physiol*, 289 : G949-59. Kufe, D., 2009. Mucins in cancer : function, prognosis and therapy. *Nature Reviews. Cancer*, 9(12) : 874-85. Sheng et al., 2011. The MUC13 cell-surface mucin protects against intestinal inflammation by inhibiting epithelial cell apoptosis. *Gut*, 60(12) : 1661-70. Vancamelbeke et al., 2017. Genetic and Transcriptomic Bases of Intestinal Epithelial Barrier Dysfunction in Inflammatory Bowel Disease. *Inflamm Bowel Dis*, 23(10) : 1718-1729.

**TRANSCRIPTOMIC PROFILE OF INFLAMED COLONIC BIOPSIES FROM NEWLY DIAGNOSED CROHN'S DISEASE AND ULCERATIVE COLITIS PATIENTS DEPEND ON THE AGE AT DIAGNOSIS.** S. Verstockt (1), B. Verstockt (2), J. Van Bouwel (3), W. Meert (3), A. Cortes Calabuig (3), V. Brys (3), V. Ballet (4), E. Glorieus (5), M. De Decker (6), G. Van Assche (4), P. Hindryckx (7), M. Ferrante (4), D. Laukens (5), F. Mana (6), M. De Vos (7), S. Vermeire (4), I. Cleyne (1) / [1] University of Leuven, Leuven, Belgium, Department of Human Genetics, [2] University of Leuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing (CHROMETA), Leuven, Belgium, [3] University Hospitals Leuven, Leuven, Belgium, Genomics Core, [4] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [5] University Hospital Gent, Belgium, Department of Gastroenterology, [6] University Hospital Brussels, Vrije Universiteit Brussel, Belgium, Department of Gastroenterology, [7] University Hospital Gent, Gent, Belgium, Department of Gastroenterology.

**Introduction :** Crohn's disease (CD) and ulcerative colitis (UC) are the most common entities of inflammatory bowel disease (IBD), both of unknown aetiology. Clinical phenotypes are heterogeneous, partly depending on age at diagnosis.

**Aim :** In this study we aimed to define the molecular profile of newly diagnosed IBD patients naïve for biologicals and immunosuppressives, and if this differs depending on the age at diagnosis.

**Methods :** Inflamed colonic biopsies were obtained from 23 CD (median age 24.0 (16.2-62.8) years ; 35% male ; 5 L2/18 L3) and 16 UC (median age 31.5 (16.7-69.0) yrs ; 29% male ; 7 E2/9 E3) patients within 6 months after diagnosis. All patients were naïve for biologicals and immunosuppressives, and without previous IBD-related surgery. Colonic biopsies from 15 non-IBD controls (median age 35.7 (20.6-68.3) yrs ; 47% male) were used to match with each patient



group according to age. Single-end RNA sequencing was performed using Illumina HiSeq4000 platform. Normalization and differential expression analysis was performed using DESeq R package. A fold change >2.0 and adjusted p-value <0.05 were considered biologically significant. Pathway analysis was performed with IPA.

**Results :** Comparative analysis identified 632 (516 up, 116 down) differentially expressed genes between CD patients and age-matched controls ; and 3796 (2542 up, 1254 down) between UC patients and age-matched controls ; 581 genes were dysregulated in both CD and UC. Common upstream regulators of overlapping genes are STAT1, IFN $\gamma$ , IFN $\alpha$  and TNF. Pathway analysis showed that Th1/Th2 activation (eg. STAT1, several MHC class II HLAs) was enriched in CD and UC, while phagosome formation (eg. FCGR2A/B, TLRs) and agranulocyte adhesion/diapedesis (eg. MMPs) were UC-specific. While in CD patients there was a fairly small difference between younger ( $\leq 30$  years, n=16) and older-onset (>30 years, n=7) patients (58 and 110 dysregulated genes, overlap of 21), younger ( $\leq 40$  years, n=11) UC patients showed more dysregulation than older-onset (>40 years, n=5) UC patients : 3550 versus 1722 genes, with an overlap of 1441. This seems to also reflect differences in disease severity between younger and older-onset, with 64% of younger UC exhibiting extended disease (E3) compared to 40% in the older group. Genes unique for younger UC were mainly involved in LPS/IL-1 mediated inhibition of RXR (eg. TNF, TLR4), while those specific for older UC were enriched for “role of macrophages, fibroblasts and endothelial cells in rheumatoid arthritis” (eg. VCAM, TLR10) as indicated by IPA.

**Conclusions :** There is a strong mRNA dysregulation in newly diagnosed CD, and even more so in newly diagnosed UC. Some pathways and upstream regulators are common for both CD and UC, while others are enriched in one of the two phenotypes. Younger and older-onset CD patients only show small molecular differences, whereas younger-onset UC patients show a prominent mRNA dysregulation compared to older-onset UC. This difference most likely reflects differences in disease severity, although this needs to be further established.

- I03 -

**BASELINE ILC1 DISTRIBUTION IN BLOOD PREDICTS RESPONSE TO USTEKINUMAB IN PATIENTS WITH REFRACTORY CROHN'S DISEASE.** B. Creyns (1), B. Verstockt (2), J. Cremer (2), M. Ferrante (2), S. Vermeire (2), J. Ceuppens (3), G. Van Assche (2), C. Breynaert (3) / [1] Laboratory of Clinical Immunology, Leuven, Belgium, Department of Microbiology and Immunology, [2] Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium, Department of Chronic Disease, Metabolism and Ageing, [3] Laboratory of Clinical Immunology, Leuven, Belgium, Department of Microbiology and Immunology.

**Introduction :** Innate lymphoid cells (ILCs) are recently identified immune cells with a high cytokine producing capacity at mucosal barriers. In patients with active Crohn's disease (CD), a shift is observed from homeostatic ILC3s towards pro-inflammatory ILC1s in the intestines. Ustekinumab (UST), targeting the IL-12/23 shared p40 subunit, was recently approved by FDA & EMA for treatment of moderate-to-severe CD. As IL-12 and IL-23 play distinct roles in the plasticity of ILC1 and ILC3s, we studied the effect of ustekinumab on ILC populations in blood.

**Aim :** Study the role of ILCs in response to ustekinumab in patients with refractory Crohn's disease.

**Methods :** We included 46 CD patients (68 % female, median age 42) refractory to anti-TNF therapy and vedolizumab with a median Simplified Endoscopic Score (SES-CD) of 16.5, initiating UST (6mg/kg IV at induction, followed by subcutaneous UST 90mg q8w thereafter). Blood samples were prospectively collected before start and at 4, 8 and 24 weeks. Endoscopic response was assessed at week 24, and defined as a  $\leq 50\%$  SES-CD decrease. ILCs were studied in isolated flow cytometry.

**Results :** Patients with (n=6) and without (n=40) endoscopic response at week 24 had a similar inflammatory burden, reflected by similar median faecal calprotectin (1800 vs 1225 $\mu$ g/g, p=0.44) and C-reactive protein (23.9 vs 10.3mg/L, p=0.10) levels at baseline. Though, baseline endoscopic activity was much higher in patients responding to UST, compared to non-responders (median SES-CD 22 vs 14, p = 0.02). Baseline contribution of ILC1s in the total ILC pool was significantly lower in responders compared to non-responders before start of therapy (7.39% vs 16.90%, p=0.017). In contrast, ILC2s were elevated in responders as compared to non-responders at baseline (70.1% vs 40.8%, p = 0.02). There was no significant difference in NCR- ILC3s (p=0.12). After week 4 treatment a significant increase in NCR- ILC3 frequency was observed as compared to baseline independent of response (p<0.001). This trend persisted at 8 weeks (p=0.02) but could no longer be observed after 24 weeks (p=0.19).

**Conclusions :** This study is the first to show how biological therapy impacts ILC populations in peripheral blood. Increased levels of ILC1s in peripheral blood at baseline may be a predictive biomarker for non-response to UST. Non-response may be explained by an increased reservoir of pro-inflammatory ILC1s in the circulation which can migrate towards the gut to annihilate treatment effects. Validation is needed in a larger and independent cohort with inclusion of biopsies. Overall these findings may guide individualized selection of biological agents in Crohn's disease, and provide mechanisms of primary (non-) response to UST.

ENDOPLASMIC RETICULUM STRESS IN BORDERING EPITHELIUM OF CROHN'S DISEASE PATIENTS WITH INTESTINAL FIBROSIS. S. Hu (1), N. Blétard (2), C. Massot (3), N. Pierre (1), F. Quesada Calvo (1), G. Paulissen (1), G. Mazzucchelli (4), N. Smargiasso (5), D. Baiwir (6), E. De Pauw (5), P. Delvenne (2), M. Meuwis (7), E. Louis (3) / [1] Giga-R, University of Liège, Liège, Belgium, Translational Gastroenterology, [2] CHU de Liège, Liège, Belgium, Pathological anatomy and cytology, [3] CHU de Liège -GIGA-R, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology and Translational Gastroenterology, [4] University of Liège, Belgium, Laboratory of Mass Spectrometry, Chemistry Dep., [5] University of Liège, Belgium, Laboratory of Mass Spectrometry, Chemistry Dep., [6] GIGA facility ULiège, Liège, Belgium, GIGA-proteomics, [7] CHU de Liège -GIGA-R, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology Department and Translational Gastroenterology.

**Introduction :** Intestinal fibrosis in Crohn's Disease (CD) is complex and its initiation and progression are linked to chronic inflammation and lead to bowel damages. Bordering epithelium involvement in this process remains unravelled.

**Aim :** Our purpose was to address proteomic changes occurring in the bordering epithelium of regions with increasing degrees of sub-mucosal inflammation and fibrosis. Proteins differentially abundant could be potential actors eliciting fibrogenic pathways and potential therapeutic targets.

**Methods :** Formalin fixed paraffin embedded tissue sections from CD patients with ileal stenosis (n=5) were treated by laser capture microdissection to isolate bordering epithelial cells. Paired regions were selected in Normal (NL), inflammatory and mildly fibrotic (IF1) as well as inflammatory and moderately to severely fibrotic (IF2/3) areas. Protein digests were analysed by label free proteomics. Immunohistochemical (IHC) evaluation on independent CD cases was done (n=32). Moreover, the epithelial colonic cell line HT29 was used for in vitro culture experiments in order to characterise the selected protein in the epithelium and its potential impact on a simple model of intestinal fibrosis.

**Results :** Proteomics identified 1249 proteins from which 257 showed a distribution varying significantly with the degree of fibrosis. Anteriority gradient protein homolog 2 (AGR2), related to endoplasmic reticulum (ER) stress and mucus secretion, was the most significant one. AGR2 IHC confirmed a significant increase in ileal CD (n=19) with inflammation and a stronger one with fibrosis. In the colon (n=13) there was no significant difference between simple inflammation and inflammation with fibrosis. ER stress induction in HT29 cells enabled AGR2 increase as measured by RT-Q-PCR and WB, while TGFβ, the main fibrogenic elicitor, induced a decrease of this protein.

**Conclusions :** AGR2 increase in the epithelium of fibrotic CD ileum and in epithelial cell line upon ER stress induction suggest a potential role for epithelium and ER stress (including AGR2) in the development of surrounding submucosal fibrosis in ileal CD.

SERUM PROTEOMIC ANALYSIS CHARACTERIZES NEWLY DIAGNOSED CROHN'S DISEASE AND ULCERATIVE COLITIS DEPENDING ON THE AGE AT DIAGNOSIS. S. Verstockt (1), E. Glorieus (2), M. De Decker (3), B. Verstockt (4), N. Ardeshir Davani (4), V. Ballet (5), G. Van Assche (5), P. Hindryckx (2), M. Ferrante (5), D. Laukens (2), F. Mana (3), M. De Vos (2), S. Vermeire (5), I. Cleynen (1) / [1] University of Leuven, Leuven, Belgium, Department of Human Genetics, [2] University Hospital Gent, Belgium, Department of Gastroenterology, [3] University Hospital Brussels, Vrije Universiteit Brussel, Belgium, Department of Gastroenterology, [4] Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing (CHROMETA), Leuven, Belgium, [5] Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium., Leuven, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** Inflammatory bowel disease (IBD) is characterized by a chronic inflammation of the gut with a poorly understood ethiopathogenesis. Clinical features differ among patients and have also been shown to be dependent on the age at diagnosis.

**Aim :** To get a better understanding of the underlying mechanisms at the time of diagnosis, and possible age-related differences, we studied the inflammatory serum protein profiles of patients newly diagnosed with Crohn's disease (CD) or ulcerative colitis (UC), naïve for biologicals and immunosuppressives.

**Methods :** We prospectively included newly diagnosed CD (n=76) and UC (n=31) patients across three Belgian IBD centres (University Hospitals Brussels, Ghent and Leuven). New diagnosis was defined as within 3 months after diagnosis, naïve for biologicals and immunosuppressives, and without previous IBD-related surgery. Each patient was matched to a healthy control (n=80) according to gender and age ( $\pm$  3.6 years). A panel of 91 inflammatory proteins was quantified in serum samples using the Proximity Extension Assay technology (OLINK). Wilcoxon rank-sum and t tests were used as appropriate, and correction for multiple testing applied using the Benjamini-Hochberg method (R 3.4.2). An adjusted p value <0.05 was considered significant.

**Results :** The included CD and UC patients showed a similar age distribution at diagnosis, while CD patients were more frequently of male gender than UC patients (median age at diagnosis 26.2 years (16.0-74.0) in CD, 25.5 years (16.7-69) in UC ; 53% male in CD, 45% male in UC). Comparison of protein expression levels in CD patients with matched controls identified 44 significantly different proteins, including OSM (fold change (FC)=4.0, p=1.73E-12) and IL-6 (FC=3.7, p=3.91E-12) as the most dysregulated proteins. When comparing UC with controls, 39 significantly different proteins were observed, 29 of which were also differentially expressed in CD, including IL-6 and OSM (ranked 9th and 10th respectively). The most dysregulated protein in UC was CXCL1 (FC=1.7, p=4.48E-07). We then stratified the CD and UC patient groups into quartiles based on their age at diagnosis ( $\leq 21.5$ , 21.5–25.5, 25.5–33.5 and  $>33.5$  years for CD ;  $\leq 20.6$ , 20.6–26.0, 26.0–33.7 and  $>33.7$  years for UC), and compared each subgroup with its age-matched control group. A comparable number of differentially expressed proteins were observed for quartiles 1 to 3 in CD (n=25-30 proteins), of which 12 overlapped in all 3 quartiles, including OSM and IL-6. Only one protein, FGF-19, was significantly different in the oldest CD group. For UC patients, quartiles 1 and 2 showed comparable results (13 and 8 differentially expressed proteins, with overlap of 7), while no significant differences were observed for the two oldest UC groups.

**Conclusions :** We identified panels of inflammatory markers characterizing newly diagnosed CD and UC, with some common for both (OSM, IL-6), while others appear to be specific for either CD (eg. FGF-19) or UC (eg. CCL11). Stratifying by age at diagnosis showed a decrease in inflammatory burden with increasing age, providing further evidence for the less severe clinical symptoms in late-onset compared with early-onset IBD. These findings will now need to be correlated with disease severity, and validated in independent cohorts to get better insights in the main inflammatory markers at (age of) diagnosis such as OSM, IL-6 and FGF-19.

- I06 -

SERUMPROTEOMICPROFILINGREVEALSCHANGESININFLAMMATORYPROFILESWITHCONSECUTIVE BIOLOGICAL THERAPIES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE. M. De Bruyn (1), V. Ballet (2), S. Verstockt (3), B. Verstockt (1), G. Van Assche (2), M. Ferrante (2), K. Machiels (1), S. Vermeire (2) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Chronic Diseases, Metabolism and Ageing (CHROMETA), [2] University Hospitals Leuven, Leuven, Belgium, Gastroenterology and Hepatology, [3] Laboratory of Complex Genetics, Leuven, Belgium, Human Genetics.

**Introduction :** The last decade, besides anti-TNF (infliximab/IFX, adalimumab/ADM), anti-a4b7 (vedolizumab/VDZ) and anti-p40 (ustekinumab/UST) antibodies became available for patients with inflammatory bowel disease. Biological-naïve patients consistently had better outcomes compared to exposed patients. It is unclear if this is due to more refractory disease or alterations in immune pathways triggered by biological exposure.

**Aim :** Using serum proteomics and mucosal transcriptomics, we evaluated differences in immune profiles at start and after switch of different types of biologicals.

**Methods :** Consecutive serum samples were collected at start of biological treatment (Timepoint/T1) and at time of switch to another biological (T2, T3) from 176 anti-TNF treated patients (137 IFX, 39 ADM), 41 VDZ treated patients, 5 UST treated patients, 40 patients consecutively treated with IFX, ADM and VDZ, and 13 patients consecutively treated with anti-TNF, VDZ and UST. All patients starting anti-TNF were biological-naïve. Using the Proximity Extension Assay technology, 79 inflammatory markers were measured with the Proseek Inflammation Panel (OLINK). RNA sequencing on matched baseline mucosal biopsies (n=54) was performed with Illumina HiSeq 4000NGS. Normalization and differential expression analysis was performed using DESeq. Significance was reported after correction for multiple testing (False Discovery Rate).

**Results :** In patients failing IFX, 34 serum markers involved in cell migration and immune response significantly higher at T2 compared to T1. In contrast, patients failing ADM had significantly lower levels of 23 markers involved in immune process stimulation and chemotaxis at T2. Interestingly, IL-17A was significantly higher at T2 after both IFX and ADM. At ADM T1 versus IFX T1, 9 markers involved in cell migration were significantly different, regardless of disease activity. In patients failing VDZ, 5 markers involved in cytokine signaling (e.g. GDNF, IL-8) were lower at T2. Similar trends were observed at mRNA level. Patients failing UST had lower levels of 14 markers involved in immune system regulation (e.g. TNF, CCL25) at T2. At VDZ T1 versus UST T1, higher levels of markers involved in apoptosis and NF- $\kappa$ B signaling were observed. Patients switching from IFX to ADM (T2) and VDZ (T3) had significantly higher levels of 21 markers involved in cell migration (e.g. CCL7) at T2 and most markers decreased at T3. Patients switching from anti-TNF to VDZ (T2) and UST (T3) had higher levels of apoptotic markers at T2, and altered levels of lymphocyte differentiation markers (e.g. IL-12B) at T3.

**Conclusions :** Exposure to different types of biological treatments is associated with specific changes in immune profiles. Future studies should now prospectively characterize these profiles on a larger scale to see if they can aid clinicians in personalized therapeutic decision making.

PROTEIN BIOMARKERS IDENTIFY SUBCLINICAL INFLAMMATION PATTERNS IN FIRST-DEGREE RELATIVES OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE. M. Vancamelbeke (1), V. Ballet (2), N. Ardeshir Davani (3), G. Van Assche (3), M. Ferrante (3), I. Cleynen (4), S. Vermeire (3) / [1] KU Leuven, Leuven, Belgium, Department Chronic Diseases, Metabolism and Ageing (CHROMETA), Translational Research Center for Gastrointestinal Disorders (TARGID), [2] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [3] KU Leuven, Leuven, Belgium, Department Chronic Diseases, Metabolism & Ageing (CHROMETA), Translational Research Center for Gastrointestinal Disorders (TARGID), [4] KU Leuven, Leuven, Belgium, Department of Human Genetics, Laboratory of Complex Genetics.

**Introduction :** First-degree relatives (FDR) of patients with Crohn's disease (CD) and ulcerative colitis (UC) have the highest risk of developing inflammatory bowel disease (IBD). Although it is accepted that genetic and environmental factors contribute to the disease risk, the exact determinants are unclear.

**Aim :** We here investigated the serological profiles of IBD patients and their healthy FDR, and compared these with non-IBD control families to study whether serum proteomics can help in defining individuals at risk.

**Methods :** Serum and faeces were obtained from 80 individuals of 20 multiple-affected IBD families (47 IBD (38 CD/9 UC, 29.8% male, median [interquartile range, IQR] age 51.4 [42.5-59.5] years), 33 FDR (48.5% male, 45.5 [28.5-59] years)), and 39 healthy controls (HC) (53.8% male, 45.5 [27.1-56.6] years) from 8 non-IBD families. Protein biomarkers were measured in serum using the Proseek Multiplex Inflammation panel (OLINK). A total of 77 proteins (given as normalized protein expression (NPX)) were analysed following quality control and excluding markers with >75% missing data. Faecal calprotectin was measured using Bühlmann ELISA. Non-parametric statistical analyses were performed in SPSS and R with Benjamini-Hochberg correction for multiple comparisons. Protein-protein interactions were identified with STRING.

**Results :** Diagnosis, age and family ID significantly influenced the proteomic profiles (envfit,  $p < 0.01$ ). Individual comparisons according to diagnosis identified 21 protein markers with differential expression between IBD patients and HC ( $p < 0.05$  and fold change  $> 1.2$ ). Ten of these were also different in FDR compared to HC (IL8, MCP3, IL6, OSM, TGF $\alpha$ , HGF, ENRAGE, CASP8, IL17A, CXCL9). The top pathways associated with the IBD-specific and IBD-FDR overlapping proteins were regulation of leukocyte migration and cell chemotaxis, respectively. Calprotectin was higher in IBD patients compared to FDR and HC ( $p < 0.01$ ). The differentially expressed proteins correlated well with calprotectin, although this effect was only pronounced in patients. Nine FDR had NPX values above the median seen in IBD patients for at least 11 of the 21 differentially expressed proteins. These FDR, serologically being similar to IBD patients, did not share specific phenotypic traits nor had higher calprotectin levels, though three of them were from the same family.

**Conclusions :** Several proteins with significant difference between IBD patients, FDR and HC were identified. The fact that some were also increased in FDR, confirms previous evidence of a subclinical state in this group. Interestingly, a subgroup also showed biomarker levels comparable to those in patients. These FDR and the identified markers merit close follow-up to confirm if they trigger actual disease.

DECREASED LEUKOCYTE TRAFFICKING MAY CONTRIBUTE TO VEDOLIZUMAB REFRACTORY DISEASE AFTER ANTI-TNF EXPOSURE IN PATIENTS WITH ULCERATIVE COLITIS. B. Verstockt (1), S. Verstockt (2), M. De Bruyn (3), K. Machiels (3), H. Bleui (3), V. Ballet (4), G. Van Assche (5), S. Vermeire (5), M. Ferrante (5) / [1] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing, [2] KU Leuven, Leuven, Belgium, Laboratory for Complex Genetics, [3] KU Leuven, Leuven, Belgium, Translational Research in Gastrointestinal Disorders, Department of Chronic Diseases, Metabolism and Ageing, [4] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [5] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing.

**Introduction :** Vedolizumab (VDZ) limits lymphocyte recruitment to the gut by targeting the  $\alpha 4\beta 7$  integrin and has shown efficacy in patients with ulcerative colitis (UC). Real-life and controlled trial data suggest that VDZ is more effective in anti-TNF naïve patients.

**Aim :** We studied proteomic and transcriptomic differences between patients with and without anti-TNF exposure prior to VDZ initiation.

**Methods :** Serum samples of 63 UC patients (50.8% female, median disease duration 8.3 years) with baseline endoscopic active disease were prospectively collected prior to VDZ treatment, as well as serum from 69 healthy controls. Using Proximity Extension Assay technology (Olink Inflammation), proteomic analysis was performed on baseline serum

samples. Biopsies from inflamed colon in 16 UC patients were taken prior to VDZ initiation. Mucosal total RNA was isolated, and next-generation sequencing performed using Illumina HiSeq 4000NGS. Differential gene expression was evaluated by DESeq R package and pathway analysis by Ingenuity Pathway Analysis.

**Results :** Prior to VDZ therapy, 80.6% of patients received  $\geq 1$  anti-TNF agents. By comparing anti-TNF experienced and naïve patients before first VDZ administration, 5 proteins were significantly overexpressed in the naïve population ( $p < 0.05$ ), including CCL25 (fold change (FC) 1.43) (Figure 1). This association was mainly driven by previous infliximab (IFX) exposure ( $p = 0.031$ ). Pathway analysis revealed a significant upregulation of regulatory pathways involved in leukocyte chemotaxis, cell migration and leukocyte migration in the naïve population ( $p < 0.005$ ). CCL25 levels in all UC patients were similar compared to healthy controls ( $p = 0.35$ , FC 1.0), thus not reflecting disease activity. No significant correlation between CCL25 and disease duration or duration of anti-TNF therapy could be observed. In patients exposed only to IFX prior to VDZ, CCL25 was significantly lower when IFX was stopped less than one year prior to VDZ initiation ( $p = 0.021$ ). Inflamed colonic biopsies from anti-TNF naïve patients expressed numerically more CCL25, compared to anti-TNF experienced patients (FC 25.0). Serum prior to both anti-TNF and subsequent VDZ therapy was available in 11 patients. Paired-analysis showed that patients who responded to VDZ ( $n = 6$ ) had overall a stable CCL25 from start of anti-TNF to start of VDZ ( $p = 0.88$ ), whereas patients who failed VDZ therapy ( $n = 5$ ) experienced a drop in CCL25 ( $p = 0.12$ ).

**Conclusions :** Prior administration of IFX significantly influences leukocyte trafficking and may therefore mechanistically explain lower VDZ response rates after prior anti-TNF therapy in UC. Although further experimental evidence is warranted, we hypothesise that IFX downregulate CCL25, which has shown to influence a4b7-MADCAM1 adhesion.

- I09 -

THIOPURINE MONOTHERAPY STILL HAS A PLACE IN THE TREATMENT OF PATIENTS WITH MILD-TO-MODERATE CROHN'S DISEASE IN THE BIOLOGICAL ERA. L. Boets (1), B. Verstockt (2), G. Van Assche (3), S. Vermeire (3), M. Ferrante (3) / [1] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [2] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing, [3] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing.

**Introduction :** For more than half a century, thiopurines have been the first line maintenance therapy in patients with Crohn's disease (CD). With the increasing availability of biological drugs, thiopurines are often considered less potent, though in mild-to-moderate disease they may be a valid, safe and less expensive alternative. Genetic determinants including HLA, TPMT and NUDT15 have been associated with response and/or side effects to thiopurines.

**Aim :** We aimed to report outcome of thiopurine monotherapy in CD patients, and evaluated genetic associations with response.

**Methods :** The medical records of all genotyped CD patients (Illumina ImmunoChip) who ever received thiopurine monotherapy at our tertiary referral centre were retrospectively assessed. All patients had TPMT-screening prior to thiopurine initiation. Response was defined as continuation of thiopurines for more than 1 year in monotherapy, with minimal corticosteroid use (max 1 course/year) and no need for other rescue therapy. Allelic association was assessed using PLINK v1.07.

**Results :** Over the past 18 years, 852 CD patients (median disease duration 4.0 years) received thiopurine monotherapy (99.8% azathioprine, 9.8% mercaptopurine), of whom a median (IQR) follow-up of 13.3 (8.3-18.3) years is available. One third of patients (35.5%) responded, whereas 35.5% experienced no response. Thiopurine withdrawal due to side-effects occurred in 29.0% of patients, early after initiation (29.2, 14.6-73 days), including pancreatitis ( $n = 62$ ), abnormal liver tests ( $n = 18$ ) and GI intolerance ( $n = 52$ ). Three lymphomas were diagnosed during follow-up. One quarter of responding patients (26.1%) never discontinued therapy during median follow-up of 7.9 (3.1-11.9) years. The other 73.9% initial responders stopped thiopurine therapy after 5.5 (2.8-9.2) years. Ileal disease location ( $p = 0.001$ ), older age ( $p = 0.04$ ), longer disease duration ( $p < 0.001$ ), absence of perianal disease behaviour ( $p = 0.004$ ) and absence of active perianal disease at time of thiopurine initiation ( $p < 0.0001$ ) were significantly associated with response. Genetic analysis revealed 3 loci significantly associated with response to thiopurines, including rs10196508 located at a regulatory region within chromosome 2 ( $p = 2 \times 10^{-5}$ , OR 2.6).

**Conclusions :** In this large retrospective series, thiopurine monotherapy could safely maintain clinical response in up to 35.5% of patients after one year, similar to previous prospective data observed during the SONIC-trial. We identified a genetic marker associated with response to thiopurines, which needs validation in an independent cohort before its clinical use can be evaluated.

USTEKINUMAB INDUCES CLINICAL AND BIOLOGICAL REMISSION IN BIOLOGIC REFRACTORY CROHN'S DISEASE PATIENTS. C. Liefferinckx (1), B. Verstockt (2), A. Gils (3), M. Noman (4), C. Van Kemseke (5), E. Macken (6), M. De Vos (7), W. Van Moerkercke (8), J. Rahier (9), P. Bossuyt (10), J. Dutré (11), E. Humblet (12), D. Staessen (13), H. Peeters (14), P. Van Hootegeem (15), E. Louis (5), D. Franchimont (1), F. Baert (16), S. Vermeire (4) / [1] Hopital Erasme, ULB, Belgium, Department of Gastroenterology, [2] University Hospitals KU Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [3] KUL, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [4] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [5] Centre Hospitalier Universitaire Sart-Tilman, ULG, Belgium, Department of Gastroenterology, [6] Universiteit ziekenhuis Antwerpen, Belgium, Department of Gastroenterology, [7] Universitair ziekenhuis Gent, Belgium, Department of Gastroenterology, [8] AZ Groeninge, Kortrijk, Belgium, Department of Gastroenterology, [9] Centre Hospitalier Universitaire Mont-Godinne, UCL, Belgium, Department of Gastroenterology, [10] Imeldaziekenhuis, , Belgium, Department of Gastroenterology, [11] Ziekenhuis Netwerk Antwerpen, Belgium, Department of Gastroenterology, [12] Ziekenhuis Oost-Limburg - Campus Sint-Jan, Belgium, Department of Gastroenterology, [13] GZA Sint-Vincentius ziekenhuis, Antwerpen, Belgium, department of Gastroenterology, [14] Algemeen Ziekenhuis Sint-Lucas, Belgium, department of Gastroenterology, [15] Algemeen Ziekenhuis Sint-Lucas, Brugge, Belgium, Department of Gastroenterology, [16] AZ Delta, Roeselare, Belgium, Department of Gastroenterology.

**Introduction :** Ustekinumab (UST), a fully humanized IgG1 monoclonal antibody targeting IL12/23p40, was recently approved for moderate to severe Crohn's disease (CD). We report real world short-term efficacy data in a Belgian cohort (14 centres) with prior exposure to both anti-TNF and vedolizumab and correlate outcome with week 8 UST serum levels

**Aim :** We report real world short-term efficacy data in a Belgian cohort (14 centres) with prior exposure to both anti-TNF and vedolizumab and correlate outcome with week 8 UST serum levels

**Methods :** Prospectively collected data were retrospectively analysed according intention-to-treat. Patients received IV UST (induction) and 90 mg SC q8 weeks from week 8. Primary endpoints were clinical response/remission at week 8 and 16. Clinical response/remission were defined as a reduction in Harvey Bradshaw Index (HBI) of  $\geq 3$  and a HBI  $\leq 4$  respectively. Biological response/remission were defined as 50% drop of C-reactive protein (CRP) and CRP  $< 5$  mg/L respectively if CRP  $\geq 5$  mg/l at baseline. Serum UST samples were available in 94 patients at week 8 and were measured with an ELISA developed by KU Leuven with the same specificity, selectivity, accuracy and precision as the J&J assay. Paired analysis was performed for faecal calprotectin (fCal) at baseline and week 8 (=60) and week 16 (n=33)

**Results :** Our study population of 157 patients has a median age of 40 years with a median age of diagnosis of 22 years. 40,7% of CD cohort has an history of peri-anal disease. Patients are highly refractory with failure to 1 anti-TNF, 2 anti-TNF and 2 anti-TNF + anti-integrin in 99,4%, 77,1 and 70,7% of cases, respectively. At the baseline, 43,9%, 10,8% and 5% of patients are treated by steroids, azathioprine and methotrexate, respectively. The cohort presents a baseline HBI of 11 (IQR 8-14) with median CRP of 12,5 mg/l (IQR 5-23,6, n= 144 ; n  $< 5$  mg/l = 37) and median fCal of 795,5 (IQR 141,75- 1800, (n=88 ; n  $< 50$   $\mu$ g/g= 6). 142 patients reached week 16. At week 8, clinical response and remission were achieved in 56.7% (89/157) and 27.4% (43/157) of patients, respectively. At week 16, clinical response and remission was achieved in 53.5% (76/142) and 31.7% (45/142). Biological response and remission was achieved in 25.8% (31/120) and 8.3% (10/120) respectively at week 8 and in 23.8% (25/105) and 10.5% (11/105) at week 16 (Figure1). CRP significantly decreased from baseline (14.7 mg/L, IQR [8.8-27.7]) to 6.2 mg/L at week 8 (IQR [2.85-11.85], p $< 0.0001$ ) and 6.6 mg/L (IQR [2.2-14.9] at week 16, p $< 0.0001$ ). In subset with available paired samples, a 50% drop in fCal was observed in 33% (20/60) and in 39.4% (13/33) of patients at week 8 and 16. Week 8 UST levels were not significantly associated with (short-term) clinical response (p=0.15). However, a significant inverse correlation was seen between UST levels and CRP at week 8 (r=-0,322 ; p=0.002). At induction, 33.3% of patients (47/141) experienced arthralgia (excluding patients with ankylosing spondylitis (n=16)), disappearing in 25.5% and 34% of them at week 8 and 16 respectively. By week 16 only 3.2% of patients (5/157) had reported side effects (Clostridium and CMV infection, intense myalgia, pregnancy, deep venous thrombosis) and 5.7% of patients (9/157) required surgery associated to CD.

**Conclusions :** UST is effective in inducing short term clinical response and remission in this highly refractory CD cohort, including a significant reduction in CRP levels and calprotectin (when available). UST levels at week 8 inversely correlate with CRP but not with short-term outcome

RISK OF CMV REACTIVATION IN UC PATIENTS WITH PREVIOUS HISTORY OF CMV INFECTION FOLLOWING INFLIXIMAB OR VEDOLIZUMAB TREATMENTS. C. Hommel (1), X. Roblin (2), L. Briche (2), B. Bihin (3), S. Pillot (4), J. Rahier (1) / [1] CHU UCL Namur, Yvoir, Belgium, Gastroenterology, [2] University Hospital Saint Etienne, France, Gastroenterology, [3] CHU UCL Namur, Yvoir, Belgium, Scientific Support Unit, [4] University Hospital Saint Etienne, France, Laboratory of Infectious Agents and Hygiene.

**Introduction :** Cytomegalovirus (CMV) persists in the colonic mucosa throughout the lifetime of infected subjects and reactivation with viral replication can occur especially in case of immunosuppression. Anti-integrin drugs, while depleting the intestine of circulating lymphocyte, may favour CMV reactivation due to diminished constant immune surveillance.

**Aim :** The aim was to compare in UC patients with prior CMV immunization the risk of CMV reactivation and colectomy rates on vedolizumab (VZ) compared to infliximab (IFX). Secondary aims were to identify risk factors for CMV reactivation and characterize CMV reactivation in both groups

**Methods :** In a single tertiary centre, UC patients with CMV IgG seropositivity prior to intravenous treatment with VZ or IFX were evaluated clinically and endoscopically. Patients with absence of CMV replication prior to treatment, assessed by quantitative PCR for CMV DNA load, were included. Primary endpoint was CMV reactivation with colitis detected by tissue colonic PCR.

**Results :** Between January 2008 and September 2016, 33 patients with positive CMV IgG but no signs of active CMV colitis started either VZ (n=16) or IFX (n=17). Baseline characteristics of patients, concomitant treatments and endoscopic disease severity were similar in both groups except for prior lines of treatments, disease extension and duration which were higher in the VZ group. CMV colitis reactivation occurred in 10 patients (median time : 5.9 months (VZ) and 2.5 months (IFX)). Incidence rates of CMV colitis were 5/14.2 patient-years in the VZ group compared to 5/54.4 patient-years in the IFX group. Using a Cox model and correcting for disease severity (assessed by endoscopic and total Mayo score), our data support an increased risk of CMV reactivation in patients treated with VZ (HR [95 CI] : 2.3 [0.5-9.3]) compared to IFX and in case of concomitant steroid use (HR [95 CI] : 5.1 [0.6-41]). During CMV reactivation, clinical, endoscopic and biological severity were higher in the VZ group. Quantification of tissue CMV replication levels were heterogeneous in both groups but median tissue viral load was higher in the IFX group (6482 IU/100 000 cells [iQR 263-6945] vs 225 [iQR 77-961]). Colectomy was observed in 3 VZ patients (2 with reactivated CMV) but not in IFX patients.

**Conclusions :** In UC patients, seropositive for CMV, our data support a higher risk of CMV reactivation when treated with VZ compared to IFX. CMV reactivation was clinically and endoscopically more severe in patients treated with VZ. Whether this is reflecting a negative effect of VZ or the consequence of uncontrolled disease is unknown. CMV reactivation and the risk for colectomy in patients under VZ warrants further investigation.

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USTEKINUMAB INDUCES LIMITED MUCOSAL HEALING AFTER 6 MONTHS IN A REAL-LIFE, PROSPECTIVE COHORT OF PATIENTS WITH REFRACTORY CROHN'S DISEASE. B. Verstockt (1), M. Noman (2), I. Aerden (2), M. Peeters (3), E. Brouwers (4), V. Ballet (5), L. Vandersmissen (3), G. Van Assche (6), A. Gils (3), S. Vermeire (6), M. Ferrante (6) / [1] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing, [2] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [3] KUL, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies, Department of Pharmaceutical and Pharmacological Sciences, [4] KU Leuven, Leuven, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies, Department of Pharmaceutical and Pharmacological Sciences, [5] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [6] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing.

**Introduction :** Ustekinumab (UST), targeting the IL-12/23 shared p40 subunit, was recently approved by FDA & EMA in moderate-to-severe Crohn's disease (CD). Real life data in patients IV induced with UST are currently lacking.

**Aim :** We aimed to report efficacy of UST during induction and maintenance, including patient-reported outcome (PRO2), CRP, faecal calprotectin (fCal) and endoscopy (SES-CD). Additionally, we assess association between UST serum levels (SL) and outcome.

**Methods :** Forty-seven CD patients, all refractory to anti-TNF and vedolizumab, were prospectively included. All received UST 6mg/kg IV at induction, with SC UST 90mg q8w thereafter. Patients were endoscopically assessed at baseline and week 24. Clinical remission was defined as average daily stool frequency  $\leq 2.8$  and average abdominal pain score  $\leq 1$ . Biochemical remission was defined as CRP  $\leq 5$ mg/L and response as CRP decrease of at least 50% or CRP  $\leq 5$  mg/L, in patients with elevated CRP at baseline. Endoscopic response was defined as minimal 50% SES-CD decrease compared to baseline, mucosal healing as SES-CD  $\leq 2$ . UST SL were measured using an in-house developed ELISA with the same operational performance as the assay developed by JnJ.

**Results :** All patients were prospectively followed up for a median of 24 (IQR 16-31) weeks. Twenty patients (43%) discontinued therapy after a median of 24 (19-24) weeks, all because of endoscopically confirmed primary non-response. Although SES-CD decreased from 14 (9-19) at baseline to 12 (7-16) at week 24 (p=0.04), this resulted in low endoscopic response (19%) and mucosal healing (3%) rates. Overall fCal dropped significantly from baseline (1741mg/g) to week 4 (1074mg/g) and 8 (603mg/g), whereafter it started to increase by week 16 (747mg/g) and 24 (988mg/g). CRP decreased from 17 to 6mg/L at week 24 (p=0.005), resulting in biological response and remission rates of 46% and 21%. Similarly,

PRO2 dropped significantly, leading to a clinical remission rate of 26% by week 24. UST SL at week 8 (6.3, 2.7-9.3ml/L) and 24 (1.6, 0.6-3.3ml/L) showed substantial interindividual variability ; and correlated well between both timepoints ( $r=0.7$ ,  $p<0.001$ ). Week 8 and 24 SL were numerically higher in patients with endoscopic response and biological remission at week 24. Quartile analysis showed that all biological remitters were in the upper quartiles, whereas the majority of non-remitters were in the lower. Similarly, patients with the highest fCal decrease were in the upper quartiles. Healing rates were too low to determine predictive thresholds.

**Conclusions :** In biologics refractory CD patients, UST IV induction followed by 90 mg SC q8w showed good clinical and biochemical remission rates, but limited mucosal healing after 6 months. Although larger prospective cohorts are needed to validate this, it seems that higher drug exposure is needed in refractory patients to achieve mucosal healing.

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EFFECTIVENESS AND PERSISTENCE OF VEDOLIZUMAB IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE : RESULTS FROM THE BELGIAN REAL-LIFE STUDY WITH VEDOLIZUMAB (BE-RELIVE). C. Reenaers (1), A. Cremer (2), O. Dewit (3), B. De Vroey (4), W. Van Moerkercke (5), P. Bossuyt (6), V. Muls (7), J. Imschoot (8), S. Block (8), A. Hantson (8), V. Philippe (9) / [1] Centre Hospitalier Universitaire de Liège, Liège, Belgium, Department of gastroenterologie, hepatology and digestive oncologie, [2] Erasme Hospital, Brussels, Belgium, Gastroenterology, [3] Clin universitaires St-Luc, UCL, Brussels, Belgium, Gastroenterology, [4] Centre Hospitalier de Jolimont-Lobbès., La Louvière, Belgium, hepato-gastroenterologie, [5] AZ Groeninge, Kortrijk, Belgium, Kortrijk, Belgium, gastroenterology and hepatology, [6] Imelda Hospital, Bonheiden, Belgium, Gastroenterology, [7] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology, [8] Takeda Belgium, Brussels, Belgium, Medical Affairs, [9] AZ Sint-Lucas Brugge, Assebroek/ Brugge, Belgium, Gastroenterology.

**Introduction :** Vedolizumab (VDZ) was efficacious in inducing and maintaining remission in Crohn's disease (CD) and ulcerative colitis (UC) in the Phase III GEMINI studies. Real-world evidence (RWE) studies with VDZ published to date included only a small proportion of biologic-naïve patients.

**Aim :** The aim of this retrospective study was to assess effectiveness and treatment persistence of VDZ in a Belgian real-world cohort of patients with CD or UC, including more than 25% of biologic-naïve patients.

**Methods :** CD and UC patients who started VDZ between 01/09/2015 and 31/07/2016 and who attended at least 1 visit after 1st infusion were included from 15 Belgian centers. Data were collected at baseline (before 1st infusion), week (W)10, W14 (CD patients only), and month (M)6. Last data were collected in January 2017. Treatment response and remission rates were assessed based on the changes in disease activity scores. Data analyses were performed according to disease type (UC/CD), and further stratified by treatment history (biologic-naïve/failure patients). Treatment persistence was assessed using Kaplan-Meier analysis. Adverse events (AEs) recorded in patients' files were collected.

**Results :** Of the 418 patients who started VDZ (safety population), 325 (202 CD and 123 UC) eligible patients were included in data analyses (effectiveness population). 22.2% of UC and 34.2% of CD patients were biologic-naïve. About three quarters of the patients achieved clinical response at W10/W14 (CD : 71.4% ; UC : 77.2%) that persisted up to M6 (CD : 75.6% ; UC : 83.9%). At M6, 66.7% of CD patients were in remission ; the response and remission rates were numerically higher among biologic-naïve patients (UC, respectively additional 9% and 24% ; CD, additional 22% and 35.8%). At M6, 87.6% of CD and 86.1% of UC patients were still on VDZ treatment. For 7.7% of patients, VDZ dose was escalated to every 4W. The most common AEs (N=418) were arthralgia (3.8%), fatigue (3.6%), skin eruption (3.1%), headache (2.9%) and gastroenteritis (2.6%).

**Conclusions :** After 6 months of treatment with VDZ, about 85% of patients were still on treatment, of whom more than 40% achieved remission. Treatment effectiveness appeared higher in biologic-naïve compared to biologic-failure patients. No new safety signals were raised. These results are consistent with findings from the Phase III and real-world evidence studies with VDZ.

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VEDOLIZUMAB TROUGH LEVELS DURING INDUCTION IN IBD PATIENTS : A LONGITUDINAL OBSERVATIONAL RETROSPECTIVE STUDY. C. Liefferinckx (1), A. Cremer (1), C. Minsart (1), A. Gils (2), L. Amininejad (1), V. Tafciu (3), E. Quertinmont (3), J. Devière (1), A. Van Gossum (1), D. Franchimont (1) / [1] Hopital Erasme, ULB, Belgium, Gastroenterology, [2] KUL, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [3] ULB, Brussels, Belgium, Laboratory of Experimental Gastroenterology.

**Introduction :** Vedolizumab (VDZ) is effective for the treatment of moderate to severe ulcerative colitis (UC) or Crohn's disease (CD). Yet, a significant proportion of patients will experience loss of response (LOR) to VDZ over time. Few real-world experience data are available on the relevance of measuring trough levels (TLs) early on to predict LOR in patients treated with VDZ.



**Aim :** Our objective is to evaluate VDZ TLs early on at induction in IBD patients

**Methods :** 86 IBD patients (45 CD, 32 UC and 9 IBD unclassified) have been treated with VDZ. 400 samples were prospectively collected from September 2015 to Augustus 2017 and measured retrospectively by Ridascreen VDZ Monitoring ELISA in parallel with clinical, biological and endoscopic data (when available). Induction analyses pool 2nd and 3rd infusion excepted if infusion is specifically named ; optional dose at week 10 was not included. Treatment failure was defined by the need to optimize VDZ and/or to swap because of active disease. Sustained response was defined by clinical response without need of optimization in the follow-up. Statistical analyses were performed using T-Student test after determination of normality of compared distributions by Shapiro-Wilk test. Results were expressed as mean +/- standard error.

**Results :** 34% of patients (n=29/86) stopped VDZ because of treatment failure during maintenance. The mean duration of VDZ treatment is shorter in patients experiencing treatment failure (145 days +/- 25 days) than patients with sustained response (263 days +/- 27 days, p=0.004). At the third infusion (week 6), the sustained response group had higher TLs (38.1 +/- 4.7mg/ml) than the failure group (24.7 +/- 3.1mg/ml) (p=0.03) but not at the second infusion (week 2) (36.3 +/- 2.35mg/ml VS 29.7 +/- 2.94mg/ml, p=0.65). At induction, patients previously treated with anti-TNF had significant lower TLs (30.4 +/- 1.75mg/ml) compared to anti-TNF naïve patients (35.5 +/- 2.3mg/ml, p=0.04). There was significant more VDZ failure in patients previously treated with anti-TNF compared to anti-TNF naïve patients (24/63 VS 2/23, p=0.008). Finally, 31% of the cohort (n=27/86) had combination treatment with immunomodulators (IMM) but no difference was observed in terms of TLs at induction (29.9 +/- 2.7mg/ml with IMM VS 31.7 +/- 1.7mg/ml without IMM, p=0.5). Likewise, there was not more VDZ failure without IMM than with IMM use (18/59 VS 11/27, p=0.46)

**Conclusions :** This study suggests that patients who lose response to VDZ during maintenance have lower VDZ TLs at induction. VDZ TLs before the third infusion (week 6) seem to be the most indicative time point. The presence of IMM does not seem to be associated to high TLs at induction or to generate a reduction of VDZ failure in the follow-up.

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VEDOLIZUMAB CAN INDUCE CLINICAL REMISSION IN PATIENTS WITH CHRONIC ANTIBIOTIC-REFRACTORY POUCHITIS : A RETROSPECTIVE SINGLE CENTRE EXPERIENCE. C. Claeys (1), B. Verstockt (2), G. Van Assche (2), A. D'hoore (3), A. Wolhuis (3), S. Vermeire (2), M. Ferrante (2) / [1] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [2] University Hospitals KU Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing, [3] University Hospitals Leuven, Leuven, Belgium, Department of Abdominal Surgery.

**Introduction :** Chronic antibiotic-refractory pouchitis affects up to 15% of patients with ulcerative colitis (UC) following colectomy with ileal pouch-anal anastomosis (IPAA). Therapy with anti-TNF agents has demonstrated efficacy in retrospective series, whereas data on vedolizumab (VDZ) therapy are scarce.

**Aim :** We aimed to report efficacy data of VDZ in patients with chronic antibiotic-refractory pouchitis.

**Methods :** We retrospectively assessed all records from UC patients who underwent IPAA and were exposed to VDZ thereafter in our tertiary referral centre. Patients enrolled in a placebo controlled phase IV program with VDZ were excluded, as well as patients with a baseline modified pouchitis disease activity index (mPDAI) < 5 or with Crohn's disease related complications of the pouch. All patients received VDZ 300mg IV at weeks 0, 2 and 6, whereafter maintenance therapy q8 was continued. The primary endpoint, clinically relevant remission defined as a mPDAI <5 and a reduction of overall score <sup>2</sup> points from baseline, was assessed at week 14.

**Results :** Twelve patients were identified (median (interquartile range) mPDAI 8.0 (7-8) at baseline). All but two patients (83.3%) underwent colectomy because of refractory UC and two for high grade dysplasia. All but one J-pouches were 2-stage procedures, constructed 6.4 years (2.8-12.3) prior to inclusion. All developed chronic antibiotic-refractory pouchitis after a median of 1.5 years (0.9-7.8), for which they were previously treated with several courses of antibiotics (100%), thiopurines (16.7%), infliximab (50.0%) or adalimumab (33.3%). mPDAI decreased from 8 (7-8) at baseline to 3 (1.5-6) at week 14 (p=0.016), resulting in a clinical relevant remission rate of 81.8%. Endoscopic PDAI sub-score dropped from 6 (5-6) to 3 (2-4 p=0.03). Steroid free clinical remission was observed in 63.6% of patients, and antibiotic free remission rate was 54.5% at week 14. No differences in C-reactive protein, haemoglobin or albumin could be found between baseline and week 14. After a median follow-up of 46 weeks (14.0-105.3), 63.6% of patients were still in clinical remission. Four (33.3%) patients stopped therapy because of primary non-response (n=2), loss-of response (n=1) or clinical and endoscopic remission (n=1). Two patients reported new onset of arthralgia and no other adverse events were reported.

**Conclusions :** In this case series, VDZ was efficacious and safe to induce clinical remission in patients with Chronic antibiotic-refractory pouchitis. Final confirmation is expected via an ongoing phase IV, placebo-controlled randomized controlled trial (NCT02790138).

OUTCOME OF PREGNANCIES IN VEDOLIZUMAB TREATED FEMALE IBD PATIENTS. A. Moens (1), K. Van Hoeve (2), E. Humblet (3), J. Rahier (4), P. Bossuyt (5), S. Dewit (6), D. Franchimont (7), E. Macken (8), J. Nijs (9), A. Posen (10), A. Van Hootegeem (11), W. Van Moerkercke (12), S. Vermeire (13), M. Ferrante (13) / [1] UZ Leuven, Leuven, Belgium, Internal medicine, [2] University Hospitals Leuven, Leuven, Belgium, Department of Paediatric gastroenterology, [3] Ziekenhuis Oost-Limburg, Genk, Belgium, Department of Gastroenterology and Hepatology, [4] CHU UCL Namur, Yvoir, Belgium, Université catholique de Louvain, [5] Imeldaziekenhuis, , Belgium, Department of Gastroenterology and Hepatology, [6] Mariaziekenhuis Noord-Limburg, Overpelt, Belgium, Department of Gastroenterology and Hepatology, [7] Hopital Erasme, ULB, , Belgium, Université Libre de Bruxelles, [8] University of Antwerp, Antwerp, Belgium, Department of Gastroenterology and Hepatology, [9] Sint-Trudo ziekenhuis, Sint-Truiden, Sint-Truiden, Belgium, Department of Gastroenterology and Hepatology, [10] AZ Vesalius Tongeren, Tongeren, Belgium, Department of Gastroenterology and Hepatology, [11] AZ Klina, Belgium, Department of Gastroenterology and Hepatology, [12] AZ Groeninge, Kortrijk, Belgium, Department of Gastroenterology and Hepatology, [13] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** Vedolizumab (VDZ) is a gut-targeted IgG1 anti- $\alpha 4\beta 7$  integrin approved for treatment of inflammatory bowel disease (IBD). As IBD typically affects women at a childbearing age, studies reporting on pregnancy outcomes in patients under VDZ are important. Animal studies showed that MAdCAM-1, the ligand for  $\alpha 4\beta 7$ -integrin, is expressed by maternal vessels during placental development and  $\alpha 4\beta 7$ -expressing cells of the macrophage/monocyte lineage are therefore considered to play an important role in maternal/fetal tolerance. Blocking this interaction by VDZ might affect this process.

**Aim :** The aim of this study was to evaluate the outcome of pregnancies in IBD patients treated with VDZ.

**Methods :** We conducted a retrospective, national observational study. Details on disease activity, prenatal complications, delivery and neonatal outcome were collected. Data are expressed as median with interquartile range (IQR).

**Results :** A total of 23 pregnancies were reported. Twelve women had Crohn's disease and six ulcerative colitis. All but five patients had disease remission during conception. There were 18 live births (72% female, including 2 twins), two interrupted pregnancies and five pregnancies are still ongoing. The median age at diagnosis of IBD and conception was 23 (17-27) and 31 (26-34) years, respectively. The median duration of VDZ therapy at conception was 12 months (6-14). Up to three months before conception, patients were also taking systemic 5-ASA (n=3) and immunomodulators (n=1). Furthermore, three women smoked, one used a limited amount of alcohol and all, but one patient took folic acid supplementation during pregnancy. Only five patients had a caesarian section, which were all Crohn's disease patients with a history of perianal disease or prior surgery. Patients, who remained in remission (n=12), reported the following complications : intra-uterine growth retardation (n=1), eclampsia (n=1), premature rupture of the membranes (n=2) and congenital malformation (n=2, hip dysplasia and pulmonary valve stenosis). Of the five patients with active disease at conception, three pregnancies were unaffected, one female lost her fetus due to chorioamnionitis at week 22 and one had an active termination due to relational problems. One patient had an IBD flare during pregnancy and delivered a child with Hirschsprung's disease. VDZ was continued throughout pregnancy in two females and was stopped in the 1st, 2nd and 3rd trimester in 4, 11 and 1 patient, respectively. The median gestational age, Apgar score at birth and birth weight were respectively 39 (37-39.4) weeks, 9 (9-9) and 3305 (2823-3698) grams. Eight children were breastfed and this for a median of 10 (4-26) weeks. All newborns were vaccinated according to the standard Belgian regimen, but only 44% received Rotavirus vaccination. No serious infections or malignancies were reported in the newborns during the first year of life.

**Conclusions :** This is the largest cohort study reporting on pregnancy outcomes in patients treated with VDZ. Although the number of pregnancies remains low, we observed a number of prenatal complications and congenital malformations, which urges more studies on the function of  $\alpha 4\beta 7$ -MAdCAM1 interaction in the placenta. In the meanwhile, vigilance and strict follow-up of pregnant IBD patients treated with VDZ is necessary.

IMMUNOSUPPRESSIVE CO-TREATMENT WITH INFlixIMAB AND ADALIMUMAB IS NOT SUPERIOR TO ANTI-TNF MONOTHERAPY TO PREVENT TREATMENT FAILURE AND TREATMENT DISCONTINUATION IN ULCERATIVE COLITIS. S. Vieujean (1), E. Louis (1), C. Reenaers (2) / [1] CHU Sart Tilman, Liège, Belgium, Gastroenterology, [2] CHU Sart Tilman, Liège, Belgium, Gastroenterology.

**Introduction :** In Crohn's disease there is clear benefit from combination therapy with infliximab (IFX) and immunosuppressive drugs (IS), while the benefit seems more limited for adalimumab (ADA). Although some studies suggest a benefit of combination therapy with IFX in ulcerative colitis (UC) few data are available.

**Aim :** Our aim was to compare real life efficacy of anti-TNF monotherapy (IFX and ADA) and anti-TNF+IS for UC maintenance.

**Methods :** Retrospective study of patients with UC treated with IFX or ADA in 2 Belgian academic and regional Hospitals. Treatment periods were divided into 6-month semesters. A combination therapy semester was defined as anti-TNF+IS for at least 3 months, a failure semester as anti-TNF withdrawal for secondary loss of response, intolerance or surgery, a treatment optimisation semester as anti-TNF dose escalation or steroids start. Logistic regression analysis was used to compare patients with IS and patients without IS and to construct a propensity score (PS) for matching the two groups to account for their difference. The incidence of failure was recorded and the OR was calculated. To adjust OR with respect to differences between patients with and without IS, the PS was included in the multivariate logistic regression of the outcome.

**Results :** 478 semesters in 60 patients with IFX and 175 semesters in 33 patients with ADA were included. The mean IFX and ADA treatment duration were respectively 49 ( $\pm$ 33) months and 38 ( $\pm$ 19) months. Within patients treated with IFX, 32/60 patients received IFX+IS during the first semester. IFX was administrated as monotherapy in 361/478 semesters (76%). Respectively 206/478 (43%) and 78/478 semesters (16%) with IFX required dose escalation and corticosteroids course. IFX+IS was not associated with less semesters with failure (9% vs 3%,  $p=0.22$ ) or less corticosteroid intake (21% vs 15%,  $p=0.24$ ) but was associated with more semesters with dose escalation (64% vs 38%,  $p<0.001$ ,  $OR=3.06$ ). IS during the first semester was not associated with lower risk of IFX failure ( $p=0.41$ ) nor with a longer survival without IFX withdrawal ( $p=0.20$ ). Within patients treated with ADA, 19/33 patients received IFX+IS during the first semester. ADA was administrated as monotherapy in 93/175 semesters (53%). Respectively 84/175 (48%) and 42/175 (24%) semesters with ADA required dose escalation and corticosteroids course. ADA+IS was not associated with less semesters with failure (7% vs 5%,  $p=0.89$ ) or less semesters with corticosteroids use (34% vs 17%,  $p=0.56$ ). More semesters with ADA+IS required ADA dose escalation (61% vs 30%,  $p=0.008$ ,  $OR=3.3$ ). IS during the first semester was not associated with lower risk of ADA failure ( $p=0.84$ ) nor with a longer survival without ADA withdrawal ( $p=0.78$ ). Continuing the IS treatment beyond the first semester with IFX or ADA was not associated with a clinical benefit.

**Conclusions :** In this real life experience, combination therapy of IFX or ADA with IS during the first semester or prolonged after the first semester was not associated with less dose escalations, steroid courses or treatment failures.

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DRIED BLOOD SPOT SAMPLING CAN FACILITATE THERAPEUTIC DRUG MONITORING OF VEDOLIZUMAB THERAPY. S. Bian (1), L. Vandersmissen (1), S. Tops (1), E. Dreesen (1), M. Ferrante (2), S. Vermeire (2), A. Gils (1) / [1] University of Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [2] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** An association between vedolizumab (VDZ) trough concentrations and outcome has been observed in patients with inflammatory bowel diseases. This association was more pronounced in patients with ulcerative colitis (UC) compared to patients with Crohn's disease (CD). Dried blood spot (DBS) sampling by finger prick is easier and less invasive than venous sampling.

**Aim :** We aimed to develop and validate a DBS sampling method to facilitate intensive sampling for exploring the pharmacokinetics of VDZ in more detail.

**Methods :** First, DBS were prepared through spotting of 40  $\mu$ L of whole citrated blood spiked with VDZ (2-50  $\mu$ g/mL) onto a Protein Saver Card. Blood was extracted from DBS cards and the extracts were analyzed on ELISA. In addition to routine method validation (precision, accuracy, sensitivity, selectivity), DBS-related parameters including blood volumes, storage stability and impact of hematocrit were also assessed. Second, DBS derived from finger prick and serum samples obtained via venipuncture were taken concurrently at trough from 15 patients (7 UC and 8 CD) on at least one occasion and VDZ concentrations were compared. Statistical analyses were performed using R.

**Results :** Spiking VDZ to citrated whole blood followed by DBS sampling and extraction revealed an average extraction efficiency of  $70\pm 2\%$  ( $n=23$ ) with an accuracy of 98–104% and an imprecision of 7-11% for each concentration analyzed. Residual anti-TNF and antibodies towards anti-TNF did not impact the VDZ concentration whereas the addition of anti-VDZ antibodies to spiked VDZ samples caused a similar decrease in VDZ concentration in the DBS-based as in the serum-based measurements. Blood spot volumes between 15  $\mu$ L and 50  $\mu$ L produced comparable results. Storing the DBS papers at room temperature for one month or the extracts at  $-20^{\circ}\text{C}$  for 3 months did not impair DBS recovery (within 80-120% compared with the first measurements). Median VDZ serum-to-DBS ratio of 2.03 (IQR 1.89-2.01 ; Spearman's rank  $\rho=0.93$ ,  $p<0.0001$ ) was obtained across the therapeutic relevant range (7.5-39  $\mu$ g/mL serum concentration, 17-paired patient samples). DBS-converted serum concentrations showed no significant differences with analyzed serum concentrations ( $p=1.00$ ). No analytically relevant impact of hematocrit was observed in the range of 33.6% to 48.9%.

**Conclusions :** VDZ blood concentrations highly correlate with VDZ serum concentrations over a broad concentration range. The developed tool and the derived conversion ratio can be used to perform VDZ monitoring with improved flexibility by sampling at home, patient convenience and robustness.

ADAPTIVE DOSING DURING INFLIXIMAB INDUCTION THERAPY CAN IMPROVE MUCOSAL HEALING RATES IN PATIENTS WITH ULCERATIVE COLITIS. E. Dreesen (1), R. Faelens (1), G. Van Assche (2), M. Ferrante (2), S. Vermeire (2), A. Gils (3), T. Bouillon (3) / [1] KU Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [2] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [3] KU Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences.

**Introduction :** Papamichael et al. reported short-term mucosal healing (STMH, i.e., Mayo endoscopic sub-score  $\leq 1$ ) in 53% of patients with ulcerative colitis (UC) after infliximab (IFX) induction therapy and demonstrated a correlation between IFX trough concentrations (TC) and STMH (1).

**Aim :** To explore opportunities for IFX treatment optimisation during induction therapy in order to avoid primary non-response related to insufficient drug exposure.

**Methods :** A population pharmacokinetic (popPK) and pharmacodynamic (popPD) model was developed (sequential approach) to describe correlations between IFX exposure (area under the curve, AUC) and the post-induction Mayo endoscopic sub-score, using retrospectively collected data from 204 patients with UC during IFX induction therapy (1). All calculations were done with NONMEM 7.3. The model was recoded in SIMULO to perform simulations.

**Results :** IFX exposure was best described by a one-compartment popPK model (typical clearance 0.365 L/day and typical volume of distribution 8.1 L). The popPD model was a logistic regression model that described the relation between IFX dose, exposure and the probability of attaining STMH based on ordered transitions (pre-treatment versus post-induction) between Mayo endoscopic sub-score states 3, 2 and  $\leq 1$ . In the best model, cumulative AUC (cAUC) from the first dose up to time of endoscopy was identified as the dominant predictor of STMH. This model predicted a 75% STMH rate when the cAUC[week 0-12] is 4380  $\mu\text{g}\cdot\text{day}/\text{mL}$ . Simulations were performed with five different dosing regimens (200 patients each) and rates of STMH and drug expenditure were calculated and compared : (A) 3x 5 mg/kg at weeks 0, 2 and 6. (standard dosing regimen, fixed dosing) : - 55% STMH rate - 1080 mg average cumulative dose (B) 10 mg/kg at week 0, followed by 5 mg/kg at weeks 2 and 6 (fixed dosing) : - 60% STMH rate - 1420 mg average cumulative dose (C) 3x 10 mg/kg at weeks 0, 2 and 6 (fixed dosing) : - 70% STMH rate - 2160 mg average cumulative dose (D) 10 mg/kg at week 0, if TC[week 2]  $\geq 40 \mu\text{g}/\text{mL}$  : 5 mg/kg at weeks 2 and 6 ; if TC[week 2]  $< 40 \mu\text{g}/\text{mL}$  : 10 mg/kg at weeks 2 and 6 (TDM) : - 67% STMH rate - 1820 mg average cumulative dose (E) 10 mg/kg at week 0, doses at weeks 2 and 6 are proportionally adjusted to the TC[week 2] target of 40  $\mu\text{g}/\text{mL}$  (max. dose 10 mg/kg) (TDM) : - 68% STMH rate - 1940 mg average cumulative dose Simulation of dosing regimen A confirmed the STMH rate observed in our study population (55%) where most patients indeed received 3x 5 mg/kg, lending credibility to the model. The therapeutic drug monitoring (TDM) based dosing regimens D and E started from a 10 mg/kg dose at week 0 for all patients, followed by a dose optimisation at weeks 2 and 6 based on an IFX TC[week 2] target of 40  $\mu\text{g}/\text{mL}$ . TDM based dosing regimen D (10 mg/kg at week 0 with down-titration to 5 mg/kg based on the IFX TC[week 2] target of 40  $\mu\text{g}/\text{mL}$ ) yielded a 67% expected probability of STMH, compared to standard dosing regimen A. Clinical trial simulation demonstrated a probability of 75% to detect a significant improvement (regimen A versus regimen D) in a prospective study enrolling 200 patients per arm (paired t-test,  $p < 0.05$ ).

**Conclusions :** We developed the first popPK-PD model of IFX in UC, capturing the relation between IFX exposure and the rate of STMH. Based on a simulation exercise, TDM based dose optimisation during induction was clearly superior to treatment according to label for achieving STMH. Justification of the increased drug expenditure depends on available resources, although improved outcomes of higher exposure should be balanced against this decision. References : (1) K. Papamichael, T. Van Stappen, N. Vande Casteele, A. Gils, T. Billiet, S. Tops, K. Claes, G. Van Assche, P. Rutgeerts, S. Vermeire, M. Ferrante. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. Clin Gastroenterol Hepatol 2016 ; 14(4) : 543-9.

REACTIVE DOSE ESCALATION OF INFLIXIMAB IN PATIENTS WITH CROHN'S DISEASE IN TAILORIX LEADS TO IMPROVED OUTCOMES. E. Dreesen (1), D. Laharie (2), G. Lambrecht (3), P. Bossuyt (4), A. Buisson (5), J. Filippi (6), P. Van Hootegem (7), G. D'Haens (8), S. Vermeire (9), A. Gils (1) / [1] KU Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [2] Hospital Haut-Lévêque, Bordeaux, France, Service d'Hépatogastro-entérologie et oncologie digestive, [3] Damiaan Hospital, Oostende, Belgium, Maag-, darm- en leverziekten - Digestieve oncologie, [4] Imelda Hospital, Bonheiden, Belgium, Dienst gastro-enterologie, [5] Hospital Estaing, Clermont-Ferrand, France, Microbes, Intestine, Inflammation and Susceptibility of the host, UMR 1071 Inserm/Auvergne University ; USC-INRA 2018, [6] Hospital Archet, Nice, France, Département de Gastroentérologie et Nutrition Clinique, [7] Sint-Lucas Hospital, Brugge, Belgium, Department of Gastroenterology, [8] Academic Medical Centre, Amsterdam, Netherlands (the), Department of Gastroenterology and Hepatology, [9] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** In the TAILORIX study, “proactive” dose escalation based on infliximab (IFX) serum concentrations (TDM groups) had no added value to “reactive” dose escalation based on symptoms alone (TDM groups and control group) (1). In patients randomised to the TDM groups, reactive dose escalation was only allowed in the presence of elevated serum C-reactive protein (CRP, >5 mg/L) and/or faecal calprotectin (FC, >250 µg/g).

**Aim :** To evaluate the performance of reactive dose escalation in terms of restoring IFX exposure and the associated response in patients with Crohn’s disease (CD) in TAILORIX.

**Methods :** Prospectively collected data from 122 patients in TAILORIX were analysed to explore the effect of reactive dose escalation on IFX trough concentrations (TC), the CD activity index (CAI), CRP, FC and the CD endoscopic index of severity (CDEIS).

**Results :** A total of 71 dose escalations was performed in 122 patients, of which 37 were reactive, i.e., based on symptoms alone (control group, n=13) or on a combination of symptoms and biomarkers (TDM groups, n=24). IFX TC just before reactive dose escalation (at T0) varied widely (from below limit of quantification to 23.5 µg/mL) and were <3.0 µg/mL in only 11/37 cases. Eight weeks after dose escalation (at T+1), 4/11 patients did not achieve an IFX TC ≥3.0 µg/mL. Nevertheless, a significant increase in IFX TC was observed (+2.2 [+0.5-4.7] µg/mL, p=0.0001). CAI dropped significantly from 204 [174-292] at T0 to 151 [123-224] at T+1 (p=0.002), resulting in a restored clinical remission (CAI <150) in 13/26 patients. Median CRP and FC concentrations were not elevated at T0 and were also not found to change significantly after dose escalation : - IFX TC : 4.4 [3.3-6.8] µg/mL at T0 --> 8.1 [4.8-10.6] µg/mL at T+1 (p=0.0001, n=29) ; - CAI : 204 [174-292] at T0 --> 151 [123-224] at T+1 (p=0.002, n=26) ; - FC : 170 [100-371] µg/g at T0 --> 130 [100-249] µg/g at T+1 (p=0.060, n=21) ; - CRP : 2 [1-7] mg/L at T0 --> 2 [1-5] mg/L at T+1 (p=0.273, n=19). (n : number of data pairs. Changes between T0 and T+1 were evaluated using the Wilcoxon matched-pairs signed rank test.) Of all pharmacokinetic (PK ; i.e., IFX TC) and pharmacodynamic (PD ; i.e., CAI, CRP or FC) markers at T+1, a FC <237 µg/g was found to best predict endoscopic remission at week 54 of IFX therapy (13% misclassification error rate). Patients in endoscopic remission at week 54 (CDEIS <3) had significantly lower FC at T+1 compared to the patients with endoscopically active disease at week 54 (p=0.035). IFX TC, CAI and CRP at T0 or T+1 did not significantly differ between patients with and without endoscopically active disease at week 54. Using regression tree analysis, the strongest PK-PD relation was observed between IFX TC and FC (pooled T0 and T+1). IFX TC were significantly higher at time points when FC ≤250 µg/g (8.1 [4.9-15.1] µg/mL) compared to when FC >250 µg/g (4.4 [3.3-7.5] µg/mL) (p=0.041).

**Conclusions :** Reactive dose escalation resulted in a clinically relevant drop in CAI. Higher IFX TC were associated with lower FC, which was found to be a predictor of endoscopic remission after the first year of IFX therapy.

**References :** (1) D’Haens et al. 2016 Gastroenterology (692)

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INFLIXIMAB EXPOSURE PREDICTS SUPERIOR ENDOSCOPIC OUTCOMES IN PATIENTS WITH ACTIVE CROHN’S DISEASE : PHARMACOKINETIC-PHARMACODYNAMIC ANALYSIS OF TAILORIX. E. Dreesen (1), G. D’Haens (2), F. Baert (3), B. Pariente (4), Y. Bouhnik (5), J. Vander Woude (6), J. Moreau (7), D. Laharie (8), S. Vermeire (9), A. Gils (10) / [1] KU Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [2] Academic Medical Centre, Amsterdam, Netherlands (the), Department of Gastroenterology and Hepatology, [3] AZ Delta, Roeselare, Belgium, Maag-darm-leverziekten (gastro-enterologie), [4] Hospital Claude Huriez, Lille, France, Gastroenterology Unit, [5] Hospital Beaujon, Hospital Beaujon, France, Department of Gastroenterology, [6] Erasmus MC, Rotterdam, Netherlands (the), Afdeling Maag- Darm- leverziekten, [7] CHU Toulouse, Toulouse, France, Gastro-enterologie et hepatologie, [8] Hospital Haut-Lévêque, Bordeaux, France, Service d’Hépatogastro-entérologie et oncologie digestive, [9] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [10] KU Leuven, Leuven, Belgium, Departement of Pharmaceutical and Pharmacological Sciences.

**Introduction :** In the TAILORIX study, “proactive” dose escalation based on infliximab (IFX) serum concentrations (TDM groups) had no added value to “reactive” dose escalation based on symptoms alone (TDM groups and control group) (1). In patients randomised to the TDM groups, reactive dose escalation was only allowed in the presence of elevated serum C-reactive protein (CRP, >5 mg/L) and/or faecal calprotectin (FC, >250 µg/g).

**Aim :** To explore the value of pharmacokinetic (PK) and pharmacodynamic (PD) monitoring of IFX therapy in patients with Crohn’s disease (CD) in TAILORIX.

**Methods :** We studied associations between PK markers (i.e., IFX concentrations), PD markers (i.e., CD activity index or CAI, CRP and FC) and their predictive value for endoscopic remission (CD endoscopic index of severity, CDEIS <3), using prospectively collected data from 122 patients with CD in TAILORIX.

**Results :** During induction therapy, IFX trough concentrations (TC) were significantly higher in patients achieving endoscopic remission by week 12 compared to patients who did not : Endoscopic remission at week 12 (n=52) ↔ No endoscopic remission at week 12 (n=54) : \*Week 2 : - IFX : 26.5 [23.8-34.9] µg/mL ↔ 22.5 [17.8-27.9] µg/mL (p=0.002) - CAI : 159 [109-215] ↔ 194 [145-241] (p=0.056) - FC : 218 [100-716] µg/g ↔ 768 [171-1729] µg/g

(p=0.001) - CRP : 2 [1-6] mg/L ↔ 3 [2-6] mg/L (p=0.079) \*Week 6 : - IFX : 19.4 [14.8-26.3] µg/mL ↔ 15.6 [8.5-21.3] µg/mL (p=0.013) - CDAI : 122 [72-198] ↔ 138 [73-186] (p=0.455) - FC : 116 [100-289] µg/g ↔ 447 [194-934] µg/g (p<0.0001) - CRP : 1 [1-4] mg/L ↔ 3 [1-7] mg/L (p=0.123) An IFX TC ≥23.1 µg/mL at week 2 and ≥10.0 µg/mL at week 6 predicted endoscopic remission by week 12 (specificity 80%, sensitivity 57%, AUROC 0.67, p=0.002 and specificity 89%, sensitivity 37%, AUROC 0.64, p=0.013 for week 2 and week 6, resp.). Also, FC ≤250 µg/g at weeks 2 and 6 was associated with 69% and 68% endoscopic remission by week 12, resp., while only 44% and 26% of the patients with FC >250 µg/g demonstrated endoscopic remission by week 12 (p=0.021 and p=0.0002). During maintenance therapy, FC was significantly lower in patients achieving endoscopic remission by week 54 (p<0.0001). Using classification tree analysis, endoscopic remission at weeks 12 and 54 was found to be best predicted by FC. Overall, the strongest PK-PD correlation was found between IFX concentrations and FC at the same time point. IFX concentrations were significantly higher when FC was ≤250 µg/g (p<0.0001). Out of 43 dose escalation opportunities based on CDAI in the TDM groups, 23 (53%) were avoided per protocol as biomarkers were not elevated. This additional biomarker criterion did not apply to the control group, where normal CRP and/or FC was observed in nine out of 15 (60%) of the CDAI based dose escalation events.

**Conclusions :** In TAILORIX, a clear exposure-response relation was observed during IFX induction therapy. The additional value of IFX concentration based dose escalation during maintenance therapy might be blurred due to CDAI based dose escalations that increased the background IFX exposure and response. References : (1) D’Haens et al. 2016 *Gastroenterology* (692)

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POTENTIAL DIAGNOSTIC BIOMARKERS OF ULCERATIVE COLITIS-ASSOCIATED COLORECTAL DYSPLASIA. A. Merli (1), C. Massot (2), N. Blétard (3), F. Quesada Calvo (1), D. Baiwir (4), G. Mazzucchelli (5), N. Smargiasso (5), L. Servais (6), C. Oury (6), M. De Pauw-Gillet (7), E. De Pauw (5), C. Coimbra Marques (8), A. Colard (9), A. Vijverman (10), P. Delvenne (3), M. Meuwis (2), E. Louis (2) / [1] GIGA-R, University of Liège, Liège, Belgium, Translational Gastroenterology, [2] CHU de Liège -GIGA-R, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology and Translational Gastroenterology, [3] CHU de Liège, Liège, Belgium, Pathological anatomy and cytology, [4] GIGA facility ULiège, Liège, Belgium, GIGA-proteomics, [5] University of Liège, Belgium, Laboratory of Mass Spectrometry, Chemistry Dep., [6] GIGA-R, University of Liège, Liège, Belgium, Laboratory of Thrombosis and Hemostasis, [7] University of Liège, , Belgium, Mammalian Cell Culture Laboratory, [8] CHU de Liège, Liège, Belgium, Abdominal Surgery Department, [9] CHC de Liège, Liège, Belgium, Gastroenterology, [10] CHR Citadelle de Liège, Liège, Belgium, Gastroenterology and Digestive oncology.

**Introduction :** In Ulcerative Colitis (UC), dysplasia can develop in areas that are or have been affected by chronic inflammation and are identified as Dysplasia Associated to Inflammation (DAI). Dysplasia may also develop independently of chronic inflammation and be defined as Sporadic Dysplasia (DSp). Anatomopathological diagnosis of DAI remains difficult, especially when tissue inflammation is present, as mucosal regenerative remodelling impairs dysplasia confirmation.

**Aim :** The aim of this study is to highlight specific proteins of UC-DAI.

**Methods :** We performed a study on Formalin-Fixed Paraffin-Embedded (FFPE) samples from UC-DAI (n=5). To compare the proteomes of dysplastic (DAI), inflammatory (I) and normal (NL) paired tissues, we collected epithelial cells by Laser Capture Microdissection (LCM) before differential analysis using label free proteomics. Confirmation of tissue distribution of one selected protein differentially distributed between DAI and I or NL was done by Immunohistochemistry (IHC) on UC-DAI (n=11). Colonic tissues of a colitis-associated cancer mouse model (AOM/DSS) (Thaker Al et al, *J Vis Exp* 2012) were evaluated by IHC encompassing Low Grade Dysplasia (LGD - n=39), High Grade Dysplasia (HGD - n=12), Adenocarcinoma (ADC - n=6), I (n=30) and NL (n=6) tissues.

**Results :** Proteomic analysis enabled confident identification of 1070 proteins. Nineteen proteins showed differential abundance between DAI and I or NL, among which Solute Carrier Family 12 member 2 (SLC12A2) that was only detected in DAI. SLC12A2 IHC on UC cases confirmed significantly different distributions with DAI>I (p=0.0001 for bordering epithelium and p=0.002 for crypts epithelia) and DAI>NL (p<0.0001 for bordering epithelium and p=0.001 for crypts epithelia). In the AOM/DSS model, SLC12A2 was significantly increased in dysplasia and ADC compared to I and NL tissues (LGD>I with p<0.0001, LGD>NL with p=0.004, HGD>I with p<0.0001, HGD>NL with p=0.007, ADC>I with p=0.0002 and ADC>NL with p=0.009). SLC12A2 was significantly higher in advanced lesions (HGD>LGD with p=0.012 and ADC>LGD with p=0.038).

**Conclusions :** SLC12A2 could be a potential marker of DAI in UC as being able to identify dysplasia from surrounding tissues with inflammation. It requires proper validation to evaluate its power as a specific IHC marker that could be used to clarify difficult cases diagnosed as “indefinite for dysplasia”.

GOLIMUMAB DRIED BLOOD SPOT ANALYSIS (GOUDA): A PROSPECTIVE TRIAL TO VALIDATE GOLIMUMAB CONCENTRATION ANALYSIS USING THE DRIED BLOOD SPOT METHODOLOGY. I. Detrez (1), E. Dreesen (1), G. Van Assche (2), S. Vermeire (2), M. Ferrante (2), A. Gils (1) / [1] KU Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [2] UZ Leuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing.

**Introduction :** Therapeutic drug monitoring of golimumab (GLM) is performed by measuring trough concentrations, obtained by venous sampling. Sampling via dried blood spots (DBS) allows multiple determinations within a dosing interval and thereby gives a more complete insight in the total drug exposure (here expressed as area under the curve or AUC).

**Aim :** We assessed the robustness and user-friendliness of the DBS method and the relation between GLM trough concentration (TC) and exposure during induction and maintenance regimens.

**Methods :** Ten patients with ulcerative colitis (UC) were recruited prospectively (NCT02910375). For patients initiating GLM therapy (n=5), 39 finger punctures and 13 corresponding venepunctures (6 at trough and 7 at intermediate time points) were performed over a period of 18 weeks. For patients on  $\geq 2$  years GLM maintenance therapy (n=5), the sampling schedule consisted of 20 finger punctures and 8 corresponding venepunctures (4 at trough and 4 at intermediate time points) over a period of 12 weeks. At the end of the study, user-friendliness was evaluated using a questionnaire. GLM and anti-GLM antibody concentrations were measured using in-house developed ELISA's. (1) Non-compartmental pharmacokinetic evaluation was performed using the PKNCAR package. Mucosal healing (Mayo endoscopic sub-score  $\leq 1$ ) was evaluated at week 14. Data are expressed as mean $\pm$ SD.

**Results :** A total of 79 matched pairs of serum and DBS sample GLM concentrations showed a very good correlation (Spearman  $r=0.990$ ,  $p<0.0001$ ). Nine out of 10 patients reported DBS sampling as user-friendly. For patients initiating therapy, TC were not linearly correlated with AUC ( $R^2=0.29$ ). In these patients, a significant decrease in TC was observed from w2 ( $11\pm 4.1 \mu\text{g/mL}$ ) to w10 ( $3.3\pm 1.9 \mu\text{g/mL}$ ) ( $p=0.005$ ) but not in AUC within the respective dosing intervals (AUC[0-2]= $212\pm 82.4 \mu\text{g}\cdot\text{day/mL}$  vs. AUC[6-10]= $175\pm 50.6 \mu\text{g}\cdot\text{day/mL}$ ) ( $p=0.085$ ). This decrease in TC was more pronounced in patients without mucosal healing than in patients with mucosal healing ( $p=0.028$ ). During maintenance therapy, a trend for lower TC and AUC were observed in patients starting therapy (week 6-18) than in patients who were successfully treated for  $\geq 2$  years ( $p=0.064$  and  $p=0.053$ ). Using a drug-tolerant assay, anti-GLM antibodies were detectable in two starters and in one patient on maintenance therapy.

**Conclusions :** The GOUDA study showed that DBS sampling is a robust and patient-friendly alternative to venous blood collection. DBS sampling provides also better insights into GLM exposure, as exposure was not captured well by the TC during induction. The GOUDA data are currently pooled with two other datasets to determine the GLM exposure-response relationships. (1) Detrez, et al. 2016. Journal of Crohns & Colitis, 10(5) :575-81.

INFLIXIMAB AND VEDOLIZUMAB SHOW A DIFFERENT EFFECT ON CLOT FORMATION IN INFLAMMATORY BOWEL DISEASE PATIENTS. I. Detrez (1), V. Ballet (2), M. Peeters (1), G. Van Assche (2), S. Vermeire (2), M. Ferrante (2), A. Gils (1) / [1] KU Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, [2] UZ Leuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing.

**Introduction :** Inflammation and thrombosis are intertwined. Therefore, ulcerative colitis (UC) and Crohn's disease (CD) patients tend to have an altered clot-lysis (CL) profile, which may reflect their higher risk for venous thromboembolic events (VTE). Blocking TNF by infliximab (IFX) has been shown to normalise the CL profile of IBD patients responding to the therapy. (1)

**Aim :** We aimed to investigate whether the gut-specific, anti-integrin vedolizumab (VDZ) exhibits a similar effect on the CL profile of IBD patients upon treatment response.

**Methods :** Forty-two IBD patients initiating IFX (n=20) or VDZ (n=22) therapy for active UC (median total Mayo score 8) or CD (median Harvey-Bradshaw Index (HBI) 9), and 22 healthy controls (HC) were prospectively included. None of the patients had a history of VTE. Plasma was collected before the first infusion (week 0, w0) and after induction therapy (w14). From the CL profile, area under the curve (AUC ; global marker for coagulation/fibrinolysis), 50% clot-lysis time (CLT ; marker for fibrinolytic capacity), amplitude (marker for clot formation) and time to peak (tmax ; marker for clot formation rate) were deduced. (1) Disease remission (w14) was defined by Partial Mayo Score  $\leq 2$  and Mayo endoscopic sub-score  $\leq 1$  (UC) or HBI  $\leq 5$  and C-reactive protein concentration (CRP)  $\leq 5 \text{ mg/L}$  (when baseline CRP was elevated) (CD). Results were expressed relative to the values of the plasma pool of HC (=100%).

**Results :** Prior to biological treatment, AUC and amplitude were significantly higher in IBD patients as compared to HC (161 [111-211] % vs. 101 [79-133] % ;  $p=0.001$  and 127 [104-148] % vs. 94 [85-114] % ;  $p=0.001$ , respectively). Upon

induction therapy, response to either IFX or VDZ therapy was accompanied by a significant decrease in AUC (167 [78-212] % vs. 85 [68-100] % ; p=0.014 and 125 [96-180] % vs. 104 [78-145] % ; p=0.010) and amplitude (126 [98-166] % vs. 89 [65-99] % ; p=0.027 and 116 [103-139] % vs. 101 [89-120] % ; p=0.020) to values observed as those in HC. Baseline AUC and amplitude were already lower in w14 VDZ responders compared to non-responders (p=0.096 and p=0.048, respectively). From w0 to w14, tmax was significantly prolonged in IFX responders (26 [21-39] min vs. 36 [27-45] min ; p=0.004), whereas the opposite was observed for VDZ responders (34 [16-61] min vs. 31 [18-47] min ; p=0.044). No patient developed a VTE during one-year study follow-up.

**Conclusions :** Response to both IFX and VDZ induction therapy is reflected in a diminution of the CL profile of the IBD patient. Upon response, time to clot formation was prolonged by IFX but shortened by VDZ responders. Inhibition of the  $\alpha 4\beta 7$  integrin :fibronectin interaction by VDZ might play a role and deserves further investigation. (1) Bollen, et al. 2015. *Inflamm Bowel Dis*, 21(3) :570-8.

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EPIDEMIOLOGY OF CLOSTRIDIUM DIFFICILE INFECTIONS IN IBD OVER TWO DECADES. A. Moens (1), B. Verstockt (1), K. Machiels (2), P. Bossuyt (3), A. Verdonck (4), K. Lagrou (4), S. Vermeire (1), M. Ferrante (1) / [1] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [2] KU Leuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing, [3] Imeldaziekenhuis, Belgium, Department of Gastroenterology and Hepatology, [4] University Hospitals Leuven, Leuven, Belgium, Department of Laboratory Medicine.

**Introduction :** The incidence of Clostridium difficile infection (CDI) has been rising in the overall population as well as in patients with inflammatory bowel disease (IBD). However, it stands to reason that in the era of biologic IBD treatments, the incidence of CDI in IBD may be changing.

**Aim :** A retrospective observational study to establish the incidence of CDI in IBD over a two-decade period.

**Methods :** The electronic database of the Department of Laboratory Medicine of our hospital (tertiary referral center) was reviewed for all stool samples received from patients, admitted on gastroenterology wards or visiting the gastroenterology outpatient clinic, from 2000 until 2017 for the diagnosis of CDI. In 2000, CDI was defined as diarrhea with positive toxin A and from 2005 a positive toxin A/B. Currently, diagnosis is based on positive enzyme immunoassays (EIAs) for glutamate dehydrogenase and toxin A/B or positive PCR for toxin producing Clostridium difficile in case of discordant EIAs.

**Results :** Out of 538 stool samples, 220 patients were diagnosed with CDI of whom 22.3% had IBD [30 Crohn's disease, 17 ulcerative colitis (UC) and 2 IBD unclassified]. By comparing baseline characteristics, IBD patients were found to be younger (p<0.0001), had less cardiovascular comorbidity (p=0.02), fewer prior hospitalizations (p=0.04) and fewer prior antibiotic use (p=0.003). In addition, the need for hospitalization for CDI was lower (p<0.0001) and duration of hospitalization was shorter (p<0.0001) compared to non-IBD patients. At CDI diagnosis more IBD patients were on biologic therapy (p<0.0001), immunomodulators (p<0.0001) or steroids (p<0.0001). However, they were less likely to be taking proton pump inhibitors (p=0.001). There was no difference in the use of endoscopy for diagnosis of CDI in both groups (p=0.2), but when used pseudomembranes were only seen in non-IBD patients (0% vs. 32%, p=0.006). The median number of CDI (IQR) in IBD patients from 2000-2008 was 2 (1.5-5) and from 2009-2017, 4 (1.5-5). However, the median number of CDI (IQR) in non-IBD patients was 9 (5-13) in the first and 17 (11-19.5) in the second period. A linear-by-linear test showed a trend towards increasing number of CDI in non-IBD patients (p=0.078), whereas the number of CDI in IBD patients remained constant over time (p=0.59). There was no difference in the choice of antibiotics between the IBD and non-IBD group [metronidazole (49% vs 46%), vancomycin (27% vs 28%)] or in the number of recurrent CDI (rCDI) (18% vs. 17%, p=0.8). Furthermore, rCDI was independent of the antibiotics used for the first CDI in both groups. The outcome of CDI in IBD was favorable with only two UC patients needing semi-urgent colectomy (after one and four weeks). The one-year mortality was lower in the IBD patients (4%) compared to the non-IBD patients (56%) (p<0.0001), probably explained by younger age and less comorbidity.

**Conclusions :** The last two decades, despite the increasing use of biologic medication, the incidence of CDI in IBD remained stable in contrast to the general population where, although not statistically significant, a trend towards a higher incidence was seen. The overall outcome of CDI in IBD patients was favorable and only two patients needed colectomy.

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PROTEOMIC ANALYSIS HIGHLIGHTS DIVERGENCES AND CONVERGENCES BETWEEN ILEAL AND COLONIC PATHOLOGICAL PROCESSES INVOLVED IN CROHN'S ULCERS. N. Pierre (1), C. Reenaers (2), C. Van Kemseke (2), J. Loly (2), G. Mazzucchelli (3), N. Smargiasso (3), D. Baiwir (3), D. Morsa (3), E. De Pauw (3), M.



Meuwis (4), E. Louis (4) / [1] University of Liege, GIGA-R, Liège, Belgium, Translational Gastroenterology, [2] CHU de Liège, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology, [3] University of Liège, Belgium, Laboratory of Mass Spectrometry, Chemistry dep, [4] CHU de Liège -GIGA-R, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology and Translational Gastroenterology.

**Introduction :** Crohn disease (CD) affects predominantly the ileum and/or the colon. Previous genome wide association studies have revealed that patients with ileal or colonic disease present partly distinct risk loci. This finding opens new perspectives for the development of personalised treatments and biomarkers based on disease location. To this end, protein-based approaches are needed to discover new tissue-specific proteins associated with CD.

**Aim :** The goal of our study was to decipher the relation linking disease location and physiopathological processes by comparing the proteomic picture of ileal/colonic CD ulcers with normal tissues.

**Methods :** CD patients (n=16) with ileum (n= 8) or colon (n=8) ulcers were included. Paired biopsies were taken at the edges of the ulcer (U) and in the nearby endoscopically normal mucosa (N). Label free proteomic differential analysis was run using protein digests obtained with the 16 paired biopsies. Identifications and quantification of proteins were performed using MaxQuant. Paired t-test with Benjamini-Hochberg correction was applied for selection of proteins differentially abundant between N and U tissues. Pathway enrichment analysis was performed with the Database for Annotation, Visualization and Integrated Discovery (DAVID) bioinformatics tool.

**Results :** We identified and quantified 4652 and 5422 proteins in ileum and colon samples, respectively. Among these proteins, 440 (ileum) and 409 (colon) were differentially distributed between N and U tissues. The well-recognised fecal marker of CD activity, calprotectin, was increased in U, showing consistency of our results with clinical observations. When proteins were ranked by increasing p-value, the calprotectin subunits S100-A9 and S100-A8 appeared respectively at the 266-300th (ileum) and the 142-165th (colon) positions, suggesting that our dataset could reveal new relevant proteins in CD. In both ileum and colon ulcers, pathway enrichment analysis showed that the proteins decreased in lesions, were related to energetic metabolism, whereas the increased ones were mainly involved in the endoplasmic reticulum-golgi protein processing and the immune response. In the ileum, the over-abundant proteins found in U were also involved in mRNA maturation and protein translation, this was not observed in the colon.

**Conclusions :** Our proteomic experiment highlights common and distinct physiopathological processes between ileal and colonic CD ulcers, thus indicating a partial segment specificity of the disease. Further investigations are required to confirm these results. Among the 849 proteins differentially abundant between N and U mucosa, new therapeutic targets and new biomarkers could emerge for CD patient management.

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SERUM PROTEOMIC PROFILING IN CROHN'S DISEASE PATIENTS UNDERGOING ILEOCOLONIC RESECTION REVEALS DISCRIMINATIVE INFLAMMATORY MARKERS FOR ENDOSCOPIC RECURRENCE.

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**Introduction :** Although not curative, intestinal resection is often required in Crohn's disease (CD) patients. Postoperative recurrence (POR) is common and early postoperative endoscopy is considered the gold standard for detection of POR. The recent expansion of proteomics provides an attractive way to identify new biomarkers of early inflammation.

**Aim :** We investigated serum inflammatory profiles for their predictive and discriminative value for POR in CD patients undergoing ileocolonic resection. We also studied if combination of proteomics with metagenomics including our recent association of *Fusobacterium* spp with POR, may improve diagnostic accuracy.

**Methods :** Serum samples were prospectively collected from 70 healthy subjects (HS) and from 57 CD patients (median age 46.3 years, 47.4% male) undergoing ileocecal resection with ileocolonic anastomosis before surgery and at month 1, 3 and 6 after surgery. POR - defined by a Rutgeerts score  $\geq 2$  on endoscopy was assessed at month 6. Relative levels of 92 inflammation-related proteins were measured using the Proximity Extension Assay (PEA) (Olink Bioscience, Sweden). Fecal calprotectin (ELISA, Buhlmann) and relative abundance of *Fusobacterium* spp (16S RNA sequencing) were available in a subset of 47 and 37 patients respectively. Logistic regression and receiver operating characteristic curve analysis were used to evaluate the discriminative power of significant biomarkers. Analyses were conducted in SPSS with false discovery rate (FDR) correction for multiple testing. Results were validated in a second cohort of 41 patients (median age 39.5 years, 36.6% male).

**Results :** Comparisons of the serological markers between both patient groups with and without POR were not significantly different after FDR correction at baseline, month 1 and month 3. At month 6, 6 markers including CCL3, CCL4, OSM, FGF21, ST1A1 and TGF- $\alpha$  were significantly increased in recurrence patients (N=29) compared to patients remaining in remission (N=28). A model combining these 6 proteins showed an accuracy of 78.9% and AUC of

0.844 ( $p < 0.001$ ). Validation of the model in a second cohort of 41 CD patients (of whom 7 remained in remission and 34 developed recurrence) showed an accuracy of 87.8% and AUC=0.962 ( $p < 0.001$ ). Calprotectin and Fusobacterium spp each showed lower discriminative power (AUC 0.653,  $p=0.072$  and AUC 0.629,  $p=0.18$  resp). Combination with the 6 serum proteins showed an improved discriminative capacity for Fusobacterium spp (AUC 0.888  $\rightarrow$  0.929) but not for calprotectin (AUC 0.801  $\rightarrow$  0.804).

**Conclusions :** Using a panel of inflammation-related proteins, we identified a combination of 6 serological biomarkers able to discriminate early endoscopic POR. These surrogate markers performed better than faecal calprotectin and incorporation of a microbial marker further improved its discriminatory capacity. Quantitative validation is required to test its clinical utility.

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QUANTITATIVE MICROBIOME PROFILING CHANGES THE DESCRIBED DYSBIOTIC STATE IN INFLAMMATORY BOWEL DISEASE. C. Caenepeel (1), S. Vieira-Silva (2), J. Sabino (3), K. Machiels (3), G. Falony (4), M. Ferrante (5), G. Van Assche (5), J. Raes (4), S. Vermeire (5) / [1] KU Leuven, Leuven, Belgium, Departement Chronische Ziekten, Metabolisme en Veroudering, [2] KU Leuven, Leuven, Belgium, Department of Microbiology and Immunology, [3] KU Leuven, Leuven, Belgium, Department of Chronic Diseases, Metabolism and Ageing, [4] Rega Institute, Leuven, Belgium, Department of Microbiology and Immunology, [5] UZ Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology.

**Introduction :** Gut microbiota play a crucial role in the pathogenesis of inflammatory bowel disease (IBD). The usage of culture-independent techniques leads to the identification of dysbiosis in IBD, but generate only relative microbiome profiles (RMP) with no ability to provide information on the extent or directionality of changes in taxa abundances. Quantitative microbiome profiling (QMP) combines microbiome sequencing with flow cytometric counting of microbial cells to quantitatively assess microbiota variation (Vandeputte et al, 2017).

**Aim :** We aimed to investigate the differences in microbial load in patients with active Crohn's disease (CD). We compared the distribution of the different enterotypes and hypothesized that microbial load may be associated with the inflammatory status in IBD

**Methods :** Fecal samples of 69 CD patients with endoscopically active disease were collected prior to biological therapy. Fecal samples of 66 healthy controls (HC) from the Flemish Gut Flora Project (FGFP) were used as comparison. Microbiota phylogenetic profiling was conducted by using 16S rRNA gene amplicon sequencing, and microbial loads of frozen fecal samples were measured using flow cytometry. These cell counts were used to transform the sequencing data into an absolute microbiome abundance matrix that allowed QMP by modifying sequencing depth rarefying procedures and generated QMP expressed as number of cells per gram feces.

**Results :** Our flow cytometric analysis data confirms a significant lower microbial load (Wilcoxon  $r = -0.49$  ;  $p < 0.001$ ) in active CD, up to a hundred-fold lower, compared to HC. Enterotypes distribution varies between the active CD and HC. Notably, 10.6% of the FGFP samples were typed as Bacteroides2, compared to a much higher prevalence of 88.2 % in our patients with active CD. Furthermore, we compared the microbial load between clinical responders (defined as a HBI score of  $\leq 4$  points) and non-responders (defined as no decrease from the study baseline HBI score of at least 4 points) prior to biological therapy. Baseline microbial density was not significantly different between these clinical responders (N=54) and non-responders (N=15) (Wilcoxon  $p=0.48$ ).

**Conclusions :** The introduction of QMP, as recently published, leads to a revisiting of the known dysbiosis in IBD microbiome research. Using QMP, we confirm previous observations of lower microbial loads and a high Bacteroides2 prevalence in CD, even more pronounced due to the active disease state. No difference in microbial density is seen between clinical responders and non-responders to biological therapy, but further investigation is needed.

- I29 -

ILEAL GENE EXPRESSION CHANGES ARE ASSOCIATED WITH COLONIC DISEASE ACTIVITY IN PATIENTS WITH ULCERATIVE COLITIS. M. Vancamelbeke (1), S. Verstockt (2), M. Ferrante (1), G. Van Assche (1), S. Vermeire (1), I. Cleynen (2) / [1] KU Leuven, Leuven, Belgium, Department Chronic Diseases, Metabolism & Ageing (CHROMETA), Translational Research Center for Gastrointestinal Disorders (TARGID), [2] KU Leuven, Leuven, Belgium, Department of Human Genetics, Laboratory of Complex Genetics.

**Introduction :** Ulcerative colitis (UC) is a chronic, relapsing disorder characterised by inflammation limited to the colon and rectum. From a pathophysiologic point of view, there is no explanation for the spatial restriction of inflammation, and studies on the involvement of ileal changes in patients with UC are scarce.

**Aim :** Here we therefore aimed to investigate gene expression profiles of the unaffected ileum of UC patients, and compare these to non-IBD controls to see if these factors contribute to disease perpetuation.

**Methods :** Biopsies were collected from normal terminal ileum of 16 patients with UC (50% male, median [interquartile range, IQR] age 49.5 [29.4-66.7] years, median [IQR] disease duration 11 [7-15.5] years, Montreal disease extent 1 E1/8 E2/7 E3) ; and 14 controls (42.9% male, age 56.7 [45.7-60.6] years) who underwent endoscopy for polyp screening. Patients with backwash ileitis were excluded. Disease activity for UC was based on endoscopic findings, with active disease defined as Mayo endoscopic subscore  $\geq 2$ . Next-generation single-end sequencing was performed using the Illumina HiSeq 4000 NGS platform. One sample was removed from analysis due to suboptimal read counts. Differential expression analysis was performed using DESeq.

**Results :** One-fourth of UC patients had active colonic disease at the time the biopsy was taken. Comparative analyses of gene expression levels between active UC patients and controls identified seven genes with significant different expression (false discovery rate (FDR)  $\leq 0.1$  and fold change (FC)  $\geq 2$ ). The top signals were seen for MUC4 which was significantly upregulated (FC=3.89, FDR=0.01), and FAM21B which was significantly downregulated (FC=0.06, FDR=0.05) in ileum of active UC compared to controls. All other significant genes were upregulated (CEACAM20, CASP10, LRG1, PDZK1IP1 and GRAMD2). Pathway analysis showed association with antiviral innate immunity and apoptosis signalling. When comparing ileal samples from inactive UC patients with controls, however, we did not observe any differentially expressed genes after adjustment for multiple testing. Also among UC patients, no differentially expressed genes were seen for those with active colonic disease versus those without.

**Conclusions :** Our study showed that - while no overt inflammation is generally seen in ileum of UC patients - subtle ileal gene expression changes do occur in patients depending on disease activity of the colon. The identified genes are involved in a range of UC-associated biological processes including barrier function, cell trafficking, apoptosis, angiogenesis and immune signalling. Whether ileal changes in these processes should be seen as a driving factor in UC or secondary epiphenomenon remains to be confirmed with functional studies.

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LOW ADALIMUMAB SERUM LEVELS AT WEEK 4 PROVOKE IMMUNOGENICITY AND INFLUENCE THERAPY OUTCOME IN ANTI-TNF NAÏVE CROHN'S DISEASE PATIENTS. B. Verstockt (1), G. Moors (2), S. Bian (3), T. Van Stappen (3), S. Tops (3), V. Ballet (2), G. Van Assche (1), S. Vermeire (1), A. Gils (4), M. Ferrante (1) / [1] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing, [2] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology and Hepatology, [3] KU Leuven, Leuven, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies, Department of Pharmaceutical and Pharmacological Science, [4] University Hospitals KULeuven, Leuven, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies, Department of Pharmaceutical and Pharmacological Sciences.

**Introduction :** Adalimumab (ADM) serum levels (SL) during maintenance are associated with treatment outcome and need for dose-escalation in Crohn's disease (CD) patients. Little is known about the clinical relevance of proactive testing of ADM SL during induction.

**Aim :** We aimed to evaluate correlation between ADM SL at week 4, ADM anti-drug antibody (ADA) presence and outcome.

**Methods :** Serum samples from biologically naïve CD patients were prospectively collected at trough at week 4 and 12 after ADM initiation. Clinical remission was defined as an average daily stool frequency  $\leq 2.8$  and an average abdominal pain score  $\leq 1$ . In patients with an elevated baseline C-reactive protein (CRP), biochemical remission was defined as a CRP  $\leq 5.0$ mg/L and response as a decrease of at least 50% or CRP normalisation. ADM SL were measured with a novel ADM RIDA@QUICK lateral flow assay (LFA, R-biopharm) and benchmarked with the RIDASCREEN<sup>®</sup> ELISA. ADA presence was determined using a drug-resistant assay, allowing detection in presence of high concentrations of ADM (Bian S. et al. AAPS J 2017).

**Results :** Ninety-two patients with active CD were included. Median SL at week 4, measured by LFA (11.2 $\mu$ g/mL, IQR 8.2-14.5), correlated well with median ELISA SL at week 4 (10.0mg/ml, IQR 7.7-12.9) ( $r=0.96$ ,  $p<0.001$ ). Lower median SL at week 4 were significantly associated with the presence of ADA at week 12 (8.4 in ADA positive vs 12.8mg/ml in ADA negative patients,  $p=0.006$ ). Only 3 out of 15 ADA+ patients at week 12, had detectable ADA at week 4 already. Similarly, a trend towards lower median SL at week 2 could be observed in these 3 ADA+ patients at week 4, compared to the remaining ADA- patients (4.4 vs 9.9mg/ml,  $p=0.2$ ). Although median weighted patient reported outcome, PRO2, significantly decreased from baseline to week 12 (15.0 vs 8.0,  $p<0.001$ ), SL at week 4 were not significantly associated with clinical remission at week 12. However, SL at week 4 were associated with biological response and remission at week 12 ( $p=0.002$ ,  $p=0.005$ ), and with the need for dose-escalation in symptomatic patients within the first year ( $p=0.01$ ). In patients given dose-escalation, discontinuation of ADM thereafter, due to loss-of-response (LOR), was associated with lower SL at week 12 ( $p=0.02$ ) and ADA positivity at week 12 ( $p=0.001$ ).

**Conclusions :** Lower SL at week 4 are associated with ADA development later on, and seem to be the cause rather than the consequence of lower SL afterwards. ADM SL during induction may predict the need for and the success of

dose-escalation. Although these findings need prospective validation, availability of an ADM rapid assay creates the opportunity for optimizing therapy early during induction.

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FILGOTINIB (GLPG0634, GS-6034), A JAK-1 SELECTIVE INHIBITOR, SIGNIFICANTLY REDUCES GUT TISSUE PSTAT3 IN CROHN'S DISEASE PATIENTS. G. De Hertogh (1), G. Chen (2), D. French (3), E. Huntzicker (3), A. Van Der Aa (4), T. Van Kaem (4), P. Harrison (4), C. Tasset (5), R. Galien (6), Y. Pan (3), B. Feagan (7), W. Sandborn (8), S. Vermeire (9) / [1] University Hospitals Leuven, Leuven, Belgium, Department of Pathology, [2] Gilead Sciences, Inc, Foster City, United States (the), Department of biostatistics, [3] Gilead Sciences, Inc, Foster City, United States (the), Biomarker Sciences, [4] Galapagos NV, Mechelen, Belgium, Research and Development, [5] Galapagos NV, Mechelen, Belgium, Rsearch and Development, [6] Galapagos SASU, Romainville, France, Research and Development, [7] Robarts Research Institute, London, Ontario, Canada, Clinical Trials, [8] University of California San Diego, CA, United States (the), Division of Gastroenterology, [9] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology.

**Introduction :** Janus kinases (JAK) are a family of tyrosine kinases that play a key role in the signalling of more than 60 cytokines and growth factors. Many of these cytokines display pro-inflammatory activity in Crohn's Disease (CD). The selective JAK1 inhibitor filgotinib blocks cytokine signalling through the inhibition of STAT phosphorylation and has shown clinical efficacy in a double-blind, placebo-controlled Phase 2 study in CD (FITZROY). In order to understand the mechanism of action of filgotinib in CD patients, we measured the level of phosphorylated STAT3 (pSTAT3) in gut biopsies from this study.

**Aim :** To present the effects of filgotinib on levels of pSTAT3 in pre-and post-treatment intestinal biopsies.

**Methods :** CD patients were randomized 3 :1 to receive 200mg filgotinib or placebo QD for the first 10 weeks. Two biopsies, one each from the most and least affected mucosa, were collected during screening and at Wk 10 from each of the 6 predefined segments of the lower gastrointestinal tract. Samples from 60 patients with complete set of paired biopsies were selected. pSTAT3 was evaluated by IHC using an antibody specific to phosphorylated Y705. H-Score was quantified using Definiens Tissue Studio software. The mixed effect ANOVA method was used for evaluating the treatment effect and difference between patients achieving clinical remission (defined as CDAI < 150) and those who did not.

**Results :** Basal pSTAT3 level was comparable for the filgotinib and placebo groups. Following filgotinib treatment, pSTAT3 level was significantly reduced in the most affected mucosa from all segments combined : -36% (95% CI : -51%, -17%), whereas reduction in the placebo arm was not significant (although with less subjects) : -24% (95% CI : -49%, +14%). In patients with clinical remission at Wk 10, pSTAT3 levels showed a significant reduction from baseline in each group : -62% (95% CI : -83%, -16%) with placebo, and -42% (95% CI : -57%, -21%) with filgotinib. In patients not achieving clinical remission, pSTAT3 from the placebo arm showed an average numerical increase of +12% (95% CI : - 21%, +94%) whereas pSTAT3 was on average reduced with filgotinib : -28% (95% CI : -51%, +7%). Similar observations were made in the least affected mucosa of different segments.

**Conclusions :** Significant reduction of pSTAT3 by filgotinib on inflamed gut of CD patients provides direct evidence of its anti-inflammatory effect. Clinical remission status is associated with a decrease in pSTAT3. In non-remitters, the observed pSTAT3 reduction with filgotinib illustrates its pharmacodynamic effect through JAK1 inhibition. A large phase 3 program in CD and UC is ongoing.

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EFFECT OF DISEASE DURATION AND LOCATION ON CLINICAL REMISSION IN CROHN'S DISEASE PATIENTS TREATED WITH FILGOTINIB, A SELECTIVE JAK1 INHIBITOR : POST-HOC ANALYSIS FROM THE PHASE 2 FITZROY STUDY. S. Vermeire (1), A. Colard (2), V. Muls (3), M. De Vos (4), A. Vijverman (5), O. Dewit (6), A. Van Der Aa (7), C. Jamoul (7), C. Tasset (7), P. Harrison (7), G. D'Haens (8) / [1] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology, [2] Clinic Saint-Joseph, Liege, Belgium, Department of Gastroenterology, [3] CHU Saint-Pierre, Brussels, Belgium, Department of gastroenterology, [4] University Hospital Gent, Belgium, Department of gastroenterology, [5] Citadelle Hospital, Liege, Belgium, Department of gastroenterology, [6] Saint-Luc University Hospital, Brussel, Belgium, Department of gastroenterology, [7] Galapagos NV, Mechelen, Belgium, Research and Development, [8] Academic Medical Center, Amsterdam, Netherlands (the), Department of Gastroenterology.

**Introduction :** Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor, with demonstrated efficacy in rheumatoid arthritis. This 20-week Phase 2 study evaluated the efficacy and safety of filgotinib in patients with active Crohn's disease (CD). The primary endpoint (CDAI remission at Week 10) was met with an acceptable safety profile.

**Aim :** The effect of disease duration and location has been assessed post-hoc on the primary endpoint.

**Methods :** 174 patients with moderate-to-severely active CD (CDAI : 220 to 450) and ulcerations confirmed by centrally read endoscopy were randomized 3 :1 to receive 200mg filgotinib (FIL) or placebo (PBO) QD for 10 weeks. Immunosuppressants were discontinued prior to treatment initiation but corticosteroid-treated patients remained stable until Week 10 (W10). Patients naïve to anti-TNF therapy as well as patients previously exposed to anti-TNF with no response or loss-of-response were included. Clinical remission at W10 was analysed by disease duration (< 5 years (yrs), 5-10 yrs and > 10 yrs) and historical location (ileal, ileo-colonic, colonic).

**Results :** Baseline disease characteristics were similar in both initial treatment groups, showing a population of active Crohn's patients (mean CDAI 293, mean SES-CD 14.6, mean CRP 15.6 mg/L, 41% > 10mg/L, oral corticosteroids use 51%, mean daily dose 21.6 mg). Forty-two % of patients were anti-TNF naïve, 58% were anti-TNF non-responder. Forty-three % were diagnosed for less than 5 yrs, 30% between 5 and 10 yrs and 27% for > 10 yrs. Most anti-TNF naïve patients (63%) had <5 yrs CD, whereas 71% of anti-TNF non-responders were diagnosed > 5 yrs. A total of 62% of patients had ileo-colonic disease, whereas 18% had ileal involvement only and 20% had only colonic involvement. The percentage of FIL-treated patients in clinical remission at W10 is not impacted by longer disease duration (53%, 43% and 43% for respectively <5 yrs, 5-10 yrs and >10 yrs) while for PBO-treated patients the percentage of remitters was lower with disease duration of >10 yrs (24%, 27% and 17% for respectively <5 yrs, 5-10 yrs and >10 yrs). In FIL-treated patients, consistently high remission rates in both anti-TNF naïve and (to a lesser extent) anti-TNF non-responders were seen, independently of disease duration (anti-TNF naïve : 59%, 60%, 62% ; anti-TNF non-responders : 42%, 37%, 32%, for respectively <5 yrs, 5-10 yrs and >10 yrs). FIL treatment effect was also shown independent of disease location, although a higher percentage of remitters was observed in the subgroup with colonic disease only (FIL : 42%, 41% and 68%, and PBO : 14%, 26% and 17% for respectively ileal, ileo-colonic, and colonic disease).

**Conclusions :** This post-hoc analysis of the Phase 2 FITZROY study indicates that inhibition of JAK1 with filgotinib in Crohn's patients is consistently associated with clinical remission, independently of disease duration and location.

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SERUM MARKERS PREDICT OUTCOME TO USTEKINUMAB IN PATIENTS WITH REFRACTORY CROHN'S DISEASE AND PROVIDE INSIDES IN THE MECHANISM OF ACTION. B. Verstockt (1), S. Vermeire (1), S. Verstockt (2), B. Creyns (3), N. Ardeshir Davani (4), C. Breyneart (5), G. Van Assche (1), M. Ferrante (1) / [1] University Hospitals KULeuven, Leuven, Belgium, Department of Gastroenterology and Hepatology - Department of Chronic Diseases, Metabolism and Ageing, [2] KU Leuven, Leuven, Belgium, Laboratory for Complex Genetics, [3] University Hospitals KULeuven, Leuven, Belgium, Laboratory for Clinical Immunology, Department of Microbiology and Immunology, [4] KU Leuven, Leuven, Belgium, Translational Research in Gastrointestinal Disorders, Department of Chronic Diseases, Metabolism and Ageing, [5] KU Leuven, Leuven, Belgium, Laboratory for Clinical Immunology, Department of Microbiology and Immunology.

**Introduction :** Ustekinumab (UST), targeting the IL-12/23 shared p40 subunit, was recently approved by FDA & EMA for treatment of moderate-to-severe Crohn's disease (CD).

**Aim :** We aimed to identify potential predictive immunological biomarkers for response which may guide treatment strategies with ustekinumab.

**Methods :** Serum samples of 36 CD patients (73% female, median disease duration 15.9 years), all refractory to anti-TNF therapy and vedolizumab and with baseline endoscopic active disease, were prospectively collected prior to UST initiation. Patients received UST 6mg/kg IV at induction, with subcutaneous UST 90mg q8w thereafter. Endoscopic response was assessed at week 24, and defined as minimal 50% decrease in SES-CD. Proteomic analysis (OLINK) was performed on baseline serum samples. Inflamed ileal (n=10) and colonic (n=17) biopsies, prior to UST therapy, were collected. Mucosal total RNA was isolated, and next-generation sequencing performed. Differentially gene expression was evaluated by DESeq R package.

**Results :** Patients with (n=7) and without (n=29) endoscopic response at week 24 had a similar inflammatory burden, reflected by similar median faecal calprotectin (1800 vs 1721mg/g, p=0.22), C-reactive protein (20.3 vs 9.4mg/L, p=0.36) and IL-6 (p=0.37, fold change (FC)=1.06) before start of UST. Baseline endoscopic activity was much higher in patients responding to UST, compared to non-responders (median SES-CD 21 vs 13, p<0.001). Several proteins significantly correlated with baseline SES-CD, but only one protein, CD40 (r=0.87, p=0.05), also significantly differed between responders and non-responders before UST initiation (p=0.029 with corresponding FC 1.46). At baseline, CCL11 also varied between responders and non-responders (p=0.06, FC 1.45), but did not correlate with baseline SES-CD (p=0.97). Receiver operator characteristics showed a significant area under the curve (81.5%, p=0.011) for prediction of response based on the combination of both. On mucosal level, a non-significant increase in both CD40 and CD40L could be observed in colonic biopsies of responders at baseline (FC 1.6 and 1.5 respectively). Ileal biopsies also expressed increased CD40L in responders (FC 2.0).

**Conclusions :** Two potential predictive biomarkers for response to UST were identified, which need validation in larger and independent cohorts. Because it has been shown that CD40/CD40L-triggering of dendritic cells induces expression

of high levels of IL-23 and not IL-12, low CD40 levels in non-responders suggest another mechanism, apart from the IL-12/23 pathway, driving inflammation in these patients. These findings may aid in individualized selection of biological agents in Crohn's disease, and provide mechanisms of primary (non-)response to UST.

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THE INTERACTION BETWEEN INTESTINAL PERMEABILITY DISTURBANCES AND INFLAMMATION IN A CHRONIC COLITIS MOUSE MODEL, STUDIED OVER TIME. H. Van Spaendonk (1), J. De Man (1), S. Francque (2), H. De Schepper (2), B. De Winter (1) / [1] University of Antwerp, Antwerp, Belgium, Gastroenterology and Hepatology, [2] University Hospital Antwerp, University of Antwerp, Antwerp, Belgium, Gastroenterology and Hepatology.

**Introduction :** The pathogenesis of inflammatory bowel diseases (IBD) is multifactorial. Although not fully understood, it involves environmental or microbial factors which provoke an exaggerated immune response in genetically susceptible individuals. Recently there is renewed interest in the involvement of a mucosal barrier defect, as evidenced by an increased intestinal permeability in IBD patients. On the one hand, a defective intestinal barrier increases the contact between luminal components and the mucosal immune system, causing a pro-inflammatory response. Inflammatory cytokines on the other hand perpetuate this barrier defect, resulting in a cycle of increased intestinal permeability and chronic mucosal inflammation.

**Aim :** We aimed to investigate the timely relationship between changes in intestinal permeability and colonic inflammation.

**Methods :** Colitis was induced in immunodeficient SCID mice by the adoptive transfer of CD4+CD25-CD62L+ T-cells, isolated from the spleens of donor BALB/c mice. Mice were sacrificed at fixed time points to study disease progression resulting in the following groups : control mice (WEEK 0 ; n=10) colitis mice after 1 week 1 (WEEK 1 ; n=10), colitis mice in week 2 (WEEK 2 ; n=10), colitis mice in week 4 (WEEK 4 ; n=10) and colitis mice in week 6 (WEEK 6, n=10). Prior to sacrifice, mice were orally gavaged with FITC-dextran. Four hours later, FITC concentration was measured in the serum to assess intestinal permeability. After sacrifice, colonic inflammation was assessed by macroscopic and microscopic scoring, myeloperoxidase (MPO) activity and cytometric bead array (CBA) for TNF- and IL-1. Messenger RNA of transcription factors that regulate T helper (Th) cell differentiation including T-bet (Th1), GATA-3 (Th2), ROR- $\gamma$  (Th17) and tight junction proteins (Claudin-1, Occludin) were quantified using RT-qPCR technique. Data are represented as mean $\pm$ SEM.

**Results :** Intestinal permeability, measured by FITC-dextran concentration in the serum, was significantly elevated at WEEK 1 (1056254 vs. 17372 ng/mL at WEEK 0) and remained elevated at WEEK 2, 4 and 6. Mucosal inflammation appeared gradually in the colon of the diseased mice from WEEK 2 onwards. The macroscopic score significantly increased from 0.00.0 at WEEK 0 to 5.50.3 at WEEK 2 and to 10.22 at WEEK 6. This was completely mirrored in the MPO activity : from 0.10.1 U/g tissue at WEEK 0 to 3.70.6 U/g tissue at WEEK 2 and 4.51.1 and 6.01.7 at respectively WEEK 4 and 6. Microscopically however, the first significant signs of inflammation were observed at WEEK 1 (2.20.2 vs 0.60.3 for WEEK 0) gradually increasing at WEEKS 2, 4 and 6 (respectively 5.30.3, 6.40.4 and 8.70.6). The colonic inflammation in these mice is mainly Th1/Th2-driven, shown by the qPCR results of the T-helper cell transcription factors (respectively T-bet and GATA3). The relative mRNA expression of T-bet was significantly upregulated in WEEK 2, 4 and 6 versus WEEK 0 (respectively 6.41.0, 9.00.7 and 7.91.2 versus 1.10.2). For GATA-3, significance was reached from WEEK 4 onwards (2.90.6 versus 1.10.1 for WEEK 0). Cytokine levels (TNF- and IL-1) were significantly elevated starting from WEEK 1 (respectively 41.85.5 and 95.725.3 pg/mL versus 0.90.5 and 0.30.2 at WEEK 0) and gradually increased further as disease progressed.

**Conclusions :** Our results show a gradual increase of intestinal inflammation over time reaching significance for most parameters from WEEK 2. However, we also observed a sharp early increase in intestinal permeability starting from WEEK 1 of the experimental protocol. This shows that the mucosal barrier function might be an initiating factor of inflammation and could be an interesting treatment target.

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BECLOMETHASONE DIPROPIONAAT IS EFFECTIVE FOR MICROSCOPIC COLITIS : RESULTS OF AN OPEN LABEL MULTICENTER STUDY (COLCO). T. De Corte (1), E. Janssens (2), K. Thorrez (3), A. D'hondt (1), K. Dejaegher (4), F. D'heygere (5), B. Van Besien (3), L. Harlet (1), H. Peeters (6), W. Vanmoerkercke (5), P. Van Hootegem (7), F. Baert (1) / [1] AZ Delta, Roeselare, Belgium, Gastroenterology, [2] AZ Delta, Roeselare, Belgium, Gastroenterology, [3] Jan Yperman Hospital, Ieper, Belgium, Gastroenterology, [4] Sint-Jozefskliniek, Izegem, Belgium, Gastroenterology, [5] AZ Groeninge, Kortrijk, Belgium, Gastroenterology, [6] AZ Sint-Lucas, Ghent, Belgium, Gastroenterology, [7] AZ Sint-Lucas Brugge, Assebroek, Brugge, Belgium, Gastroenterology.

**Introduction :** Microscopic colitis (MC, consisting of collagenous (CC) and lymphocytic colitis (LC)) is a benign but bothersome disease, characterized by chronic watery diarrhea, potentially with fecal incontinence. Budesonide is shown to be effective for both CC and LC : the two current commercially available budesonide preparations (Budenofalk® and Entocort®) are topically released in the ileum and not in the colon. Beclomethasone dipropionaat (Clipper®) is a synthetic corticosteroid with topical colonic release and hence potentially superior.

**Aim :** We hereby report the first series of MC patients treated with open label beclomethasone.

**Methods :** Prospectively collected data of 23 patients with CC or LC from 6 participating centers were retrospectively analyzed. In order to qualify for this analysis, patients had to have a confirmed diagnosis of CC or LC (newly diagnosed or with prior diagnosis) and had to be symptomatic (defined as a disease activity index of  $\geq 21$  over a 7-day period, i.e. an average of 3 or more loose stools per day). Drug induced cases were excluded, as well as patients on anti-inflammatory or anti-diarrheal treatment. Treatment consisted of beclomethasone 10 mg/d for 4 weeks, followed by 5 mg/d for another 4 weeks. Patients filled out a Bristol stool scale diary at baseline, week 4 and week 8. Four weeks after discontinuation of treatment, patients were contacted again by telephone for follow-up. The primary endpoint of this study is the proportion of patients in remission (defined as a disease activity index of  $\leq 11$ , i.e.  $\leq 11$  loose stools over a 7-day period) after an 8 week treatment period. Secondary endpoints are the proportion of patients responding to therapy (response defined as subjective improvement by physician global assessment) at week 4 and week 8, the proportion of patients in remission at week 4 and 12 and the proportion of patients with relapse at week 12. Reported adverse events were collected.

**Results :** A total number of 23 patients (17F, median(range) age 69 (42-84)) were included from 6 hospitals. Of these 23 patients, 16 had LC (11F, median age 69 (42-78)), 6 CC (5F, 69yrs (64-84)) and 1 patient had an overlap syndrome (OVS) (M, 53 yrs). At baseline, mean number of stools a day was 7,0 (range 3 - 30). Other main symptoms included fecal incontinence (n=12), abdominal pain (n=11) and abdominal distension (n = 11). A total number of 9 previous episodes of LC or CC were reported in 7 patients. All patients were started on 10 mg beclomethasone/d. At week 8, 2 patients had prematurely stopped treatment due to constipation (1 patient at week 4, 1 during week 7). At week 8, 16 patients (70%, LC 63%, CC 83%, OVS 100%) were found to be in remission, 18/23 (78%, LC 75%, CC 83%, OVS 100%) were responding to their treatment. The mean number of stools a day had decreased from 7,0 (range 3 - 30) at baseline to 1,72 (range 0 - 5) with 0,73 (range 0 - 5) diarrhea. After 4 weeks of treatment with 10 mg beclomethasone, 22/23 patients (95%, LC 94%, CC 100%, OVS 100%) were responsive, 18 patients (78%, LC 75%, CC 83%, OVS 100%) were in remission. Four weeks after stopping treatment 15 patients (65%, LC 63%, CC 67%, OVS 100%) were still in remission, 4 of the initial responders (3 LC, 1 CC) had relapsed. Of the 7 patients that received prior treatment with budesonide during another flare, 4 reported a subjective better and/or faster response with beclomethasone and 3 reported a similar response. A total of 11 patients reported 14 adverse events : constipation (n = 4) facial flushing (n = 2), muscle cramps (n = 2), hyperglycemia (n = 1), hyperactivity (n = 1), vaginal discharge (n = 1), headache (n=1) and hoarseness (n=1). All adverse events were graded as mild and transient, except for 2 adverse events (hyperglycemia (with diabetes) and muscle cramps) still ongoing at the end of the study.

**Conclusions :** This open label study suggests that an 8-week course of beclomethasone is a promising and relatively safe treatment for microscopic colitis. A controlled study is warranted.

- I36 -

THE CLINICAL UTILITY OF A MULTI-MARKER SERUM TEST FOR ASSESSMENT OF ULCERATIONS IN INFLIXIMAB TREATED PATIENTS WITH CROHN'S DISEASE. M. De Bruyn (1), T. Bessissow (2), V. Kondragunta (3), A. Jain (3), I. Arijs (4), G. Van Assche (5), M. Ferrante (5), G. Opdenakker (6), S. Vermeire (5) / [1] Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium, Chronic Diseases, Metabolism and Ageing (CHROMETA), [2] McGill University, Montreal, Canada, Gastroenterology, [3] Prometheus Laboratories Inc., San Diego, United States (the), Research and Development, [4] Jessa Hospital, Hasselt, Belgium, Faculty of Medicine and Life Sciences, [5] University Hospitals Leuven, Leuven, Belgium, Gastroenterology and Hepatology, [6] Rega Institute for Medical Research, , Belgium, Microbiology and Immunology.

**Introduction :** Resolution of ulcerations is an important component of mucosal healing (MH) in Crohn's disease (CD) that is typically assessed with ileocolonoscopy, although this is an invasive, expensive and uncomfortable procedure. A non-invasive and accurate multi-marker serum test yielding a mucosal healing index (MHI) score in CD patients has recently been developed and validated based on the CD endoscopic index of severity (CDEIS).

**Aim :** The aim of this study was to assess the clinical utility of the multi-analyte MH algorithm in two independent real-life cohorts of CD patients under infliximab (IFX).

**Methods :** In cohort 1 (n=104, median age 36.5 years, 58% female, 11% ileal disease, 25% colonic disease, 64% ileocolonic disease), cross-sectional serum samples were obtained after a median of 32 weeks post-IFX. In cohort 2 (n=65, median age 36.1 years, 58% female, 11% ileal disease, 20% colonic disease, 69% ileocolonic disease), consecutive serum samples were taken within 20 days before start of IFX and after a median of 23 weeks post-IFX. All serum samples were taken within 30 days of ileocolonoscopy. At time of ileocolonoscopy, complete MH, partial MH

and no MH were defined as absence of ulcerations, >50% endoscopic improvement but with ulcerations still present, and no endoscopic improvement, respectively. The MH index (MHI) was constructed based on 13 markers (Ang1, Ang2, CEACAM1, VCAM1, TGF- $\beta$ , CRP, SAA1, MMP-1, -2, -3, -9, EMMPRIN and IL-7) and ranged from 0-100. Non-parametric tests were performed and the established cut-offs of MHI<40 (low endoscopic disease activity) and MHI>41 (medium to high endoscopic disease activity) were used. P-values <0.05 were considered significant.

**Results :** In cohort 1, 42.3% of the patients had no MH, 18.3% had partial MH and 39.4% had complete MH after IFX. MHI scores were significantly lower in patients with complete MH compared to patients with partial (p=0.049) and no (p<0.001) MH who still had ulcerations post-IFX. Moreover, 78% of the patients with MHI scores >41 had ulcerations post-IFX. In cohort 2, 34% of the patients had no MH, 32% had partial MH and 34% had complete MH post-IFX. No significant differences in MHI scores were found at baseline, whereas MHI scores were significantly lower in patients with complete MH compared to patients without MH post-IFX (p=0.009). 88% of patients with MHI scores >41 had persistent ulcerations post-IFX. The MHI decreased in 85% of the patients post-IFX, but in 80% of the patients with an increased MHI persistent ulcerations were observed.

**Conclusions :** We validated the clinical utility of the MHI for the assessment of ulcerations in CD patients in two independent real-life cohorts. This novel non-invasive test will be a useful tool to monitor MH in CD patients and help avoid unnecessary repetitive endoscopic evaluations.

- I37 -

A PROSPECTIVE TRIAL TO EVALUATE THE FEASIBILITY OF A MOBILE APP IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE UNDER MAINTENANCE THERAPY. S. Coenen (1), E. Weyts (1), P. Geens (1), E. Nijns (2), R. Van Durm (2), M. Ferrante (1), S. Vvermeire (1), B. Van den Bosch (2), G. Van Assche (1) / [1] UZ Leuven, Leuven, Belgium, IBD, [2] UZ Leuven, Leuven, Belgium, ICT.

**Introduction :** The chronic character of Inflammatory Bowel Diseases (IBD) requires close monitoring and evaluation by specialized IBD providers. Furthermore, patients increasingly seek to take part in their disease management.

**Aim :** Telemonitoring can be implemented to enhance monitoring of disease activity, improve adherence and contribute to optimal care.

**Methods :** An IBD mobile App was designed at a tertiary referral center through close collaboration between the IT and gastroenterology department. Data of this mobile App are directly integrated in the electronic medical record (EMR) and a trial was established to assess the feasibility of this App. Between May and Aug 2017, the mobile App was proposed to IBD patients on maintenance therapy. Informed consent was signed, and patients were followed for 6 months with weekly mobile monitoring of disease activity (patient reported outcomes, PRO-2), and monthly monitoring of adherence (MMAS-8), quality of life (SHS) and work/school productivity (WPAI). Alerts were generated in the EMR when patients experienced a flare, were hospitalized or failed to adhere. No reminders were sent to urge patients to fill out the e-questionnaires.

**Results :** Data were collected for 45 patients (58% male, median age 34 years, 80% Crohn's disease, 20% ulcerative colitis). Twenty-five (56%) patients showed good to excellent (80-100%) completion of the weekly and monthly questionnaires during complete follow-up. Six (13%) patients showed good to excellent completion for 2-3 months, but lost compliance over time. Between May and Nov, 16 flare alerts were generated for 7 different patients. For 5 of them PRO-2 was increased at one occasion due to gastroenteritis. For 1 patient PRO-2 was increased twice due to low self-reported adherence. One patient reported consecutive PRO increases, endoscopy confirmed an IBD flare and therapy was switched. Monthly reporting of medication adherence showed that 4 patients had low compliance once or twice. During the study period, no hospitalizations for IBD were reported.

**Conclusions :** We report on the feasibility of a fully EMR integrated mobile PRO-based IBD App that promises to reduce clinic visits of socially and professionally active patients with IBD. Integrating reminders in the App should help to improve reporting compliance over time.

- I38 -

RIGHT COLECTOMY AND ILEOCAECAL RESECTIONS FOR COLORECTAL CANCER AND CROHN'S DISEASE : ASSESSMENT OF POSTOPERATIVE RESULTS OVER A 5-YEAR PERIOD. D. Leonard (1), Y. Hamida (2), S. Barbois (2), C. Remue (2), R. Bachmann (2), N. Abbes Orabi (2), M. Blanco (2), O. Dewit (3), M. Denis (3), A. Kartheuser (2) / [1] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Unité de Chirurgie Colorectale, [2] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Unité de Chirurgie Colorectale, [3] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Service d'Hépto-gastro-entérologie.

**Introduction :** Right hemicolectomy and ileocaecal resections are common colorectal procedures, typically indicated for the management of right colorectal cancer (RCC) and Crohn's disease. These interventions can give rise to postoperative



events, of which the most life-threatening is the anastomotic leak (AL). Observation of the last decade shows that the complication rate for this type of operation seems not to be decreasing.

**Aim :** The aim of this study is to analyse the complication rate in patients undergoing right hemicolectomies and ileocaecal resections and compare the results between patients presenting right colon cancer versus Crohn's disease.

**Methods :** Data of consecutive patients undergoing right hemicolectomies and ileocaecal resections between 2007 and 2011 have been collected. Demographic information, preoperative and operative data, follow-up and postoperative data including complication rate and histological features were collected. Univariate and multivariate analysis was performed to determine the predictive factors of complications.

**Results :** 178 patients have been operated for right hemicolectomies or ileocaecal resections with 30.33% (54) of them for Crohn's disease and 60.11% (107) for RCC. The mean age for these 2 groups was 36.80 and 70.25 years-old respectively. 38.89% (21) of the Crohn's patients and 21.50% (23) of the RCC were smokers. The most frequent symptom in the Crohn patients was abdominal pain (79.63%) while this one was the second most frequent symptom (33.64) after anemia (34.57) in the RCC patients. The main surgical approach was laparoscopy in the Crohn patients (75.93%) while laparotomy was as frequently used (47.66%) as the laparoscopic approach (52.34%) in the RCC patients. The immediate postoperative complication rate was 9.55% for all the patients, with 14.81% of the Crohn patients having complications and 8.41% out of the CCR group. The AL rate was 3.93% (7/178) out of all the operations, with 6 of them in Crohn patients and 1 in a RCC patient.

**Conclusions :** Right hemicolectomies and ileocaecal resections are operations that can give rise to a major postoperative complication which is the AL and this one remains a challenge for the surgeon. In this series, the rate reaches 3.9% and Crohn's patients are at higher risk of complications compared to colon cancer.

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- K01 -

INFLIXIMAB TROUGH LEVELS AFTER INDUCTION THERAPY ARE PREDICTIVE FOR THE OUTCOME IN PAEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE. K. Van Hoeve (1), I. Hoffman (1), E. Dreesen (2), M. Ferrante (3), A. Gils (2), S. Vermeire (3) / [1] University Hospitals Leuven, Leuven, Belgium, Department of Paediatric gastroenterology, [2] KU Leuven, Leuven, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies, Department of Pharmaceutical and Pharmacological Sciences, [3] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology & Hepatology.

**Introduction :** Loss of response (LOR) to biological therapies is a big concern in inflammatory bowel disease (IBD) management and especially among paediatric patients where treatment options are limited. Therapeutic drug monitoring has been proposed as one of the ways to improve outcome, but its role remains unclear.

**Aim :** The aim of this study was to determine whether infliximab (IFX) trough levels (TL) correlated with clinical and biological remission. We hypothesized that IFX TL after induction are predictive for IFX efficacy.

**Methods :** All paediatric IBD patients with IFX TL available at their first maintenance infusion and a follow-up of at least 54 weeks were included. IFX induction regimens could be intensified at the discretion of the treating physician based on disease severity. All children received pro-active drug monitoring in the maintenance phase with the therapeutic window defined between 3-7  $\mu\text{g/mL}$  (conform adult studies). Demographics, disease activity indices and inflammatory biomarkers were recorded retrospectively. Clinical remission was defined as PUCAI/PCDAI <10 and biological remission as CRP  $\leq 5$  mg/L and ESR  $\leq 10$  mm/h at week 54. Patients were considered in deep remission if both criteria (clinical and biological remission) were met. IFX TL were measured by Ridascreen IFX Monitoring ELISA. Results were analysed using Mann-Whitney U-test. All data are presented as median [IQR] and alpha was set at 0.05.

**Results :** We included 25 children (15 with Crohn's disease and 10 with ulcerative colitis ; 40% male). IFX was stopped in only 1 patient before week 54 due to LOR. Median age at start of IFX was 12.7 years [9.7- 15.0] with a median disease duration prior to starting IFX of 7 months [4- 12] and a median follow-up under IFX of 23 months [16- 43]. At start of maintenance therapy, 76% was on concomitant immunosuppressants, which dropped to 36% at week 54. Median IFX TL at the time of the first maintenance infusion were significantly higher in children who were in clinical remission (3.4  $\mu\text{g/mL}$  [2.4-6.0] vs 1.5  $\mu\text{g/mL}$  [0.7-3.2],  $p=0.014$ ), biological remission (3.8  $\mu\text{g/mL}$  [2.7-9.0] vs 1.4  $\mu\text{g/mL}$  [0.3-3.0],  $p=0.003$ ) and deep remission (4.8  $\mu\text{g/mL}$  [2.4-12.0] vs 2.3  $\mu\text{g/mL}$  [0.9-3.2],  $p=0.008$ ) at 54 weeks.

**Conclusions :** Paediatric IBD patients with enough exposure during induction therapy (deduced by the IFX TL at start of maintenance) have better chance for clinical and/or biological remission at week 54. This illustrates that sufficient exposure during induction is essential for a long and better response.

- K02 -

INFLIXIMAB TROUGH LEVELS DURING MAINTENANCE ARE PREDICTIVE FOR INFLIXIMAB EFFICACY IN PAEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE. K. Van Hoeve (1), I. Hoffman (1), E. Dreesen (2), M. Ferrante (3), A. Gils (2), S. Vermeire (3) / [1] University Hospitals Leuven, Leuven, Belgium, Department of Paediatric gastroenterology, [2] KU Leuven, Leuven, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies, Department of Pharmaceutical and Pharmacological Sciences, [3] University Hospitals Leuven, Leuven, Belgium, Department of Gastroenterology & Hepatology.

**Introduction :** The role of therapeutic drug monitoring during maintenance treatment in paediatric inflammatory bowel disease (IBD) is poorly studied.

**Aim :** The aim was to determine whether infliximab (IFX) trough levels (TL) correlate with long-term remission in children receiving maintenance IFX.

**Methods :** In this cross-sectional study all children with Crohn's disease (CD) or ulcerative colitis (UC) receiving maintenance IFX at our referral centre were included. All children received pro-active drug monitoring with the therapeutic window defined between 3-7  $\mu\text{g/mL}$  (conform adult studies). IFX TL were analysed using the Ridascreen IFX Monitoring ELISA. Demographics, disease activity indices, biochemical values and endoscopic reports were recorded retrospectively. Clinical remission was defined as PUCAI/PCDAI <10 and biochemical remission as CRP  $\leq 5$  mg/L and ESR  $\leq 20$  mm/h. Patients were considered in deep remission if both criteria (clinical + biochemical remission) were met. Endoscopic remission was defined as absence of ulceration. Mann-Whitney U-test was used to compare responders from poor-responders and correlations were analysed with Spearman's rho. All data are presented as median [IQR] and alpha was set at 0.05.

**Results :** A total of 45 patients (30 CD and 15 UC ; 47% male ; median age of 15.4 years [12.2-16.6]) and 617 IFX TLs (median 10 per patient [5.5-21]) were included. Median age at start of IFX was 12.8 years [9.6-15] with a median disease

duration prior to starting IFX of 5.0 months [2.0-9.5]. Mean administered IFX dose was 6.8 mg/kg [5-10] and the mean maintenance interval 5.6 weeks [4-6]. At start of maintenance 76% was on concomitant immunosuppressants. Median IFX TL during maintenance were significantly higher in children who were in clinical remission (5.4 µg/mL [3.8-8.1] vs 4.1 µg/mL [2.6-6.7], p=0.0001), biochemical remission (5.2 µg/mL [3.7-7.7] vs 4.2 µg/mL [2.5-6.6], p=0.0001), deep remission (5.7 µg/mL [3.9-8.4] vs 4.2 µg/mL [2.6-6.7], p=0.0001) and endoscopic remission (6.2 µg/mL [3.9-9.5] vs 3.2 µg/mL [2.3-5.7], p=0.005). With a median follow-up of 24 months [10-40] under IFX, 36/45 (80%) patients were in clinical and 27/37 (73%) patients in endoscopic remission at last follow up. IFX TL correlated significantly with CRP, ESR, albumin and PUCAI/PCDAI (all p≤ 0.005).

**Conclusions :** In this paediatric IBD cohort treated with IFX maintenance, children who demonstrated clinical and/or endoscopic remission had significantly higher IFX TL. Our data support the value of proactive drug monitoring in children to improve long-term outcome. Whether the same therapeutic window as in adults needs to be pursued in children, needs to be investigated in prospective studies.

- K03 -

MEDICAL DEVICES IN EU CLAIMING OROPHARYNGEAL OR GASTROINTESTINAL BARRIER ACTION : BARRIER PRODUCTS OR HIDDEN PHARMACOLOGICAL AGENTS? S. Huijghebaert (1), P. De Bruyne (2), K. Allegaert (3), M. Van Winckel (4) / [1] Independent researcher, Belgium, Pharmacist PhD, [2] Ghent University, Ghent, Belgium, Clinical Pharmacologist, Paediatrics, [3] KU Leuven, Leuven, Belgium, Department of Development and Regeneration, [4] Ghent University, Ghent, Belgium, Paediatric Gastroenterology.

**Introduction :** In deciding whether a product falls under EU drug regulations (EMA reviewed and approved) or EU medical device (MD) regulations (a national competence requiring CE certification only), the EU Directive states that particular account shall be taken of the principal mode of action of the product ; in MDs, pharmacological actions are ancillary to the primary MD function. Hence ‘medicine’ products are increasingly launched in the EU as medical devices (MDs), claiming effective treatment primarily through a barrier function, while making multiple pharmacological claims.

**Aim :** To analyse the evidence for barrier and/or pharmacological actions of barrier-claiming MDs, by analysing package inserts, published evidence and promotional claims of 3 MDs and their ingredients : gelatin tannate (GT, Tasectan®, Gelenterum®) for diarrhea ; hyaluronic acid/chondroitinsulphate/poloxamer 407 HACSPol (Ziverel®, Esoxx®) for GORD ; glycerin/trypsin (GlyTS) oral mouth spray (Viruprotect®, Coldzyme®) for common cold.

**Methods :** Extensive literature search on pubmed and internet in general (extensive reference list available).

**Results :** None of the studies claiming barrier function were unambiguously conclusive : the claimed film effect was never observed/visualized. For all 3 MDs, mapping the experimental design illustrated that the claimed barrier was at the wrong side (contradicting pathophysiology) : oral GT (=in gut lumen) was claimed to function as barrier against LPS toxins administered intraperitoneally (=serosal) ; HACSPol reduced the protein extravasation from inflamed oesophageal wall to lumen (Evans blue used, instead of testing a bioadhesive barrier against luminal acid/pepsin diffusion/aggression as proven for alginates). It is recognized that Pol407 and modified HA/Pol407 composites can form (film)barriers by thermogelling (e.g. FDA-approved LeGoo® for endovascular occlusion on cardiac surgery and Seprafilm® against surgical adhesions, yet excluding GI-sutures) ; however, for thermogelling about 10-fold higher concentrations Pol 407 are needed ; they are stable MDs requiring single application only ; submucosal HACSPol(80%)-injected oesophageal cushions disappeared in 20 min. GlyTS, sprayed in the throat, was claimed to form a barrier against rhinoviruses : however, rhinoviruses cause infection via nasal and not oral cavity, while glycerol is a good solvent mixing with water ; 1-day prophylactic treatment with GlyTS could not prevent rhinovirus infection following nasal viral challenge. The assessed effects were always explainable by pharmacological actions of single ingredients, or physicochemical effects specific to the test model : 1) In GT models, effects were observed at caustic 37% HCl (tanning action ; no significance at 3.7%-10% HCl) or pH was close to the isoelectric point (iP) of G (pH 4.7) keeping GT precipitated, which however cannot guarantee barrier function at the pH range of human gut and its secretions : GT hydrolyses above and below iP. Tannins are moreover hydrolysable and bacterially degraded, gelatine digested. Tannins have been found to exert many bio/pharmacological actions at (very) low concentrations (tannate-specific ; range 0.1-100 µg/mL ; 0.1-1% of GT dose in the models) : all but one model (using aberrantly high toxic TA doses) failed to validate the claimed barrier effect by including relevant TA controls. TA also precipitates dextran in presence of protein at iP 5 (= pH in mice gut), invalidating the GT dextran sulphate-induced colitis model. 2) For HACSPol, pharmacological actions of HA (fragments) can be mediated by binding to HA-binding receptors, abundantly present in the human oesophagus ; they include angiogenic, immunostimulatory and anti-inflammatory actions (0.2% topical solutions heal buccal ulcers (= 6x less)). The effect may also be poloxamer-mediated alone, as Pols have been shown to reduce leakage by counteracting cell integrity deterioration, or simply to inhibit influx of Evans blue. 3) TS acts as signalling molecule on PAR in many complex processes of the body (including viral infection). For all MDs, pharmacological claims were made either in patent, developer-associated publications, leaflet or promotion, to support action and efficacy : a recent review listed HACSPol under ‘Drugs’ for GORD (Savarino 2017).

**Conclusions :** Evidence provided for barrier effect of MDs is non-conclusive. The barrier claim lacks either a scientific rationale (wrong barrier side), or is not tested in a validated model applicable in humans. As MDs escape claim control of medicinal drugs, vague barrier claims allow them making largely pharmacological and non-proven efficacy claims. Hence, CE marking of such MDs does not represent medicinal quality.

- K04 -

NATURAL HISTORY OF DIARRHOEA AMONG UNDER-FIVE CHILDREN IN NALCHITY, BANGLADESH.  
M. Khanam (1) / [1] Centre for Injury Prevention and Research, Bangladesh (CIPR, B), Medical Sociology, Dhaka, Bangladesh, Medical Sociology.

**Introduction :** There is a lack of comparative information on the severity of diarrhoeal diseases with aetiologic agents in Bangladesh.

**Aim :** The study aimed to compare the aetiology of under-five children with moderate-to-severe diarrhoea (MSD) and mild diarrhoea (MD).

**Methods :** MSD was defined if any of the following was present - sunken eyes and /or wrinkled skin and/or visible or reported blood in stool ; or a child is hospitalized with diarrhoea or dysentery ; or a child needs/received intravenous rehydration. Children below 5 years without any signs of MSD constituted mild diarrhoea (MD). Overall, 2,324 under 5 children were enrolled from January 2016 - December 2016 from the area of rural Nalchity Upazila, Jhalkati, Bangladesh.

**Results :** Rotavirus (33%) was the leading cause of diarrhoea for children >5 years ; 90% belonged to >2 years. Shigella represented 14% of total isolates and 45% children aged 24-59 months (45%) suffered from shigellosis. In Nalchity, Shigella was the commonest isolated pathogen (27%) followed by rotavirus (16%) among >5 years children who presented with MSD. Rotavirus was the commonest cause (43%) among those who had reported with MD. Under-5 children infected with Shigella flexneri (17% vs. 2% ;  $p<0.01$ ) and Shigella sonnei (8% vs. 1%  $p<0.01$ ) were more common in those who presented with MSD compared to their counterparts with MD. Isolation rates of ETEC (3% vs. 3%) and V. cholerae (3% vs 2%) were found to be similar in both the cases. MD cases often presented with watery stool. Conversely, straining and sunken eye were frequently manifested by individuals with MSD infected with ETEC, rotavirus, Shigella and Vibrio cholerae. Fever was a common presenting feature of MSD compared to cases with MD in >5 years children except children infected with Vibrio cholerae.

**Conclusions :** Shigella was the leading pathogen that caused MSD ; whereas, rotavirus often caused MD among children less than 5 years old in Bangladesh.

- K05 -

MEDICAL DEVICES MARKETED AS MEDICINES : SAFETY AND REGULATORY CONCERNS IN CHILDREN.  
S. Huijghebaert (1), P. De Bruyne (2), M. Van Winckel (3), K. Allegaert (4). [1] Independent researcher, Belgium, Pharmacist, PhD, [2] Ghent University, Ghent, Belgium, Clinical Pharmacologist, Paediatrics, [3] Ghent University, Ghent, Belgium, Paediatric Gastroenterology, [4] Erasmus MC, Rotterdam, Netherlands (the), Intensive Care and Department of Pediatric Surgery.

**Introduction :** Some medical devices (MDs) claim safe, effective treatment by enteral barrier mechanisms, as if it were medicinal drugs. MDs enter the EU market for direct dispensing through (drug)stores and pharmacies as OTC products, through free movement of goods via CE-labelling, self-marked by the manufacturer, or after national notification via an EU-accredited notifying body (private companies contracting with manufacturers to supply certification to enter the market for a fee, assuring 'conformity'). They escape in-depth review by national medicinal authorities or EMA for regulatory medicinal approval and control of promotional claims.

**Aim :** To analyse the regulatory quality (non-clinical and clinical) of 3 gastrointestinal products for paediatric use. For diarrhea : Tasectan®/Gelenterum® (gelatin tannate, GT) and Tasectan®/Gelenterum Duo® (GT+tyndalized heat-killed probiotics ; GTTP) . For GORD : Ziverel®, Esoxx® (hyaluronic acid/chondroitinsulphate/poloxamer 407 ; HACDSPol).

**Methods :** Analyse information of package inserts and extensive literature search for published evidence at time of entering EU.

**Results :** I. Product characteristics are inaccurately defined in the package insert : sachets GT contain 250mg powder, but the tannate is not specified (tannic acid (TA), gallic acid, bark gallotannins, Chinese, Turkish or other galls?), neither G bloom strength, ratio and free fraction of TA (added to 5 mL milk, 3 layers). GTTP powder additionally contains heat-killed L. acidophilus, L. plantarum, L. casei, L. rhamnosus, Bifidobacterium bifidum, Streptococcus thermophiles (units undisclosed). For HACDPol gel, the doses of HA, CS and Pol 407, origin (rooster comb/bacterial?) and polymerization grade of HA are missing. II. All leaflets allow unlimited use in children from birth onwards : GT and GTTP for effective relief of diarrhea of various origin within 12hrs, HACSPol for promoting mucosal repair/relieving GORD symptoms.

Whereas medicines require placebo-controlled studies to support claims, overall clinical documentation was poor, even lacking for children with GTTP and HACSPol. For GT, efficacy was claimed based on ‘observations’ in 2 ‘cohorts’ (97 children with acute diarrhea (>3months) receiving ORS+GT and 114 children on ORS) for 48hrs ; antibiotic use was allowed but not documented, neither diarrhea diagnosis and rating scales ; although groups didn’t match for baseline stool number (ORS worse), efficacy at 12hrs was based on this parameter, yet no longer statistically significant at 24hrs. A poster disclosed observational data at 12hrs in 97 (same?) children. The only placebo-controlled study in adults (20/group) did not confirm the 12hr claim. For GTTP, studies in adults were even not retrieved ; for HACSPol, gel or placebo was given add-on to standard-dose PPIs, even in PPI-naïve adults : there are no data confirming efficacy as single product, neither in comparison to PPI (so no rationale to switch children from PPI to HACSPol). III. Safety : Rare AEs are difficult to detect if there is no prescription follow-up. MD leaflets mention “no known” or “no observed side effects”. Yet, literature calls for attention : 1) GT : TA ( $\mu\text{g}$  range) is cytotoxic to intestinal cell lines and not chemically classifiable as safe with regard to carcinogenicity ; 2) TPs were shown to give more diarrhea and Aes ; 3) HA-dose is 5 to 20-fold the EFSA approved food supplement dose ; oral experience with Pol407 (surfactant) is limited to ~5-6 mg/caps/day as excipient for delayed release tablets, yet surpassing >1000 mg/day in the gel [no chronic oral toxicity available ; Pol407 abandoned in injectables, due to nephrotoxicity and effects on lipid balance]. Septrafilm® (HA 700mg/Pol407 300mg) sheets for ‘single’ use against surgical adhesions, were abandoned for gastrointestinal sutures due to increased abscesses, fistulae and sepsis. IV. None assessed or referred to potential drug-drug interactions : 1) TA is known to adsorb many drugs and identified as CYP450 and P-gp inhibitor ; 2) HA/surfactant complexes change drug absorption ; Pol 407 inhibits efflux transporters and can affect drug absorption.

**Conclusions :** EU regulation requires only national notification of MDs. This results in the marketing of poorly investigated and poorly labelled oral MDs claimed on ‘barrier’ effects, but hardly or not evaluated in children. They do not guarantee effective and safe ‘medical’ treatment of children, as for a medicinal drug registered though EMA or medicinal authorities. Children currently serve as test subjects by exposure to these MDs, be it without effective pharmacovigilance.

## BELGIAN WORKING GROUP ON PROCTOLOGY

- M01 -

DYNAMIC TRANSRECTAL ULTRASOUND VERSUS MR DEFECOGRAPHY IN PATIENTS WITH CONSTIPATION. K. Van Malderen (1), M. Somers (2), M. Spinhoven (3), H. De Schepper (2)/ [1] University of Antwerp, Antwerp, Belgium, Gastroenterology & Hepatology, [2] University Hospital Antwerp, Antwerp, Belgium, Gastroenterology & Hepatology, [3] University Hospital Antwerp, Antwerp, Belgium, Radiology.

**Introduction :** Both transrectal ultrasound and magnetic resonance (MR) defecography are frequently used to evaluate constipation. MR defecography is considered the more reliable alternative in determining the presence of celes, intussusception and muscle relaxation. Ultrasound is cheaper, quicker and easier to use than MR.

**Aim :** Our aim was therefore to evaluate the agreement between transrectal ultrasound and MR defecography in functional constipation.

**Methods :** We retrospectively evaluated the medical record of patients presenting with constipation at our pelvic clinic and who underwent both transrectal ultrasound and MR defecography. The presence of rectoceles, cystoceles, rectoanal intussusception and relaxation of the musculus puborectalis was recorded.

**Results :** 74 patients underwent both transrectal ultrasound and MR defecography. 18 patients were excluded because good dynamic images were not obtained. 56 patients were included for analysis. We calculated the positive agreement, negative agreement, overall agreement and cohens kappa for all four domains of evaluation. For the presence of a rectocele the positive agreement between the two tests was 70,8%, the negative agreement 59,6% and the overall agreement 66,1%. Cohens kappa was 0,33 which means a fair agreement. The positive agreement for the presence of intussusception was 36,4%, the negative agreement 73,4% and the overall agreement 58,9%. Cohens kappa was 0,58 which means moderate agreement. For the presence of cystocele, the positive agreement was 37,5%, the negative agreement was 31,8% and the overall agreement was 28,6%. Cohens kappa was 0,02 which means slight agreement. The positive agreement for the relaxation of the musculus puborectalis was 20,4%. The negative agreement 31,6% and the overall agreement 30,2%. Cohens kappa was -0,10 which means no agreement.

**Conclusions :** The agreement between transrectal ultrasound and MR defecography is acceptable for the detection of rectocele and rectoanal intussusception but poor for cystocele and relaxation of the musculus puborectalis. The agreement between the two tests is best for rectoceles.

- M02 -

INJECTION OF BOTULINUM TOXIN IN THE TREATMENT OF ANAL FISSURE CAN BE PERFORMED SAFELY IN PATIENTS ACTIVELY RECEIVING CHEMOTHERAPY. P. Roelandt (1), G. Coremans (1), J. Wyndaele (1) / [1] UZ Leuven, Leuven, Belgium, Gastroenterology and Hepatology.

**Introduction :** Injection of botulinum toxin in the anal sphincters is a well-documented option to reduce anal hypertonia in the treatment of anal fissures. In patients receiving chemotherapy painful anal diseases are frequent due to change in bowel habits and reduced immunity ; however injection of botulinum toxin is often not offered out of fear of complications.

**Aim :** In this study complication rate of injection of botulinum toxin in patients actively receiving chemotherapy was studied, as well as patient characteristics and outcome.

**Methods :** A retrospective longitudinal observational study was performed using keyword queries in the electronic patient files of a tertiary hospital. Type of anal pathology, underlying malignancy and current treatment as well as follow-up data were retrieved.

**Results :** Twenty-six patients were treated with 20-50 IU botulinum toxin while actively receiving chemotherapy. The average age was 54.5 years (range 24 to 77 years) with equal gender distribution (female :male 54% :46%). All patients were treated because of intractable pain and hypertonia, in the majority of patients caused by dorsal (69%, n=18) or ventral fissure/ulceration (19%, n=5), while in 3 patients (12%) no fissure was documented. The most frequent malignancies were colorectal cancer (35%, n=9) and haematological malignancies (35%, n=9), followed by gynaecological malignancies (19%, n=5), hepatobiliary cancer (8%, n=2) and lung cancer (4%, n=1). The majority of the patients (88%, n=23) had complete (61%, n=14) or at least partial (39%, n=9) relief of pain. In three patients complications occurred in the weeks following botulinum toxin injection, namely thrombosis of grade IV haemorrhoids, perianal haematoma and intersphincteric abscess, although there might be no direct causal link with the injections.

**Conclusions :** Injection of botulinum toxin in the anal sphincters is a safe and effective analgetic option in patients with anal fissure while actively receiving chemotherapy.

HEMORRHOIDAL DISEASE IN BELGIAN CLINICAL PRACTICE : RESULTS OF THE CHORUS STUDY (CHRONIC VENOUS AND HEMORRHOIDAL DISEASES EVALUATION AND SCIENTIFIC RESEARCH). H. De Schepper (1), M. Somers (1), D. De Looze (2) / [1] University Hospital Antwerp, Antwerp, Belgium, Gastroenterology & Hepatology, [2] University Hospital Gent, , Belgium, Gastroenterology.

**Introduction :** Hemorrhoidal disease is a common reason to consult a gastroenterologist. Symptoms are often vaguely reported. Clinically, the coexistence of hemorrhoidal disease with chronic venous disease can be assumed but was never thoroughly studied. Finally, there is considerable variation in the treatment of hemorrhoidal disease.

**Aim :** To determine the demographics, nature and treatment of hemorrhoidal disease in secondary/tertiary care in Belgium, and to assess coexistence with chronic venous disorders.

**Methods :** Multicentre observational study (CHORUS) in which patients presenting with symptomatic hemorrhoidal disease were screened during two consecutive months. Case report forms including patient demographics, history of anal complaints, presence of concomitant chronic venous disorders and type of prescribed treatment for hemorrhoids were completed. Data of the proctological exam were also collected.

**Results :** 45 gastroenterologists participated in the CHORUS survey, including a total number of 604 patients. 54.8% of patients were older than 50 years. There was a slight female predominance (52.8%). Of these women, 82.1% had given birth a mean of 2 times. 55.6% of the patients had a BMI  $\geq$  25. Most common complaints were bleeding (in 68% of patients), swelling (46%) and pain (45%). The majority of patients did not report constipation and had a normal Bristol stool type (3-4). 63.1% patients already consulted for hemorrhoids in the past. 44.7% of patients reported a concomitant venous leg disorders. Most common signs in these patients were telangiectasia and reticular veins in 41% of patients (C1 according to CEAP classification), followed by varicose veins in 24.2% (C2 according to CEAP). Proctological examination showed grade 1 hemorrhoids in 24.1% of cases, grade 2 in 39.3%, grade 3 in 31.7% and grade 4 in 5.0%. Most patients were started on venoactive drugs for at least one week (77.2% of total cohort). Other conservative therapies were dietary fiber (50.4%) and topical therapy (48.5%). Only 52.8% of patients received interventional treatment (unspecified instrumental or surgical). There were significant regional differences regarding the proposed treatment. Surgical therapy was applied more often in the northern part of Belgium (53% of patients in Flanders) compared to the southern part (43% of patients in Brussels and Wallonia),  $P < 0.05$ , Chi-square analysis. There was also a regional difference concerning the use of venoactive medication (66.9% of patients in the north, 82.7% of patients in the south,  $P < 0.01$ , Chi square analysis).

**Conclusions :** This patient sample provides an overview of hemorrhoidal disease management in Belgian GI practice. Of note, BMI over 25 and multiparity are present in more than half of patients with symptomatic hemorrhoids, while self-reported constipation is not. Hemorrhoidal disease and chronic venous disease coexist in almost half of patients. Management of hemorrhoidal disease varies a lot amongst caregivers and we even observe significant regional differences. Efforts should be made to improve adherence to guidelines on hemorrhoidal disease treatment. \*This observational study was funded and organized by Servier Benelux.

THUNDERBEAT®-ASSISTED HAEMORRHOIDECTOMY IN SYMPTOMATIC PROLAPSING HAEMORRHOIDS. A PILOT TRIAL. L. Heyerick (1), D. Van De Putte (1), M. De Visschere (1), P. Pattyn (1), H. Van Vlierberghe (1), D. De Looze (1) / [1] Ghent University Hospital, Ghent, Belgium, Department of Gastroenterology and Coloproctology.

**Introduction :** Excisional haemorrhoidectomy is an effective technique in the treatment of haemorrhoids, but may be complicated with intraoperative bleeding, thereby hampering the visualisation of the surgeon and increase operation time. Olympus (Japan) developed the Thunderbeat®-technology which simultaneously delivers ultrasonic and bipolar energy to cut, coagulate and dissect tissue with a single instrument by which thermofusion of vessels up to 7 mm diameter is possible. In case of intraoperative bleeding, bipolar energy can be applied for secondary haemostasis. The technology is already being used widely in laparoscopic surgery, but its use in the resection of haemorrhoids has never been investigated before.

**Aim :** To determine the efficacy and safety of Thunderbeat®-assisted haemorrhoidectomy.

**Methods :** Patients selected for excisional haemorrhoidectomy were operated using Thunderbeat® (Open Fine Jaw). Data from the pre-, per- and postoperative situation were prospectively collected. Two follow-up visits were analysed to evaluate the postoperative situation. Additionally, after initiation of this study, not-standardized questionnaires were sent to all patients to evaluate the current situation.

**Results :** 35 patients (28 male, 7 female) with a mean age at operation of 51.5 years were included. 28 (80%) patients presented with blood loss, of which 11 (39%) had anaemia. 1 patient was treated with anticoagulants preoperatively. 10 (29%) patients complained about pain. 2 (6%) patients had some degree of prolapse-associated anal incontinence

preoperatively. There was a grade 2 prolapse in 9 (26%), grade 3 in 17 (49%) and grade 4 in 9 (26%) patients. 25 (72%) patients had undergone prior instrumental treatment and 5 (14%) were already operated. The mean surgery-duration was 20.6 minutes (range 9-41) and the amount of haemorrhoids resected was 1 in 1 (3%) patient, 2 in 10 (29%) patients, 3 in 15 (43%) patients and 4 in 9 (26%) patients. During 12 (34%) interventions, additional haemostasis with bipolar coagulation was necessary. No immediate postoperative urinary retention developed in any patient and no one presented with severe haemorrhage within the first 14 postoperative days. A subgroup analysis (n=18) of mean VAS scores (0-10) showed increasing pain up to postoperative day 4 (mean VAS 5.78) whereafter the pain gradually diminished. At postoperative day 7 and 14, 6% and 59% of patients had a VAS score of 2 or less, respectively. Analysis of painkillers-usage (paracetamol, diclofenac, tradonal) revealed a steady decrease from the 7th day after surgery. The mean follow-up visits were scheduled at 34.2 (5 weeks) and 82.0 days (12 weeks) postoperatively. At 5 weeks, anal pain was still present in 14 (43%) patients, 12 (36%) had minimal blood loss and 1 (3%) had unchanged blood loss. Only 1 (3%) patient still had some prolapse feeling. 1 (3%) patient was anal incontinent (same patient as preoperatively). Another patient only had flatus incontinence. At 12 weeks, only 1 (5%) patient still had pain and 6 (29%) still had some minimal blood loss. No single patient had prolapse feeling anymore and 1 (5%) was incontinent for gas. During clinical examination after 5 weeks, active wound defects were observed in 20 (61%) patients and intra-anal erosions were present in 21 (64%). 7 (21%) patients had anal edema. After 12 weeks, 2 (10%) patients still had wound defects and 3 (14%) had intra-anal erosions, while edema was not observed anymore. 1 (5%) patient developed anal stenosis for which dilations were started. The mean long-term follow-up period for respondents to the questionnaire (n=30) was 19.9 months (range 4.1-35.4). 27 (90%) reported no blood loss and 26 (87%) had no feeling of anal prolapse. Only 1 (3%) patient had anal pain only during stool passage. 5 (17%) patients had difficulties evacuating stool, but only 2 (7%) effectively reported narrowing of their anus. As for incontinence 12 (40%) reported flatus incontinence and 1 (3%) patient reported liquid stool incontinence. Urgency was reported by 9 (30%) patients.

**Conclusions :** Thunderbeat®-assisted haemorrhoidectomy seems to be an effective, safe and quick treatment option for symptomatic haemorrhoids. Long-term results are also promising. Comparative prospective studies are needed to reliably compare classical haemorrhoidectomy and other vessel sealing devices in haemorrhoidectomy in order to determine the real value of Thunderbeat®.

- M05 -

CURIOUS INTRA-RECTAL “LATERALLY SPREADING TUMOR” IN IMMUNOSUPPRESSED PATIENT WITH ULCERATIVE COLITIS. S. Vieujean (1), P. Latour (1), C. Coimbra Marques (2), E. Louis (1), C. Van Kemseke (1) / [1] CHU Sart Tilman, Liège, Belgium, Gastroenterology, [2] CHU Sart Tilman, Liège, Belgium, Abdominal surgery.

**Introduction :** A 46-year-old man was admitted in June 2015 for the first time in our department for a colonoscopy in a context of ulcerative colitis, diagnosed 4 years earlier (ulcerative proctitis). At time of diagnosis (2011), he was treated by oral Mesalazine, 5ASA suppositories and enema, Budesonide enema and then Azathioprine. Patient was asymptomatic for a long-time but no follow-up had been achieved for at least 3 years. A colonoscopy was performed prior to potential immunosuppressive treatment discontinuation. This examination showed a kind of circumferential “laterally spreading tumour” with villous appearance located in the rectum 4 to 7 centimeters from the anal margin with a little triangular extension to the dentate line. Surprisingly rectal biopsies revealed a condyloma acuminatum with very focally high-grade intra-epithelial lesion and an overexpression of the p16 protein (cell marker induced by oncogenic HPV). Azathioprine was stopped and a transanal surgical resection was performed. This led to a scarring rectal substenosis and further rectoscopies permitted destruction of some little condylomatous persistent lesions. At guided anamnesis on sexual behavior, patient confirmed to be an active “men who have sex with men” (MSM). No recurrence of active ulcerative proctitis occurred despite Azathioprine discontinuation.

**Conclusions :** Condyloma acuminatum is a manifestation of Human Papillomavirus (HPV) infection and usually occurs in the genital and perianal regions. Involvement of the rectal mucosa is a rare condition and treatment strategy is not well established. This may have been in this case promoted by immunosuppressive treatment. As sexually transmitted anorectal disease may mimic inflammatory bowel disease, first diagnosis of ulcerative proctitis may be questioned even more with absence of recurrence despite absence of treatment.



## NUTRITION

- N01 -

SHIFTING PARADIGMS IN INTESTINAL TRANSPLANTATION : FROM RESCUE THERAPY TO STANDARD OF CARE FOR INTESTINAL FAILURE? E. Canovai (1), L. Ceulemans (1), G. De Hertogh (2), M. Hiele (3), M. Sainz-Bariga (1), D. Monbaliu (1), I. Jochmans (1), T. Vanuytsel (3), J. Pirenne (1) / [1] UZ Leuven, Leuven, Belgium, Abdominal Transplantation, [2] UZ Leuven, Leuven, Belgium, Pathology, [3] UZ Leuven, Leuven, Belgium, Gastroenterology.

**Introduction :** Intestinal Transplantation (ITx) is standard treatment for intestinal failure patients with life-threatening complications of home parenteral nutrition (HPN). Furthermore, refractory diffuse portomesenteric thrombosis (DPMT) is a growing indication for multivisceral transplantation (MVTx). Traditionally, ITx has had lower long-term survival compared to other solid-organ transplants (due to higher risk of rejection /infection) and compared to HPN. This often leads to late referral for ITx when malnourishment and vascular access problems increase perioperative risks.

**Aim :** To study the results of a single-center cohort of ITx patients and discuss possible change/evolution in indications for ITx.

**Methods :** A retrospective analysis of a prospectively maintained database of a single-center cohort of ITx patients transplanted from 2000-2017 was performed. Demographics, indication, graft type, rejection episodes, survival, costs versus HPN ; and quality of life (QoL) were recorded.

**Results :** In the study period, 17 patients (13 adults (median age 43 years (23-57)) and 4 children (median age 6 years (range : 3-17))), were included. In adults, majority of indications were short bowel syndrome (SBS) (61%) and diffuse portomesenteric thrombosis (31%). Two children had SBS after volvulus and 2 had congenital diseases. Seven patients underwent isolated ITx, 5 combined Liver-ITx, and 4 MVTx (including stomach, liver, pancreas and small intestine). Patients were treated according to a previously described immuno-suppressive (basiliximab, tacrolimus, azathioprine, steroids) and immunomodulatory protocol (Donor-specific blood transfusion & interventions aimed at reducing inflammation and endotoxin load) (Ceulemans et al. Am J Tx 2016). Cold ischemia times were kept short by synchronizing donor and recipient operations (median : 5.35 hrs.). Parenteral nutrition was stopped before discharge in all survivors. There were 10 episodes of acute rejection in 6 patients which all resolved with medical treatment. One patient developed sclerosing mesenteritis 14 years after ITx which was successfully treated with everolimus and high dose corticosteroids. Two patients died in the first year post-ITx due to invasive aspergillosis infections. One patient died more than 11 years after ITx due to NSAID induced enteropathy. The 10-year patient survival was 87%. Median Karnofsky score amongst survivors was 90-100%. The first-year cost of ITx was € 185.662 (122.483-571.301) versus € 59.524 (58.731-65.807) in stable HPN patients. However, in subsequent years, the cost of ITx was dramatically reduced while HPN costs remained stable (Y2 : €44.893, Y3 : €18.976) than HPN.

**Conclusions :** In this series, results of ITx compare favorably to HPN and other solid organ transplants. Diffuse splanchnic thrombosis is an expanding indication for MVTx. Excellent long-term results in addition to cost effectiveness and excellent QoL indicate that ITx may be offered earlier in the course of intestinal failure.

## BELGIAN GROUP FOR DIGESTIVE ONCOLOGY (BGDO)

- 001 -

PROGNOSTIC VALUE OF TUMOR LOCATION IN COLORECTAL CARCINOMA : A BELGIAN POPULATION-BASED STUDY. K. Janssens (1), N. Boeckx (2), K. Op De Beeck (2), E. Fransen (3), F. Calay (4), N. Van Damme (4), M. Peeters (5) / [1] University of Antwerp, Antwerp, Belgium, Internal Medicine, [2] Center for Oncological Research (CORE), Edegem, Belgium, [3] StatUa Center for Statistics, Antwerp, Belgium, [4] Belgian Cancer Registry, Brussel, Belgium, [5] Antwerp University Hospital, Edegem, Belgium, Department of Oncology.

**Introduction :** In recent years, the difference in survival between right-sided and left-sided colorectal cancer (CRC) has been extensively studied. Various studies have convincingly shown that patients with tumours originating on the left side of the colon have a significantly better prognosis than those with tumours originating on the right side of the colon, in all CRC stages. However, these conclusions are mostly based on data of clinical trials and therefore based on data of selected patients. These findings need to be confirmed in population-based studies.

**Aim :** The aim of this study is to compare survival rates in left-sided and right-sided CRC in the (non-selected) Belgian population.

**Methods :** In Belgium, data on patient and tumour characteristics of all new diagnosed cancers is collected in a national and population based cancer registry, the Belgian Cancer Registry (BCR). Patients diagnosed with CRC between 2004 and 2015 were included in our analysis. We obtained information on age, sex, stage, location of the primary tumour and survival. The vital status was retrieved by the BCR from the Crossroads Bank of Social Security. Cancers were classified as right-sided cancer if they were located in the caecum, ascending colon, hepatic flexure and transverse colon. Left-sided colon cancer is defined as cancer of the splenic flexure, descending colon, sigmoid and rectosigmoid colon.

**Results :** The study included 93,011 patients : 27,863 (30%) with right-sided CRC, 35,815 (38.5%) with left-sided CRC, 27,359 (29.4%) with rectal cancer and 1,974 (2.1%) with an overlapping lesion of the colon or unknown localization. Overall, the observed 5-year survival rate for patients with right-sided colon cancer was 49.9% (95% CI : 49.3% to 50.5%) compared with 55.3% (95% CI : 54.8% to 55.9%) for patients with left-sided colon cancer and 54.8% (95% CI : 54.2% to 55.4%) for patients with rectal cancer, in all stages combined. The 5-year relative survival rate for patients with right-sided colon cancer was 65.6% (95% CI : 64.7% to 66.4%) compared with 68.4% (95% CI : 67.7% to 69.1%) for patients with left-sided colon cancer and 66.1% (95% CI : 65.4% to 66.9%) for patients with rectal cancer, in all stages combined. In stage IV colon cancer, the observed 5-year survival rate for patients with right-sided colon cancer was 11.1% (95% CI : 10.2% to 12.1%) compared with 16.9% (95% CI : 15.9% to 17.9%) for patients with left-sided colon cancer and 17.6% (95% CI : 16.4% to 18.9%) for patients with rectal cancer. The 5-year relative survival rate in stage IV was 13.4% (95% CI : 12.2% to 14.5%) in right-sided colon cancer compared with 19.6% (95% CI : 18.4% to 20.7%) for patients with left-sided colon cancer and 20.2% (95% CI : 18.8% to 21.6%) for patients with rectal cancer.

**Conclusions :** We present the survival data of all colorectal cancer patients diagnosed between 2004 and 2015 in Belgium according to tumour location, age, sex and stage. Currently, we can conclude that observed survival is numerically lower in patients with right-sided colorectal cancer compared to left-sided CRC. This corresponds with findings of previous research. Extended analysis will be available in February.

- 002 -

CLINICAL APPLICATION AND POTENTIAL USEFULNESS OF TARGETED NEXT-GENERATION SEQUENCING ON RESECTED PANCREATIC DUCTAL ADENOCARCINOMA. F. Puleo (1), N. Rémy (2), Y. Blum (2), J. Cros (3), L. Marisa (2), P. Demetter (4), E. Quertinmont (5), M. Svrcek (6), N. Elarouci (2), D. Franchimont (7), L. Verset (4), J. Devière (7), A. De Reyniès (2), P. Laurent-Puig (8), J. Bachet (9), R. Maréchal (7), J. L. Van Laethem (7) / [1] Institut Jules Bordet, Brussels, Belgium, Gastroenterology, [2] Ligue Nationale Contre Le Cancer, Paris, France, Carte d'Identité des Tumeurs, [3] Hôpital Beaujon, Clichy, France, Pathology, [4] Erasme Hospital, Brussels, Belgium, Pathology, [5] Erasme Hospital, Brussels, Belgium, Laboratory of Experimental Gastroenterology, [6] Hôpital Saint Antoine, Paris, France, Pathology, [7] Erasme Hospital, Brussels, Belgium, Gastroenterology, [8] Hôpital Européen Georges Pompidou, Paris, France, UMRS 1147, [9] Hôpital Pitié Salpêtrière, Paris, France, Gastroenterology.

**Introduction :** Pancreatic ductal adenocarcinoma (PDA) carries a dismal prognosis. Virtually all PDA are characterized by mutation of four driver genes : KRAS, TP53, CDKN2A and SMAD4 and a long tail of rarely mutated genes. Application of targeted next-generation sequencing (NGS) has entered clinical routine for colon, lung and other cancers. Among patients with resected PDA, usefulness, applicability and prognostic significance of NGS results are still a matter of debate.

**Aim :** To evaluate : 1) the alterations of the 4 main driver genes and patient outcomes after resection 2) the usefulness of targeted NGS in finding targetable alterations.

**Methods :** We analyzed DNA alterations in FFPE tumors among 279 patients with curatively resected PDA who were treated at 4 Academic Hospitals (Franco-Belgian consortium). Sequencing libraries were prepared using a 50 genes panel (Ion AmpliSeq™ Cancer HotSpot Panel v2, Life Technologies). Sequencing was performed on an Ion Proton™ System using an Ion PITM Sequencing 200 Kit and an Ion PITM Chip Kit v3 (Life Technologies). Associations of driver gene alterations with disease-free survival (DFS) and overall survival (OS) were evaluated using Cox proportional hazards regression with estimation of hazard ratios (HRs) and 95% CIs and adjusted for age, sex, tumor characteristics and institution.

**Results :** Of the 279 patients analyzed, 163 (58.4%) were men and 116 (41.6%) were women, with a median age of 64.59 (36.9-87.5) years. KRAS, TP53, CDKN2A and SMAD 4 were mutated in 246, 193, 45 and 44 patients respectively. Patients with KRAS mutant tumors did not have worse DFS (median [95% CI], 12.2 [11.35–14.6] months) and OS (23.9 [21.1–30.1] months) compared to patients with KRAS wild-type tumors (DFS, 14.3 [9.64-19.4] months ; OS, 31.8 [19.4-53.5] months). The mutational status of TP53 or SMAD4 was not associated with DFS or OS as well. CDKN2A mutations were associated with a lower OS (mutation : 20.5 [14.6-33.0] versus wild-type 26.5 [21.9-33.3] months OS, log-rank <1% HR 1.65 [1.124-2.436]) but not to a lower DFS. Patients had slightly worse DFS and OS if they had a greater number of altered driver genes. Compared with patients with 0 to 2 altered genes, those with 3 to 4 altered genes had worse DFS (HR, 1.377 [95% CI, 1-1.89 ; P=.05]) and OS (HR, 1.476 [95% CI, 1.04-2.09 ; P=.028]). For some patients (n=27, 9.68%), we found mutations that could be targeted (i.e PTEN, STK11, GNAS, PIK3CA, FLT3, BRAF, IDH1/2, RET, FGFR3, KIT, AKT1).

**Conclusions :** Analysis of the four main driver gene alterations introduces weak prognostic information with little added clinical value. However, application of NGS in resected PDA is quite feasible and is able to find targetable mutations. KRAS and CDKN2A deserve future attention for targeting specific mutations.

- O03 -

PREOPERATIVE GEMCITABINE-NAB-PACLITAXEL (G-NP) FOR (BORDERLINE) RESECTABLE (BLR) OR LOCALLY ADVANCED (LA) PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) : A FEASIBILITY AND PROOF OF CONCEPT STUDY. L. Mans (1), I. Borbath (2), M. Bali (3), G. Verset (1), A. Demols (1), F. Puleo (1), L. Annet (4), M. Komuta (5), P. Demetter (6), J. Van Laethem (1), R. Marechal (1) / [1] Erasme Hospital, Brussels, Belgium, Gastroenterology, Hepatopancreatology and Digestive Oncology Department, [2] Cliniques universitaires Saint-Luc, Brussels, Belgium, Gastroenterology and Hepatology Department, [3] Erasme Hospital, Brussels, Belgium, Radiology Department, [4] Cliniques universitaires Saint-Luc, Brussels, Belgium, Radiology Department, [5] Cliniques universitaires Saint-Luc, Brussels, Belgium, Department of anatomopathology, [6] Erasme Hospital, Brussels, Belgium, Department of anatomopathology.

**Introduction :** Neoadjuvant/induction therapy is emerging in resectable/borderline resectable pancreatic cancer (PDAC) aiming to control micrometastases, R0 resection and outcome. Recently the combination of gemcitabine and nab-paclitaxel has shown significant activity in PDAC to be proposed in the preoperative setting. Gem-nab-P has been reported to decrease tumor stroma and enhance intratumoral drug delivery when delivered preoperatively.

**Aim :** G-NP has recently emerged as an effective combination treatment for metastatic PDAC. We aimed to evaluate tolerability and activity of induction/neoadjuvant G-NP before surgery.

**Methods :** Patients with ECOG PS 0/1, cytologically proven PDAC, normal bilirubin level and BLR or LA disease were included and received at least one cycle of G 1000 mg/m<sup>2</sup> and NP 125 mg/m<sup>2</sup>, weekly 3week/4. Additional cycles were indicated according to sequential tumor restaging for resectability evaluation ; complementary chemoradiation (CRT) (50.4 Gy in 28 fractions) with capecitabine (825 mg/m<sup>2</sup> BID) was administered in case of persisting non resectability. Adjuvant chemotherapy was given if indicated. Feasibility, toxicity, kinetic of CA 19.9, radiological response (RECIST criteria), R0 resection rate, pathological response (pR), recurrence and survival were assessed.

**Results :** 23 patients received therapy (M/F : 13/10 ; median age : 63 (range 42-77), ECOG 0/1 : 12/11), 13 with BLR and 10 with LA PDAC ; median number of cycles was 3 (range : 1-6). Eight patients received additional CRT. The most common AEs were hematological disorder, asthenia, diarrhea and decrease appetite mostly grade 1 or 2. Sixteen (69%) patients had grade 3 toxicity (n=15, mainly hematologic) or grade 4 (n=1, thrombopenia). No toxic death occurred during the whole sequence. During the preoperative treatment, the best RECIST responses were 8 PR, 12 SD and 3 PD. Among the 16 patients with an elevated CA19.9 level at baseline, 10 (62%) decreased CA 19.9 levels by at least 50 %. R0 (n=7)/R1(n=6) resection could be performed in 13/23 patients (56%). There were 0 pCR, 3 major pR and 10 minor/ no pR. Outcome was available for 16 patients : median progression-free survival was 10.9 months (95% CI : 5.0-16.8) and median overall survival 19.4 months (95% CI : 13.8-25.0).

**Conclusions :** Induction chemotherapy with G-NP is feasible, well tolerated and active before surgery. Our data suggest a potential interest of this combination to increase the R0 resection rate in BLR or LA pancreatic adenocarcinoma that can be evaluated more deeply.

IMPACT OF INTRODUCTION OF AN ENHANCED RECOVERY PATHWAY IN ESOPHAGEAL CANCER SURGERY: A PROSPECTIVE COHORT STUDY AND PROPENSITY SCORE MATCHING ANALYSIS. Y. Mandeville (1), J. Moons (1), A. Ringoet (1), L. Depypere (1), W. Coosemans (1), H. Van Veer (1), P. Naftoux (1) / [1] UZ Leuven, Leuven, Belgium, Thoracic Surgery.

**Introduction :** Enhanced recovery pathways (ERP) are well established in several surgical disciplines and have the potential to improve clinical outcome even after complex procedures, such as esophagectomy. In a stepwise implementation of ERP in esophagectomy patients, early mobilization (transition period-TP) was introduced in September 2016 in our department. Subsequently, a complete ERP was implemented in May 2017.

**Aim :** Purpose of this study was to determine the impact of a new ERP on perioperative results as compared to our traditional care after esophagectomy (TC).

**Methods :** For this observational study independent samples t-test and Fisher's exact test were used to calculate statistical differences between groups. A propensity score matching was performed to reduce the bias due to confounding variables. The nearest neighbour matching procedure (1 :1) was used. Differences were considered to be significant when  $p < 0.05$ .

**Results :** There were 160 TC and 50 ERP patients. No differences were found neither in patient demographics, comorbidities, tumour characteristics nor in treatment types (table 1). A significant decrease in complications was found between the two groups, especially pneumonia and respiratory failure requiring reintubation (38% in TC and 16% in ERP ;  $p = 0.0007$  and 16% versus 4% ;  $p = 0.026$  respectively) and postoperative blood transfusion (26%-4% ;  $p = 0.003$ ). Furthermore, a clear but non-significant reduction in anastomotic leak rates (12%-4% ;  $p = 0.11$ ), delirium (6%-2% ;  $p = 0.24$ ), central line infections (10%-0%) was found (table 2). Consequently, CCI% was statistically different between the groups : TC 38.1% vs. ERP 28.2% ( $p = 0.03$ ). Furthermore, median LOS was also significantly shortened from 13 days (IQR 10-20) in TC to 9 days (IQR 8-13) in ERP patients ( $p = 0.009$ ). The 30-day readmission rate (10% in TC and 10% in ERP) was not significantly affected. Forty-seven ERP-patients could be matched to 47 TC-patients in a propensity analysis in which 11 variables were used to ensure an even distribution of confounders between groups (table 3). This analysis confirmed the significant impact on pneumonia ( $p = 0.032$ ) ; blood transfusion ( $p = 0.021$ ) and LOS ( $p = 0.022$ ) (table 4).

**Conclusions :** In this prospective observational study, a clear decrease in complication rate (especially respiratory complications) and CCI% were observed after ERP introduction, leading to a shortening of LOS without affecting the 30-day readmission rate. A propensity analysis confirmed the positive impact of ERP on pneumonia and LOS without impact on readmission rate. ERP for esophagectomy in a tertiary referral centre is associated with a significant decrease in postoperative (respiratory) complications which results in a significant decrease of LOS without affecting readmission rate.

LONG TERM ONCOLOGICAL RESULTS AND QUALITY OF LIFE AFTER HIPEC FOR CARCINOMATOSIS OF COLORECTAL ORIGIN. S. Barbois (1), D. Leonard (2), A. Souchet (1), C. Remue (1), N. Abbes Orabi (1), R. Bachmann (1), M. Van Den Eynde (3), X. Wittebole (4), E. Cotte (1), E. Danse (5), A. Jouret-Mourin (6), A. Dragean (5), G. Leclercq (7), A. Kartheuser (1) / [1] Cliniques universitaires Saint-Luc, Brussels, Belgium, Unité de Chirurgie Colorectale, [2] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Unité de Chirurgie Colorectale, [3] Cliniques universitaires Saint-Luc, Brussels, Belgium, Department of Hepato-gastro-enterology, [4] Cliniques universitaires Saint-Luc, Brussels, Belgium, Intensive Care Department, [5] Cliniques universitaires Saint-Luc, Brussels, Belgium, Department of Radiology, [6] Cliniques universitaires Saint-Luc, Brussels, Belgium, Department of Pathology, [7] Cliniques universitaires Saint-Luc, Brussels, Belgium, Department of Pharmacy.

**Introduction :** Peritoneal carcinomatosis (PC) of colorectal origin remains the most advanced form of colorectal cancer and is still associated with poor outcome. Cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC) has deeply modified patients' prognosis.

**Aim :** This study aims to review our results of CRS and HIPEC based on Oxaliplatin and using a closed abdomen technique as treatment of peritoneal carcinomatosis of colorectal origin. Beside oncologic outcome, this study examines the long-term quality of life (QoL) of patients treated by CRS and HIPEC.

**Methods :** This is a retrospective monocentric study based on consecutive patients presenting colorectal cancer with peritoneal carcinomatosis and treated by CRS and HIPEC. Demographic, operative, post-operative and pathological data have been collected. Long term oncological results have been computed and quality of life has been evaluated using the EORTC QLQ C-30 and GIQLI questionnaires.

**Results :** Between October 2007 and December 2015, 82 patients have undergone 92 HIPEC, of which 70 patients underwent 75 CS with Oxaliplatin HIPEC using a closed abdomen technique. Among the 38 patients alive at the time

of the study, 34 had not benefited from a redo-HIPEC after December 31, 2015. Of the 82 patients operated between October 2007 and December 2015, 10 (10.9%) received prophylactic HIPEC. There were 44 women and 38 men with a median age of 60 (18-77). Twenty-one patients (32.6%) had synchronous resectable liver metastases. The median level of carcinoembryonic antigen was 2,7 ng / mL. The CC-0 and CC-1 resection scores were obtained for 75 (87.2%) and 10 (11.6%) procedures, respectively. The median index of peritoneal carcinomatosis (PCI) was 6 (0 to 30). Twenty-two patients (23.9%) had a Dindo-Clavien complication > 2 and the postoperative mortality was 1,6%. The median follow-up time is 35 months. Twenty-seven patients (29.3%) received neoadjuvant chemotherapy and 48 (53.3%) received adjuvant chemotherapy. Twelve patients (13.0%) had isolated recurrence of CP and 35 patients (38.0%) presented distant metastases. Overall survival (OS) and 5-year survival without recurrence (DFS) were 45.7% and 8.7%, respectively. The deterioration of the quality of life in the long term is related to the presence of an invasion and to the occurrence of distal recurrences. The EORTC and GIQLI questionnaires showed a high incidence and intensity of diarrhea.

**Conclusions :** HIPEC with Oxaliplatin using a closed abdomen technique to treat CP of colorectal origin offers acceptable oncological results. This treatment strategy should therefore be considered for all patients with peritoneal carcinomatosis, while ensuring that patients live not only longer but also enjoy a good quality of life.

- 006 -

A NOVEL POST-SURGICAL PROGNOSTIC SYSTEM FOR COLORECTAL LIVER METASTASES TREATED BY PREOPERATIVE SYSTEMIC TREATMENT, USING TUMORAL AND NON TUMORAL PATHOLOGICAL CHANGES, RAS MUTATION AND IMMUNOSCORE. P. Baldin (1), M. Van Den Eynde (2), B. Mlecnik (3), G. Bindea (3), G. Beniuga (4), J. Carrasco (5), C. Hubert (6), B. Navez (7), G. Pairet (8), A. Jouret-Mourin (9), G. Galon (3), M. Komuta (9) / [1] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Pathology, [2] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Medical Oncology, [3] INSERM UMRS1138 Laboratory of Integrative Cancer Immunology, Paris, France, Université Paris Descartes, Sorbonne Paris Cité, [4] IPG, Charleroi, Belgium, Department of Pathology, [5] GHDC, Charleroi, Belgium, Department of Medical Oncology, [6] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Department of Abdominal Surgery and Transplantation, [7] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Department of Abdominal Surgery and Transplantation, [8] Centre Hospitalier de Jolimont-Lobbes, La Louvière, Belgium, Department of Pathology, [9] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Department of Pathology.

**Introduction :** Surgical control of colorectal liver metastasis (CRLM) combined with systemic treatment in patients aims to maximize survival. However, around 40% of patients develop recurrence in one-year post operation. Moreover, chemotherapy-related liver injury (CALI), such as sinusoidal obstruction syndrome (SOS), nodular regenerative hyperplasia (NRH), and steatohepatitis, have been reported to worsen operative mortality and morbidity rates.

**Aim :** We aim to develop a prognostic scoring system to stratify patient prognosis post-hepatectomy by identifying the significant prognostic clinico-pathological-molecular factors in patients with resected CRLM.

**Methods :** We investigated 143 patients with 403 CRLM operated from 2005-2013, including patients untreated (19 patients with 29 lesions) and treated with chemotherapy alone (33 patients with 91 lesions), chemotherapy with anti-VEGFR (47 patients with 157 lesions), and chemotherapy with anti-EGFR (44 patients with 126 lesions). All specimens were reviewed to assess tumour regression grading (TRG), histological growth pattern (HGP), and CALI. Genomic DNA from the lesions was extracted and purified from Formalin-fixed, paraffin-embedded slides. Immunoscore was assessed by the immune densities (cells/mm<sup>2</sup>) of CD3- and CD8 positive lymphocytes in the center and the invasive margin of the tumour by using morphometry. Comparisons were made using the Wilcoxon-Mann-Whitney test. Cumulative disease-free (DFS) and overall survival (OS) were analysed using the Kaplan-Meier estimator and compared by log-rank tests. Cox proportional hazards models were used for uni- and multi-variate analysis. P-value of less than 0.05 was considered statistically significant.

**Results :** Multivariate analysis showed that a high TRG (TRG 3-5), the worst HGP (replace growth pattern, mixed pattern),  $\geq 4$  lesions, positive surgical margin, CALI (steatohepatitis, NRH), RAS mutation and the worst Immunoscore were the significant prognostic factors. The prognostic scoring system combining these parameters significantly stratified post-operatively treated patients' prognosis into three groups (high risk group : 81.3% (63.1%-90.3% 95CI) one-year recurrence rate, intermediate risk group : 41.3% (26.8%-52.9% 95CI) one-year recurrence rate, low risk group : 13.8% (0.3%-25.5% 95CI) one-year recurrence rate).

**Conclusions :** Our novel prognostic scoring system of CRLM assessed by tumour and non-tumour pathological changes, Ras mutation and Immunoscore, allowed us to identify the patient population with high risk of recurrence post-hepatectomy.

INTER-CENTER HETEROGENEITY IN THE QUALITY OF CARE FOR RECTAL ADENOCARCINOMA IN BELGIUM. N. Van Damme (1), J. Vandeven (1), J. Verbeeck (1), J. Xicluna (1), F. Penninckx (2), A. Kartheuser (3), K. Haustermans (4), J. Van Laethem (5), H. De Schutter (1), L. Van Eycken (1) / [1] Belgian Cancer Registry, Brussel, Belgium, Research, [2] UZ Leuven, Leuven, Belgium, Abdominal Surgery, [3] Cliniques Universitaires St-Luc, UCL, Brussels, Belgium, Colorectal Surgery Unit, [4] UZ Leuven, Leuven, Belgium, Radiation Oncology, [5] Hopital Erasme, ULB, Belgium, Medical Gastroenterology.

**Introduction :** The Belgian Cancer Registry (BCR) conducts studies on quality of care indicators (QCI) for specific cancers by linking its population-based cancer registration database with administrative databases. These projects aim to compare and finally improve quality of care in Belgian hospitals.

**Aim :** In the present study, QCI on rectal cancer were calculated at the Belgian population and hospital level and individual feedback was provided to all Belgian hospitals.

**Methods :** All patients registered by the BCR with unique rectal adenocarcinoma between 2009 and 2011 were selected (n=6,776). After assigning patients to a hospital, different process and outcome indicators were calculated at the national and hospital level : participation in multidisciplinary team meetings (MDT), administration of (neo)adjuvant chemo/radiotherapy, postoperative mortality and observed and relative survival. QCI were adjusted for differences in case-mix between hospitals, including sex, age, stage and WHO performance score.

**Results :** All 103 Belgian hospitals treated rectal cancer in this period, ranging from 7 to 344 cases per hospital (median : 49 cases). The largest center treated 5.1% of all cases. An MDT meeting was reimbursed for 40.7% to 100% of the patients. Neo-adjuvant radiotherapy was given to 43.5% to 100% of cStage II-III diseases and adjuvant chemotherapy was administered to 16.7% to 80.0% of the patients in (y)pStage II-III. Postoperative 30-day and 90-day mortality ranged from 0.0% to 19.4% and 0.0% to 20.8%, respectively. The 5-year observed and relative survival ranged from 29.6% to 71.4% and from 47.3 to 81.0%, respectively. This large inter-center variation in QCI results remained present after case-mix adjustments.

**Conclusions :** Even for common cancers such as rectal adenocarcinoma, substantial variability in treatment and outcome is observed between centers. By providing individual feedback to all Belgian hospitals, foreseeing regular monitoring of QCI results and the possibility to make the results publicly available, centers are encouraged to take further initiatives for quality improvement.

IDENTIFICATION OF NEW PATHWAYS DRIVING MUSCLE ATROPHY AND BIOMARKERS REFLECTING MUSCLE ATROPHY IN CANCER CACHEXIA. G. Paulissen (1), R. De Walque (2), L. Bindels (3), N. Delzenne (3), J. Thissen (4), E. De Pauw (5), M. Meuwis (6), E. Louis (6) / [1] GIGA-R, University of Liège, Liège, Belgium, Translational Gastroenterology, [2] Catholic University of Louvain, Brussels, Belgium, Pole Endocrinology, Diabetes & Nutrition, [3] Catholic University of Louvain, Leuven, Belgium, Louvain Drug Research Institute, [4] Catholic University of Louvain, Leuven, Belgium, Pole Endocrinology, Diabetes & Nutrition, [5] University of Liège, Belgium, Laboratory of Mass Spectrometry, Chemistry, [6] CHU de Liège -GIGA-R, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology Department and Translational Gastroenterology.

**Introduction :** Cancer cachexia is a complex metabolic syndrome characterized by weight loss, in particular skeletal muscle. Loss of muscle mass in advanced cancer is recognized as an independent predictor of mortality and its reversal leads to prolonged survival in animal models. Therefore, maintaining muscle mass seems per se helpful in improving survival in cancer cachexia. However, reliable parameters for early diagnosis of muscle atrophy are still lacking.

**Aim :** We aim at highlighting new pathways driving muscle atrophy during cancer cachexia and at identifying new potential biomarkers in mice and potentially in humans. The secondary goal is to develop a signature of early cancer cachexia markers detectable in the plasma.

**Methods :** To assess muscle atrophy in cancer cachexia, an experimental mouse model was used : C26 carcinoma cells were injected in male CD2F1 mice on day 0 (Bindels et al, ISME Journal, 2016). Mice were sacrificed 10 days later and gastrocnemius samples were collected for protein extraction and fractionation. The sarcoplasmic fraction (SF) (=soluble proteins) and the myofibrillar fraction (MF) (=insoluble proteins) were prepared and provided for the proteomic discovery study. Differential label free proteomics was used to compare muscle peptide extracts from cachectic (n=6) and control mice (n=6). Tissue peptide extracts were analyzed on an instrumental system composed of a 2Dnano UPLC (Waters) coupled to a QExactive Plus Hybrid Quadrupole-Orbitrap mass spectrometer (ThermoFisher Scientific). Protein identifications and relative label free quantitations (LFQ) were obtained using MaxQuant and the differential analysis was performed using Perseus (Tyanova et al, Nature Methods, 2016).

**Results :** We obtained 974 proteins identified and quantified in SF and 948 in MF. The comparison of the two groups : “cachectic” versus “control mice” allowed the selection of a total of 232 proteins found differentially distributed in SF

and 203 in MF and being potential biomarkers. Proteins that focused our attention were the most significant ones with the highest difference between both groups. Gene Ontology, Reactome and the David tools were used and showed that the significant proteins were involved in the metabolism of lipids and carbohydrates with potential global perturbations. Many pathways were affected, as well as some structural muscle proteins, and the general inflammatory response. The most abundant proteins in cachectic muscles were involved in coagulation and complement cascades and in the insulin signaling pathway. The less abundant proteins in cachectic muscles were implicated in energy metabolism as the oxidative phosphorylation, the citrate cycle, as well as in protein degradation. In addition, the significant proteins were searched on the Plasma Proteome Database, leading to 204/232 proteins in SF and 177/203 in MF, that were found detectable in plasma. Some of these will be targeted for further development of a blood test for detecting early cachexia in both mice and humans. The selection of the potential biomarkers is under progress with their empirical detection/ quantitation by a technique of targeted proteomics : Selected Reaction Monitoring (SRM). This SRM method development using mice (cachectic and control) and humans is ongoing for the pragmatic selection of the most relevant biomarkers accessible in the plasma matrix. While the most significant proteins of our lists appear to be linked to inflammation and probably to the inflammatory response driven in cachectic muscles, the markers involved in the SRM signature should also represent the status of the other impacted pathways and perturbed metabolisms that have been highlighted in our muscle analyses.

**Conclusions :** From the proteomic analysis of muscles showing atrophy induced by cancer cachexia in a mouse model, we highlighted some potential biomarkers which require confirmation on blood samples. The development of a targeted proteomic method using SRM should enable this confirmation on mouse plasma. Such SRM signature should also be tested on samples of patients suffering from cancer cachexia.

- 009 -

A CENTRE-BASED STUDY OF CLINICAL AND MOLECULAR CHARACTERISTICS OF POST-COLONOSCOPY COLORECTAL CANCER. C. Severi (1), G. Van Roey (2), J. Janssens (3) / [1] UZ Leuven, Leuven, Belgium, Internal Medicine, [2] AZ Turnhout, Turnhout, Belgium, Gastro-Enterology, [3] AZ Turnhout, Turnhout, Belgium, Gastro-Enterologie.

**Introduction :** Studies showed evidence for the prevention of colorectal cancer (CRC) by colonoscopy with eventual polypectomy, and as such of the general low risk of CRC and advanced adenomas after negative colonoscopy. More recently, the importance of good quality colonoscopy has been highlighted, with special attention to bowel preparation and scope withdrawal time. However, a lot of features of post-colonoscopy colorectal cancer (PCCRC) are still undefined. Obviously, the colonoscopy quality is of great importance in occurrence of post-colonoscopy CRCs. Studies have already shown that physician and patient characteristics have an influence on the incidence of PCCRC. Regarding molecular characteristics, the majority of CRCs progress by the chromosomal instability pathway. Microsatellite instability (MSI) accounts for 15% of all CRCs, including 3% of cancers associated with Lynch syndrome.

**Aim :** To examine the characteristics of patients with PCCRC, we looked at the data of a cohort in our centre. During a three-year time period we made a registry of all patients with CRC who underwent a prior colonoscopy within 10 years (for all reasons) to observe and compare clinical attributes, molecular characteristics (RAS, BRAF, MSI), tumour location (right or left) and time interval between diagnosis of the CRC and the last previous colonoscopy.

**Methods :** Study design : Characteristics of 24 PCCRC patients in a registry of a three-year period (2015-2017) in a single non-university hospital (all colonoscopies performed by members of staff). Patient group : For the aim of this study, a centre-based subset of 24 PCCRC cases was registered during a three-year period. Medical records and colonoscopy reports were reviewed to assess indication of last prior colonoscopy, quality of bowel preparation, completeness of examination, findings and advice for re-evaluation. A pathological examination was performed to detect the presence of MSI, RAS- and B-RAF mutations in near all PCCRCs. Statistical Analysis : We used descriptive statistics to analyse patients, examinations, tumour and molecular characteristics among post-colonoscopy CRC.

**Results :** The index colonoscopy was complete in 100% of the examinations, with no mentioning of insufficient bowel preparation. The average age at diagnosis of PCCRC was 70,5 years and didn't differ significant from average age of all CRC. There was a slight majority of women (13 vs 11). In PCCRC, tumours were more likely to be located in the right colon (62,5%) as compared to the left colon (37,5%). In 9 cases the tumour exhibited MSI (37,5%). All of these tumours were located in the right colon. In two of these patients the diagnosis of Lynch Syndrome was confirmed by genetic examination (not known before diagnosis PCCRC). B-RAF mutations were found in 6 patients (19 examinations - 32%). The B-RAF mutations were all in right-sided tumours. RAS mutations were found in 3 patients (19 examinations - 16%). Of these patients 1 had a right-sided tumour and two patients had a tumour located in the left colon. The average period between index colonoscopy and diagnosis of PCCRC was 3,7 years. There was no significant difference between distal (3,46 yrs) and proximal (3,94 yrs) locations, and between MSI-positive (3,81 yrs) and MSI-negative (3,73 yrs) cancers. CRC associated with Lynch syndrome had a significant shorter interval period of 2,52 years.

**Conclusions :** Our analysis of 24 PCCRCs offers an insight in clinical and molecular characteristics. Our study confirms recent results, that PCCRCs are far more likely to be located in the proximal colon. Moreover, our data showed that

MSI as well as tumours with B-RAF mutations are significantly overrepresented among PCCRCs. The median interval between index colonoscopy and PCCRC is short.

- O10 -

ESTIMATION OF THE FUTURE LIVER REMNANT FUNCTION SUPPORTS PARENCHYMA-SAVING HEPATECTOMY COMBINED WITH HEPATIC VEIN RESECTION AND RECONSTRUCTION. T. Chapelle (1), B. Op De Beeck (2), G. Roeyen (3), V. Hartman (3), B. Bracke (3), D. Ysebaert (3) / [1] Universiteit Antwerpen / Antwerp University Hospital, Wilrijk (Antwerpen), Belgium, Hepatobiliary, Transplantation and Endocrine surgery, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Radiology, [3] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Hepatobiliary, Transplantation and Endocrine surgery.

**Introduction :** Liver tumours invading hepatic vein(s) often lead to major hepatectomy because of the need to resect liver segments drained by the affected vein(s). Hepatic vein resection and reconstruction (HVRR) allows parenchyma-saving hepatectomy (PSHX) with a consequential lower incidence of post-hepatectomy liver failure (PHLF). The choice for combined PSHX/HVRR may be supported by a tool estimating the future liver remnant function (eFLRF), itself a predictor of PHLF.

**Aim :** To demonstrate that combined PSHX/HVRR is technically feasible and can avoid PHLF

**Methods :** Nine patients with tumoural invasion of hepatic vein(s) were reviewed in whom combined PSHX/HVRR was performed instead of major hepatectomy. eFLRF was calculated for different surgical treatment strategies : major hepatectomy without preoperative portal vein embolization (PVE) (option 1), major hepatectomy with PVE with hypothetical degrees of liver hypertrophy of 10% (option 2) and 15% (option 3) and combined PSHX/HVRR (option 4).

**Results :** With this PSHX/HVRR approach, 2/9 developed PHLF grade A and no postoperative mortality occurs. 8/9 had R0 resection. eFLRF was significantly higher in option 4 compared to options 1, 2 and 3 (p= 0.008).

**Conclusions :** Combined PSHX/HVRR can be performed safely and is a good alternative for major hepatectomy. Higher eFLRF implies that this approach is able to reduce the risk of PHLF and its related mortality.

- O11 -

ESTIMATION OF THE FUTURE LIVER REMNANT FUNCTION PRIOR TO HEPATECTOMY MAY GUIDE THE INDICATION FOR PORTAL VEIN OCCLUSION AND AVOID POST-HEPATECTOMY LIVER FAILURE : A PROSPECTIVE INTERVENTIONAL STUDY. T. Chapelle (1), B. Op De Beeck (2), G. Roeyen (3), B. Bracke (3), V. Hartman (3), I. Huyghe (4), S. Francque (5), P. Michiels (5), D. Ysebaert (3) / [1] Universiteit Antwerpen / Antwerp University Hospital, WILRIJK (Antwerpen), Belgium, Hepatobiliary, Transplantation and Endocrine surgery, [2] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Radiology, [3] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Hepatobiliary, Transplantation and Endocrine surgery, [4] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Nuclear Medicine, [5] UZA, Universitair Ziekenhuis Antwerpen, Edegem, Belgium, Gastroenterology and Hepatology.

**Introduction :** Estimation of the future liver remnant function (eFLRF) can avoid post-hepatectomy liver failure (PHLF). In a previous study, a cut-off value of 2.3%/min/m<sup>2</sup> for eFLRF was a better predictor of PHLF than future liver remnant volume (FLRV%). In this prospective interventional study, investigating a management strategy aimed at avoiding PHLF, this cut-off value was the sole criterion assessing eligibility for hepatectomy, with or without portal vein occlusion (PVO).

**Aim :** To demonstrate that eFLRF cut-off of 2.3%/min/m<sup>2</sup> is a good indicator for PVO and helps to avoid PHLF.

**Methods :** In 100 consecutive patients, eFLRF was determined using the formula : eFLRF = FLRV% x total liver function (TLF). Group 1 (eFLRF >2.3%/min/m<sup>2</sup>) underwent hepatectomy without preoperative intervention. Group 2 (eFLRF <2.3%/min/m<sup>2</sup>) underwent PVO and re-evaluation of eFLRF at 4-6 weeks. Hepatectomy was performed if eFLRF had increased to >2.3%/min/m<sup>2</sup>, but was considered contraindicated if the value remained lower.

**Results :** In group 1 (n=93), 1 patient developed grade B PHLF. In group 2 (n=7) no PHLF was recorded. Postoperative recovery of TLF in patients with preoperative eFLRF <2.3%/min/m<sup>2</sup> occurred more rapidly when PVO had been performed.

**Conclusions :** A predefined cut-off for preoperatively calculated eFLRF can be used as a tool for selecting patients prior to hepatectomy, with or without PVO, thus avoiding PHLF and PHLF-related mortality.

- O12 -

NEXT- GENERATION SEQUENCING IN CHOLANGIOCARCINOMA : THE QUEST FOR APPLICABILITY AND PRECISION THERAPY! A. Bucalau (1), N. D'Haene (2), P. Demetter (2), V. Lucidi (3), G. Verset (1), J. Van Laethem



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**Introduction :** Cholangiocarcinoma (CC) involves a group of related but heterogeneous malignances with different clinical and biological presentation for intrahepatic (IH) and extrahepatic (EH) localization as well as gallbladder (GB). Its prognosis remains poor and treatment is currently scarce. Next-generation sequencing (NGS) technology may provide some answers regarding the molecular landscape of CC and identify subgroups for targeted therapy.

**Aim :** We are seeking the most common genomic alterations in CC. We hope, in the future, to be able to identify distinct molecular subsets of this malignancy, with better-defined prognostic classification and therapeutic implications in case of finding druggable gene alterations.

**Methods :** Since May 2015, all patients from Erasme University Hospital with advanced/metastatic CC at diagnosis or recurrence after surgery were considered for DNA alterations analysis. The NGS research was launched during the first line of chemotherapy (Gemcitabine-Cisplatin) in order to offer a targeted therapy in the 2nd line or subsequently. Mutation profiling was performed on biopsy, surgical (primary or metastatic nodules) or fine needle aspiration (FNA) samples using a 50-gene panel (PGM, Ion Torrent with Kit AmpliSeq).

**Results :** NGS-based testing was successfully achieved in 18 out of 34 patients diagnosed with advanced CC, who completed one line of chemotherapy. Population age ranged between 35 and 80 years (median of 65, 5), with M/F ratio 1 :1 (9 men and 9 women). Of the 18 samples that were analyzed, 8 (44, 4%) presented an intrahepatic localization, 3 (16, 7%) extrahepatic and 7 (38, 8%) were located in the gallbladder. Three patients were initially curatively resected, the remaining being locally advanced/metastatic from diagnosis. Several differences were noticed in the three localizations regarding the genetic aberrations : IDH 1 and 2 were found only in the intrahepatic group (2/8 patients), ERBB2 in the extrahepatic and gallbladder group (2/10 patients), meanwhile TP53 was observed in all three categories (6/18 patients). The other genes detected were CDKN2A, ATM and PIK3CA in the intrahepatic category, the extrahepatic population being poorer in mutation with KRAS in one patient and no other anomaly in the gallbladder subgroup. One patient with intrahepatic CC presented a fusion FGFR2 and received consequently a targeted therapy with stable disease at this time. IDH1/2, PIK3CA, ATM and ERBB2 mutations could be targeted in the future according to the clinical evolution of these patients. Additionally, Microsatellite instability (MSI) was researched by immunohistochemistry in 8 patients and was negative.

**Conclusions :** NGS technology is feasible for CC on different tissue sampling. Its applicability for precision therapy is to be evaluated individually and incorporated in the management of patients with advanced disease.

- O13 -

AMOCT : A SINGLE CENTER EXPERIENCE IN PATIENT REPORTED OUTCOME (PROM) REGISTRATION DURING TREATMENT OF GASTRO-INTESTINAL CANCER PATIENTS. M. Rasschaert (1), S. De Keersmaecker (2), J. Ravelingien (3), M. Peeters (1) / [1] University Hospital Antwerp, University of Antwerp, Antwerp, Belgium, Medical Oncology, [2] University Hospital Antwerp, Antwerp, Belgium, Medical Oncology, [3] Remedus, Aartselaar, Belgium, Home Care.

**Introduction :** Monitoring of symptoms and performance status during chemotherapy is a cornerstone of medical oncology routine care, and is standard for patients (pts) enrolled in clinical trials. As pts experience various adverse effects, needs for therapy alteration, supportive care, or informational services often change. The use of PROMS is superior to physician assessed toxicity scoring and improves overall survival regardless of tumour type or treatment.

**Aim :** This study assesses patients use a device/smartphone designed for cancer pts to self-record toxicity-related symptoms (PROMs) based on the PRO-CTCAE (NCI Patient-reported outcomes Common Terminology Criteria for Adverse Events). Secondary outcomes include the rate and grade of toxicities encountered, the use of emergency resources, hospitalizations and unscheduled consultations.

**Methods :** The device is linked with an electronic platform as well as the pts EPF (Electronic ptn file). Real time data / Proms are collected by the pts and processed by an algorithm. This algorithm allows automated responses to graded toxicity and interaction with care givers when toxicity exceeds predefined thresholds ( $\geq$  grade 3).

**Results :** From April 2015 to June 2017, sixty-nine pts with cancer of digestive origin were enrolled (41 men, 29 women). Median age was 65 years (yrs) in men (range 42- 88yrs) and 60yrs in women (range 27-80yrs). Median time on AMOCT was 171 days (d) (range 0-704d). 32 % of pts still continued PROM registration at the end of the study, 33% pts stopped therapy, while 9% dropped out because of clinical deterioration and 4% changed therapies. 29 pts (42%) were hospitalized (41 instances) and 22 pts (32%) visited the ER during enrolment. Frequently scored severe (Gr3) toxicities were dyspnoea, arthralgia an asthenia in 38%, 15% and 13% of pts respectively.

**Conclusions :** The use of an interactive Self-Report tool is feasible, reliable and acceptable to outpatients. A comparison to a historical control group will be presented at the final meeting and will further elucidate the secondary outcomes.

## BELGIAN PANCREATIC CLUB (BPC)

- P01 -

ENDOSCOPIC NECROSECTOMY A SINGLE CENTER EXPERIENCE. A. Taha (1), T. Aouattah (1), R. Yeung (1), T. Moreels (1), H. Piessevaux (1), P. Deprez (1) / [1] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Hepato-Gastroenterology Department.

**Introduction :** Pancreatic necrosis occurs in 15% of acute pancreatitis with mortality in infected necrosis up to 20%. With the emerged endoscopic drainage techniques, there has been an evolution in the treatment of infected pancreatic necrosis and during the last decade several studies showed better outcome for less invasive treatment approaches.

**Methods :** A retrospective review of patients that underwent endoscopic necrosectomy at our centre between 2007 and 2017. Primary end point was treatment clinical success with improvement in symptoms and no further treatment needed, and secondary end points radiological success with complete resolution of the collection or small residual collection with no further treatment, survival, major adverse events, and outcomes on long term follow up.

**Results :** A total of 16 patients (mean age 54 years ; 13 males) underwent 35 sessions of endoscopic necrosectomy. The most frequent etiology was biliary (43.7%) followed by alcohol (37.5%). The mean time for the intervention was 2.7 months (range 1-6) from the initial presentation. Initial clinical success was achieved in 14 patients (87.5%), and two patients were referred to surgical necrosectomy for colonic fistula and faecal peritonitis. Complete radiological success was achieved in 12 patients (75%) : 9 patients had complete resolution of the collection, and 3 other had residual small collections (<2cm) asymptomatic with no further intervention. 2 patients had partial residual collections, treated with endoscopic EUS drainage with favourable outcome. 15 patients survived (93.7%). Adverse events were non-life-threatening bleeding in 2 patients (12.5%) and one stent migration (6.2%). 6 patients developed type II diabetes (37.5%), 4 developed disconnected pancreatic duct syndrome (25%), 4 had splenic vein thrombosis (25%), and 2 cases of portal vein thrombosis (12.5%).

**Conclusions :** Endoscopic necrosectomy as a step-up approach is a minimally invasive and effective method with a high clinical and radiological success rate, with acceptable risk of adverse events. It is however seldom used in a centre in a medical approach is preferred as initial treatment after acute necrotizing pancreatitis, and when WONs are first treated with EUS guided endoscopic drainage.

- P02 -

LONG-TERM OUTCOME OF PATIENTS WITH PANCREATIC DUCT DISRUPTION. M. Arvanitakis (1), A. Bourguignon (2), M. Delhaye (1), J. Deviere (1), C. Matos (3) / [1] Erasme Hospital, Brussels, Belgium, Gastroenterology, [2] Erasme Hospital, Brussels, Belgium, Radiology, [3] Champalimaud Clinical Center, Portugal, Radiology.

**Introduction :** Pancreatic fluid collections (PFCs) associated with disconnected pancreatic ducts syndrome (DPDS) represent a difficult clinical situation in which endoscopic transmural approach has become the first line treatment. Prolonged transmural stenting has been suggested to reduce the risk of relapse after initial treatment but has not been unanimously adopted for potential safety reasons.

**Aim :** The current study focuses on long-term outcome after endoscopic transmural PFC drainage in DPDS.

**Methods :** We present a retrospective study of patients undergoing endoscopic transmural drainage of PFCs (associated with acute, chronic or post-traumatic pancreatitis) over a twelve years period with identification of those having a DPDS (review of imaging and clinical data) and long term analysis with a minimum of 4 years after initial treatment.

**Results :** Five hundred and two patients who underwent endoscopic transmural drainage were identified. Among them, 168 were formally associated with a DPDS and 71 of these patients had a minimal follow-up of 4 years. The main causes of pancreatitis were acute on chronic (n=35), biliary (n=18) and alcoholic pancreatitis (n=10). The median duration of follow-up was 74 (48-177) months. Thirteen patients died a median of 76 (49-161) months after initial treatment. None of them were related to the initial procedure. Symptomatic relapses were observed in 19 patients (26,8%) and were associated in 17 cases with stent migration or removal. All these relapses were successfully treated endoscopically. Over the 503 patient-year follow-up, only 5 complications were observed and all of them resolved after stent removal.

**Conclusions :** The maintenance of plastic stents is safe and associated with a lower risk of symptomatic relapse of PFC in patients with DPDS. Scheduled removal of the stents should be avoided.

- P03 -

IMPROVEMENT OF PANCREATIC ENDOCRINE FUNCTION AFTER ENDOSCOPIC TREATMENT OF CHRONIC PANCREATITIS. P. Deprez (1), M. Hermans (2), T. Moreels (3), T. Aouattah (3), E. Perez-Cuadrado-Robles

(3), S. Kautbally (3) / [1] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Gastro-entérologie, [2] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Endocrinology, [3] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Hepato-Gastroenterology.

**Introduction :** Studies reporting on function after endoscopic treatment of chronic pancreatitis are scarce and with conflicting results.

**Aim :** The aim of the study was to investigate prospectively the evolution of pancreatic endocrine function in patients undergoing endoscopic treatment.

**Methods :** Between November 2013 and December 2016, patients requiring endoscopic drainage for chronic pancreatitis with ductal obstruction were enrolled in the study and had a prospective evaluation of their endocrine function. Endocrine function was evaluated by HbA1c, fasting blood insulin level, C-peptide level and HOMA test before endotherapy and at 1,3,6 and 9 months following endotherapy. A comparative analysis between follow-up points (1,3,6 and 9 months) and baseline values of variables was performed.

**Results :** Thirty-four patients (age : 54+12 yr, 67.6% male) were included. Statistically significant improvement in HbA1c was attained at 1 (6.6 vs. 6.2, p=0.001), 3 (6.6 vs. 6.1, p=0.005) and 9 months (6.6 vs. 6.0, p=0.006) compared to before drainage. HOMA-B values were statistically higher at 1 (53.0 vs. 67.2, p=0.002), 3 (53.0 vs. 68.6, p=0.001), 6 (53.0 vs. 75.4, p<0.001) and 9 months (53.0 vs. 75.0, p<0.001). Clinical success of endoscopic drainage defined as 50% reduction in VAS score as compared to before drainage was recorded in 72, 84, 80 and 77% of patients at 1,3,6 and 9 months, respectively. To our knowledge, our study is the first to evaluate prospectively the effect of endoscopic treatment on the endocrine function of the pancreas as the principal aim. Our study has shown significant improvement in endocrine function at 1,3,6 and 9 months following endoscopic drainage. Considering maximum follow-up in each patient, all endocrine function variables (HbA1C, FPG, FBIL, C-peptide, HOMA-B) improve their values at each follow-up point. Similar results were obtained in diabetic patients under insulin therapy or oral antidiabetic medications as well as in non-diabetic patients.

**Conclusions :** Successful endoscopic therapy in chronic pancreatitis improves pancreatic endocrine function, even in non-diabetic patients.

- P04 -

SEVERE PANNICULITIS AND POLYARTHRITIS. A. Raptis (1), M. Plier (2), N. Jabbour (3), P. Durez (4), M. Komuta (5) / [1] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Pathology, [2] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Rheumatology, [3] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Department of Hepatobiliopancreatic surgery, [4] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Department of Rheumatology, [5] Cliniques Universitaires Saint-Luc, Brussels, Belgium, Pathology.

**Introduction :** The pancreatitis, panniculitis and polyarthritis (PPP) syndrome is a rare condition caused by pancreatic diseases, such as acute or chronic pancreatitis or pancreatic carcinoma. We report the first case of PPP syndrome caused by metastatic acinar cell carcinoma from an ectopic pancreas. The symptoms were successfully managed by the treatment of the metastatic carcinoma.

**Methods :** Case report

**Conclusions :** Pancreatic diseases such as pancreatic cytosteatonecrosis, pancreatic carcinoma, and/or acute or chronic pancreatitis should be considered in a patient who is showing symptoms of panniculitis and polyarthritis.

- P05 -

ARARE VARIANT OF CONVENTIONAL PANCREATIC DUCTAL ADENOCARCINOMA. L. Verset (1), S. Debroux (2), P. Eisendrath (3), E. Toussaint (4), R. Marechal (2), J. Van Laethem (5), F. Charara (6), J. Closset (7), P. Loi (7), M. Pezzullo (8), M. Delhay (5), M. Arvanitakis (5), P. Demetter (1) / [1] Hopital Erasme, ULB, Belgium, Pathology, [2] CHU Tivoli, La Louvière, Belgium, Gastroenterology, [3] CHU Saint-Pierre, Brussels, Belgium, Gastroenterology, [4] CHU de Charleroi, Hôpital Marie Curie, Charleroi, Belgium, Gastroenterology, [5] Hopital Erasme, ULB, Belgium, Gastroenterology, [6] CHU Tivoli, La Louvière, Belgium, Digestive Surgery, [7] Hopital Erasme, ULB, Belgium, Digestive Surgery, [8] Hopital Erasme, ULB, Belgium, Radiology.

**Introduction :** Undifferentiated carcinoma with osteoclast-like giant cells of the pancreas (UCOGCP) accounts for less than one percent of all pancreatic malignancies. This rare entity is characterized by pleiomorphic neoplastic mononuclear cells intermixed with large non-neoplastic multinucleated giant cells. Due to small number of cases, variable outcomes are reported in the literature and the biologic behaviour of such tumours is still controversial.

**Aim :** To analyse clinicopathological characteristics of UCOGCP cases detected between 2010 and 2017 by cytologic examination at the Erasme University Hospital in Brussels.

**Methods :** Cases were searched for in the files of the Department of Pathology. Clinical characteristics and follow-up data were obtained through patient files.

**Results :** We identified five cases of UCOGCP (four from the Erasme Hospital and one from CHU Tivoli). All of them were diagnosed by echoendoscopic fine-needle aspiration and cytology. We observed male predominance (four men and one woman) and an average age of 50 years (range 25-70). Echoendoscopic assessment evaluated average tumour size at 49 mm (range 24-90). Two patients were operated and tumour stage was pT3N0 for both of them. UCOGCP was associated with conventional ductal adenocarcinoma (PDAC) in one of them. Three cases were metastatic at time of diagnosis (two with liver metastases and one with pleural effusion and peritoneal carcinomatosis). Gene alterations have been searched for by next generation sequencing in 2 cases. These cases harboured mutations in both KRAS and TP53. In one of these cases, there was also a CDKN2A mutation. Three patients died within 3 months after diagnosis. One patient with metastatic disease received Folfirinox, followed by a combination of gemcitabin and cisplatin and, finally, a monotherapy of gemcitabin because of neurotoxicity. This patient currently presents disease progression after fifteen months of follow-up. The fifth patient, treated by surgery and adjuvant gemcitabine, is still free of recurrence after 12 months of follow-up.

**Conclusions :** UCOGCP is a rare type of pancreatic tumour that can be diagnosed by cytological examination. Whereas in this small cohort median survival was less than 3 months, one-year survival is possible in chemosensitive tumours, even in patients presenting with metastases at time of diagnosis. Genetic alterations in UCOGCP seem similar to those detected in conventional ductal adenocarcinoma, further supporting the classification of UCOGCP as a ductal adenocarcinoma variant.

- P06 -

A RARE CAUSE OF REPETITIVE ACUTE PANCREATITIS. A. Dupin (1), J. Loly (2), P. Gast (3), T. Mesureur (3), E. Louis (3) / [1] CHU de Liège, Liège, Belgium, [2] CHU Liège, Liège, Belgium, [3] CHU Liège, Liège, Belgium.

Congenital anomalies have to be excluded in recurrent pancreatitis in young adults without risk factors. Many variants of pancreas like ectopic tissue, annular pancreas and pancreas divisum are described in literature. A complete duplication of both the pancreatic duct and pancreatic parenchyma is rarely documented. We report the case of a 46 years old female with recurrent abdominal pain for 15 years. The patient, otherwise healthy, had a history of cholecystectomy 20 years ago. Recently she was diagnosed twice time with acute cephalic pancreatitis. Evaluation by CT and MRI showed an inflammatory cephalic pancreas tissue and a dilatation of the cephalic duct. Due to artifact movement, MRI was suboptimal. An ERCP was performed and revealed a duplication of the corporeal and caudal duct as well as stenosis and ectasia of the cephalic duct. This rare variant anatomy probably leads to acute pancreatitis by a mechanism which is not well known. In the other types of anatomical abnormalities like pancreas divisum for example, an incomplete ductal drainage is suspected to predispose to the onset of acute pancreatitis. There is no literature for management of this anomaly, endotherapy may be discussed to prevent recurrence.

- P07 -

EUS GUIDED PANCREATICOGASTROSTOMY. C. Amicone (1), J. Loly (2), P. Gast (2) / [1] CHU Sart Tilman, Liège, Belgium, Gastro-Entérologie, [2] CHU Sart Tilman, Liège, Belgium, Gastro-enterology and Hepatology.

We report the case of a 70-year-old-woman with recurrent acute pancreatitis caused by stenosis of the pancreatojejunostomy anastomosis after a cephalic pancreaticoduodenectomy. The first symptoms occurred during the beginning of 2017's year. The CPD was performed for a suspicion of a neoplasia five years ago. Finally, the pathology results described an inflammatory process. Symptomatic stenosis of the pancreatojejunostomy anastomosis is a late complication of cephalic pancreatoduodenectomy. We performed by EUS-guided a pancreaticogastrostomy in August 2017. Two months later, the patient is still asymptomatic, has a stable weight. The prothesis were replaced to sustain the pancreaticogastrostomy.

## BELGIAN WORKING GROUP ON DIGESTIVE PATHOLOGY

- R01 -

AN UNUSUAL GASTRIC POLYP. C. Van Paesschen (1), E. Macken (2), P. Pauwels (1), A. Snoeckx (3), M. Ruppert (4), A. Driessen (1) / [1] University Hospital Antwerp, Antwerp, Belgium, Department of Pathology, [2] University Hospital Antwerp, Antwerp, Belgium, Department of Gastroenterology and Hepatology, [3] University Hospital Antwerp, Antwerp, Belgium, Department of Radiology, [4] University Hospital Antwerp, Antwerp, Belgium, Department of Surgery.

**Introduction :** Gastric polyps are diagnosed in approximately 5% of the endoscopies. These polyps are usual asymptomatic and an incidental finding during endoscopy. Large polyps may cause symptoms such as anaemia due to bleeding and pain as a result of an obstruction. The most common gastric polyps are e.g. hyperplastic polyps and adenomas. Other tumoural masses may also present as a polyp, such as e.g. lymphomas, mesenchymal tumours.

**Aim :** We present a case of an unusual gastric polyp, which causes a diagnostic problem.

**Methods :** Gross examination and microscopy.

**Results :** A 24-yrs old female presented with abdominal pain in the upper part of the abdomen, fatigue and weakness due to a severe anaemia, for which she received several blood transfusions. Gastroscopy and radiological examination revealed a large polypoid mass in the distal part of the stomach. A partial gastrectomy was performed. Gross examination of the specimen showed a large polypoid submucosal mass (maximal size 5.5 cm), covered by a mucosa with two ulcers. On section the mass had a white soft appearance with some tiny holes, filled with mucus. Microscopically this mass was situated in the submucosa and extended into the muscularis propria and serosa. The mass had an unusual appearance and consisted of 2 different components : a mesenchymal and epithelial component. The major component was the mesenchymal part, which was composed of spindle cells, intermingled with smooth muscle cells. Different types of inflammatory cells were dispersed into this stroma, that had in some areas a myxoid aspect. Mitotic figures were uncommonly seen. In the mesenchymal part numerous cystic holes were present. These holes, which extended deeply in to the mass, consisted of the epithelial component, corresponding to irregular dilated glandular structures. These structures were delineated by a mucussecreting epithelium, most commonly of the gastric type. A series of immunohistochemical stainings was performed with positivity for SMA and desmin in the mesenchymal part. The epithelial marker pancytokeratin highlighted the irregular glandular structures.

**Conclusions :** The morphological features of the mass raise a differential diagnostic problem between a regenerative and neoplastic lesion. The appearance of the myxoid stroma may suggest an inflammatory fibroid tumour. This type of tumour may occur throughout the whole gastrointestinal tract, in which the stomach, especially the antrum, a common location is. Although there is some debate about the nature of this tumour, the presence of different types of mutations, a.o. PDGFRA, favours a neoplastic origin. Unusual for this type of tumour is however the presence of irregular dilated glandular structures, which may suggest a hamartomatous lesion. Despite the origin of these lesions is different, both diagnostic entities are associated with a benign behaviour with no recurrence after complete resection.

- R02 -

GRANULAR CYTOPLASMIC EXPRESSION OF CALRETININ IN SCHWANN CELL HAMARTOMAS. L. Libbrecht (1), C. Hamoir (2), R. Sciot (3), A. Jouret-Mourin (4) / [1] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, pathology, [2] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Gastroenterology, [3] University Hospitals KU Leuven, Leuven, Belgium, Pathology, [4] Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Pathology.

**Introduction :** Schwann cell hamartoma is a very rare Schwann cell-derived lesion of the gastrointestinal mucosa for which there exists an extensive differential diagnosis with other lesions of neural origin, including neurofibroma, Schwannoma, ganglioneuroma and granular cell tumour.

**Aim :** To describe calretinin as a new marker in the immunohistochemical diagnostic panel for Schwann cell hamartoma.

**Methods :** Previously diagnosed cases of Schwann cell hamartoma were retrieved from the archives of the pathology departments of the KU Leuven and UCLouvain University Hospitals.

**Results :** 3 cases were identified, presenting as incidental small polyps in the mucosa of the sigmoid, which is in line with the clinical-endoscopic presentation described in the literature. Patients (1 male, 2 female) were 62, 65 and 80 years old. Immunohistochemistry for calretinin was performed on automated stainers from Ventana and Dako using polyclonal antibody ILP2303 (Immunologic) and the DAK-Calret 1 clone. The stainings with both clones showed a diffuse and strong granular cytoplasmic expression in all 3 lesions. The nuclei were consistently negative. The consistent expression of calretinin, which belongs to the same family as S100, supports the idea that Schwann cell hamartoma is a lesion of Schwannian origin. Since calretinin expression is not seen in non-tumoural Schwann cells, we suggest that this lesion

actually might be a benign tumour rather than a hamartoma. In contrast with the reported combined nuclear and non-granular cytoplasmic expression of calretinin in Schwannomas and granular cell tumours, Schwann cell hamartomas show an exclusively cytoplasmic and distinctly granular expression. This peculiar expression pattern can be used as a diagnostic tool to resolve the differential diagnosis when one is confronted with a possible Schwann cell hamartoma.

**Conclusions :** The cytoplasmic granular expression of calretinin in Schwann cell hamartoma can be used as an easy diagnostic tool and raises questions regarding the proposed hamartomatous nature of this lesion.

- R03 -

MYXOID HEPATOCELLULAR ADENOMA, A RARE VARIANT OF LIVER CELL ADENOMA, OFTEN CLINICALLY MISDIAGNOSED AS CAVERNOUS HAEMANGIOMA. A. Hoorens (1), A. Candaele (1), M. Van Der Linden (1), P. Smeets (2), C. Lecluyse (2), N. De Vos (2), R. Troisi (3), J. Van Dorpe (1) / [1] Ghent University Hospital, Ghent, Belgium, Pathology, [2] Ghent University Hospital, Ghent, Belgium, Radiology, [3] Ghent University Hospital, Ghent, Belgium, General and Hepatobiliary Surgery, Liver Transplantation Service.

**Introduction :** A 53-year-old woman was referred to our hospital because of a large liver mass. Her past medical history included an appendectomy as well as a hysterectomy with bilateral adnexectomy. There was no history of malignancy. She was treated with thyroxine.

**Aim :** The large liver mass was an incidental finding on computed tomography imaging after trauma. It was located in the left liver lobe and had a maximal diameter of 20 cm. In addition, a smaller lesion was observed in liver segment VI. On magnetic resonance imaging, the large lesion in the left liver lobe resembled a giant cavernous haemangioma, while the small lesion in the right liver lobe was suggestive of a hepatic adenoma.

**Methods :** Physical examination revealed the liver mass in the right hypochondrium, extending to below the umbilicus. It was slightly painful on palpation. Hand-assisted laparoscopic liver resection was performed of the left liver lobe in combination with resection of the lesion in segment VI.

**Results :** Macroscopically the left lobectomy specimen measured 20x16x8cm. A whitish red large liver mass was observed through the liver capsule. On cutting it had a varied appearance with cystic mucoid areas alternating with small fibrotic areas and haemorrhagic areas. The mass occupied almost whole the resection specimen and was sharply delineated from the surrounding liver parenchyma. The resection of segment VI measured 8x3x2cm. It contained an irregularly delineated mass with a maximal diameter of 2 cm. Microscopically, the tumour in the left liver lobe consisted of strands and nests of polygonal hepatocytes embedded in an abundant myxoid/mucinous matrix. The smaller lesion consisted of normal appearing hepatocytes arranged in cords, with focal peliosis and small foci of hepatocytes embedded in myxoid/mucinous stroma. None of the lesions contained portal tracts. Histology and immunohistochemistry was compatible with hepatocellular adenomas. The largest lesion was compatible with a myxoid hepatocellular adenoma. The smaller lesion was a more conventional type of hepatocellular adenoma, however, displaying some small foci of myxoid change, next to more prominent foci of sinusoidal dilatation and peliosis. Both tumours displayed inactivation of HNF-1-alpha expression, as demonstrated by loss of LFABP expression by immunohistochemistry. None of the tumours showed nuclear staining for beta-catenin, but the largest lesion expressed diffuse increased glutamine synthetase expression compared to non-tumoural liver parenchyma. Overexpression of glutamine synthetase was not observed in the smaller lesion.

**Conclusions :** Only very few cases of myxoid hepatocellular adenomas have been reported in the literature until now. Almost all described cases were associated with adenomatosis, and the myxoid change was present in multiple adenomas. Myxoid hepatocellular adenomas seem to be biologically distinct from other HNF-1-alpha mutated adenomas, as in addition to their typical morphology, malignant degeneration seems to be more common. Reporting incidental cases is important to better understand the natural history of myxoid adenomas. Molecular characterization of these lesions may contribute to better predict the risk for malignant degeneration.

- R04 -

FREQUENCY OF EPIDERMAL METAPLASIA IN A RETROSPECTIVE MONOCENTRIC SERIES OF MUCOSECTOMY FOR ESOPHAGEAL INTRAEPITHELIAL NEOPLASIA AND/OR SUPERFICIAL SQUAMOUS CELL CARCINOMA. F. Al Zubi (1), H. Dano (1), H. Nassereddine (1), L. Libbrecht (1), P. Deprez (2), A. Jouret-Mourin (1) / [1] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Anatomopathologie, [2] Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Gastroenterologie.

**Introduction :** Epidermoid metaplasia (leukoplakia) is defined by the presence of a granular layer accompanied by hyperkeratotic orthokeratosis. It is sometimes concomitant with squamous cell carcinoma (SCC) of the oral mucosa. Esophageal epidermoid metaplasia is rare and its relationship with SCC is poorly studied.

**Aim :** To evaluate the frequency of epidermoid metaplasia (EM) in association with intraepithelial neoplasia and / or esophageal SCC and to evaluate its possible association with the HPV virus.

**Methods :** Seventy-two mucosectomies (ESD) performed at Clinic Saint-Luc university hospital for intraepithelial neoplasia or superficial SCC between 2005 and 2015 were reviewed by two pathologists for the presence of EM. An infection with the HPV virus was sought by PCR amplification.

**Results :** The mean age of the patients was 67 years (range : 46-89). the following lesions were present in these 72 of mucosectomies : 55 SCC (76.3% : 32 pT1a and 23pTb), 3 carcinomas in situ pTis (4.1%), 11 High grade intraepithelial neoplasia (15.2%) and 3 Low grade intraepithelial neoplasia (4.1%). EM was found in 6 cases (8.3%) with female predominance (4/6). The mean age of patients with EM was 65.8 years (range : 55-87) and metaplasia was observed in the distal third of the esophagus. There was no evidence of HPV infection in the 4 cases tested ; the remaining two cases could not be tested because Bouin fixative was used.

**Conclusions :** The results of our study allow us to suggest a causal relationship between EM and malignant degeneration and to consider it as precancerous lesion. These results must be consolidated by increasing the number of samples.

- R05 -

ENDOTHELIAL INDOLEAMINE 2,3-DIOXYGENASE EXPRESSION IN COLORECTAL CANCER : AN EARLY MARKER OF DISEASE RELAPSE. A. Meireson (1), I. Chevolet (1), E. Hulstaert (1), L. Ferdinande (2), P. Ost (3), K. Geboes (4), M. De Man (4), D. Van De Putte (5), L. Verset (6), V. Kruse (7), P. Demetter (6), L. Brochez (1) / [1] University Hospital Gent, Belgium, Dermatology, [2] University Hospital Gent, Belgium, Pathology, [3] University Hospital Gent, Belgium, Radiation-Oncology and Experimental Cancer Research, [4] University Hospital Gent, Belgium, Gastroenterology and Digestive Oncology, [5] University Hospital Gent, Belgium, Gastrointestinal Surgery, [6] Hopital Erasme, ULB, Belgium, Pathology, [7] University Hospital Gent, Belgium, Medical Oncology.

**Introduction :** Targeting immune checkpoint molecules has become a major new strategy in the treatment of several cancers. Indoleamine 2,3-dioxygenase (IDO)-inhibitors are a potential next-generation immunotherapy, currently investigated in multiple phase I-III trials. IDO is an intracellular immunosuppressive enzyme and its expression/activity has been associated with worse prognosis in several cancers.

**Aim :** The aim of this study was to investigate the expression pattern of IDO in colorectal cancer (CRC).

**Methods :** In a cohort of 94 CRC patients, primary tumours (PTs) with corresponding tumour-draining lymph nodes (TDLNs, n=38) and extranodal/distant metastases (n=19) were retrospectively analysed by immunohistochemical staining for IDO, CD8 and Foxp3. 45 MSS and 37 MSI-H tumours were selected to compare IDO expression, as these tumours are considered to have different immunogenicity.

**Results :** A highly consistent expression pattern of IDO was observed in the PT, TDLNs and metastases. IDO was expressed both by tumoural cells and host endothelial cells and these expressions were highly correlated ( $p < 0.001$ ). IDO expression was observed more frequently in the MSI-H subset compared with the MSS subset (50% vs 24% for tumoural expression ( $p = 0.042$ ) and 44% vs 15% for endothelial expression ( $p = 0.021$ )). Endothelial IDO expression was demonstrated to be a negative prognostic marker for recurrence free survival.

**Conclusions :** IDO expression is highly consistent in the PT, TDLN and metastatic tissue of patients with colorectal cancer, indicating that immune tolerance may be determined very early in the disease course. MSI-H tumours had higher IDO expression especially by endothelial cells compared to MSS tumours. Endothelial IDO expression was a negative prognostic marker for recurrence free survival.