ABSTRACTS

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ABSTRACTS

BELGIAN ASSOCIATION FOR THE STUDY OF THE LIVER (BASL) - BLIC

- A01 -

IMPACT OF INTENSIVE ENTERAL NUTRITION IN ASSOCIATION WITH CORTICOSTEROIDS IN THE TREATMENT OF SEVERE ALCOHOLIC HEPATITIS : A MULTICENTER RANDOMIZED CONTROLLED TRIAL.

C. Moreno (1), E. Trepo (1), A. Louvet (2), D. Degré (1), B. Bastens (3), A. Hittelet (4), M. Piquet (5), W. Laleman (6), H. Orlent (7), L. Lasser (8), T. Sersté (9), P. Starkel (10), X. Dekoninck (11), S. Negrin (12), J. Delwaide (13), I. Colle (14), C. De Galocsy (15), S. Francque (16), P. Langlet (17), V. Putzeys (18), H. Reynaert (19), T. Gustot (1), P. Deltenre (20). (1) CUB Hôpital Erasme, Brussels, Belgium, Department of Gastroenterology, Hepatogastroenterology and Digestive oncology ; (2) Centre Hospitalier Régional Universitaire de Lille, Hôpital Claude Huriez, Lille, France, Service des Maladies de l'Appareil Digestif ; (3) Hôpital Saint-Joseph, Liège, Belgium, Department of Gastroenterology ; (4) Hôpital Ambroise Paré, Mons, Belgium, Department of Gastroenterology ; (5) CHU de Caen, Caen, France, Service d'Hépatogastroentérologie ; (6) University Hospitals Leuven, Leuven, Belgium, Department of Liver and Biliopancreatic Disorders ; (7) AZ Sint-Jan Brugge-Oostende, Brugge, Belgium, Department of Gastroenterology and Hepatology ; (8) CHU Brugmann, Brussels, Belgium, Department of Hepatogastroenterology ; (9) CHU Saint-Pierre, Brussels, Belgium, Department of Hepatogastroenterology ; (10) UCL, Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Gastroenterology ; (11) Hôpital Saint-Pierre, Brussels, Belgium, Department of Gastroenterology ; (12) Hôpital Saint-Joseph, Liège, Belgium, Department of Gastroenterology ; (13) CHU Sart Tilman, Liège, Belgium, Department of Hepatogastroenterology ; (14) UZ Gent, Gent, Belgium, Department of Hepatogastroenterology ; (15) Hôpitaux Iris Sud Bracops, Brussels, Belgium, Department of Gastroenterology ; (16) UZ Antwerpen, Edegem, Belgium, Department of Gastroenterology and Hepatology ; (17) CHIREC-Site Cavell, Uccle, Belgium, Department of Gastroenterology ; (18) CHR La Citadelle, Belgium, Department of Gastroenterology ; (19) UZ Brussel, Jette, Belgium, Department of Hepatogastroenterology ; (20) Hôpital de Jolimont, Haine-Saint-Paul, Belgium, Service d'Hépatogastroentérologie.

Introduction : Severe alcoholic hepatitis (AH) is associated with a high risk of short-term mortality. Although adequate nutritional support is recommended in these patients, the recommended protein-caloric intake is often difficult to achieve orally in this population.

Aim : Our objective was to evaluate the impact of intensive enteral nutrition in addition to steroid therapy on 6-month survival in patients with severe AH.

Methods : This multicenter randomized, controlled trial was performed in 18 Belgian and 2 French hospitals. Two groups were included : 1) intensive enteral nutrition and methylprednisolone (intensive group) or 2) conventional nutrition and methylprednisolone (control group). In the intensive group, enteral nutrition was given using a feeding tube for 14 days and patients received Fresubin HP Energy® (1.5 kcal/ml, 7.5 g prot/100 ml) as it follows : 1L/day if body weight (BW) < 60 kgs, 1.5L if BW between 60 and 90 kgs, 2L if BW > 90 kgs. Nutrition intake was recorded for 14 days in both groups.

Results : A total of 136 patients with a severe biopsy-proven AH (Maddrey discriminant function [mDF] ≥ 32) were randomized, 68 in each group. At baseline, there were no significant difference between the two groups (intensive vs. control) for age (49.5 ± 8.7 vs. 51.5 ± 8.6), male gender (69.1 vs. 58.8%), bilirubin (13.3 [8.9-23.5] vs. 11.9 [6.9-21.5] mg/dL), INR (1.8 [1,6-2.1] vs. 1,8 [1.6-2.1]), mDF (52.3 [40.9-70.2] vs. 54 [42-68.5]) and MELD score (22.8 [21.4-26.3] vs. 22.4 [20.2-25.1]). Mean kcal intake was 2206 ± 754 vs. 1754 ± 656 kcal/day ($p = 0.001$) and mean protein intake was 106 ± 37 vs. 80 ± 32 g/day ($p < 0.001$). In intention-to-treat (ITT) analysis, 6-month survival was not statistically different between the two groups : 55.9 vs. 47.0% ($p = 0.316$). In the intensive group, 43/68 (63.2%) patients received at least 80% of the planned kcal intake defined by the protocol, and were considered in the per-protocol analysis. In per-protocol analysis, 6-month survival was higher in the intensive group : 69.8 vs. 46.8% ($p = 0.015$). In addition, mean kcal intake/kg/day > 26.4 (median value) was associated with a higher 6-month survival (68.3 vs. 42.4%, $p = 0.002$). In ITT multivariable analysis, a mean kcal intake/kg/day > 26.4, age, baseline serum sodium, baseline MELD and the Lille scores remained independently associated with 6-month survival.

Conclusions : Intensive enteral nutrition by feeding tube does not improve 6-month survival in patients with severe AH. However, adequate nutritional support is associated with a better short-term prognosis. Adequate nutritional intake should be targeted in AH patients treated with corticosteroids.

- A02 -

OBETICHOLIC ACID, AN FXR AGONIST, REDUCES HEPATIC FIBROSIS IN A RAT MODEL OF TOXIC CIRRHOSIS. L. Verbeke (1), I. Mannaerts (2), R. Schierwagen (3), S. Klein (3), I. Vander Elst (1), P. Windmolders (1), R. Farre (4), M. Wenes (5), M. Mazzone (5), F. Nevens (1), L. Van Grunsven (2), J. Trebicka (3), W. Laleman (1). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Hepatology ; (2) Laboratory of Liver Cell Biology, VUB, Brussels, Belgium ; (3) University Hospital, Bonn, Germany, Department of Internal Medicine I ; (4) Translational Research Center for Gastrointestinal Disorders (TARGID), KULeuven, Leuven, Belgium ; (5) KU Leuven, Leuven, Belgium, Laboratory of Molecular Oncology and Angiogenesis, Vesalius Research Center, Department of Oncology.

Introduction : Hepatic stellate cells (HSC) drive hepatic fibrosis following chronic liver injury. Although controversial, the bile acid-responsive farnesoid-X receptor (FXR) might antagonize hepatic fibrogenesis via inhibition of HSC activation.
Aim : We aimed to investigate both the preventive and therapeutic effects of the FXR agonist obeticholic acid (INT-747) on fibrosis in a rat model of toxic cirrhosis.
Methods : Cirrhosis was induced by thioacetamide (TAA) intoxication for 18 weeks. INT-747 was given during the last 4 weeks of (prophylactic) or for 4 weeks after ending (therapeutic) intoxication. Vehicle-treated rats served as controls. At sacrifice, degree of fibrosis (image analysis, hydroxyproline), hemodynamic (liver perfusion) and biochemical parameters were assessed. HSC activation, proliferation, apoptosis, hepatic nuclear-factor kappa B (NF-κB) activation, pro-inflammatory and pro-fibrotic cytokines were determined (RT-PCR, western blot). The effect of INT-747 was further evaluated on these latter parameters on isolated HSC, Kupffer cells, hepatocytes and liver sinusoidal endothelial cells.
Results : INT-747 significantly decreased fibrogenesis during TAA-administration and reversed fibrosis in established cirrhosis. As a consequence, portal pressure decreased through reduced total intrahepatic vascular resistance. These beneficial effect related to HSC de-activation by decreased expression of pro-fibrotic (transforming growth-factor β, connective tissue growth factor, platelet-derived growth factor β-receptor, tissue inhibitor of metallopeptidase-1) and pro-inflammatory cytokines (e.g. monocyte chemo-attractant protein-1) via down-regulated NF-κB. INT-747 also affected hepatic markers of cell turn-over. In vitro, a direct effect of INT-747 on HSC was excluded.
Conclusions : FXR agonist INT-747 reverses fibrosis in toxic cirrhotic rats by decreased HSC activation, indirectly via decreased hepatic inflammation.

- A03 -

MULTICENTER BELGIAN EXPERIENCE OF SOFOSBUVIR (MEDICAL NEED PROGRAM) IN VERY DIFFICULT-TO-TREAT HCV PATIENTS : SAFETY AND EFFICACY RESULTS. D. Degré (1), W. Laleman (2), X. Verhelst (3), A. Lamproye (4), T. Vanwolleghem (5), T. Gustot (6), P. Starkel (7), N. Lanthier (7), P. Michielsen (5), J. Delwaide (4), H. Vanvlierberghe (3), F. Nevens (2), C. Moreno (6). (1) CUB Hôpital Erasme, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology ; (2) University Hospitals Leuven, Leuven, Belgium, Department of Liver and Biliopancreatic disorders ; (3) UZ Gent, Gent, Belgium, Department of Hepatogastroenterology ; (4) CHU Sart Tilman, Liège, Belgium, Department of Hepatogastroenterology ; (5) UZ Antwerpen, Edegem, Belgium, Department of Gastroenterology and Hepatology ; (6) CUB Hôpital Erasme, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology ; (7) UCL, Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Gastroenterology.

Introduction : Severe hepatitis C (HCV) recurrence after liver transplantation (LT), HCV in cirrhotic patients listed for LT, and HCV in patients with severe extra-hepatic manifestations have a negative impact on patient survival and current treatment options are clearly suboptimal. Sofosbuvir (SOF), Daclatasvir (DCV) and Simeprevir (SMV) have been recently approved in Europe but there are limited data on the use of these drugs in the treatment of very difficult-to-treat patients with severe HCV.
Aim : The aim of this study was to evaluate the safety and efficacy of SOF treatment in combination with DCV, SMV, ribavirin (RBV) or Peginterferon (PegIFN) in very difficult-to-treat HCV patients.
Methods : We performed a retrospective analysis of patients with either severe HCV recurrence after LT, listed for LT or having severe extra-hepatic manifestations receiving SOF with SMV, DCV, Peginterferon (PegIFN) + ribavirin (RBV) or RBV in compassionate use or medical need in Belgium.
Results : 42 patients were enrolled in this data collection : 14 cirrhotics listed for LT, 17 LT recipients with severe recurrence, 8 with severe extra-hepatic manifestations, 2 decompensated cirrhotic patients, 1 cirrhotic IFN ineligible patient. Twenty-five patients had clinical liver decompensation. SOF was administered in combination with SMV, DCV and RBV alone in 9, 17 and 5 cases, respectively. Four patients received SOF, DCV and RBV. SOF was administrated with PegIFN and RBV in 3 cases. The majority of the patients were male (72.5%). Median age was 55 [51.2-66.7] years. Genotype distribution was : genotype 1 (n = 34), 2 (n = 1), 3 (n = 6) or 5 (n = 1). In listed for LT and post-LT patients,

median MELD and Child-Pugh scores were 13.7 [10.1-19.5] and 8 [5.5-10], respectively. At baseline, 16 patients of them had ascites and 4 of them hepatic encephalopathy. Six patients have completed the treatment course and 31 are still on therapy. W4 and W12 HCV RNA undetectable was 20% (4/20) and 71,4% (10/14) respectively. End of treatment response was 100% (5/5) (1 viral load is ongoing) and SVR12 was 100% (2/2). Final SVR results will be presented. Treatment was stopped in 5 patients. Four patients were transplanted, viral load after LT was positive in 1 patient and currently unknown for the 3 others. SAEs were reported in 3 patients, 2 (hospitalization for flu-like syndrome and hyperkaliemia) were not related to the antiviral treatment and 1 patient developed pancytopenia after 1 day of treatment (SOF+RBV) and the treatment was stopped.
Conclusions : This preliminary experience in very difficult to treat patients shows that SOF in combination with DCV, SMV, RBV or PegIFN is safe and virological response seems to be promising.

- A04 -

EARLY TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT IN CIRRHOTIC PATIENTS WITH ACUTE VARICEAL BLEEDING : A META-ANALYSIS OF CONTROLLED TRIALS. P. Deltenre (1), E. Trépo (2), M. Rudler (3), A. Monescillo (4), M. Fraga (1), A. Denys (5), C. Doerig (1), N. Fournier (6), C. Moreno (2), D. Moradpour (1), C. Bureau (7), D. Thabut (3). (1) Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, Division of Gastroenterology and Hepatology ; (2) CUB Hôpital Erasme, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology ; (3) Hôpital Pitié-Salpêtrière, Paris, France, Service d'Hépato-Gastroentérologie ; (4) Hospital Universitario Insular de Gran Canaria, Gran Canaria, Spain, Servicio de Aparato Digestivo ; (5) Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, Service de Radiologie ; (6) Université de Lausanne, Lausanne, Switzerland, Département universitaire de médecine et santé communautaires, Médecine sociale et préventive ; (7) CHU Toulouse, Toulouse, France, Service d'Hépato-Gastroentérologie.

Introduction : There is conflicting evidence regarding the benefit of early transjugular intrahepatic portosystemic shunt (TIPSS) on survival of cirrhotic patients with acute variceal bleeding (AVB).
Aim : To assess the effect of early TIPSS on patient prognosis.
Methods : We performed a meta-analysis of controlled trials evaluating TIPSS performed within 72 hours of the initial endoscopy in cirrhotic patients with AVB treated with the standard-of-care.
Results : Four studies including 252 patients were included. Early TIPSS was associated with fewer deaths (OR = 0.38, 95% CI = 0.17-0.83, p = 0.02). There was a moderate heterogeneity between studies (p = 0.15, I2 = 44%). After exclusion of a study in which patients allocated to TIPSS were compared to historical control and which included patients with very severe liver disease, there was a significant effect of early TIPSS on mortality (OR = 0.26, 95% CI = 0.13-0.51, p < 0.001) with no significant heterogeneity (p = 0.9, I2 = 0%). Among Child-Pugh B patients, early TIPSS was not significantly associated with fewer deaths (OR = 0.35, 95% CI = 0.10-1.17, p = 0.087). There was no heterogeneity between studies (p = 0.6, I2 = 0%). Among Child-Pugh C patients, early TIPSS was not significantly associated with fewer deaths (OR = 0.34, 95% CI = 0.10-1.11, p = 0.074). There was a high heterogeneity between studies (p = 0.06, I2 = 60%). After exclusion of a study in which patients allocated to TIPSS were compared to historical control, there was a significant effect of early TIPSS on mortality (OR = 0.21, 95% CI = 0.07-0.66, p = 0.007) with less heterogeneity (p = 0.22, I2 = 33%). Early TIPSS was also associated with better 6-week (OR = 3.03, 95% CI = 1.41-6.49, p = 0.004) and 1-year (OR = 2.42, 95% CI = 1.03-5.67, p = 0.04) survivals. Less patients treated with early TIPSS reached the composite endpoint defined as failure to control bleeding or failure to prevent clinically significant bleeding within one year (OR = 0.08, 95% CI = 0.04-0.17, p < 0.001), with no heterogeneity between studies (p = 0.7, I2 = 0%). Results were similar among Child-Pugh B (OR = 0.15, 95% CI = 0.05-0.47, p = 0.001) and Child-Pugh C patients (OR = 0.05, 95% CI = 0.02-0.15, p < 0.001). Early TIPSS was not associated with higher rates of encephalopathy (OR = 0.84, 95% CI = 0.50-1.42, p = 0.5).
Conclusions : Cirrhotic patients with AVB treated with early TIPSS had lower death rates and improved 6-week and 1-year survivals as compared to patients treated without early TIPSS. Child-Pugh C patients with AVB may also benefit from early TIPSS.

- A05 -

PLACENTAL GROWTH FACTOR INHIBITION MODULATES THE INTERPLAY BETWEEN HYPOXIA AND THE UNFOLDED PROTEIN RESPONSE IN HEPATOCELLULAR CARCINOMA. Y. Vandewynckel (1), D. Laukens (1), L. Devisscher (1), A. Paridaens (1), E. Bogaerts (1), A. Van Den Bussche (1), S. Raevens (1), X. Verhelst (1), C. Van Steenkiste (1), B. Jonckx (2), L. Libbrecht (3), A. Geerts (1), P. Carmeliet (4), H. Van Vlierberghe (1). (1) UZ Gent, Gent, Belgium, Department of Hepatology and Gastroenterology ; (2) ThromboGenics NV, Heverlee, Belgium, ThromboGenics NV ; (3) UZ Gent, Gent, Belgium, Department of Pathology ; (4) KU Leuven, Leuven, Belgium, Laboratory of Angiogenesis and Neurovascular link, Vesalius Research Center.

Introduction : Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality worldwide. We previously showed that inhibition of Placental growth factor (PlGF) exerts antitumour effects and induces vessel normalization in HCC, possibly reducing hypoxia. However, the exact mechanism of PlGF inhibition in HCC remains unclear.
Aim : Since hypoxia signalling and the unfolded protein response (UPR) have been implicated in tumour progression, we assessed the interaction between PlGF and these tumoural adaptation processes.
Methods : PlGF knockout mice and monoclonal anti-PlGF antibodies were used in a diethylnitrosamine-induced mouse model for HCC to investigate the effect of PlGF inhibition on tumour hypoxia and UPR activation . In addition, we examined the interaction between the UPR, hypoxia and PlGF expression in human HCC cell lines.
Results : Both genetic and pharmacological inhibition of PlGF inhibition significantly reduced diethylnitrosamine-induced chaperone levels ($p < 0.05$) and activation of the PKR-like endoplasmic reticulum kinase (PERK) pathway ($p < 0.01$). Also tumour hypoxia was attenuated by both, as shown by reduced pimonidazole staining in the tumour nodules ($p < 0.05$). Interestingly, hypoxia markedly activated the PERK pathway in human HCC cells ($p < 0.01$), suggesting PlGF inhibition may diminish PERK activation by improved oxygen delivery via vessel normalization. Finally, we found that both hypoxia and chemical ER stress inducers tunicamycin and thapsigargin increased PlGF expression in HCC cells ($p < 0.01$), predominantly via the inositol-requiring enzyme 1 (IRE1) pathway of the UPR.
Conclusions : These findings indicate that PlGF inhibition reduces UPR activation by tempering hypoxia in experimental HCC and that the UPR, in turn, is able to induce PlGF, suggesting the existence of a feedback mechanism of hypoxia-mediated UPR which stimulates PlGF-mediated angiogenesis.

- A06 -

EVOLUTION OF THE UNDERLYING MYEPROLIFERATIVE DISORDER IN BUDD-CHIARI PATIENTS TREATED WITH LIVER TRANSPLANTATION. P. Martens (1), G. Maleux (2), T. Devos (3), D. Monbaliu (4), S. Heye (2), C. Verslype (5), W. Laleman (5), D. Cassiman (5), S. Van Der Merwe (5), W. Van Steenbergen (5), I. Jochmans (4), R. Aerts (4), J. Pirenne (4), F. Nevens (5). (1) UZ Leuven, Leuven, Belgium, Division of Liver and Biliopancreatic disorders ; (2) UZ Leuven, Leuven, Belgium, Division of Interventional Radiology ; (3) UZ Leuven, Leuven, Belgium, Division of Hematology ; (4) UZ Leuven, Leuven, Belgium, Division of abdominal transplantation Surgery ; (5) UZ Leuven, Leuven, Belgium, Division of Liver and Biliopancreatic disorders.

Introduction : A myeloproliferative disorder (MPD) type Essential Thrombosis (ET) or Polycythemia Vera (PV) is the most common underlying pro-thrombotic risk factor in patients with a Budd-Chiari syndrome. ET and PV are known for their evolution towards myelofibrosis and acute myeloid leukemia. Little is known about the trajectories of evolution towards myelofibrosis and acute myeloid leukemia in ET and PV patients treated with liver transplantation receiving calcineurin inhibitors (CNI).
Aim : To investigate the evolution of the underlying MPD in Budd-Chiari patients treated with liver transplantation receiving CNI.
Methods : We retrospectively collected date from 37 Budd-Chiari patients diagnosed and treated at the University Hospital KU Leuven. Patients with an underlying myeloproliferative disorder were identified by the measurement of the JAK2V617F mutation. Median time to progression towards myelofibrosis/acute myeloid leukemia was measured. The Kaplan-Meier method was used to compare differences in time to progression between transplanted patients receiving CNI and controls not receiving CNI.
Results : A total of 22 Budd-Chiari patients with an underlying myeloproliferative disorder were identified. In total five patients (24%) progressed to myelofibrosis with a median time to progression of 17 years. Ten Budd-Chiari patients (45.5%) were treated with liver transplantation receiving CNI, two of whom progressed to myelofibrosis (9%). Twelve Budd-Chiari patients (54.5%) did not receive transplantation but best medical treatment (anticoagulation, portosystemic shunt or TIPSS), three of whom progressed to myelofibrosis (13.6%). No difference in progression rate towards myelofibrosis was found between patients receiving CNI and not receiving CNI (Log-rank $p = 0.06$, Breslow $p = 0.9$, Tarone Ware $p = 0.8$).
Conclusions : Liver transplantation remains an important treatment option for Budd-Chiari patients with ongoing liver damage despite optimal medical treatment with anticoagulation and decompressive therapy (portosystemic shunt or TIPSS). This retrospective case-control study indicates that Budd-Chiari patients with an underlying MPD treated with a CNI do not show an accelerated progression to myelofibrosis as compared to controls.

- A07 -

TISSUE AND CELL DISTRIBUTION OF FETUIN-A : EVIDENCES OF A ROLE OF KUPFFER CELLS IN ITS EXPRESSION. N. Lanthier (1), V. Lebrun (1), M. Berghmans (1), O. Molendi-Coste (1), I. Leclercq (1). (1) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Laboratory of Hepato-Gastroenterology, Institut de Recherche Expérimentale et Clinique.

Introduction : Blood levels of fetuin-A are increased in type 2 diabetic patients. Originally described as an exclusively liver-derived protein, the adipose tissue has recently been suggested as another site of production.
Aim : We wanted to explore the relationship between fetuin-A and Kupffer cell (KC) activation and its expression in insulin sensitive tissues in high fat diet fed mice as well as in the liver of non-alcoholic steatohepatitis (NASH) patients.
Methods : Fetuin-A mRNA and protein expressions were evaluated by RT-PCR, Western-blot and immunofluorescence (IF) on liver, epididymal adipose tissue and skeletal muscle of male mice fed a normal diet (ND) or a high fat diet (HFD) for 3 days, known to initiate steatosis and insulin resistance. Kupffer cell (KC) depletion was obtained by intravenous injection of clodronate-loaded liposomes and compared with PBS liposomes. Fetuin-A and CD68 (a marker of human Kupffer cells) were further analyzed in human NASH biopsies by IF.
Results : Three days HFD feeding induced liver steatosis, KC activation and hepatic insulin resistance. This regimen was associated with a significant increased expression of fetuin-A mRNA (1.5 fold, $p < 0.01$) in the liver but not in the adipose tissue or in the muscle. Kupffer cell depletion in this setting significantly improved hepatic insulin sensitivity as well as significantly decreased liver fetuin-A mRNA expression (0.7 fold, $p < 0.01$) compared to animals with KC. In contrast, short term HFD feeding and KC depletion had no impact on the liver fetuin-A protein expression. Liver IF revealed fetuin-A presence in cytoplasmic vesicular structures of centrilobular hepatocytes. Fetuin-A protein content was 3 fold higher in the adipose tissue than in the liver ($p < 0.001$). However, at the mRNA level, fetuin-A was 800 fold higher in the liver than in the adipose tissue ($p < 0.001$). In contrast, fetuin-A protein and mRNA were very low in skeletal muscles. In human NASH patients, fetuin-A was evidenced in steatotic hepatocytes and in adjacent activated Kupffer cells.
Conclusions : Fetuin-A mRNA is highly abundant in the liver and the protein is found in vesicular cytoplasmic structures within the hepatocytes. Dissociation between mRNA and protein liver levels and localisation in vesicles support secretion of fetuin-A by the hepatocytes. HFD induced KC activation enhanced while KC depletion reduced hepatic fetuin-A. In human NASH, fetuin-A is located in fatty hepatocytes as well as neighbouring activated Kupffer cells. Collectively, those data suggest a role for fetuin-A in the pathogenesis of metabolic and liver disturbances in the context of non-alcoholic fatty liver disease.

- A08 -

RETARGETING OF BILE SALT EXPORT PUMP (BSEP) AND CRITERIA OF FAVOURABLE OUTCOME IN CHILDREN WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPE II (PFIC-II). S. Varma (1), N. Revencu (2), X. Stephenne (1), I. Scheers (1), F. Smets (1), A. Beleza (2), C. De Magnée (3), R. Reding (3), T. Roskams (4), E. Sokal (1). (1) Cliniques Universitaires Sain-Luc, Brussels, Belgium, Service de Gastroentérology et Hépatologie Pédiatrique ; (2) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Centre de génétique humaine ; (3) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Unité de chirurgie pédiatrique ; (4) UZ Leuven, Leuven, Belgium, Anatomie-Pathology.

Introduction : PFIC II has a wide spectrum of presentation and the management options include UDCA, biliary diversion, liver transplantation. No factors predicting the response to non transplant measures have been identified as yet. BSEP re-targeting has never been demonstarted with UDCA or biliary diversion though its been reported with the use of 4-Phenyl Butyrate as chaperone therapy.
Aim : To investigate predictors of clinical evolution in PFIC-II patients and their relationship to BSEP expression and (re)targeting
Methods : 23 children with established PFIC-II were retrospectively included. Clinical, biochemical and histological characteristics were reviewed at presentation and following treatment with Ursodeoxycholic acid (UCDA) only (10 mg/kg TDS) ($n = 20$) or UCDA and Partial Biliary Diversion (PBD) ($n = 3$). BSEP immunostaining was obtained in 20/23 patients. Response to treatment was defined as normalization of pruritus, disappearance of jaundice, and normalisation of alanine amino transferases (ALT) (< 1.5 upper limit of normal-ULN). The duration of remission was also recorded. Six responders had a paired biopsy with BSEP immunostaining, 2 after PBD.
Results : Twelve of 23 patients were non-responders, 1 partial responder and 10 responded to treatment. Non-responders had earlier onset of jaundice (< 9months), neonatal cholestasis and higher ALT levels. ALT > 165 IU/L had sensitivity of 72% and specificity of 55% to predict non-response. 8/12 non-responders had no BSEP expression, 1 cytoplasmic, 1 canalicular, 2 not done. Amongst 10 responders, 5 had cytoplasmic BSEP expression and 5 absent. Paired biopsies were obtained after treatment in 6 /10 : De novo canalicular expression of BSEP occurred in 4/6, 2 with baseline cytoplasmic

expression and 2 with no baseline expression. Seven patients were still responders at last follow up (median 20 months, range 5-67 months), one of them died from unrelated cause, and 3 did relapse after 56, 72 and 82 months. Amongst the 9 living responders a median relapse free survival time of 72 months (CI 95% 48 to 96 months) was observed and the five years Kaplan Meier relapse free survival was of 75% (CI 95 % 33-100%)
Conclusions : PFICII children with late onset presentation, ALT < 165 IU/L and cytoplasmic BSEP are likely to respond at least transiently to non-transplant treatment while patients with neonatal cholestasis do not. All but one PFIC II patients had abnormal or no BSEP expression. De novo or retargeted canalicular expression of BSEP can occur under treatment amongst the responders.

- A09 -

TEN YEAR FOLLOW UP OF A REAL-LIFE HIV-HCV COINFECTED PATIENT COHORT IN ANTWERP. A. Boerekamps (1), S. Bourgeois (2), A. De Weggheleire (3), P. Michielsen (1), S. Francque (1), L. Lynen (3), E. Florence (3), T. Vanwolleghem (1). (1) UZ Antwerpen, Edegem, Belgium, Department of Gastroenterology & Hepatology ; (2) ZNA campus Stuivenberg, Antwerpen, Belgium, Department of Gastroenterology & Hepatology ; (3) Institute of Tropical Medicine, Antwerpen, Belgium, Department of Clinical Sciences.

Introduction : HIV-HCV coinfected patients are known to have a more rapid liver disease progression compared to HCV mono-infected patients. HCV eradication has been shown to halt disease progression and lower liver-related and overall mortality in HCV mono-infected patients.
Aim : We aimed to identify, in a large real life HIV-HCV co-infected cohort, factors associated with baseline severity of liver disease and with disease progression (evolving fibrosis, events of decompensated cirrhosis, hospitalization and overall mortality).
Methods : Patients were selected over a retrospective period of 10 years in 3 large healthcare institutes involved in the care for HIV-HCV co-infected patients. Patients were included provided they had detectable antibodies against HIV and repetitive positive HCV PCRs for at least 6 months. Patient variables and outcomes, including (but not limited to) comorbidities and liver fibrosis identified on liver biopsy or by shear wave elastography were retrieved from patient files and analysed using SPSS.
Results : A total of 154 chronic HIV-HCV coinfected patients were identified, of whom 127 were men (82.5%) and 82 (53.2%) of Belgian origin. Patients got infected by men-who-have-sex-with men (MSM) contact (57.1 %), intravenous drug use (IVDU) (24.0%), iatrogenic exposure (10.4%), heterosexual contact (4.5%) or unknown risk factors (3.9%). HCV genotype 3a infection significantly correlated with IVDU ($P < 0.001$) and HCV genotype 1a infections with MSM contact ($P < 0.001$). During follow up, 11 reinfections were diagnosed, of which all but one by MSM behaviour. 15 patiënts were HCV-HBV-HIV coinfected. 25 patiënts had excessive alcohol consumption. At first presentation in the hepatology clinic 128 (83.1%) patients were treated for their HIV infection, of whom 97 (75.6%) had an undetectable HIV viral load. Moderate to severe liver fibrosis, detected on liver biopsy or elastography was seen in 53.8% of patients upon initial presentation at the hepatology clinic. The degree of baseline fibrosis correlated with age ($P = 0.010$) and alcohol consumption ($P = 0.008$). Patients were followed for a mean of 8 years and 3 months. During follow-up, 68.2% of patients were treated for HCV with an overall success rate of 43.2%. Of those patients with severe fibrosis 79,6% has been treated with an overall success rate of 40,8%. There were 96 hospitalizations in 41 patients, of which 26 events of decompensated liver cirrhosis in 14 patients. Eleven patients died. Treatment of HCV infection was associated with lower liver fibrosis progression ($P = 0.045$), but not with a better overall outcome, including mortality and hospitalizations ($P = 0.73$).
Conclusions : In this long-term follow up, real-life HIV-HCV co-infected cohort, treatment of HCV impacts on liver fibrosis progression, but does not reduce morbidity, as evidenced by the need for hospitalization, or overall mortality. This suggests that in the HIV-HCV infected population, other comorbidities, besides HCV, determine overall outcome.

- A10 -

LIVER PROGENITOR CELLS YIELD REGENERATIVE NODULES IN THE CIRRHOTIC LIVER. R. Manco (1), R. Espanol-Suner (1), N. Feza-Bingi (1), F. Lemaigre (2), C. Sempoux (3), I. Leclercq (4). (1) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Laboratory of Hepato-gastroenterology ; (2) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Liver and Pancreas development Unit, De Duve Institute. ; (3) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Pathology Department, CHUV, University Hospital, Lausanne, Switzerland, Laboratory of Hepato-gastroenterology ; (4) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Laboratory of Hepato-gastroenterology.

Introduction : In previous studies we showed that liver progenitor cells (LPC) are capable to differentiate into mature hepatocytes in the diseased liver ; however their contribution to liver regeneration is rather small. In chronic diseases and

cirrhosis, the regenerative capacity of hepatocytes is compromised and amplification of the liver progenitor cells compartment, a reaction called the ductular reaction (DR), is often pronounced.
Aim : The role of LPC in cirrhosis has never been demonstrated and is the objective of our study.
Methods : We used tamoxifen-inducible Osteopontin-Cre (OPN-CreERT2) mice crossed with YFP reporter mice to trace, by mean of YFP expression, the fate of cells of the progenitor/biliary compartment. Chronic injury with severe fibrosis and cirrhosis was induced by repeated injections of carbon tetrachloride (CCl4) for 4 and 7 months, respectively. Livers were analyzed at the end of treatment or after a 2 weeks CCl4-free recovery period.
Results : Seven months CCl4 induced micro- and macro-nodular cirrhosis with discrete DR in fibrotic septa. Efficiency of recombination in LPC/biliary cells was 50-60%. We observed in all samples multiple patches of LPC-derived YFP+ hepatocytes. A large proportion of them (> 70%) radiated from the portal track area and some regenerative nodules were entirely composed of YFP+ hepatocytes. Some area and nodules of the cirrhotic liver strongly expressed glutamine synthase, suggesting beta-catenin activation and preneoplastic transformation, with no strict association between glutamine synthase and YFP expression. To better understand the dynamics of LPC-derived regeneration, CCl4 was applied for a shorter period (4 months) and liver examined upon injury as well as after 2 weeks recovery. Efficiency of recombination in this experiment was > 95%, enabling tracing of the almost whole LPC population. The treatment induced severe fibrosis. In all sections, we observed a mild DR and numerous patches of YFP+ hepatocytes preferentially in contact with portal structures. The size of YFP+ hepatocyte patches was however smaller compared to the 7 months experiment. After 2 weeks recovery, hepatocellular injury, inflammation, fibrosis and DR have regressed while total area of YFP+ hepatocytes tended to increase from 1,2 ± 0,4 % of the liver sections after injury to 2,3 ± 0,5% upon recovery (p = NS). There was no significant difference in the number and location of YFP+ patches, but significant increase in their size (mean size 11.71 ± 1.20 mm^2 vs 28.80 ± 2.80 mm^2 after injury vs upon recovery, respectively, $p < 0.0001$) with a decreased number of the small sizepatches and an increased number of larger ones after recovery. This is compatible with growth of YFP+ patches during recovery.
Conclusions : We provide here the first demonstration that LPC contribute to liver regeneration and to formation of regenerative nodules in the cirrhotic liver. Thus, in severe and chronic liver injury, LPC yield a number of patches of YFP+ hepatocytes organised in plates irradiating from the portal track region. Whether a regenerative nodule stems from clonal expansion of a LPC-derived hepatocyte, and whether LPC-derived regenerative nodules are preneoplastic lesions are questions currently investigated.

Invited Lecture

- A11 -

HEMOCHROMATOSIS AND WILSON'S DISEASE : WHAT'S NEW IN OLD DISEASES ? Prof. David Cassiman. UZ Leuven, KULeuven, Leuven, Belgium.

- A12 -

HUMAN 3D HEPATIC CO-CULTURE MODEL FOR IN VITRO DRUG-INDUCED FIBROSIS TESTING. S. Leite (1), T. Roosens (1), I. Mannaerts (1), A. Taghdouini (1), M. Najimi (2), E. Sokal (2), C. Chesne (3), L. Van Grunsven (1). (1) UZ Brussel, VUB, Jette, Belgium, Liver - Bmwe ; (2) Cliniques Universitaires Saint-Luc, UCL Woluwe-Saint-Lambert, Belgium, Laboratory of Pediatric Hepatology and Cell Therapy ; (3) Biopredic International, La Bretèche, Saint-Grégoire, France.

Introduction : In Europe, liver cirrhosis accounts for around 170.000 deaths a year according to WHO. The lack of clinically efficient treatment for fibrosis, together with the fact that the pro-fibrotic profile of a drug is often detected only at later stages of the preclinical phase, highlights the need for better human models to study fibrosis. Liver fibrosis is the result of scar tissue formation as a consequence of long term ECM deposition by activated hepatic stellate cells (HSCs). In vitro, HSCs can be activated directly but in the majority of the cases in vivo it is a response to hepatocyte injury.
Aim : The aim of our work is to develop an in vitro model where drug-induced liver fibrosis can be mimicked. An efficient model as such, would not only lead to an early retraction during drug development of pro-fibrotic substances but also to develop treatments for liver fibrosis.
Methods : We developed a 3D human co-culture model of primary HSCs and hepatocyte-like cells (HepaRG) with the aim of screening both pro- and anti-fibrotic compounds.
Results : Here we present the optimized 3D HepaRG/HSC co-culture conditions that allow the maintenance of non-activated HSCs for at least 21 days based on the gene expression of HSC markers Col1a1, Col3a1 and Loxl2. In parallel, no alteration of hepatocyte functionality including CYP induction, albumin secretion and hepatocyte-specific gene expression is observed as compared to 3D HepaRG monocultures. However, TGFb can still directly induce activation of the human HSCs while LPS induces a survival response (IL6, MMP1, CCL2, TNFa, ILb). When exposed to known

hepatotoxicants, HSC activation is observed by the increased mRNA expression of HSC activation markers and collagen protein accumulation and secretion. This effect is enhanced when the co-cultures are exposed to an inflammatory cytokine cocktail reflecting inflammation-induced fibrogenesis.
Conclusions : The 3D hepatic co-cultures of primary HSCs and HepaRGs are an attractive tool to predict the (anti-) fibrotic profile of a compound in vitro. This model constitutes a big step forward from the regular 2D HSC and 2D/3D HepaRG monocultures.

- A13 -

VALIDATION OF APRI AND FIB-4 SCORE IN AN ANTWERP COHORT OF CHRONIC HEPATITIS C PATIENTS. W. Verlinden (1), S. Bourgeois (2), P. Gigase (2), C. Thienpont (2), L. Vonghia (1), T. Vanwolleghem (1), P. Michielsen (1), S. Francque (1). (1) UZ Antwerpen, Edegem, Belgium, Gastroenterology Hepatology ; (2) UZ Antwerpen, Edegem, Belgium, Gastroenterology.

Introduction : Evaluation of fibrosis stage in chronic hepatitis C patients (HCV) guides decision making of follow-up and therapy and is prognostically relevant. Liver biopsy is the gold standard, but has limitations for which noninvasive markers of liver fibrosis have been developed. APRI and FIB-4 are two frequently used and easily calculated tests and respectively use AST and platelets, and AST, ALT, platelets and age. APRI uses cut-off values to predict absence (< 0.5) or presence (> 1.5) of significant (≥F2) or advanced (≥F3) fibrosis, and cut-off values to predict absence (< 1) or presence (> 2) of cirrhosis. FIB-4 uses cut-off values to exclude (< 1.45) or predict (> 3.25) advanced fibrosis.
Aim : To validate APRI and FIB-4 in a cohort of chronic hepatitis C patients using biopsy as gold standard.
Methods : We retrospectively studied chronic hepatitis C patients who underwent liver biopsy. Liver fibrosis was staged according to the METAVIR scoring system.
Results : 136 patients were included (106 HIV-negative). Distribution of fibrosis was 16.2% F0, 40.4% F1, 23.5% F2, 8.1% F3 and 11.8% F4. AUROC of APRI for differentiation between F0-1vsF2-4, F0-2vsF3-4 and F0-3vsF4 was 0.777, 0.842 and 0.936, and 0.823, 0.856 and 0.932, for all patients and HIV-negative patients respectively. Sensitivity, specificity, PPV and NPV of APRI < 0.5 in HIV-negative patients were 72.9%, 80.9%, 82.7% and 70.4%, and 59.5%, 90.9%, 96.2% and 37% to exclude significant and advanced fibrosis, respectively. Sensitivity, specificity, PPV and NPV of APRI > 1.5 to predict severe fibrosis were 45.5%, 91.7%, 58.8% and 86.5% in HIV-negative patients, respectively. Sensitivity, specificity, PPV and NPV of APRI > 2 to predict cirrhosis were 50%, 97.8%, 77.8% and 92.7% in HIV-negative patients, respectively. Sensitivity, specificity, PPV and NPV of APRI < 1 to exclude cirrhosis are 92.8%, 92.9%, 98.7% and 45.4% in HIV-negative patients, respectively. AUROC of FIB-4 for differentiation between F0-2vsF3-4 was 0.896 and 0.912, in all patients and HIV-negative patients, respectively. Sensitivity, specificity, PPV and NPV of FIB-4 < 1.45 to exclude advanced fibrosis were 79.8%, 90.9%, 97.1% and 54.1% in HIV-negative patients, respectively. Sensitivity, specificity, PPV and NPV of FIB-4 > 3.25 to predict advanced fibrosis were 50%, 97.6%, 84.6% and 88.2% in HIV-negative patients, respectively. When using the FIB-4 score in the group of HIV negative patients, 73.6% was correctly classified, 22.6% unclassified (FIB-4 between 1.45 and 3.25) and 3.8% wrongly classified (1.9% over- and 1.9% underclassified).
Conclusions : In our population, the AUROC of APRI was slightly lower and the AUROC of FIB-4 was slightly higher compared to the initial reports. Both tests have a better AUROC in HCV monoinfected patients compared to HIV-HCV coinfected patients. FIB-4 had a better AUROC compared to APRI for F0-2vsF3-4 and is therefore, considering the new Belgian reimbursement rules for the new antivirals, the preferred noninvasive fibrosis score.

- A14 -

PERK INHIBITION REDUCES ACETAMINOPHEN-INDUCED TOXICITY. A. Paridaens (1), Y. Vandewynckel (1), E. Bogaerts (1), A. Van Den Bussche (1), L. Devisscher (1), L. Thoen (2), L. Van Grunsven (2), I. Leclercq (3), X. Verhelst (1), H. Van Vlierberghe (1), A. Geerts (1), I. Colle (1). (1) UZ Gent, Gent, Belgium, Department Gastroenterology and Hepatology ; (2) UZ Brussel, VUB, Jette, Belgium, Cell Biology ; (3) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Department Hepato-Gastroenterology.

Introduction : Acetaminophen, also known as paracetamol, (APAP) is one of the most widely used analgesic and antipyretic pharmaceutical and accounts for most cases of drug-induced liver injury resulting in acute liver failure. APAP overdose in mice induces hepatic Endoplasmic Reticulum (ER) stress, which leads to activation of the unfolded protein response (UPR).
Aim : To assess the impact of ER stress in APAP-induced hepatotoxicity, we examined the effect of chemical chaperones reducing ER stress and a UPR inhibitor on the protein kinase (PKR)-like endoplasmic reticulum kinase (PERK) pathway on APAP-induced liver damage.

Methods : Mice were fasted for 20 hours prior to receiving 300 mg/kg APAP or PBS intraperitoneally. Two hours post APAP/PBS injection, the mice were treated with chemical chaperones tauroursodeoxycholic acid (TUDCA), 4-phenylbutyric acid (PBA), a highly selective inhibitor of PERK (Perki), the current standard of care N-acetylcysteine (NAC) or PBS. Mice were sacrificed 24 hours after APAP injection and liver and serum samples were collected. Liver damage was evaluated by quantification of the serum ALT and AST levels and by Haematoxylin-Eosin staining on paraffin-embedded sections. Western Blotting was performed to screen for ER stress markers. Cytochrome P450 2A1, 2E1 and 3A4, total antioxidant capacity and reactive oxygen species were measured in liver lysates.
Results : APAP overdose effectively increased the expression of Grp78, suggesting robust induction of hepatic ER stress. Interestingly, APAP overdose increased the phosphorylation of eIf2α and the expression of downstream proteins Atf4 and Chop, suggesting activation of the Perk pathway which may induce ER stress-mediated cell death. Both NAC and Perki treatment reduced the levels of Atf4, Chop and the phosphorylation of eIf2α, whereas only a small decrease was observed following TUDCA or PBA treatment. As expected, ALT and AST levels were significantly increased in the APAP-treated group compared to the PBS control group ($p < 0,001$). Both NAC and Perki treatment reduced ALT ($p < 0,05$) and AST ($p < 0,05$) levels compared to APAP treated controls. Neither TUDCA nor PBA reduced the transaminase levels in APAP-treated mice. Fewer necrotic lesions and TUNEL-positive hepatocytes were observed in APAP-mice treated with NAC ($p < 0,05$) or Perki ($p < 0,001$) compared to APAP controls. Perki significantly outperformed the standard of care NAC. Additionally, we assessed the effect of ER stress modulation on APAP-induced oxidative stress. The mRNA levels of the anti-oxidant enzyme heme oxygenase-1, were increased after APAP intoxication and were decreased by NAC, Perki and TUDCA treatment ($p < 0,05$). However, we found no differences in oxidative stress or the total antioxidant capacity between the APAP control and Perki treated group. Inhibition of Cyp enzymes by Perki treatment could not be demonstrated.
Conclusions : These data demonstrate that APAP overdose strongly activates the pro-apoptotic Perk pathway of the UPR and that pharmacological inhibition of this pathway effectively reduces APAP-induced liver damage. Further studies are in the pipeline to unravel the downstream mechanisms by which Perki exerts its hepatoprotective effect following APAP intoxication.

- A15 -

DUCTULAR BILIRUBINOSTASIS PREDICTS THE EVOLUTION TO ACUTE-ON-CHRONIC LIVER FAILURE IN PATIENTS SUSPECTED WITH SEVERE ALCOHOLIC STEATOHEPATITIS. L. Verbeke (1), T. Roskams (2), C. Verslype (1), D. Cassiman (1), S. Van Der Merwe (1), W. Van Steenbergen (1), G. Maleux (3), A. Wilmer (4), W. Laleman (1), F. Nevens (1). (1) UZ Leuven, KULeuven, Leuven, Belgium, Hepatology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Pathology ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Radiology ; (4) UZ Leuven, KU Leuven, Leuven, Belgium, Medical Intensive Care Unit.

Introduction : Current guidelines consider a liver biopsy optional to diagnose severe alcoholic steatohepatitis (ASH) and based on clinical criteria (i.e. Maddrey-score / MDF ≥32) patients are initiated on corticosteroids (CS). However, in patients with acute decompensation of alcoholic cirrhosis, this diagnosis may be challenging since it clinically resembles acute-on-chronic liver failure (ACLF). We recently identified ductular bilirubinostasis (DB) as an early risk factor for ACLF.
Aim : To evaluate the significance and prognostic role of DB on early liver biopsy in patients clinically suspected with severe ASH.
Methods : Prospective trial of 114 patients with alcoholic cirrhosis and suspicion of severe ASH (i.e. MDF ≥32) who underwent a transjugular liver biopsy within 3 days after admission. Literature-reported clinical, biochemical and histological parameters indicative of severe ASH and/or ACLF were assessed and correlated to the risk of death and the response to CS using logistic regression and survival analysis.
Results : In 76/114 patients (67%) the diagnosis of severe ASH was confirmed : 42/76 (55%) had severe ASH without and 34/76 (45%) with DB. 26/114 (23%) had DB without severe ASH. DB was predictive for evolution to ACLF (and associated with infection and multi-organ failure). Multivariate analysis revealed DB as the main independent early variable predicting 6-month-mortality (O.R. 13.5 ; $P < 0.001$). Patients without DB had the highest 6-month survival, irrespective of the presence of severe ASH (67% vs. 24% ; $P < 0.0001$). While patients with severe ASH without DB had a good response to CS, survival increased most significantly after CS in the subset of patients displaying both histological features of severe ASH and DB (median survival 81 vs. 38 days vs. untreated counterparts ; $P < 0.05$).
Conclusions : -One third of patients suspected with severe ASH were misdiagnosed without histology. -DB on early liver biopsy predicts evolution to ACLF and is associated with poor outcome. -Patients with both severe ASH and DB benefited most from CS treatment.

- A16 -

DEFECTIVE THERMOGENIC ADAPTATION TO HIGH CALORIE INTAKE : A CONTENDER IN NASH PATHOGENESIS IN FOZ/FOZ MICE. L. Poekes (1), V. Legry (2), O. Schakman (3), A. Bol (4), G. Farrell (5), I. Leclercq (6). (1) Université Catholique de Louvain, Institut de Recherche Exérimentale et Clinique (IREC), Brussels, Belgium, Laboratory of Hepato-gastroenterology ; (2) Université Catholique de Louvain, Institut de Recherche Exérimentale et Clinique (IREC), Brussels, Belgium, Laboratory of Hepato-gastroenterology ; (3) Université Catholique de Louvain, Institut de Recherche Exérimentale et Clinique (IREC), Brussels, Belgium, Institute of Neuro Science ; (4) Université Catholique de Louvain, Institut de Recherche Exérimentale et Clinique (IREC), Brussels, Belgium, Pôle d'imagerie moléculaire, radiothérapie et oncologie (MIRO) ; (5) Australian National University, Australia, Liver Research Group ; (6) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Laboratory of Hepato-gastroenterology.

Introduction : Unlike Wild Type (WT) mouse strains, foz/foz mice fed a high fat diet (HFD) develop progressive fibrosing steatohepatitis together with severe metabolic syndrome. They represent thus an appropriate model to study NASH pathogenesis. Foz/foz mice carry a spontaneous mutation in Alms1, a gene encoding for a protein of the primary cilium of yet unknown function.
Aim : The aim is to understand mechanisms contributing to the obese, metabolic and liver phenotype of foz/foz mice.
Methods : Foz/foz mice are hyperphagic. Pair feeding experiment in which foz/foz mice have restricted access to HFD to the exact equal amount of their WT counterparts was set up. Activity level, oxygen consumption and thermogenic adaptation were evaluated.
Results : Compared to WT, 4 weeks of HFD induced more severe obesity, insulin resistance, steatosis and liver and adipose inflammation in foz/foz mice. Caloric restriction to foz/foz mice partially improved but did not correct metabolic disturbances. Physical activity, circadian rhythm, basal metabolism and body temperature were unaffected in foz/foz mice. By contrast, thermogenic adaptation of their brown adipose tissue (BAT) was impaired. When fed standard chow, foz/foz mice had a larger and fatter BAT than WT mice. The content in mitochondrial DNA (mtDNA) and the level of expression of thermogenic genes UCP-1, PGC1alpha and DIO2 were however similar between the 2 genotypes. In WT mice, HFD reduced BAT fat load, increased mtDNA content and up-regulated UCP-1, PGC1α and DIO2 genes consistent with an adaptive fat burning in the face of increased energy load. Conversely, HFD in foz/foz mice markedly increased BAT lipid accumulation while up-regulation of mtDNA content and thermogenic genes was lower or blunted compared to HFD-fed WT mice. Upon exposure to 4°C for 6 hours, body temperature dropped by 2.1°C in WT mice but by 3.9°C in foz/foz mice ($p < 0.05$) and up-regulation of thermogenic genes was 40 to 60% lower in HFD-fed foz/foz than in WT mice. Thermogenic failure was further confirmed by a significant lower up-take of 18FDG (PET-Scan) by foz/foz BAT than by WT BAT upon cold exposure.
Conclusions : Overall, these results suggest that in this model, next to hyperphagia, reduced adaptive thermogenesis contributes to obesity and insulin resistance, eventually driving NASH and call upon evaluating targeting of BAT for therapeutic intervention in metabolic syndrome and NASH.

Marc Hautekeete Invited Lecture

- A17 -

BETA-BLOCKERS IN CIRRHOSIS : TO BLOCK OR NOT ? Prof. Aleksander Krag (Department of Gastroenterology and Hepatology, University of Southern Denmark & Odense University Hospital).

Non-selective beta-blockers (NSBB) have been known and studied since the 1960'ies. Landmark studies in the early 1980'ies by Lebrec and colleagues paved the path for its revolutionary impact on clinical hepatology. NSBB have since been studied intensively and become a cornerstone in portal hypertension. The clinical efficacy of NSBB in terms of preventing variceal bleeding and improving survival has been documented in several randomized trails and meta-analyses. The treatment is adapted all over the world as the standard of care in the primary and secondary prevention of variceal bleeding. More recent studies suggest that NSBB also prevent gut bacterial translocation and potentially also hepatocellular carcinoma and these effects may contribute to the beneficial effects on survival. NSBB had become the "aspirin of cirrhosis" – a holy grail. But in 2010 data came out suggesting that NSBB may not be safe in advanced cirrhosis. That subgroup of patients had not been
specifically studied in the randomized trials. It was suggested that NSBB should only be used during a certain window in the disease. A number of observational studies have investigated if such a window exists and if so when it closes. Current available data are equivocal, but the largest studies with long term follow up support a serious safety concern of NSBB in patients with cirrhosis and refractory ascites, after an episode of spontaneous peritonitis and a relation to renal failure. The exact mechanisms behind the potential harmful effects of NSBB in advanced cirrhosis have not been identified. But NSBB are titrated to reduce heart rate by 25%, which translates to a reduction in cardiac output of 25% and affects blood pressure negatively. A number of studies suggest a relation between deterioration of circulatory function and survival and this may be an important event during NSBB treatment. The sickest patients with cirrhosis and ascites under NSBB therapy walk a fine line between the detrimental effects and beneficial effects.

- A18 -

PDGFRA-MEDIATED LAMININ B1 DEPOSITION INDUCES INVASION IN HUMAN HEPATOCELLULAR CARCINOMA. O. Govaere (1), M. Petz (2), J. Wouters (1), Y. Vandewynckel (3), A. Ceulemans (1), B. Topal (4), C. Verslype (5), H. Van Vlierberghe (3), F. Nevens (5), W. Mikulits (2), T. Roskams (6). (1) UZ Leuven, KU, Leuven, Belgium, Department of Imaging & Pathology ; (2) Institute of Cancer Research, Medical University of Vienna, Vienna, Austria, Vienna, Austria, Department of Medicine I ; (3) UZ Gent, Gent, Belgium, Department of Hepatology & Gastroenterology ; (4) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Abdominal Surgery ; (5) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Hepatology ; (6) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Imaging & Pathology.

Introduction : Platelet-derived growth factor receptor α (PDGFRA) has been associated with the progression of hepatocellular carcinoma (HCC), although the exact underlying mechanism of PDGFRA still remains unclear.
Aim : In this study we aim to investigate the clinicopathological relevance of PDGFRA and unravel the underlying mechanism.
Methods : Clinicopathological value of PDGFRA was assessed in a Caucasian cohort of 136 HCC patients (resection or explant specimens) with different underlying aetiologies ; the predictive value was evaluated in an independent series of 46 pre-operative needle biopsies with a follow-up of 5 years. Microarray analysis was performed on frozen HCC tissue samples with or without microvascular invasion (n = 52). Activation or inhibition of PDGFRA (using recombinant PDGFA/B or Crenolanib respectively) and alteration of downstream targets laminin B1 (LAMB1) and its receptor integrin B1 (ITGB1) (by laminin-1 coating, shRNAs or targeted antibodies) was performed in the SNU423 and HepG2 HCC cell lines. Functional readout was done using invasion and invadopodia assays.
Results : In the cohort of surgical specimens PDGFRA expression was found in 66% of the samples and was significantly correlated with metastasis ($p < 0,001$), microvascular invasion ($p < 0,001$) and increased tumour size ($p < 0,05$), and was especially found in the invasive front. In the cohort of needle biopsies, PDGFRA was significantly linked with poor overall survival ($p < 0,05$). Microarray analysis showed that HCCs with microvascular invasion display a strong up-regulation of genes related to cytoskeleton remodelling and genes related to extracellular matrix components. In vitro activation of PDGFRA enhanced LAMB1 expression through the LA/SSB cascade and promoted invasion and invadopodia formation, whereas inhibition of PDGFRA by Crenolanib had the opposite effect. Antibodies targeting laminin-1 or ITGB1 receptor reduced the invasive potential and altered the expression of genes involved in cytoskeleton remodelling (e.g. KRT19, ANXA3, TUBB6). Moreover, inhibiting the ITGB1 receptor morphologically changed the growth pattern to a less invasive phenotype.
Conclusions : The PDGFRA-LAMB1 pathway plays an important role in the invasion of HCCs and is a promising therapeutic target.

- A19 -

BIRTH COHORT DISTRIBUTION AND SCREENING OF VIREMIC HCV INFECTIONS IN BELGIUM. C. Moreno (1), W. Laleman (2), P. Stärkel (3), P. Van Damme (4), D. Vandijck (5), S. Blach (6), H. Razavi (6), H. Van Vlierberghe (7). (1) CUB Hôpital Erasme, Brussels, Belgium, Department of Gastroenterology and Hepatopancreatology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Liver and Biliopancreatic Disorders ; (3) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Department and Laboratory of Gastroenterology ; (4) UZ Antwerpen, Antwerpen, Belgium, Vaccine & Infectious Disease Institute ; (5) UZ Gent, Gent, Belgium, Dept. of Health Economics & Patient Safety ; (6) Center for Disease Analysis (CDA), Louisville, USA, Epidemiology ; (7) UZ Gentl, Gent, Belgium, Department of Internal Medicine.

Introduction : In Belgium approximately 50% of hepatitis C virus (HCV) infected individuals have been identified (Deuffic-Burban et al. 2012). Given the significant clinical and economic burden, this rate should increase.
Aim : This project analyzes the distribution of HCV cases in the Belgian population in order to develop more innovative detection strategies.
Methods : A previously described HCV disease burden model was populated with Belgian assumptions regarding HCV prevalence, viremic rate and age distribution (Razavi et al. 2014 ;Van Damme et al. 2014). The viremic population was aged to 2014, accounting for mortality and cure rates, and was stratified according to birth cohort. The number of screenings required to identify one viremic case was calculated as 1 / (viremic HCV prevalence – (1 – diagnosis rate)). Costs (expressed in €) associated with diagnosing (anti-HCV serology and HCV RNA qualitative) and informing treatment (genotype and viral load) for one viremic case were estimated as follows – [€ 8 * (# anti-HCV tests administered)] + [€ 65 * (# HCV-RNA tests administered for anti-HCV positive cases)] + [€ 228 * (# treatment informing tests administered for HCV-RNA positive cases)].
Results : More than 50% of the viremic HCV infected population was calculated to be born between 1955-1974, with 70% born between 1950-1979. Random screening would require 300 anti-HCV tests (in addition to further confirmatory

tests) to diagnose one current HCV case, while targeted screening in the 1950-1979 cohort (35-64 years of age) could diagnose one case per 150 persons screened. Targeted screening in the 1950-1979 cohort would cost about € 1,730 per positive diagnosis, as compared with a € 2,760 cost for random screening. Screening within 5-year cohorts could identify one case per 150 persons screened (1960-1964 cohort, 15% of the viremic population) to one case per 34,540 persons screened (2010-2014 cohort, < 1% of the viremic population).
Conclusions : Considering only the direct cost of diagnosis, the most efficient birth-year screening strategy would particularly target persons born between 1950 and 1979 (35 - 64 years of age), as this cohort accounts for over 70% of viremic cases and requires screening of only 140 individuals to identify one viremic HCV infected case. Targeted birth cohort screening is more efficient and cost effective than random screening.

- A20 -

A GLOBAL RISK GENE SCORE PREDICTS EARLY AND LATE TUMOR RECURRENCE AFTER RESECTION OF HEPATOCELLULAR CARCINOMA. J. Dekervel (1), D. Popovic (2), H. Van Malenstein (1), P. Windmolders (1), L. Libbrecht (3), A. Bulle (1), B. De Moor (2), E. Van Cutsem (4), F. Nevens (5), C. Verslype (5), J. Van Pelt (1). (1) UZ Leuven, KU, Leuven, Belgium, Lab of Hepatology ; (2) UZ Leuven, KU, Leuven, Belgium, Department of Electrical Engineering (ESAT) ; (3) UZ Gent, Gent, Belgium, Department of Pathology ; (4) UZ Leuven, Leuven, Belgium, Department of Digestive Oncology ; (5) UZ Leuven, Leuven, Belgium, Department of Hepatology.

Introduction : Patients undergoing treatment with curative intent for hepatocellular carcinoma (HCC) remain at high risk for tumor recurrence by the emergence of intrahepatic metastasis (“early recurrence”) or the formation of new lesions (“late recurrence”).
Aim : We aimed to develop and validate a gene expression signature that could predict this risk.
Methods : HepG2 liver cancer cells made resistant to sorafenib during several months were used as a model for hepatocyte dedifferentiation and aggressive tumor biology. The differential expressed genes between this cell line and its non-resistant parental lineage were determined using an Affymetrix microarray platform. To form a score, the number of genes was subsequently downsized by assessing the performance of each one in published microarray data sets of HCC samples (GSE25097, GSE9843) and samples of non-tumoral surrounding liver (GSE40873). This resulted in a 7 gene score (Global Risk Score, GRS) which was validated in two independent data sets (LEC cohort, GSE1898/ GSE4024, n = 67 and NCI cohort, GSE14520, n = 247) using a tumor- and liver-specific cut-off for GRShigh and GRSlow.
Results : The GRS, when assessed in tumor tissue of patients treated with resection, identified patients at low and high recurrence risk at 3 years in the LEC (GRShigh 68 +/- 10% vs GRSlow 35 +/- 7%, p = 0.03) and NCI (GRShigh 62 +/- 5% vs GRSlow 37 +/- 4%, p < 0.001) cohort. Moreover, assessment of the GRS in non-cancerous surrounding liver tissue of the NCI patients revealed that, starting at about 19 months after resection, the score was correlated with the formation of new lesions in the cirrhotic liver (p = 0.03). Taken together, based on the tumor and liver score value, the GRS identified 4 patient groups (GRS I – IV) with differences in recurrence rates and time patterns of recurrence (overall p-value by log rank testing < 0.001). Patients in GRS I, who are GRSlow in liver and tumor tissue, had a 3 year recurrence rate of 32% (SD 6%) compared to 65% (SD 6%) in patients in GRS IV (GRShigh in both tissues). Patients with GRSlow in tumor and GRShigh in liver (GRS III) had similar recurrence risk as tumor GRShigh/liver GRSlow patients (GRS II) with differences in median time to recurrence (46 months (95% CI 32 – 59) versus 26 months (95% CI 8 – 45) p = 0.03 by breslow testing). Multivariable analysis by Cox regression showed that GRS group was a significant predictor of recurrence, independent from BCLC stage (p = 0.007).
Conclusions : We present the first gene score validated in both HCC tissue and surrounding liver based on an in vitro model. By identifying aggressive tumor biology as well as tumorigenic potential of the underlying liver disease, the Global Risk Score allows calculating a prognostic estimate for an individual patient facilitating therapeutic decisions.

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PARITAPREVIR/RITONAVIR, OMBITASVIR AND DASABUVIR WITH OR WITHOUT RIBAVIRIN ACHIEVES 98.6% SUSTAINED VIROLOGIC RESPONSE IN BELGIAN GT1 INFECTED PATIENTS. H. Van Vlierberghe (1), C. Moreno (2), S. Bourgeois (3), J. Mulkay (4), H. Reynaert (5), S. Francque (6), Y. Horsmans (7), F. Nevens (8). (1) UZ Gent, Gent, Belgium, Department of Gastroenterology and Hepatology ; (2) CUB Hôpital Erasme, Brussels, Belgium, Department of Gastroenterology and Hepatology ; (3) ZNA Stuivenberg Hospital, Antwerp, Belgium, Department of Hepatology ; (4) CHU Saint-Pierre, Brussels, Belgium, Clinic of Hepato-gastroenterology ; (5) UZ Brussel, VUB, Brussels, Belgium, Department of Gastroenterology and Hepatology ; (6) UZ Antwerpen, Antwerp, Belgium, Department of Gastroenterology and Hepatology ; (7) Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, Department of Gastroenterology and Hepatology ; (8) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Hepatology.

Introduction : The interferon-free regimen of paritaprevir (ABT450) boosted with ritonavir, ombitasvir and dasabuvir with or without ribavirin has been extensively studied in 6 phase III trials involving over 2300 HCV genotype 1 infected patients. Belgian patients were included in 3 Phase III trials : PEARL II (NCT01704755), a multicentre, open-label phase 3 trial assessing the need for ribavirin in GT1b treatment-experienced noncirrhotic patients ; PEARL III (NCT01767116), a multicentre, double-blind phase 3 trial investigating whether ribavirin is needed in treatment-naive GT1b noncirrhotic patients ; TURQUOISE II (NCT01704755), a multicentre open-label phase III study, evaluating the efficacy and safety of paritaprevir/ritonavir/ombitasvir, combined with dasabuvir and ribavirin for 12 or 24 weeks in HCV genotype 1 patients with compensated cirrhosis.
Aim : To evaluate virologic response in Belgian GT1 infected patients treated with paritaprevir/ritonavir, ombitasvir and dasabuvir with or without ribavirin .
Methods : Sixty nine Belgian patients (pooled data from 3 phase III studies) infected with HCV GT1 were randomly assigned to receive either 12 (n = 57) or 24 weeks (n = 12 ; Turquoise II only) of treatment with paritaprevir/ritonavir/ombitasvir (at a once daily dose of 150 mg of paritaprevir, 100 mg of ritonavir and 25 mg of ombitasvir), and dasabuvir (twice daily dosing of 250 mg) with or without weight-based ribavirin. The primary efficacy endpoints were a sustained virologic response (SVR) 12 weeks after the end of treatment.
Results : A total of 68 of 69 patients (including 27.5% patients with compensated cirrhosis) had a sustained virologic response at post-treatment week 12, for a rate of 98.6% (97.5% CI, 95.3 to 100%). All GT1b infected patients achieved SVR12 (100% ; n = 62), independent of the presence of ribavirin, fibrosis stage or previous treatment response. None of the reported adverse events were severe ; the three most common side effects were fatigue (53.6%), headache (37.7%) and diarrhoea (26.1%). Decreases in haemoglobin level were significantly more common in patients receiving ribavirin, though ribavirin dose modifications were uncommon (4.3%) and did not affect SVR12 (100%). No severe or serious adverse events have been reported and no patients discontinued treatment owing to adverse events or virologic failure.
Conclusions : In these three phase 3 trials of an oral, multitargeted interferon-free therapy, the use of paritaprevir boosted with ritonavir, ombitasvir and dasabuvir with or without ribavirin resulted in high rates of sustained virologic response in Belgian patients, including those with compensated cirrhosis. Antiviral therapy was well tolerated, as shown by the absence of treatment-related discontinuations and absence of severe adverse events.

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THE HIPPO PATHWAY EFFECTOR YAP CONTROLS MOUSE HEPATIC STELLATE CELL ACTIVATION.
I. Mannaerts (1), S. Leite (1), S. Verhulst (1), L. Thoen (1), S. Claerhout (2), G. Halder (2), L. Van Grunsven (1). (1) Vrije Universiteit Brussel (VUB), Jette, Belgium, BMWE - Liver Cell Biology Lab ; (2) Katholieke Universiteit Leuven, Leuven, Belgium, VIB Center for the Biology of Disease, and KU Leuven Center for Human Genetics.

Introduction : Hepatic stellate cell activation is a wound-healing response to liver injury. However, continued activation of stellate cells during chronic liver damage causes excessive matrix deposition and the formation of pathological scar tissue leading to fibrosis and ultimately cirrhosis. The importance of sustained stellate cell activation for this pathological process is well recognized, and several signaling pathways that can promote stellate cell activation have been identified, such as the TGFβ-, PDGF-, and LPS-dependent pathways.
Aim : The mechanisms that trigger and drive the early steps in activation are not well understood, identification of those is the aim of our study.
Methods : Primary HSCs are isolated from healthy and fibrotic BalbC mice. Microarray analysis on in vitro and in vivo activated HSCs (unseeded), identified significant changes in genes related to the Hippo pathway. 2D and 3D spheroid cultures are used to investigate the contribution of the hippo-effector protein YAP.
Results : We identified the Hippo pathway and its effector YAP as a key pathway that controls stellate cell activation. YAP is a transcriptional co-activator and we found that it drives the earliest changes in gene expression during stellate cell activation. Activation of stellate cells in vivo by CCl4 administration or activation in vitro, caused rapid activation of YAP as revealed by its nuclear translocation and induction of target genes. Importantly, knock-down of YAP expression or pharmacological inhibition of YAP prevented hepatic stellate cell activation in vitro. Moreover, in vivo inhibition of YAP activity with a pharmacological inhibitor impeded fibrogenesis in mice.
Conclusions : YAP activation is thus a critical driver of hepatic stellate cell activation and inhibition of YAP presents a novel approach for the treatment of liver fibrosis.

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A DETAILED SYSTEMS BIOLOGY STUDY IDENTIFIES UNAPPRECIATED ROLES FOR THE INNATE IMMUNE RESPONSE AND B-CELLS IN THE DIFFERENTIATION BETWEEN HBV CLINICAL PHASES. T. Vanwolleghem (1), J. Hou (2), G. Van Oord (2), A. Andeweg (3), A. Osterhaus (3), S. Pas (3), H. Janssen (4), A. Boonstra (2). (1) UZ Antwerpen, Edegem, Belgium, Gastroenterology & Hepatology ; (2) Erasmus Medical Center, Rotterdam, Netherlands, Department of Gastroenterology and Hepatology ; (3) Erasmus Medical Center, Rotterdam, Netherlands, Viroscience ; (4) University Health Network, Canada, Liver Clinic.

Introduction : Host factors that identify distinct clinical phases of a chronic HBV infection, -immune tolerant (IT), immune active (IA), inactive carrier (IC) and HBeAg negative (ENEG) hepatitis phases- are poorly defined.
Aim : We performed a systems biology study to identify host markers that can differentiate between these disease phases.
Methods : Serum samples from untreated chronic HBV patients (n = 71) were used for multiplex cytokine measurements, quantitative HBsAg, HBeAg levels, HBV genotype and mutant analysis. Leukocytes were phenotyped using multicolour flowcytometry and whole blood transcriptome profiles were generated.
Results : HBV viral load, HBeAg and HBsAg levels ($P < 0.001$), but not leukocyte composition differed significantly between distinct phases. Serum MCP-1, IL-12p40, IP-10, MIP-1β levels were different between two or more clinical phases ($P < 0.05$). The lowest number of HBV precore mutations was found in IT patients ($P < 0.01$). Comparison of blood transcriptomes identified 64 differentially expressed genes between clinical phases. The gene signature distinguishing IA from IT and IC patients was predominantly composed of highly upregulated immunoglobulin encoding genes. Furthermore, gene-set enrichment analysis corroborated abundant expression of B cell function-related genes in IA patients, and pointed towards increased ISG transcript levels in IT patients compared to subsequent phases. Finally, NK cell activities were clustered in clinical phases with biochemical liver damage (IA and ENEG phases).
Conclusions : HBV clinical phases are characterised by distinct blood gene signatures. Innate interferon and B cell responses are highly active during the IT and IA phases, respectively. This suggests that the presumed immune tolerance in chronic HBV infections needs to be redefined.

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LIVER FIBROSIS PROMOTES HEPATOCARCINOMA GROWTH ACCORDING TO THE SEVERITY OF FIBROSIS IN AN ORTHOTOPIC TUMOR MODEL IN MOUSE. B. Delire. Cliniques Universitaires Saint-Luc, Brussels, Belgium, Gastroenterology.

Introduction : HCC is associated in 90% of cases with cirrhosis. However, the fibrosis-dependent mechanisms of hepatocarcinogenesis remain poorly understood. MMP-2,-9 and Membrane-Type 1 (MT1)-MMP are endopeptidases that cleave the extracellular matrix and are related to HCC invasiveness.
Aim : Our aim was to study the impact of fibrosis and its severity on HCC development and to evaluate the tumor expression of MMP-2,-9 and MT1-MMP according to the liver fibrosis status in an orthotopic transplantation model.
Methods : The HCC cell line Hepa 1-6 is syngenic with the C57Bl/6 mouse strain and is characterized by a constitutive expression of αFP. Hepa 1-6 cells (1x106) were injected into the liver by direct puncture in 3 groups of mice (n = 10/ group) : in non-fibrotic liver (normal liver group-NLG), in mild fibrotic liver (mild fibrosis group-MFG) and in severe fibrotic liver (severe fibrosis group-SFG). Mild and severe fibrosis were induced by CCl4 injections for 2 and 7 weeks respectively. Mice were sacrificed 2 weeks post HCC cell injection. The liver was sliced and examined for the presence of tumor (nodule ≥ 1mm). The tumor volume (TV) and the liver to body weight ratio (LW/BW) were used as parameters of tumor burden. A part of each tumor was used for histological analysis and the other for RNA preparation.
Results : A tumor nodule was observed in 60%, 80% and 100% of animals in the NLG, MFG and SFG respectively. The TV was significantly higher in the MFG compared to the NLG ($p < 0,05$) and in the SFG compared to the MFG ($p < 0,001$) and to the NLG ($p < 0,0001$). The LW/BW was significantly higher in the SFG compared to the MFG ($p < 0,05$) and to the NLG ($p < 0,01$). In all tumors, αFP mRNA expression was high and significantly higher in SFG tumors compared to NLG tumors ($p < 0,05$). Intra-tumor expression of MMP-2,-9 and MT1-MMP gradually increased with fibrosis severity at the time of tumor implantation. Furthermore, there was a positive and significant correlation between TV and LW/BW and the intra-tumor expression of all MMPs.
Conclusions : Our results demonstrate that liver fibrosis promotes HCC development in our model and suggest a link between the severity of fibrosis and the ability of liver cancer to develop. Moreover, we have shown an enhanced MMP-2,-9 and MT1-MMP expression in the tumors of the fibrosis group suggesting a role of the MMPs and matrix remodeling in the fibrosis-dependent promotion of HCC development.

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ASSESSMENT OF SERUM GLYCOMICS (GLYCOCIRRHOTEST) FOR RISK PREDICTION OF HEPATOCELLULAR CARCINOMA DEVELOPMENT IN PATIENTS WITH CIRRHOSIS. X. Verhelst (1), D. Vanderschaeghe (2), L. Castéra (3), A. Geerts (4), N. Goutté (5), C. Francoz (5), F. Durand (5), N. Callewaert (2), H. Van Vlierberghe (4). (1) UZ Gent, Gent, Belgium, Department of Gastroenteroly and Hepatology ; (2) VIB, Gent, Belgium, Unit for Medical Biotechnology, Inflammation Research Center ; (3) Hôpital Beaujon, Clichy, France, Department of Hepatology ; (4) UZ Gent, Gent, Belgium, Department of Gastroenterology and Hepatology ; (5) Hôpital Beaujon, Clichy, France, Department of Hepatology.

Introduction : Cirrhosis, whatever the cause, is a major predisposing factor for the development of hepatocellular carcinoma (HCC) with a yearly incidence ranging from 1 to 8%. Both EASL and AASLD guidelines recommend systematic screening with liver ultrasound at 6 months interval in cirrhotic patients. It has been shown previously that the GlycoCirrhoTest, corresponding to the respective abundance of bisecting GlcNAc residues and triantenarry glycans in the serum, had a 79% sensitivity and 86% specificity for the diagnosis of cirrhosis among patients with chronic liver diseases.
Aim : The aim of the present study was to determine whether serum glycomics are predictive for the development of HCC in patients with compensated cirrhosis.
Methods : We analysed blood samples of 132 cirrhotic patients collected between 1995 and 2005. All patients had biopsy proven cirrhosis at the moment of serum sampling and had CHILD A or CHILD B cirrhosis. Seventy percent of the patients had hepatitis C virus (HCV) infection. In the remaining patients, the cause of cirrhosis was hepatitis B virus infection, alcohol and autoimmune diseases. The patients were followed until the appearance of a HCC, death or liver transplantation. At the moment of serum sampling there was no evidence of HCC. GlycoCirrhoTest was performed using capillary electrophoreses as previously described by Callewaert et al (Nature Medicine 2004).
Results : Thirty five (26.5%) of the patients developed a HCC after a median follow up of 4 years (IQR : 3.6 – 8.06). Mean follow up in the patients who did not develop HCC was 3.7 years (IQR : 3.4-9.9 ; ns) . There was a significant increase of the mean baseline GlycoCirrhoTest value in the patients who developed a HCC during follow up ($p < 0.001$) as compared to those who did not. ROC Curve analysis showed an AUC of 0.716 (95% CI : 0.611-0.820) for the prediction of HCC in the patients with a follow up of at least 1 year. An 0.1 increase in the value of the GlycoCirrhoTest was associated with a 27% increase in the risk for developing HCC (OR 1,27 ; 95%CI : 1,098-1,475). In 81 patients (65 without HCC and 16 with HCC) baseline AFP values were available. Combining GlycoCirrhoTest and AFP using logistic regression increased the predictive value (AUC = 0.789 ; 95% CI : 0.677-0.900).
Conclusions : This study suggests that a glycomic based biomarker could represent a useful biomarker for the identification of patients with cirrhosis at high risk for developing HCC. GlycoCirrhoTest may help stratify cirrhotic patients according to the risk of HCC and optimize screening.

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PERFORMANCE OF THE AFP MODEL IN PREDICTING PROGNOSIS AFTER LIVER TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA : A SINGLE CENTER RETROSPECTIVE VALIDATION. J. Dekervel (1), H. Poels (2), C. Duvoux (3), J. Van Pelt (1), D. Monbaliu (4), W. Laleman (2), S. Van Der Merwe (2), W. Vansteenbergen (2), F. Nevens (2), J. Pirenne (4), C. Verslype (2). (1) UZ Leuven, KU Leuven, Belgium, Lab of Hepatology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Hepatology ; (3) Hôpital Henri Mondor, Créteil, France, Service d'Hépatologie ; (4) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Abdominal Transplant Surgery and Transplant Coordination.

Introduction : Different criteria that identify patients with hepatocellular carcinoma at low risk for disease recurrence after liver transplantation have been developed. In an attempt to take a marker of tumor biology into account, a model partly based on alpha-foetoprotein (aFP) level at time of listing has been developed and is now being used for the allocation of patients in France. The model gives points based on tumor number (0 or 2 points for 1-3 or > 3 nodules respectively), largest diameter in centimeter (0, 1 or 4 points for < 3, 3-6 or > 6 cm respectively) and aFP level (0, 2 or 3 points for < 100, 100 – 1000 or > 1000 ng/ml respectively) with a total of > 2 points indicating high risk.
Aim : We investigated the performance of the aFP model in a Belgian center and we compared the prognostic ability of the aFP model with the widely used Milan criteria.
Methods : We retrospectively assessed 159 patients that underwent OLT for HCC in our center between 2000 and 2013. Patients who died in the first three months after OLT were excluded unless they had HCC recurrence. Patients were mostly male (77%) with underlying alcoholic liver disease (35%) or chronic hepatitis C infection (32%). Median number of lesions at listing was 1 (5-95% percentile 1 - 5) with the size of the largest lesion being 25 mm (5-95% percentile 10 - 70). Most patients (87%) had aFP levels < 100 μg/l, only 4 (2.5%) had levels > 1000 μg/l. During a follow-up of 46 months (range 3 – 157) 25 patients (16%) showed HCC recurrence and 52 patients (33%) died.

Results : At time of listing, so before downstaging was performed in appropriate cases, 37 patients (23%) were outside Milan criteria, whereas 22 (14%) were outside aFP model. As expected, patients inside Milan had significant lower recurrence rates at 5 years after transplantation compared to patients outside Milan (10% (SD 3%) vs 40% (SD 9%), $p < 0.001$). Similar, the aFP model identified a subgroup of patients with high 5 year recurrence risk (11% (SD 3%) vs 47% (SD 11%), $p < 0.001$). There were no differences in recurrence rates between patients inside Milan/outside aFP model ($n = 8$) and patients outside Milan/inside aFP model ($n = 23$) ($p = 0.75$). Within the patient cohort with aFP < 100μg/l (which are the patients that do not receive any points for their aFP level), the aFP level was still prognostic for recurrence resulting in a ROC curve with AUC of 0.7 ($p = 0.007$).
Conclusions : In this cohort of patients with mainly low aFP levels at time of listing, the recurrence rate of those within Milan criteria was similar to that of patients within the aFP model. Because the latter criteria are less stringent, more patients could theoretically be considered for transplantation without resulting in higher recurrence rates. However, even lower aFP levels were significantly associated with recurrence suggesting that a lower cut-off could increase the power of an allocation model based on this parameter.

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TAUROURSODEOXYCHOLIC ACID DAMPENS ONCOGENIC APOPTOSIS INDUCED BY ENDOPLASMIC RETICULUM STRESS DURING HEPATOCARCINOGEN EXPOSURE. Y. Vandewynckel (1), D. Laukens (2), L. Devisscher (2), A. Paridaens (2), E. Bogaerts (2), X. Verhelst (2), A. Van Den Bussche (2), S. Raevens (2), C. Van Steenkiste (2), M. Van Troys (3), C. Ampe (3), B. Descamps (4), C. Vanhove (5), O. Govaere (6), L. Libbrecht (7), A. Geerts (2), H. Van Vlierberghe (2). (1) UZ Gent, Gent, Belgium, Hepato-gastroenterology ; (2) UZ Gent, Gent, Belgium, Department of Hepatology and Gastroenterology ; (3) UZ Gent, Gent, Belgium, Department of Biochemistry ; (4) UZ Gent, Gent, Belgium, Infinity imaging lab ; (5) UZ Gent, Gent, Belgium, Infinity imaging lab ; GROUP-ID Consortium ; (6) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Cell and Tissue Research, Department of Imaging and Pathology ; (7) UZ Gent, Gent, Belgium, Department of Pathology.

Introduction : Hepatocellular carcinoma (HCC) is characterized by accumulation of unfolded proteins in the endoplasmic reticulum (ER) which activates the unfolded protein response. However, the role of ER stress in tumour initiation and progression remains a contentious topic.
Aim : To determine the impact of ER stress, we applied tauroursodeoxycholic acid (TUDCA), a cytoprotective bile acid with chaperone properties reducing ER stress.
Methods : The effect of TUDCA on hepatic tumour burden, apoptosis, ER stress, autophagy, oxidative stress and inflammation was assessed in the diethylnitrosamine-induced orthotopic mouse model for HCC in a preventive and therapeutic setting. The effect on MTT metabolic activity and BrdU incorporation was investigated in vitro and the effect on tumour progression was assessed in a HepG2 xenograft model.
Results : Administration of TUDCA in a preventive setting reduced the carcinogen-induced elevation of aspartate and alanine aminotransferase levels and apoptosis of hepatocytes and, surprisingly, also the tumour burden in the preventive setting. TUDCA markedly reduced the phosphorylation of eukaryotic initiation factor 2α, the expression of the pro-apoptotic C/EBP homologous protein (CHOP) and caspase-12 activation in the DEN-treated livers, suggesting that TUDCA suppressed terminal unfolded protein response signalling. Although no significant effects were observed on oxidative stress or autophagic flux, TUDCA alleviated hepatic inflammation associated with repeated carcinogen exposure. Furthermore, TUDCA dose dependently enhanced the cellular MTT metabolic activity, but not the cell proliferation rate in vitro. Importantly, administration of TUDCA in a therapeutic setting after tumour development did not alter the growth of orthotopic tumours or HepG2 xenografts.
Conclusions : These findings indicate that TUDCA attenuates hepatocarcinogenesis by suppression of carcinogen-induced ER stress-mediated cell death and inflammation without stimulation of tumour progression. Therefore, the chemical chaperone TUDCA could represent a novel chemopreventive agent for HCC.

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EFFECT OF A DIETARY WEIGHT LOSS INTERVENTION ON THE LIPID PROFILE OF OBESE INDIVIDUALS WITH SIGNS OF NON-ALCOHOLIC FATTY LIVER DISEASE : BEYOND STANDARD LIPIDS. A. Verrijken (1), S. Francque (2), H. Hilden (3), I. Mertens (4), C. Van Gils (4), E. Dirinck (4), K. Wouters (5), E. Van Marck (6), P. Michielsen (2), M. Taskinen (3), L. Van Gaal (4). (1) UZ Antwerpen, Edegem, Belgium, Endocrinoloy, Diabetology and Metabolic Diseases ; (2) UZ Antwerpen, Edegem, Belgium, Gastroenterology and Hepatology ; (3) Helsinki University Central Hospital and Biomedicum, Helsinki, Finland, Division of Cardiology, Department of Medicine ;

(4) UZ Antwerpen, Edegem, Belgium, Endocrinology, Diabetology and Metabolic Diseases ; (5) UZ Antwerpen, Edegem, Belgium, Scientific Coordination and Biostatistics ; (6) UZ Antwerpen, Edegem, Belgium, Pathology.

Introduction : Cardiovascular disease (CVD) is an important cause of morbidity and mortality in patients with non-alcoholic fatty liver disease (NAFLD). Different mechanisms linking CVD and NAFLD are being proposed including hyperinsulinemia, impaired thrombolysis, inflammation and dyslipidaemia.
Aim : The aim of this study was to assess an extensive lipid profile in obese patients with signs of NAFLD and to look at the impact of dietary weight loss.
Methods : Patients presenting at the obesity clinic underwent a metabolic and liver assessment. If NAFLD was suspected, liver biopsy was proposed (NASH CRN scoring system). After 6 months of dietary intervention, patients were re-evaluated, including an extensive lipid profile with various apolipoproteins, LDL and HDL subspecies, adiponectin and β-hydroxybutyrate.
Results : We selected 73 patients (75.3% female) that completed a 6-month weight loss program, with at baseline median BMI 35.1 kg/m² (Q1-Q3 : 32.4-39.8) and mean age 48 ± 12 y. In 69 patients (94.5%) at least one standard lipid parameter was disturbed at baseline. Biopsy proven liver steatosis was associated with smaller LDL ($p = 0.056$) and HDL particle size ($p = 0.040$). This was also reflected by the inverse associations between the liver scores for NAFLD/NASH and the LDL and HDL particle size. Serum levels of GGT ($p < 0.001$), Fatty Liver Index ($p < 0.001$), calculated liver percentage ($p < 0.001$) and NAFLD liver fat score ($p = 0.001$) were significantly higher in patients with a hypertriglyceridemic waist (marker of the atherogenic metabolic triad). After 6 months of diet patients achieved a mean weight loss of 9.1 ± 5.6% and most parameters of the lipid metabolism improved significantly, except for the HDL subspecies HDL2a ($p = 0.083$), HDL3a ($p = 0.487$) and HDL3c ($p = 0.342$) and ApoA1 ($p = 0.762$) which remained unchanged. Changes in lipids (TG, HDL, HDL2b, HDL3a, HDL3b, HDL mean particle size, ApoB, ApoE and RLP) were closely related to changes in visceral adipose tissue.
Conclusions : We confirm the proatherogenic lipid profile in NAFLD, with high total cholesterol, high LDL and smaller LDL peak particle size. This lipid profile is associated with markers of steatosis and fibrotic NASH, suggesting that dyslipidaemia may play a role in the link between NAFLD and CVD. Investigating the effect of weight loss on lipid metabolism in an obese population with evidence of NAFLD, we observed that weight loss improves most parameters of lipid metabolism during the first 6 months of diet.

INFUSION OF THIRD-PARTY MESENCHYMAL STROMAL CELLS AFTER LIVER TRANSPLANTATION : A PHASE I, OPEN-LABEL, CLINICAL STUDY.

O. Detry (1), M. Vandermeulen (2), M. Delbouille (2), A. Deroover (2), J. Somja (3), N. Bletard (3), A. Briquet (4), C. Lechanteur (5), Y. Beguin (5). (1) Centre Hospitalier Universitaire de Liège, Liège, Belgium, Dpt of Abdominal Surgery and Transplantation ; (2) Centre Hospitalier Universitaire de Liège, Liège, Belgium, Dpt of Abdominal Surgery & Transplantation ; (3) Centre Hospitalier Universitaire de Liège, Liège, Belgium, Dpt of Pathology ; (4) Centre Hospitalier Universitaire de Liège, Liège, Belgium, Dpt of Hematology ; (5) Centre Hospitalier Universitaire de Liège, Liège, Belgium, Dpt of Hematology.

Introduction : Mesenchymal stromal cells (MSC) are multipotent bone marrow progenitors that have demonstrated significant immunosuppressive effects in various in vivo and in vitro studies.
Aim : This study aimed to be the first evaluation of the safety and tolerability of MSC infusion after liver transplantation in a prospective, controlled phase-1 study.
Methods : Clinical grade MSCs were locally collected from the bone marrow of unrelated healthy donors. They were cultured in a GMP-compliant lab, underwent extensive quality controls and were frozen for storage in a MSC bank. When needed for patient treatment, MSC were thawed and intravenously injected into patients. 10 liver transplant recipients under standard immunosuppression (TAC-MMF-low dose steroids until day 30) received 1.5-3x106/kg MSC on post-operative day 3 ± 2. These patients were prospectively compared to a group of 10 control (MSC-) liver recipients. Primary endpoints were MSC infusion toxicity, and incidence of cancer and opportunistic infections at month 6. Secondary endpoints were patient and graft survivals and rejection at month 6, as well as the effects of MSC on recipients' immune function and on immunohistology of at month 6 graft biopsies.
Results : Results : No MSC infusional toxicity was observed. Both groups were comparable in terms of donor and recipient characteristics. There was no difference in primary end-points between control and MSC groups. No patient developed de novo cancer. There was no statistical difference in patient and graft survivals or in rejection rates. There was no graft rejection in the MSC group. Month-6 graft biopsies were not different according to Banff and fibrosis scores.
Conclusions : This phase 1 study showed excellent tolerability and safety of a single infusion of third-party MSC after liver transplantation. There were no graft safety issues and no excess of immunosuppression after MSC injection. Further analyses of consequences of MSC injection on the immune profile are needed. The possibility of avoiding calcineurin-

inhibitors with repeated MSC injections as main immunosuppressive therapy and/of tolerance induction by MSC infusion should be investigated by further studies.

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LIVER FIBROSIS EVALUATION USING REAL-TIME SHEAR WAVE ELASTOGRAPHY IN CHRONIC HEPATITIS C. W. Verlinden (1), S. Bourgeois (2), P. Gigase (2), C. Thienpont (2), L. Vonghia (1), T. Vanwolleghem (1), P. Michielsen (1), S. Francque (1). (1) UZ Antwerpen, Edegem, Belgium, Gastroenterology Hepatology ; (2) UZ Antwerpen, Edegem, Belgium, Gastroenterology.

Introduction : Evaluation of fibrosis stage in chronic hepatitis C patients (HCV) guides decision making of follow-up and therapy and is prognostically relevant. Liver biopsy is the gold standard, but has limitations which necessitate the search for noninvasive reliable methods of liver fibrosis assessment. Real-time shear wave elastography (SWE) is a recent, noninvasive tool to assess liver fibrosis by measuring liver stiffness (LS). Few studies have evaluated the accuracy of SWE in HCV, but excluded HIV co-infected patients.
Aim : To assess the diagnostic performance of LS, measured by SWE, as a noninvasive predictor of liver fibrosis in HCV using liver biopsy as a gold standard and to evaluate a potential difference between mono-infected and co-infected patients.
Methods : We measured LS in patients with HCV undergoing liver biopsy. Fibrosis was staged according to the METAVIR scoring system. Analyses of receiver operating characteristic (ROC) curve were performed to calculate optimal area under the ROC curve (AUROC) for F0-F1 vs F2-F4, F0-F2 vs F3-F4 and F0-F3 vs F4.
Results : 80 patients (53 mono-infected, 27 co-infected) were included. Distribution of fibrosis was 12% F0, 41% F1, 20% F2, 18% F3 and 9% F4. There was a significant correlation between LS and fibrosis stage (Spearman's Rho 0.69, $p < 0.0001$). AUROCs were 0.84, 0.88 and 0.98 when comparing F0-F1 vs F2-F4, F0-F2 vs F3-F4 and F0-F3 vs F4, respectively. Suggested cut-off values are 8.5kPa for F2, 10.4kPa for F3 and 11.3kPa for F4 with a sensitivity and specificity of 81% and 84%, 81% and 95% and 100% and 90%, respectively. There was no significant difference between LS values of mono-infected compared to co-infected patients ($p = 0.811$).
Conclusions : This is the first study of LS by SWE that includes HCV-HIV co-infected patients. SWE of the liver is a reliable noninvasive predictor of liver fibrosis in HCV patients. There is no significant difference between mono- and co-infected patients, hence the same cut-off values can be used for both groups.

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HEALTH-RELATED QUALITY OF LIFE IS IMPROVED AFTER LIVER TRANSPLANTATION AND IS RELATED TO DISEASE ACCEPTANCE, HELPLESSNESS AND PERCEIVED DISEASE BENEFITS. W. Develtere (1), L. Onghena (1), X. Rogiers (2), R. Troisi (2), F. Berrevoet (2), A. Vanlander (2), A. Geerts (1), H. Van Vlierberghe (2), X. Verhelst (3), C. Poppe (4). (1) UZ Gent, Gent, Belgium, Department of Gastroenterology and Hepatology ; (2) UZ Gent, Gent, Belgium, Department of Hepatobiliary Surgery and Transplant Surgery ; (3) UZ Gent, Gent, Belgium, Department of Gastroenteroly and Hepatology ; (4) UZ Gent, Gent, Belgium, Transplantation Center.

Introduction : Liver transplantation (LT) is the only curative treatment for end-stage liver disease with excellent long-term outcomes, regarding morbidity and mortality rates. However, an important outcome parameter is health-related quality of life (QoL). Improvement of QoL has been described after liver transplantation.
Aim : We wanted to confirm these findings with specific attention for psychological parameters such as acceptance, helplessness and perceived disease benefits.
Methods : We performed a cross-sectional study (pre-post design) in a liver transplant unit. Self-report questionnaires were conducted in 120 patients with end-stage liver disease (ESLD) : 60 patients pre-transplantation and 60 post-transplantation. A control group of 57 patients with ESLD without the perspective of a transplantation also completed the same questionnaires on QoL (SF-36), acceptance (ICQ), helplessness (ICQ) and disease benefits (ICQ). Clinical and socio-demographical data were collected from the medical files. Data were analysed using the Mann-Whitney U test and Spearman's rank correlation coefficient.
Results : The studied groups of patients were comparable regarding age and MELD score, but the control group was significantly older ($p = 0.09$). We observed a significant increase in QoL as soon as 3 months after LT ($p = 0.046$) as well regarding the mental component summary scale ($p = 0.029$) as the physical component summary scale ($p = 0.033$). After liver transplantation, patients report more acceptance ($p < 0.01$) and disease benefits ($p < 0.0001$) and a decrease in helplessness ($p < 0.05$). General QoL is positively significant correlated ($p < 0.001$) with acceptance ($rs = 0.737$) and disease benefits ($rs = 0.494$), and negatively with helplessness ($rs = -0.828$).

Conclusions : These data confirm an increase of QoL starting from 3 months after liver transplantation. We observed a better acceptance of their illness and more benefits of the illness after transplantation. Patients also report to feel less helpless, but the decrease is less distinct. We also found a high association between the QoL and helplessness.We assume that these findings indicate that patients receive a lot of attention and support for their illness after transplantation but still feel slightly uncertain and helpless about the future, regarding coping with it (medication, diet,...). These aspects deserve more attention and could give new directions in the approach of liver patients after transplantation. Further research on this matter is necessary.

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MEASUREMENT OF SPLEEN AND LIVER STIFFNESS BY SHEAR WAVE ELASTOGRAPHY TO NON-INVASIVELY EVALUATE HEPATIC VENOUS PRESSURE GRADIENT AND PORTAL HYPERTENSION. L. Vonghia (1), W. Verlinden (1), T. Vanwolleghem (1), P. Michielsen (1), S. Francque (1). (1) UZ Antwerpen, Edegem, Belgium, Gastroenterology Hepatology.

Introduction : Hepatic venous pressure gradient (HVPG) is the gold standard used to determine the degree of sinusoidal portal hypertension and an important prognostic factor for patients with cirrhosis. HVPG can only be determined invasively in specialized centers. Recent data demonstrated that measurement of spleen stiffness (SS) and liver stiffness (LS) by transient elastography correlates with HVPG levels. To date, the performance of swear wave elastography (SWE) in this setting has not been reported.
Aim : To assess the diagnostic performance of SS and LS, measured by SWE, as noninvasive predictor of portal hypertension (PH) using HVPG as the gold standard.
Methods : We measured SS and LS in patients with liver disease undergoing HVPG measurement.
Results : Between September 2013 and October 2014, 63 patients were consecutively included. 67% were male and mean age was 55.3 ± 12.4 years. Main aetiologies of liver disease were alcohol (41%), non-alcoholic fatty liver disease (29%), hepatitis B (14%) and autoimmune hepatitis (8%). Linear regression showed a significant correlation between HVPG and SS (R2 0.433, $p < 0.001$), LS (R2 0.468, $p < 0.0001$) and SS/LS combined (R2 0.540, $p < 0.0001$). AUROC of SS for HVPG < 10 mmHg versus ≥10 mmHg and HVPG < 12 mmHg versus ≥12 mmHg was 0.86 and 0.84, respectively. A SS cut-off value of 29.6 kPa had a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 74%, 90%, 85% and 81%, and of 78%, 82%, 70% and 88% for HVPG ≥10 mmHg and HVPG ≥12 mmHg, respectively. AUROC of LS for HVPG < 10 mmHg versus ≥10 mmHg and HVPG < 12 mmHg versus ≥12 mmHg was 0.85 and 0.80, respectively. A LS cut-off value of 15.9 kPa had a sensitivity, specificity, PPV and NPV of 96%, 69%, 73% and 96%, and of 95%, 56%, 54% and 96% for HVPG ≥10 mmHg and HVPG ≥12 mmHg, respectively.
Conclusions : This is the first study of SWE measurement of SS and correlation with HVPG. Measurement of SS can be used for noninvasive assessment of PH, and is a slightly better predictor than LS.

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SIMEPREVIR WITH PEGIFN/RIBAVIRIN FOR CHRONIC HCV INFECTION SHORTENS TIME WITH PATIENT-REPORTED SYMPTOMS AND IMPAIRMENT IN QOL : ATTAIN STUDY RESULTS. J. Scott (1), K. Cerri (2), U. Sbarigia (2), C. Corbett (3), M. Fu (4), W. Jessner (3). (1) Janssen Global Services LLC, High Wycombe, United Kingdom ; (2) Janssen Pharmaceutica NV, Beerse, Belgium ; (3) Janssen Research and Development, Beerse, Belgium ; [4] Janssen Research and Development, PA, USA.

Introduction : Fatigue, skin and depressive symptoms are common in chronic hepatitis C virus (HCV)-infected patients, and can impair functioning and quality of life (QoL). Patient-reported outcomes (PRO) provide the patient's perspective on HCV therapy.
Aim : ATTAIN, a Phase III, randomised, double-blind study compared simeprevir (SMV) plus peginterferon/ribavirin (PR) vs telaprevir (TVR) plus PR in HCV genotype 1-infected patients with compensated liver disease who were null or partial responders to prior PR.
Methods : Patients received SMV (150mg once-daily) or TVR (750mg three-times-daily) plus PR for 12wks, then PR alone for 36wks. Patients completed PRO questionnaires to rate severity of fatigue (Fatigue Severity Scale [FSS]), skin symptoms (Skindex-16), depressive symptoms (Center for Epidemiologic Studies Depression [CES-D]), work productivity and daily activity impairment (hepatitis C-specific version of Work Productivity and Activity Impairment score, WPAI) and QOL (EuroQoL 5 Dimension, EQ-5D) at baseline (BL) and throughout the study. PRO data analyses compared area-under-the-curve (BL to Wk60, AUC60 ; BL to Wk12, AUC12).
Results : Mean scores for all PRO scores (763 patients, SMV = 379, TVR = 384) worsened in both groups from BL to Wk12, were generally stable from Wk16 to Wk48 and returned close to BL values from Wk60 onwards. As AUC60

analyses did not show a statistically significant difference between groups in FSS, treatment comparisons for other PRO endpoints were not analysed statistically in keeping with the hierarchical testing procedure specified in the statistical analysis plan. Post-hoc AUC12 analyses significantly favoured SMV vs TVR for FSS ($p = 0.003$, clinically meaningful difference), WPAI Daily Activity Impairment ($p = 0.022$), EQ-5D VAS ($p < 0.001$), and maximum Skindex-16 score ($p = 0.0087$). Trends for lower CES-D and WPAI Work impairment scores were observed for AUC12. There were fewer serious adverse events (AEs), treatment-related AEs, AEs leading to permanent stop and anaemia AEs (grade 3 and SAEs) reported with SMV vs TVR.
Conclusions : During the initial 12-week triple treatment period, patients on SMV/PR reported significantly less fatigue and skin symptoms, and less impairment in daily activities and QoL vs TVR/PR patients, consistent with the better safety profile of SMV vs TVR. Significant differences in AUC12 in favour of SMV were not replicated in AUC60 analyses due to longer PR therapy duration, which dominated the overall results.

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ONCE-DAILY SIMEPREVIR (TMC435) WITH PEGINTERFERON/RIBAVIRIN IN TREATMENT-NAÏVE OR TREATMENT-EXPERIENCED CHRONIC HCV GENOTYPE 4-INFECTED PATIENTS : SVR12 RESULTS OF A PHASE III TRIAL. C. Moreno (1), C. Hezode (2), P. Marcellin (3), S. Bourgeois (4), S. Francque (5), D. Samuel (6), F. Zoulim (7), J. Grange (8), U. Shukla (9), O. Lenz (9), S. Ouwerkerk-Mahadevan (10), M. Peeters (11), M. Beumont-Mauviel (11), W. Jessner (11). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium ; (2) Hôpital Henri Mondor, Créteil, France ; (3) Hôpital Beaujon, Clichy, France ; (4) ZNA Campus Stuivenberg, Antwerp, Belgium ; (5) UZ Antwerpen, Edegem, Belgium ; (6) Hôpital Paul-Brousse, Villejuif, France ; (7) Hôpital de la Croix Rousse, Lyon, France ; (8) Hôpital Tenon, Paris, France ; (9) Janssen Infectious Diseases BVBA, Beerse, Belgium ; (10) Janssen Research & Development, Beerse, Belgium ; (11) Janssen Infectious Diseases BVBA, Beerse, Belgium,

Introduction : Simeprevir (SMV) is a one pill, once-daily (QD) HCV NS3/4A protease inhibitor with antiviral activity against HCV genotype (GT) 1 and 4 infection.
Aim : We present SVR12 results from RESTORE, a Phase III, multicentre, uncontrolled, open-label study evaluating SMV+peginterferon-α-2a/ribavirin (PR) in treatment-naïve/-experienced patients with chronic HCV GT4 infection (NCT01567735).
Methods : Treatment-naïve patients and relapsers received SMV 150mg QD+PR (12 weeks), followed by PR alone (12/36 weeks), using response-guided therapy (RGT) criteria. Prior non-responder patients received SMV 150mg QD+PR (12 weeks), followed by PR (36 weeks). Primary efficacy endpoint : SVR12.
Results : 107 patients received treatment (male, 78.5% ; median age, 49 years ; Black, 28.0% ; METAVIR F4, 28.8% ; IL28B non-CC, 92.5% ; GT4a/4d/4 other, 42.5/23.6/33.9% ; treatment-naïve, n = 35 ; relapsers, n = 22 ; partial responders, n = 10 ; null-responders, n = 40). The percentage of patients reaching SVR12 overall was 65.4% (70/107), 82.9% (29/35) for the treatment naïve, 86.4% (19/22) for the relapsers, 60% (6/10) for the partial responders and 40% (16/40) for the null responders. Among METAVIR F4 patients, 46.7% and 62.1% achieved SVR12 and RVR, respectively. SVR12 rates in IL28B CT and TT patients were 65.6% and 59.5%, while 65.5% and 62.2% had RVR, respectively. Among those meeting RGT criteria, no patients experienced on-treatment failure and 3 patients experienced viral relapse (treatment-naïve, n = 2 ; relapsers, n = 1). Adverse events (AEs, Weeks 1–12) were mainly grade 1/2. Serious AEs were infrequent (5 patients [4.7%] ; no deaths) and considered unrelated to SMV. Most frequent (> 30% of patients) AEs included influenza-like illness, asthenia and fatigue.
Conclusions : SMV 150mg QD (12 weeks+PR) was well tolerated and effective in HCV GT4-infected patients, consistent with previous observations in HCV GT1-infected patients.

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SIMEPREVIR (TMC435) WITH PEGINTERFERON/RIBAVIRIN FOR TREATMENT OF CHRONIC HCV GENOTYPE 1 INFECTION IN EUROPEAN PATIENTS WHO RELAPSED AFTER PREVIOUS INTERFERON-BASED THERAPY : THE PROMISE TRIAL. X. Forns (1), E. Lawitz (2), S. Zeuzem (3), E. Gane (4), J. Bronowicki (5), P. Andreone (6), A. Horban (7), A. Brown (8), M. Peeters (9), O. Lenz (9), S. Ouwerkerk-Mahadevan (10), G. De La Rosa (11), R. Kalmeijer (12), M. Beumont-Mauviel (9). (1) Liver Unit, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain, 2] Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA ; (3) J.W. Goethe University Hospital, Frankfurt, Germany ; (4) Auckland Hospital Clinical Studies Unit, Auckland, New Zealand ; (5) INSERM U954, Université de Lorraine, Centre Hospitalier Universitaire de Nancy, Vandoeuvre Les Nancy, France ; (6) Dipartimento di Scienze Mediche e Chirurgiche, University of Bologna, Bologna, Italy ; (7) Medical University of Warsaw, Wolska, Warsaw, Poland ; (8) Imperial College Healthcare NHS Trust,

London, UK ; (9) Janssen Infectious Diseases BVBA, Beerse, Belgium ; (10) Janssen Research & Development, Beerse, Belgium ; (11) Janssen Global Services, LLC, Titusville, NJ, USA ; (12) Janssen Research & Development, Titusville, NJ, USA.

Introduction : Simeprevir (SMV) is a one pill, once-daily (QD), oral HCV NS3/4A protease inhibitor.
Aim : PROMISE was a randomised, double-blind, Phase III trial evaluating SMV plus peginterferon α-2a/ribavirin (PR) vs placebo (PBO)/PR in genotype (GT)1 HCV patients who relapsed after previous interferon-based therapy. Efficacy and safety data from PROMISE are presented for European patients.
Methods : Patients received SMV 150mg QD (12wks) with PR (24 or 48wks ; based on response-guided therapy), or PBO (12wks) plus PR (48wks). Patients were stratified by HCV GT1 subtype and IL28B GT. Primary efficacy endpoint : sustained virological response at 12wks (SVR12).
Results : 274/393 (69.7%) patients were European (male 64.6%, white 97.8%, HCV GT1a/1b 29.2/70.4%, IL28B CC/CT/TT 22.6/65.3/12.0%, METAVIR F3/F4 14.7/14.0%) ; 18.5% of European HCV GT1a patients had Q80K. SVR12 was higher with SMV/PR versus PBO/PR in the European population overall (87.5% (161/184) vs. 44.4% (40/90)) ($p < 0.001$). For all patients these numbers were : 206/260 (79.2%) vs. 49/133 (36.8%) ($p < 0.001$). In patients on SMV/PR who met response-guided therapy criteria, SVR12 was 90.8% (157/173). SVR12 for SMV/PR vs. PBO/PR in IL28B genotype CC was 38/41 (92.7%) vs. 13/21 (61.9%) ; in IL28B genotype CT : 106/121 (87.6%) vs. 25/58 (43.1%) ; in IL28B genotype TT : 17/22 (77.3%) vs. 2/11 (18.2%). For genotype subgroups these numbers were : HCV GT 1a 52/59 (88.1%) vs. 8/22 (36.4%) ; HCV GT 1a with Q80K : 6/8 (75.0%) vs. 4/7 (57.1%) ; HCV GT 1a without Q80K : 45/50 (90.0%) vs. 4/15 (26.7%) ; HCV GT 1b : 109/125 (87.2%) vs.32/68 (47.1%). For METAVIR subgroups, these numbers were : METAVIR score F0-F2 : 105/119 (88.2%) vs. 34/70 (48.6%) ; METAVIR score F3 : 26/30 (86.7%) vs. 2/9 (22.2%) ; METAVIR score F4 : 23/27 (85.2%) vs. 3/10 (30.0%). 173/184 SMV/PR patients (94.0%) were eligible for 24wks PR ; 90.8% of these patients achieved SVR12. 81.5% of SMV/PR- and 3.4% of PBO/PR-treated patients achieved rapid virological response. On-treatment failure (3.3% vs 20.0%) and viral relapse rates (11.9% vs 43.5%) were lower with SMV/PR versus PBO/PR. In the SMV/PR arm (Wks1–12), most common AEs included fatigue, headache and influenza-like illness. Most were Grade 1/2 (Grade 3/4, 19.6%) ; no AEs resulted in SMV withdrawal. SAEs possibly related to SMV were infrequent (1.1%). No fatal AEs occurred.
Conclusions : SMV confers clinical benefit and is generally well tolerated in European HCV GT1-infected patients.

SIMEPREVIR (TMC435) WITH PEGINTERFERON/RIBAVIRIN FOR TREATMENT OF CHRONIC HCV GENOTYPE 1 INFECTION IN TREATMENT-NAÏVE EUROPEAN PATIENTS IN THE QUEST-1 AND QUEST-2 PHASE III TRIALS. G. Foster (1), I. Jacobson (2), G. Dore (3), M. Fried (4), M. Manns (5), P. Marcellin (6), F. Poordad (7), E. De Araujo (8), M. Peeters (9), O. Lenz (9), S. Ouwerkerk-Mahadevan (10), G. De La Rosa (11), R. Kalmeijer (12), R. Sinha (9), M. Beumont-Mauviel (9). (1) Queen Mary's, University of London, London, UK ; (2) Weill Cornell Medical College, New York, NY, USA ; (3) The Kirby Institute, University of New South Wales, Darlinghurst, NSW, Australia ; (4) University of North Carolina at Chapel Hill, NC, USA ; (5) Medizinische Hochschule Hannover, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany ; [6] Hôpital Beaujon, Service d'Hépatologie, INSERM U-481, Clichy, France ; (7) Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA ; (8) Hospital das Clinicas of the University of São Paulo School of Medicine, Faculty of Medicine, University of São Paulo, Sao Paulo, SP, Brazil ; (9) Janssen Infectious Diseases BVBA, Beerse, Belgium, Belgium ; [10] Janssen Research & Development, Beerse, Belgium ; (11) Janssen Global Services, LLC, Titusville, NJ, USA ; [12] Janssen Research & Development, Titusville, NJ, USA.

Introduction : Simeprevir (SMV) is a one pill, once-daily (QD), oral HCV NS3/4A protease inhibitor.
Aim : QUEST-1 and QUEST-2 were randomised, double-blind, Phase III trials evaluating SMV plus peginterferon α-2a (QUEST-1) or peginterferon α-2a/2b (QUEST-2) plus ribavirin (PR) versus placebo (PBO)/PR in treatment-naïve genotype (GT) 1 HCV patients. Pooled efficacy and safety data from QUEST-1/QUEST-2 are presented for European patients.
Methods : Patients received SMV 150 mg QD (12wks) with PR (24 or 48 wks ; based on response-guided therapy, RGT), or PBO (12wks) plus PR (48wks). Primary efficacy endpoint : sustained virological response at 12wks (SVR12).
Results : 418/785 (53.2%) patients were European (male : 57.7%, white 96.4%, HCV GT1a/1b 30.1/68.7%, 5.3% GT1a Q80K, IL28B CC/CT/TT 28.0/59.8/12.2%, METAVIR F3/F4 12.7/7.3%). SVR12 was higher with SMV/PR versus PBO/PR in European patients overall 86.6% (239/276) versus 52.8% (75/142) ($p < 0.001$). For all patients, these numbers were 80.4% (419/521) vs. 50.0% (132/264) ($p < 0.001$). In patients on SMV/PR who met response-guided therapy criteria, SVR12 was 91.7% (231/252). SVR12 for SMV/PR vs. PBO/PR in IL28B genotype CC was 72/75 (96.0%) vs. 33/42 (78.6%) ; IL28B genotype CT : 143/166 (86.1) vs. 37/84 (44.0) ; IL28B genotype TT : 24/35 (68.6%) vs. 5/16 (31.3%). For genotype subgroups, these numbers were : HCV GT 1a/other : 67/84 (79.8%) vs. 23/47 (48.9%) ; HCV GT 1a with Q80K : 9/14 (64.3%) vs. 4/8 (50.0%) ; HCV GT 1a without Q80K : 56/68 (82.4%) vs. 17/36 (47.2%) ; HCV GT

1b : 172/192 (89.6%) vs. 52/95 (54.7%). For METAVIR subgroups, these numbers were : METAVIR score F0–F2 : 191/217 (88.0%) vs. 64/110 (58.2%) ; METAVIR score F3 : 29/36 (80.6%) vs. 7/16 (43.8%) ; METAVIR score F4 : 10/14 (71.4%) vs. 4/16 (25.0%). 91.3% of SMV/PR-treated patients were eligible for 24 weeks of PR ; 91.7% of these patients achieved SVR12. 82.2% and 13.7% of SMV/PR- and PBO/PR-treated patients, respectively, achieved rapid virological response. Fewer SMV/PR-treated patients experienced on-treatment failure (5.8% vs PBO/PR 29.6%) or viral relapse (8.1% vs PBO/PR 24.2%). During SMV/PR treatment (Wks 1–12), 62.0% of patients had ≥1 AE possibly SMV-related. AEs (SMV/PR group) were mostly Grade 1/2 (Grade 3/4, 25.0%). SAEs possibly SMV-related (0.4%) and SMV discontinuations due to ≥1 AE (2.2%) were infrequent. No fatal AEs occurred.
Conclusions : SMV/PR confers clinical benefit versus PBO/PR and is well tolerated in European HCV GT1-infected patients.

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RENAL FUNCTION IN HCV GENOTYPE 1-INFECTED TREATMENT-NAÏVE PATIENTS RECEIVING SIMEPREVIR IN COMBINATION WITH PEG-IFN AND RIBAVIRIN : A POST-HOC ANALYSIS. S. Mauss (1), M. Buti (2), C. Moreno (3), G. Foster (4), R. De Masi (5), A. Baldini (6), M. Schlag (7), G. De La Rosa (8), J. Witek (5). (1) Center for HIV and Hepatogastroenterology, Duesseldorf, Germany ; (2) Liver Unit, Department of Internal Medicine, Hospital Valle Hebron and Ciberehd del Institut Carlos III, Barcelona, Spain ; (3) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology and Hepatopancreatology ; (4) Queen Mary, University of London, the Liver Unit, London, UK ; (5) Janssen Research & Development LLC, Titusville, New Jersey, USA ; (6) Janssen, Paris, France ; (7) Janssen Cilag, Vienna, Austria ; (8) Janssen Global Services, LLC, Titusville, NJ, USA.

Introduction : Several studies have reported on an association between chronic hepatitis C (CHC) and the development of chronic kidney disease. Treatment with certain HCV protease inhibitors has been associated with a reduction in glomerular filtration rate (GFR) during treatment.
Aim : This analysis examined the renal function in patients treated with simeprevir, an NS3/4A HCV protease inhibitor, or placebo in combination with Peg-IFN/ribavirin (PR) in HCV genotype-1-infected, treatment-naïve patients.
Methods : Data were pooled from two trials of treatment-naïve patients with CHC who received simeprevir and PR for 12 weeks then PR alone for 12 or 36 weeks (n = 521), or placebo and PR for 48 weeks (n = 264) (QUEST-1 and -2). Estimated GFR (eGFR) (Modification of Diet in Renal Disease [MDRD]) was measured at baseline and at regular intervals during the studies. Exclusion criteria included plasma creatinine levels of > 1.5 mg/dL, patients with disease that could be exacerbated by PR therapy (judged by clinical investigator), and any clinically significant disease or findings during screening that could compromise patient safety or could interfere with the patient's participation/ completion of the study.
Results : Baseline characteristics for the pooled population (n = 785) were well balanced. In summary, 44% were female and 91% were Caucasian (7% Black or African American). Median age was 47 years (range : 18–73 years). Fibrosis stage for the pooled population was : 74% METAVIR F0–F2, 16% F3 and 10% F4. There was a balance of genotype 1 subtypes (49% genotype 1a and 51% 1b). The majority of patients had non-CC IL28B (71%). Mean (SE) eGFR at baseline was 87.22 (0.73) [n = 521] and 87.51 (1.08) [n = 264] mL/min/1.73m2 for simeprevir + PR and placebo + PR, respectively. By on-treatment Week 12, eGFR increased in both treatment groups (94.46 (0.91) [n = 496] and 92.03 (1.27) [n = 256] mL/min/1.73m2 for simeprevir + PR and placebo + PR, respectively), with a change from baseline of 7.47 (0.61) and 4.59 (0.90). By on-treatment Week 24, the increase in eGFR had plateaued in both groups (94.34 (0.91) [n = 481] and 93.36 (1.43) [n = 210] mL/min/1.73m2 for simeprevir + PR and placebo + PR, respectively), with a change from baseline of 7.14 (0.66) and 5.71 (1.02).
Conclusions : Triple therapy with simeprevir was associated with an increase in renal function as was placebo + PR. These findings indicate that simeprevir has a good renal safety profile.

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PREVALENCE OF THE HEPATITIS C VIRUS POLYMORPHISM Q80K IN A POOLED ANALYSIS OF G1 PATIENTS FROM TELAPREVIR AND SIMEPREVIR PHASE II/III CLINICAL TRIALS. O. Lenz (1), C. Sarrazin (2), E. Lathouwers (1), M. Peeters (1), A. Buelens (1), J. Witek (3), Y. Wyckmans (4), B. Fevery (1), T. Verbinnen (1), A. Ghys (1), M. Schlag (5), A. Baldini (6), S. De Meyer (1). (1) Janssen Infectious Diseases BVBA, Beerse, Belgium ; (2) Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, Germany ; [3] Janssen Research & Development LLC, Titusville, USA ; [4], Janssen, Beerse, Belgium [5] Janssen-Cilag, Vienna, Austria ; [6] Janssen, Paris, France.
Introduction : The hepatitis C (HCV) NS3 polymorphism Q80K can be found in patients with HCV genotype 1 (G1) and has been associated with a reduced treatment response to simeprevir (SMV) + pegylated interferon/ribavirin (PR) in

HCV G1a patients (1). However, the prevalence of the Q80K polymorphism at baseline varies significantly between G1 subtypes and geographical regions (2).
Aim : We conducted a post-hoc meta-analysis of Q80K polymorphism prevalence among European patients enrolled in SMV and telaprevir (TVR) studies.
Methods : Demographic and baseline patient characteristics were pooled from 14 phase II and III SMV and TVR clinical studies. Data from patients enrolled from European countries were analysed. Baseline HCV NS3/4A protease sequences (population sequencing) were analysed to determine the prevalence of the Q80K polymorphism.
Results : The analysed population comprised 3462 patients. Countries included in the analysis were Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, Ukraine and UK. Of the pooled population, 35.9%, 63.5% and 0.7% had G1a, G1b and other HCV G1 subtypes, respectively. Sequencing data were available for 3349 (96.7%) patients. Of these patients, 250 (7.5%) had the Q80K polymorphism at baseline. In patients with G1a, G1b and other HCV G1 subtypes, 19.8% (237/1200), 0.5% (11/2138) and 18.2% (2/11) had the Q80K polymorphism, respectively. Twelve countries had sequencing data available for ≥20 patients with G1a. Among these countries, the prevalence of the Q80K polymorphism at baseline in HCV G1 patients ranged from 2.7% (7/263) in Spain to 18.2% (36/198) in the UK, though there was a greater variation in Q80K polymorphism prevalence when G1a patients were considered alone (4.8% (1/21) in Norway to 75.0% (15/20) in Poland). Prevalence of the Q80K polymorphism was not associated with any other baseline factor besides HCV G1 subtype and country.
Conclusions : A previous study reported a Q80K polymorphism prevalence of 34.4% (185/538) in North American HCV G1-infected patients (2). Based on our extensive analysis, there is a considerably lower prevalence of the Q80K polymorphism at baseline among patients infected with HCV G1 in European countries. Within Europe, the prevalence varies considerably.

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SENSING OF CARBOHYDRATES BY THE GHRELIN CELL IS POLARIZED AND OCCURS IN THE SMALL INTESTINE. S. Steensels (1), L. Vancleef (1), I. Depoortere (1). (1) KU Leuven, Leuven, Belgium, Targid.

Introduction : Carbohydrate administration in healthy volunteers results in the decrease of the 'hunger hormone' ghrelin, an octanoylated 28 amino acid peptide produced in the stomach, which stimulates food intake and increases body weight. Recent evidence suggests that taste receptors on endocrine cells, similar to those on the tongue, regulate the release of hormones in response to nutrients. Studies have shown that the ghrelin cell is co-localized with the sweet taste receptor, TAS1R2-TAS1R3, and the gustatory G-protein, gustducin, both involved in the sensing of carbohydrates by endocrine cells.
Aim : 1) To compare the dose-dependent effects of glucose on ghrelin release in the stomach and duodenum in vitro and in vivo in mice and 2) to determine whether sensing of glucose by the ghrelin cell is mediated via a-gustducin and occurs via the luminal or blood-born direction.
Methods : Mouse stomach ghrelinoma cells were stimulated with D-glucose at different concentrations (1-200mM) for 3 hours. Mouse intestinal stomach and jejunal segments were stimulated with 200mM D-glucose. In vivo, wildtype (WT) and a -gustducin knockout mice (a-gust-/-) were gavaged with 4g/kg D-glucose. In addition, WT mice were intravenously (IV) injected with 1g/kg D-glucose. Ghrelin levels were determined in culture medium, plasma and gut tissue extracts by radioimmunoassay.
Results : In ghrelinoma cells, D-glucose increased octanoyl ghrelin release with 32% at low concentrations (10mM) and decreased octanoyl ghrelin levels with 41% at high concentrations (200mM). Incubation of jejunal segments with 200 mM D-glucose decreased ($P < 0.05$) octanoyl ghrelin release from 36 ± 6 to 17 ± 2 pg/mg dry weight but did not affect octanoyl ghrelin release from segments of the corpus (control : 7.2 ± 0.5 vs D-glucose : 7.6 ± 0.4 pg/mg dry weight). In both WT and a-gust-/- mice gavage of D-glucose decreased ($P < 0.05$) plasma octanoyl ghrelin levels to a similar extent (WT : 54%, a-gust-/- : 67%). In both genotypes this was accompanied by an increase ($P < 0.05$) in duodenal ghrelin content from 692 ± 26 to 962 ± 105 pg/mg protein in WT and from 899 ± 99 to 1364 ± 112 pg/mg protein in a-gust-/- mice. Stomach ghrelin content was not affected (WT : from 85 ± 4 to 100 ± 13, a-gust-/- : from 83 ± 16 to 75 ± 12 ng/mg protein in a-gust-/-). IV administration of D-glucose neither affected plasma octanoyl ghrelin levels (control : 191 ± 31, D-glucose : 156 ± 56 pg/ml) nor tissue octanoyl ghrelin content.
Conclusions : D-glucose inhibits ghrelin release after acute administration. The sensing of D-glucose is polarized and occurs via the lumen, where it is sensed by ghrelin cells in the duodenum. a-gustducin is not involved in the sensing of D-glucose.

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SPECTRUM OF LIVER FUNCTION TESTS AMONG THE PATIENTS WITH HEPATITIS AT THE TIME OF DIAGNOSIS. P. Risal. Dhulikhel Hospital, Kathmandu University Hospital, Dhulikhel, Kavre, Nepal, Department of Biochemistry.

Introduction : Viral hepatitis remains silent or may show sign of jaundice, but if untreated, hepatitis B and C may become chronic, leading to cirrhosis or cancer of liver. Although, hepatitis A and E gets better on its own, children and pregnant women are at high risk of acute liver failure. Thus, early diagnosis and management is very important. Liver function tests are usually done to diagnose and monitor disease. Due to ignorance and other factors, health care utilization is limited among people of Nepal. Therefore, some patients may have severe impairment of liver functions at the time of its diagnosis.
Aim : This study was conducted so that public awareness could be made and on time management could be done to reduce morbidity and mortality.
Methods : Retrospective study was conducted at Kathmandu University hospital. Blood samples were obtained by vein puncture and diagnosis of viral hepatitis was done by using ELISA method. Liver function tests were carried out by using automated techniques. Patients with different viral infections were divided into two groups : hepatitis A and E (Group A) and hepatitis B and C (Group B).
Results : Serum bilirubin level was significantly higher in Group A, compared to Group B. Liver enzyme, aspartate transaminase (AST) and alanine transaminase (ALT) was found high in Group A (100% vs. 48%), compared to Group B. Patients in Group A exhibit significantly higher ALT (1318.3 ± 1472 IU/L vs. 99.1 ± 123.8 IU/L), AST (1318.3 ± 1472 IU/L vs. 85.7 ± 111.8 IU/L) and alkaline phosphatase (ALP) (211.8 ± 104.2 IU/L vs. 142.4 ± 74.2 IU/L), compared to Group B.
Conclusions : In conclusion, majority of the patients with viral hepatitis showed deranged liver function tests at the time of its diagnosis and among which ALT and AST being most altered parameters.

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THE RELATIONSHIP BETWEEN THE DISTRIBUTION OF SUSHEPATIC VEIN INVOLVEMENT AND THE UNDERLYING PRO-THROMBOTIC RISK FACTOR IN PATIENTS WITH BUDD-CHIARI SYNDROME. P. Martens (1), G. Maleux (2), T. Devos (3), D. Monbaliu (4), S. Heye (2), C. Verslype (5), W. Laleman (5), D. Cassiman (5), S. Van Der Merwe (5), W. Van Steenbergen (5), W. Van Steenbergen (5), I. Jochmans (4), R. Aerts (4), J. Pirenne (4), F. Nevens (5). (1) UZ Leuven, Leuven, Belgium, Division of Liver and Biliopancreatic disorders ; (2) UZ Leuven, Leuven, Belgium, Division of Interventional Radiology ; (3) UZ Leuven, Leuven, Belgium, Division of Hematology ; (4) UZ Leuven, Leuven, Belgium, Division of Abdominal Transplantation Surgery ; (5) UZ Leuven, Leuven, Belgium, Division of Liver and Biliopancreatic Disorders.

Introduction : Literature suggests that patients with an underlying myeloproliferative disorder (MPD) as pro-thrombotic risk factor are challenged with a more severe form of Budd-Chiari syndrome. However this more severe form can be mitigated with available therapies. Transhepatic intrajugular portosystemic shunt (TIPSS) has become mainstay of treatment for patients with Budd-Chiari syndrome. TIPSS however becomes technically less feasible when all hepatic veins are occluded.
Aim : The aim of our study was to investigate the relationship between the underlying pro-thrombotic condition and the distribution of sushepatic vein involvement.
Methods : We retrospectively collected date from Budd-Chiari patients diagnosed and treated at the University Hospital KU Leuven. All patients were diagnosed with Budd-Chiari syndrome according to criteria published in the AASLD 2009 guideline for vascular disorders of the liver. Additional tomographic imaging was used to delineate the distribution of the sushepatic veins. Patients were subdivided in two dichotomous groups, presence of a MPD as pro-thrombotic risk factor (yes or no), and presence of ≥1 patent sushepatic vein (yes or no). Statistical analysis was done with the Chi-square test.
Results : A total of 33 patients with Budd-Chiari syndrome were identified in which all aforementioned data was available. Table 1 shows the dichotomous distribution according to the presence of a MPD and sushepatic vein involvement. Chi-square analysis indicates that patients presenting with all three sushepatic veins occluded more often have an underlying MPD (p = 0,011). Hepatic vein patency 0 ≥1 Affected patients 20/33 (61%) 13/33 (38%) Underlying JAK2 14/20 (70%) 3/13 (23%)
Conclusions : This analysis indicates that Budd-Chiari patients presenting with all sushepatic veins occluded more often have an underlying MPD. This date extends the current knowledge that patients with an MPD not only have a propensity towards a more severe form of Budd-Chiari, but also are less suitable candidates for classic “Transhepatic TIPSS”. Because “Transhepatic TIPSS” is not technically possible with all three occluded sushepatic veins, these patients often require “Transcaval TIPSS” (associated with more morbidity) or liver transplantation to halt ongoing hepatic injury.

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DISCONTINUATION OF VITAMIN K ANTAGONIST IN BUDD-CHIARI PATIENTS WITH A WELL MANAGED Underlying Myeloproliferative Disorder : Lessons From A Small Case-Series. P. Martens (1), G. Maleux (2), T. Devos (3), D. Monbaliu (4), S. Heye (2), C. Verslype (5), W. Laleman (5), S. Van Der Merwe (5), W. Van Steenbergen (5), I. Jochmans (4), R. Aerts (5), R. Aerts (5), J. Pirenne (4), F. Nevens (5). (1) UZ Leuven, Leuven, Belgium, Division of Liver and Biliopancreatic Disorders ; (2) UZ Leuven, Leuven, Belgium, Division of Interventional Radiology ; (3) UZ Leuven, Leuven, Belgium, Division of Hematology ; (4) UZ Leuven, Leuven, Belgium, Division of Abdominal Transplantation Surgery ; (5) UZ Leuven, Leuven, Belgium, Division of Liver and Biliopancreatic Disorders.

Introduction : A large European case-series from the European Network for Vascular Disorders of the Liver (EN-VIE group) illustrates that 50% of Budd-Chiari patients' foster only one pro-thrombotic risk factor. The most common underlying pro-thrombotic risk factor in patients with Budd-Chiari is a myeloproliferative disorder (MPD). With current available cytoreductive therapies, a MPD seems to be a well manageable pro-thrombotic risk factor. Still no data is available about the possible discontinuation of vitamin K antagonist (VKA) in Budd-Chiari patients with a well-managed MPD.
Aim : To evaluate the discontinuation of VKA therapy in Budd-Chiari patients with a well managed underlying MPD
Methods : We retrospectively collected date from 37 Budd-Chiari patients diagnosed and treated at the University Hospital KU Leuven. All patients underwent thorough screening at presentation for the presence of underlying acquired and inherited pro-thrombotic conditions. Patients with a MPD without co-existing pro-thrombotic conditions were included. The treatment, response to therapy and rate of recurrence of this subgroup was analyzed.
Results : Of the 37 retrospectively collected Budd-Chiari patients, we identified 12 patients (32%) with an underlying MPD without other coexisting pro-thrombotic conditions. Within this subgroup we identified 6 patients with an underlying MPD well managed with cytoreductive therapy (consisting of hydroxycarbamide, anagrelide, or a JAK2-inhibitor) not receiving a VKA but aspirin instead. Median follow-up was 12 years (range : 3 years to 29 years). During follow-up not a single patient had a recurrence of Budd-Chiari syndrome.
Conclusions : In patients with Budd-Chiari syndrome a MPD is the most salient underlying pro-thrombotic condition. This pro-thrombotic condition is also well-manageable with current available therapies. This small case-series suggests that patients with a well-managed underlying MPD as sole pro-thrombotic risk factor can safely discontinue VKA-therapy. Aspirin therapy however remains desirable when discontinuing the VKA.

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AN INTEGRATED SAFETY AND EFFICACY ANALYSIS OF > 500 PATIENTS WITH COMPENSATED CIRRHOSIS TREATED WITH LEDIPASVIR/SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN. H. Van Vlierberghe (1), M. Bourlière (2), M. Sulkowski (3), M. Omata (4), S. Zeuzem (5), E. Lawitz (6), J. Feld (7), P. Marcellin (8), S. Tomasovic (9), R. Hyland (10), X. Ding (10), J. Yang (10), S. Knox (11), P. Pang (10), M. Subramanian (10), W. Symonds (10), J. Mchutchison (11), A. Mangia (12), E. Gane (13), R. Reddy (14), M. Mizokami (15), S. Pol (16), N. Afdhal (17). (1) UZ Gent, Gent, Belgium, Department of Gastroenterology and Hepatology ; (2) Hôpital Saint-Joseph, Liège, Belgium, Hepato-Gastroenterology department ; (3) John Hopkings University, USA, Viral Hepatitis Center ; (4) Yamanashi Prefectural Hospital Organization, Japan, Department of Gastroenterology ; (5) Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, Germany, Department of Internal Medicine ; (6) Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA, Departement of Gastroenterology ; (7) Sandra Rotman Centre for Global Health, University of Toronto, Canada, Department of Hepatology ; (8) Hôpital Beaujon, Clichy, France, Service d'Hépatologie ; (9) Gilead Sciences, Brussels, Belgium, Medical Department ; (10) Gilead Sciences, Foster City, USA, Clinical Research ; (11) Gilead Sciences, Foster City, USA, Clinical Research ; (12) Casa Sollievo Sofferemza Hospital, San Giovanni Rotondo, Italy, Liver Unit ; (13) Auckland City Hospital, Auckland, New Zealand, Liver Transplant Unit ; (14) University of Pennsylvania, USA, Department of Gastroenterology ; (15) National Center for Global Health and Medicine, Japan, Research Center for Hepatitis and Immunology ; (16) Université Paris-René Descartes, France, Department of Hepatology ; (17) Beth Israel Deaconess Medical Center, Boston, USA, Liver Center

Introduction : Patients with HCV and Cirrhosis represent a population in most need of treatment ; however, with interferon based therapy, such patients are difficult to cure and consequently often underrepresented in clinical trials.
Aim : Ledipasvir/sofosbuvir (LDV/SOF) Phase 2 and Phase 3 studies included > 500 patients with compensated cirrhosis. We analyzed the safety and efficacy of the regimen in this population.
Methods : Treatment-naïve or treatment-experienced patients with chronic HCV genotype 1 infection and compensated cirrhosis who had participated in Phase 2 or Phase 3 studies receiving LDV/SOF+/-ribavirin (RBV) for 12 or 24 weeks were included in this pooled analysis.

Results : 514 subjects with compensated cirrhosis were identified. The majority (91%) of patients had cirrhosis diagnosed by biopsy or fibroscan (> 12.5 kPa). Of the 293 patients on whom a fibroscan was performed, 137/293 (47%) had a value > 20 kPa. The majority were treatment-experienced (353, 69%), male (343, 67%), GT 1a (307, 60%), and IL28B non-CC (405, 79%). 238 (67% of the treatment-experienced patients) had previously received a protease inhibitor-containing regimen. 91 (18%) initiated therapy with a baseline platelet count of < 90,000 cells/μL. 59 (11%) initiated therapy with a baseline albumin < 3.5 g/dL. The patients received one of four regimens : 12 weeks of LDV/SOF (118, 23%), or LDV/SOF+RBV (206, 40%), or 24 weeks of LDV/SOF (132, 26%) or LDV/SOF+RBV (58, 11%). Safety in patients with cirrhosis was similar to that previously reported in patients without cirrhosis. Adverse events including anemia were more frequent in patients who received RBV. No other trends in adverse events or serious adverse events were noted. To date, 284 patients have available post-treatment week 12 data ; of these, 269 (95%) have achieved SVR12. Safety and efficacy for all 514 subjects will be presented.
Conclusions : Based on results from over 500 patients, LDV/SOF is effective, safe, and well-tolerated for the treatment of compensated cirrhotic patients with HCV genotype 1.

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HBSAG LOSS WITH TENOFOVIR DISOPROXIL FUMARATE (TDF) PLUS PEGINTERFERON ALFA-2A (PEG) IN CHRONIC HEPATITIS B (CHB) : RESULTS OF A GLOBAL RANDOMIZED CONTROLLED TRIAL. H. Reesinck (1), P. Marcellin (2), S. Ahn (3), X. Ma (4), F. Caruntu (5), W. Tak (6), M. Elkashab (7), W. Chuang (8), F. Tabak (9), R. Mehta (10), J. Petersen (11), S. Tomasovic (12), E. Martins (13), P. Dinh (13), A. Corsa (13), P. Charuworn (13), M. Subramanian (13), J. Mchutchison (13), M. Buti (14), G. Gaeta (15), G. Papatheodoridis (16), R. Flisiak (17), H. Chan (18). (1) Academic Medical Center, Amsterdam, The Netherlands, Department of Gastroenterology and Hepatology ; (2) Hôpital Beaujon, Clichy, France, Service d'Hépatologie ; (3) Yonsei University College of Medicine, Republic of Korea, Division of Gastroenterology ; (4) Drexel University College of Medicine, USA, Department of Gastroenterology ; (5) National Institute for Infectious Diseases "Matei Bals", Romania ; (6) Kyungpook National University Hospital, Daegu, Republic of Korea ; (7) Toronto Liver Center, Canada ; (8) Kaohsiung Medical University Chung-Ho Memorial Hospital, Taiwan, China ; (9) University of Istanbul, Istanbul, Turkey ; (10) Liver Clinic, India ; (11) IFI Institute for Interdisciplinary Medicine at the Asklepios Klinik St. George, University of Hamburg, Hamburg, Germany, Liver Unit ; (12) Gilead Sciences, City of Brussels, Belgium, Medical Department ; (13) Gilead Sciences, Foster City, USA ; (14) Hospital Universitario Val d'Hebron, Barcelona, Spain, Hepatology Unit ; (15) Viral Hepatitis Unit, Department of Infectious Diseases, Second University, Naples, Italy ; (16) Athens University Medical School, Athens, Greece ; (17) Medical University of Bialystok, Bialystok, Poland ; (18) The Chinese University of Hong Kong, Hong Kong, Department of Medicine and Therapeutics and Institute of Digestive Disease.

Introduction : Rates of HBsAg loss in CHB patients treated with nucleos(t)ide analogues (NA) or PEG therapy are relatively low. Studies comparing PEG+NA combination therapy versus PEG alone are inconclusive.
Aim : Here we present the Week 48 analysis of an ongoing trial evaluating TDF+PEG as combination therapy.
Methods : 740 patients with non-cirrhotic CHB were randomized 1 :1 :1 :1 to receive TDF+PEGx48 weeks (Arm A) ; TDF+PEG x16 weeks followed by TDF x32 weeks (Arm B) ; continuous TDF (Arm C) ; PEG x48 weeks (Arm D). The primary hypotheses compared the rates of HBsAg loss, estimated by Kaplan-Meier method, at Week 72 for arms A vs C, A vs D, B vs C, and B vs D. The Week 48 analysis was pre-specified.
Results : Of the 740 patients randomized and treated, 58.4% were HBeAg(+), mean age 37 years, 74.9% Asians and HBV genotype distribution (A, B, C, D, E-H) was 8.2%, 27.3%, 42.3%, 20.8% and 1.1%, respectively. At week 48, patients receiving PEG+TDF for 48 weeks had significantly higher rates of HBsAg loss than either TDF or PEG alone . Arm A had higher rates of HBs seroconversion (5.9%) than Arms B (0.6%), C (0%) or D (1.8%). Of the subjects with HBsAg loss, 73% were HBeAg(+) at baseline and had the following genotype distribution : 31.8% A, 36.4% B, 18.2% C, and 13.6% D. Rates of HBeAg loss were also higher in arms receiving PEG+TDF(Arm A 24.3%, Arm B 20.2%, Arm C 8.3%, Arm D 12.5%). HBV DNA suppression (HBV DNA < 15 IU/ml) was higher in the TDF-containing arms (Arm A 69.2%, Arm B 71.2%, Arm C 60.5%, Arm D 20.8%). No unexpected AEs were observed in the combination arms.
Conclusions : CHB patients treated with TDF and PEG combination therapy for 48 weeks achieved significantly higher rates of HBsAg loss than either therapy given alone.

SOMATOSTATIN (Eumedica®) INFUSION ALLOWS MODULATING GRAFT FLOWS AND GRADIENTS IN LIVER TRANSPLANTATION. RESULTS OF A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL. M. Sainz-Barriga (1), A. Croo (2), E. Codarin (3), E. De Wolf (4), G. Antoniali (5), J. Van Limmen (6), B. Heyse (7), L. De Baerdemaeker (8), I. Colle (9), A. Geerts (9), H. Van Vlierberghe (10), G. Tell (11), R. Troisi (12). (1) Centre Hospitalier Régional Universitaire de Tours, Tours, France, Digestive Surgery and Liver Transplantation ; (2) UZ Gent, Gent, Belgium, General Hepatobiliary and Liver Transplantation Surgery ; (3) University Of Udine, Udine, Italy, Dept. of Medical & Biological Sciences ; (4) UZ Gent, Gent, Belgium, General Hepatobiliary and Liver Transplantation Surgery ; (5) University Of Udine, Udine, Italy, Dept. of Medical & Biological Sciences ; (6) UZ Gent, Gent, Belgium, Anesthesiology ; (7) UZ Gent, Gent, Belgium, Anestesiology ; (8) UZ Gent, Gent, Belgium, Anesthesiology ; (9) UZ Gent, Gent, Belgium, Gastroenterology ; (10) UZ Gent, Gent, Belgium, Gastroenterology ; (11) University of Udine, Udine, Italy, Dept. of Medical & Biological Sciences ; (12) UZ Gent, Gent, Belgium, General, Hepatobiliary and Liver Transplantation Surgery

Introduction : Somatostatin (SST) infusion decrease portal pressure in acute variceal bleeding in cirrhotic patients. Despite liver transplantation (LTx), recipients with portal hypertension (PHT) display different degrees of portal hyperperfusion especially after receiving segmental grafts (SG). Little data are available in clinical LTx regarding the use of SST as inflow modulator.
Aim : To evaluate the safety and the pharmacological properties of SST a prospective RCT was conceived.
Methods : A randomized double blind, placebo-controlled study (NCT 01290172, EUDRACT 2008-008318-24) was designed to allocate patients with measured PHT in a 1 :2 ratio to either the placebo group (P) or the SST group (S). SST patients received a continuous infusion of 6-mg/24 hrs. during 5 days starting at the anhepatic phase. The primary objective was to assess the safety and efficacy of SST in decreasing portal vein flow (PVF) and hepatic vein pressure gradients (HVPG = portal vein pressure - central vein pressure), eventually increasing the hepatic artery flow (HAF). A secondary objective was to investigate the SST effects on ischemia/reperfusion injury (IRI) as measured by expression levels of known stress-responsive proteins.
Results : Twelve patients were included in the P group and 21 in the S group. At a median follow up of 17 months (IQR 13-25), all patients but one were in good health with normally functioning grafts. PVF decrease ($p = 0.02$), with a trend for higher HAF was observed ($p = 0.058$) and HVPG decrease ($p = 0.016$) in the S group compared to the P group was observed. No vascular thrombosis was observed. No significant differences in AST and INR peaks between both groups were observed as well as in proteomic expression.
Conclusions : Somatostatin has proven to be a safe and useful drug to consistently reduce PVF and HVPG. The trend for HAF increase could be particularly interesting in SG transplantation where its value can be decreased. Further studies must be addressed to understand its role in IRI.

FEASIBILITY AND SAFETY OF LIVER SURGERY AFTER TUMOR TRANSARTERIAL RADIOEMBOLIZATION. G. Katsanos (1), V. Lucidi (1), F. Bouazza (2), J. Van Laethem (3), A. Hendlisz (4), P. Flamen (5), V. Donckier (1). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Hepatobiliary Surgery and Abdominal Transplantation Department ; (2) Institut Jules Bordet, Brussels, Belgium, Digestive Surgery Department ; (3) CUB Hôpital Erasme, Brussels, Belgium, Digestive Oncology Department ; (4) Institut Jules Bordet, Brussels, Belgium, Digestive Oncology Department ; (5) Institut Jules Bordet, Brussels, Belgium, Nuclear Medicine Department.

Introduction : Transarterial radioembolization (TARE) has been recently developed as a loco-regional treatment for liver cancers. Limited data are available on the use of TARE as a preoperative treatment for tumor downstaging before surgical treatment.
Aim : The aim of this study is to evaluate the feasibility and safety of liver surgery after TARE for liver cancer.
Methods : We retrospectively analyzed 8 patients that were treated with TARE prior to resection or liver transplantation. Primary endpoints were perioperative and 90 day morbidity and mortality. Standard statistical methods were used.
Results : Primary diagnosis for liver tumor was hepatocellular carcinoma (5 patients), peripheral cholangiocarcinoma (1 patient), colorectal metastasis (1 patient) and metastasis of an oesophageal adenocarcinoma (1 patient). Among patients with hepatocellular carcinoma, 2 were treated by liver transplantation and 3 by resection. The remaining 3 patients were treated by liver resection. American Society of Anesthesiology psysical status classification was 1 for 1 patient, 2 for 3 patients and 3 for 4 patients. Six patients received whole liver transarterial radioembolisation prior to surgery. Overall morbidity was 37.5% and 2 patients developed grade III complication. There was no postoperative liver failure, no pulmonary specific complications and no deaths within the 90 day postoperative period.
Conclusions : These preliminary data suggest that preoperative TARE before liver resection is not responsible for additional operative morbidity or mortality. The oncological benefit of this approach remains to be determined.

CASE PRESENTATION : OVERWEIGHT AND ELEVATED LIVER ENZYMES : NOT ALWAYS NAFLD.
J. Schreiber (1), C. Moreno (1). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology Department.

Introduction : We present the case of a 35-year-old Caucasian female addressed to the liver outpatient clinic for elevated liver enzymes. Her general practitioner did a workup after a recent EBV infection after which liver enzymes stayed elevated 6 months after the infectious phase.
Aim : The workup included an ultrasound of the abdomen, which showed steatosis of the liver, absence of bile stones and duct dilatation and presence of two ovarian cysts. Blood samples showed : GOT 36 UI/L, GPT 58 UI/L, GGT 55 UI/L, total bilirubin 1,2 mg/dl. She did not consume alcoholic beverages and smoked 1 packet of cigarettes every 2 weeks. Her medical history showed hypercholesterolemia, urticaria of unknown origin, 2 pregnancies (1 child in good health/1 hemiplegic). Her medications included : Simvastatine 20 mg, Ibuprofen (on demand), and anti-histaminics (on demand).
Methods : Physical examination showed eczema like lesions on her legs and was normal otherwise. Her weight was 80 kg for 1m70, giving a BMI of 27,7. Her blood pressure was 110/70 mmHg. A Fibroscan was performed and showed a value of 6,5 kPa and CAP of 395 dB/m. Viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson disease, α-anti-trypsin deficiency were excluded. Total cholesterol was 296 mg/dl and HDL cholesterol was 33 mg/dl. Fibrotest was 0,48. NAFLD was suspected and a liver biopsy was performed. Biopsy showed septal fibrosis (Metavir : A1-2/F2), slight microvesicular steatosis, ballooning of hepatocytes and lymphocytic infiltration.
Results : LAL deficiency belongs to a family of diseases called Lysosomal Storage Disorders. The LAL enzyme breaks down fatty material (cholesteryl esters and triglycerides), and the lack of the LAL enzyme results in a build-up of these materials in the liver and other organs. Clinical findings of this disease include elevated liver enzymes, high LDL-cholesterol, very low HDL cholesterol and hepatomegaly. This disease can lead to liver fibrosis, cirrhosis and elevates the risk of cardiovascular events.
Conclusions : We hereby present the first case of LAL deficiency in an adult patient in Belgium. This case shows how challenging this diagnosis is in a patient with a clinical metabolic profile. The patient will soon be included in an enzyme replacement study.

OG-FWO

RESEARCH GROUP "GASTROINTESTINAL REGULATORY MECHANISMS"

- B01 -

S100B IN THE DEVELOPING ENTERIC NERVOUS SYSTEM. E. Capoccia (1), M. Hao (1), W. Boesmans (1), G. Esposito (2), P. Vanden Berghe (1). (1) Translational Research Center for Gastrointestinal Disorders (TARGID), Lab for Enteric Neuroscience (LENS), KU Leuven, Leuven, Belgium, Department of Clinical and Experimental Medicine ; (2) Sapienza University, Rome, Italy, Department of Physiology and Pharmacology "Vittorio Erspamer".

Introduction : Introduction : S100B is a diffusible Ca2+ and Zn2+ binding protein which is predominantly expressed by glial cells in the nervous system. S100B plays important roles in the control of cell proliferation, survival, differentiation and Ca2+ homeostasis in both the central nervous system and enteric nervous system (ENS), exerting either pro-survival or pro-apoptotic effects depending on its extracellular concentration. The ENS is vital for the control of gastrointestinal function, including motility and secretion. All the neurons and glia of the ENS arise from neural crest cells that migrate into the gastrointestinal tract during development. S100B is expressed by post-mitotic glial cells of the ENS, however, currently little is known about its function in development.
Aim : In this study, we are investigating the development of glia in the ENS. We aim to identify whether S100B plays a role in guiding the proliferation, survival and differentiation of enteric neurons and glia during development.
Methods : Methods : To examine enteric glia, we used the Wnt1-CRE ;R26R-GCaMP transgenic mouse line, where the reporter protein, GCaMP3 is expressed by all neural crest cell derivatives, including all the neurons, glia and progenitors of the ENS. Immunohistochemistry was performed on embryonic (E14.5, E16.5) and postnatal day (P)0 mice using anti-GFP (to identify GCaMP-expressing cells), as well as S100B, glial fibrillary acidic protein (GFAP) and Sox10 antisera to label glial cells. S100B and GFAP were used to identify post-mitotic glia, whereas Sox10 is also expressed by neuronal and glial progenitors. To examine the effect of inhibiting S100B expression, in vitro organ culture of intact embryonic gut was used in the presence of arundic acid, a well-known inhibitor of S100B protein synthesis.
Results : The earliest S100B-immunoreactive positive cells were detected at embryonic day (E)14.5 where they made up 10% of the total number of the GFP+ cells in the rostral small intestine. The number and proportion of S100B+ cells increased through embryonic development, to 50% of GFP+ cells at P0. Interestingly, at all different aged analyzed (E14.5, E16.5 and P0) a small percentage of cells were immunoreactive for S100B but not for Sox10 in both the small intestine and the colon. GFAP expression was not identified until P0. To investigate the effect of modulating S100B expression, we have begun preliminary experiments to culture E13.5 embryonic gut in vitro in the presence of arundic acid (300 μM). After 2 days in vitro, control cultures showed abundant S100B expression, however, no S100B-immunoreactive cells were identified in the arundic acid cultures. In addition, exposure to arundic acid appeared to completely eliminate Sox10+ progenitor cells and there was a reduction in the overall number of GFP+ cells in the ENS network.
Conclusions : S100B expressing cells are present as early as E14.5 in developing gut and its expression increases during embryonic development. Our preliminary experiments suggest that S100B could be important for the maintenance of both glial cells and progenitors during ENS development.

- B02 -

HYPERPLASIA OF INTERSTITIAL CELLS OF CAJAL IN SPROUTY HOMOLOG 4 DEFICIENT MICE. A. Thys (1), P. Vandenberghe (1), P. Hague (1), O. Klein (2), C. Erneux (3), J. Vanderwinden (1). (1) ULB Faculty of Medicine, Anderlecht, Belgium, Neurophysiology ; (2) UCSF, San Franscisco, USA, Department of Pediatrics and Institute for Human genetics, University of California, Department of Orofacial Sciences and Program in Craniofacial and Mesenchymal Biology, University of California, San Francisco ; (3) ULB Faculty of Medicine, Anderlecht, Belgium, IRBHM

Introduction : Gastrointestinal stromal tumors, which are thought to derive from interstitial cells of Cajal or their precursors, often harbor an oncogenic mutation of the KIT tyrosine kinase receptor. Sprouty homolog 4, a known negative regulator of ERK pathway, has been identified in the interstitial cells of Cajal in the KitK641E murine model of gastrointestinal stromal tumors. Sprouty homolog 4 was upregulated both at the mRNA and protein level in these cells, suggesting that Sprouty homolog 4 is downstream of oncogenic KIT activation and potentially engaged in the negative feedback loop of ERK activation in this model.
Aim : To investigate the role of SPRY4 in vivo using a Spry4 KO mouse model

Methods : KitK641E heterozygous and Sprouty homolog 4 null animals were used to quantify interstitial cells of Cajal in situ, using quantitative immunofluorescence. Furthermore, carmine red was administered by gavage in order to measure total gastrointestinal transit time.
Results : In the antrum of Sprouty homolog 4 null mice, hyperplasia of interstitial cells of Cajal was reminiscent of the KitK641E heterozygous mice antrum. Additionally, the density of interstitial cells of Cajal was higher in the colon of adult Sprouty homolog 4 null mice than in WT littermates, although hyperplasia was more severe in KitK641E heterozygous mice. Functional transit studies also show similarities between Sprouty homolog 4 null and KitK641E heterozygous mice, as the total transit time in 9 months old animals was significantly increased in both genotypes compared to WT littermates.
Conclusions : We conclude that the lack of Sprouty homolog 4 expression leads to hyperplasia of the interstitial cells of Cajal and is functionally associated with a delayed transit time in aging mice.

- B03 -

PHOSPHODIESTERASE 3A : MORE THAN AN ICC MARKER ? P. Vandenberghe (1), A. Thys (1), P. Hague (1), C. Erneux (2), J. Vanderwinden (1). (1) ULB Faculty of Medicine, Anderlecht, Belgium, Laboratory of Neurophysiology ; (2) ULB Faculty of Medicine, Anderlecht, Belgium, IRIBHM.

Introduction : The cGMP inhibited phosphodiesterase 3A (PDE3A) regulates the levels of cyclic nucleotides and thus controls biological responses in several tissues and cell types such as brain, heart, vascular smooth muscle cells (VSMC), platelets and oocyte. We have previously shown that PDE3A is a marker of Kit+ interstitial cells of Cajal (ICC) in adult mouse gut and that its expression is upregulated in the mouse WK641E GIST model (Gromova.P et al. JCMM 2009).
Aim : To unravel the expression profile of PDE3A during mouse gut development, with emphasis on ICC and their progenitors.
Methods : Gut of E14.5 and E17 wild type (WT) mouse embryos were dissected out, fixed with paraformaldehyde and processed as wholemounts. Antrum of P2 and P24 WT mouse were dissected out, fixed with paraformaldehyde, cryopreserved in graded sucrose solutions, embedded in OCT and cut on a cryostat. Immunofluorescence was performed using specific antibodies for PDE3A, Kit and smooth muscle actin (α-SMA). qPCR experiments were performed on postnatal (P2 and P24) WT mouse antrum.
Results : At E14.5, PDE3A-ir was detected in mesenchymal Kit+ cells as well as in Kit+/α-SMA+ common progenitors of ICC and smooth muscle cells (SMC). At E17, Kit+/PDE3A+ and Kit+/α-SMA+/PDE3A+ were observed while Kit-/α-SMA+/PDE3A+ cells start to appear. At P2, Kit-/α-SMA+/PDE3A+ form the longitudinal muscle layer while the Kit+/PDE3A+ ICCs surround myenteric plexus. At P24, the SMC are α-SMA+/PDE3A- and PDE3A-ir is detected only in the Kit+ ICC. qPCR indicated a decreased PDE3A expression in the antrum of P24 compared to P2 animal while Kit expression didn't change.
Conclusions : PDE3A is expressed early during development of the gut mesenchyme in precursor cells forming the future longitudinal muscle layer and ICC-MP. Its expression changed over time while ICC/SMC differentiation occurs, suggesting a potential role in that process. Further studies of other phosphodiesterase, cyclic nucleotides, their targets and cyclase expression are envisioned to better understand the underlying mechanisms controlled by PDE3A.

- B04 -

CHRONIC ENTERITIS IN HORSES. A RETROSPECTIVE STUDY IDENTIFYING THE DIAGNOSTIC VALUE OF DIFFERENT APPROACHES. C. Delesalle (1), J. Dewulf (2), S. Klooster (3), M. De Bruijn (4), T. Picavet (5), K. Palmers (6), B. Boshuizen (4), A. Popovic (7), M. Ploeg (8). (1) Gent University, Gent, Belgium, Department of Comparative Physiology and Biometrics. Faculty of Veterinary Medicine. ; (2) Gent University, Gent, Belgium, Department of Reproduction, Obstetrics and Herd Health. Unit for Veterinary Epidemiology, Faculty of Veterinary Medicine ; (3) Utrecht University, Netherland, Equine Science, Faculty of Veterinary Medicine ; (4) Wolvega Equine Clinic, Netherland, Equine Internal Medicine ; (5) De Bosdreef Equine Clinic, Belgium, Equine Internal Medicine ; (6) De Morette Equine Clinic, Belgium, Equine Internal Medicine ; (7) Gent University, Gent, Belgium, Department of Comparative Physiology and Biometrics, Faculty of Veterinary Medicine ; (8) Utrecht University, Netherland, Department of Pathobiology, Faculty of Veterinary Medicine

Introduction : Chronic enteritis (IBD) is often a real challenge in horses. At this point there is no conclusive diagnostic test available.
Aim : The objective of this retrospective study was to provide an overview of patient data such as breed, gender, age, symptoms, dietary management before and after diagnosis of IBD, applied diagnostic tests, applied treatment protocol and outcome in a group of 78 horses and ponies admitted to 4 large equine referral clinics*, suspected of having IBD and

subjected to an oral glucose absorption test (OGAT) between 2008 and 2013. To our knowledge, this is the first large scale study to evaluate the diagnostic value of duodenal and rectal biopsies, despite their increasing popularity. * the Utrecht University Equine Clinic, The Netherlands ; The Wolvega Equine Clinic, The Netherlands ; De Morette Equine Clinic, Belgium ; The Bosdreef Equine Clinic, Belgium.

Methods : Case history, diagnostic approach, therapy and outcome was mapped out for all horses. OGAT results were recorded, together with the different types of IBD identified in duodenal or rectal biopsies. Findings of rectal examination, transabdominal ultrasound, gastroscopy and blood work were recorded. Harvested duodenal and rectal biopsies were labeled for quality and depth. Long term follow-up was performed by means of a telephone questionnaire at least one year after establishment of diagnosis.

Results : 80% of horses was admitted in the age range between 5-15 years. There was no gender predisposition, nor seasonality in the pattern of admittance. 'Lethargy', 'diarrhea', 'recurrent colic' and 'weight loss despite good appetite' were recorded in respectively 21,8% ; 14,1% ; 28,2% and 76,9% of cases. None of these clinical symptoms as such or as a combination had a significant positive predictive value for OGAT test results, low blood TP or biopsy based diagnosis of IBD. There was no significant correlation between the diet prior to diagnosis and OGAT results, nor biopsy results. In 31 (51,7%) out of 60 horses abnormalities like presence of stomach ulcers or an aberrant aspect of the duodenum was reported during gastroscopie. Biopsies were deemed of good quality in 93,3% (rectal) and 59,5% (duodenal) of cases. In respectively 21 horses (56,8%) the duodenal biopsy and in 38 horses (84,4%) the rectal biopsy was aberrant. There was no correlation between OGAT test results, or enteral biopsy test results on one hand and blood TP, gastric ulcer disease or an aberrant endoscopic duodenal aspect. There was no correlation between an aberrant duodenal or rectal biopsy result and a disturbed OGAT test. Treatment approach encompassed prednisolone (69%), dexamethasone (2%), omeprazole (34%) and adapted diet (63%). There was no correlation between either treatment and positive outcome.

Conclusions : Histopathological results of enteral biopsies, either duodenal or rectal should be interpreted with caution in cases suspected of IBS since they show no correlation with OGAT results, currently viewed as golden standard. Likewise, gastroscopic identification of an aberrant aspect of the entrance of the duodenum can't be viewed as a diagnostic tool. Treatment and management approach of these cases needs more finetuning.

- B05 -

SENSING OF CARBOHYDRATES BY THE GHRELIN CELL IS POLARIZED AND OCCURS IN THE SMALL INTESTINE. S. Steensels, L. Vancleef, I. Depoortere. KU Leuven, Leuven, Belgium, TARGI.

Introduction : Carbohydrate administration in healthy volunteers results in the decrease of the 'hunger hormone' ghrelin, an octanoylated 28 amino acid peptide produced in the stomach, which stimulates food intake and increases body weight. Recent evidence suggests that taste receptors on endocrine cells, similar to those on the tongue, regulate the release of hormones in response to nutrients. Studies have shown that the ghrelin cell is co-localized with the sweet taste receptor, TAS1R2-TAS1R3, and the gustatory G-protein, gustducin, both involved in the sensing of carbohydrates by endocrine cells.

Aim : 1) To compare the dose-dependent effects of glucose on ghrelin release in the stomach and duodenum in vitro and in vivo in mice and 2) to determine whether sensing of glucose by the ghrelin cell is mediated via a-gustducin and occurs via the luminal or blood-born direction.

Methods : Mouse stomach ghrelinoma cells were stimulated with D-glucose at different concentrations (1-200 mM) for 3 hours. Mouse intestinal stomach and jejunal segments were stimulated with 200 mM D-glucose. In vivo, wildtype (WT) and a -gustducin knockout mice (a-gust-/-) were gavaged with 4 g/kg D-glucose. In addition, WT mice were intravenously (IV) injected with 1 g/kg D-glucose. Ghrelin levels were determined in culture medium, plasma and gut tissue extracts by radioimmunoassay.

Results : In ghrelinoma cells, D-glucose increased octanoyl ghrelin release with 32% at low concentrations (10 mM) and decreased octanoyl ghrelin levels with 41% at high concentrations (200 mM). Incubation of jejunal segments with 200 mM D-glucose decreased ($p < 0.05$) octanoyl ghrelin release from 36 ± 6 to 17 ± 2 pg/mg dry weight but did not affect octanoyl ghrelin release from segments of the corpus (control : 7.2 ± 0.5 vs D-glucose: 7.6 ± 0.4 pg/mg dry weight). In both WT and a-gust-/- mice gavage of D-glucose decreased ($p < 0.05$) plasma octanoyl ghrelin levels to a similar extent (WT : 54%, a-gust-/- : 67%). In both genotypes this was accompanied by an increase ($p < 0.05$) in duodenal ghrelin content from 692 ± 26 to 962 ± 105 pg/mg protein in WT and from 899 ± 99 to 1364 ± 112 pg/mg protein in a-gust-/- mice. Stomach ghrelin content was not affected (WT : from 85 ± 4 to 100 ± 13, a-gust-/-: from 83 ± 16 to 75 ± 12 ng/mg protein in a-gust-/-). IV administration of D-glucose neither affected plasma octanoyl ghrelin levels (control : 191 ± 31, D-glucose: 156 ± 56 pg/ml) nor tissue octanoyl ghrelin content.

Conclusions : D-glucose inhibits ghrelin release after acute administration. The sensing of D-glucose is polarized and occurs via the lumen, where it is sensed by ghrelin cells in the duodenum. a-gustducin is not involved in the sensing of D-glucose.

- B06 -

THE EFFECT OF SCHISTOSOMIASIS ON THE DISTRIBUTION OF CX3CR1-POSITIVE DENDRITIC CELLS AND MONONUCLEAR PHAGOCYTES IN THE ILEUM AND MESENTERIC LYMPH NODES OF THE MOUSE.

K. Alpaerts (1), R. Buckinx (1), N. Cools (3), M. Heylen (4), S. Nullens (4), Z. Berneman (3), B. De Winter (4), L. Van Nassauw (5), J.P. Timmermans (2). (1) University of Antwerp, Antwerpen, Belgium, Laboratory of Cell Biology and Histology, (2) University of Antwerp, Antwerp, Belgium, Department of Veterinary Sciences, (3) University of Antwerp, Antwerpen, Faculty of Medicine and Health Sciences, Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute, (4) University of Antwerp, Antwerp, Belgium, Faculty of Medicine and Health Sciences, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology, (5) University of Antwerp, Antwerp, Belgium, Faculty of Medicine and Health Sciences, Laboratory of Human Anatomy and Embryology.

Introduction : The gastrointestinal (GI) tract is continuously exposed to many different antigens ranging from harmless commensals and food antigens to potential pathogenic organisms and must be able to mount an active immune response only when necessary. The intestinal dendritic cells (DCs) are key regulators in preserving this delicate immune homeostasis. There are two main DC subsets in the lamina propria (LP) of the mouse ileum, i.e. CD11c+CD103+ LP-DCs and CD11c+CX3CR1+F4/80- LP-DCs. The CD103+ DCs are able to migrate to the mesenteric lymph nodes (MLNs) and induce Foxp3+ regulatory T cells or interferon-γ-producing T cells. The CX3CR1+ subtype was recently shown to also migrate to the MLNs. They continuously sample the gut lumen and circulation, placing them in a unique position in both intestinal and circulatory immune surveillance. To date, there is no information about the distribution and behavior of the LP-DCs and other mononuclear phagocytes in the ileum or MLNs during trematode-induced inflammation.
Aim : To study the distribution of the mononuclear phagocyte subsets, with a particular focus on the CD11c+CX3CR1+ F4/80- DCs, in the ileum and MLNs of the mouse during Schistosoma mansoni-induced inflammation. In addition, we evaluated which subsets are responsible for the uptake and processing of S. mansoni-derived antigens in vivo.
Methods : The different DC and macrophage (MΦ) subsets were quantified in the ileum and MLNs of CX3CR1+/GFP C57BL/6 mice using a combined strategy of immunohistochemistry (IHC) and multiparametric flow cytometry (FACS). The antigen uptake and processing capacity of the DCs and MΦs was evaluated at different time points after intraperitoneal (i.p.) injection with S. mansoni soluble worm proteins (SmSWP) or S. mansoni egg antigens (SmSEA) and the mononuclear phagocytes involved were visualized using IHC and confocal microscopy.
Results : FACS analysis of MLN showed a decrease of CD103+ cells and CD11c+CD103+ DCs while the general CD11c+ and F4/80+ population significantly expanded during inflammation. Within the CX3CR1+ population, the CD11c+CX3CR1+F4/80+ MΦ subset showed no changes and the CD11c+CX3CR1+F4/80- DCs significantly increased during schistosomiasis. Immunohistochemical analysis of the ileal LP revealed a significant increase in CD11c+CX3CR1+ F4/80- DC numbers during intestinal schistosomiasis. SmSWP and SmSEA injections showed that these antigens were rapidly engulfed in the ileum and MLNs mainly by CX3CR1-positive phagocytes, i.e. CX3CR1+CD11c-, CX3CR1+ F4/80-, CD11c+CX3CR1+ and F4/80+CX3CR1+ cells.
Conclusions : Our findings provide, for the first time, an accurate analysis of the distribution of the LP-DC and MΦ subsets in the ileum and MLNs during S. mansoni-induced infection. In addition, our data point to an important role of CX3CR1-expressing cells and more specifically of the CD11c+CX3CR1+F4/80- DC subset in the uptake of parasitic antigens. Taken together, our results highlight the likely involvement of CD11c+CX3CR1+F4/80- DCs in immune surveillance and in initiating active immune response towards trematode invasion.

- B07 -

BENEFICIAL EFFECTS OF THE SELECTIVE ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONIST GTS-21 ON SEPSIS-INDUCED ILEUS AND IMPAIRED MUCOSAL BARRIER FUNCTION.

S. Nullens (1), C. Peleman (1), M. Staessens (1), P. Pelckmans (2), C. Lammens (3), S. Malhotra-Kumar (3), J. De Man (1), B. De Winter (1). (1) (1) University of Antwerp, Antwerp, Belgium, Laboratory of Experimental Medicine and Pediatrics, Gastroenterology and Hepatology, (2) UZ Antwerpen, Edegem, Belgium, Gastroenterology and Hepatology, (3) University of Antwerp, Antwerpen, Belgium, Laboratory of Medical Microbiology ; (2) University Hospital Antwerp, Antwerp, Belgium, Gastroenterology and Hepatology ; (3) University of Antwerp, Antwerpen, Belgium, Laboratory of Medical Microbiology.

Introduction : Sepsis remains a leading cause of mortality in Intensive Care Units. Ileus, the inhibition of the propulsive motility of the gastrointestinal (GI) tract, together with mucosal barrier dysfunction will maintain sepsis by the translocation of bacteria. The alpha7 nicotinic acetylcholine receptor (α7nAChR) represents a final step in the vagal anti-inflammatory pathway, an endogenous reflex pathway that suppresses inflammation.
Aim : We investigated the effect of GTS-21, a selective α7nAChR agonist, on ileus, colonic permeability and translocation of intestinal bacteria in blood and mesenteric lymph nodes (MLN).

Methods : Sepsis was induced in Swiss-OF1 mice by cecal ligation and puncture (CLP). Sham-operated animals served as controls. Mice received either GTS-21 8 mg/kg i.p. (GTS) or vehicle (veh) 1h before the CLP procedure, and subsequently once daily. In the GI study, occurrence of ileus was confirmed by studying the geometric center (GC) of beads following gavage. In the permeability study, mice were anesthetized at day 2 following CLP, and underwent a laparotomy during which the colon was ligated and injected with 100μL of a 9% Evans blue (EB) solution. Mice were sacrificed 1h later via cardiac puncture and serum samples were analyzed for the proinflammatory cytokine IL-6. Colons were rinsed and incubated for 24h in formamide to extract the EB from the colon wall. Whole blood and homogenized MLN were plated directly onto agar plates and cultured for 24h to quantify bacterial translocation. RT-PCR was performed on colons for proteins of cell adhesion.
Results : CLP resulted in a significant prolongation of GI transit times, while GTS was able to reverse this (GC : sham+veh 4.9 ± 0.3, sham+GTS 4.2 ± 0.3, CLP+veh 2.5 ± 0.4*, CLP+GTS 4.3 ± 0.4). IL-6 levels rose significantly after CLP, GTS was able to reduce this (sham+veh 2.6 ± 0.5, sham+GTS 3.5 ± 0.7, CLP+veh 243.6 ± 54.9*, CLP+GTS 90.3 ± 31.3 pg/mL). Sepsis resulted in an increased colonic permeability, as demonstrated by a significant rise in the amount of EB extracted from the colon, whereas GTS-21 was able to ameliorate the impaired colonic barrier (sham+veh 56.2 ± 4.3, sham+GTS 43.7 ± 3.8, CLP+veh 105.6 ± 22.1*, CLP+GTS 49.5 ± 6.9 μg EB/100mg colon). GTS appears to reduce the number of positive blood and MLN cultures following CLP-induced sepsis (Blood : CLP+veh 67% and CLP+GTS 30%* positive cultures ; MLN : CLP+veh 100% and CLP+GTS 40%* positive cultures). Sepsis caused a significant increase in the mRNA expression of the cell adhesion molecules occludin, zonulin-1, claudin-1, desmoglein-2 and E-cadherin, with a significant additional increase in the mRNA expression of claudin-1 by GTS (relative mRNA expression of claudin-1 : sham+veh 1.00, sham+GTS 4.5 ± 1.2, CLP+veh 4.1 ± 1.6, CLP+GTS 11.5 ± 1.9 ; significant effect of CLP and GTS).
Conclusions : CLP resulted in the occurrence of septic ileus with an increased colonic permeability and subsequently increased bacterial translocation. GTS was able to ameliorate GI motility, suppress inflammation, normalize the permeability of the colonic wall, and decrease the number of positive cultures. The increase in mRNA expression of cell adhesion proteins following CLP has been described in other organs affected by sepsis, and presumably represents an attempted repair response. Targeting the α7nAChR appears to be an interesting therapeutic strategy in inflammatory conditions.

- B08 -

FACILITATION OF CHOLINERGIC NEUROTRANSMISSION VIA 5-HT4 RECEPTORS IN THE MURINE GASTROINTESTINAL TRACT. V. Pauwelyn (1), E. Van Deynse (1), R. Lefebvre (1). (1) Gent University, Gent, Belgium, Heymans Institute of Pharmacology.

Introduction : Recent data in rats with mosapride and in mice with prucalopride, both selective 5-HT4 receptor agonists, showed that these agents activate the cholinergic anti-inflammatory pathway in the rodent small intestine. This was suggested to be due to activation of 5-HT4 receptors on cholinergic myenteric neurons dampening activation of resident macrophages. Till now however, even the presence of 5-HT4 receptors on cholinergic enteric neurons inducing smooth muscle contraction, a location established in the pig and human gastrointestinal (GI) tract, was not firmly established in the murine GI tract.
Aim : The aim of this study was therefore to investigate the influence of prucalopride on submaximal cholinergic contractions in different regions of the murine GI tract.
Methods : Circular smooth muscle strips were prepared from the fundus, jejunum and colon (mucosa removed for jejunum and colon) and mounted between 2 stimulation electrodes in an organ bath with oxygenated Krebs solution ; isometric tension was registered. For each tissue, electrical field stimulation (EFS) was performed with different stimulation parameters (voltage, frequency and interstimulus interval) to select those parameters inducing neurogenic cholinergic on-contractions as checked with tetrodotoxin (3 μM) and atropine (1 μM) respectively. EFS at these parameters induced reproducible contractions ; the contraction amplitude was halved by decreasing the voltage (V50%) to study the influence of prucalopride (0.003 to 0.03 μM). The 5-HT4 receptor antagonist, GR113808 (0.3 μM), was studied versus 0.03 μM prucalopride.
Results : EFS-induced cholinergic on-contractions were obtained in the presence of guanethidine (4 μM) and L-NAME (300 μM) to exclude noradrenergic and nitrergic influences respectively. Additionally, for colon strips the P2Y1 receptor antagonist MRS 2500 (1 μM) had to be added to avoid influences of the relaxant neurotransmitter ATP. EFS with 10 s trains (500 μs pulse duration ; maximal voltage ; 4 [fundus] or 8 Hz [jejunum and colon]) at 5 (fundus and colon) or 10 min (jejunum) interval induced reproducible contractions. Upon reduction of the stimulation voltage to V50%, reproducible submaximal contractions were obtained ; after adding prucalopride, contractions by EFS at V50% were followed for 50 min. Prucalopride concentration-dependently increased contractions at V50%. The mean contraction force (%) 50 minutes after administration of prucalopride (0.003, 0.01 and 0.03 μM) was 133, 181*, 204*** in the fundus ; 122*, 124**, 138*** in the jejunum ; 133, 136, 152** in the colon (*P < 0.05 ; **P < 0.01 ; ***P < 0.001 versus control ; one-way ANOVA with Bonferroni correction ; n = 6-9). The effect of 0.03 μM prucalopride was abolished by the selective 5-HT4 receptor antagonist GR113808 (0.3 μM).

Conclusions : These data suggest the presence of 5-HT4 receptors on cholinergic neurons innervating circular smooth muscle in murine fundus, jejunum and colon. The effective concentrations of prucalopride are lower than those needed at 5-HT4 receptors in the human and porcine GI tract.

- B09 -

EVALUATION OF A NEW SERINE PROTEASE INHIBITOR ON VISCERAL PAIN IN A RAT MODEL OF ACUTE COLITIS. H. Ceuleers (1), A. Deiteren (1), J. Joossens (2), K. Augustyns (2), P. Van Der Veken (2), P. Pelckmans (1), J. De Man (1), B. De Winter (1). (1) University of Antwerp, Antwerpen, Belgium, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology ; (2) University of Antwerp, Antwerpen, Belgium, Antwerp Drug Discovery Network.

Introduction : Inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis are characterized by an intermittent inflammation of the gastrointestinal tract. Serine proteases are likely to be involved in modulating the inflammatory process and the associated visceral hypersensitivity. The latter is believed to contribute to chronic abdominal pain in patients with IBD.
Aim : In this study, the preclinical potential of a new serine protease inhibitor was evaluated in a rat model of acute colitis.
Methods : Colitis was induced in male Sprague-Dawley rats by intrarectal administration of 0.25 ml of 7.5 mg trinitrobenzenesulfonic acid (TNBS) in 50% ethanol. The control group received a saline enema. Three days later, visceral sensitivity was objectified by quantifying visceromotor responses (VMRs) to colorectal distension (10-80 mmHg, 20 s, 4 min interval) and expressed as total area under the curve (AUC, expressed in μV) for visceral allodynia (10-30mmHg) and hyperalgesia (40-80mmHg). Rats were administered either the serine protease inhibitor (1 or 5 mg/kg intraperitoneally) or vehicle, 30 minutes before the VMR registration. Colon compliance was assessed by inflating a colorectally inserted balloon with graded water volumes (0-2 ml, 80 s interval) while recording the corresponding pressures in the colon. Finally, inflammation was scored by colonoscopy, macroscopy, microscopy and myeloperoxidase activity.
Results : TNBS enema resulted in colitis in all rats. Compared to vehicle-treated controls, vehicle-treated colitis rats displayed significant visceral hypersensitivity, characterized by visceral allodynia (10-30 mmHg ; total AUC : 1112 ± 190 in colitis rats vs 353 ± 69 in control rats ; $n = 11$; $p < 0.001$) as well as hyperalgesia (40-80mmHg ; total AUC : 2726 ± 307 in colitis rats vs 1307 ± 256 in control rats ; $n = 11$; $p < 0.001$). The serine protease inhibitor in a dose of 1 mg/kg had no significant effect on visceral hyperalgesia : total AUC was 2445 ± 291 in drug-treated colitis rats vs 2726 ± 307 in vehicle-treated colitis rats ($n = 11$; ns). The 5 mg/kg dose however significantly reduced visceral hyperalgesia : total AUC was 1792 ± 294 in drug-treated colitis rats vs 2726 ± 307 in vehicle-treated colitis rats ($n = 10$-11 ; $p < 0.05$). The serine protease inhibitor thus reduced visceral hyperalgesia in a dose-dependent manner, without affecting visceral allodynia in colitis rats. The serine protease inhibitor had no effect on VMRs in control rats and had no effect on colonic compliance in control and colitis rats. The serine protease inhibitor in a dose of 5 mg/kg had no significant effect on the inflammatory parameters.
Conclusions : Direct inhibition of serine proteases significantly reverses inflammation-induced visceral hyperalgesia and thus seems to be a new and promising strategy in the search for potent modulators of visceral hypersensitivity and abdominal pain in patients with IBD.

- B10 -

ABERRANT BYSTANDER IMMUNE RESPONSE TRIGGERS VISCERAL HYPERSENSITIVITY IN A TH2 PREDOMINANT POST-INFECTIOUS IBS MOUSE MODEL. S. Mondelaers (1), J. Aguilera-Lizarraga (1), S. Theofanous (1), G. Boeckxstaens (1), M. Wouters (1). (1) KU Leuven, Leuven, Belgium, TARGID.

Introduction : Approximately 10% of patients with irritable bowel syndrome (IBS) develop symptoms and abnormal pain perception or visceral hypersensitivity (VHS) following an episode of infectious gastroenteritis. Although persistent low-grade immune and/or mast cell activation have been proposed to underlie VHS, the exact mechanism involved remains unclear. As mast cell involvement suggests a Th2-mediated disease mechanism, we hypothesized that during infection, an aberrant immune response to innocent bystander antigens would lead to recurrent immune activation upon re-exposure of the respective antigen with the development of VHS, especially against a Th2 background.
Aim : To study this hypothesis, we developed a post-infectious (PI-IBS) model using ovalbumin (OVA) as bystander antigen and evaluated VHS development in Th1 predominant C57BL6 and Th2 predominant Balb/c mice.

Methods : Mice were infected with C. rodentium or vehicle in the presence of OVA and orally re-challenged with OVA 5 weeks post-infection (PI). Visceral pain was assessed by quantification of the visceromotor response (VMR) during colorectal distension before the infection and at 2, 4, 6 and 7 weeks post-infection. Oral tolerance was studied in infected or control mice exposed to OVA 2 weeks before s.c. OVA immunization. To check for oral tolerance, footpad swelling to OVA challenge s.c and diarrhea development after oral OVA re-challenge were evaluated.
Results : Infection with C. rodentium induced VHS 2 weeks PI recovering to normal within 4 weeks PI in Balb/c mice. Of note however, VHS was re-installed by oral feeding of OVA (week 5) in infected Balb/c but not C57Bl6 mice compared to uninfected controls, indicating loss of tolerance against OVA in infected Balb/c mice. In line, s.c. OVA resulted in footpad swelling in infected immunized mice while oral OVA re-challenge resulted in diarrhea in infected immunized Balb/c but not C57BL6 mice.
Conclusions : Our data show that infection with C. rodentium prevents the induction of oral tolerance and triggers the induction of an immune response to the "innocent" bystander antigen OVA. Re-exposure to this antigen in the PI phase results in reactivation of this immune response leading to VHS in mice with a Th2 genetic background. Based on these data, we propose that this mechanism may contribute to the development of post-infectious IBS, especially in Th2 prone individuals.

- B11 -

EVIDENCE FOR HISTAMINE-MEDIATED POTENTIATION OF TRPV4 AND TRPA1 SIGNALING IN SUB-MUCOSAL NEURONS OF IBS PATIENTS AND MOUSE DRG NEURONS. D. Balemans (1), J. Aguilera-Lizarraga (1), W. Vanbrabant (1), A. Moonen (1), C. Cirillo (1), M. Florens (1), S. Van Der Merwe (2), P. Vanden Berghe (1), M. M. Wouters (1), G. E. Boeckxstaens (1). (1) KU Leuven, Leuven, Belgium, TARGID ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Hepatology.

Introduction : Mast cell activation and sensitization of neuronal TRP channels have been proposed to underlie visceral hypersensitivity in preclinical models. We previously showed evidence for histamine-mediated sensitization of TRPV1 in patients with irritable bowel syndrome (IBS) : incubation of dorsal root ganglia (DRG) with supernatant of rectal biopsies of patients with IBS resulted in H1R-mediated sensitization of TRPV1, while rectal submucosal neurons of IBS patients were more sensitive to the TRPV1 agonist capsaicin compared to healthy volunteers (HV).
Aim : As TRPV4 and TRPA1 may also play a role in visceral hypersensitivity, we compared TRPV4 and TRPA1-induced neuronal activation in IBS and HV, and evaluated the effect of histamine on these nociceptors in human submucosal neurons and murine DRG.
Methods : The submucosal plexus was isolated from rectal biopsies taken from 16 HV (4M, median age of 44 yrs IQR [36-53]) and 13 IBS patients (7M, median age of 40 yrs IQR [31-48]), and was loaded with Fluo-4 for calcium imaging. Responses to the TRPV4 agonist GSK1016790A (0.001 and 0.01 nM) and the TRPA1 agonist cinemaldehyde (0.1 and 10 nM) were compared between IBS and HV. In addition, the effect of pre-incubation with 10 μM histamine on the GSK1016790A and cinemaldehyde response was studied in HV. In parallel, murine DRGs were isolated and loaded with Fura-2 to study the effect of histamine (10 μM, 10 min) on cinemaldehyde (10 μM) and GSK1016790A (1 nM) responses.
Results : Application of the TRPV4 agonist GSK1016790A as well as the TRPA1 agonist cinemaldehyde evoked significantly higher peak amplitudes in submucosal neurons of IBS patients compared to HV (GSK1016790A : 0.001 nM : HV : 0.14 ± 0.07 % response (n = 8) vs IBS : 1.99 ± 0.41 % response (n = 6), p = 0.0045 ; 0.01 nM : HV : 0.38 ± 0.13 % response (n = 9) vs IBS : 3.02 ± 0.19 % response (n = 5), p = 0.003 ; cinemaldehyde : 0.1 nM : HV : 0.18 ± 0.08 % response (n = 7) vs IBS : 2.00 ± 0.55 % response (n = 6), p = 0.0051 ; 10 nM : HV : 0.34 ± 0.08 % response (n = 7) vs IBS : 1.20 ± 0.16 % response (n = 10), unpaired t-tests). Moreover, pretreatment with histamine significantly increased the response to GSK1016790A and cinemaldehyde in submucosal neurons from HV (GSK1016790A before histamine : 0.27 ± 0.08 % response (n = 6) vs GSK1016790A after histamine : 1.00 ± 0.27 % response (n = 6), p = 0.037 ; cinemaldehyde before histamine : 0.46 ± 0.13 % response (n = 6) vs cinemaldehyde after histamine : 4.27 ± 0.66 % response (n = 6), p = 0.0027, paired t-tests). Murine DRG neurons responded to the TRPA1 agonist cinemaldehyde but not to the TRPV4 agonist GSK1016790A. In line with human submucosal neurons, incubation with histamine significantly potentiated the calcium response to cinemaldehyde (cinemaldehyde + Krebs : 72 ± 16 nM (n = 43) vs cinemaldehyde + histamine : $422 \pm .9$ nM (n = 70), $p < 0.0001$, unpaired t-test)
Conclusions : Our data illustrate sensitization of TRPV4 and TRPA1 in submucosal neurons of IBS patients compared to HV, an effect that can be mimicked by histamine. In line, histamine increases the response to TRPA1 in murine DRG neurons. Our results suggest that the mucosal microenvironment in IBS contains mediators, most likely including histamine, that sensitize nociceptors such as TRPV1, TRPV4 and TRPA1, potentially contributing to increased visceral pain perception observed in these patients.

- B12 -

EVIDENCE FOR A NEW MECHANISM UNDERLYING PERSISTENT VISCERAL HYPERSENSITIVITY AND INCREASED PERMEABILITY IN A MODEL OF POST-INFECTIOUS IBS. J. Aguilera-Lizarraga (1), S. Mondelaers (1), M. Florens, D. Balemans, S. Theofanous, P. Perna, M. Wouters, G. Boeckxstaens. KU Leuven, Leuven, Belgium, Translational Research in Gastrointestinal Disorders (TARGID).

Introduction : Infectious gastroenteritis is associated with an increased risk to develop irritable bowel syndrome (IBS). Although persistent low-grade immune and/or mast cell activation have been proposed to underlie the increased mucosal permeability and visceral hypersensitivity (VHS) observed in IBS, the exact mechanism involved remains unclear. Here, we hypothesized that infection with a pathogen triggers an aberrant Th2 immune response against luminal bystander antigens with activation of the immune system upon re-exposure.
Aim : IBS features such as VHS and colonic permeability were studied upon re-exposure to OVA in Th2 predominant Balb/c mice infected with Citrobacter rodentium. Ovalbumin (OVA) was selected as bystander antigen and was introduced during an infection.
Methods : Four groups of mice were studied (n = 11-13/group). Groups 1 and 2 : mice were infected with C. rodentium in the presence (infected OVA-OVA) or absence (infected NaCl-OVA) of OVA and were re-challenged with OVA (5 weeks post-infection). Group 3 : non-infected (but exposed to OVA) mice were re-challenged with OVA (non-infected OVA-OVA). Group 4 : mice were infected in presence of OVA but "re-challenged" with saline (infected OVA-NaCl). Visceral pain was assessed by recording of the visceromotor response using abdominal muscle electromyography during colorectal distention before and at 2, 4, 6 and 7 weeks post-infection. VHS was considered when the area under the curve was > 5.04 (= 95th percentile). Thereafter, mice were sacrificed and the colon was collected to study mucosal permeability in Ussing chambers and to assess expression of pro-inflammatory cytokines.
Results : C. rodentium induced increased pain perception in all three infected groups (VMR infected OVA-OVA = 9.71, $p < 0.001$; VMR infected OVA-NaCl = 11.65, $p < 0.001$; VMR infected NaCl-OVA = 8.82, $p < 0.01$) at 2 weeks post-infection compared to the non-infected mice (VMR = 3.68), returning to normal after 4 weeks. Of note, VHS was re-installed by OVA re-challenge but only in mice that had OVA during infection (infected OVA-OVA, VMR = 7.47, $p < 0.01$) : 10 of 13 mice were VHS at week 7. In contrast, infected OVA-NaCl (VMR = 2.86) or infected NaCl-OVA (VMR = 2.82) mice all had normal pain perception. In line, only the infected OVA-OVA mice (103.6 ng fluorescein/mL/cm2, $p < 0.01$) showed increased colonic permeability compared to the other 3 groups (non-infected OVA-OVA = 35.0 ng fluorescein/mL/cm2 ; infected OVA-NaCl = 16.6 ng fluorescein/mL/cm2 ; infected NaCl-OVA = 15.6 ng fluorescein/mL/cm2). No differences in cytokines expression (IL-4, IL-10, IL-1b, IL-6, INFγ, TNFα, cKit, MCP-1 and TGFβ) were found.
Conclusions : C. rodentium infection induces a short-lasting VHS returning to normal after 4 weeks. In mice exposed to OVA during infection, re-exposure to OVA re-installed VHS and increased mucosal permeability in the absence of overt inflammation. Based on these data, we propose that infection induces a bystander immune response to intraluminal antigens resulting in post-infectious IBS upon persistent exposure to these antigens. Future studies will unravel the potential role of mast cells in this process.

- B13 -

FUNCTIONAL DYSPEPSIA : IMPAIRED INTRAGASTRIC DISTRIBUTION OR IMPAIRED GASTRIC EMPTYING-AN ATTEMPTED EVALUATION BY NUCLEAR SCINTIGRAPHY. V. Agarwal. Medanta, The Medicity Hospital, Gurgaon, India, Nuclear Medicine Department.

Introduction : Functional Dyspepsia (FD) is a heterogeneous disorder and is a diagnoses of exclusion. Many disorders namely post-prandial distress syndrome (PDS) and epigastric pain syndrome (EPS) have similar symptoms. By definition, presence of symptoms thought to originate in the gastro-duodenal region (post-prandial fullness, early satiation, epigastric pain or burning), in the absence of any organic, systemic or metabolic disorder-should explain the condition. It has been suggested that these patients may respond to gastric pro-kinetic or fundus-relaxing drugs-agents that alter gastric motility. Indeed, some patients do have delayed gastric emptying, but overall, there seems to be little relation between rate of emptying and symptoms.
Aim : This study is an attempt to find whether it is just delayed gastric emptying or maldistribution of food within gastric cavity-the cause of symptoms of FD.
Methods : We examined 18 patients, having symptoms of bloating and epigastric discomfort but without any identifiable organic cause or acid related disorder ; and 08 volunteers. All of them were served Tc-99m DTPA mixed food (consisting of wheat porridge) and were asked to have it over 20 minutes. Soon after finishing their meals, they were asked to stand upright in front of gamma camera, and imaged for 1 minute over the area of upper abdomen, every 10 minutes, for a total of 90 minutes (total 10 images). Then, the images were divided into upper 1/2 (proximal) and lower 1/2 (distal) gastric portions empirically, keeping in mind that stomach otherwise anatomically also consist of proximal :distal in the ratio of

40 :60. Being empirical gave us the freedom of being reproducible in every patient. The time-activity curves (TAC) were obtained for upper1/3rd, lower 2/3rd and total stomach region.
Results : TAC of total stomach region between patients and volunteers was not significantly different in its information, meaning that the total emptying in patients was no different from the volunteers except in 2, which showed delayed gastric emptying ; but TAC of distal stomach region (lower 2/3rd) was. In the volunteers, food remained predominantlyin the proximal half and then moved towards the distal half ; however in the patient sub-group, food moved quickly from the fundus to the antrum and showed stasis of food for longer duration (in antrum) as compared to the volunteers.

Conclusions : Our study indicates that the primary cause of FD is the intra-gastric maldistribution of food (stasis in the distal stomach and antrum) rather than the abnormal gastric emptying. This might help in tailoring better treatment in form of drugs which affect intra- gastric motility rather than drugs which simply enhance gastric emptying.

- B14 -

THE EFFECT OF A HIGH AND PROTEIN WEIGHT LOSS DIET ON COLONIC FERMENTATION AND FECAL WATER TOXICITY. K. Windey (1), E. Backx (2), V. De Preter (1), L. De Groot (2), K. Verbeke (1). (1) KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) Wageningen University, Wageningen, The Netherland, Division of Nutrition.
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Introduction : High protein diets are increasingly popular as they result, at least on the short term, in increased weight loss. However, concerns are raised considering the increase in protein fermentation induced by high protein intake. In vitro and animal studies suggest protein fermentation to be detrimental to gut health, although evidence in humans is mostly lacking.
Aim : The impact of weight loss diets differing in amount of protein on colonic fermentation and on fecal water genotoxicity and cytotoxicity was investigated in overweight subjects.
Methods : Sixty subjects (age : 62.7 ± 5, BMI = 31.2 ± 3.0 kg/m2) performed a double-blind, parallel RCT comparing a standard protein weight loss diet (SP, 15% protein) to a high protein weight loss diet (HP, 30% protein). Both diets were caloric restricted with 25%. Fecal samples were collected before the start of the diet and after 12 weeks. Colonic fermentation was characterized through an untargeted metabolomics approach using GC-MS. Fecal water genotoxicity and cytotoxicity were analyzed as parameters of gut health using the Comet Assay and WST-1 assay, respectively. Clustering techniques were applied to detect fermentation metabolites associated with cytotoxicity or genotoxicity.
Results : Weight loss after 12 weeks amounted to 9.1 ± 3.4 kg after the SP diet ($p < 0.001$) and 8.9 ± 2.9 kg after the HP diet ($p < 0.001$). Absolute protein intake during the HP diet was 116.7g/d and 83.5g/d during the SP diet. Both weight loss diets modified colonic fermentation. Short chain fatty acids and medium chain fatty acids were reduced after both diets, while aldehydes were more prevalent in the samples collected at the end of both diets. Samples collected after the HP diet are associated with higher levels of sulfides. Fecal branched chain fatty acid-concentrations were reduced after the SP-diet ($p = 0.05$) and remained unaffected after the HP-diet ($p = 0.21$). Parameters of gut health were not affected by any diet (genotoxicity : $p = 0.25$ for SP and $p = 0.22$ for HP ; cytotoxicity : $p = 0.36$ for SP and $p = 0.32$ for HP). No correlation was found between body weight loss and fecal water cytotoxicity ($p = 0.23$) nor genotoxicity ($p = 0.69$). However, higher levels of acids and sulfides were associated with higher cytotoxicity and genotoxicity.
Conclusions : Parameters of gut health were not affected by weight loss per se nor by diet composition (protein intake). However sulfides, previously suggested as genotoxic agents1,2, were more prevalent after the HP diet and were associated with fecal water genotoxicity and cytotoxicity. Therefore, the mechanisms of sulfide-induced toxicity in the gut need further investigation. In the mean time, caution is warranted when using high protein diets to obtain weight loss. 1Attene-Ramos MS, et al. Mol Cancer Res 2007 ;5 :455-9 2Windey K, et al. PLoS One 2012 ;7 :e52387 3Russell WR, et al. Am J Ckin Nutr 2011 ;93 :1062-72

- B15 -

HIGH PROTEIN INTAKE ELEVATES FECAL WATER GENOTOXICITY IN SUBJECTS WITH HIGH LEVELS OF SULFATE-REDUCING BACTERIA. K. Windey (1), V. De Preter (1), L. Deroover (1), G. Huys (2), G. Vansant (3), K. Verbeke (1). (1) KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Gent, Gent, Belgium, Laboratory of Microbiology & BCCM/LMG Bacteria Collection ; (3) KU Leuven, Leuven, Belgium, Department of Nutrition–Public Health Medicine.

Introduction : In healthy subjects, increased fecal levels of sulfides were associated to higher fecal water genotoxicity1 confirming in vitro experiments that demonstrated the genotoxic potential of hydrogen sulfide (H2S) in colonocytes2. In the colon, H2S is produced by the sulfate reducing bacteria (SRB) from sulfur-containing amino acids or inorganic sulfate and sulfite, both frequently used additives in preserved foods.

Aim : We investigated whether levels of SRB at the start of a high protein diet (either isocaloric or caloric restricted) predispose to increases in fecal water genotoxicity.
Methods : Fecal samples were obtained from 20 normal-weight subjects before and after 2-weeks of an isocaloric high protein (HP ; 27% protein) diet and from 30 overweight subjects before and after 12 weeks of a high protein weight loss diet (HP-WL ; 30% protein, 25% energy restriction). The numbers of SRB were quantified in the fecal samples using RT-PCR. Fecal water genotoxicity was assessed using the Comet Assay and expressed as μm tail length (TL). Relative concentrations of sulfides were determined using GC-MS.
Results : Absolute protein intake amounted to 2.0g/kg BW/d during the isocaloric HP diet and to 1.7g /kg BW/d during the HP-WL diet. Fecal numbers of SRB were significantly higher after the isocaloric HP diet compared to the LP diet ($p = 0.03$). The HP-WL diet tended to increase numbers of SRB compared to baseline ($p = 0.10$). After the isocaloric HP diet, baseline numbers of SRB correlated positively with an increase in fecal water genotoxicity ($p = 0,04$; Spearman's rho = 0,46). In subject with low numbers of SRB, the effect of the HP diet on fecal water genotoxicity [-13.2 μm TL (-43.7 – 21.2)] was significantly different from the effect in the group with high SRB numbers [37.0 μmTL (-2.4 – 55.2) ; $p = 0.04$]. Relative concentrations of sulfides were higher in the group with high numbers of SRB compared to the group with low numbers. After the HP-WL diet baseline numbers of SRB were not correlated to changes in fecal water genotoxicity ($p = 0.72$; Spearman's rho = 0.071). The changes in fecal water genotoxicity after the diet were not different between the group with high SRB [-13.9 μm TL (-52.3 – 14.6)] and low numbers of SBR [0.7 μm TL (-46.2 – 5.6) ; $p = 0.57$].
Conclusions : High protein intake stimulates the number of SRB in the colon. The baseline number of SRB predisposes to increased fecal water toxicity only after an isocaloric high protein diet, but not after a high protein calorierestricted diet suggesting that a minimal absolute protein intake is required. The increased fecal water genotoxicity after increased protein intake is associated with an increased production of sulfides which are known genotoxic agents. 1Windey K, et al. PLoS One 2012 ;7 :e52387 2Attene-Ramos MS, et al. Mol Cancer Res 2007 ;5 :455-9.

- B16 -

FECAL MICROBIOTA TRANSPLANTATION IN IRRITABLE BOWEL SYNDROME WITH BLOATING : RESULTS FROM A PROSPECTIVE PILOT STUDY. T. Holvoet (1), J. Boelens (2), M. Joossens (3), J. Raes (3), M. De Vos (4), D. De Looze (4). (1) UZ Gent, Gent, Belgium, Gastroenterology ; (2) UZ Gent, Gent, Belgium, Microbiology ; (3) VIB, Leuven, Belgium, Microbiology and Immunology ; (4) UZ Gent, Gent, Belgium, Gastroenterology.

Introduction : Intestinal microbiota dysbiosis is thought to play an important role in the complex pathophysiology of irritable bowel syndrome (IBS), especially in diarrhoea-predominant IBS with severe bloating. Fecal microbiota transplantation (FMT) has been shown to be an effective means of correcting this gut microbiota imbalance and has become the preferred treatment strategy in patients with recurrent Clostridium difficile infections. In this pilot study we wanted to evaluate the effects and safety of FMT in IBS patients.
Aim : In this pilot study we wanted to evaluate the effects and safety of FMT in IBS patients.
Methods : Patients with refractory IBS symptoms and severe bloating were selected for inclusion. Donors of fecal material were screened following standard protocols used in Clostridium patients with extensive serology (HAV, HBV, HCV, Treponema, HIV) and stool examination (enteropathogens, Clostridium difficile toxin and parasites). Fecal transplants were prepared with fresh stools (< 6 hours after collection) as previously described and administered to the right colon of patients by means of colonoscopy. Treatment was considered effective if patients reported adequate relief of IBS symptoms in general and bloating in particular at week 12 posttransplantation. Secondary end points were changes in IBS related symptom scores and quality of life questionnaires. Stool samples were collected before and at different timepoints following transplantation and 16S rRNA amplicon sequencing to follow the dynamics of the gut microbiota is ongoing.
Results : Between November 2013 and April 2014 a total of 12 IBS patients underwent FMT without any reported complications. At week 4 and week 12, respectively 67% and 75% of patients reported adequate relief of general IBS symptoms and bloating in particular. At 4 weeks a statistically significant reduction was seen in discomfort (mean reduction of 35%, $p = 0.007$), urgency (-29.5%, $p = 0.038$), abdominal pain (-31%, $p = 0.012$), bloating (-32%, $p = 0.007$) and flatulence (-28%, $p = 0.017$). At week 12, general abdominal discomfort (-20%, $p = 0.037$) pain (-35%, $p = 0.008$), bloating (-25%, $p = 0.011$) and flatulence (-32%, $p = 0.005$) was significantly lowered. Additionally, a statistically significant improvement in quality of life was seen over the course of the study (mean improvement of 16.3% ($p = 0.011$)).
Conclusions : FMT with healthy donor stools might be beneficial in the treatment of refractory IBS with diarrhoea and severe bloating. Based on these results a randomised, controlled clinical trial is warranted and feasible.

- B17 -

PAN-COLONIC PRESSURIZATIONS ASSOCIATED WITH RELAXATION OF THE ANAL SPHINCTER IN MAN : A HIGHLY PREVALENT COLONIC MOTOR EVENT IDENTIFIED USING HIGH-RESOLUTION MANOMETRY.
M. Corsetti (1), G. Pagliaro (2), I. Demedts (1), E. Deloose (1), A. Gevers (1), C. Scheerens (1), N. Rommel (1), J. Tack (1). (1) KU Leuven, Leuven, Belgium, Department of Clinical and Experimental Medicine, Translational Research Center for Gastrointestinal disorders (TARGID) ; (2) Catholic University, Rome, Italy, Digestive Endoscopy Unit.

Introduction : Only few studies have applied high-resolution manometry (HRM) to the study of colonic motility in adult man and none of them have concurrently evaluated the colonic and anal motor activity.
Aim : to evaluate colonic motility and its relationship with the anal sphincter activity by means of HRM.
Methods : In 10 volunteers the HRM catheter was advanced as proximally as feasible during colonoscopy. Colonic pressures were recorded for four hours before and three hours after a meal.
Results : The catheter was clipped to the right colon in 8 out of 10 volunteers, and at least to the transverse in the remaining. In all the subjects pressure increases of 24 ± 4s, simultaneously occurring in all the colonic sensors (pan-colonic pressurizations) and associated with anal sphincter relaxation, were identified. Subjects had on average 85 ± 38 pan-colonic pressurizations which were associated with feelings of gas and desire to evacuate gas. Pan-colonic pressurizations increased significantly during meal ($p = 0.007$) and decreased afterward ($p = 0.01$). The mean number of propagating sequences was 47 ± 39, and only retrograde increased significantly postprandially ($p = 0.01$). High-amplitude propagating sequences ($n = 2$) occurred in only one subject. In all but two subjects, non-propagating motor activity was also observed.
Conclusions : This study demonstrates for the first time the occurrence of pan-colonic pressurizations associated with relaxations of the anal sphincter in healthy subjects. The occurrence of pan-colonic pressurizations is influenced by meal and is associated with sensations of gas or a desire to evacuate gas, suggesting they may represent a colonic venting system.

- B18 -

LARGEST REPORTED PROSPECTIVE EVALUATION OF A LOW FODMAP DIET IN IBS PATIENTS.
J. Arts (1), J. Tack (2), T. Lanssens (1), R. Van Schaik (1), R. Arts (1), R. Spitaels (1), A. Holvoet (1), S. Decock (1), P. Van Hootegem (1). (1) AZ Sint-Lucas, Brugge, Belgium, Gastroenterology Department ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Neuro-Gastroenterology Department.

Introduction : The irritable bowel syndrome (IBS) is a highly prevalent condition with unclear underlying pathophysiology and for which no standard effective therapy is established. A number of recent studies have shown that fermentable oligo-, di-, mono-saccharides and polyols (FODMAPS) alter intestinal physiology and can trigger gastro-intestinal symptoms, while a low FODMAP diet improves symptoms in tertiary care IBS patients
Aim : Our aim was to perform a prospective study to determine whether a low FODMAP diet improves symptoms in IBS patients in the setting of a regional hospital in Belgium.
Methods : Consecutive IBS patients, seen at the gastroenterology outpatient clinic, were instructed how to take a low FODMAP diet by an experienced dietician. All patients were asked to score their symptom severity before and 8 weeks after the implementation of a low FODMAP diet. The intensity of 5 symptoms (bloating, abdominal cramps, borborygmi, stool disturbances, fatigue) was evaluated using 0 to 100 mm visual analogue scales (VAS). The global effect of the low FODMAP diet was also evaluated by means of a VAS (0mm = no improvement to 100mm = complete symptom resolution). VAS are reported as mean+/-standard deviation. Responses were compared using the Wilcoxon signed rank test. Results were considered significant if $p < 0.001$.
Results : Eighty-two patients with IBS according to Rome III criteria, 83% females, mean age 39 ± 12 years, were included in this prospective study. After 8 weeks of low FODMAP diet, we found a significant reduction of global symptom score (sum of all evaluated symptoms) (318 ± 61 vs. 131 ± 61 ; $p < 0.001$). An improvement of > 50% of the global symptom score was observed in 65% of the patients. The low FODMAP diet also improved all cardinal IBS symptoms (abdominal pain, 63 ± 21 vs. 29 ± 20 mm ; bloating 58 ± 20 vs. 30 ± 22mm ; flatulence 69 ± 18 vs. 30 ± 20 mm and stool disturbances (64 ± 20 vs. 30 ± 20mm) (all $p < 0.001$). In addition, fatigue was significantly less with a low FODMAP diet (63 ± 20 vs. 41 ± 26mm, $p < 0.001$). The global efficacy rating was 65 ± 24mm on the VAS. Of the 82 patients, 21 had a result of > 90mm, these patients can be considered as complete responders.
Conclusions : A diet low in FODMAPs effectively reduces IBS symptoms and fatigue in secondary care practice. Robust symptom improvement occurs with a strict low FODMAP diet. To our knowledge, this prospective study is the largest reported trial and confirms the results obtained in tertiary care centers. The results support the use of dietary intervention in IBS in general clinical practice.

CASE REPORT SESSION

- C01 -

SYSTEMIC CAT SCRATCH DISEASE MIMICKING LYMPHOMA IN A PATIENT WITH CROHN'S DISEASE. F. Wuestenberghs (1), J. Depaus (2), G. Mavrogenis (1), A. Sibille (1), P. Warzée (1). (1) Grand Hopital de Charleroi, Charleroi, Belgium, Department of Gastroenterology ; (2) Grand Hopital de Charleroi, Charleroi, Belgium, Department of Oncology and Hematology.

Background : Due to the growing use of immunomodulator therapy in inflammatory bowel diseases (IBD), physicians increasingly encounter opportunistic infections in caring for patients with IBD. To the best of our knowledge, there is only one case report of a systemic Bartonella henselae infection in association with Crohn's disease, which occured during immunosuppressive treatment with infliximab.
Aim : We describe a case of systemic bartonellosis in a Crohn's disease patient treated by azathioprine. **Case report** : A 61-year-old man had been treated for ileal Crohn's disease since 2004 and had received azathioprine (2.5 mg/kg/day) for 2 years. In January 2014, he was hospitalized for high fever, night sweats and weight loss. Endoscopy disclosed active duodenal Crohn's disease. The diagnostic work-up revealed serum inflammation, mild cytolytic and cholestatic hepatitis, "biologic" pancreatitis (rapidly resolving) and a suspicion of cholangitis on endoscopic ultrasound (EUS). Common infections were excluded and no improvement was seen with antibiotic treatment (piperacillin/tazobactam). An infectious mononucleosis was suspected since anti-EBV IgM and IgG antibodies were positive, together with splenomegaly on imaging. However, Epstein-Barr Virus (EBV) Polymerase Chain Reaction (PCR) analysis was negative, indicating a false-positive test result. One month later, despite the initial clinical improvement, a necrotic submaxillary adenopathy was diagnosed, suggesting a lymphoma. Cervical node biopsy showed nonspecific subacute inflammation indicating an infectious process. Bone marrow biopsy was negative for lymphoma. Whole body 18F-FDG positron emission tomography/computed tomography (PET/CT) displayed hypermetabolic lesions in both infra- and supra-diaphragmatic lymph nodes, in the spleen and diffusely in the skeleton. Magnetic resonance imaging of the spleen revealed multiple septic lesions. The medical work-up showed doubtful Bartonella henselae serology. EUS-guided fine needle aspiration biopsies of mediastinal lymph nodes were performed and disclosed nonspecific acute adenitis with non-necrotizing granulomas. Systemic bartonellosis was confirmed by PCR analysis of the lymph node tissue. Retrospectively, the patient reported a cat scratch on his nose a few days before the beginning of his symptoms. Serologic cross-reactivity could explain the prior false-positive EBV testing. The symptoms of the patient resolved following discontinuation of azathioprine together with a five-day azithromycin regime. Lesions on 18F-FDG PET/CT imaging disappeared completely, except splenomegaly and the thickening of the common bile duct on abdominal ultrasound. At follow-up 6 months later, the patient was completely asymptomatic.
Discussion : Bartonella henselae is the agent of cat scratch disease in immunocompetent hosts. In contrast, immunocompromised patients (transplant recipients, patients with acquired immunodeficiency syndrome, cancer patients under chemotherapy, patients treated with tumor necrosis factor-alpha [TNFα] antagonists…) are at risk of developing systemic bartonellosis, with extranodal manifestations including neurologic, hepatic and/or bone involvement.
Conclusions : Systemic Bartonella henselae infection is a rare complication of immunosuppression in Crohn's disease patients, even without TNFα blockers, and should be kept in mind in the differential diagnosis of fever of unknown origin and polyadenopathy in this population.

- C02 -

A CASE OF PELLAGRA IN A PATIENT WITH WHIPPLE'S DISEASE. T. Van Nieuwenhove (1), B. Strubbe (2), K. De Boulle (3), M. Stubbe (1). (1) OLV Ziekenhuis, Aalst, Belgium, Rheumatology ; (2) OLV Aalst, Aalst, Belgium, Gastroenterology ; (3) Aalst Dermatology Group, Aalst, Belgium, Dermatology.

A 60 year old man was diagnosed with Whipple's disease in 2013. The patient had been suffering from polyarthritis since 2005. Diagnosis of seronegative rheumatoid arthritis was made and the patient treated with several DMARDs (both biologicals and non-biologicals) but none were successful. When tocilizumab was administered the patient experienced severe diarrhea and weight loss. Diagnosis of Whipple's disease was made on the basis of typical findings on gastric endoscopy and on biopsy. Treatment with intravenous ceftriaxone followed by thrimetoprim-sulfamethoxazole was started but had to be discontinued due to inefficacy. A switch to a treatment with doxycycline and hydroxychloroquine was made. After a few months the patient presented with signs of dermatitis limited to his hands. Differential diagnosis were : psoriasis, drug reaction (photosensitivity) due to chronic use of doxycycline, dermatomyositis or lupus erythematodes. Pathology of a cutaneous biopsy of the lesions revealed an interface dermatitis both clinically and histologically compatible with vitamin B3 deficiency (pellagra). The patient was given nicotinamide and after 3 months the skin lesions totally resolved. Furthermore he was free of arthritic and gastro-intestinal symptoms. Pellagra is caused by vitamin B3 deficiency and is a rare entity in industrialized countries. The most characteristic finding is the presence

of a symmetric hyperpigmented rash presenting on exposed areas of the skin. Other clinical findings are non-specific gastro-intestinal and neurologic symptoms. In our countries, this deficiency is seen in patients with inflammatory bowel diseases or other malabsorption disorders such as alcoholism. Pellagra is a challenging diagnosis because it is very rare and could be mistaken for other skin diseases. To our knowledge this is the first case description of pellagra in a patient suffering from Whipple's disease.

- C03 -

WHEN THE VIRUS GOES VIRAL. J. Nijs (1), G. Moors (1), K. Demuynck (2), J. Vanmeerbeek (3), P. Grouwels (4), H. Verbrugge (5). (1) Sint-Trudo Ziekenhuis, Sint-Truiden, Belgium, Gastroenterology ; (2) Sint-Trudo Ziekenhuis, Sint-Truiden, Belgium, Pneumology ; (3) Sint-Trudo Ziekenhuis, Sint-Truiden, Belgium, Pathology ; (4) Sint-Trudo Ziekenhuis, Sint-Truiden, Belgium, Radiology ; (5) Sint-Trudo ziekenhuis, Sint-Truiden, Belgium, Internal Medicine.

We want to present the case of a 74 year old male with a prior history of multiple abdominal surgeries i.e. Hartmann resection for perforated diverticulitis, transabdominal prostatectomy, cholecystectomy and correction of an umbilical hernia. In november 2011 he was admitted at the emergency room for gastrointestinal obstruction. Explorative laparotomy with extensive adhesiolysis was performed. Peroperative diagnoses of inflammatory Crohn's disease of the terminal ileum was made. Pathology showed the presence of granuloma's. He was treated with peroral budesonide. In february 2012 colonoscopy showed persistent inflammation of the terminal ileum. MRI enteroclysis showed multiple inflammatory lesions of the terminal and preterminal ileum with substenosis and skip lesions. We then started 6-mercaptopurine, but in april 2012 6-MP had to be stopped due to hepatotoxicity. Decision was made to start with infliximab, but tuberculosis skin test was positive. So before starting Infliximab a treatment with Nicotibine 300 mg per day was initiated. 6 weeks later Infliximab was started with standard start-up dose of 5 mg/kg week 0, 2 and 6 and maintenance therapy with 5 mg/kg every 8 weeks. 1 year later, in april 2013 patient was fine and had no abdominal complaints, but he suffered from cough with yellow expectorations. Chest radiography did not show any abnormalities. 8 weeks later, the chough was still present. We performed a new chest X-ray and now a round consolidation was shown in the right upper lobe of the lung. Differential diagnosis was made between a pneumonia, a malignant tumor or reactivation of TBC. Bronchoscopy showed 2 papillomatous tumors in the larynx. The bronchus to the right upper lobe was stenotic due to edema. Pathology proved the presence of a squamous papillomatous tumor. We immediately stopped Inflfiximab and over the next few months we saw a complete disappearance of the consolidation.

- C04 -

THE FLOW MUST GO ON. L. Vandenabeele (1), D. De Vos (2), A. Dik (3), D. De Wolf (4), P. Smeets (5), A.Geerts (6), X. Verhelst (6), H. Van Vlierberghe (6). (1) UZ Gent, Gent, Belgium, Gastroenterology ; (2) UZ Gent, Gent, Belgium, Radiology ; (3) UZ Gent, Gent, Belgium, Interventional Radiology ; (4) UZ Gent, Gent, Belgium, Pediatric Cardiology ; (5) UZ Gent, Gent, Belgium, Radiology ; (6) UZ Gent, Gent, Belgium, Gastroenterology.

We present this unusual case of a chronic Budd-Chiari syndrome with a late presentation and a quite unusual cause. A female patient (°1967) with a prior history of Behçet's disease, pulmonary embolism and deep venous thrombosis, experienced anemia as a consequence of hypermenorrhea caused by an endometrial carcinoma . Clinical examination revealed a slim lady in good general health with marked thoracic collateral veins (pictures available). Ultrasound imaging of the abdomen showed a nodular liver, typical of cirrhosis and a small amount of ascites. CT scan showed patency of the arterial, portal and venous hepatic circulation. A thorough examination to elucidate the cause of the liver disease (viral, auto-immune, metabolic...) and the reason for the underlying thrombotic disorder, did not find helpfull clues. Apart froma mild thrombopenia (127000), there were no biochemical signs of liver decompensation. (Child A 6 points). A transjugular liver biopsy with measurement of the portal venous pressure gradient was attempted. However, during femoral punction of the femoral vein, it was not possible to canulate the caval vein. Injection of contrast fluid only showed abdominal collaterals channeling blood flow to a prominent azygos vein. A jugular approach was neither succesfull. A new CT scan of the liver and abdominal was performed, showing a veinous obstruction of the blood entry in the right atrium and presence of only one large (right) hepatic vein. Further investigation with cardiac MRI reveiled a persistent Eustachian valve, which obstructed the blood flow in the caval vein. A balloon dilatation resulting in a release of the obstruction was performed. We would be happy to share this patient report of a very rare cause of a Budd Chiari syndrome, due to a persistent Eustachian valve in the heart. The case report will be illustrated by dynamic cardiac MRI images showing nicely this congenital abnormality and images of the therapeutic balloon dilatation.

- C05 -

ACUTE INTERMITTENT PORPHYRIA OFTEN MISDIAGNOSED AS FUNCTIONAL GASTROINTESTINAL DISORDER. V. Skuja (1,4), Z. Straume (1,4), S. Hasnere (3,5), A. Proskurina (4), I. Krupnova (2), M. Suvalova (2), A. Derovs (1,4), A. Lejnieks (1,4). (1) Riga East Clinical University Hospital, Gastroenterology, Hepatology and Nutrition Clinic, Riga, Latvia ; (2) Riga East Clinical University Hospital, Infectology Center of Latvia, Intensive Care Clinic, Riga, Latvia ; (3) Pauls Stradins Clinical University Hospital, Oncology Clinic, Riga, Latvia ; (4) Riga Stradins University, Riga, Latvia ; (5) University of Latvia, Riga, Latvia.

Introduction : Acute intermittent porphyria (AIP) is one of the hereditary porphyrias, presenting as direct attacks with gastrointestinal and neurological symptoms. Due to mostly predominant gastrointestinal symptoms – severe abdominal pain, nausea, vomiting and constipation with no objective diagnostic findings AIP can be easily misdiagnosed as functional gastrointestinal disorder.
Results : a 27-year old female patient presented to the emergency department with a history of generalized, severe abdominal pain, nausea and vomiting for three days. Initial physical evaluation, abdominal ultrasound and gynecological examination showed no abnormality. The patient was discharged with a diagnosis - functional gastrointestinal disorder. However, she returned to the hospital the next day with the same complaints, new onset of fever and was hospitalized. Patient reported previous episodes of abdominal pain before menstruations, but never this severe. She experienced changing bowel habits, frequently accompanied by nausea that exacerbated when using analgesic medication and severe toxicosis during the first half of pregnancy. Family history revealed that patient's father had similar unexplained symptoms that were attributed to hepatic and pancreatic dysfunction. On physical examination she presented with diffusely tender abdomen, but no signs of acute surgical pathology. Laboratory testing showed hyponatremia (124 mmol/l) that was attributed to vomiting. She was treated symptomatically for presumed functional gastrointestinal disturbances and foodborne toxicoinfection. The next day pain worsened and staff reported the patient being confused, not remembering herself and vomiting several times. Neurological examination was notable for horizontal nystagmus, tremor of tongue and hands, limb ataxia and neck stiffness. Blood tests showed worsening hyponatremia (102 mmol/l) and patient was started on hypertonic saline. Despite the treatment she remained disoriented and required emergency intubation after a seizure. She was admitted to the Intensive care unit and received continuous sedation to maintain mechanical ventilation. Cranial and abdominal computed tomography examinations were performed, but the results were unremarkable. Laboratory tests showed leukocytosis with an elevated absolute neutrophil count, alkalosis and decreased sodium level. Eventually it was noted that patient's urine developed orange color and urinary delta-aminolevulinic acid (ALA) and coproporphyrin levels were measured (increased 27- and 9-fold, respectively). Based on clinical presentation and results of urinalysis - AIP was diagnosed. The patient was started on human hemin and glucose which together with one plasmapheresis procedure, constant electrolyte monitoring and symptomatic treatment resulted in rapid clinical improvement, significant fall in urinary ALA and coproporphyrin excretion. Patient was discharged with recommendations to avoid disease-aggravating factors (smoking, alcohol, P-450 inducing drugs, diet with low carbohydrate level), receive hospital treatment during attacks, wear a medical alert bracelet and schedule a genetic consultation for the family.
Conclusion : With AIP being a rare disease with nonspecific symptoms and usually minimal physical findings that requires specific treatment, early clinical recognition is extremely important for starting an effective treatment and improving patient's prognosis. AIP should be included in the differential diagnosis in cases of recurrent episodes of unexplained severe abdominal pain that lasts for several days and are accompanied by neurologic and/or psychiatric symptoms and hyponatremia.

- C06 -

A "STARRY NIGHT". L. Vonghia (1), K. Saevels (2), G. Moorkens (2), B. Op De Beeck (3), P. Michielsen (1), S. Francque (1). (1) UZ Antwerpen, Edegem, Belgium, Department of Gastroenterolgy and Hepatology ; (2) UZ Antwerpen, Edegem, Belgium, Department of Internal Medicine ; (3) UZ Antwerpen, Edegem, Belgium, Department of Radiology.

A 54 year old man was admitted to our department because of general malaise, debilitating fatigue and myalgia since a month and fever since two weeks. The patient was known with Hashimoto thyroiditis and penicillin allergy. At admission, the patient showed elevated inflammatory parameters (leukocytosis with neutrophilia and elevated CRP) and disturbed liver tests, namely canalicular. Urine cultures and hemocultures were negative and a chest X-ray did not show any infiltrate. Also a transoesophageal echocardiography and eyefundus-examination were negative. The abdominal ultrasound did not demostrate any inflammatory/infectious focus but showed a "starry night" aspect of the liver parenchyma, due to diffuse hyperechogenic spots, without dilatation of the biliary tree. In the meantime a PET-CT was performed to investigate a possible infectious focus. On CT-scan, in accordance with the ultrasound findings, several

millimetric hypodense liver lesions without hypercaptation on PET were visualized. An empiric therapy with ceftriaxone (because of penicillin allergy) was started. To better characterize the lesions and to study the biliary tree a magnetic resonance cholangiopancreaticography (MRCP) was planned and showed multiple sub-centimeter liver nodules, without communication with the biliary tree. There were no abnormalities of the biliary tree. The morphology, diffusion pattern and absence of pathological contrast captation were all characteristic for the presence of von Meyenburg complexes (VMCs). The liver biopsy, performed to investigate the possible cause of the disturbed liver set showed the presence of active cholangitis. Cultures of the biopsyspecimen remained negative. The patient was further treated with antibiotics (ceftriaxone) and showed a good clinical and biochemical evolution and therefore could be discharged. On outpatient follow up no recurrence of the cholangitis was noted. VMCs, also called bile duct hamartomas, are a rare clinicopathologic entity, consisting of small (< 1.5cm), usually multiple and nodular cystic lesions. They originate from embryonic bile ducts that fail to involute. VMCs have a unique MRI appearance : VMCs do not enhance after intravenous contrast, thus differentiating them from metastasis. On T1-weighted MRI, von Meyenburg complexes appear as hypointense cystic lesions and hyperintense on T2-weighted imaging relative to liver parenchyma. Further they are not in connection with the biliary tree. VMCs are typically asymptomatic, therefore the diagnosis is generally incidental. In the literature currently availabe, a few cases of VMCs were associated with cholangitis (and or jaundice). This case suggests that the association between VMCs and cholangitis, athough it is a reare condition, should be considered in case of clinical suspicion.

- C07 -

ANAL BLOOD LOSS IN A HEALTHY YOUNG WOMAN. G. LAMBRECHT (1), M. COOL (1), K. HERTVELDT (2), G. DEBOEVER (1). (1) AZ Damiaan, Oostende, Belgium, Gastroenterology Department ; (2) AZ Damiaan, Oostende, Belgium, Pathology Department.

A 38 year causasian woman presented with painless intermittent bright rectal bleeding often associated with mucus during 4 months. There is no weight loss, diarrhea, fever or other general symptoms. There is no history of sexually transmitted diseases. Anal inspection is normal and colonoscopy revealed a congested mucosa without ulceration over a distance of 5 cm from the anal verge. Biopsies were taken and showed lymfoid hyperplasia. Because a rectal lymphoma needed to be excluded, deep submucosal biopsies were taken but again mucosal and submucosal hyperplastic lymphoid follikels were seen and even immunochemistry was not in favour of lymphoma. Chlamydia PCR test and serological studies for Chlamydia trachomatis were negative. A diagnosis of lymphoid follicular proctitis(LFP) was withheld and treament was started with mesalazine suppository 1 gram daily. After 2 weeks, the patient was asymptomatic and and a rectoscopy performed 4 weeks after the start of mesalazine suppository treatment already showed regression of the rectal lesions. LFP is an uncommon inflammatory condition confined to the rectum. Patients with LFP constitute a special group with clinical, endoscopic, and histological features unrelated to other types of inflammatory bowel diseases, and have been reported to be refractory to local steroid treatment or to oral sulfasalazine. Mesalazine suppository treatment is an useful therapeutic option for symptomatic patients with LFP. Lymphoid follicular proctitis is characterized by rectal bleeding, a congested and granular mucosa without ulceration and histologically abnormal and coalescing hyperplastic lymphoid follicles. Biopsies with endoscopic submucosal resection may be helpful to identify patients with lymphoid follicular proctitis or low-grade lymphoma, as large specimens sufficient to examine the broad extent of the lesion can be obtained. Endoscopic follow-up is indicated with repeated biopsies. In a Korean study of eight patients with LFP none progressed to other diseases including ulcerative proctitis or lymphoma with a maximum follow-up of 20 months. The etiology of LFP of the rectum is unknown but several case reports showed a favourable prognosis and a good response to mesalazine suppository treatment. Conclusion : lymphoid follicular proctitis of the rectum is an uncommon inflammatory condition responsible for blood loss and can be treated with mesalazine suppositories. There is need for prospective randomised evaluation with standarized follow-up and treatment. Reference : Seo GS, Jo EY, Choi CS, Kim JW, Kim TH, Yun KJ, Nah YH. The usefulness of mesalazine suppositories for the treatment of lymphoid follicular proctitis. Korean J Gastroenterol.,2006, 47 :420-4.

- C08 -

CASE PRESENTATION: OVERWEIGHT AND ELEVATED LIVER ENZYMES: NOT ALWAYS NAFLD. J. Schreiber, C. Moreno, CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology Department.

Introduction : We present the case of a 35 year old Caucasian female addressed to the liver outpatient clinic for elevated liver enzymes. Her general practitioner did a workup after a recent EBV infection after which liver enzymes stayed elevated 6 months after the infectious phase.

Aim : The workup included an ultrasound of the abdomen which showed steatosis of the liver, absence of bile stones and duct dilatation and presence of two ovarian cysts. Blood samples showed: GOT 36 UI/L, GPT 58 UI/L, GGT 55 UI/L, total bilirubin 1.2 mg/dl. She didn't consume alcoholic beverages and smoked 1 packet of cigarettes every 2 weeks. Her medical history showed hypercholesterolemia, urticaria of unknown origin, 2 pregnancies (1 child in good health/1 hemiplegic). Her medications included: Simvastatine 20 mg, Ibuprofen (on demand), and anti-histaminics (on demand).
Methods : Physical examination showed eczema like lesions on her legs and was normal otherwise. Her weight was 80 kg for 1m70, giving a BMI of 27.7. Her blood pressure was 110/70 mmHg. A Fibroscan was performed and showed a value of 6.5 kPa and CAP of 395 dB/m. Viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson disease, α-anti-trypsin deficiency were excluded. Total cholesterol was 296 mg/dl and HDL cholesterol was 33 mg/dl. Fibrotest was 0.48. NAFLD was suspected and a liver biopsy was performed. Biopsy showed septal fibrosis (Metavir: A1-2/F2), slight microvesicular steatosis, ballooning of hepatocytes and lymphocytic infiltration.
Results : LAL deficiency belongs to a family of diseases called Lysosomal Storage Disorders. The LAL enzyme breaks down fatty material (cholesteryl esters and triglycerides), and the lack of the LAL enzyme results in a build-up of these materials in the liver and other organs. Clinical findings of this disease include elevated liver enzymes, high LDL-cholesterol, very low HDL cholesterol and hepatomegaly. This disease can lead to liver fibrosis, cirrhosis and elevates the risk of cardiovascular events.
Conclusions : We hereby present the first case of LAL deficiency in an adult patient in Belgium. This case shows how challenging this diagnosis is in a patient with a clinical metabolic profile. The patient will soon be included in an enzyme replacement study.

BELGIAN SOCIETY FOR GASTROINTESTINAL ENDOSCOPY (BSGIE) AND SMALL BOWEL GROUP

- G01 -

LONG-TERM FOLLOW-UP IN PATIENTS WITH OGIB AND NORMAL CAPSULE ENDOSCOPY. C. Van De Bruaene (1), P. Hindryckx (1), C. Snauwaert (2), B. Vanduyfhuys (2), D. Dooremont (3), M. De Vos (1), D. De Looze (1). (1) UZ Gent, Gent, Belgium, Gastroenterology ; (2) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Gastroenterology Department ; (3) AZ Sint-Elisabeth, Zottegem, Belgium, Gastroenterology Department.

Introduction : Obscure Gastrointestinal Bleeding (OGIB) accounts for approximately 5% of all digestive bleeding causes. Capsule Endoscopy (CE) is a useful tool to identify an underlying etiology located in the small bowel (SB). However, data on further long-term follow-up (FU) after a negative CE are scarce.
Aim : Studying the outcome of patients who presented with OGIB and had a normal capsule endoscopy of the small bowel.
Methods : The standardized application forms of all patients that underwent CE for OGIB between 2002 and 2013 were reviewed and the subgroup of patients with a negative CE result was identified. Follow-up information of these patients was retrieved by contacting the referring physician and/or the general practitioner.
Results : Between 2002 and 2013, 458 patients underwent CE for the indication of OGIB, from which 263 (57.4%) had a normal CE. Follow-up was available for 222 patients (Male, N = 114 ; Female, N = 108) of whom 81 presented with overt bleeding and 141 with occult bleeding. Median follow-up time was 1604.5 days (range 43-4247 days). Ninety-six patients underwent further diagnostics showing a cause for OGIB in 57 (diagnostic yield 59.4%). In 45 patients a previous origin for OGIB was suspected and CE was used to exclude a SB etiology. The final cause of anemia was identified in 102 patients : 33 in the upper GI tract, 26 in the lower GI tract, 24 outside the GI tract (i.e. gynaecological, renal, urological or hematological etiology) and 19 in the small bowel. Final outcome for the complete cohort of negative CEs was : 145 (65.3%) true negative (i.e. non SB cause of bleeding/ resolved anemia), 19 (8.6%) false negative (i.e. small bowel cause of OGIB) and 58 (26.1%) ongoing bleeding without cause. The missed SB lesions were : angiodysplasia (N = 11), Meckel's diverticulum (N = 3), SB malignancy (N = 3), jejunal erosions (N = 1) and NSAID-induced SB ulcerations (N = 1). These "false negative" CEs could not be predicted by age, gender, overt/occult bleeding, hemoglobin value or relevant comorbidities at the moment of CE. Persistent anemia after CE was predictive for finding a SB lesion, compared to true negative CEs ($p < 0.05$). Bleeding resolved in 142/222 patients (64.0%) of which 83 did not undergo any specific therapy for a GI cause of bleeding.
Conclusions : Persisting anemia after negative CE warrants further diagnostics : in 59,4% of these patients a cause for anemia was identified during long-term follow-up, of which the majority was not at the level of the small bowel. Relevant small bowel lesions on the other hand (SB Angiomas, SB tumor and Meckel diverticulum) account for 8.6% of all negative CEs.

- G02 -

LONG-TERM OUTCOMES OF COLORECTAL ESD IN A WESTERN TERTIARY REFERRAL CENTRE. C. Snauwaert (1), H. Piessevaux (1). (1) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Hepatology and Gastroenterology Department.

Introduction : Colorectal endoscopic submucosal dissection (CR-ESD) enables en-bloc resection of lesions > 2 cm which would otherwise require piecemeal removal. However, CR-ESD is still considered as a technically challenging procedure and is not widespread outside Asian expert centres.
Aim : To assess efficacy, safety and long-term results of CR-ESD and identify possible risk factors for technical difficulty.
Methods : We analysed charts from 173 consecutive patients scheduled for CR-ESD between May 2006 and July 2013. Efficacy and safety endpoints were complete en-bloc resection, mucosal recurrence rates and post-procedural complications.
Results : Median age of patients was 67 years (IQR 58-76). Lesions were located throughout the colon with predominance for the caecum (21.4%) and rectum (39.9%). Median longest and perpendicular diameter of lesions was 35mm (range 10-150mm, IQR 30-50) and 30mm (range 8-130mm, IQR 20-40) respectively. Most lesions were classified as Paris 0-IIa (45.1%), 0-Is (29.5%) and 0-IIb (17.3%). Forty-eight percent of lesions were classified as LST-NG according to the Japanese classification. In 15.6% of cases a previous resection had been attempted elsewhere. Full ESD was performed in 117 (68%) patients ; the remainder was treated using a hybrid technique of circumferential submucosal incision, dissection and finally followed by en-bloc snare resection. Median procedure time was 109 minutes (IQR 70-157). The en-bloc resection rate was 74.6% (129/173). Previous attempt at resection was a significant risk factor for en-bloc resection failure (40.8% vs. 22.7% ; $p < 0.05$). Twenty-one (12.1%) perforations occurred during ESD and in 30 patients (17.3%) a dehiscence of muscular fibres was seen, which were all successfully managed by endoscopic clip closure. One

or more post-procedure complications occurred in 46 patients (26.9%) of which 15 delayed perforations (8.6%). The complication rate decreased significantly with growing experience (e.g. 14 delayed perforations for the first 87 cases vs. 1 delayed perforation for the last 86 cases ; 16% vs. 1% ; $p < 0.05$). Two patients required surgery for post-procedural perforation salvage. Median hospital stay was 2 days (IQR 2-2). The majority of lesions (114/173 ; 65%) contained high-grade dysplasia (HGD) or more advanced histopathology : HGD (62), T1m2 (31), T1m3 (3), T1sm1 (12), T1sm2 (4), T1sm3 (1) and T2 (1). Free vertical margins were achieved in 92% (160/173) of patients. Fourteen patients underwent additional surgical resection because of incomplete resection or unfavourable histology. Endoscopic follow-up was available in 147 patients. During the median follow-up period of 13 months (IQR 3-24), one mucosal recurrence occurred (0.7%).
Conclusions : CR-ESD is effective with very low local recurrence rates. Previous attempts at snare resection are predictive for en-bloc resection failure. In general, post-procedural course is favourable with short hospitalisation stays. Complications (especially delayed perforations) have to be considered, but usually can be managed conservatively. A higher level of experience significantly reduces the post-procedural complication rate.

- G03 -

ANALYSIS OF HIGH RESOLUTION MICROENDOSCOPIC IMAGES FOR AUTOMATED DIAGNOSIS OF COLON NEOPLASIA. K. T. Du (1), S. Anandasabapathy (2), Y. Tang (3), R. Richards-Kortum (3), A. D. Polydorides (2). (1) Monash University, Australia, Department of Gastroenterology ; (2) The Mount Sinai Medical Centre, New York, NY, USA, Division of Gastroenterology ; (3) Rice University, Houston, TX, USA, Department of Bioengineering, Rice University, Houston, TX, USA.

Introduction : The ability to distinguish adenomas from benign polyps during routine colonoscopy can be challenging. High-resolution microendoscopy (HRME) is an advanced optical imaging technique allowing subcellular imaging of the colorectal mucosa. There is an unmet need for a widely accessible imaging modality such as HRME that can accurately differentiate non-neoplastic from neoplastic colonic mucosa.
Aims : This study aimed to develop quantitative HRME image analysis algorithms based on pathological and architectural features. In addition, it aimed to evaluate the automated classification algorithms performance to accurately categorize neoplastic (tubular adenoma, tubulovillous adenoma and cancer) and non-neoplastic (normal, hyperplastic) mucosa in the colon.
Methods : A total of 134 patients with known or suspected colon neoplasia from Mount Sinai Hospital (NY, USA) whom underwent endoscopic or surgical resection were enrolled in the study. Real-time HRME imaging was performed *in vivo* during routine colonoscopy or *ex vivo* immediately after sample resection. HRME images extracted from the collated data were randomized for quality control review. The images that met the quality control process were digitally processed to extract image characteristics for the potential use in classification algorithms - classifying each site into neoplastic or non-neoplastic. The data was divided into an *in vivo* and *ex vivo* set. Using two-class linear discriminant analysis and the selected features, the classification algorithms delineating neoplastic and non-neoplastic categories were developed from the training set data. The proposed classification algorithms were then used to classify the test data, with sensitivity and specificity determined based on histology diagnosis as gold standard.
Results : Quantitative information from the high-resolution images were used to develop a three-feature algorithm and sequential analysis. An exhaustive search was performed to identify the three best metrics. In the *in vivo* image set, the three-feature algorithm classified neoplasia from non-neoplasia with a sensitivity of 85% and specificity of 80% with an area under the ROC curve of 0.86. The *ex vivo* image set yielded a sensitivity of 83% and 73%. The sequential classification algorithm resulted in a sensitivity and specificity of 85% and 93% respectively in the *in vivo* set and 92% and 91% in the *ex vivo* set.
Conclusion : Given the results, this study demonstrates high-resolution microendoscopy with automated image analysis can aid in the accurate identification of colonic neoplasia Automated sequential analysis and the combination of three features both exhibit high accuracy in providing an objective, quantitative framework to assist clinicians to evaluate colonic polyps. Such use of software-based image analysis may overcome issues of training and expertise in low-resource settings, allowing dissemination of ‘optical biopsy’ technologies.

- G04 -

PERORAL ENDOSCOPIC MYOTOMY : OUTCOMES AT SHORT AND MID-TERM FOR THE FIRST 25 PATIENTS TREATED FOR ESOPHAGEAL MOTILITY DISORDERS. S. Dept , J. Devière , D. Blero , H. Louis. CUB Hôpital Erasme, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology.

Introduction : Peroral endoscopic myotomy (POEM) was introduced recently as a promising minimally invasive therapeutic option for the treatment of achalasia and other esophageal spastic disorders like distal esophageal spasm (DES).
Aim : The aim of the study was to report short- and mid-term outcomes of the first 25 patients treated with POEM in a single Belgian tertiary-care center.
Methods : Patients who underwent POEM between June 2011 and October 2014 were followed prospectively. High resolution manometry (HRM) was performed pre- and post-operatively at 1 month. Symptomatic evaluation using Eckardt score was recorded pre- and post-operatively at 1 month and yearly.
Results : Twenty-five patients (15 males and 10 females) with a mean age of 50 ± 17 years (range 24-88) were included in this study. Indications for POEM were achalasia type 1 for 7 patients (28%), type 2 for 9 patients (32%), type 3 for 6 patients (24%), DES for 3 patients (12%) and achalasia variant with intact peristalsis for 1 patient (4%). Fifteen patients (60%) had been treated previously with pneumatic dilation (PD) before POEM. Myotomy was performed on a mean length of 9 ± 2 cm for type 1, 9 ± 2 cm for type 2 and 12 ± 3 cm for type 3 and DES. No complication occurred during a median hospital stay of 2 (2-5) nights post-procedure. Post-operative evaluation was obtained after 1 month for 22 patients (19 evaluated with HRM), 1 year (15 patients), 2 years (11 patients) and 3 years (4 patients). Basal and relaxation pressures of the lower esophageal sphincter decreased from 36 ± 16 and 19 ± 11 mmHg pre-operatively, to 18 ± 13 mmHg and 8 ± 8 mmHg post-myotomy ($p < 0.01$). Median Eckardt score decreased from 6 (3-11) before POEM to 0 (0-3) at 1 month, 1 (0-5) at 1 year, 1 (0-3) at 2 years and 1 (0-2) at 3 years ($p < 0.001$). Symptom recurrence (Eckardt ≥ 3) was observed in 3 patients (2 with type 3 and 1 with type 2 achalasia) between 1 and 2 years follow-up, because of gastro-esophageal junction outflow obstruction in 2 patients, treated successfully by PD, and gastro-esophageal reflux treated by proton pump inhibitors (PPI) in 1 patient. At a mean follow-up of 17 ± 13 months (1-42), 12 % of patients used PPIs on demand and 28% on daily basis.
Conclusions : POEM is a safe and effective treatment for achalasia and distal esophageal spasm. Excellent symptom efficacy is observed in 90% of patients at short- and mid-term follow-up, additional pneumatic dilation or PPI being used for the few patients with symptomatic recurrence. POEM may become the first-line therapy of esophageal spastic disorders ; especially for type 3 achalasia and distal esophageal spasm for which pneumatic dilation is usually ineffective.

- G05 -

QUALITY CRITERIA AND MORBIDITY AFTER COLOSCOPY : A PROSPECTIVE MONOCENTRIC ANALYSIS.
B. Vos (1), I. Juriens (2), J. Rigaux (2), V. Bourgeois (2), J. Cappelli (2), P. Gruselle (2), P. Hayard (2), V. Lamy (3), E. Lecocq (2), P. Ooghe (2), A. Pestiaux (2), B. Ramdani (2), J. `Van Cauter (2), M. Bergiers (4), F. Toussaint (4), V. Vincke (4), N. Chique (2), M. Pierlot (2), V. Castiau (5), D. Chianura (5), F. Delvaux (5), F. Limelette (5), H. Siemons (5), A. Vandenberghe (5), D. Blero (2). (1) CHU de Charleroi, Charleroi, Belgium, Hepato-gastroenterology and Pancreatology Department ; (2) CHU de Charleroi, Charleroi, Belgium, Gastroenterology Department ; (3) CHU de Charleroi, Charleroi, Belgium, Gastroenterology Deparment ; (4) CHU de Charleroi, Charleroi, Belgium, Secretary Department ; (5) CHU de Charleroi, Charleroi, Belgium, Medical Information Department.

Introduction : Coloscopy is actually considered as gold standard for colon investigation but also has a number of limitations. Quality criteria are used to continuously assess and improve medical practice, especially for coloscopy. Coloscopy is a safe outpatient procedure for colon examination associed with low rate of complications. Immediate complications are easily identified and diagnosed during or early (< 24 hours) after the examination but long term complications rate is frequently unknown.
Aim : The aim of this study is to analyze prospectively quality criteria of colposcopy, morbidity and mortality defined as adverse events occurring within 28 days after coloscopy.
Methods : Between 6 january and 15 october 14, information relating to prior coloscopy criteria (indication), information relating to the review (quality of preparation by Boston score, cecal intubation, number of polyps identified and resected, immediate complication), but also information on the after colonoscopy assumed by a systematic phone call at 28 days. We record pain and duration, bleeding and duration, unplanned hospitalization and any type of medical event.
Results : Between 6 january and 15 october 14, 2827 coloscopies were realized in our institution. Adenoma detection rate (ADR) is 26% (738/2827) ; 27.6% in men (437/1581) ; 24.2% (301/1246) in women. ADR in diagnosis group was 27.3% (437/1757) ; ADR in follow-up group was 21.7% (178/569) ; ADR in screening group was 21.5% (123/501), including 29.3% (17/58) in positive guaiac-based fecal occult blood testing population. Cecal intubation rate is 93.6% (2646/2827). The median (min-max) quality of bowel preparation (Boston score) was 7 (0-9). Immediate complication was present in 11 (0.4%) patients (7 bleeding post polypectomy, 4 anesthesia-related adverse event, 1 tumoral bleeding secondary to a biopsy, 1 perforation treated by macroclip). Long term follow-up was obtained in 75.9% of patient (2146/2827), including 94.6% (2030/2146) without problem and 5.4% (116/2146) with related problem in population with follow-up available. Pain occur in 35 patients with median (min-max) intensity pain (visual scale 0 to10) was 3 (1-8) ; Median (min-max) duration pain was 6 days (1-10). Bleeding occur in 29 patients with median (min-max) duration of 2 days (1-8). Follow-up at 28 days revealed that 11 patients (0.5%) was back in hospital for complication related to

coloscopy including 2 perforations treated by surgery, 3 transmural burn syndrome, 2 bleeding,2 abdominal pain, 1 sciatalgy, 1 pneumonia. Global morbidity rate was 5.9% (127/2146) and there was no mortality related.
Conclusions : Systematic prospective analyze of quality indicators and complications of coloscopy is feasible in routine practice and could help to improve institutional good medical practice of coloscopy.

Invited Lecture

- G06 -

IS THE BELGIAN COLONOSCOPY SERVICE PREPARED FOR COLORECTAL CANCER SCREENING ? LESSONS FROM THE UK. R. Valori, Gloucester, UK.

- G07 -

TRANS-FISTULARY DRAINAGE FOR POST-BARIATRIC ABDOMINAL COLLECTIONS COMMUNICATING WITH THE UPPER GASTROINTESTINAL TRACT. S. Bouchard (1), P. Eisendrath (2), E. Toussaint (3), O. Le Moine (2), A. Lemmers (2), J. Devière (2). (1) Centre Hospitalier de l'Université de Montréal, Montréal, Canada, Gastroenterology ; (2) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology, Hepato-pancreatology and Digestive Oncology ; (3) ULB CHU Brugmann, Brussels, Belgium, Department of Gastroenterology.

Introduction : Diverse endoscopic methods, such as temporary stenting, have been proven effective to treat leaks or fistulas following bariatric surgery. However, certain patients do not respond to usual endoscopic treatments because of anatomic particularities, delayed management and/or collections not properly drained surgically.
Aim : In these patients with post-bariatric surgery collections, we have hypothesized that successful treatment could be achieved using trans-fistulary drainage with double pig-tail plastic stents.
Methods : We performed a retrospective analysis of patients with post-bariatric surgery abdominal collections communicating with the upper GI tract treated by trans-fistulary stenting between May 2007 and September 2014. Clinical success was defined as a patient released from the hospital with a sustained (median 5, range 1.2-53.3 months at the time of abstract submission) clinical resolution and biological normalization. Patient's records, radiologic images and our endoscopic database were reviewed to collect baseline characteristics, interventional data and treatment response.
Results : 25 patients (17 women/8 men, mean age 45.3 ± 10.6 years) were treated by trans-fistulary drainage during the study period. Post-operative collections occured after sleeve gastrectomy in 20 patients and after gastric bypass in 5. Median maximal diameter of the collection was 70 mm (range 20-130). A median of 48 days (range 5-1071) elapsed between initial surgery and trans-fistulary stenting. Eleven patients were treated by trans-fistulary stenting as primary treatment, while 14 patients had previously failed endoscopic treatment attempts (endoprosthetics, clips and/or fistula plugs). Internal drainage was initially maintained by placement of 2 double pigtail stents (7 or 8.5 Fr) in 21 patients or by one stent and a naso-cystic catheter in 4. In 5 patients, transfistulary stenting was performed in combination with percutaneous drainage. No complication occurred during the initial drainage procedure. In 6 patients, trans-fistulary stenting was not successful and surgery was necessary. Clinical success was achieved in 19 patients (76%). The clinical success rate was 81.8% in previously untreated patients and 71.4% in patients with previous endoscopic treatment failures. In 7 successfully treated patients, stents are still in place after a median stenting duration of 102 days (range 41-1620) and no complication has occurred. In 4 patients with spontaneous stent migration, no complication has occurred after a median follow-up duration of 137.5 days (range 85-390). In 8 patients, the plastic stents have been removed after a median stent indwell duration of 186.3 days (range 24-773) and no complication has occurred after a median follow-up duration of 159.4 days (range 5-461). In these patients, stents were either removed electively (2 patients) or because of dysphagia or symptomatic stent-induced esophageal ulcerations (6 patients).
Conclusions : Trans-fistulary drainage of post-bariatric abdominal collections is safe and is associated with high success rates. This technique seems promising and can be considered either in previously untreated patients when a collection is present and not properly drained percutaneously or after failure of other endoscopic treatments.

- G08 -

TRANSANAL ENDOSCOPIC OPERATION FOR BENIGN RECTAL LESIONS AND LOW-RISK T1 CARCINOMA : A BELGIAN MULTICENTER EXPERIENCE. E. Yoshihara (1), L. Dedrye (2), K. Vindevoghel (3), M. D'hondt (1). (1) AZ Groeninge, Kortrijk, Belgium, Department of Digestive Surgery ; (2) Jan Yperman Hospital, Ieper, Belgium, Department of General and Digestive Surgery ; (3) Onze-Lieve-Vrouw van Lourdes Hospital, Waregem, Belgium, Department of General Surgery.

Introduction : Transanal endoscopic operation (TEO) has evolved as a new technique from transanal endoscopic microsurgery (TEM). TEO is a minimally invasive technique used for local excision of benign and selected malignant rectal lesions.
Aim : The aim of this study is to investigate the feasibility, safety and oncologic outcome of the procedure and report the experience in 3 Belgian centers.
Methods : We retrospectively reviewed a prospectively collected database of all patients with benign or ≤ cT1N0 rectal cancer who underwent TEO with curative intent at 3 Belgian centers between March 2012 and September 2014. Data collected included : patient demographics, medical comorbidities, preoperative diagnosis and locoregional staging (endorectal ultrasonography and magnetic resonance imaging of the pelvis), location of the lesions (distance from anal verge and direction), details of the operative procedure, length of hospital stay, intra- and postoperative complications, final pathology and oncologic outcome.
Results : Fifty-five patients underwent 56 TEOs for 61 rectal lesions (32 adenomas, 27 adenocarcinomas, 1 gastrointestinal stromal tumour and 1 neuroendocrine tumour). Median distance from the anal verge was 5.5 cm (range 2-15 cm). The median lesion diameter was 4 cm (0.5-9.2 cm). Of all the 27 adenocarcinomas preoperatively evaluated by endorectal ultrasonography and magnetic resonance imaging 33.3% (9 out of the 27) were understaged. Median operative time was 60 min (range 40-180 min). The operation time was significantly associated with the lesion size ($P < 0.001$). All lesions except one were radically excised (1 R1 resection of a large adenoma). Postoperative complications occurred in 5 patients, 3 due to hemorrhage and 2 urinary tract infections. Median hospital stay was 3 days (range 2-8 days). During a median follow-up of 13 months (range 2-27 months) 1 recurrence occurred, which was treated with a redo-TEO procedure. Based on final pathology 8 patients (29.6%), underwent completion radical surgery, Total Mesorectal Excision.
Conclusions : Although long-term follow up is still required, TEO appears to be an effective method of excising benign tumours and low-risk T1 carcinomas of the rectum. However, TEO should be considered as a part of the diagnostic work-up. Furthermore, the resected specimen of a TEO procedure allows adequate local staging in contrast to an endoscopic piecemeal excision. Nevertheless definitive histology needs to be appreciated and in cases of unfavorable histology radical salvage resection still has to be performed.

- G09 -

ENDOSCOPIC TREATMENT OF LARGE ESOPHAGEAL DIVERTICULA USING A MAGNETIC ANASTOMOSIS DEVICE : REPORT OF THREE CASES. S. Bouchard , V. Huberty , D. Blero , J. Deviere . CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology and Hepatology.

Introduction : Although benign, symptoms of esophageal diverticula can be particularly disabilitating, especially in patients with large diverticula. With the recent advancements in endotherapy, Zenker's Diverticulum can now be treated by flexible endoscopy using either a cap or a soft diverticuloscope.
Aim : A recent development in endoscopy has been the use of magnets to create magnetic compression anastomosis. Magnets could possibly have a role in treating patients with large esophageal diverticula by creating a magnetic compression anastomosis between the base of the diverticulum and the esophagus and allowing full marsupialization by completing the section of the septum.
Methods : A first magnet (14-mm diameter) is mounted on a catheter and advanced over a guidewire into the stomach. The endoscope is introduced in the esophagus with the second magnet (16-mm diameter) already attached at the tip of the endoscope using biopsy forceps. After this magnet has been placed at the base of the diverticulum, the magnet in the stomach is slowly pulled back under fluoroscopic and endoscopic guidance until the two magnets mate, thus creating a compression between the base of the diverticulum and the esophageal wall. The magnets are then left in place for 7-14 days to allow time for a complete magnetic compression anastomosis to occur. During a second endoscopic procedure, the magnets are removed. A large communication between the base of the diverticulum and the esophagus is now visible. Using a diathermic blade, the septum between the diverticulum and the esophagus is progressively cut. The cut is started at the top of the septum and continued downwards until the magnet-induced anastomosis is reached, thus completing the diverticulotomy.
Results : The first patient had a Zenker's diverticulum unsuccessfully treated with three endoscopic sessions. Then a magnetic compression anastomosis was performed and a partial section of the septum between the diverticulum and the esophagus was done. One week later, the magnets were retrieved from the base of the diverticulum and the remaining septum was cut. A barium swallow performed a month later demonstrated complete passage of barium in the stomach. The second patient had a long-standing history of a large mid-esophageal pulsion diverticulum. During an initial EGD, magnets were successfully placed. 10 days later, the magnets were easily retrieved and the remaining septum was cut. One month later, the patient presented a complete resolution of symptoms and is still asymptomatic at 5 months. Our last patient had a 10-month history of retrosternal discomfort associated with development of dysphagia. A barium swallow revealed a large 4 cm deep diverticulum of the lower esophagus. During an initial endoscopic procedure, the magnets were placed. 13 days later, another gastroscopy showed the magnets-induced communication between the base of the

diverticula and the esophagus. The magnets were retrieved and the remaining septum was completely cut. One month later, the dysphagia has significantly improved.
Conclusions : We reported the first series of patients with esophageal diverticula treated endoscopically by creation of a magnetic compression anastomosis followed by an endoscopic diverticulotomy. This approach seems promising for the treatment of selected patients with large esophageal diverticula.

- G10 -

EOSINOPHILIC ESOPHAGITIS : CLINICAL CHARACTERISTICS OF ADULT CASES DURING A 10-YEAR PERIOD IN A BELGIAN TERTIARY CARE HOSPITAL. C. Pirenne (1), G. Nkaya Kabamba (2), P. Demetter (3), O. Le Moine (1), J. Devière (1), H. Louis (1). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology ; (2) Université Libre de Bruxelles (ULB), Brussels, Belgium, Faculty of Medicine, Department of General Medicine ; (3) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Pathology.

Introduction : Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease responsible for dysphagia. Defined clinico-pathologically, EoE is probably underdiagnosed and its incidence is rising in Western countries.
Aim : The objective of the study is to analyze the adult cases of EoE diagnosed in a tertiary care hospital in Belgium during the last 10 years.
Methods : From the pathology report database and after exclusion of other causes of esophageal eosinophilia, 44 adult patients were included between 2004 and 2013 and their clinical data were analyzed retrospectively.
Results : Cases of EoE were mostly diagnosed during the last 5 years in middle-aged male patients (range18-66, mean 43 y-old, male/female ratio 28/16), during the first semester of the year. An allergic context was reported in 66% patients, both for aeroallergens and food allergens, and asthma was present in 21% of patients. Symptom prevalence (%) at diagnosis revealed heartburn (66%), dysphagia (57%), abdominal pain (39%), food impaction (18%) and chest pain (16%). Endoscopic findings disclosed reflux esophagitis (59%), white plaques (34%), longitudinal furrows (30%), esophageal rings (9%), Schatzki ring (7%) and stenosis (7%). Before diagnosing EoE, endoscopy had been previously performed (between 1 and 6 procedures) in 86% of the patients. Biopsies were performed at esophageal proximal and distal levels (43%), proximal only (36%), distal only (16%) or unspecified in the pathology report (5%). The majority of patients were treated with PPI either alone (55%) or in combination with swallowed fluticasone (25%). Fluconazole was prescribed to 7% of patients, after a wrong diagnosis of esophageal candidiasis based on the endoscopic image.
Conclusions : EoE was more often diagnosed during the last 5 years and during the first semester of the year, in young and middle-aged adults with a male predominance and an allergic context. The number of previous endoscopies performed on most patients suggests EoE might have been underdiagnosed, and the endoscopic findings can be confused with esophageal candidiasis. A better awareness of the disease should allow performance of systematic biopsies at different levels of the esophagus to increase sensitivity of endoscopy when EoE is clinically suspected.

- G11 -

ENDOSCOPIC OR COMBINED ENDOSCOPIC/PERCUTANEOUS MANAGEMENT OF PATIENTS WITH COMPLEX BILE DUCT INJURIES AND BILIARY EXCLUSION. S. Bouchard (1), D. Tan (2), T. Gupta (2), P. Eisendrath (2), A. Lemmers (2), V. Huberty (2), O. Le Moine (2), J. Devière (2). (1) Centre Hospitalier de l'Université de Montréal, Montréal, Canada, Department of Gastroenterology ; (2) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology.

Introduction : Bile duct injuries occur most often after biliary tract surgery. The most severe injuries, also known as complex bile duct injuries (BDI), are associated with significant morbidity and mortality. Although reconstructive biliary surgery is considered standard treatment for complex BDI, recent studies have suggested that an endoscopic or combined endoscopic/percutaneous approach might be an alternative to a surgical approach in selected patients.
Aim : In this study, we report our experience with a variety of endoscopic or combined endoscopic/percutaneous techniques to re-establish biliary drainage in patients with complex BDI and biliary exclusion.
Methods : We performed a retrospective study of patients with a diagnosis of complex BDI (either complete biliary transections or complete biliary strictures) treated in our endoscopy unit between July 1998 and November 2013. The diagnosis of complex BDI was confirmed by reviewing the radiologic or endoscopic images. Baseline characteristics, laboratory tests results, radiologic findings, procedural and follow-up data were collected by reviewing patient's records, our endoscopic database and radiologic database.
Results : We identified 12 symptomatic patients with complex BDI and biliary exclusion who were treated by various methods to repermeabilise the excluded bile ducts. All procedures were performed with patients under general anesthesia

by gastroenterologists with experience in endoscopic and percutaneous procedures. Successful drainage of the excluded biliary ducts with resolution of symptoms was possible in all patients, either through recreation of bilio-biliary continuity (9 patients) or by creating a bilio-enteric drainage tract (3 patients). In 5 patients, biliary repermeabilisation was performed using a TIPSS-200 set. Mean duration of the biliary repermeabilisaiton procedure was 108 min (range 70-180). No immediate severe complication occured. Complete internalization of biliary drainage was possible in all 12 patients. An average of 4.6 additionnal ERCP procedures per patient were performed after the initial repermeabilisation procedure and an average of 7.8 biliary stents were placed per patient (range 1-18). Mean duration of follow-up was 52.2 months (range 5-159). During the follow-up period, six patients developed a biliary stricture at the level of the initial BDI, three patients developed episodes of cholestasis and/or cholangitis secondary to biliary stent occlusion, biliary stones or sludge, and one patient developed a recurrent biloma. These late complications were all successfully treated by endoscopic means. All patients are free of external drainage at follow-up. Reconstructive biliary surgery was avoided in all patients. During the follow-up period, three patients died of causes unrelated to the repermeabilisation procedures.
Conclusions : In patients with complex BDI and biliary exclusion, various endoscopic or combined endoscopic/percutaneous procedures may be successfully performed to recreate bilio-biliary or bilio-enteric continuity. In experienced hands, these techniques seem safe and can prevent reconstructive biliary surgery.

BSGIE Grant 2013

- G12 -

THE PREDICTIVE VALUE OF PLEXITIS AT THE PROXIMAL RESECTION MARGIN : A PROSPECTIVE STUDY ON PREDICTORS OF EARLY POST-OPERATIVE ENDOSCOPIC RECURRENCE OF CROHN'S DISEASE. M. Ferrante.

- G13 -

DIAGNOSTIC AND THERAPEUTIC ROLE OF ENDOSCOPIC ULTRASOUND IN CHILDREN'S PANCREATICO-BILIARY DISORDERS. I. Scheers (1), M. Ergun (2), H. Piesseveaux (2), T. Aouattah (2), I. Borbath (2), X. Stephenne (1), F. Smets (1), F. Veyckemans (3), B. Weynand (4), E. Sokal (1), P. Deprez (2). (1) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Department of Pediatric Gastroenterology, Hepatology and Nutrition ; (2) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Department of Hepatogastroenterology ; (3) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Pediatric Anesthesiology ; (4) CHU Dinant Godinne, Yvoir, Belgium, Department of Pathology.

Introduction : The diagnostic and therapeutic role of endoscopic ultrasound (EUS) in children was demonstrated only recently and data on the technique's indications remain scarce.
Aim : We therefore evaluated diagnostic and interventional EUS indications and safety in children with pancreaticobiliary disorders.
Methods : We retrospectively reviewed our single pediatric center experience covering a 15-year period.
Results : Between January 2000 and December 2014, 52 EUS procedures were performed on 48 children (mean age 12yrs ; range 2-17yrs) with pancreaticobiliary disorders for the following indications : suspected biliary obstruction (n = 20/52), acute/chronic pancreatitis (n = 20), pancreatic mass (n = 3), pancreatic trauma (n = 7), and ampullary adenoma (n = 2). EUS examination precluded endoscopic retrograde cholangiopancreatography (ERCP) (n = 13 biliary ; n = 6 pancreatic), focusing on endotherapy (n = 7 biliary ; n = 14 pancreatic), or reorienting therapy towards surgery (n = 7). EUS-guided fine-needle aspiration was carried out on 12 patients for pancreatic tumor (n = 4) or pancreatic cyst fluid analysis (n = 4), autoimmune pancreatitis (n = 2), and suspicion of biliary tumor (n = 2). Thirteen therapeutic EUS procedures were conducted, nine of which (7 children, mean age 8yrs, range 4-11yrs) were combined EUS-ERCP procedures, three were EUS-guided pseudocyst drainage, and one was a EUS-guided transgastric biliary drainage. One child developed an haemorrhagic complication after the procedure.
Conclusions : We report on a large pediatric EUS series for diagnostic and therapeutic pancreaticobiliary disorders, demonstrating the impact of diagnostic EUS and affording insights into novel EUS and combined EUS-ERCP therapeutic applications. We suggest considering EUS as a diagnostic and therapeutic tool in the management of pediatric pancreaticobiliary diseases.

- G14 -

GIANT COLON AS PROMOTION TOOL FOR COLORECTAL CANCER SCREENING : POPULATION ANALYSIS AND LOCAL IMPACT. B. Vos (1), B. Ramdani (2), V. Lamy (3), P. Hayard (2), B. Louyest (4), M. Candeur (5), D. Blero (4). (1) CHU de Charleroi, Charleroi, Belgium, Hepato-gastroenterology and Pancreatology Department ; (2) CHU de Charleroi, Charleroi, Belgium, Gastroenterology Department ; (3) CHU de Charleroi, Charleroi, Belgium, Gastroenterology Department ; (4) CHU de Charleroi, Charleroi, Belgium, Gastroenterology Deparment ; (5) Centre Communautaire de Référence pour le Dépistage des Cancers, Mont-Saint-Guibert, Belgium.

Introduction : Colorectal cancer is third most frequent cancer. Since 2009, guaiac-based fecal occult blood testing (gFOBT) is used as screening intervention by French Community, but only ten percent of targeted population is finally screened. We perform a “sensibilisation day” with intra-hospital giant colon in order to inform people about colon cancer screening program.
Aim : We analyze the target population and the potential local impact after event
Methods : After an educational visit of a giant colon in the hall of the hospital, people were invited to complete a questionnaire with help of nurse. We record age, sex, postal code, colorectal cancer risk factor. After data collection, persons were classified between gFOBT (received a test) or coloscopy for high risk population. Distribution of gFOBT by postal code 6 months before and after event was analysed.
Results : 217 persons complete the questionnaire. H/F ratio was 35% (76)/ 65% (141). Median age (min-max) was 59 years (42-84) and 92% (200/217) are on target population with 10 under/ 7 over age. 64% (138) gFOBT were distribued and 36% (79)coloscopy proposed. 93 risk factors were identified in the coloscopy group : familial antecedents (43), personal adenoma (14), transit modification (12), rectoragy (11), abdominal pain (7), inflammatory bowel disease (6). gFOBT distributed (138) represent 31% (138/450) of monthly median gFOBT analyzed, by French Community per month in postal code represented . There was no significant increase of number of gFOBT analysed in represented postal code in the 6 months after event.
Conclusions : Giant colon as promotion tool against colorectal cancer is interesting to promote patient education about gFOBT in target population, but there is no impact on number of gFOBT analyzed after event.

- G15 -

FEASIBILITY OF USING A NOVEL TRIANGULATION DEVICE TO PERFORM FLEXIBLE ENDOSCOPIC SUTURING IN A PORCINE MODEL. V. Huberty (1), M. Ibrahim (1), M. Hiernaux (2), A. Chau (2), J. Deviere (1). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology and Hepatology ; (2) CUB Hôpital Erasme, ULB, Brussels, Belgium, Endotools Therapeutics.

Introduction : Endoscopic suturing was reported recently but full thickness gastric sutures are still challenging due to the complexity of suturing maneuvers and lack of instrumental handiness, the latter could be reduced with a flexible triangulation system.
Aim : To explore the technical feasibility of a novel triangulation platform “ENDOMINA ®” to perform full thickness endoscopic suturing and anterio-posterior apposition into the stomach.
Methods : ENDOMINA ® (Endo Tools Therapeutics, Belgium) is a single use triangulation platform, assembled on the endoscope into the stomach, that adds a 5 Fr bendable channel and a 5 Fr non bendable channel to an endoscope. ENDOMINA ® is used in combination with TAPES ® (Transmural Anterio-Posterior Endoscopic Stitcher) in the bendable channel with a preloaded tag and tightening system releaser. The steps of the procedure were (i) Identification of the anterior and posterior piercing points in the stomach. (ii) Mucosal ablation with argon plasma coagulation. (iii) Grasping of first point (iv) Introduction of TAPES in the bendable channel. (v) Transmural piercing and deposition of first tag. (vi) Repetition of the same technique at the second point. (vii) Release and tightening of both transmural plicatures using the preloaded knot.
Results : Three complete sutures with knot release were achieved in 2 pigs. Mean time for the procedure was 90 minutes. Endoscopy follow up at 7 and 30 days confirmed the presence of the sutures in place and persistent antero-posterior application of the 2 transmural plicatures. Both pigs were sacrificed and tissue histology of resected suture area confirmed full thickness tissue apposition and fibrosis formation. No mortality or procedure related morbidities were reported in the 2 pigs with one month follow up.
Conclusions : ENDOMINA-assisted endoscopic system can perform safely endoluminal suturing and knot-tying in live porcine models, achieving not only plicatures with serosa to serosa apposition but also antero-posterior apposition of the plicatures.

- G16 -

COLORECTAL ESD TRAINING AND LEARNING CURVE IN EUROPE. P. Dewint (1), B. Boxma-De Klerk (2), J. Haringsma (1). (1) Maasstadziekenhuis, Rotterdam, The Netherlands, Gastroenterology and Hepatology ; (2) Maasstadziekenhuis, Rotterdam, The Netherlands, Research Bureau, Maasstadacademie.

Introduction : The development of advanced endoscopic resection techniques in the late 1990s has significantly impacted on the treatment of early neoplastic lesions of the GI tract. In Europe, the role of Endoscopic Submucosal dissection (ESD) in the colorectum is still controversial, largely due the backlog in skill level as compared to Japan and Korea, and the long learning curves.
Aim : The aim of this study was to describe the learning curve of an experienced interventional endoscopist after following a well-structured course with training in both ex vivo and in vivo animal models and exposure to experts according to the current European guidelines.
Methods : The study was designed as a single-center, prospective, cohort study between February and November 2014. The decision to remove the lesion with ESD was left to the discretion of the endoscopist. A total of 12 colorectal lesions in 12 patients were resected by submucosal dissection using a DualKnife® (Olymus Optical, Hamburg). Based on the long and short axis of the excised lesions the circumference and surface was calculated.
Results : All (n = 12) lesions had a Paris 0-Is morphology. Eight out of 12 lesions were located in the rectum, 2 in the rectosigmoid and 2 in the sigmoid. 5 lesions showed low grade dysplasia, 6 high grade dysplasia and 1 was a T1sm1 adenocarcinoma. En-bloc resection rate and R0 resection rate were 100 % and 82 % respectively. Curative resection rate was 100 %. The time needed to circumcise the lesion did not change over time (range : 0,40 cm/min – 1,27 cm/min, p = ns), whereas the time needed to dissect decreased significantly over time (range : 0,06 cm2/min – 0,63 cm2/min, p = 0,026). Also the size of resected lesions became larger over time (range : 3,6 cm2 – 56,0 cm2, p = 0,07). One patient required endoscopic closure of a small perforation during dissection. This complication occurred in the fith procedure. No post-procedural bleeds occurred.
Conclusions : After training according to current guidelines a steep learning curve could be shown. Colorectal ESD is feasible in the European setting with an optimum outcome.

- G17 -

SINGLE CENTER EXPERIENCE USING ESO-CREMER STENT AS FIRST LINE ENDOSCOPIC THERAPY FOR POST SLEEVE GASTRECTOMY LEAK. S. Mupingu (1), J. Rigaux (2), D. Blero (2). (1) CHU de Charleroi, Charleroi, Belgium, Gastro-enterology ; (2) CHU de Charleroi, Charleroi, Belgium, Gastroenterology.

Introduction : Temporary endoscopic stenting is considered as a first line treatment of post bariatric leak or fistula. Different self-expanding metallic stents (SEMS) have been described, mainly depending of local abilities. The most reported policy uses a partially covered SEMS which implies a retrieval in two steps, since a fully covered plastic stent insertion into the SEMS is mandatory in order to proceed to the final removal. In case of leak after sleeve gastrectomy two anatomical and physical particularities have to be considered ; first the high intraluminal pressure in the proximal part of the sleeve which favors the opening of the leak, second the length of the sleeve which implies the precise placement of the stent into the eso-gastric neo-tract. In order to circumvent these particularities, Prof. M. Cremer designed a 20 cm long nitinol SEMS fully covered excepted on 5 mm at the level of the inflection of the both ends tulips of the SEMS.
Aim : We describe here our experience using that Eso-Cremer SEMS (Endoflex, Dusseldorf, Germany) as a primary endoscopic treatment of leak after sleeve gastrectomy.
Methods : Retrospective review of the charts of all patients with leak occuring after sleeve gastrectomy from Sep 2011 until Nov 2014, for which a Eso-Cremer SEMS was inserted (Endo-Flex Gmbh, Dusseldorf, Germany) in our center.
Results : Six patients have been included (2 women and 4 men ; 19-66 years). The delay between surgery and leak diagnosis ranged from 4 to 15 days. The delay between leak diagnosis and SEMS placement ranged from 2 to 54 days. All patients were septic and were drained (5 by surgery and 1 radiologically) before undergoing stent insertion. SEMS (Eso-Cremer length 20 cm ; diameter 20-25 mm) was deployed under fluoroscopy after placement of a stiff wire into the upper GI tract. All stents were placed successfully (success defined as complete disappearance of leak on barium swallow at the end of the procedure). Stenting periods ranged from 8 to 10 weeks. Removal of these SEMS was successful in all patients in a single session, using a rat tooth forceps. Leak healing, defined as absence of contrast extravasation after stent removal, occurred in all patients after one cycle of treatment. All patients displayed nausea and dysphagia immediately after the first endoscopic procedure with spontaneous resolution, except for one patient who had distal migration of the SEMS resulting in a persistent leak 14 days after its placement, requiring a second procedure to reposition it. Despite treatment with proton pump inhibitor, five patients developed ulcers Forrest III in the antrum, due to the impaction of SEMS at that level. One patient developed a benign stenosis at the level of the proximal hyperplasia, which required progressive CRE balloon dilations.
Conclusions : Insertion of a long, almost fullly covered SEMS is efficient to treat leak after post sleeve gastrectomy, but its use should be carefully evaluated due to the risk of traumatic ulcers

IBD RESEARCH GROUP (BIRD)

- I01-

INTESTINAL DYSBIOSIS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS. J. Sabino (1), S. Vieira-Silva (2), K. Machiels (1), M. Joossens (2), G. Falony (2), V. Ballet (1), M. Ferrante (1), G. Van Assche (1), S. Van Der Merwe (3), J. Raes* (2), S. Vermeire* (1). (1) KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) Rega Institute for Medical Research, KU Leuven, Leuven, Belgium - VIB, Department of Microbiology and Immunology - Center for the Biology of Disease ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Hepatology.

Introduction : Primary sclerosing cholangitis (PSC) is a cholestatic liver disorder very frequently associated with inflammatory bowel diseases (IBD). The intestinal microbiota seems to be essential in PSC as bacterial translocation is thought to play an important role in the pathogenesis of the disease.
Aim : Given the association with IBD and the fact that patients with IBD have a well-documented intestinal dysbiosis, we hypothesized that dysbiosis would also play a role in PSC.
Methods : Faecal samples from 52 PSC patients and 52 age, sex and BMI matched healthy controls were collected. Within the PSC cohort, 39 patients had concomitant IBD (17 Crohn's disease (CD) and 22 ulcerative colitis (UC)). After bacterial DNA extraction, 16S rDNA paired-end sequencing was performed using Illumina MiSeq sequencer. Successfully combined reads were quality-filtered (30 QS over 90% of read length) and chimeric sequences filtered out (UCHIME). Sequencing depth was downsized to 10000 reads/sample by random selection. Reads were clustered at 97% sequence similarity for species-level de novo OTU picking (USEARCH). The Ribosomal Database Project classifier was used for taxonomic assignment. Statistical analyses were performed with R package phyloseq, using non-parametric Mann-Whitney U and Kruskal-Wallis tests, with multiple testing correction (FDR).
Results : The overall microbiota diversity was significantly decreased in PSC patients compared to healthy controls ($p < 0.0001$). This reduction was observed in each subgroup of PSC patients (PSC only, PSC+CD, PSC+UC) versus healthy controls (adjusted $p < 0.0001$). At genus level, five genera were consistently more abundant in PSC patients compared to healthy controls (adjusted $p < 0.02$) : Enterococcus, Fusobacterium, Lactobacillus, Veillonela and Morganella. PSC patients with IBD versus controls showed differences in the abundance of an additional 33 genera (adjusted $p < 0.05$) including Faecalibacterium, Roseburia, Blautia and Butyricicoccus.
Conclusions : The intestinal microbiota of PSC patients is clearly different from that of healthy controls, even in the absence of intestinal inflammation such as IBD. A unique microbial signature of five genera is observed in PSC patients, irrespective of the presence of IBD. In PSC patients with concomitant IBD, a dysbiosis involving previously described IBD-related genera is also observed in addition to the PSC specific microbial signature. Our data support the hypothesis that the intestinal microbiota plays an important role in the pathogenesis of this chronic cholestatic liver disease.

- I02 -

PREDOMINANT INTESTINAL MICROBIOTA PREDICTS POSTOPERATIVE CROHN'S DISEASE RECURRENCE FOLLOWING ILEOCAECAL RESECTION WITH ILEOCOLONIC ANASTOMOSIS. K. Machiels (1), W. Vanhove (2), J. Sabino (2), M. Joossens (3), I. Arijs (2), I. Terrasson (4), V. Ballet (2), G. Van Assche (2), J. Verhaegen (5), A. Wolthuis (6), D. Anthony (6), A. D'hoore (6), M. Ferrante (2), P. Rutgeerts (2), S. Vermeire (2). (1) KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Leuven and Translational Research Center for Gastrointestinal Disorders (TARGID), Leuven, Belgium ; (3) VUB, Brussels - KU Leuven, Leuven - VIB, Leuven, Belgium, Department of Microbiology - Department of Microbiology and Immunology - Center for the Biology of Disease ; (4) University Hospitals Leuven, Leuven, Belgium, Abdominal Surgery ; (5) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Clinical Microbiology ; (6) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Abdominal Surgery

Introduction : Dysbiosis of the intestinal microbiota has been described in Crohn's disease (CD) and may play an important role in the early events triggering postoperative disease recurrence.
Aim : We hypothesized that microbiota are altered in patients with early postoperative endoscopic recurrence (ER) and evaluated if the risk for postoperative ER can be predicted based on differences in the fecal microbial composition before surgery.
Methods : Fecal samples from 30 CD patients (median age 46 years, 16 male) undergoing ileocaecal resection with ileocolonic anastomosis were prospectively collected before surgery and at month 1, 3 and 6 after surgery. Postoperative ER - defined by a Rutgeerts score ≥i2 - was assessed at month 6. The predominant microbiota was studied using denaturing gradient gel electrophoresis (DGGE) and bands of interest were sequenced. Partial Least Squares Discriminant Analysis (PLS-DA) was used to cluster the microbial profiles using Unscrambler. Statistical analysis was performed using SPSS and R software.

Results : Based on the preoperative microbial profiles, two clusters of patients were identified : those developing early ER (N = 12) and patients without ER (N = 18). Before surgery, a reduction of the Lachnospiraceae family (p = 0.05) and Clostridium XVIII genus (p = 0.032) was seen in the predominant microbiota of patients developing early postoperative ER whereas 3 members of Clostridium XIVa genus (p = 0.073), Veillonellaceae family (p = 0.028) and Bifidobacterium genus (p = 0.01) were higher in patients with ER compared to patients without ER. A score combining these five bacterial risk factors was calculated and showed an area under the curve of 0.87 (95% CI, 0.76-0.99). The occurrence of two or more risk factors had a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 56%, 60% and 100% respectively. At the time of postoperative endoscopy, we observed an overrepresentation of Lactobacillus genus (p = 0.003) and Ruminococcus gauvreauii (p = 0.01) in the patients with ER.
Conclusions : An overrepresentation of Clostridium XIVa spp., Veillonellaceae, Bifidobacteria and a lower abundance of Lachnospiraceae and Clostridium XVIII spp. in the predominant profile of preoperative fecal samples is associated with a higher risk to develop postoperative ER following ileocaecal resection. At the time of postoperative endoscopy, the predominant microbiota from patients with ER also differs from patients without recurrence, with as most prominent players lactobacilli and R. gauvreauii.

- I03 -

INFLIXIMAB TROUGH CONCENTRATIONS DURING THE INDUCTION PHASE PREDICT SHORT-TERM MUCOSAL HEALING IN PATIENTS WITH ULCERATIVE COLITIS. K. Papamichail (1), N. Vande Casteele (2), T. Billiet (1), A. Gils (2), S. Tops (2), K. Claes (1), G. Van Assche (1), P. Rutgeerts (3), S. Vermeire (4), M. Ferrante (1). (1) KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine ; (2) KU Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, Laboratory for Therapeutic and Diagnostic Antibodies ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Laboratory for Clinical Infectious and Inflammatory Disorders and Translational Research Center for Gastrointestinal Disorders (TARGID) ; (4) KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine, Labo Digestie-Absorptie, E462.
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Introduction : Mucosal healing is currently a primary goal of anti-TNF therapy in inflammatory bowel disease (IBD). Mucosal healing is an independent predictor of sustained clinical remission in patients with ulcerative colitis (UC) treated with infliximab (IFX). Although trough concentrations (TC) of both IFX and adalimumab have been associated with mucosal healing during the maintenance treatment in IBD, there are only limited data regarding the role of therapeutic drug monitoring during the induction phase.
Aim : We investigated whether IFX TC during the induction phase can predict short-term, mucosal healing (STMH) in patients with UC.
Methods : This was an observational, retrospective, single-center study. Patients who received scheduled induction therapy (week 0-2-6) and had an endoscopic evaluation both at baseline and after induction therapy (week 10-14) were eligible to be included in the study. STMH was defined as a Mayo endoscopic sub-score of 0 or 1, assessed after the induction therapy, with a baseline sub-score of 2 or 3. Infliximab TC were evaluated in prospectively collected serum samples at weeks 0, 2, 6 and 14 after IFX initiation using an in-house developed and clinically validated ELISA.
Results : From an electronic database of 411 UC patients treated with IFX, 101 were finally included in the study. Patients with STMH (n = 55) had higher IFX TC [median (IQR)] compared to those without (n = 46) at week 2 [22.7 (15.9-31.6) vs 17.6 (8.5-22) µg/ml, p = 0.016, Mann-Whitney U test], week 6 [17.3 (9.6-25.3) vs 9.3 (3.6-13.6) µg/ml, p = 0.001] and week 14 [7.4 (3.4-11.2) vs 1.5 (0.7-3.2) µg/ml, p < 0.001]. A receiver operating characteristic (ROC) curve analysis identified a cut-off of 22.5 µg/ml at week 2 (AUC : 0.642, p = 0.016) and 12.8 µg/ml at week 6 (AUC : 0.691, p = 0.001), as predictive values for STMH. Univariate (chi-square) analysis identified IFX TC > 22.5 µg/ml at week 2 [p = 0.013, OR : 3.1 (95%CI : 1.3-7.3)], IFX TC > 12.8 µg/ml at week 6 (p = 0.002, OR : 3.9 (95%CI : 1.7-9.1)], female gender [p = 0.039, OR : 2.5 (95%CI : 1.1-5.9)] and azathioprine (AZA) at start of IFX [p = 0.009, OR : 3 (95%CI : 1.3-6.9)], as parameters predicting STMH. Multiple logistic regression analysis retained IFX TC > 12.8 µg/ml at week 6 [p = 0.004, OR : 3.6 (95%CI : 1.5-8.6)] and AZA at IFX initiation [p = 0.024, OR : 2.7 (95%CI : 1.1-6.6)] as independent factors predicting STMH.
Conclusions : This study reflecting real-life clinical practice indicates that early therapeutic drug monitoring may be important for guiding therapeutic decisions in UC patients treated with IFX, while concomitant immunomodulators may play a significant role towards STMH.

- I04 -

CULTURING PATIENT-DERIVED INTESTINAL EPITHELIUM AS A VALUABLE TOOL FOR PERSONALIZED MEDICINE. W. Vanhove, S. De Schepper, D. Staelens, I. Arijs, G. Van Assche, M. Ferrante, S. Vermeire, K. Nys. KULeuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine.

Introduction : Inflammatory bowel diseases (IBD) are caused by an aberrant immune response towards intestinal microbiota in genetically predisposed persons, most likely facilitated by intestinal epithelial defects. The intestinal epithelium has an important role in the intestinal immune response by conserving host-microbial interactions and tissue homeostasis. The imminent introduction of new therapeutic classes for IBD patients emphasizes the need for personalized medicine for which the epithelial resistance or response to cytotoxic agents, therapeutics, dietary components, etc. may be essential. However, a simple epithelial model with the potential for personalized determination has not been tested.
Aim : We wanted to develop a short term culture system for IBD patient-derived intestinal epithelial cells (IECs) and validate its epithelial character.
Methods : Endoscopically-derived mucosal biopsies were obtained from both inflamed and non-inflamed regions from the colon of IBD patients. Colonic crypts from biopsies were isolated through chemical and mechanical separation (adapted intestinal organoid protocol by Sato et al. (Gastroenterology, 2011)). Intact intestinal crypts were immediately plated in collagen-coated wells containing in-house designed medium, resulting in a monolayer of IECs. The epithelial character of the cells was confirmed by ICC for epithelial tight junction protein E-cadherin and positive detection of cytokeratin (CK) 18 and 20 mRNA at different time points by qRT-PCR, whereas detection of fibroblast markers PDGFR and COL1A1 and COL1A2 mRNA remained negative. Inflammasome sensors NLPR3, AIM2 and IFI16 were assessed by ICC.
Results : Crypt isolation was successful in 80%. The crypts attached to the bottom of the wells overnight. After 24 hours, normal crypt architecture switched to a monolayer culture, observed as patches of densely packed cuboidal cells. We were able to culture the IECs for a maximum of 12 days before cell death and detachment appeared. As an initial validation, we could confirm the reported cytoplasmic localization for inflammasome sensors NLRP3 and AIM2, whereas IFI16 showed nuclear staining.
Conclusions : We have developed a simple ex vivo 2D IEC culture system complementary to the 3D organoid culture system. Endoscopy-derived IEC isolation will allow clinicians to evaluate patient-specific epithelial response to e.g. different or new classes of gastrointestinal therapeutics. This approach also provides a simple model for screening of drug effects at the site of the intestinal epithelium in a personalized manner. Moreover association of epithelial responses with patient-specific genetic profiles (eg. with mutations in inflammasome-related genes) may lead to further insights into disease biology of intestinal diseases such as IBD.

- I05 -

SOFT ROCK INHIBITION PREVENTS INTESTINAL FIBROSIS IN A MURINE COLITIS MODEL. T. Holvoet (1), S. Devriese (2), K. Castermans (3), S. Boland (3), P. Hindryckx (2), A. Borin (3), M. De Vos (3), O. Defert (3), D. Laukens (1). (1) UZ Gent, Gent, Belgium, Gastroenterology ; (2) UZ Gent, Gent, Belgium, Gastroenterology ; (3) Amakem Therapeutics, Diepenbeek, Belgium.

Introduction : Intestinal fibrosis is a common complication of Crohn's disease. Fibrotic strictures are the most important indication for surgery and current therapies are unable to prevent their development. Rho kinase (ROCK) is a key mediator in TGFß-induced activation of myofibroblasts and a promising anti-fibrotic drug target. However, systemic ROCK inhibition is known to cause significant cardiovascular (CV) side effects.
Aim : We investigated the effects of AMA0825, a ROCK inhibitor with Localized Activity (also referred to as "soft"), on the development of intestinal fibrosis
Methods : CV effects of AMA0825 were assessed in spontaneous hypertensive rats (SHR). Disease activity, intestinal fibrosis and inflammation were evaluated in chronic DSS-induced colitis. Effects on the production of fibrotic and inflammatory mediators were measured in human intestinal fibroblasts (HIF), HT29 colonic epithelial cells and THP1 macrophages. mRNA and protein expression was analyzed by qPCR, Luminex bead assays and immunocytochemistry.
Results : In SHR, AMA0825 had no CV effects at 10 mg/kg p.o. Daily treatment of mice with AMA0825 (3 mg/kg p.o.) reduced colonic weight/length ratio ($p = 0.03$) and bacterial translocation to the liver ($p = 0.02$), while no signs of toxicity were noticed (as compared to the vehicle treated group). Trichrome-positive fibrotic tissue was reduced in the muscularis mucosae, mucosa and submucosa compared to placebo ($p = 0.003$). Lower colonic protein levels of pro-fibrotic cytokines IL6, IL13 and TGFβ1-2 were observed, and DSS-induced production of matrix metalloproteinase (MMP) 2, 3 and 9, and to a lesser extent 8 and 12, was prevented in treated mice. Interestingly, transcription of COL1A1 and ACTA2 was profoundly reduced, suggesting decreased activation of colonic myofibroblasts. Inflammatory cell infiltration and myeloperoxidase activity was unaffected by AMA0825 treatment, however, local levels of pro-inflammatory CXCL2,

KC, IFNG, TNFα and MCP1 were significantly reduced. In HIFs, AMA0825 dose-dependently inhibited TGFß1-induced phosphorylation of myosin light chain (a marker of ROCK activity), formation of actin stress fibers and expression of COL1A1 and ACTA2. TGFβ1-induced production of IL6, TGFß1 and MMP 2, 3 and 12 was also abrogated, whereas TNF, IL8 and MCP1 were not induced by TGFβ1. AMA0825 did not affect IL8 secretion from TNF-stimulated HT29 cells or LPS-challenged THP1 cells either. Since these cell types largely contribute to inflammation in DSS-colitis, AMA0825 may not exert a direct anti-inflammatory effect.
Conclusions : Inhibition of ROCK by oral administration of AMA0825 in mice is safe and profoundly diminishes the development of intestinal fibrosis by suppressing pro-fibrotic expression profiles. These effects are mainly due to direct inhibition of myofibroblast formation and activation.

- I06 -

PERSISTENT DYSREGULATED COLONIC MUCOSAL GENE EXPRESSION IN ULCERATIVE COLITIS PATIENTS WITH ENDOSCOPIC HEALING AFTER INFLIXIMAB OR VEDOLIZUMAB THERAPY. I. Arijs (1), G. De Hertogh (2), L. Van Lommel (3), K. Machiels (1), J. Van Der Goten (1), M. Ferrante (1), F. Schuit (3), G. Van Assche (1), P. Rutgeerts (1), S. Vermeire (1). (1) KU Leuven, Leuven, Belgium, Clinical and Experimental Medicine ; (2) KU Leuven, Leuven, Belgium, Imaging & Pathology ; (3) KU Leuven, Leuven, Belgium, Cellular and Molecular Medicine.

Introduction : Mucosal healing on endoscopy is considered the treatment goal in inflammatory bowel diseases, including ulcerative colitis (UC). However, endoscopic healing is no cure and relapses are still observed in the majority of patients when treatment is discontinued in these patients. As the triggers for recurrence of inflammation are unknown, we studied if mucosal gene expression profiling could identify pathways important in relapse.
Aim : We, therefore, compared colonic mucosal gene expression profiles of UC patients achieving endoscopic mucosal healing induced by infliximab (IFX) or vedolizumab (VDZ) therapy to these of healthy controls.
Methods : Colonic biopsies from 23 UC patients before and W4-6 after first IFX, from 44 UC patients before and W6, W12 and W52 after VDZ (GEMINI I and LTS), and from 12 non-IBD healthy controls were studied. Endoscopic mucosal healing was assessed at the same time points as the biopsies. Total RNA from biopsies was analyzed for whole genome gene expression via Affymetrix Human Gene 1.0 ST arrays (false discovery rate < 5% and > 2-fold).
Results : In VDZ healers, there were no significant gene probe sets different at W6 and only 5 (↘ : IDO1, REG3A, KLK6, SAA2 and ↗ : PCK1) at W12 when compared to W0. As many as 593 (462↘/131↗) gene probe sets were significantly different in VDZ healers at W52 vs. W0. The majority of the observed changes at W52 by VDZ encoded genes that were involved in immune cell trafficking, cellular movement and inflammatory response, and overlapped (63%) with the probe sets identified in IFX healers at W4-6 vs. W0 [481 (388↘/93↗) significant probe sets] probe sets. After therapy at each of the studied time points, many gene probe sets remained significantly dysregulated in the IFX and VDZ healers when compared with controls, and again a great overlap was seen between IFX and VDZ of these persistent dysregulated genes (eg. ↗ : IL1B, TIMP1, CCL20, DEFA5/A6, PI3, AREG, PTGS2, C2, SERPINB5, FAM5C and ↘ : AQP8, MT1H/M).
Conclusions : This study demonstrates that VDZ and IFX restore, although incompletely, the colonic expression of many immune-related genes in UC patients achieving endoscopic healing with VDZ at W52 and with IFX at W4-6. Persistent abnormalities in gene expression remain after therapy in healers and may explain why mucosal lesions recur if patients do not receive maintenance therapy. Furthermore, the significant overlap in persistent dysregulated genes between VDZ and IFX healers suggests that unidentified triggers of inflammation are incompletely blocked by these biologic agents.

- I07 -

HLA-DRB1 IS INVOLVED IN THE DEVELOPMENT OF ANTIBODIES TO INFLIXIMAB IN INFLAMMATORY BOWEL DISEASE. T. Billiet (1), N. Vande Casteele (2), T. Van Stappen (2), I. Cleynen (1), V. Ballet (3), K. Claes (1), F. Princen (4), S. Singh (4), A. Gils (2), M. Ferrante (3), G. Van Assche (3), S. Vermeire (3). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology ; (4) Prometheus Laboratories Inc., San Diego, USA, Department of Research and Development.

Introduction : Loss of response is one of the biggest obstacles of maintenance treatment with infliximab (IFX) in patients with inflammatory bowel diseases (IBD). One of the factors driving loss of response, is the formation of antibodies to infliximab (ATI). Little is known about host factors that determine immune responses to IFX but genetic factors may play a crucial role.

Aim : We hypothesized that the formation of ATI is associated with specific HLA class II alleles.
Methods : In this retrospective single-center study, we identified 76 IBD patients (44 CD, 32 UC) who developed ATI (= cases) during maintenance therapy and matched them with 116 IBD controls (64 CD, 52 UC). All patients were anti-TNF naïve before IFX therapy was started. Controls required at least two years of maintenance therapy with at least six IFX trough level (TL) measurements and never detectable ATI. ATI and TL were measured with an in-house-developed and clinically validated ELISA. HLA-DRB1 allele groups were typed using PCR with sequence specific primers (Prometheus Laboratories Inc.). Patient and therapy factors and the number of allele carriers for the different DRB1 alleles were compared between cases and controls. Stepwise logistic regression was performed to identify independent predictors of ATI formation.
Results : At IFX start, a loading dose (at weeks 0-2-6) and a higher albumin level were protective for ATI formation ($P < 0.05$, Chi^2 and Mann Whitney test). When considering the total number of DRB1 alleles, we found that 13% of the alleles in cases were DRB1*03 positive compared to 4% in the control group ($P = 0.02$ (adjusted for multiple testing with FDR) ; OR = 3.7, 95% CI 1.6-8.7). This association was independent of disease type, use of a loading dose or concomitant immunomodulator use ($P < 0.01$; Cochran Mantel Haenszel). In a multiple logistic regression model, the presence of DRB1*03, absence of a loading dose or IFX monotherapy were independent significant predictors of ATI formation with OR (95%CI) of 6.7 (2.3-19.5), 2.9 (1.4-6.3) and 2.02 (1.0-4.2) respectively.
Conclusions : We demonstrate that ATI formation is influenced by the HLA-DRB1 locus in patients with IBD. This locus has already been associated with formation of antibodies to interferon beta therapy in multiple sclerosis and the DRB1*03 allele with formation of anti-Ro/La autoantibodies in systemic lupus erythematosus. Our results therefore further implicate a causal role for this allele group in immunogenicity. We also demonstrated that low serum albumin and absence of a loading dose are involved in ATI formation. Low albumin has previously been linked to ATI formation and might be a surrogate marker for disease burden and an aggravated immune response. The absence of a loading dose has not been previously implicated in ATI formation. Although this loading dose is now applied widely, we feel our findings are clinically important.

- I08 -

A CANDIDATE GENE STUDY OF RARE MONOGENIC DISORDERS WITH IBD-LIKE PHENOTYPE IDENTIFIED RARE VARIANTS IN XIAP GENE IN A COHORT OF EARLY-ONSET IBD PATIENTS.

L. Amininejad (1), B. Charloteaux (2), E. Theatre (3), J. Van Cauter (4), P. Hayard (4), V. Muls (5), J. Maisin (6), M. Schapira (6), J. Ghislain (6), P. Closset (7), M. Talib (8), M. Abramowicz (9), M. Mni (2), L. Karim (10), N. Cambisano (10), J. Devière (1), M. De Vos (11), E. Louis (12), S. Vermeire (13), A. Van Gossum (1), W. Coppieters (2), M. Georges (2), D. Franchimont (1). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology and Laboratory of Experimental gastroenterology ; (2) ULg, Liège, Belgium, Unit of Animal Genomic, Groupe Interdisciplinaire de génoprotéomique Appliquée (GIGA-R) and Faculty of veterinary medicine ; (3) CHU de Liege, Domaine Universitaire du Sart Tilman, Liège, Belgium, Unit of Animal Genomic, Groupe Interdisciplinaire de Génoprotéomique Appliquée (GIGA-R) and Faculty of Veterinary Medicine ; (4) CHU de Charleroi, Charleroi, Belgium, Department of Gastroenterology ; (5) CHU Saint-Pierre, Brussels, Belgium, Department of Gastroenterology ; (6) Hôpital de Jolimont, Haine-Saint-Paul, Belgium, Department of Gastroenterology ; (7) CH Etterbeek, Brussels, Belgium, Department of Gastroenterology ; (8) CHU Brugmann, Brussels, Belgium, Department of Gastroenterology ; (9) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Human Genetics ; (10) CHU de Liege, Domaine Universitaire du Sart Tilman, Liège, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology and Laboratory of Experimental Gastroenterology ; (11) UZ Gent, Gent, Belgium, Department of Gastroenterology and Hepatology ; (12) CHU de Liège, Domaine Universitaire du Sart Tilman, Liège, Belgium, Department of Gastroenterology ; (13) KU Leuven, Leuven, Belgium, Department of Clinical and Experimental Medecine, Gastroenterology section.

Introduction : Chronic granulomatous disease, glycogen storage disease Ib, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome, leukocyte adhesion deficiency, congenital, cyclic and autoimmune neutropenias, Wiskott-Aldrich syndrome, IPEX syndrome, IL10 deficiency and XIAP deficit are all rare monogenic primary immunodeficiencies (PID). These disorders are characterized by a defective innate or adaptive immune response and demonstrate chronic intestinal inflammation reminiscent of inflammatory bowel disease (IBD).
Aim : We aimed to investigate whether the causative genes identified so far for these monogenic disorders may harbor low frequency and rare variants contributing to inherited predisposition to IBD.
Methods : We analyzed 23 selected candidate genes underlying ten monogenic diseases in IBD patients, for the presence of (i) low frequency variants by association analysis using meta-data corresponding to genotypes of ~17,000 Crohn disease (CD) case /control individuals obtained from the International IBD Genetics Consortium (IIBDGC) and imputed with 1,000 Genomes Project reference panels, testing for the presence of CD-associated variants in 1Mb loci centered on the selected candidate genes, (ii) rare variants by means of high-throughput resequencing (HTS) of 4800 individuals

(2400 early-onset and adult-onset CD/ 2400 controls) and (iii) integrating the results of the association analysis with functional information (eQTL) generated in nine tissue types relevant in IBD pathogenesis.
Results : We identified rare missense coding variants in XIAP gene conferring susceptibility in early-onset CD patients, but not in adult-onset CD patients. None of the XIAP mutation carriers demonstrate the full expression of PID X-linked lymphoproliferative disease type 2 (XLP2). No significative result was found for the other candidate genes. Increasing further more the sample size of the current cohort may reveal additional rare variants in XIAP or in other candidate genes.
Conclusions : We examined 23 coding genes underlying monogenic disorders characterized by IBD-like intestinal inflammation and could identify rare missense variants in the XIAP gene in early-onset CD. XIAP gene underlies the PID X-linked lymphoproliferative disease type 2 (XLP2) and encodes for a molecule that belongs to the family of inhibitor of apoptosis proteins (IEPs). XIAP activate also the NfκB via an indirect interaction with the NOD2-interacting protein RIP2. This study emphasizes the need to perform gene testing for XIAP deficit in patients with early-onset CD.

- I09 -

SERUM NEUTROPHIL GELATINASE B-ASSOCIATED LIPOCALIN AND MATRIX METALLOPROTEINASE-9 (NGAL-MMP-9) COMPLEX AS A SURROGATE MARKER FOR MUCOSAL HEALING IN PATIENTS WITH CROHN'S DISEASE. M. De Bruyn (1), I. Arijs (2), G. De Hertogh (3), M. Ferrante (2), G. Van Assche (2), P. Rutgeerts (2), S. Vermeire (2), G. Opdenakker (1). (1) Rega Institute for Medical Research, KU Leuven, Leuven, Belgium, Microbiology and Immunology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (3) KU Leuven, Leuven, Belgium, Translational Cell and Tissue Research, Imaging and Pathology.

Introduction : The current standard to assess mucosal healing after therapy in patients with Crohn's disease (CD) is endoscopy. However, frequent assessments are uncomfortable for the patient and contain a risk for complications. Recently, we described that serum NGAL-MMP-9 is a surrogate marker for mucosal healing in patients with ulcerative colitis (UC).
Aim : To investigate whether serum NGAL-MMP-9 can also be used in CD patients as a surrogate marker for mucosal healing.
Methods : Serum NGAL-MMP-9 levels were determined with sandwich ELISA before and up to 5 years after first infliximab infusion in 108 patients with active CD (median age at first infliximab 35.8 years, 57% female) as well as in 43 healthy controls (HC, median age 27.3 years, 60% female). Endoscopic healing was defined as complete absence of ulcerations, whereas partial healing was defined as significant endoscopic improvement, but still with ulcerations present. In a subset of patients (n = 82), histological healing was defined as an absence of epithelial damage (d'Haens score). Data were analyzed with SPSS statistics 22 and R version 3.0.2 using non-parametric tests and p-values of < 0.05 were considered significant.
Results : From the 108 patients with active CD, 72 patients showed endoscopic healing (n = 38 complete, n = 34 partial) whereas 36 patients showed no signs of endoscopic healing. At baseline, median [interquartile range, IQR] NGAL-MMP-9 serum levels were significantly higher in active CD patients versus HC (77.6 [36.9-141.0] vs 25.5 [17.8-42.8] ng/ml ; $p < 0.001$). After treatment, median [IQR] NGAL-MMP-9 serum levels significantly decreased in CD patients with healing (69.0 [32.6-135.5] to 35.2 [9.4-56.1] ng/ml ; $p < 0.001$), whereby only 4 patients with complete healing (10%) had an increase of NGAL-MMP-9 levels after therapy. For CD patients with no healing, median [IQR] NGAL-MMP-9 serum levels also significantly decreased after treatment (100.9 [43.4-152.6] to 43.8 [27.0-96.8] ng/ml ; $p = 0.002$). However, the decrease of NGAL-MMP-9 levels was significantly more profound in complete healers ($p = 0.020$). NGAL-MMP-9 serum levels correlated with the amount of neutrophils (Spearman's rho [r] = 0.470, $p < 0.001$), CRP levels ($r = 0.448$, $p < 0.001$), endoscopic activity (Kendall's tau [T] = 0.296, $p < 0.001$) and histological activity ($T = 0.312$, $p < 0.001$). Receiver operating characteristic (ROC) analysis defined a serum NGAL-MMP-9 cut-off level of 26.4 ng/ml corresponding to complete endoscopic healing (AUC = 0.79, 58% sensitivity, 85% specificity, 56% PPV and 85% NPV) and histological healing (AUC = 0.73, 63% sensitivity, 84% specificity, 50% PPV and 90% NPV). Of importance, CRP was not elevated (< 5 mg/L) in 33% of patients with active disease at start of treatment, whereas 81% of these patients did have elevated NGAL-MMP-9 levels.
Conclusions : In the search for surrogate markers to assess mucosal healing in IBD, measurement of serum NGAL-MMP-9 complex can supplement CRP in both UC and CD. We therefore propagate that the use of NGAL-MMP-9 serum levels can be implemented in clinical practice, thereby potentially overriding the need for endoscopy.

- I10 -

IDENTIFYING PREDICTORS OF LOW ADHERENCE IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE. S. Coenen (1), E. Weyts (1), V. Ballet (1), M. Noman (1), G. Van Assche (1), S. Vermeire (1), J. Vanemelen (2), M. Ferrante (1). (1) UZ Leuven, KU Leuven, Leuven, Belgium, IBD ; (2) MACX, Aartselaar, Belgium.

Introduction : Inflammatory Bowel Diseases (IBD) are chronic gastrointestinal conditions that often require medical therapy. However, medication can be costly, difficult to take or associated with unpleasant side effects. This may result into less optimal adherence and, consequently, poorer disease outcome. Therefore, identifying predictors of low adherence is paramount to effectively intervene and increase the adherence and outcome of IBD patients.
Aim : We investigated precise adherence figures and factors associated with low adherence in Belgian patients with IBD.
Methods : Between November 2013 and March 2014, 471 ambulatory IBD patients in our tertiary referral center were requested to complete the Morisky 8-Item medication adherence questionnaire (MMAS-8) as well as a survey containing socio-demographic data (smoking, educational level, marital status and occupation). Based on the self-reported MMAS-8, adherence was categorized as low (MMAS-8 score > 2), medium (1-2) or high (0). Using SPSS 22.0, we looked for factors independently associated with low adherence.
Results : Data were collected for 466 IBD patients (50% male, median age 41 years, 71% Crohn's disease, 29% ulcerative colitis), giving a participation rate of 99%. Univariate analysis in the IBD group showed that mesalamine was the only therapy associated with low compliance [1.572 (1.032-2.395), $p = 0.035$]. As regards occupation, low adherence was most frequently observed in students (47.6%) and employees (42.0%), and less frequently in the self-employed (20.0%). Other significant predictors of low adherence were higher educational level and being single. In multivariate analysis, factors independently associated with low adherence were higher educational level [1.867 (1.315-2.650), $p < 0.001$], being single [1.724 (1.147-2.590), $p = 0.009$], and being self-employed [0.348 (0.156-0.774), $p = 0.010$]. IBD patients who felt worse had more difficulty sticking to the treatment plan [39.1% vs. 19.5%, OR 2.652 (1.092-6.437), $p = 0.026$] and they concealed their doctor about this [21.7% vs. 8.7%, OR 2.911 (0.996-8.507), $p = 0.042$]. Patients with a higher educational level reported that they forgot more often to take their medication [35.2% vs. 17.8%, OR 2.513 (1.638-3.855), $p < 0.001$] and they stopped the intake of their medication more often when they felt well [20.9% vs. 12.6%, OR 1.836 (1.116-3.020), $p = 0.016$]. As regards occupation, students had more difficulties sticking to the treatment plan [35.9% vs. 21.5%, OR 2.047 (1.030-4.067), $p = 0.037$].
Conclusions : Approximately one third of the IBD patients were low adherers. Predictors of low adherence in this group were higher educational level, being single, and not being self-employed. More data are warranted to define a well-validated profile for IBD patients with low medication adherence requiring a tailored intervention.

- I11 -

GENETIC AND CLINICAL CHARACTERIZATION OF 62 MULTIPLE-AFFECTED IBD FAMILIES. A. Settesoldi (1), M. Vancamelbeke (2), T. Billiet (2), V. Ballet (3), S. Singh (4), S. Lockton (4), F. Princen (4), G. Van Assche (3), P. Rutgeerts (3), S. Vermeire (3), I. Cleynen (2). (1) Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy, Gastroenterology ; (2) KU Leuven, Leuven, Belgium, Translational Research in Gastro Intestinal Disorders (TARGID) ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology ; (4) Prometheus Laboratories Inc., San Diego, USA, Prometheus Laboratories Inc.

Introduction : Inflammatory bowel disease (IBD) pathogenesis comprises genetic, environmental and immunological factors. 163 genetic loci have been associated with the risk of IBD.
Aim : Multiple-affected families (≥ 3 first-degree relatives affected) may have a higher genetic risk burden. We characterized these families clinically and genetically to find to what extent the 163 loci are associated with IBD in these families.
Methods : We included 62 multiplex families affected by Crohn's disease (CD), ulcerative colitis (UC) or IBD unclassified (IBD-U). We collected demographic (sex, smoking) and clinical data (age at diagnosis, disease location and behavior). We genotyped affected and unaffected members with Immunochip for the 163 loci. We analyzed serum samples for the Prometheus serology panel (ASCAA, ASCAG, CBir1, Fla2, FlaX, OmpC, ANCA).
Results : Among our families, 39 were CD, 2 UC, 17 CD/UC and 4 CD/IBD-U. They comprised in total 190 CD, 38 UC, 6 IBD-U and 307 healthy relatives. The average age at diagnosis was 25 years for CD (IQR 20-34) and 31 for UC (IQR 26-39). CD members of a same family showed high concordance in smoking habit (72%), age at diagnosis (87%), disease location (74%) and behavior (69%). The difference in average number of risk alleles (RA) between affected and unaffected members was not significant, nor between affected members and 2612 unrelated cases. Quartile analysis of the number of risk alleles showed that patients were most represented in Q4 and unaffected in Q1 ($p = 2.61x10\text{-}03$). Of

the 163 loci, 18 SNPs were nominally significant for the parenTDT test. The most significant (p = 2.08x10-03) was rs2155219, located in 11q13 between C11orf30 and LRRC32. NOD2 frameshift mutation was also significantly associated with Crohn's disease (p = 0.045). We found no enrichment of particular disease-associated pathways in any of the families. The serology panel was disease-dependent rather than family-dependent, with low intraclass correlation coefficients within families (0.06-0.21), suggesting that these antibodies increase with inflammation. Sensitivity, specificity, PPV and NPV for a diagnostic prediction of IBD vs non-IBD were 85.6%, 75.9%, 85% and 76.8%, respectively.
Conclusions : This is the largest cohort of multiple-affected IBD families studied to date. We found a high degree of concordance among CD patients of a same family in clinical features. We found nominal significance for disease association with 18 of the known IBD susceptibility loci but they do not explain much of genetic risk in these families. Exome sequencing on families with a low genetic risk score could identify additional risk loci. Serology markers could be useful to diagnose disease rather than to predict it.

- I12 -

ANTI-TNF-INDUCED SKIN MANIFESTATIONS IN IBD PATIENTS : ROLE FOR INCREASED DRUG EXPOSURE ? I. Cleynen (1), W. Van Moerkercke (2), T. Billiet (3), N. Vande Casteele (4), M. Ferrante (1), M. Noman (2), G. Van Assche (2), P. Rutgeerts (2), S. Segaert (5), A. Gils (4), S. Vermeire (1). (1) KU Leuven, Leuven, Belgium, Clinical and Experimental Medicine ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology ; (3) KU Leuven, Leuven, Belgium, Clinical and Experimental Medicine ; (4) KU Leuven, Leuven, Belgium, Therapeutic and Diagnostic Antibodies ; (5) UZ Leuven, KU Leuven, Leuven, Belgium, Dermatology Department.

Introduction : A subgroup of patients treated with anti-tumor necrosis factor (anti-TNF) develop paradoxical inflammation of the skin. While in most patients these lesions can be controlled with topical or systemic treatment, in a subset of patients anti-TNF treatment needs to be discontinued. Although the pathogenesis of these skin lesions is not fully understood, these side-effects mostly seem to occur while the intestinal inflammation is controlled.
Aim : We therefore aimed to study if drug exposure in those patients developing a skin lesion is higher than in patients without skin lesions.
Methods : We performed a retrospective study on 604 IBD patients under infliximab maintenance therapy (> = 4 infusions in > = 6 months), and studied the influence of infliximab trough concentrations (TC) and development of antibodies to infliximab (ATI) on the development of skin lesions. A skin lesion was defined as either xerosis cutis, eczema, psoriasis, psoriasiform eczema, palmoplantar pustulosis or other (folliculitis, acne, alopecia areata, tinea pedis…) with the need to consult a dermatologist. A total of 8350 TC measurements (ELISA) were available in 433 individuals with a median of 18 (IQR 5-32) per individual. 2770 ATI measurements were available in 325 individuals with a median of 5 (IQR 3-13) per individual.
Results : Of the 604 patients, 230 (38.0%) developed a skin lesion related to anti-TNF therapy. Of these, 176 (29%) developed under infliximab after a median time of 1.7 years (8.7/100 patient years, pyrs), and 54 (9%) after switch to adalimumab or certolizumab pegol with a median time of 1 year after switch (7.3/100 pyrs). The cumulative infliximab dose in patients developing a skin lesion under infliximab was 2833 [2198-3864] mg/yr, compared to 2927 [2372-3670] mg/yr in the other patients (p = NS). The median infliximab TC in skin lesion patients was 4.2 μg/ml, and 4.0 μg/ml in non-skin lesion patients (p = NS). There was no difference in the number of subtherapeutic TC (at least twice TC < 3 μg/ml), supratherapeutic TC (at least twice TC > 7 μg/ml), or ATI positive (at least once > 1 μg/ml equivalents) patients in the skin lesion group compared to the non-skin lesion group (Table 1). Quartile analysis of the median TC per individual did not show differences between skin lesion and non-skin lesion patients (table 1, p = NS).
Conclusions : Our data show that differential drug exposure, as represented by drug TC does not play a role in developing skin adverse events in patients treated with anti-TNF.

- I13 -

DISEASE BURDEN OUTWEIGHS THE IMPACT OF DRUG CONCENTRATIONS AND ANTIBODIES TO INFLIXIMAB IN PRIMARY NON-RESPONSE TO INFLIXIMAB IN CROHN'S DISEASE PATIENTS. T. Billiet (1), I. Cleynen (1), V. Ballet (2), K. Claes (1), F. Princen (3), S. Singh (3), M. Ferrante (2), G. Van Assche (2), S. Vermeire (2). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology ; (3) Prometheus Laboratories Inc., San Diego, USA, Department of Research and Development.

Introduction : The mechanisms behind primary non-response (PNR) to infliximab (IFX) in IBD are still incompletely understood. The role of IFX trough levels (TL) and early antibody formation (ATI) during the induction phase (0-2-6 weeks) are contradicting. Furthermore, the evolution of serum TNF during IFX induction has been sparsely studied.

Aim : We investigated if serum markers of inflammation or drug exposure help in understanding what is driving PNR.
Methods : In this retrospective single-center study, we identified a cohort of 201 anti-TNF naïve Crohn's disease (CD) patients who received IFX induction and had serum samples drawn at weeks 0, 2, 6 and 14. In all samples CRP, albumin, TNF (Prometheus Laboratories Inc.), ATI (measured with drug tolerant homogeneous mobility shift assay, Prometheus Laboratories Inc.) and TL (in-house-developed ELISA) were assessed. PNR was defined as complete absence of clinical improvement at week 14 (physician global assessment).
Results : The incidence of PNR was 8% (n = 16). In univariate analysis, low albumin at w6 was associated with PNR (P = 0.01, Mann Whitney test). We observed a significant increase of serum TNF after each IFX infusion with medians at w0 and w14 of 1.6 pg/ml (IQR 0.9-2.7) and 7.7 pg/ml (IQR 4.5-11.5) respectively (P < 0.0001, Kruskal-Wallis test). In patients with PNR, this rise in TNF (w14-w0) was significantly lower than in responders (P = 0.03, Mann Whitney test). In an attempt to classify inflammation driven by TNF relative to the overall inflammation, we compared TNF/CRP ratio between both groups. A stepwise multiple logistic regression model identified albumin at w6 and TNF/CRP at w0 to be independent significant predictors (P < 0.01) of PNR to infliximab at w14, with OR (95% CI) of 0.08 (0.02-0.37) and 3.10 (1.54-6.25) respectively.
Conclusions : A high disease burden (represented by low albumin, high CRP and serum TNF) and not IFX TL or ATI (detectable in 21% of patients at w14) are the most important factors driving PNR to IFX. TNF and CRP separately did not predict primary response but a higher TNF/CRP ratio before start of IFX was predictive for PNR, contradicting the theorem that PNR might be due to 'non-TNF-driven' disease. Although the median TL at w14 between both groups did not differ significantly (P = 0.48), this ratio indicates that the contribution of TNF in inflammation might even be higher in PNR before IFX start, and possibly demanding a higher loading dose. We further observed an increase of serum TNF after IFX and this was less in PNR. The mechanism behind this increase remains unclear. These results warrant further investigation for the role of disease burden in PNR to IFX.

- I14 -

PLEXITIS AS A PREDICTIVE FACTOR FOR EARLY POST-OPERATIVE ENDOSCOPIC RECURRENCE IN PATIENTS WITH CROHN'S DISEASE UNDERGOING A RIGHT HEMICOLECTOMY WITH ILEOCOLONIC ANASTOMOSIS : RESULTS FROM A PROSPECTIVE, SINGLE CENTER TRIAL. B. Lemmens (1), G. Van Assche (2), A. De Buck Van Overstraeten (3), S. Vermeire (2), A. Tertychnyy (4), S. Fieuws (5), K. Geboes (6), A. D'hoore (3), G. De Hertogh (6), M. Ferrante (2). (1) KU Leuven, Leuven, Belgium, Imaging and Pathology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Abdominal Surgery ; (4) First Moscow State Medical University, Moscow, Russia, Pathology Department ; (5) KU Leuven, Leuven, Belgium, Biostatistics and Statistical Bioinformatics Unit ; (6) UZ Leuven, KU Leuven, Leuven, Belgium, Imaging and Pathology.

Introduction : Many Crohn's disease (CD) patients will experience post-operative endoscopic recurrence (ER) within one year after surgery. Prediction of early ER is warranted, to advocate the initiation of post-operative prophylactic therapy.
Aim : In retrospective studies, plexitis was proposed as a predictive factor for early post-operative ER and we aimed to confirm this in a prospective setting.
Methods : A prospective cohort of 74 patients (30 male ; median age 45 years) undergoing a right hemicolectomy with ileocolonic anastomosis for confirmed CD was studied. As a control group, 19 patients with ulcerative colitis and 19 patients with a tumour of the caecum were included. Active smoking (n = 21), fistulising disease (n = 39) and previous bowel resections (n = 28) were selected as predefined potential clinical confounders. The proximal resection margin of every surgical specimen was histologically investigated on three consecutive slides by a pathologist. Inflammatory cells were counted stepwise within and appositioned to every ganglion of both the myenteric and submucosal plexus. Eosinophils were counted on haematoxylin-eosin stained slides, lymphocytes and mast cells on immunohistochemically CD45 and tryptase stained slides, respectively. All patients underwent ileocolonoscopy six months after surgery, and endoscopic recurrence was defined as a Rutgeerts score of ≥i2b. Statistical analyses were performed using SAS software and were based on application of Bayes' rule.
Results : At six months, ER was seen in 37 of 74 patients (50%). Prediction of ER based on the clinical confounders led to an area under the curve (AUC) of only 0.547 (95%CI :0.415–0.678). When looking at the counts, the mean count of submucosal and myenteric lymphocytes, as well as submucosal mast cells was significantly higher in CD-patients compared to the control groups (P < 0.0001). Furthermore, the submucosal lymphocyte count could discriminate between ER and no ER with an AUC of 0.640 (0.513–0.767). Adding these submucosal lymphocyte counts to the clinical parameters, resulted in a significantly higher AUC of 0.703 (0.584–0.821) (P = 0.047) compared to the use of clinical information alone. Simplifying these analyses by looking only at the percentage of non-zero counts resulted in a comparable result with an AUC of 0.677 (0.554–800).
Conclusions : Submucosal lymphocytic plexitis in the proximal section margin was significantly related with the risk for ER after right hemicolectomy. In clinical practice, the use of the percentage of non-zero counts can be used to predict

the risk for early post-operative ER. Furthermore, our data suggest that blocking lymphocyte trafficking in the post-operative bowel by anti-adhesion molecules may prevent early post-operative ER.

- I15 -

LOW AWARENESS ON THE DETRIMENTAL RISKS OF SMOKING IN BELGIAN CROHN'S DISEASE PATIENTS. EDUCATION REMAINS CHALLENGING. C. De Bie (1), V. Ballet (2), G. Van Assche (2), S. Vermeire (3), M. Ferrante (3). (1)UZ Leuven, Leuven, Belgium, Department of Internal Medicine ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID).

Introduction : The detrimental effect of smoking on development and progression of Crohn's disease (CD) is generally accepted. Although health care professionals undoubtedly spend a lot of time in education of patients, the actual awareness of smoking risks in CD patients is unclear.
Aim : The aim of this study was to evaluate the knowledge of IBD patients about the different effects of smoking on their diseases, in particular the deleterious effect on CD's course and the protecting influence of smoking on ulcerative colitis (UC).
Methods : We assessed several smoking behaviour parameters and patients' awareness on different effects of smoking, through a simple questionnaire in a single referral centre. During the outpatient clinic of gastroenterology, 625 consecutive patients with CD, 238 patients with UC and 289 patients without an inflammatory bowel disease (non-IBD controls, NC) were requested to participate. The questionnaire included questions on former and actual smoking behaviour, cessation attempts, nicotine dependence (Fagerström score), and willingness to quit smoking. Patients were questioned on their awareness of smoking-related risks on several aspects of health, including detrimental effects on CD.
Results : Participation rates were 92% for CD (n = 575, 46% male, 44 years, 44% never smoked), 93% for UC (n = 238, 57% male, 45 years, 50% never smoked) and 76% for NC (n = 221, 48% male, 48 years, 55% never smoked). At diagnosis, more CD patients were active smokers compared to UC patients (40% vs. 17%, $p < 0.001$). Previous attempts to stop smoking and nicotine dependence were similar in all groups. Remarkably, smoking cessation rates after diagnosis were not higher in CD compared to UC (both 56%, $p = 0.997$). In contrast, more CD than UC patients started smoking after diagnosis (12% vs. 6%, $p = 0.050$). The majority of patients recognized dangers of smoking on general health (98-99%), lung cancer (95-97%), myocardial infarction (89-92%), and stroke (78-87%). Although CD patients more frequently acknowledged risks of smoking on their disease, only 37% were aware of the link with CD development, 30% of increased surgical rates, and 27% of increased postoperative recurrence rates. Of note, within the CD population, awareness was unrelated to actual smoking behaviour. Increased surgery rates were acknowledged by 30% of active, 32% of former and 29% of non-smokers ($p = 0.783$). Active smokers not willing to quit smoking, most often denied a potential bad influence of smoking on their disease. Previous surgery, level of education and employment did not influence awareness. Finally, UC patients were more frequently aware of an inverse relationship between smoking and UC development (39% UC, 16% CD, 4% NC, $p < 0.001$).
Conclusions : Although CD patients were better informed on the detrimental effects of smoking, the awareness rate was still low. These data may also suggest more denial for the adverse consequences of smoking in active smokers. More efforts need to be done on informing and educating patients regarding the risks of smoking.

- I16 -

ANTI-TNF TREATMENT AND RENAL CELL CARCINOMA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE, RHEUMATOID ARTHRITIS AND SPONDYLOARTHROPATHY : TRIGGER OR CURE ? L. Wauters (1), S. Joniau (2), P. Verschueren (3), G. Van Assche (1), S. Vermeire (1), M. Ferrante (1). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Gastroenterology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Urology ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Rheumatology.

Introduction : There is limited evidence on the risk of solid cancers such as renal cell carcinoma (RCC) in chronic inflammatory conditions treated with anti-TNF therapy. Moreover, anti-TNF therapy is increasingly being used for advanced RCC in clinical trials .
Aim : We studied the occurrence of RCC in patients with inflammatory bowel disease (IBD), as well as rheumatoid arthritis and spondyloarthropathy (REU) at a tertiary referral centre.
Methods : In this retrospective cohort study using a supervised automatic search of our electronic clinical database, we included all IBD and REU patients who were diagnosed with RCC between January 1990 and September 2014. Medical records were reviewed for demographic and clinical variables, including type and duration of anti-TNF treatment. Age at diagnosis of RCC, tumour stage and surgical treatment were compared between groups.

Results : The diagnosis of RCC was confirmed in 22/2538 (0.9%) anti-TNF naïve IBD patients and in 7/1847 (0.4%) IBD patients with anti-TNF exposure (p = 0.049). IBD/RCC patients with anti-TNF had a significantly higher rate of prior immunosuppression (100% vs. 27% ; p = 0.001) and surgery (100% vs. 62%, p = 0.042) compared to anti-TNF naïve IBD/RCC patients. In anti-TNF treated IBD patients, RCC was diagnosed at a younger age (median 46.0 (IQR 42.3-56.4) vs. 63.1 (51.6-71.8) years ; p = 0.034) and early surgery (within 1 month of diagnosis) (100% vs. 23% ; p = 0.0003) and partial nephrectomy (86% vs. 33% ; p = 0.013) were more common. In the REU group, 29 patients with RCC were identified with only one patient previously exposed to anti-TNF. Compared to IBD, symptomatic RCC was more common in REU patients (41% vs. 17% ; p = 0.043) and RCC was diagnosed at a significantly older age (70.0 (60.0-77.0) vs. 58.1 (46.0-67.3) years ; p = 0.008) and in advanced tumour stages (≥T2 28% vs. 7% ; p = 0.037).
Conclusions : IBD/RCC patients with anti-TNF exposure were diagnosed at a younger age and undergoing early and nephron sparing surgery, inferring a better patient and tumour profile. Conversely, REU/RCC were diagnosed at a higher age and in more advanced stages with only one patient with anti-TNF. The higher rate of prior immunosuppression and surgery in IBD patients with anti-TNF indicates more active disease, requiring regular abdominal imaging which may lead to incidentally found low stage RCC. However, a potential treatment or disease related risk is not excluded and further long-term multicentre case-control studies are needed.

- I17 -

SUSTAINED TNF SUPPRESSION AND ADEQUATE TROUGH CONCENTRATIONS DURING INDUCTION THERAPY WITH ADALIMUMAB PREDICT REMISSION IN ANTI-TNF NAÏVE CROHN'S DISEASE PATIENTS.
N. Vande Casteele (1), A. Gils (1), M. Ferrante (2), D. Mould (3), S. Tops (1), K. Vandenbroeck (2), V. Ballet (2), G. Van Assche (2), S. Vermeire (2), F. Baert (4). (1) KU Leuven, Leuven, Belgium, Department of Pharmaceutical and Pharmacological Sciences, Therapeutic and Diagnostic Antibodies ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology Department.

Introduction : Adalimumab (ADM), a fully human TNF antagonist, is effective for treating patients with Crohn's disease (CD). A correlation between concentration and effect was observed at distinct time points.
Aim : Our aim was to evaluate the correlation of early longitudinal measurements of ADM with different biological markers for disease activity and induction of clinical remission.
Methods : Prospective two-centre open-label study in 23 anti-TNF naïve patients with moderate to severe CD induced with ADM 160/80 mg at week 0 and 2 and 40 mg every 4 weeks in monotherapy. Serum samples were taken pre and post first injection and at weeks 1, 2, 3, 4 and 12. Clinical remission was evaluated at week 12 and was defined as a Harvey-Bradshaw index (HBI) less than or equal to 4. True primary non-responders, defined as a lack of clinical response despite adequate drug exposure, were excluded from longitudinal analyses. Concentrations of ADM were measured with the Leuven assay (lower limit of quantification, LLOQ 0.3 μg/mL) and antibodies to ADM with a drug tolerant homogenous mobility shift assay (LLOQ 1.7 U/mL).
Results : Of the 23 patients, 16 (70%) achieved clinical remission at week 12. Median (IQR) HBI in remitters (R) and non-remitters (NR) was 7 (5-9) vs. 7 (5-9) at week 0 (P = 0.840) ; 1 (0-5) vs. 7 (5-9) at week 4 (P = 0.020) and 1 (0-2) vs. 6 (5-7) at week 12 (P = 0.001). CRP and TNF concentrations at baseline were similar in R and NR : respectively 6.9 vs. 8.9 mg/L (P = 0.504) for CRP and 2.9 vs. 2.9 pg/mL (P = 0.973) for TNF and decreased significantly in R but not in NR. Drug exposure as defined by area under the curve (AUC(week 0-4)) of ADM was significantly greater for R than NR (P = 0.043). One patient had an ADM exposure level in the 95th percentile and was excluded as a true primary non-responder ; this patient also had low TNF at baseline (0.56 pg/mL). Trough concentrations of ADM were better associated with clinical remission at week 12 than peak concentrations ; ROC curve analysis at week 2 revealed a cut-off of > 9.7 μg/mL (100% specificity, 69% sensitivity, AUROC 0.87, P < 0.01) and at week 4 of > 11.0 μg/mL (100% specificity, 69% sensitivity, AUROC 0.88, P < 0.01). One patient developed antibodies to ADM (detectable at week 12) and was in clinical remission at that time.
Conclusions : Primary (non-)response to ADM is not associated with immunogenicity even during monotherapy. Our results indicate that adequate exposure to ADM drives response and that in relation to TNF concentration, this might be predictive of effective disease suppression. Prospective trials to evaluate preemptive dose optimization based on exposure during induction are now needed and might increase primary remission rates.

DEVELOPMENT OF A SIMPLIFIED HISTOLOGICAL GEBOES SCORE FOR ULCERATIVE COLITIS. A. Jauregui-Amezaga (1), G. De Hertogh (2), T. Bessissow (3), B. Lemmens (2), T. Lobatón (4), M. Ferrante (1), R. Bisschops (1), G. Van Assche (1), S. Vermeire (1), K. Geboes (2). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology - Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Pathology ; (3) McGill University, Montreal, Canada, Department of Gastroenterology ; (4) Hospital Universitari Germans Trias i Pujol, Badalona, Spain, Department of Gastroenterology.

Introduction : The current goal of medical treatment in ulcerative colitis (UC) is to achieve mucosal healing assessed by endoscopic examination. However, the presence of histological activity in patients with clinical and endoscopic quiescent UC has been related to a higher risk of relapse. The Geboes histological Score is the most used in UC, but its complexity limits its applicability (Geboes, Gut 2000). As it was previously developed to assess the effect of topical therapy, some aspects have become redundant in the era of biologicals.
Aim : The aim of this study was to create a Simplified Geboes Score (SGS) and determine its accuracy to predict UC relapse.
Methods : Only variables linked to active inflammatory activity were taken from the original Geboes Score : neutrophils/eosinophils in the lamina propria and neutrophils in the epithelium were reduced to 3 subcategories, and epithelial injury at crypts and surface was combined into one category. Additionally, basal plasmacytosis was included as a scoring variable (Bitton, Gastroent 2001). All histological slides from a previous study (Bessissow, Am J Gastroent 2012) evaluating UC patients with complete mucosal healing (Mayo 0) were then re-read by two independent readers. UC relapse (clinical Mayo Score ≥3) was recorded in these patients over a 12-month follow-up period.
Results : Seventy-five UC patients (40 men, median age 40 years) with endoscopic healing were included. Histological activity was observed in 33/75 (44%) patients : 17 (23%) presented basal plasmacytosis (SGS grade 1), in 7/75 (9%) eosinophils (SGS grade 2A) were observed and in 8/75 (11%) neutrophils (SGS grade 2B) were identified in the lamina propria. Crypts were involved in 13/75 (17%) cases (SGS grade 3) and epithelial injury (SGS grade 4) was diagnosed in 18/75 (24%) patients. During follow-up 15 patients (20%) experienced a clinical relapse, and histological activity at baseline was observed in 10 of these (67%). Basal plasmacytosis (SGS grade 1, $p = 0.004$) and epithelial injury (SGS grade 4, $p = 0.02$) were significantly associated with UC relapse and identified as predictors of relapse in univariate regression analysis (SGS grade 1 OR 6.5 [1.9-22], $p = 0.003$; SGS grade 4 5.7 [1.7-19], $p = 0.005$). After multivariate regression analysis, only epithelial injury was withheld as a UC relapse predictor (OR 6.9 [CI 1.9-24], $p = 0.003$.
Conclusions : 67% of UC patients in endoscopic remission still showed histologic activity. We simplified the histological Geboes score and demonstrate that epithelial injury is a significant risk factor for relapse in these patients. Further studies should now be designed to validate this score.

IDENTIFICATION OF DSG3, MAGI1 AND TFF1 AS FUNCTIONALLY IMPORTANT GENES IN INFLAMMATORY BOWEL DISEASE PATHOGENESIS. M. Vancamelbeke, T. Vanuytsel, R. Farré, M. Ferrante, K. Verbeke, P. Rutgeerts, S. Vermeire, I. Arijs, I. Cleynen. KU Leuven, Leuven, Belgium, Clinical and Experimental Medicine.

Introduction : Genetic and functional studies have implicated an intestinal epithelial barrier dysfunction ('leaky mucosal barrier') in inflammatory bowel disease (IBD). However, it remains unclear whether this dysfunction is a causal event in IBD or rather a consequence of mucosal inflammation.
Aim : In this study, we investigated the role of intestinal epithelial barrier genes in IBD.
Methods : The mRNA expression of 128 genes involved in different aspects of intestinal epithelial barrier function was studied in 116 colonic mucosal biopsies (74 active ulcerative colitis (UC), 23 inactive UC, 8 active Crohn's disease (CD) and 11 controls) and in 78 ileal biopsies (51 active CD, 16 inactive CD and 11 controls). Disease activity was based on endoscopic findings. Total RNA from biopsies was used to analyse the gene expression with Affymetrix Human Gene 1.0 ST arrays (false discovery rate < 0.05 and > 2-fold change). We also compared allele frequencies of 3220 SNPs within 104 of the selected genes in our cohort of IBD patients ($n = 2804$; 1856 CD, 948 UC) and 1013 healthy controls using immunochip data. In addition, we tested if these SNPs influenced expression of the differentially expressed genes (eQTL).
Results : No significant difference in colonic barrier gene expression was seen between active UC and active CD. In active IBD, the colonic expression of MUC1, MUC5B, EMCN, MCAM, TFF1, CLDN1, JAM2, DSG3, LAMA4, LAMC1, TCF4 and F2RL2 was upregulated compared to controls, whereas the colonic expression of RETNLB, CLDN8, OCLN, MAGI1 and MEP1A was downregulated. In inactive colonic IBD, no significant changes were observed compared to controls. The ileal expression of MUC1, MUC4, MUC5B, MUC6, TFF1, CLDN1, CLDN18 and F2RL2 was significantly upregulated in active CD compared to controls, while only the ileal expression of CLDN8 was significantly downregulated. In inactive CD, MUC1 and MUC4 ileal expression remained upregulated, and CLDN8

downregulated compared to controls. Forty-six genes showed a significant association (> = 1 SNP with uncorrected $p < 0.05$) with IBD, of which 8 belonged to the differentially expressed genes (MUC1, MUC4, TFF1, CLDN8, DSG3, MAGI1, TCF4, MEP1A). Interestingly, SNPs in DSG3, MAGI1, and TFF1 did not only confer risk to IBD, but also were eQTLs for their expression in inflamed colon and ileum respectively.
Conclusions : Our data show a dysregulated expression of several barrier genes in active IBD patients, while only in inactive ileal CD patients few barrier genes remained dysregulated, suggesting a primary barrier defect in these patients. The expression data, but also genetic data and eQTL analysis point to DSG3, MAGI1 and TFF1 as possibly important and functional candidate genes for IBD pathogenesis.

- I20 -

SEROLOGICAL MARKERS CHANGE SIGNIFICANTLY AFTER RIGHT HEMICOLECTOMY WITH ILEOCOLONIC ANASTOMOSIS IN PATIENTS WITH CROHN'S DISEASE. M. Noben (1), A. De Buck Van Overstraeten (2), S. Lockton (3), B. Verstockt (4), G. De Hertogh (5), F. Princen (3), A. Wolthuis (2), G. Van Assche (4), S. Vermeire (4), S. Singh (3), A. D'hoore (2), M. Ferrante (4). (1) KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Abdominal Surgery ; (3) Prometheus Laboratories Inc., San Diego, USA, Research and Development ; (4) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Gastroenterology ; (5) UZ Leuven, Leuven, Belgium, Department of Pathology.

Introduction : Preventing postoperative endoscopic (ER) and clinical recurrence (CR) remains challenging in patients with Crohn's disease (CD) undergoing an intestinal resection. We previously identified a pre-operative risk panel (including smoking behavior, Fla2, and pANCA) which may guide postoperative prophylactic therapy.
Aim : We aimed to evaluate the post-operative evolution of serological markers and its association with both ER and CR.
Methods : The study population consisted of 71 consecutive patients (33 males, 20 active smokers, median age 42.7 years) undergoing an ileal resection with ileocolonic anastomosis for refractory CD, of whom a serum sample was available both ≤1 week prior to surgery and 6 months thereafter. ER was defined as an endoscopic recurrence score of i3 or i4 at month 6. Sera were analysed blindly at Prometheus laboratories Inc. for the expression of anti-Saccharomyces cerevisiae IgA and IgG antibodies, three different anti-flagellin antibodies (CBir1, Fla2 and FlaX), antibodies to the outer-membrane porin C of Escherichia coli (OmpC), and atypical perinuclear antineutrophilic cytoplasmic antibodies (pANCA). The Q3 value of each individual marker was defined as the cut-off point.
Results : At month 6, ER and CR were observed in 20 (28%) and 12 (17%) patients, respectively. During a median (IQR) follow-up of 26.8 (18.1-39.2) months, 24 (34%) of patients developed CR. We observed a significant decrease of ASCA IgA [median 21.39 (IQR 11.59-73.18) six months postoperatively vs. 34.05 (9.56-89.34) pre-operatively, Wilcoxon $p < 0.001$], ASCA IgG [25.22 (12.00-35.91) vs. 29.07 (11.10-63.86), $p < 0.001$], CBir1 [24.91 (16.37-49.60) vs. 30.31 (16.78-89.28), $p < 0.001$] and FlaX [51.47 (23.49-73.87) vs. 52.49 (25.63-95.80), $p = 0.001$], while a significant increase was noted for OmpC [12.66 (9.29-22.38) vs. 6.58 (2.63-13.17), $p < 0.001$]. The absolute and relative post-operative changes of these markers were not associated with ER or CR. However, active smoking, ASCA IgA > 72 EU, OmpC > 23 EU and positive pANCA (n = 15) at month 6, were associated with ER. In multivariate analysis, OmpC > 23 EU was associated with ER [Odds ratio 4.398 (1.379-14.028), $p = 0.012$]. In 59 patients without CR at month 6, Cox regression multivariate analysis, revealed that both ER [7.926 (2.256-27.848), $p = 0.001$] and pANCA [4.741 (1.378-16.313), $p = 0.014$] were independent predictors of long-term CR.
Conclusions : In contrast to most previous findings, we observed a clear evolution of serological markers in the postoperative phase. This observation is probably reflecting a changing microbial environment. At 6 months, OmpC antibodies were independently associated with postoperative ER. Interestingly, not only ER but also presence of pANCA at month 6 was an independent predictor of long-term CR. Validation of these results in an independent cohort is warranted.

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ENTERO-COLO MR PREDICTS CLINICAL RELAPSE IN QUIESCENT CROHN'S DISEASE. P. Meunier (1), F. Cousin (1), C. Van Kemseke (2), C. Reenaers (2), P. Latour (2), J. Belaiche (2), E. Louis (2). (1) CHU de Liège, Liège, Belgium, Department of Medical Imaging ; (2) CHU de Liège, Liège, Belgium, Department of Gastroenterology.

Introduction : Crohn's disease is a chronic relapsing disease with tissue damage accumulating over time. Therefore, deep remission including clinical remission but also tissue healing has been advocated as the therapeutic target in this disease. Yet, the definition of deep remission remains unclear. Particularly when assessed by MRI, the degree of healing to obtain is not defined.

Aim : The aim of this study was to assess the relapse predictive value of a series of characteristics at entero-coloMR (ecMR) in clinically quiescent Crohn's disease.
Methods : We performed a prospective monocenter cohort study, including consecutive patients. We included patients with clinical remission defined by a Harvey Bradshaw index ≤4. At baseline, these patients had blood test including hemoglobin, platelets count, CRP and the measurement of fecal calprotectin. They underwent an ecMR, after gut and colon repletion by enterography and enema. These patients were then followed up clinically until study end. All ecMRs were analysed by a single radiologist blindly from clinical outcome : a segmental and a mean global MaRIA score were calculated as well as a modified one (including jejunal and proximal ileal segments). Furthermore, a series of MR signs were collected. A relapse was defined by a HBI > 4 with an increase of at least 3 points. Correlations between clinical, demographic, biological parameters and ecMR signs were assessed with Pearson and Spearman tests. Time-to-relapse predictive value of the variables was assessed by the Cox regression.
Results : 29 patients were initially recruited, but two did not undergo the foreseen assessment. Twenty seven patients were finally analyzed : 16 males, median age 31 yrs, median disease duration 7 yrs, 11 ileal disease (L1), 12 ileocolonic (L3), 2 ileal + upper GI disease (L1+L4), 2 ileocolonic + upper GI disease (L3+L4). Fifteen were under anti-TNF, 7 under Immunosuppressant, 5 under 5ASA, 5 without treatment and none under steroids. Median CRP, median fecal calprotectin and median platelet counts were 2.1 mg/l, 300 microg/g and 288.000/mm3, respectively. Fecal calprotectin and platelet counts, but not CRP were significantly correlated to several MR signs and scores (Mean MaRIA, Modified MaRIA, Maximal segmental MaRIA, relative contrast enhancement, submucosal oedema). 10/27 patients relapsed over a median follow up of 27 months. In univariable analysis, variables associated with the time-to relapse were relative contrast enhancement of the maximally affected segment (HR :2.56 ;P = 0.046), presence of ulcers (HR :12.5 ;P = 0.039), presence of fistula (HR :14.1 ;P = 0.009) and the target sign (HR :3.63 ;P = 0.049). None of the clinical, demographic or biological variables was statistically significant (although CRP and platelet counts were borderline). In multivariable analysis, the only variable selected was the presence of a fistula.
Conclusions : ecMR signs correlated well with biological markers of remaining inflammation in patients with clinically quiescent Crohn's disease. ecMR signs better predicted time-to-relapse than these biomarkers.

- I22 -

GENETIC DELETION OF TISSUE INHIBITOR OF METALLOPROTEINASE-1/TIMP-1 ATTENUATES INFLAMMATION AND FIBROSIS IN A DSS-INDUCED MOUSE MODEL OF COLITIS. M. De Bruyn (1), C. Breynaert (2), I. Arijs (3), J. Cremer (2), G. De Hertogh (4), F. Schuit (5), M. Ferrante (3), S. Vermeire (3), G. Opdenakker (1), G. Van Assche (3), J. Ceuppens (2). (1) KU Leuven, Leuven, Belgium, Rega Institute for Medical Research, Microbiology and Immunology ; (2) Laboratory of Clinical Immunology, KU Leuven, Leuven, Belgium, Microbiology and Immunology ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (4) KU Leuven, Leuven, Belgium, Translational Cell and Tissue Research, Imaging and Pathology ; (5) KU Leuven, Leuven, Belgium, Gene Expression Unit, Cellular and Molecular Medicine.

Introduction : Tissue remodeling and fibrosis are hallmarks of inflammatory bowel diseases (IBD). An increased level of tissue inhibitor of metalloproteinase-1 (TIMP-1) has been reported during active inflammation and in fibrotic strictures in patients with Crohn's disease (CD).
Aim : To investigate the effect of TIMP-1 deficiency on inflammation, tissue remodeling and fibrosis in an acute and chronic mouse model of inflammatory colitis.
Methods : Colitis was induced in 8-10 week old female B6.129S4-Timp1tm1Pds/J knock-out (KO) mice and C57BL/6J control mice. Acute colitis was induced by oral administration of 3% dextran sodium sulphate (DSS) for 7 days followed by 2 days of regular water. Chronic colitis was induced by 3 cycles of 1 week of exposure to 1.75–2.0% DSS followed by a recovery phase of 2 weeks. Systemic inflammation, colonic inflammation and fibrosis were assessed by macroscopic parameters, histopathology analysis and tissue collagen levels. Gelatinase levels were determined with gelatin zymography and gene expression differences were assessed with Affymetrix Mouse Gene 1.0 ST arrays (false discovery rate < 5% and > 2-fold).
Results : In comparison with control mice, administration of DSS to TIMP-1 KO mice resulted in significantly less weight loss ($p < 0.001$ [acute model] and $p = 0.006$ [chronic model]) and less systemic inflammation ($p < 0.001$ [acute model] and $p = 0.031$ [chronic model]). After chronic DSS administration, TIMP-1 KO mice had reduced colonic inflammation (macroscopic damage : $p < 0.001$, histological inflammation : $p = 0.016$) and lower tissue collagen levels compared to control mice ($p = 0.003$). ProMMP-9 levels were higher in controls with chronic colitis ($p = 0.050$), whereas proMMP-2 ($p = 0.002$) and activated MMP-2 ($p = 0.040$) levels were higher in controls with acute colitis compared to TIMP-1 KO mice. Comparison of gene expression levels after acute DSS administration showed that TIMP-1 KO mice had an upregulation of Ido1 (Fold change [FC] = 15, $p = 0.010$), Gal3st3 (FC = 8.8, $p = 0.010$), Xpnpep2 (FC = 7.5, $p = 0.002$) and downregulation of Mmp-2 (FC = 3.3, $p = 0.020$), Mmp-9 (FC = 3.1, $p = 0.030$), Cldn1 (FC = 3, $p = 0.040$) compared to control mice. After chronic DSS administration, Xpnpep2 (FC = 4.2, $p = 0.020$) was upregulated in TIMP-1 KO mice compared to control mice. Interestingly, there were no gene expression differences between TIMP-1 KO

mice receiving water versus acute DSS administration. Chronic DSS versus water administration, however, yielded 194 genes that were more than 2-fold up/downregulated in TIMP-1 KO mice. Young TIMP-1 KO mice (10-12 weeks [acute model]) versus older animals (19-21 weeks [chronic model]) showed significantly increased expression of Reg3g (FC = 16, p = 0.030), Reg3b (FC = 12.6, p = 0.040) and Ido1 (FC = 3.5, p = 0.008), whereas the expression levels of Mir200b (FC = 2.2, p = 0.009), Ctse (FC = 1.3, p = 0.030) and Wnt2b (FC = 1.1, p = 0.002) were decreased.
Conclusions : TIMP-1 deficiency leads to upregulation of anti-bacterial and innate immunity genes, resulting in an attenuated development of acute colitis. In a chronic setting of inflammation, TIMP-1 KO mice have less remodeling and fibrosis. Unraveling the role of TIMP-1 in extracellular matrix remodeling will be necessary to understand the biology of intestinal wound healing and fibrosis in IBD.

- I23 -

SAFETY AND LONG TERM OUTCOME OF PRIMARY ILEOCECAL RESECTION FOR TERMINAL ILEAL CROHN'S DISEASE : A MULTICENTER LARGE COHORT ANALYSIS. A. De Buck Van Overstraeten (1), E. Eshuis (2), S. Vermeire (3), G. Van Assche (3), M. Ferrante (3), G. D'haens (2), C. Ponsioen (2), A. Wolthuis (1), W. Bemelman (4), A. D'hoore (1). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Clinic Gasthuisberg, Department of Abdominal Surgery ; (2) Academic Medical Center, Amsterdam, The Netherlands, Department of Gastroenterology and Hepatology ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Clinic Gasthuisberg, Department of Gastroenterology ; (4) Academic Medical Center, Amsterdam, The Netherlands, Department of Surgery.

Introduction : Despite improvement of medical therapy, majority of patients will require surgical resection at some stage of their disease. In previous series surgical recurrence has been noted between 30 and 60%.
Aim : To report current safety and long-term clinical and surgical recurrence after ileocecal Crohn's disease in a large multicenter cohort and describe predictors for recurrence.
Methods : A prospective cohort analysis of all patients undergoing surgery for ileocecal Crohn's disease in two academic centers was performed. Anastomotic leakage and risk factors were assessed. Kaplan-meier estimates were used to describe long-term clinical and surgical recurrence. Risk factors for both endpoints were identified.
Results : 538 patients underwent a primary ileocecal resection between 1998 and 2013 (male : n = 215, 40% ; median age 31 years old, IQR : 24 – 42). Indication for surgery was intractable inflammation in 7% (n = 37), fibrostenotic disease in 50 % (n = 270) and penetrating disease in 43% (n = 231) of the cases. Laparoscopy was used in 383 (71%) patients, while 47 patients (12%) were converted. Median hospital stay was 7 days (IQR : 5 – 8). Overall postoperative morbidity was reported in 122 (23%) patients. 15 patients (3%) developed an anastomotic leak, despite a low ileostomy rate. Indeed, only 7% (n = 38) had an ileostomy. All but one stomas were reversed after a median time lapse of 5 months (IQR : 4 – 7). Specimen length (p = 0.002) and preoperative anti-TNF use (p = 0.0353) increased the risk of anastomotic leakage significantly. Median follow up was 6 years (IQR : 2 – 9). Clinical recurrence after 5 and 10 years were 45% and 55% respectively. Postoperative smoking (p = 0.0047) and microscopic section margin positivity (p < 0.0001) significantly influenced clinical recurrence. Surgical recurrence after 5 and 10 years were 6.5% and 19.1% respectively. Surgical recurrence was significantly influenced by smoking (p = 0.012), postoperative treatment regimen (p = 0.0008) and microscopic resection margin positivity (p = 0.0119).
Conclusions : Ileocecal resection for Crohn's disease is safe and is more effectively keeping the patient in surgical remission than previously reported. Overall surgical recurrence rate is low. The risk of surgical recurrence is not a valid argument to delay surgery in Crohn's patients.

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NOVEL SEROLOGY PANEL FOR PREDICTION OF RELAPSE AFTER INFLIXIMAB CESSATION IN PATIENTS WITH CROHN'S DISEASE ACHIEVING CLINICAL REMISSION. K. Papamichail (1), K. Claes (1), M. De Bruyn (1), S. Hauenstein (2), F. Princen (2), S. Singh (2), G. Van Assche (1), P. Rutgeerts (1), S. Vermeire (1), M. Ferrante (1). (1) KULeuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine ; (2) Prometheus Laboratories Inc., San Diego, CA, USA.

Introduction : Stopping rules for anti-tumor necrosis factor (TNF) therapy are urgently needed. The identification of predictive markers identifying patients at low or high risk for relapse after stopping is therefore warranted. There are limited data concerning the role of non-invasive, serological factors as predictors of relapse after anti-TNF cessation in patients with Crohn's disease (CD).
Aim : We investigated whether a novel serology panel for assessment of wound healing and repair can predict relapse after infliximab (IFX) cessation for clinical remission in patients with CD.

Methods : This was an observational, retrospective, single-center study. From an electronic database we identified 100 CD patients (57 luminal CD, 40 male, median age at diagnosis 25 years) who discontinued IFX for clinical remission. The majority of patients (n = 84) continued on immunomodulators. Relapse was defined as the need to re-introduce medical therapy or surgery. The serology panel included serum TNFα, amphiregulin (AREG), epiregulin (EREG), heparin-binding EGF-like growth factor (HBEGF), hepatocyte growth factor (HGF), heregulin beta EGF domain (HRGB), betacellulin (BTC), epidermal growth factor (EGF), and transforming growth factor alpha (TGFα). These markers were determined in samples taken at the time of IFX discontinuation by Prometheus Laboratories (San Diego, CA). A test was considered positive if the titers were higher than the Q3 of the samples measurements : [TNFα, (> 12 µg/ml), AREG (> 20 U/ml), EREG (> 243 U/ml), HBEGF (> 12 U/ml), HGF (> 74 U/ml), HRGB (> 33 U/ml), BTC (> 235 U/ml), EGF (> 88 U/ml), TGFα (> 7 U/ml)].
Results : During a median (IQR) follow up of 9.7 (8.0-11.5) years, 48 out of 100 patients relapsed. A receiver operating characteristic (ROC) analysis did not identify predictive cut-off values for relapse after IFX discontinuation for any of the investigated serological markers. Univariate (Log-Rank) and multiple COX regression analysis revealed borderline significance for positive AREG in predicting relapse (p = 0.066 and 0.068 respectively). However, multiple COX regression analysis for a sub-group of patients treated mainly for luminal disease, identified positive AREG as an independent factor predicting relapse after IFX cessation [n = 34, p = 0.008, HR : 8.1 (95%CI : 1.7-38.1), SN : 80%, SP : 52%, PPV : 22%, NPV : 94%].
Conclusions : Positive amphiregulin titers may be associated with relapse in patients who discontinue IFX for clinical remission. AREG is a member of the epidermal growth factor family which is highly expressed only in the active inflamed and not in the normal mucosa of CD patients (1). Our results warrant further study of the role of serum AREG in mucosal healing and repair in IBD. (1) Nishimura T, et al. Oncol Rep 2008.

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IDENTIFICATION OF 10 REGIONS ASSOCIATED WITH IBD IN A NON- CAUCASIAN MOROCCAN POPULATION. L. Amininejad (1), M. Elansary (2), I. Hama (3), I. Ratbi (4), V. Muls (5), M. Talib (6), P. Closset (7), M. Van Gossum (5), I. Errabih (8), E. Theatre (2), B. Charloteaux (2), Y. Momozawa (2), E. Quertinmont (1), V. Wambacq (1), L. Karim (2), N. Cambisano (2), N. Ahariz (2), H. Ouazzani (8), E. Louis (9), M. Abramowicz (10), J. Devière (1), A. Van Gossum (1), A. Sefiani (4), W. Coppieters (2), M. Georges (2), D. Franchimont (1). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology and Laboratory of Experimental gastroenterology ; (2) University of Liege, Liège, Belgium, Unit of Animal Genomic, Groupe Interdisciplinaire de génoprotéomique Appliquée (GIGA-R) and Faculty of veterinary medicine ; (3) Faculté de Médecine et de Pharmacie, Université de Mohammed V, Rabat, Morocco, Centre de Génomique Humaine ; (4) Faculté de Médecine et de Pharmacie, Université de Mohammed V, Rabat, Rabat, Morocco, Centre de Génomique Humaine ; (5) CHU Saint-Pierre, Brussels, Belgium, Department of Gastroenterology ; (6) CHU Brugmann, Brussels, Belgium, Department of Gastroenterology ; (7) CH Etterbeek, Brussels, Belgium, Department of Gastroenterology ; (8) Hopital Avicenne, Rabat, Morocco, Department of Medecine B ; (9) CHU de Liège, Domaine Universitaire du Sart-Tilman, Liège, Belgium, Department of Gastroenterology ; (10) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Human Genetics.

Introduction : Genome wide association studies (GWAS) identified 163 loci associated with Caucasian Inflammatory Bowel Disease (IBD) patients.
Aim : We aimed to investigate these 163 known loci and top SNPs associated with IBD in a non- Caucasian Moroccan IBD cohort
Methods : We genotyped 549 non- Caucasian Moroccan individuals with 285 IBD patients (211 Crohn's disease (CD), 63 Ulcerative colitis (UC) and 11 Indeterminate colitis (IC)) and 264 controls on custom designed Immunochips from ILLUMINA®. We considered the 163 loci and top SNPs associated with IBD in Caucasian individuals and negative controls matched for the minor allele frequencies (MAF). After quality controls, association analysis was done using PLINK and population stratification was corrected using the first five principal components as covariates. Simulation tests with random groups of SNP (outside the 163 loci and matched for MAF) and regions (outside the 163 IBD loci and matched for the number of independent tests) were used to test the significance of the results.
Results : We identified 10 regions significantly associated with IBD and UC : rs907611(Chr11 :1.62-2.12), rs7554511 (Chr1 :200.62-201.12), rs1819333 (Chr6 :167.12-167.62), rs11465804 (Chr1 :67.4-67.95), rs9264942 (Chr7 :31.02-31.52), rs4380874 (Chr6 :107.18-107.72), rs529866 (Chr16 :11.12-11.95), rs10781499 (Chr9 :138.99-139.64), rs3749171 (Chr2 :241.31-241.83) and rs10758669 (Chr9 :4.73-5.23). Key genes related to these regions are : TNNI2, LSP1, KIF21B, CCR6, R PS6KA2, RNASET2, IL23R, HLA-C, PSORS1C1, NFKBIL1, MICB, DLD, SOCS1, LITAF, RMI2, CARD9, PMPCA, SDCCAG3, INPP5E, GPR35 and JAK2. Surprisingly, none of NOD2 variants were found to be associated with IBD moroccan population. Increasing the sample size of the used cohort will definitively help to detect more IBD loci/SNPs associated with Moroccan IBD.

Conclusions : This is the first genetic study conducted in a large population of Moroccan IBD patients. Ten loci/top SNPs were significantly associated with IBD and UC. Interestingly, none of the NOD2 variants were found to be associated to CD/UC and Moroccan IBD.

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TAUROURSODEOXYCHOLIC ACID PROMOTES BACTERIAL SULFIDE PRODUCTION AND STIMULATES THE GROWTH OF DESULFOVIBRIONACEAE. L. Van Den Bossche (1), R. De Weirdt (2), R. Vilchez Vargas (2), T. Van De Wiele (2), M. De Vos (1), D. Laukens (1). (1) University of Gent, Gent, Belgium, Department of Gastroenterology ; (2) University of Gent, Gent, Belgium, Laboratory of Microbial Ecology and Technology (LabMET).

Introduction : Inflammatory bowel disease (IBD) is characterized by gut microbiome dysbiosis and bile acid dysmetabolism. Recently, we and others demonstrated that the bile acid tauroursodeoxycholic acid (TUDCA) protects against DSS-induced colitis and bile acid therapy for IBD has been proposed. Bile acids control the gut microbiota and might affect the production of intestinal microbial metabolites. This may have consequences for human health, since bacterial metabolites can influence physiological processes, such as inflammation. Short chain fatty acids (SCFAs), especially butyrate, are known suppressors of intestinal inflammation, while sulfide acts as a pro-inflammatory agent.
Aim : The main objective of this study was to investigate the potency of TUDCA to induce changes in the large intestinal bacterial composition and metabolism.
Methods : First, 48h batch incubations of a colonic microbial community with 0.1, 1, 5 and 10 mM TUDCA or glycoursodeoxycholic acid (GUDCA) were performed. The impact on microbial functioning was evaluated by measuring SCFAs, sulfide (S2-) and ammonium. In a second experiment, C57Bl6/J mice were given 500 mg/kg/d TUDCA or PBS by oral gavage. After 7 days, the fecal microbial community was analyzed using 16S rRNA Illumina sequencing.
Results : Supplementation of TUDCA to in vitro batch incubations of a colonic microbial community decreased absolute SCFA production ($p < 0.05$) and relative butyrate levels ($p < 0.01$). In addition, protein fermentation products were decreased : ammonium production dropped from 24 mM to 18 mM ($p < 0.05$) and no branched SCFAs were detected. Sulfide production dose-dependently increased, rising from 12 mg/l (0.1 mM TUDCA) to almost 100 mg/l (10 mM TUDCA) ($p < 0.01$). Supplementation of GUDCA did not induce these high levels of sulfide, reaching only 20 mg/l in the presence of 10 mM GUDCA ($p < 0.05$). Absolute SCFA and ammonium production, however, showed a comparable decrease as was seen with TUDCA. Additionally, mice were given TUDCA for 7 days and the fecal microbiota was analyzed. Although Shannon indices were similar compared to control mice, significant phylum- and family-level alterations could be observed after oral TUDCA administration. More specifically, TUDCA treatment significantly reduced Candidate division TM7, a subgroup of gram-positive bacteria that might play a role in IBD by promoting the early stages of inflammation. In addition, the abundance of sulfide-producing Desulfovibrionaceae family members was increased ($p < 0.05$).
Conclusions : Together, these data indicate that TUDCA supplementation may negatively affect gut microbial functioning in terms of human health. These data are likely specifically associated with taurine-conjugated bile acids and raise the question whether GUDCA, the glycine-coupled conjugate of ursodeoxycholic acid, would be a better candidate therapeutic for human IBD.

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POTENTIAL PROTEOMIC BIOMARKERS ASSOCIATED WITH MUCOSAL HEALING AND RELAPSE PREDICTION AFTER IFX WITHDRAWALS IN CROHN'S DISEASE. M. Meuwis (1), F. Quesada-Calvo (2), D. Baiwir (3), G. Mazzucchelli (4), N. Smarrggiaso (4), E. De Pauw (4), M. Malaise (5), G. The (6), E. Louis (2). (1) CHU de Liège, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology Department, CHU of Liège and GIGA-R ; (2) CHU de Liège, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology, CHU of Liege, GIGA-R ; (3) University of Liège, Liège, Belgium, Proteomic facility GIGA ; (4) University of Liège, Liège, Belgium, Laboratory of Mass Spectrometry, Chemistry Dep., GIGA-R CART ; (5) CHU de Liège, Liège, Belgium, Rheumatology ; (6) Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif, Paris, France, GETAID.

Introduction : In Crohn's disease (CD), there is a discrepancy between clinical activity of the disease (symptoms) and intestinal healing. However absence of tissue healing is associated with the risk of relapse and tissue damage progression. Endoscopy is costly and invasive. Hence biomarkers correlating with intestinal healing could improve disease management and potentially decrease the number of endoscopy when patients are in clinical remission.
Aim : We aimed to identify potential biomarkers associated to CD mucosal healing and relapse after IFX withdrawal by a shotgun label-free proteomic study.

Methods : We used the STORI(1) clinical trial cohort (n = 103) Serum samples of patients in clinical remission (at baseline) were pooled according to the degree of intestinal healing seen at endoscopy or according to relapse occurrence during the 28 months follow-up. We performed depletion of the 20 most abundant plasma proteins on each serum pool and ran a proteomic label-free differential analysis using 2D-nanoUPLC-MSE HDMS Synapt G2 for data acquisition. We performed different statistical analysis. Moreover, a Gene Ontology annotation was also performed for the potential biomarkers highlighted.
Results : We identified 430 different proteins including 188 common to all samples. Among these, 40 were found with a significant differential abundance in the groups compared. We selected some among the most significant ones (ratio > 1.3) or being by nature consistent with the context of this study (sample origin and clinical question addressed). For example, the C-reactive protein (CRP) was found with a significant Ratio of 2 between Relapsers and Non Relapsers. The other potential biomarkers associated to mucosal healing or to prediction of relapse, were selected for further validation by Western Blot analysis, routine laboratory tests and also by a Mass Spectrometry based technology : multiplexed Selected Reaction Monitoring (SRM). This technique will enable quantitative analysis of these candidates in each individual patient as well as WB tests.
Conclusions : This research strategy and the validation results on potential biomarkers associated to mucosal healing or relapse after treatment cessation in this cohort of CD patients, as well as tests done on other CD patients, might provide new opportunities for patient follow-up test developments. The next step is to perform SRM validation on the STORI cohort and design signatures using these potential biomarkers SRM data for prognosis power evaluation. (1) Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 2012 ;142 :63-70.

- I28 -

FAECAL WATER SAMPLES FROM ULCERATIVE COLITIS PATIENTS HAVE INCREASED CYTOTOXIC POTENTIAL. L. Boesmans, K. Windey, L. Deroover, G. Vandermeulen, V. De Preter, K. Verbeke. KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders. (TARGID)

Introduction : Ulcerative colitis (UC) is an inflammatory bowel disease characterised by chronic inflammation of the colonic epithelium. Furthermore, UC patients have an increased risk to develop colorectal cancer (CRC). The microbiota is implicated in the initiation and the propagation of the disease. Through bacterial fermentation of carbohydrates and proteins a plethora of luminal compounds are produced in the colon, which might interact with the host's physiology.
Aim : The cytotoxic potential of faecal samples from UC patients and healthy controls was determined as a marker of gut health and future CRC risk. Furthermore, bacterial metabolites associated with faecal water cytotoxicity were identified.
Methods : Faecal samples were collected from healthy controls (HC ; n = 52, 19M/33F, age : 38 ± 16 y), UC patients with active disease (UC-A ; n = 58, 35M/23F, age : 46 ± 16 y) and UC patients in remission (UC-R ; n = 59, 34M/25F, age : 47 ± 16 y). Active disease was defined as a partial Mayo score > = 3. Faecal water (FW) was derived from these samples by ultracentrifugation. FW cytotoxicity was determined on HT-29 cells using the WST-1 colorimetric cell viability assay. Results were expressed as the FW dilution at which 50% of the cells died (IC50). Profiles of colonic fermentation metabolites were determined in the FW samples using GC-MS. Partial least squares analysis was applied to cluster samples with similar metabolite profiles and identify discriminating metabolites. Data are presented as median (IQR) and were compared by Kruskal-Wallis (KW) and Mann-Whitney-U (MW) tests.
Results : FW from UC patients (IC50 22,6 (12,9-34,5)) was significantly more cytotoxic than FW from HC (IC50 19,1 (11,9-22,5)) (MW p = 0,02). When comparing the 3 groups separately (KW p = 0,02), a significant difference was found between HC and UC-R (22,9 (15,0-33,2)) (MW p = 0,01). Samples with higher cytotoxicity (IC50 > 25) were associated with some aldehydes, furans and protein fermentation metabolites like branched-chain fatty acids and sulphides. In addition, higher cytotoxicity was associated with lower levels of medium and short chain fatty acids (SCFA). SCFA, comprising acetate, propionate and butyrate, are generally recognised to be beneficial for the host and mainly originate from carbohydrate fermentation. Indeed, SCFA levels were lower in UC patients versus HC (MW p < 0,01 for all).
Conclusions : FW samples from UC and particularly UC-R patients are more cytotoxic than HC samples. This could contribute to the higher CRC risk for UC patients. Moreover, higher cytotoxicity could lead to barrier disruption and to the induction and/or continuation of inflammation. Decreasing the levels of protein fermentation metabolites and increasing SCFA concentrations, for example by the use of prebiotics or dietary adjustments, could positively affect the colonic health in UC.

- I29 -

INTERFERENCE OF COLONIC BACTERIAL METABOLITES WITH THE BUTYRATE METABOLISM IN ULCERATIVE COLITIS. L. Deroover, L. Boesmans, G. Vandermeulen, K. Windey, E. Boets, V. De Preter, K. Verbeke. KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) and Leuven Food Science and Nutrition Research Centre (LFoRCe).

Introduction : Butyrate, a metabolite of colonic bacterial fermentation, is the major energy source for the colonic mucosa. Studies reported a decreased butyrate uptake and oxidation in patients with ulcerative colitis (UC). UC is featured by an altered composition and activity of the intestinal microbiota.
Aim : We evaluated the hypothesis that colonic bacterial metabolites decrease butyrate oxidation and expression of the genes involved in butyrate uptake (MCT1) and oxidation (ACSM3, ACADS, ECH1S, HSD17B10, ACAT2) in UC patients.
Methods : Faecal samples were collected from healthy controls (HC ; n = 49), patients with active UC (UC-A ; n = 49) and patients in remission (UC-R ; n = 54). Faecal water (FW) was derived from the samples by centrifugation. Human colonic adenocarcinoma (HT-29) cells were incubated with FW for 24h after which the butyrate oxidation rate was measured using 14C-labelled butyrate and expressed as % of oxidation rate in untreated cells. The relative expression of the genes involved in butyrate uptake and oxidation was determined by qRT-PCR. Profiles of volatile organic compounds (VOCs) were determined in FW samples using GC-MS. The metabolites present in 80% of the samples were correlated with the butyrate oxidation rate and gene expression levels.
Results : Incubation with FW from HC, UC-A or UC-R did not significantly influence the butyrate oxidation in HT-29 cells (HC : 112 ± 6% ; UC-A : 124 ± 8% ; UC-R : 110 ± 7% ; Kruskal-Wallis $p = 0,33$). The gene expression of ACSM3, encoding the first enzyme of the butyrate oxidation, was significantly lower after incubation with FW from UC-A and UC-R than from HC ($p < 0,001$ for both) whereas the expression of ACAT2, encoding the last enzyme, was significantly higher with FW from UC-A and UC-R ($p < 0,001$ for both). When combining the 3 groups, the gene expression of MCT1 was positively correlated with the expression of each oxidation enzyme (all $p < 0,01$) except for ACAT2 and the gene expression of each enzyme was positively correlated with the expression of the subsequent gene in the oxidation pathway (all $p < 0,005$). A total of 237 VOCs were identified in the FW samples with 40 VOCs present in 80% of the samples. The butyrate oxidation rate was negatively correlated with levels of 2 furan derivatives (Spearman ; furan : $r = -0,259$, $p = 0,052$; 2,5-dimethyl-furan : $r = -0,268$, $p = 0,035$). The concentrations of 11 VOCs, including butyrate were positively correlated with the expression of ACSM3 (for butyrate : $r = 0,469$, $p < 0,001$). The expression of ACAT2 correlated negatively with 6 VOCs, including butyrate (for butyrate $r = -0,621$, $p < 0,001$) and positively with 2 furans and 2 sulphides.
Conclusions : Colonic bacterial metabolites are not responsible for a decreased butyrate metabolism as observed in UC. However, gene expression of the butyrate oxidation pathway is, at least partially, regulated by substrate concentration.

- I30 -

HUMAN-LEUKOCYTE ANTIGEN TYPE IS ASSOCIATED WITH DURATION ON INFLIXIMAB THERAPY IN PATIENTS WITH ANTIBODIES TO INFLIXIMAB. T. Billiet (1), T. Van Stappen (2), N. Vande Casteele (2), I. Cleynen (1), V. Ballet (3), K. Claes (1), F. Princen (4), S. Singh (4), A. Gils (2), M. Ferrante (3), G. Van Assche (3), S. Vermeire (3). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Laboratory for Therapeutic and Diagnostic Antibodies ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology ; (4) Prometheus Laboratories Inc., San Diego, USA, Department of Research and Development.

Introduction : The contribution of antibodies to infliximab (ATI) to loss of response (LOR) in patients with IBD is well established. It was also shown that ATI may be transient and that infliximab (IFX) discontinuation is not always necessary in this occasion. The variables that influence discontinuation of IFX in patients who have developed ATI are unknown. The HLA system, responsible for processing antigens, might play an important role.
Aim : We hypothesized that HLA class II alleles influence the duration on IFX therapy in patients who develop ATI.
Methods : In this retrospective single-center study, we identified 74 IBD (42 CD, 32 UC) patients who developed ATI during maintenance IFX. Of these, 61 (82%) discontinued IFX therapy because of LOR or side effects and 13 (18%) were still receiving IFX at the end of follow-up. All patients were anti-TNF naïve before start of IFX. A total of 1889 serial serum samples were measured for ATI with an improved bridging ELISA using monoclonal antibody MA-IFX10F9 as calibrator. For each patient, the highest ATI concentration measured, was used to create ATI quartiles. HLA-DRB1 was genotyped with sequence specific primers (Prometheus Laboratories Inc.). Patient and therapy variables (e.g. presence of rescue IFX dose optimization, immunomodulator rescue), ATI quartiles and DRB1 alleles were included as possible confounders influencing total time on IFX using Cox proportional hazard regression.

Results : The median time on IFX was 100 weeks (IQR 52 - 217) and did not differ significantly depending on ATI quartile (P = 0.19, Kruskal-Wallis test). However, patients from quartile 4 showed a significant shorter time on IFX (median 72 weeks) compared to the other quartiles combined (median 111 weeks, P = 0.049). We observed clear differences in time on IFX depending on the DRB1 allele with medians ranging from 43 weeks for DRB1*13 to 169 weeks for DRB1*15 (P = 0.019, Log-rank test). Cox proportional hazard regression identified albumin at start of IFX, ATI in quartile 4, presence of DRB1*11 and presence of DRB1*15 as independent predictors (P < 0.05) of total time on IFX with hazard ratios (95% CI) of 0.34 (0.19-0.59), 3.3 (1.6-6.9), 0.45 (0.23-0.9) and 0.35 (0.16-0.77) respectively.
Conclusions : In IBD patients who develop ATI, besides the magnitude of the titer, a higher concentration of albumin at start of IFX and the HLA-DRB1 genotype prolong the time patients will remain on IFX. The concomitant use of immunomodulators or rescue IFX dose optimization did not affect time on IFX in this study. These results clearly warrant further investigation in prospectively designed studies.

- I31 -

THE CONTRIBUTION OF CLINICAL FACTORS, SEROLOGY AND GENETICS IN DIFFERENTIATING INFLAMMATORY BOWEL DISEASE TYPE UNCLASSIFIED. T. Billiet (1), I. Cleynen (1), V. Ballet (2), K. Claes (1), F. Princen (3), S. Singh (3), M. Ferrante (2), G. Van Assche (2), S. Vermeire (2). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology ; (3) Prometheus Laboratories Inc., San Diego, USA, Department of Research and Development.

Introduction : A definitive diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) in patients who initially present with inflammatory bowel disease type unclassified (IBDU) remains challenging. Usually, a combination of clinical (presence of rectal sparing without local therapy ; ileal disease/backwash ileitis ; perianal abscess ; segmental colitis ; stenotic disease), histopathological and sometimes serological markers is used in clinic.
Aim : We investigated if the combination of clinical factors, pathology, serology and genetics would improve differential diagnosis in these patients.
Methods : In this retrospective single-center study, we identified 60 patients diagnosed with IBDU. On the basis of histopathology, 21 of these were later reclassified as CD, 22 as UC and 17 remained IBDU at the end of follow-up (with a median follow-up time of 12.6 years). For each patient, a clinical score ranging from 0-5 (sum of the clinical factors mentioned above) was calculated and serum samples were analyzed for pANCA status and several antimicrobial antibodies (ASCA IgA, ASCA IgG, CBir1, OmpC, Fla2 and FlaX (Prometheus Laboratories Inc.)). The concentrations of the different antimicrobial antibodies were divided into quartiles, and quartile sum scores (QSS) were calculated for each patient. We also genotyped patients for the 163 IBD loci through immunochip and calculated a genetic risk score (GRS) for specific CD vs UC loci (higher values more indicative for CD and lower for UC). All markers were compared between the different groups.
Results : The median time (IQR) to definitive diagnosis was longer in the CD patients (9.6 (4.9-12.9) years) than in the UC patients (2.1 (0.8-8.8) years, P = 0.003). Both the clinical score and QSS could clearly distinguish the CD group from the UC and IBDU group (P = 0.03 and P = 0.04, Kruskall-Wallis test), but not the UC from the IBDU group. The GRS and pANCA status did not differ between groups (P > 0.45). Logistic regression identified the clinical score and QSS to be independent predictors for diagnosing CD (P < 0.01) with OR (95% CI) of 2.7 (1.3-5.7) and 1.3 (1.1-1.5) respectively. The accuracy of this prediction increased (AUC of 0.7 to 0.78 in ROC) when both were combined. A similar approach for the UC patients could only identify the clinical score as a predictor (P = 0.01) with an OR of 0.4 (0.2-0.8).
Conclusions : In patients with IBD-unclassified, a combination of clinical factors and antimicrobial antibodies is superior for determining evolution to CD. The current validated genetic risk panel of 163 IBD susceptibility loci does not have an added value in making this distinction. This might be due to the fact that there is a significant overlap between CD and UC-risk alleles and the fact that only very few genes are specific for CD or UC.

- I32 -

A MATRIX-BASED PREDICTION MODEL FOR PRIMARY RESPONSE TO INFLIXIMAB IN CROHN'S DISEASE PATIENTS. T. Billiet (1), M. De Bruyn (1), V. Ballet (2), K. Claes (1), F. Princen (3), S. Singh (3), M. Ferrante (2), G. Van Assche (2), I. Cleynen (1), S. Vermeire (1). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Gastroenterology ; (3) Prometheus Laboratories Inc., San Diego, USA, Department of Research and Development.

Introduction : Primary non-response (PNR) to infliximab (IFX) in IBD still holds a challenge for clinicians. Furthermore, with the advent of anti-integrin molecules, selecting the right therapeutic class for a given patient would be welcomed. Current clinical and serological predictors are insufficiently identifying patients at risk for PNR and are therefore not used in clinical practice. Identification of individual genetic markers associated with primary response has been disappointing.
Aim : We designed a matrix-based prediction model, which may avoid exposure in patients unlikely to benefit from IFX. We furthermore investigated if a combination of genetic markers, rather than individual, might have an added value in this prediction model.
Methods : In this retrospective single-center study, we used 201 anti-TNF naïve Crohn's disease patients started on infliximab (IFX) induction 0-2-6. Clinical and biological markers were collected prior to IFX. Baseline serum TNF load and the IBD serology 7 panel (Prometheus Laboratories Inc.) were also available. PNR was defined as complete absence of clinical improvement at w14 (physician global assessment). We also genotyped patients for the 163 IBD loci through immunochip and calculated a total genetic risk score (GRS) for IBD for each patient. Final predictors were selected through multiple regression based on the Akaike information criterion (AIC). These were then categorized according to a clinically relevant threshold. Predicted probabilities were calculated and were organized into a color coded matrix.
Results : The incidence of PNR was 8% (16/201). In univariate analysis, older age at first IFX and prior surgery were significantly associated with PNR ($P < 0.05$). The GRS did not differ between groups ($P = 0.44$). Multiple logistic regression withheld age at first IFX, BMI and prior surgery as independent significant final predictors with OR (95% CI) for PNR of 1.05 (1.01-1.09), 0.87 (0.74-0.99) and 4.4 (1.3-20.4) respectively. The accuracy of this prediction model decreased (AUC of 0.80 to 0.78 in ROC) when the GRS was added. BMI was categorized into < 18.5 (12% of patients), 18.5-24.9 (57%) and ≥25 (31%) and age at first IFX into ≤ 25 years (27%), 26-40 years (38%), 41-64 years (30%) and ≥ 65 years (5%). The matrix model showed a good spread of predicted response rates (99% -47%) for the different categories.
Conclusions : This matrix-based prediction tool, based on readily available clinical markers (age, BMI and prior surgery) can aid physicians in optimizing therapeutic decisions. A younger age and higher BMI have already been associated with primary response to IFX and the latter is attributed to the weight based dosing of IFX. Prior surgery has also been associated with PNR and might reflect more refractory disease. The combination of the 163 IBD risk loci has no added value over these clinical factors. Loci not involved in disease susceptibility may play a more important role. The next step is to validate this matrix and to construct a similar tool for secondary loss of response.

Invited Lecture
- I33 -

ROLE OF ADIPOSE TISSUE IN IBD**.** Fernando Magro, Porto, Portugal.

Invited Lecture
- I34 -

ROLE OF THE ENTERIC NERVOUS SYSTEM IN IBD. Karel Geboes, UZ Leuven, KU Leuven, Leuven, Belgium. Pathology Department.

The enteric nervous system (ENS) is composed of an extrinsic sympathetic and parasympathetic system including efferents and visceral afferents and an intrinsic system includng ganglionated networks (the myenteric plexus (MP) and the submucosal plexus (SMP) – Meissner and Henle) and non ganglionated networks The MP, the outer of the two major plexuses, is the network of neurons situated between the muscle layers of the GI tract, and is primarily involved in the initiation and control of smooth muscle motor patterns such as peristalsis. The SMP coordinates reflexes such as secretion and absorption, as well as motor control of smooth muscle. In additon it may influence secretion of mucins and cytokines. Cellular components of the ENS are neurons, enteroglial cells and interstitial cells of Cajal. Glial cells are involved in regulation of blood flow, intestinal barrier function and inflammatory events. Structural changes of the ENS, characterized by increased prominence of nerve fibers and ganglia, not discernible in the early phase, but detectable in the intermediate and chronic phase were already described in Crohn's disease as early as in 1932. They are observed in 53 to 90% of surgical specimens with good reproducibility and allow a distinction between CD and ulcerative colitis. Electron microscopy confirms the presence of axonal damage. The lesions are associated with inflammation and show apoptosis of neurons and enteroglial cells. Furthermore, changes in numbers of interstitial cells of Cajal have been noted. These structural changes are associated with neurochemical changes (VIP, substance P, somatostatin, amines, nitric oxide) observed with immunohistochemistry and tissue level determination and the expression of inflammatory markers. In addition in situ hybridization and laser capture micro-dissection with the search for 16S rDNA demonstrated the presence of microbial material (Coxsackie B virus (CBV) and Echovirus, and legionellaceae) at the level of the MP. Lesions of the ENS were also described in animal models of colitis.

Invited Lecture
- I35 -

ROLE OF BLOOD AND LYMPHATIC VESSELS IN IBD**.** Silvio Danese, Milano, Italy.

Invited Lecture
- I36 -

DE-ESCALATION OF IBD THERAPY. David Laharie, Bordeaux, France.

Invited Lecture
- I37 -

BIOSIMILARS IN IBD THERAPY. Silvio Danese, Milano, Italy.

Invited Lecture
- I38 -

MEDICAL MANAGEMENT OF IBD ; AT WHAT COST ? Lieven Annemans, UGent, Gent, Belgium.

RESEARCH GROUP OF CLINICAL NUTRITION AND METABOLISM (SBNC)
BeSPGHAN

- N01 -

COLON TRANSIT TIME AND ANORECTAL MANOMETRY AS A PREDICTOR FOR SPONTANEOUS FAECAL CONTINENCE IN SPINA BIFIDA PATIENTS : PROSPECTIVE STUDY IN 3 TO 6 YEAR OLD. S. Vande Velde (1), A. Notebaert (2), R. De Bruyne (1), M. Van Winckel (1), S. Van Biervliet (1). (1)UZ Gent, Gent, Belgium, Department of Paediatric Gastroenterology ; (2) UZ Gent, Gent, Belgium, Department of Paediatrics.

Introduction : A cross-sectional study (1) has shown that a normal colon transit time (CTT) associated with normal anal resting pressure in spina bifida (SB) patients is related to achieving spontaneous faecal continence.
Aim : The aim of the study was to prospectively evaluate CTT and anal resting pressure in 3 to 6 year old SB children as predictor of spontaneous faecal continence.
Methods : The study is performed at the SB Reference Center of the Gent university hospital. All SB patients between 3 to 6 years old are asked to participate before incontinence treatment is started. Data from the medical file and prospective questionnaires regarding constipation is collected. The SB patients are constipated if ≥2 of the Rome III criteria for paediatric functional constipation are fulfilled. The SB patients are incontinent if involuntary faecal loss is > once a month in children > 4 years old. The control group for CTT are 16 healthy age-matched children, not suffering from constipation or incontinence according to the Rome III criteria. The control group for anorectal manometry (ARM) is based on the results by Kumar et al (2). Total and segmental CTT is measured using the 6-day method. ARM is performed in non-sedated children with a water-perfused latex-free catheter. Non parametric tests are used and multivariate analysis is performed. Ethical approval (EC UZG 2010/348) is obtained.
Results : Seventeen out of 21 eligible patients consented to perform CTT, of which 12 also performed the ARM. The Rome III criteria confirm constipation despite treatment in 5/13 SB children (4 are not included because of age < 4 years). Three patients are spontaneously continent, 6 are pseudo-continent and 4 are not considered because of young age (< 4 years old), overall 69% (9/13) is (pseudo)continent. According to a former study (1), this prospective study can confirm that SB patients have a significant (P = 0.004) longer total CTT compared to controls (median CTT 67.2h vs. 33.6h). Constipated SB patients have a significantly longer total CTT than non-constipated patients (P = 0.006) (median CTT 98.4h vs. 34.8h). Spontaneously continent patients have a normal CTT (median 31.2h) and a normal resting pressure (median 46.5 mm Hg), minimum rectal sensitivity is at a median of 15 ml. There is a significant difference of CTT in continence status (P = 0.028), with not spontaneously continent patients having an elongated CTT. For normal rectal pressure no significant difference is found (P = 0.14), but there is only one not spontaneously continent SB child with a normal resting pressure and this child has an abnormal CTT.
Conclusions : In a former study a flowchart is suggested in trying to predict spontaneous continence in SB children. This prospective study confirms this flowchart. A normal anal sphincter resting pressure is a prerequisite but not a guarantee for achieving spontaneous faecal continence. Combined with a normal CTT it predicts spontaneous faecal continence.

- N02 -

UTILIZATION OF COLONIC DERIVED PROPIONATE IN GLUCONEOGENESIS : AN IN VIVO STABLE ISOTOPE STUDY IN HUMANS. E. Boets (1), L. Deroover (1), A. Luypaerts (1), S. Gomand (2), G. Van Den Mooter (3), J. Delcour (2), K. Verbeke (1). (1) KU Leuven, Leuven, Belgium, Translational Research Center for Gastrointestinal Disorders (TARGID) and Leuven Food Science and Nutrition Research Centre (LFoRCe) ; (2) KU Leuven, Leuven, Belgium, Laboratory of Food Chemistry and Biochemistry and Leuven Food Science and Nutrition Research Centre (LFoRCe) ; (3) KU Leuven, Leuven, Belgium, Laboratory of Pharmacotechnology and Biopharmacy

Introduction : Propionate, produced in the colon during bacterial fermentation of undigested carbohydrate, is suggested to have health benefits that extend beyond the gut. Unlike acetate and butyrate, propionate can serve as a precursor for gluconeogenesis. Recent evidence suggests that gluconeogenesis not only occurs in the liver but also in the intestines and that this pathway contributes to the regulation of energy homeostasis. In humans, it is not known to what extent propionate is incorporated in glucose.
Aim : We quantified the extent by which colonic-derived propionate is used as a substrate for gluconeogenesis in vivo in healthy humans using a stable isotope technique.
Methods : Eight healthy subjects (5F/3M ; 27 ± 7y) received 13C-labelled propionate (340mg) formulated in a pH-dependent colon delivery capsule (CDC) which releases its content in the proximal colon. Together with this CDC the subjects consumed a standard breakfast labelled with inulin-14C-carboxylic acid as a marker of orocecal transit time. Upon arrival in the colon, inulin-14C-carboxylic acid and 13C-SCFA are metabolized to 14CO2 and 13CO2, respectively, which are exhaled in breath. Breath samples were collected during the day for analysis of 13CO2 and 14CO2. Blood samples were collected at regular time points for 12 h. 13C-glucose enrichment and total glucose concentrations in

plasma were measured using gas chromatography combustion isotope ratio mass spectrometry and allowed to calculate the plasma concentration of 13C-glucose over time as well as the total recovery in plasma (the area under the curve (AUC) of the concentration-time curve). Using the AUC and the glucose clearance the fraction of administered 13C-propionate incorporated in glucose was calculated. Results are expressed as medians and interquartile ranges.
Results : The rise of 13CO2 in breath upon opening of the CDC coincided with an increase in 14CO2, indicating that the CDC released its content in the colon. Up to 45.5 [33.8-53.0] % of the 13C label of propionate was recovered in breath as 13CO2 and reflects the fraction of propionate that is oxidized either in the colonocytes or in the liver. The total recovery (AUC) of 13C-glucose in plasma 12 h after consumption of the 13C-propionate CDC amounted to 20.9 [8.7-41.1] μmol.h/l. The fraction of the colonic administered 13C-propionate recovered in glucose was calculated to be 6.3 [1.9-11.4] %.
Conclusions : Compared to values reported in literature for other mammals (cows : 60%, sheep : 37% and mice : 60%), the extent of incorporation of colonic-derived propionate in glucose is more limited. More detailed knowledge on the nutrikinetics of propionate in humans will enhance the understanding of its physiological effects. Further research is required to determine to what extent gluconeogenesis from propionate occurs in the intestine or in the liver.

- N03 -

SEQUENTIAL VERSUS 10-DAY TRIPLE THERAPY TARGETED TO ANTIMICROBIAL SUSCEPTIBILITY FOR HELICOBACTER PYLORI ERADICATION IN CHILDREN. K. Kotilea (1), J. Mekhael (1), A. Salame (1), N. Genis (1), Y. Miendje-Deyi (2), S. Cadranel (1), P. Bontems (1). (1) Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Brussels, Belgium, Department of Paediatric Gastroenterology ; (2) CHU Brugmann, Brussels, Belgium, Department of Microbiology.

Introduction : The sequential regimen appeared to be more effective than a 7-day triple therapy in the eradication of Helicobacter pylori in children, but not better than the 10 or 14 days triple therapies, as it was shown in a recent meta-analysis. The bias in this review were the small number of children given the 10-day triple therapy and the absence of interpretation of factors known to increase the risk of failure such as antimicrobial resistance and adherence to therapy.
Aim : To compare, in naïve infected children, the eradication rates with a sequential regimen and a 10-day tailored triple therapy, as well as factors that may affect the treatment outcome.
Methods : A prospective randomized controlled trial was conducted between November 2010 and December 2013 in a tertiary hospital in Brussels, Belgium, included children aged 2 to 17 years with a positive Helicobacter pylori culture. Children infected with a strain susceptible to clarithromycin and to metronidazole were randomly assigned to receive either a sequential regimen or a 10-day triple therapy. Children infected with a strain resistant to clarithromycin or metronidazole received a 10-day triple regimen tailored to the antimicrobial susceptibility. The eradication rate was assessed by a negative 13C- Urea breath test performed at least 8 weeks after the end of the treatment.
Results : One hundred seventy-seven children (85 girls/92 boys, median age 9.7 years) were enrolled in the study. One hundred forty-seven were infected with mutisensitive, 11 with clarithromycin resistant and 19 with metronidazole resistant strains. The eradication rate was significantly higher in the sequential regimen arm compared to the triple therapy arm in the Intention-To-Treat (60/73, 82.2% - 70/104, 67.3% - OR 2.24, p = 0.037) and in the Full-Analysis-Set analysis (60/68, 88.2% - 70/93, 75.2% - OR 2.46, p = 0.044) but not significantly higher in the Per-Protocol analysis (55/59, 93.2% - 60/80, 85% - OR 2.43, ns). In a multivariate analysis, a higher eradication rate was observed with the sequential regimen (OR 3.73, p = 0.036) and in children that adhere more strictly to the treatment (compliance > = 90% vs < 90% OR 23.6, p < 0.001).
Conclusions : The sequential therapy, when administered to naïve children infected with multisensitive strains is more effective than the 10-day tailored triple therapy and should be proposed as first-line treatment. When infected with a strain resistant to at least one antimicrobial agent, a tailored triple therapy can be proposed but the eradication rate remains below the target of 85% in per-protocol analysis (the same was observed for the sequential regimen in a previous study performed in the same center).

- N04 -

FIBROSIS AND INFLAMMATION HISTOLOGY SCORES PREDICT DISEASE REMISSION IN PAEDIATRIC AUTOIMMUNE HEPATITIS UNDER IMMUNOSUPPRESSIVE THERAPY. G. Jannone (1), X. Stephenne (1), C. Sempoux (2), D. Castanares (3), F. Smets (1), I. Scheers (1), E. Sokal (1). (1) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Department of Paediatric Hepatogastroenterology ; (2) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Department of Paediatric Hepatogastroenterology ; (3) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Department of Paediatric Hepatogastroenterology.

Introduction : Autoimmune hepatitis (AIH) is a chronic inflammatory liver disorder, leading to progressive fibrosis and cirrhosis. The influence of standard immunosuppressive treatment on this evolution has not been precisely defined in children yet.
Aim : To investigate the fibrosis evolution and indicators of disease remission in paediatric AIH under immunosuppressive treatment.
Methods : Retrospective analysis of a cohort of 40 children (24 females, median age 10.5 years, range 9m-15y) with established AIH (9 type I, 7 type II, 2 seronegatives, 4 coombs+, 18 overlap) and immunosuppressive therapy (median follow-up 4 years, range 0-19y). Biopsy histology scores (ISHAK and LUDWIG) were compared at baseline (n = 38) and follow-up (n = 19) (median 4 years, range 3m-16y). Remission was defined as normalisation of AST, ALT and gammaglobulin levels, and absence of clinical symptoms. Long term prognostic indicators for remission and fibrosis progression were analysed by logistic regression, including baseline and follow-up demographic, clinical, biochemical, immune, histological and treatment parameters. The subgroup of overlap syndrome was also analysed separately for fibrosis progression.
Results : In the entire series, fibrosis score decreased from 3.2 ± 1.6 to 2.2 ± 1.9 ($p = 0.03$) and inflammation decreased from 3.1 ± 1 to 2.4 ± 1.1 ($p = 0.02$). Logistic regression showed that inflammation evolution was predictive of fibrosis progression (OR16.2 ; $p = 0.03$). Disease remission was predicted by (1) fibrosis score at diagnosis (OR1.9 ; $p = 0.03$), (2) fibrosis score at follow-up biopsy (OR2.6 ; $p = 0.03$), and (3) inflammation score at follow-up biopsy (OR3.8 ; $p = 0.04$). The best predictive factor for disease remission was the follow-up fibrosis score (ROC 85% ; $p < 0.05$). When overlap syndrome group was analysed separately, the fibrosis score remained unchanged over time (3.71 ± 1.25 to 3.57 ± 2.23 ; $p = 0.99$), while the improvement was confirmed in the other categories (3.25 ± 1.22 to 1.42 ± 1.08 ; $p = 0.001$).
Conclusions : Under immunosuppressive treatment both fibrosis and inflammation scores decreased significantly. Improvement of inflammation significantly predicted fibrosis regression. Pre-treatment and follow-up fibrosis scores as well as follow-up inflammation score were predictive factors for the long term disease remission. The subcategory of overlap syndrome had no favourable progression of fibrosis. We conclude that fibrosis regresses under treatment in paediatric AIH except for overlap syndrome, and that the fibrosis and inflammation scores at follow-up biopsy are predictive of long term outcome.

- N05 -

FECAL MICROBIOTA TRANSPLANTATION FOR RECURRENT CLOSTRIDIUM DIFFICILE INFECTION IN A CHILD VIA A PERCUTANEOUS GASTROJEJUNOSTOMY. X. Stephenne (1), D. Van Der Linden (2), I. Scheers (1), D. Hermans (2), F. Smets (1), E. Sokal (1). (1) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Department of Paediatric Gastroenterology, (2) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Department of Paediatrics.

Introduction : Clostridium difficile infection is a common cause of infectious healthcare –associated diarrhea. Fecal microbiota transplantation has recently shown to be safe and effective treatment for recurrent or refractory Clostridium difficile infection in adults.
Aim : We report the case of a 6-years old patient with chromosome 18q21.3 deletion. The patient has dysmorphia, cleft palate, Pierre Robin syndrome, and is followed in our hospital for mulitdiscipinary follow-up, feeding problems but also recurrent diarrhea related to Clostridium difficile infection. Clostridium difficile-associated diarrhea was refractory to metronidazole treatment, and the patient required long term vancomycin treatment due symptoms recurrence and detection of Clostridium difficile toxin in the stools at each vancomycin interruption. A gastrojejunostomy was endoscopically inserted in 2012 for enteral feeding. Familial donor fecal microbiota transplantation was proposed with the aim to cure Clostridium difficile infection.
Methods : The fecal microbiota transplantation has been approved by the local ethical committee. Both parents signed an informed consent. The blood of the parental donor was screened for HIV, HTLV-1-2, Hepatitis A-B-C, cytomegalovirus, Ebstein-Barr virus, Strongyloides stercoralis, Treponema pallidum, and Entamoeba histolytica. Donor feces were screened for parasites (including Blastocystis hominis and Dientamoeba fragilis), Clostridium difficile and enteropathogenic bacteria. Feces were collected by the donor on the day of infusion and immediately transported to the hospital. Feces were diluted, in a laminar flow hood, with 250 ml of sterile infusion water. This solution was centrifugated at 1200 rpm for 5 minutes, and the supernatant strained and poured in a sterile bottle. The solution was infused through the gastrojejunal tube within 20 minutes under general anaesthesia.
Results : The procedure was well tolerated without infusion related side-effects. At the 6-months follow-up, no recurrence of Clostridium difficile-associated diarrhea and infection occurred.
Conclusions : Fecal microbiota transplantation is a feasible and effective procedure in children under strict quality control. Randomized controlled clinical studies have to confirm the advantage of this technique.

- N06 -

EVOLUTION OF HELICOBACTER PYLORI ASSOCIATED GASTRO-DUODENAL ULCERS OR EROSIONS IN CHILDREN OVER THE LAST 23 YEARS : DECLINE OR STEADY STATE ? M. Burgard (1), K. Kotilea (1), J. Mekhael (1), Y. Miendje-Deyi (2), C. De Prez (3), J. Vanderpas (4), S. Cadranel (1), P. Bontems (1). (1) Huderf, Brussels, Belgium, Paediatric Gastroenterology ; (2) CHU Brugmann, Brussels, Belgium, Department of Microbiology ; (3) CHU Brugmann, Brussels, Belgium, Pathology ; (4) Scientific Institute of Public Health, Brussels, Belgium, Statistic Department.

Introduction : Recent data suggest that, in children, the proportion of gastro-duodenal ulcers/erosions associated with Helicobacter pylori infection is currently lower than expected.
Aim : In this study, we trace this proportion over two decades.
Methods : Retrospective review of the reports of all upper GI endoscopies with biopsies for culture over the last 23 years. Helicobacter pylori status was evaluated using a combination of several invasive methods and its rate compared in different time periods between children with lesions and controls.
Results : A total of 7849 endoscopies were performed in 5983 children (2874F/3109M, median age 7.6 y, range 0.1-17.9 y). At their first endoscopy 12.2% of the children presented gastric and/or duodenal ulcers or erosions (35.4% of them infected by Helicobacter pylori) while no such lesions were identified in 87.8% (controls, 21.3% being infected). The exposure factors associated with such lesions were older age ($p < 0.001$), male gender (p 0.002) and Helicobacter pylori infection ($p < 0.0001$). Gastric ulcers were not significantly associated with Helicobacter pylori (23% infected) while only 55% of duodenal ulcers are associated with an infection, 33% of gastric erosions and 48% of duodenal erosions. The proportion of gastro-duodenal lesions associated with Helicobacter pylori remained stable over time. Children with Helicobacter pylori infection and ulcers were older than those with Helicobacter pylori without ulcers ($p < 0.001$).
Conclusions : Our study confirms that, in our paediatric population, the proportion of ulcers without Helicobacter pylori infection is higher than previously suggested and that this prevalence has not changed over the two last decades.

- N07 -

DEVELOPMENT AND VALIDATION OF A SPINA BIFIDA SPECIFIC PAEDIATRIC QUALITY OF LIFE QUESTIONNAIRE : THE SPINA BIFIDA PAEDIATRIC QUESTIONNAIRE, SBPQ. S. Vande Velde (1), J. Laridaen (2), E. Van Hoecke (2), R. De Bruyne (1), S. Van Biervliet(1), M. Van Winckel (1), L. Goubert (3). (1) UZ Gent, Gent, Belgium, Pediatric Gastroenterology ; (2) UZ Gent, Gent, Belgium, Department of Psychology ; (3) UZ Gent, Gent, Belgium, Department of Psychology.

Introduction : A search on ‘pubmed’ resports several studies on the quality of life (QoL) in spina bifida (SB) patients. Most studies use the general health related QoL questionnaire, HRQoL, some report disease-specific QoL instruments but score a certain aspect of the SB impairments. First of all, for children the pediatric QoL (PedsQL) is not applicable in children with mental and motor impairments. Secondly, SB patients present a broad spectrum of health problems, all having an impact on QoL, leading to difficulties for interpreting the general life quality when scoring only one aspect. Hence, an instrument is needed to reliably measure the general QoL in these patients.
Aim : The aim of the study was to develop and validate a Dutch SB HRQoL questionnaire.
Methods : Based on existing questionnaires such as PedsQL 4.0, and patient interview a HR QoL questionnaire in SB children is created, the Spina Bifida Paediatric Questionnaire (SBPQ). Inclusion criteria were : SB patients between 6 and 18 years, Dutch-speaking patients and their parents. Exclusion criteria were : the presence of another disease (trauma, tumor) and a mental age lower than 6 years of age. Written informed consent was obtained. Ten SB patients of different ages and their parents, were asked to complete an ‘extended pilot questionnaire’ of 35 items. A final questionnaire was retained when 3 consecutive patients did not give any suggestions for item modification. Parents and children with a mental development of at least 10 years answered on a 5-point Likert-scale. Younger children with developmental age of 6 to 10 years answered on a visual 3-point Likert-scale and were given additional visual clues. Lower scores designated better QoL. Validation was performed in patients, parents and controls : the same questionnaire was completed twice with a time-interval of 2 weeks.
Results : Thirty-nine patients and parents answered the questionnaire once, 20 patients and their parents the test-retest. Thirty-five controls answered the questionnaire once, 34 controls and their parents the test-retest. The final questionnaire was retained when 3 consecutive patients approved all items. Visual clues were added for children with a mental ability below 10 years of age. The test-retest showed a good to excellent agreement for child self-report in 5 domains (not for social functioning), for parent proxy report in all domains (6), for control self-report in 4 domains (not for domain home) and for control parent proxy report in all domains (5). Internal consistency reliability was good in child self-report and in parent proxy report, except for physical functioning in child self-report. There was parent-child agreement for 4 out of 6 domains. Regarding social and emotional functioning, QoL was rated lower by parents than by children themselves.

Conclusions : the SBPQ has been developed. The questionnaire is tested, well accepted by children and parents and validated (after omitting one question from the social domain). This questionnaire is easy to complete and can be used by both young children and adolescents due to the visual clues. Parents provide an extra dimension to the HR QoL in SB patients.

BELGIAN GROUP FOR DIGESTIVE ONCOLOGY (BGDO)

- O01 -

68GA-DOTATOC UPTAKE AT BASELINE PREDICTS GOOD PROGNOSIS AFTER PRRT IN NEUROENDOCRINE TUMORS PATIENTS. S. Van Binnebeek (1), B. Vanbilloen (1), K. Baete (1), K. Bogaerts (2), C. Terwinghe (1), M. Koole (1), F. Mottaghy (3), P. Clement (1), L. Mortelmans (1), K. Haustermans (4), K. Nackaerts (5), A. Verbruggen (6), E. Van Cutsem (7), C. Verslype (7), C. Deroose (1). (1) UZ Leuven, Leuven, Belgium, Nuclear Medicine ; (2) KU Leuven, Leuven, Belgium, Public Health and Primary Care ; (3) Maastricht UMC, Maastricht, The Netherlands, Department of Nuclear Medicine ; (4) UZ Leuven, Leuven, Belgium, Department Radiation Oncology ; (5) UZ Leuven, KU Leuven, Leuven, Belgium, Respiratory Oncology Unit ; (6) KU Leuven, Leuven, Belgium, Radiopharmacy ; (7) UZ Leuven, Leuven, Belgium, Department of Digestive Oncology.

Introduction : Considering the variable survival data of PRRT as well as the possible side effects and costs of this high radioactive treatment, there rises a growing need to identify those patients who will respond to PRRT, before the start of therapy or on an early time point during PRRT.
Aim : This prospective study evaluated if semi-quantitative analysis of pre-therapeutic uptake on 68Ga-DOTATOC-PET can predict outcome of peptide receptor radionuclide therapy(PRRT) in neuroendocrine tumors(NETs).
Methods : Forty-four disseminated-NET-patients were treated with maximum 4cycles of 1.85GBq/m²/cycle 90Y-DOTATOC (fixed dose) every 8weeks up to a maximal kidney biological effective dose of 37Gy. A 68Ga-DOTATOC-PET/CT was performed before and 40weeks after the first cycle of PRRT(PRRT1). Response was assessed by the CT of 68Ga-DOTATOC-PET/CT at 40weeks after PRRT1 ; progression free survival(PFS) was based on follow up CT and clinical information. Three to six target lesions were prospectively chosen on PETbaseline and median SUVmax of all lesions was assessed. The relationship between median SUVmax-baseline and PFS, Ki67-proliferation-index and tumor grade were examined and ROC-analysis was performed among others.
Results : At 40weeks post PRRT1, stable and progressive disease were found in 23 and 21 patients, respectively. The median PFS was 14months. A significant correlation was found between median SUVmax on PETbaseline and tumor grade($p = 0.035$,$r = -0.32$) ; no significant correlation was found with Ki67-proliferation-index($p = 0.064$,$r = -0.29$) ; PFS was significantly stratified using a median SUVmax of 12.4 on PETbaseline($p = 0.0235$), a median PFS of 9.1months(95%CI,1.7-13.9) was shown for the group with median SUVmax ≤12.4 and 17.7months(95%CI,9.3-21.4) if median SUVmax > 12.4. ROC-analysis for median SUVmax-baseline showed an area under the curve of 0.72.
Conclusions : Median SUVmax of 12.4 on 68Ga-DOTATOC-PETbaseline could be used as a potential pre-therapeutic predictive factor for PRRT.

- O02 -

YTTRIUM-90 RADIOEMBOLISATION FOR THE TREATMENT OF CHEMO-REFRACTORY COLORECTAL LIVER METASTASES : TECHNICAL RESULTS, CLINICAL OUTCOME AND FACTORS POTENTIALLY INFLUENCING SURVIVAL. G. Maleux (1), C. Deroose (2), A. Laenen (3), C. Verslype (4), S. Heye (1), K. Haustermans (5), G. De Hertogh (6), V. Vandecaveye (1), E. Van Cutsem (5). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Radiology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Nuclear Medicine ; (3) KU, Leuven, Belgium, Interuniversity Centre for Biostatistics and Statistical Bioinformatics ; (4) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Digestive Oncology ; (5) UZ Leuven, Leuven, Belgium, Department of Radiation Oncology ; (6) UZ Leuven, Leuven, Belgium, Department of Pathology.

Introduction : Colorectal cancer is the second most common cancer in Europe and 15 – 25% of patients develop liver metastases. If these patients are ineligible for local ablative therapies like radiofrequency ablation (RFA) or for surgical resection, chemotherapeutic treatment remains the therapeutic mainstay for this patient population with an overall survival beyond 2 years. In case of liver-only or liver-predominant metastatic disease, transarterial infusion of yttrium-90 loaded microspheres into the hepatic artery might be another tool in the treatment of these chemo-refractory patients.
Aim : The purpose of the study was to retrospectively assess the technical and clinical outcome, overall survival and prognostic factors for prolonged survival after yttrium-90 radioembolisation as a salvage therapy for patients with chemo-refractory liver-only or liver-dominant colorectal metastases.
Methods : From January 2006 till January 2014, all patients selected for yttrium-90 radioembolisation to treat chemo-refractory colorectal liver metastases were identified. Demographic, laboratory, imaging and dosimetry data were collected. Post-treatment technical and clinical outcome were analysed as well as overall survival ; finally several factors potentially influencing survival were analysed.
Results : 88 patients were selected for angiographic work-up ; 71 patients (81%) finally underwent catheter-directed yttrium-90 microsphere infusion into the hepatic artery on average 25.5 days (standard deviation 12.9 days) after angiographic work-up. Median infused dose was 1809.5 Bq ; 30-day toxicity included : fatigue (n = 39 ; 55%), abdominal

discomfort (n = 33 ; 46.5%), nausea (n = 5 ; 7%), fever (n = 14 ; 19.7%), diarrhea (n = 6 ; 8.5%). Gastric ulcer was found in 5 patients (7%). Late complication was liver fibrosis associated with symptomatic portal hypertension in 3 patients (4.2%). Estimated survival at 6 and 12 months was 65.3% and 29.5%, respectively, with a 50% estimated survival after 8.0 months in this chemo-refractory group of patients. Prognostic factors for worse survival are high bilirubin, alkaline phosphatase and tumour volume levels.
Conclusions : Yttrium-90 radioembolisation for chemo-refractory colorectal liver metastases has an acceptable safety profile with a 50% estimated survival after 8.0 months. Pretreatment high bilirubin, alkaline phosphatase and tumour volume levels are associated with early death.

- O03 -

INHIBITION OF EPITHELIAL-MESENCHYMAL TRANSITION (EMT) : TREATMENT OPTION FOR ADVANCED PANCREATIC CANCER. A. Bulle (1), J. Dekervel (1), P. Windmolders (1), I. Vander Elst (1), E. Van Cutsem (2), C. Verslype (3), J. Van Pelt (4). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Laboratory of Hepatology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Department of Clinical Digestive Oncology ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Laboratory of Hepatology and Department of Clinical Digestive Oncology ; (4) UZ Leuven, KU Leuven, Leuven, Belgium, Liver Research Facility / Labo Hepatology.

Introduction : Epithelial-Mesenchymal Transition (EMT) has been shown to contribute significantly for the aggressiveness and chemo-resistance of several GI-cancers, including pancreatic cancer. The tumor microenvironment plays an important role in inducing EMT in tumor cells.
Aim : In the present study, we examined whether hypoxia and/or TGF-β1 can induce EMT in human PANC-1 cells and whether HIF inhibitor drugs can inhibit or reverse this EMT process.
Methods : PANC-1 cells were cultured under normoxic or hypoxic conditions (2% O2) for 48 hrs in the presence of TGF-β1 to induce EMT. To study EMT inhibition, cells were treated with a combination of hypoxia and/or TGF-β1 and different concentrations of 3 different HIF inhibitor drugs. Changes in cell morphology were captured using an inverted phase-contract microscope equipped with a digital camera. The expression of markers related to EMT was measured by quantitative PCR and Western blot analysis. Cell mobility was assessed using wound healing and invasion assay. Promoter region methylation status of the EMT related markers was tested by methylation-sensitive high-resolution melting (MS-HRM).
Results : We found that the morphology of the cells changed to spindle type and the number of cell-cell contacts was reduced in PANC-1 cell exposed to hypoxia and/or TGF-β1. Hypoxia alone had no significant effect on gene or protein expression of the EMT markers we investigated. qRT-PCR analysis showed, for TGF-β1 and TGF-β1 + hypoxia stimulated PANC-1 cells, that SPARC and the epithelial marker E-cadherin were downregulated and that SPOCK1, the transcription factor SNAI1 and the mesenchymal marker Vimentin were upregulated. Concomitantly, at the protein level E-cadherin expression was dowregulated and SNAI1 expression was upregulated. There was no noticeable change in VIM expression. Two HIF inhibitors could reverse the EMT in a dose dependent manner that we are now investigating in detail. We found that neither TGF-β1, hypoxia or HIF inhibitor drug treatment had effect on the promoter methylation signature of the EMT related markers under study.
Conclusions : These results show that we have developed an in vitro model for EMT. Using this model we are now studying in detail the molecular pathways involved in EMT induction and of its inhibition with the aim of identifying novel therapeutic strategies for advanced pancreatic cancer.
*) A.B. is a recipient of a bursary from the Interfaculty Council for Development Co-operation (IRO, KUL).

- O04 -

LYMPH NODE RATIO AND SURGICAL QUALITY ARE STRONG PROGNOSTIC FACTOR OF RECTAL CANCER : RESULTS FROM A REFERRAL SINGLE-CENTRE EXPERIENCE. D. Leonard (1), C. Remue (1), N. Abbes Orabi (1), A. Van Maanen (2), A. Medina-Benites (3), E. Danse (4), A. Dragean (5), D. Debetencourt (3), Y. Humblet (6), A. Jouret-Mourin (7), F. Maddalena (3), P. Scalliet (8), C. Sempoux (7), M. Van Den Eynde (9), A. Kartheuser (1). (1) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Colorectal Surgery Unit and Cliniques des Pathologies Tumorales du Colon et de Rectum (CPTCR), King Albert II Institute ; (2) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Statistical Support Unit, King Albert II Institute ; (3) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Cliniques des Pathologies Tumorales du Colon et de Rectum (CPTCR), King Albert II Institute ; (4) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Radiology and Cliniques des Pathologies Tumorales du Colon et de Rectum (CPTCR), Institut Roi Albert II ; (5) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Radiology and Cliniques des Pathologies Tumorales du Colon et de Rectum (CPTCR), King Albert II Institute ; (6) Cliniques

Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Medical Oncology and Cliniques des Pathologies Tumorales du Colon et de Rectum (CPTCR), King Albert II Institute ; (7) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Pathology, Cliniques des Pathologies Tumorales du Colon et de Rectum (CPTCR), King Albert II Institute ; (8) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Radiation Oncology and Cliniques des Pathologies Tumorales du Colon et de Rectum (CPTCR), King Albert II Institute ; (9) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Medical Oncology, Cliniques des Pathologies Tumorales du Colon et de Rectum (CPTCR), King Albert II Institute.

Introduction : Different prognostic factors of oncological outcome after rectal cancer treatment have been described. Circumferential resection margin and total mesorectal excision quality have been in the foreground but both tumour staging and particularly the nodal stage remain the mainstay. In order to compensate for the variation in total number of harvested node, lymph node ratio (LNR), adjusting the number of positive to the total number of nodes, has been advocated.
Aim : To assess the impact of LNR, compared to other predicting factors of rectal cancer outcome, particularly TME quality and circumferential resection margin, on the long-term oncological outcomes.
Methods : In the setting of a tertiary referral centre, consecutive patients operated for non-metastatic rectal cancer were extracted from a prospectively maintained database. A retrospective uni- and multivariable analysis was performed based on patient-, surgical- and tumour-related factors.
Results : Over the period between 1998 and 2013, 456 patients were operated for rectal adenocarcinoma. Patients with synchronous metastatic disease (n = 99, 21.7%) were excluded, leaving 357 patients in this analysis. Overall, neoadjuvant radio(chemo)therapy was administered to 66.7% of the patients. A sphincter saving operation (SSO) was performed in 78.2% of the patients. The anastomotic fistula rate was 6.8% and there were two post-operative deaths (0.6%). The mean number of lymph nodes removed was 12.8 ± 8.78 per specimen and the mean number of positive nodes was 0.8 ± 1.97. The mean LNR was 0.74 ± 0.16. A lower lymph node yield was reached in patients who received neoadjuvant chemoradiotherapy (11.8 vs. 14.2, p = 0.014). On multivariable analysis age, surgical approach, TME quality, and the administration of chemoradiotherapy were independently associated with the total number of lymph nodes retrieved. The overall 5-year recurrence-free survival (ORFS) was 71.8% and the 5-year overall survival (OS) was 80.1%. Multivariable analysis confirmed LNR, TME quality, absence of symptoms, peri-neural infiltration and age as independent prognostic factors of OS. LNR and extramural vascular infiltration were independently associated to ORFS. LNR reached the highest hazard ratios in both models.
Conclusions : In our experience, LNR is the most prominent prognostic factor of OS and OR. The only “controllable variable” was the surgical quality, which is in line with the principles of optimal surgical management.

- O05 -

WAIST HIP RATIO BETTER PREDICTS ONCOLOGICAL QUALITY OF RESECTION AND OUTCOME AFTER COLON CANCER SURGERY THAN BODY MASS INDEX.

N. Hetsch (1), A. Kartheuser (1), D. Leonard (1), A. Van Maanen (2), F. Penninckx (3), H. Paterson (4), N. Abbes Orabi (5), S. Achkasov (6), P. Ambrosetti (7), J. Baulieux (8), P. Bouteloup (9), D. Brandt (10), F. Bretagnol (11), R. Chamlou (12), C. Coimbra (13), E. Cotte (14), A. D’hoore (3), E. Dozois (15), R. Droissart (12), J. Etienne (16), J. Etienne (17), J. Faucheron (18), P. Frileux (19), O. Glehen (14), C. Jehaes (20), J. Kayser (21), Z. Krivokapic (22), C. Laurent (23), P. Lehur (24), J. Loriau (25), J. Mabrut (8), B. Majerus (26), P. Matthiessen (27), F. Mboti (28), G. Meurette (24), F. Michot (29), B. Monami (30), N. Mortensen (31), D. Nagele-Moser (32), Y. Panis (11), Y. Parc (33), J. Pfeifer (32), F. Pierard (34), M. Pocard (35), F. Ris (36), P. Rouanet (37), F. Rulli (38), E. Rullier (23), J. Saey (39), Y. Shelygin (6), C. Soravia (40), L. Stainier (26), N. Tinton (10), E. Tiret (41), J. Tuech (29), A. Valverde (42), J. Van De Stadt (43), Y. Van Molhem (44), B. Vinson-Bonnet (45), T. Yeung (31). (1) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Unité de Chirurgie Colorectale ; (2) Institut Roi Albert II, Brussels, Belgium ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Abdominale Heelkunde ; (4) Western General Hospital, University of Edinburgh, UK, Department of Colo-proctology ; (5) Centre hospitalier régional de Mons, Mons, Belgium, Service de Chirurgie Digestive ; (6) State Research Centre of Coloproctology, Russia ; (7) Clinique Générale, Beaulieu, Switzerland, Service de Chirurgie Générale et Digestive ; (8) Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Lyon, France, Service de Chirurgie et Transplantation Viscérale ; (9) Centre Hospitalier Privé, Saint-Grégoire, France, Cabinet de Chirurgie Digestive et Viscérale ; (10) Grand Hôpital de Charleroi, Hôpital Saint-Joseph, Gilly, Belgium, Service de Chirurgie Digestive ; (11) Hôpital Beaujon, Clichy, France, Unité de Chirurgie Colorectale ; (12) Clinique Saint-Jean, Brussels, Belgium, Service de Chirurgie Digestive, Thoracique et Endocrine ; (13) CHU de Liège, Domaine Universitaire du Sart Tilman, Liège, Belgium, Service de Chirurgie Abdominale, Sénologique, Endocrine et de Transplantation ; (14) Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Pierre-Bénite, France, Service de Chirurgie Générale, Digestive et Cancérologique ; (15) Mayo Clinic, Rochester, USA, Division of Colon and Rectal Surgery ; (16) Clinique Sainte-Elisabeth, Namur, Belgium, Service de Chirurgie Générale ; (17) Centre Hospitalier Intercommunal de Poissy, Poissy, France, Service de Chirurgie Générale et Digestive ; (18) Hôpital A. Michallon, La Tronche, France, Service de Chirurgie Digestive et de l’Urgence ;

(19) Hôpital Foch, Suresnes, France, Service de Chirurgie Digestive ; (20) Clinique St-Joseph, Liège, Belgium, Service de Chirurgie Digestive, Endocrinienne et Générale ; (21) Groupe Chirurgical Zithaklinik, Luxembourg, Service de Chirurgie Générale ; (22) Institute for Digestive Disease, Belgrade, Serbia ; (23) Hôpital Saint-André, Bordeaux, France, Service de Chirurgie Viscérale et de Transplantations Hépatiques ; (24) Hôtel Dieu CHU de Nantes, Nantes, France, Service de Chirurgie Digestive et Endocrinienne ; (25) Groupe Hospitalier Saint-Joseph, Paris, France, Service de Chirurgie Digestive ; (26) Clinique Saint-Pierre, Ottignies, Belgium, Service de Chirurgie Digestive ; (27) Örebro University Hospital, Örebro, Sweden, Department of Digestive Surgery ; (28) ULB Hôpital Erasme, Brussels, Belgium, Service de Chirurgie Générale et Digestive ; (29) CHU Charles-Nicolle, Rouen, France, Service de Chirurgie Générale et Digestive ; (30) Cliniques Saint-Joseph, Liège, Belgium, Service de Chirurgie Digestive, Endocrinienne et Générale ; (31) John Radcliffe Hospital, Oxford, UK, Department of Colo-proctology ; (32) University Clinic of Surgery, Graz, Austria, Department of Surgery Section for Surgical Research ; (33) Hôpital Saint-Antoine, Paris, France, Service de Chirurgie Générale et Digestive ; (34) Clinique Saint-Luc, Bouge, Belgium, Service de Chirurgie Digestive ; (35) Hôpital Lariboisière, Paris, France, Service de Chirurgie Digestive ; (36) HUG, Hôpital Cantonal de Genève, Genève, Switzerland, Service de chirurgie viscérale et transplantation ; (37) ICM Institut du Cancer de Montpellier, Montpellier, France, Service de Chirurgie Oncologique ; (38) University of Rome "Tor Vergata", Rome, Italy, Department of Digestive Surgery ; (39) Centre Hospitalier Régional de Mons, Mons, Belgium, Service de Chirurgie Digestive et Endocrinienne ; (40) Clinique Générale, Beaulieu, Switzerland, Service de Chirurgie Générale et Digestive ; (41) Hôpital Saint Antoine, Paris, France, Service de Chirurgie Générale et Digestive ; (42) Centre Hospitalier Victor Dupouy d'Argenteuil, Argenteuil, France, Service de Chirurgie Générale et Digestive ; (43) CUB Hôpital Erasme, ULB, Brussels, Belgium, Service de Chirurgie Digestive ; (44) Onze-Lieve-Vrouw Ziekenhuis, Aalst, Belgium, Dienst Algemene Heelkunde ; (45) Centre Hospitalier Intercommunal de Poissy, Poissy, France, Service de Chirurgie Digestive.

Introduction : Waist hip Ratio (WHR) has been shown to be more reliable than body mass index (BMI) to predict surgical outcome after colorectal surgery. The role of obesity on oncological short- and long- term outcome after colon surgery has been less investigated.
Aim : To determine whether body fat distribution, measured by the WHR, better predicts oncological short- and long-term outcome after colon cancer resection than BMI.
Methods : This prospective multi-centre international study explored the effect of obesity on early postoperative outcome in patients undergoing elective colorectal surgery. Patients operated for colon cancer were extracted from the database and long-term follow-up was obtained. Influence of WHR and BMI on oncological outcome was analysed using uni- and multivariable analysis. The effect of obesity on overall and recurrence-free survival was assessed using Cox proportional hazard models.
Results : Out of 1349 patients from 38 centres in 11 countries included in the initial prospective trial, 426 patients (mean age : 68y +/- 12.2), 245 males, sex ratio M/F : 1.35) from 24 centres in 5 countries underwent elective surgery for colon adenocarcinoma. Mean BMI was 26 +/- 5 and WHR 0.98 +/- 0.17. Medical complications occurred in 62 patients (14.6%), surgical complications in 75 (17,6%). In-hospital mortality was 0.9%. Median follow-up was 44.2 months (0.6 – 65.7). WHR was an independent prognosis factor of overall survival [hazard ratio : 4,54 (1,012 – 20,39), p = 0.048], but not of recurrence free survival. On multivariate analysis, BMI was not significantly associated with overall or recurrence free survival. Total number of lymph nodes retrieved, considered as a quality indicator of oncological resection, was significantly influenced by WHR on multivariate analysis [hazard ratio : 0,991 (0,986 - 0,996), p < 0,001] but not by BMI.
Conclusions : WHR was more effective than BMI in predicting oncological quality of resection and long-term overall survival after colon cancer surgery.

- O06 -

THE DNET REGISTRY : A PROSPECTIVE, NATIONAL, WEB-BASED ONLINE REGISTRY OF DIGESTIVE NEURO-ENDOCRINE TUMOURS. STATUS AFTER 2 YEARS OF INCLUSION. I. Borbath (1), D. Dresse (2), C. Verslype (3), G. Demolin (4), H. Rezai Kalantari (5), K. Geboes (6), V. Moons (7), M. Polus (8), J. Van Laethem (9), M. Peeters (10), A. Bols (11), W. Demey (12), G. Lambrechts (13), M. Simoens (14), P. Vergauwe (15), J. Janssens (16), E. Monsaert (17), J. Coche (18), S. Carton (19), E. Van Cutsem (20). (1) Cliniques Universitaires St-Luc, UCL, Brussels, Belgium, Gastroenterology Department ; (2) CHR Citadelle, Liège, Belgium, Abdominal Surgery Department ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Hepatology and Digestive Oncology Department ; (4) CHC, Liège, Belgium, Gastroenterology Department ; (5) CH Peltzer-La Tourelle, Verviers, Belgium, Medical Oncology Department ; (6) UZ Gent, Gent, Belgium, Gastroenterology Department ; (7) Imelda Hospital, Bonheiden, Belgium, Gastroenterology Department ; (8) CHU Sart Tilman, Liège, Belgium, Gastroenterology Department ; (9) CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology Department ; (10) UZ Antwerpen, Antwerp, Belgium, Medical Oncology Department ; (11) AZ St. Jan Brugge AV, Brugge, Belgium, Gastroenterology Department ; (12) KLINA, Brasschaat, Belgium, Medical Oncology Department ; (13) AZ Damiaan, Oostende, Belgium, Gastroenterology Department ; (14) ZNA Jan Palfijn, Merksem, Belgium, Gastroenterology Department ; (15) AZ Groeninge, Kortrijk, Belgium,

Gastroenterology Department ; (16) AZ Turnhout, Turnhout, Belgium, Gastroenterology Department ; (17) AZ Maria Middelares, Gent, Belgium, Gastroenterology Department ; (18) Clinique St. Pierre, Ottignies, Belgium, Gastroenterology Department ; (19) AZ Sint Maarten, Mechelen, Belgium, Gastroenterology Department ; (20) UZ Leuven, Leuven, Belgium, Digestive Oncology Department.

Introduction : Digestive Neuro-Endocrine tumours (NET) are rare and poorly understood neoplasms that deserve a better understanding. It was therefore the project of the BGDO to create a web-based registry to have an overview of incidence, diagnostic and therapeutic procedures performed in Belgian patients. A new version of the DNET was launched in 01/2012. Patients diagnosed with a NET after 01/01/2005 were included.
Aim : We report data after 2 years of inclusion.
Methods : As of 30 November 2014, 510 patients and more than 2000 visits were included in the registry, from 28/41 active sites. The sites had first to make the study approved by their ethics committee, all the patients had to sign informed consent. The registry is available upon username/password on www.bgdo.org/DNET.
Results : Patients consisted of 267 men and 243 female. Mean age was 60+/- 13 years. ECOG PS was 0 in 245 pts (47,8%), 1 in 133 (26%), 2 in 23 (4,5%), 3 in 23 (4,5%) and not known in 85. Primary tumours are mainly pancreas (n = 161, 31,4%), midgut (n = 165, 32,3%). Chromogranin A was analysed in 294 patients and NSE in 177. Functional syndrome was present in 79/510 pts (15%), among which 54 presented with carcinoid syndrome (10%). SRS imaging was positive in 104/128 pts (Se 81%). Pathology (cytology, biopsy or surgical specimen) was available for 89/165 midgut pts (54%) and 117/161 pancreas pNET (73%). Among Midgut pts, they were mainly WHO 2010 NET G1 (51/89, 57%) or NET G2 (32/89, 36%). pNET pts were more NEC G3 (29/117, 24%) and NET G2 (60/117, 51%) than NET G1 (29/117, 25%). Surgery (270 answers as of 30 Nov 2014) was performed in a curative intent in 217 pts, for palliative reasons in 31 pts. Initial systemic therapy was chemotherapy for 39 pts, SMS analogues for 120 pts and targeted therapy to 12/510. During follow-up, 26 pts died, mainly from tumour progression, after a median 12 m (2-105).
Conclusions : The new version of the DNET registry is recruiting very well, considering the high inclusion rate (20 pts/months) and is an effective tool for getting important informations on DNET therapy and follow-up in Belgium. More data on tretament and survival will be made available at the time of congress.

- O07 -

MICROSATELLITE INSTABILITY VERSUS MICROSATELLITE STABILITY IN COLON CARCINOMA : DOCUMENTATION OF TUMOUR HETEROGENEITY AND INFLAMMATION. L. De Smedt (1), J. Lemahieu (2), S. Palmans (1), O. Govaere (1), T. Tousseyn (2), E. Van Cutsem (3), H. Prenen (3), S. Tejpar (3), C. Decaestecker (4), X. Moles Lopez (4), P. Demetter (5), I. Salmon (5), X. Sagaert (2). (1) Katholieke Universiteit Leuven, (KUL), Leuven, Belgium, Imaging and Pathology ; (2) UZ Leuven, KU Leuven, Leuven, Belgium, Pathology Department ; (3) UZ Leuven, KU Leuven, Leuven, Belgium, Department Oncology ; (4) DIAPATH, Center for Microscopy and Molecular Imaging (CMMI), Charleroi, Belgium ; (5) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Pathology.

Introduction : Microsatellite instability (MSI) accounts for 15% of all colorectal tumours. Several specific clinico-pathologic (e.g. preference for the proximal colon over the distal colon, improved prognosis and altered response to chemotherapeutics) and histologic features (e.g. poor degree of differentiation, peritumoural Crohn's-like reaction and increased lymphocytic infiltration) are described for this subset of tumours.
Aim : The aim of our study was to analyse the morphology and inflammatory reaction of MSI and microsatellite stable (MSS) tumours in detail.
Methods : Twenty-seven MSS and 30 MSI colorectal tumours were selected from the archive of the department of pathology UZ Leuven. All cases were chosen to match for TNM-stage with availability of clinical data. Morphology was analysed on haematoxylin eosin sections. Immunohistochemistry for CD3, CD4, CD8, CD20 and CD68 was used to map tumour infiltration in both a digital and traditional microscope-based fashion for all distinct morphologic components of the tumour.
Results : Morphologic tumour heterogeneity was a marked feature of MSI tumours, occurring in 53% of the cases compared to 11% of the MSS tumours ($p < 0.001$). Digital immune quantification showed increased numbers of tumour infiltrating cytotoxic T-lymphocytes (CD8+) in MSI compared to MSS tumours for both the tumour ($p = 0.02$) and peritumoural area ($p = 0.03$). Traditional microscope-based quantification confirmed these results ($p < 0.001$ for both) and revealed large numbers of CD68+ macrophages in the peritumoural area of MSI cancers ($p = 0.001$). Moreover, traditional microscope-based analysis was able to distinguish between lymphocytes directly infiltrating the tumoural glands (intra-epithelial) and those infiltrating only the neoplastic stroma around the glands (intratumoural). Quantification showed high numbers of intra-epithelial CD3+, CD4+, CD8+, CD20+ and CD68+ cells in MSI compared to MSS cancers ($p < 0.001$, $p = 0.01$, $p < 0.001$, $p < 0.001$ and $p = 0.006$ respectively). Finally, lymphocytic infiltration was investigated for each distinct morphologic entity. Glandular MSS tumours showed mainly intratumoural lymphocytes, in contrast to glandular MSI tumours that presented with a combination of intratumoural and intra-epithelial infiltrating

lymphocytes. The mucinous compartment in MSI and MSS tumours showed low immune infiltration and the medullar compartment, only seen in MSI cases, presented with high levels of intra-epithelial lymphocytes.
Conclusions : Mixed morphology is an important feature of MSI tumours. New studies should investigate whether morphologic heterogeneity is linked to molecular heterogeneity, which is an important cause for failure and relapse after therapy. The inflammatory reaction in MSI and MSS colorectal tumours presented significant differences. MSI cancers showed mainly infiltration by cytotoxic T-cells in both the tumour and the close border around the tumour, as well as increased intra-epithelial infiltration. Both the type of immune cells and the compartment they reside in (intratumoural or intra-epithelial) depends on MSI status and morphology. Future studies should explore the T-cell receptor repertoire of intra-epithelial and intratumoural lymphocytes in order to unravel the capacity of T-lymphocytes to migrate into the intra-epithelial compartment in MSI tumours.

- O08 -

COMPARISON OF EARLY STAGES OF COLORECTAL CANCER BY LABEL FREE PROTEOMICS. F. Quesada Calvo (1), M. Meuwis (1), V. Bertrand (2), R. Longuespée (2), J. Somja (3), G. Mazzucchelli (2), N. Smargiasso (2), D. Baiwir (4), Ph. Delvenne (5), M. Malaise (7), M. Polus (1), M. De Pauw-Gillet (7), E. De Pauw (2), E. Louis (1). (1) CHU de Liège, Liège, Belgium, Gastroenterology, Hepatology and Digestive Oncology Department ; (2) University of Liège, Liège, Belgium, Mass Spectrometry Laboratory, GIGA-Research, Department of Chemistry ; (3) CHU de Liège, Liège, Belgium, Department Pathology ; (4) University of Liege, Liège, Belgium, GIGA Proteomic Facility ; (5) CHU de Liège, Liège, Belgium, Laboratory of Experimental Pathology, GIGA-Cancer ; (6) CHU de Liege, Liège, Belgium, Department of Rhumatology ; (7) University of Liege, Liège, Belgium, Department of Preclinical and Biomedical Sciences, Mammalian Cell Culture Laboratory, GIGA-R.
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Introduction : Colorectal cancer (CRC) is the second most frequent cancer in women and the third in men. Identification of the mechanisms of progression in these early CRC stages is important to develop new diagnostic and therapeutic tools. Formalin-Fixed Paraffin-Embedded (FFPE) specimens are materials that enable proteomic clinical research.
Aim : Hence our aim was to address the comparison of FFPE samples from early CRC stages patients using shotgun proteomic analysis.
Methods : We performed a retrospective study on 36 CRC tissue samples (pT1N0M0, n = 16 and pT2N0M0, n = 20) compared together and with 40 control tissue samples (20 patients with diverticulitis, using paired inflamed (DI) and healthy tissue (DH)). Each tissue slice was macrodissected to enrich in epithelial cells. We used FFPE-FASP kit (Expedeon) for sample preparation and protein digests were analyzed using 2D-nanoAquity UPLC separation online with Q-Tof Synapt HDMSTM G2 using ion mobility as additional separation. We performed protein identification and differential analysis using Progenesis QI for proteomics (Nonlinear Dynamics).
Results : We selected 149 proteins differentially distributed between T1 and T2 CRC stages which were not significantly different between CRC and DH or DI. Only 30 proteins were significantly more abundant in T1 versus T2 and 119 were distributed inversely, with a minimum fold ratio of 2. Among those, ATP synthase subunit beta, Aspartate-tRNA ligase, Haptoglobin and Kininogen were identified. Moreover, we validated Kininogen and 3 others proteins with a significant differential distribution between pT1N0M0 and pT2N0M0 stages by immunohistochemistry.
Conclusions : This FFPE retrospective study comparing T1 and T2 CRC highlighted proteins already previously identified as potential CRC biomarkers. These proteins may reflect important early changes in cancer development and may help understand early tumor progression.

- O09 -

TWO MECHANISMS OF EVEROLIMUS RESISTANCE IN PANCREATIC NEUROENDOCRINE TUMORS. T. Vandamme (1), M. Beyens (1), K. Op De Beeck (1), F. Dogan (2), P. Pauwels (3), P. Van Koetsveld (2), G. Mortier (4), G. Van Camp (4), W. De Herder (2), M. Peeters (1), L. Hofland (2). (1) Universiteit Antwerpen, Antwerpen, Belgium, Department of Oncology ; (2) Erasmus Medical Center, Rotterdam, The Netherlands, Section of Endocrinology, Internal Medicine ; (3) Universiteit Antwerpen, Antwerpen, Belgium, Department of Pathology ; (4) Universiteit Antwerpen, Antwerpen, Belgium, Center for Medical Genetics.

Introduction : Pancreatic neuroendocrine tumors (PNETs) are tumors arising from the endocrine pancreas. The phosphoinositide-3-kinase/Akt/mammalian target of rapamycin (PI3K-Akt-mTOR) is a target for PNET therapy using the mTOR-inhibiting drug everolimus. A recent phase III trial with everolimus shows an improved progression-free survival in PNET. However, adaptive resistance to mTOR inhibition is described in patients. To study mechanisms of resistance, everolimus resistance was induced in BON-1 and QGP-1, two human PNET cell lines, through long-term culturing in increasing everolimus concentrations.

Aim : Alterations in the PI3K-AKT-mTOR and adjacent pathways are studied to understand the mechanisms underlying adaptive everolimus resistance
Methods : Phosphorylation status of the PI3K-Akt-mTOR pathway proteins AKT, S6K, 4EBP-1 and ERK1/2, a member of the RAS-RAF-ERK pathway, was studied by western blotting in sensitive and resistant BON-1 and QGP-1 at baseline and after 1 hr everolimus (1μM) exposure. mRNA expression of PI3K-Akt-mTOR pathway genes MTOR, RAPTOR, RICTOR, S6K1, 4EBP1 and downstream genes BCL2 and HIF1A was evaluated through qRT-PCR in resistant and sensitive BON-1 and QGP-1, both at baseline and after 1 μM everolimus exposure during 3 days.
Results : When comparing everolimus-resistant and sensitive BON-1 and QGP-1 at baseline, an increased phosphorylation of ERK2 was seen. Phospho-AKT was increased in resistant QGP-1 when compared to sensitive QGP-1. In resistant BON-1, phospho-AKT and phospho-S6K were decreased in comparison to the sensitive cell line. After short-term everolimus exposure, phospho-4EBP1 and phospho-S6K decreased in resistant BON-1 and QGP-1. Phospho-AKT decreased in resistant BON-1, but increased in resistant QGP-1. On gene expression level, MTOR, HIF1A and mTOR complex elements RAPTOR and RICTOR expression decreased significantly in resistant BON-1 when compared with sensitive BON-1 at baseline. 4EBP1 expression was increased significantly in BON-1. In resistant QGP-1 at baseline, RICTOR and downstream genes BCL2 and HIF1A expression decreased significantly. After everolimus exposure, gene expression in resistant BON-1 showed an increase in MTOR, RAPTOR, RICTOR, 4EBP1 and downstream genes BCL2 and HIF1A. In resistant QGP-1, a significant increase in MTOR and a significant decrease in RAPTOR, S6K1, 4EBP1 and downstream genes BCL2 and HIF1A was observed.
Conclusions : In both resistant BON-1 and QGP-1 constitutional ERK activation appears induced, hinting at a role of the RAS-RAF-ERK pathway in everolimus resistance. In resistant QGP-1, AKT phosphorylation is constitutionally increased, in line with its more complete resistance profile (data not shown). After acute everolimus exposure, both resistant cell lines show a decreased phosphorylation of downstream S6K and 4EBP1, as expected after mTOR inhibition. However, BON-1 and QGP-1 show a different AKT phosphorylation response to acute everolimus exposure. This indicates differential regulation of the feedback mechanism of S6K on upstream AKT, possibly through interaction of PI3K and ERK. In conclusion, BON-1 and QGP-1 show different mechanisms of everolimus resistance.

- O10 -

THE CORRELATION BETWEEN IMAGING AND RESECTION SPECIMEN OF COLORECTAL LIVER METASTASES. H. Thierens (1), I. Colle (2), K. De Keukeleire (3), B. Van Den Bossche (4). (1) Gent University, Gent, Belgium, Medical Student ; (2) Gent University, Gent, Belgium, Department of Internal Medicine ; (3) ASZ, Aalst, Belgium, Department Radiology ; (4) ASZ, Aalst, Belgium, Department of Surgery.

Introduction : Colorectal liver metastases (CRLM) involves 50% of all liver metastases, if untreated, patients have a median survival of 5 to 20 months. Surgical resection on appropriate selected patients is the only treatment for CRLM that is associated with a plateau phase in a 5-years survival curve. The selection relies on imaging techniques (CT/MRI), these demonstrates the exact number, localization and size of metastases. Several studies showed that MRI is more sensitive than CT for lesions < 10mm.
Aim : This study aims to determine the correlation between the medical imaging (CT/MRI) with the anatomical pathology of the resection specimen of CRLM.
Methods : A first evaluation from September 2011 until April 2014 in ASZ contains 20 patients with CRLM who underwent a surgical resection. The diameters of the metastases on the last imaging before surgery are compared to the diameters of the resected samples.
Results : The imaging of all patients showed 35 metastases in total (mean = 1.8 per patient, range = 1-5). However, after resection anatomo-pathology (APD) revealed 38 metastases (mean = 1.95 per patient, range = 0-6). Of all metastases, 5 were not diagnosed before operation and 2 suspected lesions pre-op were not malignant at definitive pathology report. The period between the radiology and surgery was on average 33 days. The mean of the largest diameters on CT or MRI is 21.71 mm (range from 5.7-59.6 mm) compared to the size of the resection with a mean of 14.55 mm (from 3-40 mm). This represents an overestimation on CT of average 1.66 mm or 3%. Remarkably, lesions < 20 mm on CT are on average 25% underestimated on CT, > 20 mm are 37% overestimated.
Conclusions : In general, metastases are on CT on average 3% overrated. But lesions < 20 mm are on average 25% underestimated. Yet, 14.6% of the metastases were not diagnosed before the resection and 5.4% of the possible malignant lesions on pre-op CT were benign on definitive pathology report.

- O11 -

A HIGH NUMBER OF ADVANCED ADENOMAS ARE FOUND IN INDIVIDUALS REFERRED FROM THE FLEMISH COLON CANCER SCREENING PROGRAM : A PROSPECTIVE SINGLE CENTER QUALITY REGISTRY. L. Vandeputte, V. De Wilde, M. Cabooter, P. Laukens, H. Orlent; AZ St. Jan Brugge-Oostende, Campus Brugge, Departement of Gastroenterology and Hepatology.

Introduction : In October 2013, the Flemish government launched the Flemish colon cancer screening program. The assessment of key quality performance indicators is advocated by the European and national guidelines on colon cancer screening.
Aim : To monitor adenoma (ADR)- and carcinoma (CA) detection rate and adenoma detection index (ADI) in patients referred to our endoscopy unit.
Methods : Clinical patient parameters, endoscopic and pathological data on retrieved polyps, as well as follow-up on complications, surgery and staging are registered in 373 consecutive individuals with a positive immunological fecal occult blood test, referred to our center during the first 12 months from the Flemish colon cancer screening program.
Results : 373 individuals (M 227/F 146), mean age 68.7 years, were referred for index colonoscopy, representing 13.3 % of the total colonoscopy-volume of our unit in this period. 99.5 % of the procedures were performed under conscious sedation. An unadjusted caecal intubation rate of 97.9% was achieved. In total 884 lesions were detected, of which 850 were removed endoscopically. The polyp retrieval rate was 85.2% (724/850 lesions retrieved). Of the 724 retrieved lesions, 495 (68.4%) were tubular adenomas (TA), 21 (2.9%) tubulovillous adenomas (TVA), 24 (3.3%) serrated adenomas, 164 (22.7%) hyperplastic polyps, 10 (1.4%) carcinomas, and 14 (1.9%) other lesions. 34 carcinomas were not resected endoscopically. Polyp detection rate was 71.6% : in 267/373 colonoscopies, a polypoid lesion was found. We achieved an adenoma detection rate of 54.2% : in 202/373 colonoscopies, at least one adenoma, carcinomas not included, was detected. The adenoma detection index (ADI) (= Total N° adenomas/ Total N° colonoscopies) is 1.45. We found at least 1 high-risk-adenoma (TA of ≥10 mm ; and/or ≥1 TVA ; and/or ≥1 TA with high grade dysplasia ; adenocarcinomas ≥pTis not included) in 112/373 colonoscopies (30%). 44 adenocarcinomas were diagnosed in 41 individuals (11% of colonoscopies), predominantly at early stages : stage 0 in 6/41 patients (14.6%) and stage I in 22/41 (53.7%). In total, a high-risk adenoma and/or an adenocarcinoma was found in 151/373 (40.5%) of index screening colonoscopies . Two significant post-polypectomy bleedings (0.5%) occurred, both in patients under continued OAC (1) or NOAC (1). There were no perforations and no 30-day mortality.
Conclusions : A high ADR (54.2%) is found in patients referred from the Flemish colon-cancer screening-program. High-risk lesions, adenocarcinomas included, were found in 40.5% of the index screening colonoscopies. 44 CA (≥pTis) were detected in 11% of the colonoscopies.

- O12 -

DETECTION RATE OF COLORECTAL CANCER IN PATIENTS WITH POSITIVE IMMUNOCHEMICAL FAECAL OCCULT BLOOD TEST (IFOBT) IN THE FLEMISH POPULATION-WIDE SCREENING PROGRAMME FOR COLORECTAL CANCER : PRELIMINARY RESULTS FROM OLV HOSPITAL, AALST. L. Van Ginderachter (1), H. Degroote (2), J. Vandervoort (3), V. Casneuf (3), K. Hendrickx (3), P. Dobbels (3). (1) UZ Leuven, KU Leuven, Leuven, Belgium, Department Gastroenterology ; (2) UZ Gent, Gent, Belgium, Department Gastroenterology ; (3) OLV Aalst, Aalst, Belgium, Department Gastroenterology.

Introduction : Screening reduces the incidence and mortality of colorectal cancer. The Flemish government organised and implemented a population-wide screening programme for CRC in people aged 56-74 years, using the immunochemical faecal occult blood test (iFOBT). The quality of additional colonoscopy, performed in patients with positive iFOBT, is an important determinant of the success rate of the screening programme.
Aim : To report the preliminary results of colonoscopies performed in our unit in patients with positive iFOBT in the context of the Flemish population-wide screening programme for CRC. Using the caecal intubation rate and the detection rate of polyps and tumors as quality indicator.
Methods : We collected the results of colonoscopies performed in patients with positive iFOBT during a period of 4 months (March- June 2014) in the OLV hospital, Aalst.
Results : In a period of 4 months, 261 colonoscopies were performed in patients with positive iFOBT. The caecum was reached in all examinations. In 21 of 261 cases no cause of faecal occult blood was detected (8% false positive results of iFOBT). Detection rate of all-size colorectal polyps or tumors was 73% (191 of 261 cases). There were 78 polyps > 1 cm (29,8%). Resulting in 5,7% histologically proven CRC (15 cases). In 19% there was an other cause than polyps or tumors.
Conclusions : The detection rate in our center of all-size polyps or tumors is 73%. There were 29.8% polyps more than 1 cm. Resulting in 5,7% histologically proven CRC. These results are similar to the reported detection rate in the trial programme in Antwerp.

- O13 -

EXPEL : A NOVEL NON-DESTRUCTIVE METHOD FOR MINING SOLUBLE TUMOR BIOMARKERS. B. Costanza (1), A. Blomme (1), E. Mutijima (2), P. Delvenne (3), O. Detry (4), V. Castronovo (1), A. Turtoi (1). (1) University of Liège, Liège, Belgium, Metastasis Research Laboratory, Giga Cancer ; (2) CHU de Liège, Liege, Belgium, Department of Pathology, ; (3) CHU de Liège, Belgium, Department of Pathology ; (4) University of Liège, Liège, Belgium, Laboratory of Mass Spectrometry, Dept. of Chemistry.

Introduction : Secreted cancer proteins are important modulators of tumor growth and progression. This protein group has always been considered a major source of potential biomarkers. Unfortunately identification of novel and clinically useful secreted tumor-specific proteins is difficult since their concentration in serum or urine is very low. Alternatively to this, mining tissue proximal fluid has emerged as a powerful approach to identify potential candidate biomarkers. However, current methods relay on ex vivo culture that takes considerable time and exposes tissue biopsies to uncontrolled degradation through endogenous proteases.
Aim : Aim of the project is the discovery of new soluble biomarkers for early detection, diagnosis or prognosis of human cancer disease.
Methods : In the present work we have developed a novel and efficient method for the collection and analysis of tumor secretome. The approach, which we termed Expel, extracts soluble tumor biomarkers within few minutes and without altering the tissue morphology. For this purpose a small tissue biopsy is incubated in a slightly hypertonic extraction buffer while subjected to alternating pressure. Upon extraction the tissue is fixed in formalin and can be used for histological analysis. The soluble extract is further prepared for proteomic analysis using bottom-up mass spectrometry approach.
Results : In a proof of concept study we have extracted and analysed soluble biomarkers from human colorectal carcinoma liver metastases as well as primary colorectal tumors. In an extensive tissue validation study we confirm that Expel procedure does not alter tissue morphology or subsequent molecular pathology tests. The comparison of proteins identified in tumor lesions with those found in adjacent normal tissues revealed a group of differentially expressed soluble proteins. Their potential usefulness as diagnostic or predictive markers is currently being explored
Conclusions : The Expel protocol provides clinicians with a new tool enabling them to non-destructively discover new biomarkers and preserve precious tissues (like colon polyps) for pathology evaluation

- O14 -

METABOLOMIC, PROTEOMIC AND PRECLINICAL IMAGING OF PATIENT DERIVED TUMOR XENOGRAFTS FOR IMPROVING TREATMENT OF LIVER METASTASES PATIENTS. A. Pérez Palacios (1), A. Blomme (2), S. Boutry (3), G. Doumont (3), F. Sherer (3), G. Van Simaeys (3), D. Debois (4), G. Jerusalem (5), J. Collignon (6), P. Delvenne (7), O. Detry (8), E. De Pauw (4), R. Muller (9), S. Goldman (10), V. Castronovo (2), A. Turtoi (2). (1) University of Liège, Liège, Belgium, Metatasis Research Laboratory ; (2) University of Liège, Liège, Belgium, Metastasis Research Laboratory ; (3) IRSPG, Gosselies, Belgium, Center for Microscopy and Molecular Imaging ; (4) University of Liège, Liège, Belgium, Laboratory for Mass Spectrometry ; (5) CHU Liège, Liège, Belgium, Department of Medical Oncology; (6) CHU Liège, Liège, Belgium, Department of Medical Oncology ; (7) University of Liège, Liège, Belgium, Experimental Pathology Laboratory ; (8) University of Liège, Liège, Belgium, Department of Abdominal Surgery ; (9) IRSPG, Gosselies, Belgium, Center for Microscopy and Molecular Imaging (CMMI) ; (10) University of Liège, Liège, Belgium, Center for Microscopy and Molecular Imaging (CMMI),

Introduction : Successful translational research relies on animal tumor models that can veritably recapitulate the human situation. Most is done today using mouse xenografts, which are based on cultured cancer cells. However, these cell lines have considerably diverged from their original tumors, critically loosing the genetic and proteomic diversity typically found in tumors. This drawback is at the origin of the recent surge of interest in patient-derived tumor explants (PDTX), which consists in grafting human tumor directly in immunocompromised mice.
Aim : Although the PDTX model is promising, little is known on how well are the functional proteomic and metabolomic aspects conserved from the original patient to the model. Our study aims to broaden this knowledge. A further question concerns the clinical utility of this model and to what extent can functional data obtained on PDTX help improve treatment for cancer patients.
Methods : In the current study we have successfully established PDTX from 4 individual colorectal carcinoma and 4 liver metastases patients. We have used advanced pre-clinical imaging based on PET/CT (18FDG) and 9T MRI to functionally monitor tumor behavior in mice and compare this information to data obtained in the patient. All xenografts were evaluated using PERCIST criteria and compared to the original patient data. We further employ matrix-assisted laser desorption/ionization (MALDI) imaging technique to show for the first time a comparative metabolomic profile of the patient tumor and several generations of PDTX.

Results : Owing to a validated set of histological markers we confirm that the PDTX models have conserved histological features with the original tumor. With the preclinical imaging and the MALDI imaging technique we were able to determine the metabolic signature of the cancer cells and the stroma respectively, and we could assess the impact of generation-dependent evolution of the PDTX.
Conclusions : Our study contributes to a better understanding of the behavior of the tumor and its evolution in a model that can be useful for biomarker discovery, outcome prediction or treatment design.

BELGIAN PANCREATIC CLUB (BPC)

- P01 -

DOES INTRAOPERATIVE PANCREATOSCOPY AFFECT SURGICAL MANAGEMENT OF INTRADUCTAL PAPILLARY MUCINOUS TUMOR OF THE PANCREAS ? J. Navez (1), J. Gigot (2), C. Hubert (2), P. Deprez (3), C. Sempoux (4), N. Jabbour (2). (1) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Chirurgie et Transplantation Abdominale ; (2) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Chirurgie et Transplantation Abdominale ; (3) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Gastro-entérologie ; (4) Cliniques Universitaires St Luc, Brussels, Belgium, Anatomie Pathologique.

Introduction : Because of the potential malignant growth of intraductal papillary mucinous tumor of the pancreas (IPMTP), precise diagnosis of malignant lesions is essential for complete surgical resection.
Aim : The study aimed at reporting our extended experience of intraoperative pancreatoscopy for IPMTP, evaluating the impact on the perioperative therapeutic decision.
Methods : Between 1991 and 2013, 21 patients with IPMTP treated by pancreatectomy were retrospectively reviewed. Those with dilated pancreatic duct underwent intraoperative pancreatoscopy performed with an ultrathin flexible endoscope and biopsy forceps. All specimens of any suspicious lesions underwent frozen section analysis.
Results : Intraoperative pancreatoscopy with intraductal biopsies was performed safely and easily in all patients. Intraoperative pancreatoscopy detected 8 cases of IPMTP lesions, undetected preoperatively. In 5 cases (24%), initially planned surgical resection was modified secondary to intraoperative pancreatoscopy. At pathology, 3 of them had carcinoma in situ, 1 had invasive carcinoma, and 1 had invasive carcinoma with lymph nodes involvement. Mortality rate at last follow-up was 9,5%, only one patient with invasive carcinoma at initial pathology (pT3 N1) died of recurrence in the lungs.
Conclusions : Intraoperative pancreatoscopy of the Wirsung duct have significant role in the surgical management of patients with intraductal papillary mucinous tumor of the pancreas and should be used in all cases with dilated duct.

- P02 -

OBSERVATIONAL STUDY ON CHRONIC PANCREATITIS IN BELGIUM. PRELIMINARY RESULTS. M. Delhaye (1), C. Musala (1), M. Arvanitakis (1), W. Van Steenbergen (2), V. Putzeys (3), G. Roeyen (4), E. Cesmeli (5), P. Deprez (6). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology, Hepatopancreatology and Digestive Oncology ; (2) UZ Leuven Gasthuisberg, Leuven, Belgium, Gastroenterology ; (3) CHR La Citadelle, Liège, Belgium, Gastroenterology ; (4) UZ Antwerpen, Antwerp, Belgium, Department of Hepatobiliary, Endocrine and Transplantation Surgery ; (5) UZ Gent, Gent, Belgium, Gastroenterology ; (6) Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, Hepato-gastroenterology.

Chronic pancreatitis (CP) is a rare disorder with limited population-based epidemiologic data in Belgium. The aims of this multicenter observational study, including 6 university hospitals throughout Belgium, are to evaluate the prevalence and causes of CP, the associated endocrine/exocrine insufficiencies and the therapeutic management of patients with CP in Belgium. Methods All patients with CP diagnosed by imaging procedures were prospectively included in this study since September 1, 2014. At the time of out-patient visit or in-patient admission, data about etiology, age at onset of symptoms, body mass index (BMI), alcohol consumption, smoking, diabetes, clinical steatorrhea, treatment (medical, endoscopic, surgical) and Izbicki pain score were recorded. Results Between September 1, 2014 and November 30, 2014, a total of 306 patients (80 females / 226 males) with CP were included. Median age at symptoms onset was 47 y (0-87) and median duration of disease at the time of inclusion was 8 y (0-41). Etiologic risk factors according to the TIGAR-0 classification system were Toxic in 69%, Idiopathic in 17%, Genetic in 4%, Autoimmune in 4%, Recurrent and severe acute pancreatitis in 2% and Obstructive in 4% of the cases. The median Izbicki pain score assessed during the last year before inclusion was 25/100 (0-100). Diabetes was recorded in 132 patients (43%) and clinical steatorrhea in 117 patients (39%). Current smoking and ongoing alcohol abuse were reported in 57% and 16% of patients respectively ($p < 0.001$). Endoscopic therapy and surgery were performed in 83% and 18% of patients respectively ($p < 0.001$) with some significant differences between centres. Ongoing endotherapy was recorded in 131 patients (44%). Duration of disease was significantly longer for patients who developed ID diabetes (11 y vs 7 y for patients without ID diabetes ; $p < 0.001$) or exocrine insufficiency (10 y vs 8 y for patients without exocrine insufficiency ; $p = 0.041$). Idiopathic and autoimmune CP were less frequently associated with endocrine/exocrine insufficiencies than other causes of CP (29% / 24% compared to 45% / 45% respectively ; $p < 0.001$). Patients with previous or current alcohol abuse had a lower BMI (22 vs 25 ; $p < 0.001$), a higher Izbicki pain score (37 vs 25 ; $p = 0.048$), especially a higher score for the disease-related inability to work (44 vs 19 ; $p < 0.001$). Current smokers had a lower BMI (22 vs 25 ; $p < 0.001$) and a higher Izbicki pain score (38 vs 24 (no smoking) vs 17 (previous smoking) ; $p < 0.001$). Conclusions These preliminary observations provided a better knowledge regarding the prevalence of CP in Belgium, determined the most likely etiologic factors of

CP, identified the frequency of pancreatic insufficiencies and revealed significant associations between environmental factors and pain scores and significant differences between centres concerning therapeutic management of such patients.

- P03 -

REVISED CLASSIFICATION OF ACUTE PANCREATITIS : IMPACT ON CLINICAL MANAGEMENT. E. Cesmeli, UZ Gent, Gent, Belgium.

Acute pancreatitis(AP) is a heterogeneous disease which usually runs a mild clinical course. A subset of patients however develops severe disease that is independent of the degree of the initial insult or etiology, with high morbidity and mortality up to 43%. It is important at the onset of disease to categorize patients with different severity grades in order to monitor,triage and plan the best possible management strategy in an individualized manner. In this regard the clinically based 1992 Atlanta Classification was an important step to describe AP (1). Definitions were given regarding local (acute fluid collection,acute pseudocyst, pancreatic necrosis,pancreatic abscess) and systemic (shock,pulmonary insufficiency,renal failure and gastrointestinal bleeding) complications and two categories of severity(mild and severe) were recognized. Although this classification was widely accepted, some of the definitions turned out to be confusing and not universal(2). Since the initial publication of the Atlanta Classification there was also a better understanding of the pathophyiology of the disease as well as improved diagnostic imaging. After a wide consultation among pancreatologists, the Atlanta Classification was revised in 2012 (3). In the Revised Atlanta Classification(RAC) two phases of acute pancreatitis are identified: early and late. The severity is classified as mild,moderate or severe. Mild pancreatitis has no organ failure,local or systemic complications. Moderately severe acute pancreatitis is defined by the presence of transient organ failure,local complications or exacerbation of co-morbid disease. Severe acute pancreatitis is defined by persistent organ failure (> 48 h). Local complications are peripancreatic fluid collections,pancreatic and peripancreatic necrosis (sterile or infected),pseudocyst and walled-off necrosis(sterile or infected).Exacerbation of pre-existing co-morbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis is defined as a systemic complication. To define organ failure three organ systems should be assessed: respiratory,cardiovascular and renal. The aim of the RAC is to define the different local and systemic complications of the disease and predict interventions and outcomes. The clinical utility of the definitions proposed by the RAC seems to be valid and the association of this classification system with clinical outcomes of patients has already been prospectively demonstrated. It will no doubt further improve the stratification of patients and reporting of clinical research. The RAC is a major advance in standardazing the terminology, but there are some minor issues that need to be adressed in the near future: moderately severe AP includes local complications with different prognosis, patients with early persistent organ failure could represent a specific subgroup in the classification system, there are difficulties in redefining systemic complications,… (4) The co-existence of another new classification system, the so called determinant-based classification (DBC) can lead to some confusion in the clinical management of AP. This classification was also an international initiative to overcome the limitations of the initial Atlanta Classification (5). The differences of DBC with RAC are few and the two systems are probably complementary. The RAC however is broader in scope and seems to be more relevant to the day-to-day clinical care of patients. The presence of this second classification can possibly affect the widespread implementation of the RAC.

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- P04 -

IMAGING IN ACUTE PANCREATITIS. M.A. Bali, ULB Erasme, Brussels, Belgium.

- P05 -

MEDICAL TREATMENT OF SEVERE PANCREATITIS. A. Wilmer, KU Leuven, Leuven, Belgium.

To a large extent the remarkable mortality of 10-30% in patients with severe acute pancreatitis (SAP) is determined by the development of persistent organ failure (POF) and/or infected pancreatic necrosis (IPN). The absolute influence on mortality of POF and IPN is comparable but the relative risk of mortality doubles when both are present. In the intensive care unit the medical approach to SAP aims at preventing and treating POF and IPN. Goal- and disease-directed, supportive options for this purpose include adequate fluid resuscitation, monitoring of intra-abdominal pressure, instituting an adequate nutritional plan, judicious use of antimicrobials and timely choice of draining procedures including ERCP. IAP/APA guidelines from 2013 recommend an initial infusion rate of 5-10 ml/kg/h until resuscitation goals are reached, a recommendation based mainly on low-quality evidence. The most recent data support a more restrictive strategy and invasive hemodynamic monitoring can very likely optimize the achievement of both resuscitation and de-resuscitation goals and thereby improve outcome. As compared to normal saline, balanced electrolyte solutions seem to be associated with less inflammation. With a prevalence of 37-59% intra-abdominal hypertension has been again confirmed to be a risk factor for multiple organ failure. In SAP specific monitoring for IAH equates with good clinical practice. In cases of abdominal compartment syndrome surgical decompression is likely indicated. For good reasons, early enteral nutrition within 24 h of admission remains an important aspect of medical care. Recent data indicate that feeding with nasogastric tubes is not associated with more complications than with nasojejunal tubes, but trials with larger samples seem desirable before wide adoption of this practice. In a very recent large randomized trial, an oral diet initiated 72 h after admission versus early nasoenteral feeding did not show significant differences regarding the rate of infection or mortality. Obviously, in ICU patients oral nutrition is limited to those that are not mechanically ventilated. At this point, probiotics or immunonutrition have no place in SAP. Prophylactic antibiotics are not recommended by current guidelines and the evidence for full selective digestive decontamination in SAP is too limited for implementation in routine care. Positive cultures are not always necessary for the diagnosis of infection of (peri)- pancreatic necrosis. Once this event is diagnosed, multi-disciplinary consultation for the appropriate drainage procedure is mandatory. During the presentation the issues presented above will be discussed in detail.

- P06 -

RADIOLOGIC, SURGICAL, AND ENDOSCOPIC MANAGEMENT OF NECROTIZING PANCREATITIS. H.C. van Santvoort, University of Utrecht, Utrecht, The Netherlands.

- P07 -

NATURAL HISTORY OF SEROUS CYSTADENOMA. B. Bernier (1), M. Arvanitaki (2), M. Bali (3), C. Matos (3), P. Demetter (4), J. Deviere (2), M. Delhaye (2). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology, Hepatogastroenterology and Digestive Oncology ; (2) CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology, Hepatopancreatology and Digestive Oncology ; (3) CUB Hôpital Erasme, ULB, Brussels, Belgium, Radiology ; (4) CUB Hôpital Erasme, ULB, Brussels, Belgium, Pathology.

Introduction : The serous cystadenomas (SC) of the pancreas are rare tumors and almost always benign. Usually incidentally discovered, some SC may compress adjacent organs and cause various biliopancreatic symptoms. There is no consensus in the literature regarding indications of surgical resection of these tumors and about the follow-up of these patients.
Aim : The aim of this study was to identify predictive factors of tumoral growth and to clarify indications of surgery.
Methods : We retrospectively studied 54 patients (42 women, 12 men : 59.7+/- 16.6 years) diagnosed with SC of the pancreas at the Erasme Hospital between 04/2000 and 04/2013. We compared patients with SC increasing in size and those with a stable SC or decreasing in size. We also compared patients who had surgery and patients who did not have surgery.
Results : A typical SC was identified by imaging procedure (CT scan / MRI) in only 18.5% (10/54) of the cases. EUS with analysis of the cystic fluid increased the diagnostic sensitivity of SC to 78.7% (37/47). Occurrence of symptoms during a median follow-up of 6 years was statistically associated with tumor growth that was observed in 18 patients ($p = 0.049$; OR 4.4). Surgical resection was performed in 8 patients (for uncertain diagnosis in $n = 6$, for symptoms due to compression of adjacent organs in $n = 2$). Operated patients had a higher CEA level in cystic fluid as compared with non-operated patients ($p = 0.058$).
Conclusions : A correct diagnosis of pancreatic SC required usually imaging procedures as well as cystic fluid analysis. The clinical and radiological follow-up of patients with SC can identify patients at risk of tumor growth. Surgical resection should be proposed to a minority of patients.

- P08 -

NEEDLE-BASED CONFOCAL LASER ENDOMICROSCOPY FOR PANCREATIC LESIONS : PRELIMINARY RESULTS IN A TERTIARY CENTER. J. Chevaux (1), C. Galant (2), T. Aouattah (1), A. Jouret-Mourin (3), P. Deprez (1), I. Borbath (1). (1)Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium Gastro-enterology ; (2) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Pathology ; (3) Cliniques Universitaires Saint-Luc, UCL, Woluwe-Saint-Lambert, Belgium, Pathology.

Introduction : Needle-based confocal laser endomicroscopy (nCLE) is an imaging technique, which enables microscopic sighting of pancreatic lesions, in vivo and in real-time, during an EUS-FNA procedure. Recent studies (INSPECT, CONTACT I) have identified reliable nCLE descriptive features particularly for cystic lesions.
Aim : This on-going prospective study aims at evaluating diagnostic yield of nCLE in pancreatic lesions.
Methods : Nine patients with a pancreatic lesion of unknown nature were included from 06/2014 to 11/2014. After I.V. injection of fluorescein, puncture was done with a 19G needle with the nCLE probe preloaded (AQ-Flex, Cellvizio, Mauna Kea). After examination by nCLE, aspiration was done in the same track to compare images and histological results. nCLE sequences were visualized by two gastro-enterologists and histological diagnoses were assessed according to nCLE sequences. nCLE criteria were papillae for IPMN, superficial vascular network for serous cystadenoma (SCA), a field of bright and black particles for pseudocyst (PC), an epithelial border for mucinous cystadenoma (MCA) and dark cells aggregates with pseudo-glandular aspects with straight hyperdense elements more or less thick (= tumoral fibrosis) for adenocarcinoma (ADC). Final diagnoses were based on cross-sectional imaging, cytology and histology findings and clinical follow-up.
Results : Median age of patients was 62 years (IQR, 51-72) and 4 patients were male (44%). Median size of lesions was 36 mm (IQR, 25-40), 7 were cystic and 2 solid. Seven lesions were in the head and 2 in the body of the pancreas. There were 1 SCA, 2 PC, 2 IPMN, 2 MCA and 2 ADK. Median duration of procedure was 15 minutes (IQR, 10-20). EUS-FNA was feasible in every case and difficult in two cases. nCLE probe retrieval from the 19G needle was difficult in one case. One mild pancreatitis occurred. nCLE diagnosis was true in 7 lesions and indeterminate in 2 (PC and ADK). No wrong nCLE diagnosis was observed. Specificity of the nCLE criteria was 100% for the diagnosis of cystic lesion .
Conclusions : Our preliminary results are promising, particularly for cystic lesions with an excellent specificity, as observed previously. nCLE could therefore facilitate the diagnosis of these lesions by bringing real-time information. This Prospective study is still ongoing.

- P09 -

SINGLE VERSUS MULTIPLE PANCREATIC STENTS IN CHRONIC PANCREATITIS : A RANDOMIZED CLINICAL STUDY. C. Musala (1), C. Musala (2), M. Arvanitaki (1), J. Deviere (1), M. Delhaye (1). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology ; (2) CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology.

Introduction : Placement of pancreatic stents (PS) in chronic pancreatitis (CP) has been shown to improve pain.
Aim : This study aims to assess if the placement of multiple stents is associated with a better outcome than a single stent.
Methods : Thirty-three patients with painful CP and a distal stricture were randomized (1 vs 2 stents) and prospectively followed. Stents were removed after stricture resolution, if the patient was pain free (Izbicki pain score (IS) < 10/100). Patients were followed-up until the last visit, surgery or death. Data were analyzed by intention-to-treat and per-protocols analysis. The primary end points were to evaluate the rate of stent removal and the improvement in the IS at the end of follow-up (FU). Secondary end points included duration of stenting, number of procedures, need for restenting, and endocrine/ exocrine insufficiencies.
Results : 33 patients were randomized in a blinded fashion (8 women, 25 men ; median age 53). Median baseline IS was 47/100. 18 patients were enrolled in the single stent group, from which 2 were excluded (1 loss of FU, 1 duration of stenting < 6 months) and 15 patients were included in the multiple stents group, from which 7 were excluded (1 pancreatic cancer, 3 loss of FU, 3 duration of stenting < 6 months). Baseline characteristics were similar in both groups. During the study period, 10 patients changed of groups (9 passed from single to multiple and 1 from multiple to single). Migration was observed in 4 patients. Stent removal was possible in 17/24 patients (70%) without significant difference between the 2 groups in intention-to-treat (12/16, 75% vs 5/8, 62.5%, p :0.41), nor in per-protocol analysis (5/8, 62.5% vs 12/16, 75%, p :0.41). Median stenting duration was 19 months (1-68) and FU after removal was 27.5 months (1-111) with no significant difference between both groups. Surgery was required in 3 patients. We observed an improvement of IS (median :-100%(-100,+20)) at the end of FU for all patients in whom stents were removed/migrated and had not been operated on (n = 21). Median IS at the end of FU was 0/100 (0-88). The total median number of endoscopic procedures was 3 (1-13) and restenting was required after stent removal or migration in 7/21 patients (33%) without difference according to stenting group. Endocrine/ exocrine insufficiencies at the end of FU were comparable in both groups (8/24, 33%).

Conclusions : Endoscopic therapy with stenting is efficient regarding pain resolution, even after stent removal. The study failed to show any difference between single or multiple pancreatic stenting. However, a large proportion of patients randomized in single stent group changed for multiple stents because of pain at the time of first stent exchange. An important limitation of the study is the small patients number. More patients should be included for definitive results.

- P10 -

DELAYED GASTRIC EMPTYING AFTER PANCREATODUODENECTOMY. C. Vandermeeren (1), P. Loi (2), J. Closset (2). (1) CHU de Charleroi, Charleroi, Belgium, Digestive Surgery ; (2) CUB Hôpital Erasme, ULB, Brussels, Belgium, Digestive Surgery.

Introduction : Delayed gastric emptying (DGE) is one of the most frequent complication after pancreatoduodenectomy and significantly contributes to its related postoperative morbidity. Postoperative course is affected by increasing hospital length of stay, decreasing patients' quality of life and delaying neoadjuvant treatment introduction.
Aim : Clinical risk factors of DGE after pancreaticoduodenectomy remaining controversial, this study aims to investigate the factors that could influence the development of DGE in this type of surgery .
Methods : From January 2000 to December 2012, a total of 257 patients underwent, in the same centre, a pancreatoduodenectomy for pancreatic or periampullary cancer (51%), chronic pancreatitis (9%), or other indications (40%). This study included 257 patients and a total of 19 items were retrospectively extracted from their medical records. DGE (grade A, B and C) was defined by the International Study Group of Pancreatic Surgery classification. Univariate and multivariate analysis were performed to identify factors associated with DGE.
Results : Delayed gastric emptying occurred in 133 patients (51,8%), with 89 (66,9%), 27 (20,3%) and 17 (12,8%) with grade A, B and C respectively. By multivariate analysis, biliary fistula (OR = 8,87 ; IC 95% 2,07 à 37,99 ; p = 0,003), sepsis (OR = 8,02 ; IC 95% 3,22 à 19,99 ; p < 0,0001) or intra-abdominal collection (OR = 3,43 ; IC 95% 1,06 à 11,06 ; p = 0,039) were identified as independent risk factors for DGE, while reconstruction by pancreaticogastrostomy (OR = 0,32 ; IC 95% 0,16 à 0,64 ; p < 0,001) was indentified as a protective factor for DGE.
Conclusions : In our population, delayed gastric emptying was linked to the occurrence of postoperative intra-abdominal complications and reconstruction by pancreaticogastrostomy was beneficial by decreasing its incidence.. A multicentre study should be conducted.

- P11 -

QUALITY METRICS IN ONCOLOGICAL PANCREATIC SURGERY : IMPACT OF STANDARDIZATION OF SURGICAL TECHNIQUE IN A HIGH VOLUME TERTIARY CENTER. A. Vanlander (1), J. Verlinden (2), S. Libbrecht (2), F. Berrevoet (3). (1) UZ Gent, Gent, Belgium, Algemene en Hepatopancreaticobiliare Heelkunde ; (2) UZ Gent, Gent, Belgium, Algemene en Hepatopancreaticobiliaire Heelkunde ; (3) UZ Gent, Gent, Belgium, Algemene & Hepatopancreaticobiliaire Heelkunde.

Introduction : Pancreas cancer is the 4th cause of cancer death. Surgical resection is the optimal treatment. Outcome of surgical resections for pancreatic cancer seems to be superior when pancreaticoduodenectomies are performed by high-volume pancreatic surgeons practicing in high-volume hospitals. Complications following PD have a negative effect on quality of life and survival. However, acquiring accurate hospital specific data for comparison of outcomes remains a challenge. Furthermore, only recently established quality metrics have been reported.
Aim : It was the aim of this analysis to evaluate the impact of standardization of surgical technique and pre- and postoperative management on quality metrics in a tertiary referral center in Belgium.
Methods : From 1/1/2011 till 1/1/2014 all patients that underwent a pancreatic resection for oncological reasons were extracted from a prospective database. Following parameters were analysed : number of procedures per surgeon, indications, basic characteristics, operating time, type of procedure, lymph node ratio, major and minor complication rate including pancreatic fistula, delayed gastric emptying and infectious complications.
Results : In total 153 pancreatic resections for malignant disease were performed during this study period. 112 pancreaticoduodenectomies (PD), 28 body- and tail resections with splenectomy and 13 total pancreatectomies were performed. Mean operating time was 348 minutes ± 41 and mean hospital stay was 14 days. In all patients a standardized duct-to-mucosa pancreaticojejunostomy was performed. Postoperative complications consisted of 7.4% type A fistula (according to ISGPF classification), 2.6% type B and 0.7% type C fistula with reoperation. Using a standardized antecolic duodenoenterostomy delayed gastric emptying was only diagnosed in 6% of patients after PPPD. Fistula rate was higher in the tail and body- and tail resections when compared to PPPD.
Conclusions : When standardized perioperative care and surgical strategies can be implemented in large volume centers, low fistula rates can be achieved regardless the type of pancreatic anastomosis in contrast with current literature. Delayed

gastric emptying is no longer a significant problem using antecolic anastomoses and overall patient morbidity is acceptable and below 25% in this series. In current oncological care standardized treatment is the key to success.

- P12 -

(PRE-) DIABETES IS FREQUENTLY UNDIAGNOSED AND UNDERREPORTED IN PATIENTS REFERRED FOR PANCREATIC SURGERY. G. Roeyen (1), M. Jansen (2), T. Chapelle (2), K. De Greef (2), B. Bracke (2), V. Hartman (2), D. Ysebaert (2), C. De Block (3). (1) UZ Antwerpen, Edegem, Belgium, Hepatobiliairy Endocrine and Transplantation Surgery ; (2) UZ Antwerpen, Edegem, Belgium, Hepatobiliary, Endocrine and Transplantation Surgery ; (3) UZ Antwerpen, Edegem, Belgium, Endocrinology, Diabetology and Metabolic Disorders.

Aim : Since postoperative glycemic control has a major impact on outcome in pa1tients referred for pancreatic surgery, a preoperative evaluation of this glycemic status seems justified. Preoperative evaluation of glucose metabolism might also predict the postoperative glycemic control.
Methods : In a period of 21 months, 79 patients referred for oncologic pancreatic surgery or surgery for chronic pancreatitis have prospectively been screened for glycemic disturbances. The proportion of these patients not known with glycemic abnormalities, underwent an oral glucose tolerance test (OGTT) with a 75 gram glucose solution per os after an overnight fasting. Blood sampling for glucose, C-peptide, insulin and glucagon determination on 0, 15, 30, 45, 60, 90, 120 minutes and HbA1c level were evaluated. To interpret the results, the American Diabetes Association criteria for (pre-) diabetes have been used.
Results : 79 patients have been included in this study. 20/79 were diabetes patients known before referral and consequently 59/79 had no known glycemic disturbances. The OGTT was performed in all these 59 patients. OGTT results were normal in 42.4% and 57.6% of patients had abnormal results (18.6% Impaired Glucose tolerance, 6.7% a combination of Impaired Fasting Glucose and Impaired Glucose Tolerance and 32.2% newly diagnosed diabetes). HbA1c level was < 6.5% in 79.4% of the patients diagnosed with glycemic abnormalities by this OGTT. 20.6% has an HbA1c level ≥ 6.5 %.
Conclusions : In patients referred for oncologic pancreatic surgery or surgery for chronic pancreatitis and not known preoperatively with glycemic disturbances, 57.6% has prediabetes or diabetes (criteria American Diabetes Association). This (pre-)diabetes is frequently undiagnosed and therefore underreported.

PATHOLOGY

- R01 -

CORRELATION OF ENDOSCOPIC AND PATHOLOGICAL FEATURES OF GASTRO-INTESTINAL LYMPHOMAS. A. Camboni (1), G. Mavrogenis (2), H. Piessevaux (3), P. Deprez (4), M. Denis (3), O. Dewit (3), A. Jouret-Mourin (5). (1) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Pathology ; (2) Grand Hopital de Charleroi, Charleroi, Belgium, Department of Gastroenterology ; (3) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Hepato-Gastroenterology ; (4) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Hepato-Gastroenterology ; (5) Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, Department of Pathology.

The gastrointestinal (GI) tract is the most common extranodal site of lymphoma involvement. Primary lymphomas of the GI tract are rare, while secondary GI involvement is relatively common. Despite their rarity, primary lymphomas of the GI tract are important since their evaluation, diagnosis, management and prognosis are distinct from that of lymphoma at other sites and other cancers of the GI tract. In the last years many improvements have been done in the management of GI lymphomas. The new and more accurate endoscopic techniques enabled to better describe the endoscopic features of GI lymphomas with important contributions in the diagnosis, therapy and follow-up. Moreover, a better insight into GI lymphomas etiology and molecular signaling pathways also allowed an improvement in their management, in particular for the diagnosis and for the treatment strategies. We describe the endoscopic presentation of GI lymphomas according to the involved site and lymphoma subtypes. We also discuss the histo-pathological and molecular aspects of all subtypes of GI lymphomas. A. Camboni and G. Mavrogenis contributed equally to this work.

- R02 -

UNUSUAL MASS IN THE MESENTERY OF THE ILEUM. N. Nathalie. Hôpital Civil Marie Curie, Lodelinsart, Belgium, Pathology.

Introduction : We report the case of a 69-year-old female admitted for repetitive occlusive syndrome.
Aim : A total colonoscopy was performed and revealed two tubular adenoma polyps with low grade dysplasia in the large intestine and a polypoid aspect of the ceacum.
Methods : A pelvic-abdominal CT SCAN revealed small bowel distention associated with thickening of the distant part of the ileum wall and caecum, submucosal edema and fat infiltration. A coelioscopic ileocolectomy was performed.
Results : Macroscopic examination revealed a 10cm poorly defined fatty tumor of the ileal mesentery. Microscopically, the lesion was characterized by an irregulary admixture of mature adipose tissue and smooth muscle fibers leading to the diagnosis of myolipoma.
Conclusions : Myolipomas are very rare benign lipomatous soft tissus tumors, mostly located in the abdominal cavity, inguinal areas or retroperitoneum.

- R03 -

IPILIMUMAB-INDUCED ENTEROCOLITIS : DESCRIPTION OF HISTOPATHOLOGICAL OBSERVATIONS IN 6 CASES AND SELECTED LITERATURE REVIEW. A. Hoorens (1), Y. Janssen (2), B. Neyns (2). (1) UZ Brussel, Brussels, Belgium, Pathology ; (2) UZ Brussel, Brussels, Belgium, Medical Oncology.

Introduction : Ipilimumab is a fully human IgG1 monoclonal antibody that blocks the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) receptor, a key negative regulator of the anti-tumour immune response. Ipilimumab at a dose of 3 mg/kg every 3 weeks for a total of 4 administrations, improves the overall survival in patients with advanced melanoma and is registered for this indication. During ipilimumab treatment a unique set of adverse effects may occur (commonly referred to as “immune-related adverse effects” [irAE]). Across clinical trials irAE have been reported to occur in up to 40% of patients. The second most commonly reported ipilimumab-related side effect, after dermatologic toxicities, is diarrhoea associated with enterocolitis. If left unrecognized or untreated, ipilimumab-related enterocolitis can rapidly escalate in severity and lead to serious life-threatening complications such as bowel perforation.
Aim : To describe the histopathological spectrum of ipilimumab-induced enterocolitis in Belgian patients treated with ipilimumab.
Methods : The files of six patients diagnosed with ipilimumab-related colitis in our hospital were reviewed. Slides were re-evaluated and all alterations were reported. In addition, the literature was reviewed for enterocolitis associated with ipilimumab treatment to provide a fully detailed description of the histopathological alterations observed with this type of irAE related to ipilimumab.

Results : In most patients diffuse colitis with relative rectal sparing was observed during endoscopy. Microscopically there was an increase in inflammatory cells with cryptitis, without significant architectural alterations or other signs of chronicity, discriminating it from IBD. Colitis was usually more severe and more diffuse, compared to what is normally observed in acute self-limited (infectious) colitis. The inflammatory process has, however, also been reported as patchy and segmental in distribution. In one of our patients microgranulomas were observed. One of our patients developed toxic megacolon and subsequent small bowel perforation requiring colectomy and partial resection of the small bowel, despite adequate treatment with high dose corticosteroids and infliximab.
Conclusions : As the use of ipilimumab, an anti-CTLA-4 directed immune modulating antibody, for treatment of advanced melanoma becomes more common, pathologists must be aware of its potential to induce immune-related enterocolitis and of the histologic appearance of ipilimumab-iduced bowel toxicity. If left unrecognized these adverse effects can rapidly escalate in severity and even lead to intestinal perforation.

- R04 -

DIAGNOSIS OF CROHN'S DISEASE OF THE ILEAL POUCH. H. Vafa (1), M. Ferrante (2), A. Van Gossum (1), D. Franchimont (1), R. Maréchal (1), L. Amininejad (1), G. De Hertogh (3), P. Demetter (4). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology Department ; (2) UZ Leuven Gasthuisberg, Leuven, Belgium, Gastroenterology Department ; (3) University of Leuven, Leuven, Belgium, Pathology Department ; (4) CUB Hôpital Erasme, ULB, Brussels, Belgium, Gastroenterology Department.

Introduction : Crohn's disease (CD) of the pouch in patients with an ileal pouch-anal anastomosis (IPAA) for refractory ulcerative colitis (UC) or dysplasia is poorly described and therefore a debated entity. The only available definition of CD related complications of the pouch in literature includes patients presenting with pouch or perineal fistula, prepouch ileitis or pouch stenosis. Since these complications often lead to pouch failure, it is important to establish clinical, endoscopic and histological diagnostic criteria which are currently lacking.
Aim : We aimed to precise diagnostic criteria for CD related complications of the pouch.
Methods : Patients with UC who underwent total proctocolectomy with IPAA in two tertiary centres were identified retrospectively. Patients with a diagnosis of pouchitis having available pouch biopsy samples were selected among them. Three group of patients were distinguished : acute pouchitis (n = 8), chronic refractory pouchitis (refractory to four weeks of antibiotics (n = 11)) and CD related complications of the pouch (n = 23). CD related complications of the pouch was defined based on the only available definition (perineal or pouch fistula, prepouch ileitis and/or pouch stenosis). Pouch biopsies were reviewed by two separate pathologists using the histological 14-point Heidelberg Pouchitis Activity scoring system including villous atrophy, ulcers, polymorphonuclear cells, monocytes, pseudopyloric metaplasia and granulomas. Univariate and multivariate analysis were performed using SPSS comparing the demographic and histological findings in the pouch between the three groups.
Results : In univariate and multivariate analysis no single clinical variable came out as a specific factor predicting CD related complications of the pouch, and no single histological item was found to be a specific hallmark for CD related complications of the pouch. By using a ROC curve, a cut-off value of 10 was found with a specificity of 88.2% and a sensitivity of 43.4% for the diagnosis of CD related complications of the pouch. The Positive Predictive Value (PPV) for this test was 83.3% and the Negative Predictive Value (NPV) was 53.6%.
Conclusions : No single histological item was found to be a specific hallmark for CD related complications of the pouch. A cut-off of 10 on the histological Heidelberg Pouchitis Activity Score showed a high specificity and PPV for the diagnosis of CD related complication of the pouch. This cut-off should be validated in a large prospective study.

- R05 -

PROGNOSTIC IMPACT OF QUALITY CONTROL OF TOTAL MESORECTAL EXCISION SPECIMEN EVALUATION. P. Demetter (1), A. Jouret-Mourin (2), C. Sempoux (2), A. Hoorens (3), N. Nagy (4), C. Cuvelier (5), T. Vandendael (6), N. Van Damme (6), G. Silversmit (6), F. Penninckx (7). (1) CUB Hôpital Erasme, ULB, Brussels, Belgium, Pathology Department ; (2) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Pathology Department ; (3) UZ Brussel, Jette, Belgium, Pathology Department ; (4) CHU de Charleroi, Charleroi, Belgium, Pathology Department ; (5) UZ Gent, Gent, Belgium, Pathology Department ; (6) (7) UZ Leuven Gasthuisberg, Leuven, Belgium, Abdominal Surgery Department.

Introduction : In order to audit the quality of total mesorectal excision (TME), a central pathology review has been organised within the framework of the Belgian PROCARE (Project on Cancer of the Rectum) project. A fair to moderate concordance in interpretation of the TME plane by local pathologists, sensibilised for the aims and procedures of PROCARE by workshops and communications at national meetings, and the review panel has been observed.

Aim : We wanted to explore the potential impact of TME grading by an expert panel on oncological outcome.
Methods : Based on photographic material, TME quality was reviewed in 482 patients. For the present study, 53 patients with a stage IV tumour and 2 patients with unknown incidence date were excluded, resulting in a study population of 427 patients. Quality assessment was based on the classic three-graded score : mesorectal, intramesorectal and muscularis propria resection. Both local and expert panel TME quality grading were used as predictors in univariable Cox regression models for 4 outcome variables : local recurrence, distant metastasis, overall survival and disease-free survival. Prediction error differences between local and expert grading were tested using the method of van de Wiel (van de Wiel et al, Biostatistics 2009). Brier scores at 1, 3 and 5 years for both predictors were used as a measure for the prediction error.
Results : Resection planes were concordant in 238 cases (56%). Downgrading from mesorectal to muscularis propria resection was noted in 28 cases (7%). There were no significant differences in the prediction error between the two models ; both local and expert TME quality grading predicted equally well the outcome variables.
Conclusions : Grades of TME quality as reported by local pathologists can be used for outcome analysis. Differences in judgement of the TME resection plane are limited and do not have a significant impact on predicting the oncological outcome of a patient cohort. Quality control of TME assessment does not seem to be warranted in the context of improvement projects if pathologists are adequately trained.

- R06 -

PREOPERATIVE TREATMENT MODIFIES THE IMMUNE MICROENVIRONNEMENT OF LIVER COLORECTAL METASTASES. M. Vandeneynde (1), B. Mlecnik (2), J. Machiels (3), D. Debetancourt (4), G. Bindea (2), G. Pairet (5), A. Jouret-Mourin (5), C. Sempoux (5), J. Gigot (6), C. Hubert (6), Y. Humblet (3), J. Carrasco (7), N. Haicheur (8), F. Marliot (8), F. Pagès (8), J. Galon (2). (1) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Gastroenterology, Oncology ; (2) Centre de Recherche des Cordeliers, Paris, France ; (3) Cliniques Universitaires Saint-Luc, Belgium, Oncology ; (4) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Centre du Cancer ; (5) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Pathology ; (6) Cliniques Universitaires Saint-Luc, Brussels, Belgium, Hepato-bilio-pancreatic Surgery ; (7) Grand Hopital de Charleroi, Charleroi, Belgium, Oncology ; (8) Hôpital Européen Georges Pompidou, Paris, France, Immunology.

Introduction : We previously reported that an adaptive Th1 immune response (CD3/CD8/CD45RO T-cells) observed in resected primary colorectal tumor and liver colorectal metastases (LCM) is an important prognostic factor. B and FoxP3 regulatory lymphocytes participate to the modulation of this response.
Aim : We aimed to investigate whether the preoperative treatments influenced the quality and the density of the immune infiltrates previously reported in the LCM.
Methods : We used a cohort of metastatic colorectal patients (n = 107) engaged for curative liver surgery with available FFPE blocks for all resected LCM to confirm the prognostic impact of the immune response. Among this cohort of 338 LCMs, 46 were completely resected after chemotherapy (CT) alone, 130 after CT + anti-VEGF, 118 after CT + anti-EGFR and 44 after surgery alone. LCMs were analyzed for histological response according the Tumor Regression Grade (TRG) and regrouped as Response (R, TRG1-3) or No Response (NR, TRG4-5). The density of CD3+ (T-cells), CD8+ (cytotoxic), CD45RO+ (memory), CD20+ (B-cells) and FoxP3+ (regulatory) in the core (CT) and invasive margin (IM) of all LCM was quantified on immunostained slides. The mean density value (CT/IM) was calculated for each marker with a dedicated image analysis software on whole-slide imaging. Comparisons were made using the Wilcoxon-Mann-Whitney test.
Results : LCMs showing R (compared to NR and untreated LCM) were more frequently associated with a high immune infiltrate for CD3+ (CT : $p < 0.005$; IM : $p < 0.05$), CD8+ (CT : $p < 0.005$; IM : $p < 0.005$) and CD20+ (CT : $p < 0.05$). Conversely, high FoxP3+ density in the CT and IM was related to NR and untreated LCMs ($p < 0.01$). LCMs treated with an anti-EGFR therapy showed higher densities of CD3+ (CT : $p < 0.005$; IM : $p < 0.01$), CD8+ (CT : $p < 0.005$), CD45RO+ (CT : $p < 0.005$), CD20+ (CT : $p < 0.005$) and FoxP3+ (CT : $p < 0.05$; IM : $p < 0.005$) compared to other treatments and untreated LCMs.
Conclusions : Preoperative treatment modifies the LCM immune microenvironnement. LCMs with a histological response show a cytotoxic immune response (CD3+/CD8+) with associated B-cells (CD20+) and downregulated Tregs (FoxP3+). The use of an anti-EGFR therapy significantly increases immune infiltration in the CT.

- R07 -

GENETIC DISSIMILARITY BETWEEN PRIMARY COLORECTAL CARCINOMA AND THEIR LYMPH NODE METASTASES : PLOIDY, P53, BCL-2 AND C-MYC EXPRESSION. A. Foda (1), K. Zalata (1), M. Elshal (2). (1) Mansoura Gastroentrology Center, Mansoura, Egypt, Pathology Department ; (2) Sadat City University, Egypt, Molecular Biology Department, Genetic Engineering and Biotechnology Institute.

Introduction : The current paradigm of metastasis proposes that rare cells within primary tumors acquire metastatic capability via sequential mutations, suggesting that metastases are genetically dissimilar from their primary tumors. Metastasis to regional lymph nodes (LNs) is an important prognostic factor and is used for the staging of colorectal carcinoma (CRC). p53, bcl-2 and c-myc are important regulating elements for apoptosis of the tumor. Mutations affecting these genes have many roles in cancer development and progression. Additionally, it is proposed that DNA aneuploidy is ultimately responsible for the activation of proto-oncogenes and the inactivation of tumor suppressor genes leading to uncontrolled proliferative activity. It has been suggested that characterization of the genomic abnormalities acquired during colorectal tumorigenesis might provide additional prognostic information. Greater understanding of the metastatic phenotype from cellular and molecular analyses will provide a rational approach for controlling cancer.
Aim : To date, studies of aneuploidy, p53, Bcl-2 and c-myc expression in CRC have focused on their expression in primary tumors. Currently, there are no data regarding the expression of these markers in the corresponding LN metastases. Therefore, our goal was to compare aneuploidy, the expression of p53, Bcl-2 and c-myc in primary CRC and their corresponding LN metastases from the same patients.
Methods : This retrospective study was carried out in surgical pathology lab at Gastroenterology Center, Mansoura, Egypt. Thirty-six primary CRCs and their corresponding LN metastases were studied. All clinicopathological data of these 36 cases were revised with re-examination of all their slides. The patients didn't receive any neoadjuvant therapy. DNA flow cytometry and immunostaining of p53, Bcl-2 and c-myc were carried out on the primary tumors and their corresponding LN metastases.
Results : It was found that there is very low probability that the histological patterns of primary tumors and LN metastases are independent ($p < 0.001$). Metastatic tumors were significantly more diffusely positive for p53 than the primary tumors ($p < 0.001$). Conversely, primary tumors were significantly more diffusely positive for c-myc than metastatic tumors ($p = 0.011$). No significant difference was found between the LNs and the primary tumors in Bcl-2 positivity ($p = 0.538$) and DNA aneuploidy ($p = 0.35$), with a tendency towards negative bcl2 and less aneuploidy in LN metastases than primary tumors.
Conclusions : LN metastatic colorectal carcinoma have a tendency of being less differentiated, with a higher incidence of diffuse p53 staining, lower incidence of bcl-2 staining and less aneuploidy in comparison to their primary counterparts suggesting a more aggressive biological behavior, which could indicate the necessity for more aggressive adjuvant therapy. This incomplete concordance in gene expression observed could be explained by gene expression modulation by the microenvironment in which the cancer cells reside.

- R12 -

ABERRANT EXPRESSION OF C-KIT AND DOG-1 IN MUCINOUS AND NON-MUCINOUS COLORECTAL CARCINOMAS AND RELATION TO CLINICOPATHOLOGICAL FEATURES AND PROGNOSIS. A. Foda (1), M. Mohamed (1). (1) Mansoura Gastroentrology Center, Mansoura, Egypt, Pathology Department.

Introduction : c-KIT and DOG-1 are two highly-expressed proteins in gastrointestinal stromal tumors (GISTs). It is now well known that some genes and proteins are aberrantly expressed in colorectal carcinoma (CRC) as IGF2, CD133, E-cadherin, and S100A4 among others, with relations to prognosis. We hypothesized that c-KIT and DOG-1 can be aberrantly expressed in a considerable proportion of CRC cases. To the best of our knowledge, c-KIT and DOG-1 were not investigated in large number of CRC cases.
Aim : This study aims to investigate expression of c-KIT and DOG-1 in colorectal mucinous adenocarcinoma (MA) and non-mucinous adenocarcinoma (NMA) using manual tissue microarray technique.
Methods : Files of all resected CRC cases in surgical pathology lab at Gastroenterology Center, Mansoura, Egypt, were revised during the period from 2007 to 2011. MA cases were selected and revised. Cases with incomplete clinical data and those that were composed completely of pools of mucin with very few epithelial cells were excluded. Seventy five cases with MA were fulfilling selection criteria. Another 75 cases of NMA were chosen randomly for comparison from the same period. The patients didn't receive any neoadjuvant therapy. All clinicopathological data of these 150 cases were revised with re-examination of all their slides. Three high density manual tissue microarrays were constructed using modified mechanical pencil tips technique and immunohistochemistry for c-KIT and DOG-1 was done.
Results : We found that aberrant c-KIT expression was detected in 12 cases (8%) ; 6 cases (4%) showed strong expression. Aberrant DOG-1 expression was detected in 15 cases (10%) among them only 4 cases (2.7%) showed strong expression. NMA showed a significantly high expression of c-KIT, but not DOG-1, than MA. Aberrant c-KIT and DOG-1 expressions were significantly unrelated. All 6 cases (100%) that showed strong c-KIT expression were DOG-1 negative. Similarly, 3 cases that showed strong DOG-1 expression were totally negative for c-KIT, only one case with strong DOG-1 expression showed weak c-KIT expression. Of the 6 cases with weak c-KIT expression and the 11 cases with DOG-1 expression, only 2 cases showed co-weak expressions. Aberrant c-KIT and DOG-1 expressions were associated with excessive peri- and intra-tumoral neutrophilic infiltrate (microscopic abscess formation). Neither c-KIT nor DOG-1 expression showed a significant impact on disease-free survival or overall survival.

Conclusions : Aberrant c-KIT and DOG-1 expression in CRC is a rare event, either in NMA or MA. NMA showed a significantly higher expression of c-KIT, but not DOG-1, than MA. The expressions of both in CRC are significantly unrelated, but are associated with microscopic abscess formation. Neither c-KIT nor DOG-1 expression showed a significant impact on DFS or OS. So, c-KIT and DOG-1 immunostaining is not a cost-effective method of identifying patients with CRC who may benefit from treatment with tyrosine kinase inhibitors.

- R13 -

RELATION OF GLYPICAN-3 AND E-CADHERIN EXPRESSIONS TO CLINICOPATHOLOGICAL FEATURES AND PROGNOSIS OF MUCINOUS AND NON-MUCINOUS COLORECTAL ADENOCARCINOMA. A. Foda (1), M. Mohamed (1), A. Abdelaziz (1), A. El-Hawary (1). (1) Mansoura Gastroentrology Center, Mansoura, Egypt, Pathology Department.

Introduction : Glypican-3 (GPC3) is a member of the membrane-bound heparin sulfate proteoglycans. It is highly expressed in embryonic intestine and is silenced in the corresponding normal adult tissues, suggesting that in this organ GPC3 is behaving as an oncofetal protein. E-cadherin is an adhesive receptor that is believed to act as a tumor suppressor gene, with a proved interplay with GPC3 in hepatocellular and breast carcinomas. GPC3 complexes with Wnt pathway components (including E-cadherin) and thus promotes proliferation of tumor cells. Moreover, GPC3 induces a higher expression of E-cadherin in mammary tumor cell line. However, to the best of our knowledge, interplay between GPC3 and E-cadherin in colorectal carcinogenesis was not yet discovered.
Aim : We aimed at the current study to investigate the interplay between GPC3 and E-cadherin in colorectal carcinoma (CRC) by testing immunohistochemical expression of both in a large number of colorectal mucinous adenocarcinoma (MA) and non-mucinous adenocarcinoma (NMA) cases using manual tissue microarray technique.
Methods : This retrospective study was carried out in surgical pathology lab at Gastroenterology Center, Mansoura, Egypt. Files of all resected CRC cases were revised during the period from 2007 to 2011. MA cases were selected and revised. Cases with incomplete clinical data and those that were composed completely of pools of mucin with very few epithelial cells were excluded. Seventy five cases with MA were fulfilling selection criteria. Another 75 cases of NMA were chosen randomly for comparison from the same period. The patients didn't receive any neoadjuvant therapy. All clinicopathological data of these 150 cases were revised with re-examination of all their slides. Three high density manual tissue microarrays were constructed using modified mechanical pencil tips technique and immunohistochemistry for GPC3 and E-cadherin was done. All relations were analyzed using established statistical methodologies.
Results : NMA showed a significantly higher E-cadherin expression than MA ($P = 0.001$). However NMA also showed higher expression of GPC3 than MA, this was not statistically significant ($P = 0.099$). GPC3 and E-cadherin positivity rates were significantly interrelated in NMA ($P = 0.001$), but not MA groups ($P = 0.673$). In NMA group, there was no significant relation between GPC3, E cadherin expressions and the clinicopathological features. Conversely, high E-cadherin expression in MA cases was associated with old age ($P = 0.004$), fungating tumor configuration ($P = 0.048$), mucoid adenocarcinoma rather than signet ring carcinoma subtypes ($P < 0.001$) and lack of intra-tumoral lymphocytic response ($P = 0.049$). Neither GPC3 nor E-cadherin expression showed a significant impact on disease-free survival (DFS) or overall survival (OS).
Conclusions : GPC3 and E-cadherin expressions are not independent prognostic factors in CRC. However, expressions of both are significantly interrelated in NMA patients, suggesting an excellent interplay between both, in contrast to MA. Further molecular studies are needed to explore the relationship between GPC3 and E- cadherin in colorectal carcinogenesis.

Friday February 27, 2015

PLENARY SESSION, Auditorium SILVER

Brohée Lecture/Prize, (To be determined by I. Borbath). J. Tack, KU Leuven, Leuven, Belgium.

XXVIIth Belgian Week of Gastroenterology
February 25-28, 2015

ABSTRACTS

A01 — A47 BASL - BLIC - BeSPGHAN
B01 — B19 OG-FWO
P01 — P12 Belgian Pancreatic Club (BPC)
G01 — G17 Belgian Society for Gastrointestinal Endoscopy (BSGIE) and Small Bowel Group
I01 — I38 IBD Research Group (BIRD)
N01 — N07 Research Group of Clinical Nutrition and Metabolism (SBNC)
O01 — O14 Belgian Group for Digestive Oncology (BGDO)
R01 — R13 Pathology Club, Radiology, Nuclear Medicine
C01 — C07 Case Report Session

CONTRIBUTORS

A

B

C

DELCOUR Jan	N02
DELESALLE Cathérine	B04
DELHAYE Myriam	P02, P07, P09
DELIRE Bénédicte	A24
DELOOSE Eveline	B17
DELTENRE Pierre	A01, A04
DELVAUX Frédéric	G05
DELVENNE Philippe	O08, O13, O14
DELWAIDE Jean	A01, A03
DEMEDTS Ingrid	B17
DEMETTER Pieter	G10, O07, P07, R04, R05
DEMEY Wim	O06
DEMOLIN Gauthier	O06
DEMUYNCK Koen	C03
DENIS Marie-Armelle	R01
DENYS Alban	A04
DEPAUS Julien	C01
DEPOORTERE Inge	B05
DEPREZ Pierre	G13, P01, P02, P08, R01
DEPT Séverine	G04
DEROOSE Christophe	O01, O02
DEROOVER Arnaud	A29
DEROOVER Lise	B18, I28, I29, N02
DEROVS Aleksejs	C05
DESCAMPS Benedicte	A27
DETRY Olivier	A29, O13, O14
DEVELTERE Wouter	A31
DEVIERE Jacques	G09, G15, P07, P09
DEVIÈRE Jacques	G04, G07, G10, G11, I08, I25
DEVISSCHER Lindsey	A05, A14, A27
DEVOS T.	A06, A41, A42
DEVRIESE Sarah	I05
DEWINT Pieter	G16
DEWIT Olivier	R01
DEWULF Jeroen	B04
D'HAENS Geert	I23
D'HONDT Mathieu	G08
D'HOORE André	I02, I14, I20, I23, O05
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DOZOIS Eric	O05
DRAGEAN Anca	O04
DRESSE Damien	O06
DROISSART Raphaël	O05
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DURAND François	A25
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