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1

Hepatitis C Virus and Lipid Droplets: Role of Adipose Differentiation-Related Protein in Lipid Droplet Morphology and Viral Life Cycle

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Background and aims: Hepatitis C virus (HCV) is a positive-strand RNA virus of the *Flaviviridae* family, whose life cycle is tightly associated with lipid metabolism. To better understand the relationship between HCV and lipid metabolism, we analyzed the impact of lipid droplets on HCV life cycle with a particular focus on Adipose Differentiation-Related Protein (ADRP), a lipid droplet-associated protein. **Methods:** We transduced human hepatoma cells (Huh-7) with a lentiviral vector expressing ADRP and monitored the impact of ADRP overexpression on (i) lipid droplet morphology and (ii) HCV viral particle production in the setting of infection with a cell cultured-derived HCV. We assessed the effect of ADRP on HCV entry with the HCV pseudoparticles system and we measured the HCV receptors level by quantitative RT-PCR. **Results:** ADRP mRNA expression level was increased by 2-fold during the course of HCV infection. The ADRP overexpression induced the appearance of large lipid droplets and an increase of main lipid droplet components (1.5- and 5-fold increase of triglycerides and cholesterol esters respectively). The HCV particles production and their infectivity were significantly increased by this overexpression (by 2-fold and 4-fold, respectively). Interestingly, ADRP overexpression likewise increased the HCV entry (by 17-fold) probably through an increase of the entry receptor occludin (by 2-fold). **Conclusion:** These findings suggest that ADRP is a critical factor for HCV life cycle.

3

Inhibition of the insulin-mediated AS160 activation is an important event leading to increased HCV egress

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Background and aims: Hepatitis C virus (HCV) infection induces insulin resistance. We recently found that insulin activation of AS160, the main PKB target involved in Glut4 translocation, is specifically inhibited in uninfected cells (myocytes, adipocytes and liver cells) cocultured with HCV-infected cells, leading to impaired glucose uptake and substantially contributing to insulin resistance. We then decided to challenge the potential role of AS160 in HCV life cycle. In addition, as activation/inactivation cycle of AS160 is regulated by insulin, we also tested the ability of insulin to impact HCV life cycle. ***Methods:*** The effect of silencing of AS160, as well as of a physiological concentration of insulin (1 nM) on HCV secretion, was assessed in Huh-7 cells expressing the genomic-length Jc1 construct. HCV replication was assessed using the subgenomic replicon pFK_i389LucNS3-3'JFH1. ***Results:*** Insulin treatment for 6 or 16 hours leads to a 50% inhibition of HCV secretion, while unaffecting the absolute number of HCV genomes secreted. While the silencing of AS160 increased the number of infectious particles secreted by more than 1 log in a dose dependent manner, it induced only a four-fold increase of viral particle number and of HCV replication. In a mirror experiment, overexpression of AS160 significantly reduced HCV virion secretion. ***Conclusion:*** These results suggest that, in HCV infection, inhibition of insulin-mediated AS160 activation may lead to an increased infectious viral particle production, suggesting that HCV may benefit from the insulin resistant state.

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Tissue specific overexpression of the transcription factor Nrf2 increases mucosal inflammation in an acute DSS model.

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Backround: The transcription factor Nrf2 is a major modulator of the cellular antioxidative response. Its cytoprotective impact is well established, but recent reports indicate that Nrf2 overexpression can also cause adverse effects.
Methods: To study the role of Nrf2 on mucosal inflammation we used transgenic mice conditionally expressing a constitutively active form of Nrf2 (caNrf2) either in epithelial cells (VilCre-CMVcaNrf2 mice) or in the myeloid cell lineage (LysMCre-CMVcaNrf2 mice). An acute colitis was induced by DSS in transgenic and control animals.
Results: Mice overexpressing Nrf2 in epithelial cells lost 11.6 +/- 0.8% of their body weight during colitis, whereas control animals showed a significant lower weight loss (4.8 +/- 0.9%). Additionally, the colon length was significantly shortened compared to control (4.8 +/- 0.3 versus 6.1 +/- 0.2 cm). Also further parameters showed a tendency towards more inflammation in VilCre-CMVcaNrf2 mice, such as MPO activity and histological score.
Mice overexpressing Nrf2 in the myeloid lineage lost significantly more weight (13.7 +/- 1.4 versus 6.4 +/- 1.7%). Histological score of colon sections was 7.4 +/- 0.4 in LysMCre-CMVcaNrf2 mice compared to 4.9 +/- 0.6 in control mice, indicating more severe inflammation. However, colon length and MPO activity did not differ between groups.
Conclusion: Our findings show that overexpression of Nrf2 in epithelial cells as well as in myeloid cells leads to a higher susceptibility to DSS induced acute colitis in mice. Further studies aim at investigating whether these effects are due to a reduced antibacterial defense by reactive oxygen species.

4

Simplified two-timepoint FDG-PET/CT imaging for pancreatic lesions. Is it helpful in determining pancreatic tumors?

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Abstract
Background: Predicting the dignity of pancreatic lesions is still a diagnostic challenge. Therefore the aim of this study was to evaluate, whether early two-timepoint kinetics of pancreatic lesions in FDG PET may be helpful to differentiate between benign and malignant pancreatic lesions.

Methods: We prospectively analyzed 64 patients (pancreatic cancer n=45, chronic pancreatitis n=19) scheduled for two-timepoint FDG-PET/CT scan for pancreatic lesions in our hospital between 2005-2011. Studies were performed 60 and 90 minutes after application of the radioactive substance. Histological samples were collected for all patients, either by resection or by biopsy. Semi-quantitative analysis was performed using the minimal, the maximal and the average standardized uptake value (SUV) from the two different sets of images and a SUV change was calculated as difference between the two measurements in percent. SUV changes of patients with pancreatic cancer and chronic pancreatitis were compared using the student t-test.

Results: Mean change of $SUV_{min.}$ was 12.04 % for pancreatic cancer vs. -4.66 % for chronic pancreatitis respectively (p=0.00012). Mean change of $SUV_{avg.}$ was 12.13 % for pancreatic cancer vs. -5.65 % for chronic pancreatitis respectively (p<0.0001). Mean change of $SUV_{max.}$ was 18.18 % for pancreatic cancer vs. -4.92 % for chronic pancreatitis respectively (p=0.00026).

Conclusions: The present analysis shows a statistically highly significant difference comparing the changes in $SUV_{min.}$, $SUV_{avg.}$ and $SUV_{max.}$ in early two-timepoint PET/CT images of pancreatic cancer and chronic pancreatitis. This is one of the first analyses of two-timepoint PET/CT performed as early as 30 minutes after the initial study. In patients with suspicious pancreatic lesions the simplified two-timepoint FDG-PET/CT represents an excellent diagnostic option and is helpful in characterizing pancreatic lesions.

Prevalence and etiologies of cholestasis in inflammatory bowel diseases patients in the Swiss IBD cohort. 5

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Background: Patients with inflammatory bowel diseases (IBD) may present with cholestasis during the course of their disease. Causes are multiple including drug-induced liver toxicity (e.g. Azathioprine), specific liver diseases complicating IBD (e.g. primary sclerosing cholangitis (PSC)) or para-inflammatory (TNF-α induced). Prevalence of cholestasis in IBD is unknown. Cholestasis, plays a significant role in the absorption of vitamins and drugs; bile acids are thought to play a role in dysplasia, intra-cellular signalling as well as interaction with the intestinal flora. The aim of this study is to establish the prevalence of clinical and biological cholestasis in IBD patients using the clinical data and bio-samples of the Swiss IBD Cohort (SIBDC). Methods: All patients of the SIBDC with serum samples available were included. Total bile acid (TBA) assay was performed (ELISA). Cholestasis was defined as a TBA > 8 µmol/l. In a second time bile acid profile, using HPLC, was performed in serum samples from patients with high TBA as well as in a cohort of patients with low TBA. Clinical data were collected from the SIBDC. Results: 1342 patients were included; 96 patients had TBA > 8 µmol/l with a mean level of 21.8 µmol/l (8-483). This represents a prevalence of 7.15% cholestasis in the SIBDC. In univariate analysis, cholestasis (TBA>8) was associated with male sex (63% vs 51%, p=0.034), less smoking (17% vs 27%, p=0.023), a higher alcalin phosphatase (108 vs 70, p=10E-12), a lower albumin (38 vs 40, p=0.016), more PSC (5% vs 1%, p=0.00007), supplementation with calcium or vitamin E (p=0.047) and treatment with tacrolimus (3% vs 1%, p=0.038) or ursodesoxycholic acid (10% vs 1%, p=10E-8). Age, IBD subtypes and mean activity index were comparable. In multivariate analysis, PSC (OR=4.64, p=0.012) and treatment with tacrolimus (OR=5.5, p=0.017) were significant factor associated with cholestasis. Conclusions: Prevalence of cholestasis in the SIBDC was high (7%). PSC, IBD inflammatory flare or adverse effect of treatments could be an explanation. In some cases, the exact cause of the cholestasis remains unclear. Further analysis on the subtypes of biliary acids is underway and should help understanding the causes of cholestasis.

Factors associated with durable response to infliximab 5 years and beyond: a multi center international cohort 7

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Background: Infliximab (IFX) have been used for about a decade worldwide. Little is known about the natural history of infliximab use beyond a few years and whether there is a subgroup which has a more sustained benefit. Methods: Data from CD Patients exposed to infliximab (IFX) in 3 different sites (US, France and Swiss IBD cohort study) were compared. Results: We collected data on 1014 CD patients (56% females), of whom 250 were identified as LTUI. In the comparison group were 290 CD patients who had to stop treatment: 48 for non response, 97 for loss of response and 147 for adverse events, whereas 474 could not be classified as they were actively receiving IFX but for less than 5 year (potential future LTUI) or the reason for therapy cessation remained unclear. The clinical characteristic of these patients showed, among the LTUI patients, more colonic and perianal involvements and an earlier age at the start of IFX. The prevalence of active smokers and obese patients differed markedly, but inversely, between American and European centers (smoking: 10% vs. 39% and obesity 16% vs. 8%), but did not impact outcome. After one year, the LOR/AE rate was stable around 3 -6%, each year till year 10. The multivariate regression analysis confirmed the LTUI patients' characteristics, however a poor prognosis was associated with thiopurines exposure (<0.001) and with previous surgical resections (NS). Conclusion: Young age at start of IFX, colonic Crohn's disease are factors associated with a long term use of IFX. After 5 years of IFX, there is still a 3-5% discontinuation rate annually. Previous resections are suggestive of poor prognosis. These results need to be interpreted cautiously due to potential confounding by indication.

Structure and Function of the N-Terminal Portion of Hepatitis C Virus Nonstructural Protein 4B 6

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Background: Nonstructural protein 4B (NS4B) is an integral endoplasmic reticulum (ER) membrane protein that acts as an oligomer and plays a central role in the formation of the hepatitis C virus (HCV) replication complex. The N-terminal portion of NS4B contains two α-helices designated as AH1 and AH2. The aim of this study was to investigate the structure and the function in the HCV life cycle of AH1.

Methods: A synthetic peptide corresponding to amino acid (aa) 1-33 of NS4B was analyzed by circular dichroism (CD) and nuclear magnetic resonance (NMR). Mutants generated in subgenomic replicons and full-length HCV genomes were analyzed by replication and virus production assays. The membrane topology was investigated by selective permeabilization and immunofluorescence analyses.

Results: Structural analyses revealed that AH1 folds into an amphipathic α-helix. AH1 displays a dual ER luminal and cytosolic membrane topology in a replicative context. While most of the mutants investigated impacted viral replication, mutation of two conserved acidic residues on the hydrophilic side impaired virus production without affecting HCV RNA replication.

Conclusions: These results provide an atomic resolution structure of an essential segment of NS4B and highlight its important roles in genome replication and virus production.

A TLR5 agonist inhibits ischemic reperfusion injury in a mouse model. 8

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Background
CBLB502 (aka Entolimod, provided by Cleveland BioLabs, Inc.) is a pharmacologically optimized derivative of bacterial protein flagellin, an agonist of toll-like receptor 5 (TLR5). Stimulation of TLR5 with CBLB502 was shown previously to have a radioprotective property in mouse and primate models. Here we investigated its stimulation of innate immune responses in mice and its potential hepatoprotective effect in a liver ischemia reperfusion (I/R) model.
Methods
Expression of TLR5 was determined in isolated liver cell populations and whole liver by RT-qPCR and immnuohistochemistry. Alterations in gene expression were determined in mice treated with CBLB502 for 2 and 6 hours by RT-qPCR of liver tissue. Activation of an innate immune response was assessed by a CD62L shedding assay. A mouse model of partial liver I/R was used to assess the hepatoprotective effect of CBLB502 against acute liver injury. Injury was assessed by serum ALT/AST levels, leukocyte infiltrate and myeloperoxidase activity.
Results
Hepatic expression of TLR5 was found on hepatocytes, biliary cells and infiltrating mononuclear cells. CBLB502 was a more potent monocyte activator than flagellin, LC_{50} 0.02 vs. 0.68 ng/ml respectively. After 2 hrs, CBLB increased inflammatory (TNF; 22-fold), neutrophil chemoattractant (CXCL1; 77-fold, CXCL2; 51-fold), TH2 (IL-10; 25-fold) and cytoprotective (TNFAIP3; 350-fold, HMOX1; 19-fold) gene expression, but not TH1 genes (IFN_gamma and IL2; not detectable). Preliminary data show that in mice treated with $0.2mgkg^{-1}$, s.c., CBLB502 there is a beneficial influence on clinical symptoms of hepatic ischemia reperfusion injury by reduced serum transaminases ($p<0.05$) and reduced myeloperoxidase activity reflecting reduced neutrophil infiltration ($p<0.0005$).
Conclusions
I/R injury associated with hepatic resections and liver transplantation remains a serious complication in clinical practice. Hepatic damage could potentially be diminished by prior activation of an innate immune response targetingTLR5.

Outcome After Neoadjuvant Therapy for Locally Advanced Rectal Cancer of the Upper Third

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Background: There is a controversy if patients with upper rectal cancer will benefit from neoadjuvant chemoradiotherapy (CRT). The present study demonstrates perioperative results and morbidity for patients with upper rectal cancer after CRT. 3- and 5-year-disease-free (DFR) and –overall survival (OSR) rates were calculated for all patients and separately for responders and non-responders. Results were compared with patients with mid/lower rectal cancer and CRT.
Methods: Patients with rectal cancer stage II or III were treated by CRT with 50.4 Gy and Capecitabine followed by surgery. If tumor was >= 10 cm from anal verge it was defined as upper rectal carcinoma. All patients underwent total mesorectal excision with coloanal anastomosis or rectal amputation. Follow-up was documented in our tumor data base.
Results: From 5/2005 – 8/2012 164 patients were treated by neoadjuvant CRT, 30 of them had a tumor of the upper third. A major complication was seen in 7% of the upper rectal cancer group and in 8% of the mid/lower group. We had 3 anastomotic insufficiency in the mid/lower group. Complete response was seen in 33% of the upper rectal cancer group and in 14% of the mid/lower group ($p<0.05$). The 3- and 5-year OSR were 96%/60% for upper rectum and 89%/83% for mid/lower rectum (p=ns). The 3- and 5-year DFR were 92 %/76% for upper rectum, 84%/74% for mid/lower rectum (p=ns). For responders to CRT 3-year OSR was 100% (upper rectal group) and 86% (lower rectal group), for non-responders 93% and 87% (p=ns).
Conclusions: Neoadjuvant CRT for upper rectal cancer is as successful as for rectal cancer located in the mid/lower third. Surgery after CRT can be performed safely with low morbidity (7%). Complete histopathologic response in upper rectal was exceptional high in our collective (33%). Long-term-results are comparable to patients with mid/lower rectal cancer and are excellent for responders to the neoadjuvant CRT.

TARGETING THE HIPPO PATHWAY TO IMPROVE THE REGENERATIVE CAPACITY OF THE LIVER

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Background: Protein kinases MST1 & MST2 are the core of the Hippo pathway, which inactivate the transcriptional co-activator YAP through LATS phosphorylation. Inhibition of MST1& MST2 leads to the activation of YAP where it translocates to the nucleus and promotes the transcription of pro proliferative genes (BIRC5/surviving and Foxm1). We hypothesize that knockdown (KD) of MST1 & MST2 will push hepatocytes into cell cycle through activation of YAP.

Methods: We are exploring a gene therapy approach using siRNAs coupled with liposomes to target the Hippo pathway to promote hepatocyte proliferation in non-regenerating livers.

Results: We first identified siRNA sequences that lead to 92% and 89% KD of MST1 and MST2 in a mouse liver hepatoma cell line in vitro. siRNA:liposome complexes injected i.v. resulted in >80% KD of expression in the liver using FVII as a control gene target. Using siRNAs targeting MST1 & MST2 coupled with liposomes reduced expression to 66 and 40%, respectively in liver after 72 hours. Efficiency of the KD was confirmed by RT-qPCR and immunoblot. KD of MST1 and MST2 in healthy mouse liver resulted in an increase of nuclear Yap localization and subsequent hepatocyte proliferation measured by incorporation of EdU and Ki67 immunostaining. Moreover, after MST1 and MST2 KD there was a remarkable 3 and 5-fold increase of BIRC5/survivin and Foxm1, respectively –both YAP target genes normally up-regulated in a regenerating liver.
Conclusion: The femoral vein injection of siRNAs coupled with liposomes is a valid method to target with high efficiency the hepatocytes *in vivo*. The KD of MST1 & MST2 using the mentioned methodology provoked nuclear YAP translocation and hepatocyte proliferation in wild-type mice. Finally to determine if targeting MST1 & MST2 is clinically relevant, we will demonstrate that there is impairment of these protein/signalling pathways in diseased or small-for-size livers during regeneration.

Real Life Experience of HCV Triple Therapies in two Tertiary Swiss Centers: An Increase in Adverse Effects, Patient Referrals and Unscheduled Visits

10

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Background/Aims: HCV triple therapies including the protease inhibitors (PI) telaprevir or boceprevir improved virological responses significantly. However, the new treatment regimens are associated with increased rates of adverse effects (AEs) and clinical burden for nursing and medical staff. Our aim was to assess the extent of additional use of health resources with current triple therapies in a real life setting.
Methods: Retrospective analysis of patients undergoing therapy for chronic hepatitis C at two tertiary centers since PI introduction in 2011. Frequencies of regular and unscheduled visits, referrals to other specialists due to AEs and absence from working place in HCV genotype 1 (GT1)-infected patients receiving PI were compared to patients receiving dual therapy (PEG-IFN-α and ribavirin in non-GT1 patients).
Results: *Demographics:* Fourty-five patients with HCV GT1 infection were analyzed (13 females, 32 males; age 34-61 years; 64% ≥F3). Of these, 22 started with a lead-in (49%) and 37 received a PI (82%). Seventeen finished treatment, 10 are still under treatment, and 18 stopped treatment due to AEs or attainment of a stopping rule. The control group consisted of 10 patients with GT3 or GT6 (3 females, 7 males; age 29-69 years; 80% ≥F3). Of these, 6 finished treatment, 3 are still ongoing, and 1 stopped due to AE. *Regular visits* done in 37 GT1-infected patients treated with a PI showed no differences in amount and distribution to the control group (a total of 597 visits in this group, 58% by nurse, 23% by physician, 19% together). *Unscheduled visits* were noted in 19/37 patients treated with a PI (51%; 30 visits in total; 1-4 visits per patient). No unscheduled visits were noted in non-GT1 patients. *Referrals to other specialists* were done in 20/37 patients treated with a PI (55%; 71 visits in total; 1-14 visits per patient), most often to dermatologists, ophthalmologists, and psychiatrists. No referrals were noted in non-GT1 pts. *Serious AEs* were noted in 15/45 pts, seven of them needed hospitalization. No deaths occurred. No serious AEs or hospitalization were noted in non-GT1 pts. *Absence from working place:* Of the 37 patients treated with a PI, 22 (60%) had no absence, 6 (16%) had absences up to 50%, 4 (11%) had absences up to 100%, and 5 (13%) were unemployed. In non-GT1 patients, 5 (50%) had no abscence, 3 (30%) had absences up to 50%, 1 (10%) had absences up to 80%, and 1 (10%) was unemployed.
Conclusions: Current PI-based HCV triple therapies put a significant burden on patients and health systems: 33% had serious AEs, 40% showed absences at work of more than one month, 50% required unscheduled visits, and 55% required referrals to other specialists due to AEs. Specialized nurses can take a key role in the care of these patients.

OPTIMIZE trial: Non-inferiority of twice-daily telaprevir versus administration every 8 hours in treatment-naïve, genotype 1 HCV infected patients

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Background: The ADVANCE study showed that telaprevir (TVR) every 8 hours (q8h) combined with pIFNα-2a (P) and ribavirin (R) had superior efficacy to PR alone. OPTIMIZE, a Phase III, randomized, open-label, international, non-inferiority study compares twice daily (bid) vs q8h TVR (NCT01241760). **Methods:** HCV G1 treatment-naive patients were randomized to 750mg q8h or 1125mg bid TVR plus PR for 12 weeks, then PR alone for 12 weeks (RVR) or 36 weeks. The primary endpoint was SVR12. **Results:** 740 patients were treated. 15% had bridging fibrosis, 14% compensated cirrhosis, 85% HCV RNA ≥800,000 IU/mL and 29% had IL28B CC. TVR bid vs q8h was non-inferior: difference 1.5% (95% CI: –4.9%, 12.0%). 69% for TVR bid vs 67% for q8h achieved RVR. The adverse event (AE) profile was generally similar between arms, with fatigue (47.3%), pruritus (42.7%), anemia (41.6%), nausea (36.5%) and rash (35.3%) as most frequent AE during the TVR phase. SAE occurred in 8.5%. **Conclusions:** In this study, with a high proportion of patients with bridging fibrosis or compensated cirrhosis, the efficacy of bid TVR was non-inferior to q8h offering the potential of simplified dosing to HCV G1 patients.

Triple therapy in patients with HCV recurrence after liver transplantation: a pilot study on efficacy and safety

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Background

HCV induced liver cirrhosis is a major indication for liver transplantation (OLT). If sustained virological response (SVR) cannot be achieved prior to OLT, HCV recurrence in the graft is universal. SVR rates after transplantation are low, but might improve with protease inhibitor (PI) based triple therapy (TT). This retrospective study aimed to evaluate the feasibility of TT in OLT patients with recurrent HCV genotype 1 infection with respect to efficacy, drug-drug interactions and adverse events.

Methods

The study included 16 patients from 2 transplant centers. Demographic, clinical, biochemical and virological data were collected at baseline and during treatment. The immunosuppressive regimen remained unchanged during TT; however the dosage was adjusted when a PI was started. In patients on boceprevir (BOC) as well as in 1 patient treated with telaprevir (TEL), a four week lead-in phase with PEG and ribavirin was performed.

Results

In 16 patients (14 male, 12 genotype 1b, 6 METAVIR F3/4, median age: 61 years) antiviral treatment was initiated 3 to 190 months after OLT. 11 patients received TEL, 3 BOC and 2 received both. 9 patients were on tacrolimus (TAC), 6 on cyclosporine (CsA) and 1 on an everolimus (ERL) TAC dosages had to be reduced by a median factor 13, CsA by a median factor 4 and ERL by a median factor 14. 9 patients achieved RVR4, 14 patients a cEVR, 7/9 patients an EOTR. SVR12 was achieved in 4/8 patients, SVR24 in 3/7 patients. The most frequent side effect was anemia occurring in all patients, ten patients required erythropoietin treatment, 7 additional blood transfusions. 8 patients were hospitalized during treatment, 1 patient died.

Conclusion

TT can be used after OLT with EVR results comparable to non-transplant patients. However, therapy requires close clinical monitoring due to drug-drug interactions and high rates of anemia requiring erythropoietin treatment and blood transfusions.

Activation and Apoptotic-Priming of Cancer-Associated Fibroblasts in Cholangiocarcinoma is mediated by PDGF-BB

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Background and Aims: Cholangiocarcinoma (CCA) is a highly desmoplastic tumor containing abundant cancer associated myofibroblasts (CAF). Increased numbers of CAF correlate with poor prognosis and are considered an important factor in aggressive tumor biology. CAF display an activated phenotype which renders the cells sensitive to apoptotic stimuli. The BH3 mimetic navitoclax induces cell death in cells primed for apoptosis. It selectively depletes CAF in an animal model of CCA resulting in reduction of tumor growth and improved survival. In this study, we examine the role of stromal PDGF-BB in cellular activation and apoptotic priming of CAF. **Methods**: Human cholangiocarcinoma specimens were examined by immunofluorescence, Western-Blot and qRT-PCR. Human quiescent fibroblasts (hFB), hepatic stellate cells (HSC) and CCA cell lines were used for in vitro studies. **Results:** PDGF-BB is highly expressed in human CCA. CAF in human CCA display activation of the pro-apoptotic Bcl-2 effector protein Bax. Treatment of quiescent hFB or HSC with PDGF-BB in vitro induces an activated cellular phenotype, results in Bax activation, and sensitizes cells to navitoclax. This indicates that PDGF-BB triggers apoptotic priming. Co-cultivation of quiescent hFB or HSC with CCA cells, similarly leads to apoptotic priming and increased cell death with navitoclax treatment. In addition to the observed Bax activation, a Bcl-2 protein profiling of PDGF-treated hFB demonstrated an increase in pro-apoptotic BH3 only proteins Bid and PUMA.
Conclusions: PDGF in CCA stroma activates and sensitizes CAF to navitoclax-induced apoptosis. The proposed mechanism is PDGF – mediated Bax activation and the upregulation of pro-apoptotic BH3 only proteins Bid and PUMA.
Apoptotic priming of CAF via a receptor tyrosine kinase pathway represents a novel mechanism in apotptosis regulation. This could be a valuable therapeutic approach in human CCA.

The gut antimicrobial peptide angiogenin-4 is upregulated in mice with portal hypertension in the absence of bacterial flora.

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Background
Gut microbial flora exerts a wide range of metabolic functions that are relevant for the host. Bacterial translocation and vascular proliferation are important mechanisms in the pathophysiology of portal hypertension (PHT).
The aim of our study was to assess the consequences of bacterial colonization in a mouse model of portal hypertension.
Methods
We induced PHT by partial ligation of the portal vein (PPVL) in germ-free and colonized mice. After two and seven days we measured hemodynamic parameters and collected tissues for microbiology, immunohistochemistry and gene expression studies.
Groups of n=10 were compared using the Mann-Whitney test.
Results
In PPVL, colonized mice presented significantly higher portal pressure levels compared to germ-free mice, while mesenteric artery blood flow, heart rate and systemic arterial pressure remained unchanged. The presence of bacterial flora was also associated with significantly increased porto-systemic shunts and spleen weight. However, there were no hemodynamic differences between sham-operated mice with or without intestinal bacterial flora.
Bacterial translocation to the spleen was demonstrated for GRAM+ (Lactobacillus), but not for GRAM- bacteria.
PHT was associated with a significant upregulation of angiogenin-4, but not of other angiogenic factors, in intestinal tissue of germ-free mice. Additionally, intestinal blood and lymphatic vessels, identified by CD31 and Lyve-1 immunohistochemistry, respectively, were more abundant in colonized and in portal hypertensive mice as compared to germ-free and sham-operated mice.

Conclusions
Portal hypertension is attenuated in the absence of gut microbial flora. Bacterial translocation and overexpression of the intestinal peptide angiogenin-4 (an antimicrobial and angiogenic factor stimulated by intestinal bacteria) may contribute to the proliferation of blood and lymphatic vessels, and hence to the development of portal hypertension.

Equal effectiveness of laparoscopic Sleeve Gastrectomy and Roux-Y-Gastric Bypass: one year Results of the prospective randomized Swiss Multicentre Bypass Or Sleeve Study (SM-BOSS)

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Background: Laparoscopic Sleeve Gastrectomy (LSG) has been proposed as an effective alternative to the current standard procedure, the laparoscopic Roux-Y- Gastric Bypass (LRYGB). Prospective data comparing both procedures are rare. Therefore, we performed a randomized clinical trial assessing the effectiveness of the two operative techniques.

Methods: Two hundred and seventeen patients were randomized at four bariatric centres in Switzerland. Hundred and seven patients underwent a LSG and 110 patients underwent a LRYGB. The mean BMI of all patients was 44 ±11.1 kg/m^2, the mean age was 43 ±5.3 years, and 72% were female. We looked at weight loss, reduction in co-morbidities, increase of quality of life according to GIQLI, and complications one year postop.

Results: Follow-up rate was 100%. Excessive BMI loss one year after the operation was similar between the two groups (LSG: 72.3±22%and LRYGB: 76.6±21%, p=0.2). Except for GERD, which showed a higher resolution rate after LRYGB, the comorbidities were significantly improved after both procedures. Quality of life increased significantly in both groups (LSG: 99 to 127, LRYGB 99 to 127.5 points). Complications during the first postoperative year were equal in terms of the incidence of micronutrient deficiencies, and no reoperations. Two patients of the LSG group suffered from extreme GERD, in the LRYGB group there was one anastomotic ulcer and one stricture at the gastroenterostomy.

Conclusions: The two procedures are almost equally efficient regarding weight loss, improvement of comorbidities and quality of life one year after surgery.

Inhibition of SIRT1 impairs tumor-associated angiogenesis 17

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Objective: Sirtuins, NAD+ dependent deacetylases, control key metabolic processes by targeting histone and non-histone regulatory proteins. We recently demonstrated that SIRT1 is strongly overexpressed in human hepatocellular carcinomas (HCC). Knock-down of SIRT1 in HCC cells resulted in a decrease in tumor cell proliferation in vitro and tumor xenograft growth in vivo. The goal of the present study was to investigate the impact of SIRT1 inhibition on tumor-associated angiogenesis in HCC. SIRT1 activity was impaired using EX527, a potent ,small-molecule inhibitor of its catalytic activity.

Methods: SIRT1 activity was inhibited with EX27 in human HCC cell lines (HepG2, Hep3B) and in a human endothelial cell line (HMEC-1). Markers of angiogenesis and cell proliferation were monitored by a RT-qPCR and by in vitro proliferation assays and in vivo with an orthotopic xenograft tumor model.

Results: Inhibition of SIRT1 activity with EX527 was associated with a change in morphology and with a decrease in oncogenic markers such as AFP, GPC3, EPO and CA9. Furthermore, EX527 impaired the proliferation of HCC and HMEC-1 cells in vitro. In HMEC-1 cells, EX527 inhibited ERK1/2 phosphorylation in the MAPK pathway. EX527 decreased the expression of the pro-angiogenesis factor VEGF in cells cultured under hypoxic conditions.. Using an in vivo model, tumor growth was impaired in animals treated with EX527 with an associated decrease in vessel formation.

Conclusions: Our data suggests that SIRT1 favors tumor angiogenesis therefore supports HCC tumor growth in vivo. With these findings, we conclude that SIRT1 is an attractive target in order to block not only the tumor cells but also endothelial cells of the tumor microenvironment.

Sorafenib shows inhibitory efficacy in a newly established murine hepatic angiosarcoma cell line 19

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Objectives: Liver angiosarcoma (AS) is a rare and highly aggressive tumor of endothelial origin with dismal prognosis. Studies of the molecular biology of AS are limited since animal models are missing. We have previously shown that knockout of Notch1 in mice leads to spontaneous formation of hepatic AS (Gastroenterol. 2012) and we have established three cell lines from these animals. The aim of this study is 1) to study the molecular pathogenesis and therapeutic targets and 2) to evaluate the effect of targeted therapies in the treatment of AS.
Methods: Gene expression of AS cell lines vs. normal liver sinusoidal endothelial cells (LSEC) from control and Notch1 KO mice without AS was profiled by Affymetrix Mouse Gene 1.0 ST array. Expression levels were analyzed including gene set enrichement analysis (GSEA). In one AS cell line the effects of treatment with increasing sorafenib concentrations (1-20 μM) were analyzed. Time-lapse microscopy of sorafenib exposed AS cells grown on matrigel was performed. Cell proliferation was monitored using the real-time cell analyser system xCELLigence. Apoptosis was measured by Nicoletti assay using the PI flow cytomertric assay. Western blot was performed to assess the impact of sorafenib on ERK signalling.
Results: Transcriptome analysis showed massive changes in gene expression identifying FGFRs, TGFβ, met proto-oncogene, PlGF, and VEGF A as potential drivers in malignant transformation of hepatic AS. Moreover, GSEA revealed that six of the top 20 upregulated chemical and genetic perturbation gene sets were related to myc targets (FDR<0.25). C-myc is a downstream transcription factor target of the Raf/MEK/ERK pathway, which can be blocked by sorafenib, a multikinase inhibitor. Timelapse imaging revealed that sorafenib treatment dramatically reduced migration of AS cells. Differences in filopodia dynamics were significant (p=0.0201) after 6 h with a decrease in filopodial extensions. Sorafenib inhibited cell proliferation in a time and dose-dependant manner, whereas the number of apoptotic cells was only slightly elevated with increasing concentrations. In addition, sorafenib suppressed ERK phosphorylation in the AS cell line.
Conclusion: We identified Notch1 as LSEC tumor suppressor gene and established three hepatic AS cell lines as a useful *in vitro* tool. Our data demonstrate antitumor activity of sorafenib in AS cells with potent inhibition of migration, filopodia formation, and cell proliferation, which support further evaluation of sorafenib as a novel treatment strategy.

Drug-induced liver injury (DILI) with auto-immune features: is it drug-induced auto-immune hepatitis (DIAIH) or immune-mediated DILI (IMDILI)? A case series 18

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Background: DILI may be associated with features of autoimmune hepatitis (AIH), requiring immunosuppression in addition to drug discontinuation. As IMDILI shows a good response to steroids with maintained remission after withdrawal, DIAIH may relapse and need prolonged immunosuppression due to an underlying predisposition to, or unrecognized AIH (J Hepatol 2011; 55:747). We describe a case series of DILI with AIH features. **Methods**: Data from 10 patients (HUG, 2008-2012) were collected. Information on viral serologies, autoantibodies, γglobulins, liver histology were obtained prior to immunosuppressive therapy. Other causes of liver disease were excluded. **Results**: Patients' median age: 60 yrs, 60% female, 40%: concomitant autoimmune diseases (Lupus, thyroiditis, vitiligo, Sjögren). The drug incriminated were renine-angiotensine inhibitors (40%), NSAID (20%), nitrofurantoine (10%), trazodone (10%), biphosphonate (10%), natural product (10%). All patients showed elevated transaminases (>25 ULN) and serum bilirubin (> 25 ULN). Hyperγglobulinemia was present in 90%, as well as autoantibodies (anti-smooth muscle and/or anti-nuclear titer >1:80) in 70% of cases. At histology, centrilobular necrosis was evident in all cases, with pleiomorphic infiltration rich in plasmocytes in 90% of cases. Immunosuppressors (80% steroids) with slowly tapered doses normalized liver function tests at 3 months. However, during follow-up, 70% showed a relapse (in the absence of drug re-exposure) that necessitates reintroduction of immunosuppressive therapy. At 1 year of the initial presentation, 60% were still under immunosuppression. **Conclusion**: In spite of a similar initial presentation, patients with IMDILI or DIAIH may not share the same outcome and prognosis. Due to the connections between DILI and AIH, patients should be followed-up and biological tests closely monitored after an acute episode.

Therapeutic Escalation in Patients with Ulcerative Colitis: Systematic Analysis of the Prevalence and Risk Factors in the Swiss IBD Cohort 20

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Background: We aimed to assess the percentage of patients with ulcerative colitis (UC) undergoing therapeutic escalation over time and to identify escalation-associated risk factors. **Methods:** Data from the Swiss IBD Cohort were analyzed. Patients were stratified according to disease duration, and the fraction of patients undergoing treatment with the following regimens were assessed: 5-aminosalicylates (5-ASA), steroids, immunomodulators (IM) (azathioprine and 6-mercaptopurine), anti-TNF drugs (infliximab, adalimumab), and calcineurin-inhibitors (cyclosporine, tacrolimus). **Results:** 901 UC patients were included (42% pancolitis, 42% left-sided colitis, 16% proctitis). Treatment regimens related to disease duration: 5-ASA 28.0%, steroids and/or IM 51.0%, anti-TNF and/or calcineurin inhibitors 18.3%, surgery 2.3%, no therapy 0.4% for disease duration of 0 to 2 years; 5-ASA 18.9%, steroids and/or IM 49.5%, anti-TNF and/or calcineurin inhibitors 28.6%, surgery 2.0%, no therapy 1.0% for disease duration of 3-6 years; 5-ASA 16.3%, steroids and/or IM 57.5%, anti-TNF and/or calcineurin inhibitors 20.4%, surgery 5.0%, no therapy 0.8% for disease duration of 7-14 years; 5-ASA 15.0%, steroids and/or IM 60.9%, anti-TNF and/or calcineurin inhibitors 9.7%, surgery 14.0%, no therapy 1.4% for disease ≥15 years. Young age at UC diagnosis (OR 0.955, 95% CI 0.929-0.981, p=0.001) as well as pancolitis (OR 2.404, 95% CI 1.261-4.584, p=0.007) were the main risk factors for a rapid therapeutic step-up requiring treatment with anti-TNF drugs and/or calcineurin inhibitors within the first two years after UC diagnosis. **Conclusions:** Less than 20% of UC patients were treated solely by 5-ASA after a disease duration of ≥3 years. Young age at disease onset and pancolitis are the major risk factors requiring a rapid step-up within the first two years of disease course.

Occurrence of Stricturing And Penetrating Complications Is Diminished In Crohn's Disease Patients Treated By Immunomodulatory And/or Anti-TNF Therapy Within the First Two Years Of Disease Duration When Corrected For Diagnostic Delay

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Background: We aimed to assess if treatment with immunomodulators (IM, includes azathioprine, 6-mercaptopurine, methotrexate) and/or anti-TNF drugs (infliximab, adalimumab, certolizumab pegol) within the first two years of Crohn's disease (CD) symptom onset (diagnostic delay is taken into account, "early therapy") is associated with a reduced risk to develop complications when compared to initiating these therapies > 2 years after CD onset ("late therapy"). **Methods:** Data from the Swiss IBD Cohort were analyzed. The following outcomes were assessed using logistic regression modelling: stenosis, internal fistulas, perianal fistulas, intestinal surgery, and perianal surgery. **Results:** 181 CD patients on "early therapy" were compared to 269 CD patients on "late therapy". "Early therapy" was negatively associated with stricture formation (OR 0.431, 95% CI 0.251-0.739, p=0.002) and development of perianal fistulas (OR 0.490, 95% CI 0.256-0.935, p=0.031). The overall disease duration was positively correlated with stricture formation (OR 1.037, 95% CI 1.014-1.060, p=0.001) and intestinal surgery (OR 1.091, 95% CI 1.061-1.121, p<0.001). **Conclusions:** Treatment with IM and/or anti-TNF therapy during the first two years of CD onset is associated with a reduced risk for development of bowel stenosis and perianal fistulas. Disease duration, adjusted for diagnostic delay, is positively correlated with the increased risk of developing bowel stenoses and undergoing intestinal surgery. Future studies evaluating the relationship between treatment efficacy and disease duration should consider assessing a true disease duration that takes into account the length of diagnostic delay.

A distinct pattern of fundus and gastroesophageal junction pressure changes during motion-induced nausea

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Background: Nausea is the unpleasant sensation that precedes vomiting. Studies using barostats suggest that fundus and LES relaxation precede vomiting. High-resolution manometry (HRM) allows less invasive, detailed measurements of fundus pressure (FP) and axial movement of the gastroesophageal junction. **Methods:** Nausea was induced in 12 healthy volunteers by a motion video (rotating view of a landscape) and rated on a VAS scale (1-4). A 15 min baseline (BL) recording was followed by the motion video (until the volunteer perceived nausea VAS≥3) and 30min recovery recording. Pressure and anatomical changes were assessed with HRM. Results correspond to measurements at peak nausea and late recovery (last 5min of the recovery period). **Results:** 10/12 subjects showed a drop in FP during nausea compared to BL (-4.0±0.8mmHg; p=0.005), and 8/10 a drop in LES pressure (-8.8±2.5mmHg; p=0.04). Peak nausea preceded peak fundus and LES relaxation. 8/10 subjects showed lengthening of the esophagus (+0.8±0.2cm; p<0.05) and shortening of the LES during nausea (-0.8±0.3cm; p<0.05). The number of TLESRs was greater during the recovery period compared to nausea (p=0.01). **Conclusions:** FP drop and LES relaxation may be preparations for vomiting. The configuration changes (esophageal lengthening, LES shortening) during nausea are most likely secondary to anatomical changes occurring with fundus and LES relaxation. Whether these pressure changes provoke the sensation of nausea or vice versa is unknown, however the time sequence in our experiment suggests the latter.

Accuracy of contrast - enhanced ultrasound in focal liver lesions in a tertiary Swiss GI center

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Background: In prospective multicenter trials with high volume contrast-enhanced-ultrasound (CEUS), accuracy of CEUS for differentiation focal liver lesions (FLL) is comparable to CT and MRI (1,2). CEUS is cost-effective and severe adverse effects are very uncommon (0,06 – 0,4%) (3, 4). Our aim was to assess whether CEUS in everyday clinical routine is practicable with adequate accuracy in terms of tumor dignity.

Methods: We analyzed all CEUS for FLL between 1/2011 – 3/2013 performed by one examinator (level II of training according to European Federation Society for Ultrasound on only one ultrasound device (Acuson Sequoia 512^{R}, Siemens) to avoid interobserver variation. All patients were examined according the international guidelines (5) with SonoVue^{R} (Bracco). Group A included all patients with histology as gold standard, if not available (e.g. benigne FLL) convergent CEUS with multislice CT or MRI (with intravenous contrast application) results or follow up (mean 15 months) were gold standard. Group B contains only histology as gold standard.

Results: In 112 patients (age 16-86 years, n=25 cirrhotics) no complications occurred after CEUS. The 37 malignant FLL included 18 HCC and 17 patients with metastasis, one cholangiocarcinoma and one primary B-cell lymphoma. The 75 benign FLL included 20 hemangioma, 9 FNH, 9 cystic lesions and 6 regenerative nodules. CEUS performance in groups A and B are demonstrated in tables 1 & 2. CEUS failed to diagnose only one HCC (MRI and histology positive) as malignant FLL. All other malignant FLL were classified correctly by CEUS showing excellent sensitivity (96-97%) and negative predictive value (npV: 94-98%). In contrast (MRT n=4/CT n=2) failed to identify 4 metastasis, one HCC and one primary lymphoma in the liver (6 false negative results with lower npV: 79-90%). Benign FLL were diagnosed slightly more accurate by MRI/CT (respectively slightly better specificity (94%) and positive predictive value (ppV: 89-94%). In 75 benign FLL CEUS demonstrated 4 false positive results and 3 lesions remained undetermined (specificity 83-90% and ppV 84-89%)

Conclusions: In our setting CEUS is practicable with no adverse effects and good accuracy for differentiation of malignant or benign FLL. CEUS is not inferior to MRI/CT and can avoid false negative results (figure 3-5). CT/MRI can avoid false positive results by CEUS and improved specificity. Therefore CEUS should be used complementary with MRI/CT.

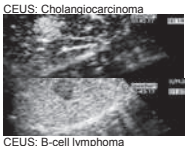
Table 1, group A, n = 112

	sensitivity	npV	specificity	ppV	accuracy
CEUS	96	94.1	84.2	88.8	90.9
MRT/CT	80.9	78.9	93.7	94.4	86.4

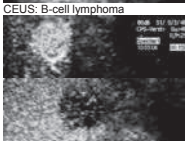
Table 2, group B (gold standard histology), n = 44

	sensitivity	npV	specificity	ppV	accuracy
CEUS	97.2	98.5	90.6	83.7	92.8
MRT/CT	80.6	89.8	94.6	89.2	89.6

CEUS: Cholangiocarcinoma



CEUS: B-cell lymphoma



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Treatment of genotype 1 Hepatitis C patients with severe fibrosis or compensated cirrhosis: the Telaprevir early access program in patients from Austria and Switzerland

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Background: HEP3002 is an ongoing, open-label, early access program (EAP) of telaprevir (TVR) in 16 countries, for adult patients with HCV G1 with severe fibrosis or compensated cirrhosis. **Methods:** Patients were treated with TVR, pegIFN-alpha and ribavirin (PR) for 12 weeks, followed by PR alone. Severe fibrosis or cirrhosis (F3, F4) and platelet count >90 000/mm^3 were required at entry. This interim (ITT) analysis included 16-week data from 36 patients currently enrolled in Switzerland (n=15) and Austria (n=21). **Results:** 69%/31% had severe fibrosis/cirrhosis, 67% HCV RNA levels ≥800,000 IU/mL. 10 (28%) developed drug-related grade 1-4 anemia (Hb<11 g/dL or >2.5 g/dL reduction), 17 (47%) grade 1-3 rash, and 17 (47%) pruritus. 5 (14%) discontinued TVR for adverse events, including 4 (11%) who discontinued for rash and 2 (6%) for anemia. In the Intent-to-Treat analysis, the percentage of patients who had HCV RNA <25 IU/mL (or undetectable) at week 4 was 82% (59%) for treatment naïve and prior relapsers combined, and 79% (36%) for prior non-responders and viral breakthroughs. At week 12, the percentage was 91% (91%) for treatment naïve and prior relapsers, and 86% (79%) for prior non-responders and viral breakthroughs. **Conclusions:** In this TVR EAP for patients in Austria and Switzerland with severe fibrosis or compensated cirrhosis, 86% of patients had undetectable HCV RNA by week 12 (ITT). 5 patients (14%) discontinued TVR for adverse events.

Treatment of HCV G1 patients with severe fibrosis or compensated cirrhosis: the international Telaprevir early access program 25

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Background: HEP3002 is an ongoing, open-label, early access program of telaprevir (TVR) in 16 countries, for patients with HCV G1 with severe fibrosis or compensated cirrhosis. **Methods:** Patients were treated with TVR, pIFN-α and ribavirin (PR) for 12 weeks, followed by PR. Severe fibrosis or cirrhosis (F3, F4) and platelet count >90,000/mm^3 were required at entry. This interim (ITT) analysis included 16 week data from the first 609 patients. **Results:** 45%/55% had severe fibrosis/cirrhosis, 66% HCV RNA levels ≥800,000 IU/mL. 59% developed grade 1-4 anemia, with 31% severe cases (Hb<9 g/dL or >4.5 g/dL reduction); 42% developed grade 1-3 rash, including 4% severe cases (Grade 3) and 1 SJS (resolved); 30 (5%) discontinued treatment for rash, 19 (3%) for anemia. 85 (14%) developed serious adverse events (SAE). 3 cirrhotic patients died (in PR phase) due to hepatic failure or ischemic colitis with subsequent multi-organ failure. **Conclusions:** 79% of patients had undetectable HCV RNA by Week 12 (ITT). SAE occurred in 14%, discontinuation due to anemia/rash was similar to phase III registration trials.

Loss of PTPN22 regulates MDP induced signaling, cytokine release and autophagy 27

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Background: Variations within the gene locus encoding protein tyrosine phosphatase non-receptor type 22 (PTPN22) are associated with the risk to develop inflammatory bowel disease (IBD). However, the functional link between PTPN22 variants and IBD is still not well understood. Aberrant activation of the muramyl-dipeptide (MDP) sensor, nucleotide-binding oligomerisation domain 2 (NOD2) and autophagy induction are both involved in IBD pathogenesis. Here we studied whether loss of PTPN22 interferes with MDP-induced NOD2 signaling, cytokine secretion and autophagy in human THP-1 monocytes.

Methods: Knockdown of PTPN22 was induced by shRNA transfection. Protein levels were analyzed by Western blot, mRNA expression by quantitative PCR, cytokine secretion by ELISA, autophagosome formation by immunofluorescent staining. THP-1 cells were used for all studies.

Results: MDP (500ng/ml) treatment enhanced PTPN22 mRNA levels ($p<0.01$), protein expression ($p<0.05$) and phosphatase activity ($p<0.01$). In turn, loss of PTPN22 enhanced MDP-induced phosphorylation of c-Jun N-terminal kinases (JNK) and p38 ($p<0.001$ each) as well as the canonical nuclear factor (NF)-kB-isoforms, p65 and p50 ($p<0.05$ each) by 30 min treatment. Consistent with elevated JNK/p38/NF-kB activation we detected enhanced secretion of interleukin (IL)-6 ($p<0.01$) and IL-8 ($p<0.001$) after 24 h MDP treatment.

Additionally, loss of PTPN22 resulted in increased protein levels of microtuble-associated protein light chain 3 (LC3)B-II ($p<0.01$) and autophagy-like (ATG)7 ($p<0.05$), but reduced p62 ($p<0.05$) protein levels, indicative for increased autophagy activation. This observation could be fully supported by immunofluorecent staining for LC3B showing increased LC3B levels in PTPN22 deficient cells.

Conclusion: In summary, our data demonstrates that PTPN22 controls NOD2 signaling, and loss of PTPN22 renders monocytes more reactive towards bacterial products, what might explain the association of PTPN22 variants with IBD pathogenesis.

The Comprehensive Complication Index (CCI) A Novel Continuous Scale to Measure Surgical Morbidity 26

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Background: Reporting of surgical complications is inconsistent and often incomplete. Most studies fail to provide information about the severity of complications, or only report the most severe event, ignoring events of lesser severity. The aim was to develop and validate a comprehensive complication index (CCI) summarizing all events with their respective severity.

Methods: We used an established classification of complications, adopting methods from operation-risk-index analysis in economy to develop a formula that considers all complications that may occur in a patient. The weights of each grade of complication, defined as median-reference-values (MRV), were obtained from 472 participants, who rated 30 different complications. Validation to assess sensitivity to treatment effects and validity of the CCI was performed through four different approaches based on 1299 patients.

Results: The CCI is calculated as the sum of all complications that are weighted for their severity (multiplication of the MRVs from patients and physicians). The final formula yields a continuous scale to rank any combination of complications from 0-100 in a single patient. The CCI was highly sensitive in detecting treatment effect differences. It also showed a negative correlation with postoperative health status ($r=-0.24$, $p=0.002$), and high correlation with the results of patient-rated single and multiple complications on conjoint analysis ($r=0.94$, $p<0.001$).

Conclusions: The CCI summarizes all postoperative complications and is more sensitive than existing morbidity endpoints. It may serve as a standardized and widely applicable endpoint in surgical trials and other interventional fields of medicine. The CCI can be computed on the online calculator at www.assessurgery.com.

Determinants for Substrate Selectivity of the Hepatitis C Virus NS3-4A Protease 28

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Background: The hepatitis C virus (HCV) NS3-4A protease is not only an essential component of the viral replication complex and prime target for antiviral intervention but also a key player in the pathogenesis of HCV. It cleaves the viral polyprotein at the consensus sequence D/E-X-X-X-X-C/T↓S/A-X-X-X. However, the recent identification of cellular substrates of the NS3-4A protease has revealed a more complex scenario. Indeed, a vast number of cellular proteins display this consensus sequence but are not cleaved. In addition, the cellular substrates identified thus far (MAVS, TRIF, TC-PTP and DDB1) have less canonical cleavage sites. Hence, the aim of this ongoing study is to characterize the determinants for substrate selectivity of the NS3-4A protease.

Methods: Different chimeric constructs generated by exchanging transmembrane domains and other regions between the known as well as newly identified cellular substrates and uncleaved proteins were examined for cleavage by the NS3-4A protease.

Results: Our analyses revealed that not only the sequence of the cleavage site is important but that the topology of the cleavage site with respect to intracellular membranes as well as the transmembrane domain contribute to substrate selectivity of the NS3-4A protease.

Conclusions: Our study identifies new determinants for substrate recognition by the HCV NS3-4A protease. Advances in our understanding of the determinants for selectivity of the HCV NS3-4A protease should provide further insights into an important aspect of the pathogenesis of hepatitis C.

Isolated tumor cells in node-negative colon cancer patients are a negative prognostic factor for disease-free and overall survival. A propensity score analysis 29

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Background: Lymph node (LN) involvement represents the strongest prognostic factor in colon cancer patients. We tested the prognostic value of isolated tumor cells (ITC) in LN of stage I & II colon cancer patients applying propensity-scoring methods.

Methods: 74 stage I & II colon cancer patients were operated at a single institution (2005-2011). LN at high risk of harboring ITC were identified via an in vivo sentinel lymph node procedure. These LN underwent multilevel sectioning and CK-19 staining. The correlation between ITC and survival was assessed using Cox regression and propensity score analyses.

Results: Median follow-up was 4.6 years (range: 1 month to 8.0 years). In 23 patients (31.1%) ITC were detected. The presence of ITC was associated with an increased risk for recurrence in unadjusted (hazard ratio [HR] = 2.82, p=0.043), in risk-adjusted (HR = 4.73, p=0.005) and in propensity score-adjusted analysis (HR = 5.24, p=0.022). Similarly, ITC were correlated with an increased risk of death (HR = 4.12, p=0.041)

Conclusions: This is the first propensity-score based analysis providing compelling evidence that ITC in stage I & II colon cancer patients are associated with shortened disease-free and overall survival. The presence of ITC should be classified as a high risk factor in stage I & II colon cancer patients who might benefit from adjuvant chemotherapy.

Oncological quality of emergency resection of colon cancer is not inferior to elective procedures 30

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Background: Up to one third of colon cancer (CC) patients are first diagnosed at the emergency department. Conflicting results have been reported considering the overall survival. Little has been published about the quality of these emergency operations. The objective of this study is to compare the quality of CC resection in an emergency setting with the standard oncological resection and its effect on overall survival.

Methods: Retrospective review of 521 patients, operated for CC in the period from 1996 to 2011 at the University Hospital Basel. Baseline characteristics, number of harvested and involved lymph nodes (LN), as quality indicators for oncologic resection, and overall survival were collected from the clinical electronic database. Statistical analyses were performed using SPSS (version 21).

Results: Of the 521 patients, 12.7% received emergency surgery. Mean age was 72.1 years (range 26.3 - 99.9). LN harvest in the emergency group (mean=20.5) did not differ from the elective group (mean=18.2) (p=0.081). Detection of nodal positive LN was not inferior in the emergency or elective group with a mean of 2.4 and 1.8 affected LN, respectively (p=0.39). Overall survival was 116.4 months for the emergency group and 143.9 months for the elective group with no significant difference (p=0.28).

Conclusions: This study does not support the reported evidence of poorer survival in patients undergoing emergency operation for CC. The performance of a high quality oncologic resection in an emergency setting is feasible and ensures that no differences in overall survival will be observed.

Posters Gastroenterology

Effects of retinoid treatment on murine gut microbiota and experimental colitis G1

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Background: *In-vitro* and *in-vivo* data have shown that retinoid treatment promotes an anti-inflammatory milieu with few adverse effects towards the gastrointestinal tract, yet there is current debate about a causal relation between retinoid treatment and inflammatory bowel disease (IBD). Here we studied the effects of retinoid treatment on murine gut microbiota and on intestinal inflammation in two mouse models of IBD.
Methods: Animals were treated with isotretinoin for 2 weeks. Faecal samples were collected before, directly after and 4 weeks after the treatment period, and gut microbiota was analysed by 16S rRNA sequencing. Chronic DSS colitis was induced by four cycles of DSS with retinoid treatment starting with the last DSS cycle and continuing until the end of the study 5 weeks later. Transfer colitis was induced by transfer of naïve T cells and treated by transfer of regulatory T cells with both types of T cells isolated from vehicle or isotretinoin treated donors. Assessments included endoscopic/histological scores, colon length, spleen weight, myeloperoxidase activity, serum cytokines, and plasma isotretinoin levels.
Results: Retinoid treatment did not influence the course of colitis in both murine IBD models. Microbiota analysis shows that retinoid treatment has no significant effects on the composition of murine gut microbiota.
Conclusion: Retinoid treatment has no adverse effects on experimental colitis and leads to no fundamental changes in murine gut microbiota composition.

Perianal abscesses in Crohn's disease – it's not always just perianal Crohn's disease G2

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Background: Many patients with Crohn's disease (CD) suffer from severe perianal disease with fistulas and abscesses. We describe a patient with therapy-resistant perianal disease who was suffering from an unexpected differential diagnosis. **Methods and Results:** Case report of a 58 year old female smoker with CD diagnosed more than 20 years ago, with ileocaecal and perianal disease activity leading to repetitive perianal fistulas and abscesses. Previous treatments of perianal disease included infliximab 13 years ago (stopped because of alopecia as possible side-effect) and repetitive courses of antibiotics and surgical incisions. 10 years ago, right hemicolectomy was performed because of caecal cancer pT3pN1MoG3. Postoperatively, the patient had a mild but ongoing chronic perianal disease and no evidence of cancer recurrence so far. The last colonoscopy 2 years ago showed only mild ulcerations at the iloetransversostomy. Recently, the patient presented again in autumn 2012 with severe perianal swelling and pain. Pelvic MRI described a transphincteric fistula without evidence of large abscesses. After non-response to a combined therapy with antibiotics and adalimumab for 6 months, the indication was given for surgical seton drainage. Intraoperatively, the anal canal showed no evidence of CD, especially no evidence of fistulas. Suspecting acne inversa, multiple perianal abscesses were treated with wide local excision and left open for secondary wound healing. The clinical suspicion of acne inverse was supported by histology compatible with acne inverse, but without granulomas suggestive of CD. **Conclusions:** Perianal abscesses in CD do not necessarily reflect perianal fistulising CD. Acne inverse (or hidradenitis suppurativa) is associated with CD, and smoking is a risk factor for both diseases. Especially patients with "skin problems" in the axilla or genital region, acne inverse should be kept in mind as differential diagnosis to perianal CD.

Periodontitis and gingivitis in inflammatory bowel disease: a case-control study

G3

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Background: The oral cavity is frequently affected in patients with inflammatory bowel disease (IBD), especially in patients with Crohn's disease (CD). Periodontitis is thought to influence systemic autoimmune or inflammatory diseases. We aimed to analyze the relationship of periodontitis and gingivitis markers with specific disease characteristics in IBD patients and to compare these data with healthy controls. **Methods:** In a prospective 8-month study, systematic oral examinations were performed in 113 IBD patients, including 69 CD patients and 44 ulcerative colitis (UC) patients. For all patients, a structured personal history was taken. 113 healthy volunteers served as a control group. Oral examination focussed on established oral health markers for periodontitis (bleeding on probing, loss of attachment, periodontal pocket depth) and gingivitis (papilla bleeding index). Additionally, visible oral lesions were documented. **Results:** Both gingivitis and periodontitis markers were higher in IBD patients than in control-patients. In univariate analysis and logistic regression analysis, perianal disease was a risk factor for periodontitis. Non-smoking decreased the risk of having periodontitis. No clear association was found between clinical activity and periodontitis in IBD. In only the CD subgroup, high clinical activity (HBI >10) was associated with one periodontitis marker, the loss of attachment at sites of maximal periodontal pocket depth. Oral lesions besides periodontitis and gingivitis were not common, but nevertheless observed in about 10 percent of IBD patients. **Conclusions:** IBD and especially perianal disease in CD is associated with periodontitis. Optimal therapeutic strategies should focus on treating both local oral and systemic inflammation.

High variety of symptoms in patients with different pattern of dyssynergic defecation

G5

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Background: Dyssynergic defecation (DD) is reported to be the main defecation disorder in patients with pelvic floor dysfunction due to different etiologies. According ROME III guidelines patients must satisfy diagnostic criteria for functional constipation and have DD patterns in at least two of the following studies: anorectal highresolution manometry (aHRM); anal sphincter EMG; MR defecography (MRD); and impaired balloon expulsion test (BET). The aim of this study was to analyse different DD patterns in functional tests in relation to variable clinical features. **Methods:** The electronic data base of the interdisciplinary pelvic floor center was used to extract 37 (23%) from 161 consecutive patients from 1.1.2010 to 30.4.2013. All patients had a workup with EMG, aHRM and BET, pathologic tests were compared with clinical features. **Results:** 37 patients showed a DD pattern in one functional test, in 26 patients two tests were pathologic. Symptoms of functional constipation were present in 28 (75%) of these patients. The other 9 (25%) patients suffered from anal incontinence or urge symptoms. 4 (11%) patients had comorbidities as neurological disorders (parkinson disease, multiple sclerosis), 12 (32%) had structural abnormalities (intussusception, sphincter damage, etc.). **Conclusion:** In our study population defecation symptoms vary greatly among patients with different DD patterns on functional testing, depending on comorbidities or structural abnormalities. Which group of patients will benefit most from specific biofeedback therapy will now be investigated.

Distinct pathophysiological profiles for discrimination of autoimmune pancreatitis subtypes.

G4

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Background:
Autoimmune pancreatitis (AIP) is a newly described and rare form of chronic pancreatitis. Two different subtypes with distinct clinical presentation have been recently individualized. However, diagnosis of AIP remains still a challenge and discrimination between both subtypes is only possible on histological specimen. For these reasons, we proposed here to assess cytokine expression in both, type 1 and type 2 AIP and compare them to pancreatic cancer and chronic pancreatitis, both difficult differential diagnosis of AIP.
Methods:
Using the **Bio-Plex system®**, that allows the multiplexing of different ELISA-type assays, we assessed cytokines concentrations in the sera and the pancreatic tissues.
Results:
We showed that IL-8, MIP-1b and MCP-1 are significantly more expressed in type 2 than type 1 AIP. These pro-inflammatory cytokines induce infiltration and activation of leukocytes -mainly neutrophils- into the sites of inflammation of pancreas. This results into a continuous activation and amplification of the cytokine cascade that might be the origin of the specific histological characteristic of type 2 AIP that is the destruction of the pancreatic duct epithelium by invading granulocytes.
Conclusions:
These three cytokines may help to distinguish both types of AIP. However, further studies are required to explain the role of activated macrophages in type 2 AIP and the origin of this activation.

Increased lymphocyte apoptosis upon ABT-737 during inflammatory conditions

G6

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Background: In Crohn's disease (CD), mucosal T cells escape normal apoptosis due to enhanced expression of the pro-survival protein B-cell lymphoma-2 (BCL-2) when compared with controls. ABT-737 (Abbvie) is an inhibitor of BCL-2 and has been shown to induce apoptosis.
Methods: 50 mg/kg/day ABT-737 was applied upon DSS-induced acute colitis and in a model of spontaneous colitis.
Results: In both models of colitis spleen weight was significantly decreased upon ABT-737 indicating an ameliorated inflammation compared to vehicle control. A significantly increased colon length, reduced histological and colonoscopy score confirmed ameliorated inflammation upon ABT-737. Total number of lymphocytes was significantly decreased upon ABT-737. In contrast percentage of $CD4^+CD25^+FoxP3^+$ Tregs was increased.
Conclusions: Treatment with BCL-2 inhibitor ABT-737 alters lymphocyte survival during inflammatory conditions and ameliorates experimental colitis. Inducing apoptosis of autoreactive lymphocytes may be a new therapeutic strategy for CD patients.

Treatment Duration with anti-TNF-α Drugs in the Swiss IBD Cohort Study

G7

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Background: Anti-TNF-α drugs (infliximab [IFX], adalimumab [ADA], certolizumab pegol [CZP]) are effective in inducing and maintaining response and remission in inflammatory bowel disease (IBD). Insufficient response or side effects may lead to a switch of the anti-TNF-α drug. We aimed to evaluate the frequency of anti-TNF-α drug use and the prevalence of anti-TNF-α switches in the Swiss IBD Cohort Study (SIBDCS).
Methods: Data from the SIBDCS were analyzed. Only patients naïve to anti-TNF-α drugs at inclusion were considered.
Results: A total of 1,731 patients (956 with Crohn's disease [CD], median disease duration 9 years; 775 with ulcerative colitis [UC], median disease duration 8 years) were analyzed. Thirty-six percent (347/956) of CD patients were ever treated with an anti-TNF-α, whereof 84.8% received one, 12.0% two and 3.0% three anti-TNF-α drugs. Of the 775 UC patients a total of 129 (16.6%) were ever treated with an anti-TNF-α, whereof 84.5% were treated with one, 13.2% with two and 2.3% with three anti-TNF-α drugs. Frequencies of the first used anti-TNF-α in CD and UC, respectively, were 68.3% and 76.7% for IFX, 13.3% and 7.8% for ADA, and 3.2% and 0% for CZP. Median treatment duration (in months) was longest for the first anti-TNF-α (CD: 25 [12-41]; UC: 14 [6-33]), followed by the second (CD: 13 [4-22]; UC: 4 [2-22]), and by the third anti-TNF-α (CD: 11 [1-11]; UC: 15 [1-26]). For all three anti-TNF-α, treatment duration was longer for CD patients compared to UC patients.
Conclusion: Anti-TNF-α were used in 36% of CD patients and in 17% of UC patients. Median treatment duration was longest for the first anti-TNF-α used, followed by the second and third one. Patients with CD sonsistently had longer treatment durations compared to UC patients for all anti TNF-α drugs.

Oral DSS induces a Cecum Localized Colitis in Rabbits

G8

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Background: Some therapeutic strategies for IBD cannot be adequately studied in rodent models. We describe a rabbit colitis model that allows to evaluate the therapeutic potential of helminth species (such as *T. suis* ova-TSO) that fail to colonize rodents whilst hatching in the human and rabbit intestine.

Methods: White Himalayan rabbits (n=12) were feed with 0.1% DSS in the daily beverage (fennel tea) during five days. Control rabbits (n=5) received tea only. Clinical symptoms were monitored daily and rabbit were sacrificed at different time points.

Results: The Disease activity index (DAI) of control rabbits remained below the baseline (DAI < 0.5); whilst the DAI of DSS rabbits increased up to 2.1 ± 0.4 at day 10 (n=6) post start of the DSS treatment. DSS caused a cecum localized pathology characterized by disruption of mucosal morphology, crypt loss, epithelial damage and infiltration of immune cells. Quantification of the histopathology showed a progressive increase in the histology score from a baseline value of 7.6 ± 0.9 in control rabbit (n=5) to an average score of 14.2 ± 4.9 at day 10 (n=4) and a further increase until day 14. Gene expression analysis of inflammatory markers in the cecum showed a transient increase of IL-12p35 expression. The neutrophils infiltration into the cecum of DSS treated rabbits transiently increased at day 5-7 before returning to baseline levels at day 14. DSS administration did not affect the other tracts of the intestine.

Conclusions: Administration of 0.1% DSS for 5 days induces an acute cecum localized inflammation that mimics some features of ulcerative colitis. The localization of the inflammation in the cecum makes the DSS model suitable to study the effects of a TSO treatment as the cecum is the site of *T. suis* colonization in rabbits.

Long-term efficacy of lubiprostone demonstrated in patients with constipation regardless of age, gender or race

G9

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Encore abstract (presented at: UEGW 2009, BSG 2013)
Background: In 24- and 48-week trials, lubiprostone demonstrated safety and efficacy in long-term treatment of adults with chronic idiopathic constipation. Analyses of lubiprostone's (24 mcg BID) efficacy in age, gender and race subgroups were performed.
Methods: Pooled data from three Phase 3 open-label safety studies were reviewed to analyse efficacy in the following subpopulations: non-elderly (<65 years) and elderly (≥65 years); male and female; and non-white and white. Constipation severity, abdominal bloating, and abdominal discomfort were rated on a 5-point scale ranging from absent to very severe.
Results: In the non-elderly and elderly, lubiprostone improved constipation severity (p≤0.0001) each week Week 1 through Week 48. Among males and females, lubiprostone improved (p≤0.0001) constipation severity each week with similar findings (p≤0.0001) for non-whites and whites, For abdominal discomfort, significant changes were seen at all weeks in the non-elderly (p≤0.0001) and for all weeks in the elderly (p≤0.0001 to p=0.0150) except Week 8 (p=0.0530). Among the genders, improvements occurred at all weeks in males (p≤0.0001 to p=0.0220) and in females (p≤0.0001). Significant changes in abdominal bloating were seen in the non-elderly (p≤0.0001) and for the elderly (p≤0.0001 to p=0.0180) at all weeks. Abdominal bloating improved at all weeks for males (p≤0.0001 to p=0.0010) and females (p≤0.0001). For non-whites and whites, abdominal bloating improved (p≤0.0001) at all weeks.
Conclusions: Lubiprostone demonstrated long-term efficacy through an overall improvement in constipation severity for up to 12 months regardless of age, gender, or race.

Lubiprostone treatment improves constipation and related symptoms in patients refractory to other constipation therapies

G10

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Encore abstract (presented at: UEGW 2009, BSG 2013)
Background: Many patients are dissatisfied with currently-available laxative treatments for constipation, with most interested in access to other treatment options[1]. Lubiprostone (24 mcg BID) has been shown to be effective and well-tolerated in patients with refractory constipation.
Methods: Patients with a history of constipation despite the use of constipation medication during the 90 days prior to initiation of study medication were included. Response rates and symptomatic improvements in this subpopulation of refractory patients were analysed based on treatment assignment in the clinical trial: lubiprostone (24 mcg BID) or placebo.
Results: Full response to treatment ranged from 52.8 to 67.2% across the 4 weeks of treatment, as compared to 32.3% to 47.4% for placebo patients. Lubiprostone produced a significant and full response over placebo, respectively, among the refractory patients who previously took contact laxatives 50.9–64.9% vs. 21.3–42.6%; PEG solutions 57.5–75.0% vs. 32.5–52.5%; or enemas 50.0–71.4% vs. 23.3–50.0%. For symptoms of constipation such as stool consistency and straining, lubiprostone treatment resulted in statistically significant improvements compared to placebo at each study week (p≤0.001).
Conclusions: Given the statistically significant response to lubiprostone in patients refractory to other constipation therapies, lubiprostone may be a helpful addition to the armamentarium for patients suffering from chronic idiopathic constipation.
References: Müller-Lissner et al. Aliment Pharmacol Ther 2013;37(1):137-145.

Lubiprostone demonstrates efficacy in adult patients with constipation regardless of age, gender or race G11

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Encore abstract (presented at: UEGW 2009, BSG 2013)

Background: Lubiprostone has demonstrated safety and efficacy in treating adults with chronic idiopathic constipation. Through an analysis of the subgroups of two Phase 3 studies, the efficacy of lubiprostone based on factors such as age, gender, and race was reviewed.

Methods: Combined data from two Phase 3 well-controlled studies were used to analyse the following subpopulations: non-elderly (<65 years) and elderly (≥65 years); male and female; and white and non-white. The efficacy endpoints for spontaneous bowel movement (SBM) frequency, stool consistency, and straining were compared between placebo and lubiprostone (24 mcg BID) groups within each subpopulation.

Results: Among non-elderly patients, lubiprostone produced a greater increase ($p \leq 0.001$) in SBM frequency each week over placebo. Statistically significant increases were observed in the elderly ($p \leq 0.0268$) at each week except Week 2 ($p = 0.0806$). Statistically significant improvements were noted in females ($p \leq 0.001$) at all weeks and in males at all weeks ($p \leq 0.05$) except Week 3 ($p = 0.0758$). Stool consistency was improved with lubiprostone in the non-elderly ($p \leq 0.0441$) and the elderly ($p \leq 0.001$) at all weeks. Straining was also improved with lubiprostone treatment at all weeks in non-elderly patients ($p \leq 0.001$). Stool consistency and straining were statistically significantly improved with lubiprostone at all weeks ($p \leq 0.001$) in females.

Conclusions: Treatment with lubiprostone resulted in increased SBM frequencies and improvement in related symptoms in patients with chronic idiopathic constipation regardless of age, gender, or race.

Pooled analysis of the most frequent adverse events associated with the use of lubiprostone G12

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Encore abstract (presented at: ACG 2006, BSG 2013)

Background: Lubiprostone, a novel ClC-2 activator, has been shown to be efficacious and well-tolerated by patients with chronic constipation in short- and long-term clinical trials. To better characterize the most frequent adverse events (AEs) associated with the use of lubiprostone 24 mcg BID, we examined pooled results of patients enrolled in Phase 2 and 3 trials of 3 to 48 weeks' duration.

Methods: Data for all safety-evaluable patients were pooled and compared between treatment groups (placebo vs lubiprostone 24 mcg BID). Nausea, headache, and diarrhea AEs were analyzed in terms of severity, duration, frequency, action taken (*e.g*, drug withdrawn, dose reduced), and outcome. In addition, nausea-related variables were explored in subpopulations of elderly (≥65 years of age) and male patients.

Results: The pooled population included 1113 lubiprostone and 316 placebo patients. At least 1 AE occurred in 79.1% of lubiprostone patients, which included 31.1% with nausea, 13.2% with headache, and 13.2% with diarrhea. At least 1 AE occurred in 39.6% of placebo patients, which included 5.1% with nausea, 6.6% with headache, and 0.9% with diarrhea. Of those lubiprostone patients who experienced nausea, 88.7% reported nausea to be mild or moderate in severity. Similarly, the majority of lubiprostone patients experiencing headache and diarrhea had mild-to-moderate symptom severity (89.8% and 82.3%, respectively). Discontinuation rates due to nausea, headache, and diarrhea were 8.7%, 3.7%, and 2.2%, respectively.

Conclusions: Nausea, headache, and diarrhea associated with lubiprostone use are generally mild to moderate in severity, intermittent, and limited in duration.

Low-lactose diet has a poor effect on functional bowel symptoms in lactose-intolerant patients G13

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Background: Lactose intolerance is a common (about 15%) finding in the work-up of patients with functional bowel disease. The impact of low-lactose diet (LLD) on functional bowel disorders appears to be inconsistent. The aim of the study was therefore to investigate the effect of LLD on lactose-related bowel symptoms in lactose intolerant (LI) and -tolerant patients (Non-LI).

Methods: 134 consecutive patients underwent a lactose-H2-methane-breath-test (12/2011-03/2013). The breath-test consisted of an oral intake of 25 g lactose followed by an analysis of H2 and methane over 180 minutes by Quintron Breath Tracker SC®, USA. All patients received a standardized questionnaire at least 3 months after the test was performed assessing demographics, diagnosis, symptoms, and dietary habits.

Results: 100 (75%) questionnaires were answered, 92 (69%) were sufficient for analysis (40 LI, 52 Non-LI). A history of IBS-symptoms was more frequent in Non-LI vs. LI (34% vs. 25%, ns). Despite test results LLD was as frequently performed in Non-LI as in LI (67% vs. 82%, ns). Symptoms persisted on LLD in 73% of LI and 77% (ns) of Non-LI. Similar symptoms as with lactose were reported on a fibre-rich diet in both groups (LI: 42%, Non-LI: 37%, ns). A glass of milk was tolerated by 18% of LI vs. 57% of Non-LI ($p < 0.001$)

Conclusions: A low-lactose diet in lactose-intolerant patients appears less efficacious than expected. High prevalence of IBS-symptoms without response to LLD may explain these conflicting results. General changes in diet may be responsible for the therapeutic response of lactose-tolerant patients on low-lactose diet.

Rifaximin Treatment Leads to Long Lasting Symptom Improvement in Lactulose Hydrogen Test Positive IBS G14

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Background: A positive lactulose hydrogen breath test (LHBT) can be found in 43% to 78% of patients with irritable bowel syndrome (IBS). Symptoms in LHBT+ IBS patients may respond to rifaximin. However, there is a lack of studies having evaluated these patients for longer than 3 months. We aimed to assess the IBS symptom evolution and rifaximin retreatment frequency over two years. **Methods:** Enrolled patients fulfilled Rome III criteria. All patients underwent LHB testing. LHBT+ patients were treated with rifaximin for 14 days. Before, at week 6, and year 2 after rifaximin treatment, patients completed a questionnaire, where the following criteria were assessed using 10-point Likert scales: bloating, flatulence, abdominal pain, diarrhea, and overall well-being. Patients with symptomatic recurrence in the follow-up period were treated again with rifaximin. **Results:** A total of 150 patients were included whereof 73 (48.7%, 76% female, mean age 49 ± 15 years) were LHBT+ and treated with rifaximin. Twenty four patients (32.9%) were treated twice with rifaximin within the first 6 weeks (mean 1.33 rifaximin treatments/patient). Rifaximin treatment significantly reduced the following symptoms at week 6 and year 2 compared to baseline: bloating (5.5 ± 2.7 before *vs.* 3.1 ± 2.4 at week 6 [$p < 0.001$] and 3.1 ± 2.7 at year 2, respectively [$p < 0.001$]), flatulence (5.4 ± 2.7 before *vs.* 3.2 ± 2.2 at week 6 [$p < 0.001$] and 3.4 ± 2.7 at year 2 [$p < 0.001$]), diarrhea (3.3 ± 2.6 before *vs.* 1.7 ± 1.6 at week 6 [$p < 0.001$] and 1.8 ± 1.9 at year 2 [$p < 0.001$]), abdominal pain (5.3 ± 2.7 before *vs.* 2.9 ± 2.2 at week 6 [$p < 0.001$] and 3.0 ± 2.6 at year 2 [$p < 0.001$]) and resulted in less impaired well-being (4.3 ± 2.1 before *vs.* 2.6 ± 2.2 at week 6 [$p < 0.001$] and 2.5 ± 2.1 at year 2 [$p < 0.001$]).

Conclusions: Rifaximin significantly improves IBS symptoms during a two-year follow-up. One third of patients needed rifaximin treatment twice during the two-year follow-up.

Development of a Standardized Method to assess Symptoms in Adult Patients with Eosinophilic Esophagitis G15

Safroneeva E[1], Panczak R[1], Haas N[1], Kuehni C[1], Zwahlen M[1], Bussmann C[2], Straumann A[3], Schoepfer AM[4]; International EEsAI study group. [1]ISPM, University of Bern, [2]Viollier Pathology, Basel, [3]University Hospital Basel, [4]University Hospital Lausanne/CHUV

Background: Assessment of disease activity is required for performing clinical trials. We are developing for Eosinophilic Esophagitis (EoE) a composed, modular assessment instrument (EEsAI = EoE Activity Index) fulfilling the methodological and regulatory requirements for readouts. The purpose of this study is to evaluate the symptom (= patient reported outcomes = PRO) module in an adult cohort of patients with Eosinophilic.

Methods: The development of the EEsAI comprises three phases: 1. Selection of candidate items by Delphi rounds; 2. Evaluation of the activity index in a first patient cohort; and 3. Validation in a second EoE patient cohort. Here we describe the evaluation of the PRO module which was developed in collaboration with regulatory authorities (FDA).

Results: A total of 156 patients were prospectively included in EoE centers from the United States, Canada, and Switzerland (114 males, median age at enrolment 38 [29-46] years). Each visit consisted of a completion of the PRO module (by patients themselves), an upper endoscopy, histology, and a blood sample. Patients preferred the 7 day symptom recall period over the 30 day or 24 hours recall period. Gold-standard for symptom severity was a 10-point Likert scale reporting clinical activity over the last 7 days. Median symptom severity was 2 (interquartile range 1-4). A total of only five items assessing different qualities of dysphagia explained 65.2% of the entire variability of EoE symptom presentation.

Conclusions: The EEsAI PRO module is being developed by an international team in collaboration with regulatory authorities. It is the first instrument assessing severity of EoE symptoms in a standardized and reproducible way.

Development of a Standardized Method to assess Symptoms in Adult Patients with Eosinophilic Esophagitis G16

Safroneeva E[1], Panczak R[1], Haas N[1], Kuehni C[1], Zwahlen M[1], Bussmann C[2], Straumann A[3], Schoepfer AM[4]; International EEsAI study group. [1]ISPM, University of Bern, [2]Viollier Pathology, Basel, [3]University Hospital Basel, [4]University Hospital Lausanne/CHUV

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Conclusions: The EEsAI PRO module is being developed by an international team in collaboration with regulatory authorities. It is the first instrument assessing severity of EoE symptoms in a standardized and reproducible way.

The influence of the 5-HTTLPR genotype on the cerebral processing of oesophageal pain in healthy volunteers – a pilot study G17

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Background: Serotonin plays an important role in the regulation of pain and emotion. Carriers of the s-allele of the serotonin transporter linked polymorphic region (5-HTTLPR) have been linked with anxiety and functional gastrointestinal disorders and show greater activation of emotion-regulating brain regions in response to colorectal distension. We aimed to study the relationship of the 5-HTTLPR genotype and brain processing of oesophageal pain. **Methods:** The personality traits neuroticism and anxiety and 5-HTTLPR genotype were assessed in 30 healthy volunteers. Brain activity was acquired using functional MRI during painful oesophageal distension (20 stimuli of a 1 second balloon inflation at pain tolerance threshold). Brain activity between genotypes (l/l, l/s, s/s) was compared using ANOVA and linear trend analysis. **Results:** The distribution of the 5-HTTLPR polymorphism was: 7 s/s, 11 l/s, 12 l/l. Sensory and tolerance thresholds to balloon inflation, mean pain ratings, neuroticism and anxiety scores did not differ between the 5-HTTLPR genotypes. Subjects with the s/s genotype showed enhanced activation of the cerebellum, insula, inf. frontal gyrus, supplementary motor area (SMA) and precentral gyrus during oesophageal pain. Trend analysis showed greater activation in l-carriers (ll>ls>ss) in the peri-genual ant. cingulate cortex and greater activation in s carriers (ss>ls>ll) in the primary somatosensory cortex, motor cortex and SMA. **Conclusion:** These preliminary findings are contrary to previous work showing increased activity in emotion-regulating brain regions in s-carriers. However, unlike previous studies, the subjects in this pilot work are all healthy volunteers and not different in personality trait and pain sensitivity, which could explain the disparity in the current observations.

Positive and negative mood modulate esophageal pain perception in healthy volunteers G18

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Background: It is generally accepted that mood plays an important role in the altered perception of visceral sensations in functional gastrointestinal disorders (FGID). Compared to somatic pain, evidence supporting this hypothesis for visceral pain is sparse. We aimed to investigate the effect of positive and negative mood on esophageal pain perception. **Methods:** Positive, negative, and neutral mood were induced in 68 healthy volunteers (36 men, mean age 26.7 years) using a combination of Velten mood induction statements, validated emotional pictures and music. Visceral pain was evoked by balloon distensions in the esophagus at individually determined pain toleration levels. Participants rated mood at the beginning/end of the experiment, and pain intensity/unpleasantness after each stimulus. Data were analyzed using repeated measures ANOVA. **Results:** Compared to neutral, ratings of mood were significantly lower following negative and higher following positive mood induction ($p<.0001$) which confirms the efficacy of the mood induction procedure. A significant effect of mood on pain ratings was found, with higher and lower pain ratings during negative and positive mood, respectively ($p<.0001$, compared to neutral). **Conclusion:** We are the first to report that both negative and positive mood modulate esophageal pain perception in healthy volunteers. We observed large inter-individual differences in the effect of mood on visceral pain perception. This might represent a susceptibility factor or 'endophenotype' for the development of FGIDs. Extensions of this study will explore possible mechanisms that underlie this variability such as genetics (serotonin transporter polymorphism) and central mechanisms (functional MRI).

Peripheral Blood Eosinophil Counts Correlate with Esophageal Peak Eosinophil Counts In Non-Allergic but not in Allergic Patients with Eosinophilic Esophagitis

G19

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Background: There is a need to evaluate non-invasive biomarkers regarding a potential correlation with histologic activity of eosinophilic esophagitis (EoE). Until now, EoE patients have to undergo endoscopy with biopsy sampling to monitor histologic activity under anti-eosinophil therapy. We aimed to evaluate the correlation between peripheral blood eosinophil counts with histologic activity.

Methods: Adult EoE patients were prospectively included and underwent history taking, an upper endoscopy with at least 6 esophageal biopsies, and blood sampling. Peripheral blood eosinophils are reported in G/l (normal range 0.05-0.3). Results are reported as correlation coefficient rho and p-values.

Results: A total of 90 adult EoE patients were included, whereof 55 (61.1%) had one or multiple allergies towards airborne allergens and/or food allergens. Median blood eosinophil values were not different in the group with versus without allergies (0.29 vs. 0.28 G/l, p=0.64). Peripheral blood eosinophil counts correlated with esophageal peak eosinophil counts in non-allergic EoE patients (rho 0.34, p = 0.05), but not in allergic patients (rho 0.05, p = 0.71). If all EoE patients were taken together, peripheral blood eosinophil counts did not correlate with esophageal peak eosinophil values (rho 0.16, p = 0.14).

Conclusions: Peripheral blood eosinophil values correlate with esophageal peak eosinphil counts in non-allergic EoE patients but not in the ones with allergies. Peripheral blood eosinophil counts may serve as biomarker to monitor histologic activity in non-allergic EoE patients.

A Rare Cause For a Bleeding Ventricular Ulcer

G22

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A 73 year old man presented with melena to our endoscopy unit. He complained about upper abdominal pain, fatigue, and weight loss. His vital signs were stable and the haemoglobin was slightly decreased with 113 g/l. The remaining blood tests were normal. Upper endoscopy showed a large bleeding ulcer along the lesser curvature, macroscopically suspect of malignancy. To control the bleeding and to rule out gastric cancer, the patient was referred to surgery. Two thirds of the stomach, a segment of the transverse colon with mesocolon had to be resected en bloc. Final histology revealed a chronic ventricular ulcer with a distinct lymphofollicular, lymphoplasmacellular and eosinophilic inflammation. The number of IgG4 plasma cells was increased (60 IgG4 positive cells per microscopic visual field, 70-80% IgG4 out of all IgGs). Storiform fibrosis and obliterating phlebitis were found not only within the ulcer base but also extensively in the adjacent soft tissue.

Summarizing, our patient suffered from a rare form of a chronic gastric ulceration as a manifestation of IgG4-related disease.

IgG4-related disease is an increasingly recognized condition presenting with specific pathological, serologic and clinical features. Its hallmark is the typical histopathological finding as in our case. Type 1 autoimmune pancreatitis and salivary gland disease are the two typical presentations, but IgG4-disease can affect each organ.

Because of no further organ involvement, consecutive immunosuppressant treatment was not required. Seven months later gastroscopy showed no signs of recurrence.

A gastric ulcer can be the first presentation of IgG4 related disease which needs to be considered as a differential diagnosis in refractory gastritis and cancer suspicious lesions.

Association study of *IL23R* and *ATG16L1* variants in IBD Moroccan patients

G20

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Background: IBD (Crohn's disease and Ulcerative Colitis) is chronic and multifactorial disease of the gastrointestinal tract. Although several studies have tried to explore these diseases, their pathogenesis is still unclear. Recently, CD has been associated with the variants in interleukin 23 receptor (*IL23R*) and autophagy-related 16-like 1 (*ATG16L1*) genes. The aim of our study was to assess the frequency of ATG16L1 (T300A) and IL23R (L310P) variants in Moroccan IBD patients and to determine a possible effect of these variants on Disease's phenotype and clinical course.

Methods: we genotyped a group of 96 Moroccan IBD patients and 114 unrelated volunteers for *ATG16L1* (T300A) and *IL23R* (L310P) variants.

Results: Our results showed no significantly increased risk of Crohn's disease among individuals carrying the GG genotype or the G allele for the (Thr300Ala) polymorphism, in contrast to the (L310P) polymorphism which confers a protective effect. We also noticed the presence of a positive correlation between Crohn's disease Type and ATG16L1 polymorphism. For UC, the carriage of the mutated allele in the ATG16L1 gene confers a protective effect.

Conclusion: Our results showed a limited role of *ATG16L1* and *IL23R* variants in the Moroccan population.

Characterisation of Extraintestinal Manifestations in Inflammatory Bowel Disease, and Chronology of Extraintestinal relative to Intestinal Manifestations in the Swiss Inflammatory Bowel Disease Cohort

G23

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Background: Inflammatory bowel disease (IBD) affects mainly the GI-tact, but extraintestinal organs are often involved as well. There is a lack of data evaluating the chronology between occurrence of IBD and of extraintestinal manifestations (EIM).

Aim: To assess type and prevalence of EIM in IBD patients and to evaluate their chronologic behavior.

Methods: Database-analysis from the Swiss Inflammatory Bowel Disease Cohort (SIBDCS) which collects since 2006 nationwide, prospectively data of IBD patients from hospitals and private practices.

Results: A total of 1,249 patients were analysed (49.8% female, median age 40 (IQR 30-51 years), 735 (58.8%) with Crohn's disease, 483 (38.7%) with ulcerative colitis, and 31 (2.5%) with indeterminate colitis. Of these, 366 (29.3%) presented one to five EIM (67.8% with CD, 28.7% with UC, 3.5% with IC). Of those patients suffering from EIM, 26.5% presented two, 4.9% three, 2.5% four, and 2.7% five EIM during lifetime. The initial EIM presented with the following frequencies: peripheral arthritis 70.0%, aphthous stomatitis 21.6%, ankylosing spondylitis 16.4%, uveitis 13.7%, erythema nodosum 12.6%, primary sclerosing cholangitis 6.6%, pyoderma gangrenosum 4.9%, and psoriasis 2.7%. In 25.8 % of cases, the first EIM manifested before IBD diagnosis was made (median time 5 months before IBD diagnosis, range 0-25 months), in 74.2% the first EIM manifested after established IBD diagnosis (median 92 months, range 29-183 months).

Conclusion: In one quarter of patients EIM was the first manifestation of IBD. Occurrence of EIM-compatible signs should prompt searching for underlying intestinal IBD.

Hepatitis C Triple Therapy of Monoinfected Patients in Switzerland: Multicentre Real Life Experience H1

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Background: Hepatitis C (HCV) triple therapies with boceprevir (BOC) and telaprevir (TVR) are available since 2011 in Switzerland.

Method: Retrospective analysis of 205 monoinfected hepatitis C patients (pts) treated with triple therapy at 7 Swiss hepatology centres (Basel, Bern, Geneva, Lausanne, Lugano, St. Gallen, Zurich).

Results: A total of 205 pts (149 male (76%)/56 female (24%), age 26-76 yrs (mean 51 yrs)) were treated since 2011. Genotyp distribution showed 98 GT1a, 83 GT1b, 20 GT1, 2 GT1a/b and 2 GT2. IL28B genotype was available in 75 (36%) pts: 12 CC, 53 CT, 10 TT. 117 (57%) pts had high viral load (>800'000 IU/ml) at treatment start. Fibrosis staging showed 7 F0 (3%), 14 F1 (6%), 46 F2 (22%), 48 F3 (23%), 88 F4 (43%), 2 (1%) not staged: a total of 136 (66%) with ≥F3. Among treated cirrhotics 5 pts had Child Pugh B, MELD score ranged from 5 to 15 including 6 pts with MELD ≥10. Cirrhotics showed mean albumin of 38 g/L (range 22-41 g/L) with 12 patients <35 g/L; platelets in cirrhotics ranged 49-354 G/L (mean 134) with 23 patients <100 G/L. Pretreatment experience showed 121 (59%) pts with prior HCV therapies (45 (22%) relapser, 55 (27%) null responder, 7 (3%) partial responder, 9 (4%) breakthrough, 5 (2%) undetermined) leaving 84 (41%) naive pts. 49 (24%) patients received BOC, 146 (73%) TVR. 22 pts with lead-in prior to TVR (5 null responder, 3 partial responder, 2 relapser, 10 naive, 2 breakthrough). 60 (29%) pts were eligible for shortened treatment duration with 57/60 achieving eRVR or RVR8, respectively. 50 (24%) pts stopped treatment prematurely so far (16 stopping rule, 21 SAE, 4 breakthrough, 2 malcompliance, 7 undetermined) and one cirrhotic patient died after lead-in due to tumor related bleeding. 83 (40%) pts developed anemia of <100g/L with a minimum of 64g/L; 57 (28%) pts received ribavirin dose reduction, 25 (12%) received blood transfusions and 34 (17%) received EPO. 56 (27%) developed rash (44 TVR,12 BOC). 85 pts reached an end of treatment response, 44 pts reached SVR24, 43 pts failed treatment; in the remaining pts treatment is ongoing and SVR24 pending.

Conclusion: Currently most patients under HCV triple therapy are treatment experienced and show advanced fibrosis. Treatment failure and adverse events are frequent in this real life population.

Characterization of the Proteins Encoded by Hepatitis E Virus Open Reading Frame 1 H2

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Hepatitis E virus (HEV) is believed to be the most common cause of acute hepatitis in the world. Until recently, it has been considered to affect only developing countries. However, autochthonous hepatitis E due to zoonotic transmission of HEV genotype 3 from pigs and other animal species has been recognized as an emerging challenge in industrialized countries. Despite a growing interest, current knowledge of the molecular virology of HEV is scarce. Its positive-strand RNA genome harbors 3 open reading frames (ORF), including ORF1 which encodes the proteins involved in viral RNA replication. The aim of our ongoing studies is to investigate the processing, structure and function of these putative replicase components. To this end, we generated constructs for genotype 1 and 3 HEV ORF1 and individual proteins and are currently characterizing these in different expression systems, including subgenomic replicons. In addition, we produced recombinant ORF1-derived proteins and are developing antibodies as a tool for subcellular localization and polyprotein processing studies. These ongoing efforts should yield new insights into the life cycle of HEV.

Autochthonous Acute Hepatitis E in Switzerland: Increased Rate of Symptomatic Manifestation in Men > 50 Years H3

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Background and aim: Hepatitis E virus (HEV) genotype 3 infection has emerged as a cause of autochthonous acute hepatitis in developed countries. High seroprevalence rates have been reported in Europe and the US. However, available serologic assays have limited reliability and PCR essays are not commonly available. On this background, we established nucleic acid testing for HEV RNA to diagnose and characterize autochthonous acute hepatitis E in Switzerland.

Methods: Viral RNA was purified from plasma or serum and converted to cDNA prior to multiplex real-time PCR for HEV RNA quantification and multiplex PCR coupled to DNA sequencing for HEV genotype determination.

Results: Twelve cases of symptomatic, autochthonous, HEV RNA-positive acute hepatitis E were diagnosed within the last year. Autochthonous infection was probable in the absence of travel to endemic regions. Nine of the 12 patients were men. Of these, all were > 50 years old and 6 were > 60 years old. The clinical course was particularly severe in patients with underlying chronic liver disease, some of whom developed transient liver failure.

Conclusions: In this initial series, men above 50 constituted the majority of patients presenting with symptomatic, autochthonous acute hepatitis E in Switzerland. Data are continuously being updated as more cases are being identified.

Safety of simeprevir (SMV) with PegIFNα-2a/ribavirin (PR) in HCV genotype 1-infected patients: PILLAR and ASPIRE trials H4

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Background: SMV is a once-daily (QD), oral HCV NS3/4A protease inhibitor. SMV/PR demonstrated superior SVR compared to PR in patients with chronic HCV genotype 1 infection in Phase IIb, randomized, double-blind, placebo-controlled trials (PILLAR and ASPIRE). **Methods:** In PILLAR, 156 treatment-naïve patients received PR and SMV 150 mg QD for 12 or 24 weeks; PR duration was response guided (24 or 48 weeks). In ASPIRE, 199 treatment-experienced patients received PR and SMV 150 mg QD for 12, 24 or 48 weeks. Controls received PR for 48 weeks (n=143). This pooled analysis compared safety for SMV 150 mg QD vs PR control during the first 12 weeks of treatment. **Results:** SMV was well tolerated in combination with PR, with no novel AEs observed over those of PR. AEs were mainly grade 1/2 and occurred during early treatment. Rates of serious AEs were 2.3% and 4.2% in the SMV and PR control groups; rates of discontinuation of SMV or PR control due to AEs were 2.8% and 0.7%. Most rash AEs were grade 1/2 (99.6%). Neutropenia was reported more frequently with SMV than with PR control (20.3% vs 14.0%). Incidence of anemia and thrombocytopenia with SMV was similar to PR control. Mild, transient increases in total bilirubin were seen with SMV. **Conclusions:** This pooled analysis showed SMV with PR to be well tolerated in treatment-naïve and -experienced patients with chronic HCV genotype 1 infection. Phase III trials of SMV 150 mg QD are ongoing.

The performance of Fibroscan in assessing liver fibrosis in chronic hepatitis B: the HUG experience H5

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Gastroenterology/Hepatology, Clinical Pathology, HUG, Geneve

Introduction: Liver biopsy is the gold standard for assessing liver fibrosis in chronic liver diseases, but is invasive and associated with potential adverse events. Liver elastography (LE) by Fibroscan® is a non invasive method to evaluate liver fibrosis, validated mainly in chronic hepatitis C. In chronic hepatitis B (CHB), cut-off values of LE for fibrosis stages are more heterogeneous, with a meta-analysis reporting: 7.9 kPa for F2, 8.8 for F3 and 11.7 for F4 (Chon et al, PLoS One, 2012). We report here the performance of LE in consecutive outpatients with CHB with a liver biopsy over a 4-year period. **Methods:** All CHB patients explored using both LE and liver biopsy were considered. Elevated transaminases (>5N); interval LE/liver biopsy > 6 mo; concomitant steatohepatitis; poor liver biopsy specimen, and non validated LE values were considered exclusion criteria. Liver biopsy was interpreted while blinded to LE data, and fibrosis evaluated semi-quantitatively/staged according to METAVIR. Patients were classified as absent/moderate fibrosis (Metavir F0-F1-F2) or advanced fibrosis (F3-F4). Thus, we included 58/198 CHB patients (mean age 42.3 yrs). **Results:** At histology, 21 patients (36%) had significant fibrosis. In this group, mean LE value was 12.1 kPa (median 10.2, SEM 1.4). However, 29% of these patients showed LE values < 8.8 kPa. In the group of absent/moderate fibrosis, mean LE value was 5.8 kPa (median 5.6, SEM 0.3). In this group, 11% of patients had LE values exceeding 7.9 kPa. The values for the prediction of advanced fibrosis were: sensitivity 71% and specificity 89%. **Conclusion:** In this group of CHB patients, and in the absence of extrinsic factors influencing LE values, the performance of Fibroscan® to assess liver fibrosis was overall good but not absolute. Due to the risk of underestimation of advanced fibrosis by LE in a subset of patients, one should consider liver histology as a gold standard in clinical situations with discordant LE values.

Invasive measurement of pulmonary artery pressure in cirrhosis: a study on 127 patients. H6

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Background: In cirrhosis, pulmonary arterial hypertension (PAH) can be due to fluid overload, cardiac failure, or in relation with elevated pulmonary vascular resistance. This condition named portopulmonary hypertension (POPH) carries a poor prognosis beyond that predicted by the MELD. We studied the prevalence of PAH and POPH in patients with cirrhosis who underwent right heart catheterization. **Methods**: Patients examined between 10/2008 to 10/2012 were included. Right heart catheterization was performed together with hepatic hemodynamic study as part of evaluation for liver transplantation or TIPS. **Results**: In the 127 patients (mean age 54.1 yrs, MELD score 15±7, alcoholic cirrhosis: 52%), cardiac output (CO) correlated to the MELD (r=0.41, p<0.001). Among the 19 patients (15%) with elevated PAH (defined by a mean pulmonary artery pressure >25mmHg), 4 (3.2%) fulfilled the criteria for POPH, with the following values: MELD score 11 [8-13], hepatic pressure gradient HVPG 18 mmHg [11-20], mean pulmonary artery pressure 48 mmHg [43-52], CO 7L/min [5-8] and pulmonary vascular resistance 581 dyne/s/cm^{-5} [374-762]. None showed hemodynamic response to inhaled nitric oxide. Two patients were started on sildenafil, one was commenced on sildenafil and bosentan therapy and the last one was treated only with long term oxygen therapy. After a follow-up ranging 2-76 months, all were alive but none were transplanted. **Conclusion**: In patients with cirrhosis, the degree of liver failure correlates with CO as a marker of systemic circulatory changes. Right heart catheterization allows to discriminate between POPH from PAH of other causes. Elevated pulmonary vascular resistance in cirrhosis is a rare event, as reported (Gastro 1991; 100 (2) , but the diagnosis of this condition is clinically relevant.

The secretion of IL-22 by hepatic innate lymphoid cells is modulated by CD39/NTPDase1 H7

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Background: The cytokine IL-22 exhibits specific hepatoprotective properties in various models of liver injury and repair. Nucleotides, such as ATP, are released by such cellular injury, bind to purinergic receptors expressed on hepatic parenchymal and non-parenchymal cells. Levels of extracellular nucleotides are regulated by NTPDase1/CD39, the major vascular ectonucleotidase. We have now explored the cellular fractions in the liver that secrete IL-22 and if extracellular nucleotides impact upon IL-22 secretion of various subsets of innate lymphoid cells in the liver.
Methods: The impact of extracellular nucleotides on cytokine secretion was assessed using surface and intracellular markers. The impact of CD39 on cytokine secretion was tested using CD39 null mice in vitro and in vivo post partial hepatectomy.
Results: Hepatic fractions that secrete IL-22 are mainly innate lymphoid cells including conventional NK cells. Interestingly, all fractions that secrete IL-22 express CD39. Deletion of CD39 is associated with a significant reduction of IL-22 secretion by hepatic lymphocytes that is paralleled by decreased fraction of immature IL-22 positive cells. In vivo, absence of CD39 is associated with significant reduced levels of IL-22 in the serum and reduced liver regeneration post partial hepatectomy.
Conclusion: IL-22 is secreted by specific subsets of hepatic innate lymphoid cells that express CD39. Deletion of CD39 is associated with reduced levels of IL-22 positive hepatic innate lymphoid cells and impaired liver regeneration.

Title: Virus-specific CD4 T cells in acute and chronic hepatitis B virus infection H8

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T cell-mediated response against Hepatitis B virus (HBV) has been recognized as one of the key factors conditioning the infection outcome. While it is well established that HBV-specific CD8 T cells are dysfunctional in chronic infection, much less is known about the phenotype and function of HBV-specific CD4 T cells. In this study we set out to dissect the CD4 T cell response to HBV antigens using a high throughput T cell screening assay, based on selection and expansion of functionally distinct memory T-helper cell subsets identified according to the expression of chemokine receptors. T cells were seeded in replicate cultures, each containing a limited number of cells (100-500), polyclonally activated by PHA and feeder, and expanded for three weeks in IL-2-containing medium. Each culture was then tested for antigen specificity by measuring the proliferative response to HBV antigens (pools of overlapping 18-20mer peptides for core, envelope, or polymerase, or core and envelope recombinant proteins. The analysis is being performed on patients with acute self-limited infection (after seroconversion and with negative viremia), patients with chronic infection at different disease stage, and healthy HBV vaccinated donors. The frequencies of HBV-specific CD4 T cells, albeit variable between the donors analyzed, were consistently higher in patients who successful controlled infection. Memory anti-HBV specific T cells were more prominently found in the CCR6^{-} subset and, within this subset, almost equally distributed in the CXCR3^{+} subset, enriched in Th1 cells, and in the CXCR3^{-} subset, enriched in Th2 cells. In spite of the high sensitivity of the experimental approach, the frequency of HBV^{+} CD4 cells was low or undetectable in chronic patients, irrespective of the clinical status. An unusual strong response was detected in a chronically infected patient under antiviral treatment at the time of test. In patients with chronic infection, stimulation with core and S protein and antigen presenting cells (APCs) was more efficient than stimulation with peptides and APCs. Interestingly, EBV-immortalized B cells (carrying either BCR specific for HBV antigens or of unrelated specificities) were superior to monocytes in presenting antigen to HBV-specific T cells. The role of B cells as antigen-presenting cells deserves further analysis, and may provide new insights in the interplay between B and T cells in chronic HBV infection, and help clarifying the mechanism of immune impairment that characterize chronic HBV infection.

Production of Recombinant Hepatitis C Virus Nonstructural Protein 4B in Mammalian Cells H9

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Background: Nonstructural protein 4B (NS4B) is the master organizer of hepatitis C virus (HCV) replication complex formation. It is a multispanning membrane protein that acts as an oligomer and has been reported to possess NTPase and RNA binding activities. However, important aspects of its structure and function remain elusive. The availability of functional recombinant HCV NS4B should facilitate advances in this important field.

Methods: U-2 OS human osteosarcoma cells inducibly expressing FLAG-tagged NS4B were expanded to large scale, followed by hypotonic lysis, fractionation, differential membrane extraction, solubilization by the nonionic detergent n-dodecyl-β-D-maltoside, and FLAG affinity purification on magnetic beads.

Results: Careful optimization of the different steps involved in this new expression and purification protocol allowed for the production of 1 mg of recombinant HCV NS4B from 10^9 cells. Enzymatic assays and circular dichroism structural studies as well as the production of monoclonal antibodies have been initiated with this recombinant protein. Furthermore, we successfully adapted the protocol to transiently transfected cells, allowing the study of NS4B proteins from different viral strains as well as engineered mutants.

Conclusions: The availability of recombinant HCV NS4B produced in mammalian cells should yield further insights into the structure and function of this essential viral nonstructural protein. In addition, the protocol developed may be applied to other integral membrane proteins.

The Endocannabinoid System in Human Chronic Liver Diseases H10

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Background: The endocannabinoid (EC) system is implicated in chronic alcoholic liver disease (ALD), hepatitis C virus (HCV) progression and may influence the anti-HCV therapy.

Methods: AEA and 2-AG serum levels were measured by GC-MS in serum from healthy controls (n=25), patients with ALD (n=33) and HCV (n=57). Expression analysis was measured by TaqMan PCR. IFNγ release from PBMCs was measured by ELISpot. Apoptosis and viability tests were performed using flow cytometry.

Results: AEA and 2AG levels were a two-fold higher in the serum of HCV and ALD patients ($p<0.005$) whereas FAAH and MGLL mRNA from liver biopsies were downregulated by a 3- and 10-fold ($p<0.05$), respectively, compared to healthy controls. Stimulation of PBMCs with 2-AG and THC showed an induction of FAAH, MGLL. CB1, CB2, FAAH and MGLL were downregulation by acetaldehyde. This expression was not affected by specific CB1 and CB2 inhibitors. The IFNγ, TNFa, and IL2 release from PHA stimulated PBMCs was significantly decreased ($p<0.05$) by AEA and 2AG and this effect was not due to cell apoptosis or reduced viability as shown by Tyrpan blue, Annexin V and 7-AAD assay. CB1 and CB2 inhibitors did not reverse this effect.

Conclusion: Serum EC levels are increased in HCV and ALD patients probably as a result of reduced expression of EC degradation enzymes in liver and PBMCs, suggesting an immunomodulatory role of ECs in CLD.

Complex anastomotic leaks following esophageal resections: the new stent over sponge (SOS) approach S1

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Background
Leakage of the anastomosis after esophageal resections is a potentially life threatening situation. The endoscopic placement of self-expanding stents with/without additional drainage was successfully implemented in the treatment of such leakages. Failure of this treatment however, usually demands a reoperation with substantial morbidity. We present a new technique for the management of complex leakages which combines stenting with an endo-vacuum-therapy.

Methods
Two complicated anastomotic leakages to the chest cavity refractory to stenting alone were treated with the combination of an endo-sponge-assisted device covered by a self-expanding covered stent. An endosponge system designed for perirectal abscesses was trimmed and endoscopically placed at the site of the anastomotic leak. A covered stent was placed over the sponge system (SOS). The suction tube was retrieved by the nose, put under suction and the system was regularly exchanged until closure of the leakage.

Results
We successfully treated two complicated anastomotic leakages to the chest refractory to stenting alone with the combination of an endosponge-vacuum device covered by a self-expanding covered stent.

Conclusions
If stent therapy fails or the peri-anastomotic abcess cavity is large and complex to drain from outside following anastomotic leakage after esophageal resection, our new SOS treatment can be considered. This is not an approach for a simple leak but a rescue maneuver for complex uncontained leaks.

Hiatal hernia after Ivor-Lewis esophagectomy: incidence and operative approach. S2

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Background. Thoracoabdominal esophagectomy (Ivor-Lewis approach) is a standard surgical procedure for esophageal cancer. Hiatal widening is necessary to allow the gastric conduit to pass freely into the chest. Hiatal hernia is a possible complication after esophagectomy.
Methods. We reviewed our patients of a 21-year period for incidence, presentation and surgical treatment of hiatal hernia after esophagectomy for esophageal cancer.
Results. From 1992-2012 we performed 266 esophagectomies. We encountered 4 patients with hiatal hernia (1.5%). One of these patients developed an asymptomatic hernia and died 17 months after esophagectomy of local recurrence. The 3 other patients became symptomatic 8, 19 and 50 months after esophagectomy. Age of these patients was 52, 54 and 65 years and they had all received neoadjuvant chemo- or chemoradiotherapy. One patient presented with signs of acute small bowel obstruction and accompanying bilateral pneumonia, the 2 other patients suffered from intermittent obstructive symptoms. Diagnosis of hiatal hernia was confirmed by computed tomography in all cases. The 3 symptomatic patients were operated via a transabdominal approach. Herniation of small bowel and the left transverse colon into the left chest was found in all cases. The patient with acute small bowel obstruction presented an incarcerated jejunal loop with necrosis and perforation. After adhesiolysis, successful hernia reduction was performed in all patients. Segmental small bowel resection was necessary in the patient with jejunal necrosis. The hiatus was closed using a half-moon shaped PTFE mesh in all cases. The postoperative course was complicated by pleural effusion in one patient and was uneventful in the other two cases. All patients fully recovered. No recurrence was noted at 6-month follow-up.
Conclusions. Hiatal hernia is a rare complication after esophagectomy. Typical symptoms are pain, nausea and vomiting due to bowel obstruction. Incarcerated hernia can lead to bowel ischemia and extensive herniation may significantly compromise pulmonary function. Hiatal hernia repair should be performed because of the risk of incarceration. We recommend a transabdominal approach and hiatus closure with a mesh. Particular attention should be paid to a meticulous preservation of the gastric conduit.

Self expanding metal stents in malignant colonic obstruction: a one year single center observation S3

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BACKGROUND: Self expanding metal stents (SEMS) are a treatment option in malignant colonic obstruction permitting reduction of stoma rates and surgery-induced mortality. Two settings have to be distinguished: palliative stenting or stenting as a bridge to surgery. METHODS: We analysed retrospectively our local endoscopical and intra-hospital patients database to identify patients having undergone colonic stenting (Taewoong Niti-S™ Enteral Colonic Stent) for malignant obstruction in our hospital from february 2012 to january 2013. Immediate, 30 and 90 days stent-related adverse events were recorded. Phone check-up with the treating oncologist was done when data was missing. RESULTS: 10 patients (7 males, 3 females, median age 68,5 years; ASA score 1-2) underwent elective colonic stenting (through the scope technique) by two well experienced gastroenterologists for stage IV colonic cancer obstruction (5 rectal, 4 sigmoidal and 1 in the right colon). Six stents were placed in palliative setting and four to permit neo adjuvant chemotherapy before tumour resection (bridge to surgery). All patients received chemotherapy before and after stent placement (30% with cetuximab and 10% with bevacizumab association). No immediate and no 30 days complication due to colonic stenting were observed beside minor self limiting lower digestive haemorrhage 24 hours after stent positioning in one case. 89% (8 of 9 patients) had no stent-related complication on day 90. One patient sustained colonic perforation on day 76 and died on day 77 when under high dose corticoid therapy for metastasis progression. Another one was excluded as he had elective rectal tumour resection on day 38. CONCLUSIONS: We investigated 30 and 90 days adverse events after colonic stenting, showing only one serious complication. Of course, our analysis is limited by the little number of patients included, but suggests that colonic stenting by experienced endoscopists is a secure treatment option in malignant colonic obstruction.

Endoscopic treatment of intra-gastric migration of adjustable ring (AR) or calibration strip of vertical banded gastroplasty (CS-VBG). Report of 6 cases S5

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Introduction The intra gastric migration of AR or CS-VBG is a late complication of bariatric surgery occurring in 0.8-2.9%. The surgical treatment of this complication has a high morbidity. Alternatively endoscopic treatment has been proposed. We report the experience of our two endoscopy units in the treatment of this complication (2009-2013). **Patients and Methods** Three patients, 3 W, mean age 39.7 years (28-55) were referred for a migration of AR and 3 patients, 1W, 2M, mean age 55.3 years (54-60) for a migration of CS- VBG. Therapeutic endoscopies were performed under general anesthesia with tracheal intubation. Disconnection between AR and injection catheter were performed the day before. Migrated device were cut using a guide wire inserted into a Lithotripter (Sohendra ®) under endoscopic and radiological control. After the section, AA and CS-VBG were retrieved with a crocodile foreign body forceps or with a standard loop. **Results** The overall success rate of migrated device retrieval was 100%, with a single procedure in 5/6 patients. In one patient with 1 AR visible but deeply incarcerated into the gastric wall, 2 endoscopic procedure were required. During the 1st procedure a covered metallic stent was slipped between the AR and the stomach wall to induce a more complete migration. The 2nd endoscopy was performed 9 days after with a successful extraction of the stent and the AR. No complications were reported in the six patients. The average duration of the procedure was 45' for the 5 patients with single procedure (36'–55'). The average length of hospitalization stay per procedure was 5.2 days (3-9). **Conclusion** In our experience, the endoscopic section and retrieval of intra-gastric migration of AA and CS- VBG is efficient and safe. These results suggest that endoscopy is the first line therapeutic treatment for this type of bariatric surgery complication.

Five year results of laparoscopic sleeve gastrectomy. S4

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Background: Laparoscopic Sleeve Gastrectomy (LSG) is gaining popularity, yet long-term results are still rare. We present the five-year outcome concerning weight loss, modification of co-morbidities and late complications.

Methods: This is a retrospective analysis of a prospective cohort with a minimal follow-up of 5 years. A total of sixty-eight patients underwent LSG either as primary bariatric procedure (n=41) or as redo-operation after failed laparoscopic gastric banding (n=27) between August 2004 and December 2007. At the time of LSG the mean body mass index (BMI) was 43.0 ±8.0 kg/m^2, the mean age 43.1 ±10.1 years, and 78% were female. The follow-up rate one year postoperatively was 100%, 97% after 2, and 91% after 5 years; the mean follow-up time was 5.9 ±0.8 years.

Results: The average excessive BMI loss after 1 year was 61.5 ±23.4%, 61.1 ±23.4% after 2, and 57.4 ±24.7% after 5 years. Co-morbidities improved considerably; a remission of type 2 diabetes could be reached in 85%. The following complications were observed: one leak (1.5%), 2 incisional hernias (2.9%), and new onset gastroesophageal reflux in 11 patients (16.2%). Reoperation due to insufficient weight loss was necessary in 8 patients (11.8%).

Conclusions: LSG was effective five years postoperatively in terms of weight loss and improvement of co-morbidities and, therefore, seems to be a valid alternative to laparoscopic Roux-en-Y gastric bypass.

From referral for a rectal prolapse to the diagnosis of rectal cancer: a case report S6

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Objective
A 59-year-old male patient has been referred to our clinic for a symptomatic rectal prolapse. During the last 6 years the patient has been suffering from the recurrent prolapses, and also from progressive diarrhoea and anal bleedings.
At the clinical examination we found, after abdominal pressing, a 10cm long complete prolapse. Macroscopally the discrimination between an adenoma of the rectal mucosa and a rectal prolapse was not possible.
Methods
After the colo- and rectoscopy with biopsies a MRIdefecography, an endoscopic ultrasound and further biopsies, as well as a CT-scan of the abdomen/pelvis and analysis of the tumour markers were organized. Due to the results as listed underneath, an oncological low anterior resection in combination with the creation of a Colon-J-Pouch and protective loop colostomy was performed.
Results
In the rectoscopy a nearly circular polypous rectal mucosa expanding over a length of 12cm from the linea dentata was described. In the endorectal ultrasound a hypo-echogenic tumour with infiltration up to the submucosa was found. The MRI-defecography showed similar findings. In the CT-scan a very well vascularised tumour of 9,5cm diameter in the lumen of the rectum was found. CA 19-9 was elevated with 58,5kU/l. The biopsies of the tumour showed high grade intraepithelial neoplasia. Postoperatively a well differentiated carcinoma (pT1(sm3)pN0(0/30)L0V0Pn0R0) in a 14cm diameter polyp with a high grade intraepithelial neoplasia was found.
Conclusion
This case shows the importance of the establishment of individual concepts of preoperative examinations in case of suspicious clinical findings in order to plan and perform a suitable surgical strategy. Once again this is a very good clinical example for the well known adenoma-carcinoma-sequence.

Incision length for kidney transplantation does not influence short or long-term outcome: a prospective randomized controlled trial

S7

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Abstract

Background: While previous studies suggest advantages of minimally invasive surgery in living donor kidney transplantation, similar data is lacking for kidney transplant recipients. Our aim was to prospectively evaluate short- and long-term outcome for kidney transplant recipients, comparing a short transverse (ST) to a classical hockey stick (HS) incision.

Methods: 66 patients were randomized into two groups: ST vs. HS from 01/2008 - 05/2010. ST was defined as incision length ≤ 9cm, HS as >14cm. Perioperative data was collected, with evaluation of intra- and postoperative complications and Quality of Recovery (QoR) score.

Results: There were no significant differences in patient demographics, early or long-term postoperative pain. There were no significant differences in QoR scores between the ST and HS group. Predictive for a worse QoR were persisting incisional pain at the 30-month follow-up. 30-day mortality, morbidity and long-term kidney function did not differ between the two groups (p=1.00, p=0.62 and p=0.66, respectively).

Conclusions: Patient satisfaction as well as graft function and patient mortality was not influenced by incision length. With patient and graft safety being paramount, especially in times of organ shortage, incision length should reflect the requirement for a successful transplantation and not be a measure of feasibility.

The Pathologist influences significantly the Number of Lymph Nodes after Standardized Colorectal Cancer Surgery

S8

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Background: Although techniques of lymph node harvest in colorectal tumor specimens have improved significantly, the numbers still vary considerably. Differences can be explained by the surgeon, the pathologist and / or the patient.

Methods: Number of retrieved lymph nodes in surgical specimen of 54 patients with colorectal cancer, who underwent surgery (01/2010–07/2011) at a university hospital (hospital A), were compared to the number of retrieved lymph nodes in specimen of 49 patients operated at a cantonal hospital (hospital B) (08/2011–12/2012). All 103 operations were performed by one surgeon with equal extent of tumor resection. Surgical and histopathological parameters were compared.

Results: No significant differences between both cohorts were observed for gender, BMI, tumor location, resected bowel length, tumor stage and R-status. For all patients, the total number of resected lymph nodes differed significantly with 17.8 +/- 7.9 in hospital A and 25.7 +/- 12.4 in hospital B (p<0.001). The difference was still observed in subgroup analysis of patients with colon cancer (19.9 +/-7.8 versus 27.5+/-12.9; p=0.015), rectal cancer (16.1 +/-7.6 versus 22.7+/-10.0; p=0.014) and rectal cancer after preoperative treatment (13.3+/-5.4 versus 19.4+/-9.5; p=0.046). Multivariable analysis confirmed the pathological institute (HR 6.22; 95%CI 2.17-10.27; p=0.003) and the pT-category (3.42; 1.1-5.74; p=0.004) as independent prognostic factors for lymph nodes number.

Conclusions: Retrieved lymph node numbers differ significantly between pathology institutes with highly experienced staff. This study confirms the pathologist and his technique as one of the most important reason for differences in lymph node numbers.

Serial measurements of serum lactacidosis in acute mesenteric ischemia: "Does it predict the extent of ischemic bowel and outcome of patients?"

S9

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Background: Acute mesenteric ischemia (AMI) is a life-threatening surgical emergency with a reported mortality rate exceeding 50%. In clinical practice, detection of AMI continues to be a major challenge. Little is known on the role of serial serum lactate and pH measurements in the diagnosis of AMI. The aim of this study was to assess the correlation of preoperative serial serum lactate and pH levels with bowel necrosis. In addition, pre-, intra- and postoperative parameters were analyzed in order to identify risk factors for lethal outcome in patients with AMI.

Methods: A retrospective study of patients with AMI from 01/2006-12/2012 was performed. Numbers are reported as mean ± standard deviation. Proportions and continuous variables were compared using the Fisher exact, Mann-Whitney U test and ANOVA, respectively.

Results: A total of 91 patients with AMI were analyzed. All patients underwent laparotomy with an in-hospital mortality rate of 42.9% (n=39). Overall mean length of necrotic bowel was 90.8 ± 99.6 cm. Among the preoperative and demographic characteristics a significantly higher ASA score was found for the non-survivors compared to the survivors (4.0±0.7 vs. 3.5±0.7, p=0.003). The length of ischemic bowel did not correlate with mortality, as long as either small bowel or large bowel was affected. However, ischemia of small and large bowel combined was significantly more common in non-survivors compared to survivors (46.3% vs. 13.5%; p=0.001). The single highest serum lactate value measured within 24h before surgery in individual patients showed a moderate correlation with the length of bowel necrosis, however, did not reach statistical significance (R^2=0.257, p=0.058). When analyzing the serial lactate measurements for the period of 48h prior to surgery, a significant increase at 6h before surgery was found. At this time, the lactate level significantly increased (p=0.006) and the pH level decreased (p=0.001) when compared to the values measured >6h before surgery. A total of 34 patients (37.4%) had at least two serum lactate measurements within 24h before surgery. Of those, 17 patients had an increase, and 17 patients a decrease of serum lactate. Serial serum CRP and white blood cell counts revealed no predictive value for none of the outcomes.

Conclusion: AMI remains a serious surgical emergency with a very high mortality. Serial serum lactate and pH measurements are of limited value in the detection of AMI. Multiple variables likely impact the level of lactacidosis in patients suffering AMI. Involvement of both, small and large bowel is a significant risk factor for lethal outcome in this population.

The numbers refer to the pages of this supplement.