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Protection of pharmacological postconditioning in liver surgery. Results of a prospective randomized controlled trial.

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Background: Targeted organ protection has gained increasing interest to improve perioperative outcomes. Inflow occlusion is an established procedure to reduce blood loss during liver transection in selective patients, which is, however, potentially harmful due to the associated ischemia-reperfusion injury. Preventive strategies include the use of repetitive short periods of ischemia interrupted by a reperfusion phase (*intermittent clamping*), and the application of short period of ischemia prior to transection (*ischemic preconditioning*) or some drugs prior to transection (*pharmacological preconditioning*). However, whether interventions after resection (postconditioning) may confer protection is unknown.

Methods: A 3 arm-prospective randomized trial was designed in patients undergoing liver resection with inflow occlusion comparing the effects of *pharmacological postconditioning* with the volatile anesthetic sevoflurane (n=48), *intermittent clamping* (n=50) and no protective intervention (*continuous inflow occlusion*, n=17) based on proper sample size calculation. Endpoints included serum transaminase levels (AST), postoperative complications and hospital stay. All patients were intravenously anesthetized with propofol. In patients with postconditioning, propofol infusion was stopped upon reperfusion, and replaced by sevoflurane for 10 min.

Results: Compared to the control group, both postconditioning (p=0.04) and intermittent clamping (p=0.01) significantly reduced AST levels. The risk of any complications was significantly decreased by postconditioning (odds ratio 0.08 [0.02 to 0.36, p=0.001]) and intermittent clamping (odds ratio 0.50 [0.26 to 0.96, p=0.038]) compared to controls. Both interventions reduced length of hospital stay (postconditioning -4 days [-6 to -1, p=0.009], and intermittent clamping -2 days, [-4 to 0, p=0.019]).

Conclusions: This is the first trial demonstrating that pharmacological postconditioning reduces organ injury and importantly postoperative complications. This easily applicable strategy with clinically relevant benefits should be used in patients with prolonged continuous inflow occlusion.

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PTEN protein phosphatase activity regulates HCV secretion through modulation of cholesterol metabolism

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Background: Hepatitis C virus (HCV) infection is dependent on lipid metabolism. Hepatocyte steatosis, i.e. excess neutral fat stored in large lipid droplets (LD), occurs frequently in HCV infection, but the relationship between steatosis, HCV replication and virion production is unclear. We have shown that HCV induces steatosis via the downregulation of the phosphatase and tensin homologue deleted on chromosome 10 (PTEN). We now investigated how PTEN may affect HCV virion production. **Methods:** The effect of overexpression or silencing of PTEN on HCV secretion was assessed in Huh-7 cells expressing the genomic-length Jc1 construct. The role of PTEN protein and lipid phosphatase activities on lipid metabolism and secretion of infectious viral particles was investigated using dominant-negative PTEN mutants. The importance of cholesterol metabolism on PTEN-dependent LD biogenesis and viral particle secretion was examined using statins. **Results:** PTEN silencing in Huh-7 cells infected with HCV stimulated viral particle secretion, while PTEN overexpression decreased virus egress. Viral secretion was also increased by overexpression of protein phosphatase-deleted ($PTEN_{Y138L}$), but not lipid phosphatase-deleted ($PTEN_{G129E}$), PTEN mutant, thus indicating that the protein phosphatase activity of PTEN controls viral secretion. Similarly, $PTEN_{Y138L}$, but not $PTEN_{G129E}$, mutant induced the formation of large LDs in the cytoplasm. $PTEN_{Y138L}$ mutant did not affect biosynthesis of triglycerides (TG), but promoted the biosynthesis of cholesterol esters (CE). Consistently, statins prevented the increased CE production, large LD formation and viral secretion in Huh-7 cells expressing the $PTEN_{Y138L}$ mutant. **Conclusion:** Downregulation of PTEN protein phosphatase activity by HCV affects cholesterol metabolism thereby increasing CE synthesis, appearance of large LDs and release of viral particles.

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Biotransformation of budesonide via cytochrome P450 3A enzymes in active eosinophilic esophagitis

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Background: Budesonide, a synthetic glucocorticoid with high local anti-inflammatory activity, has shown efficacy in patients with active eosinophilic esophagitis (EoE). However, clinical pharmacology of that model substrate of cytochrome P450 (CYP) 3A has not yet been investigated in this special population. **Methods:** Twelve adult patients with active EoE and twelve healthy adults received single and multiple dose treatment with budesonide containing orodispersible tablets (4 mg/day). Molar ratios of CYP3A dependent metabolite formation in plasma ($AUC_{metabolite}/AUC_{budesonide}$) were used as indices of CYP3A activity. Differences between subject groups were tested for significance using the Mann-Whitney test. **Results:** Metabolite formation was significantly impaired in patients with EoE as compared to healthy subjects. E.g., 1.9 ± 0.9 vs. 3.5 ± 1.1, $P<0.01$, 6β-hydroxybudesonide following 4 mg budesonide single dose; 11.4 ± 6.2 vs. 20.5 ± 11.4, $P<0.05$, 16α-hydroxyprednisolone following 4 mg budesonide single dose. In parallel, systemic exposure to the parent compound ($AUC_{budesonide}$) following 4 mg of budesonide was significantly higher in patients with EoE than in healthy subjects. A patient reported outcome score showed significant relief of dysphagia following one week of continuous treatment with the new dosage form. **Conclusions:** Our data supports the new dosage form of budesonide as being a promising drug candidate in active EoE. Active eosinophilic inflammation of the esophageal mucosa is associated with reduced biotransformation of budesonide via CYP3A, the major subfamily of drug-metabolizing enzymes in humans.

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Despite persistent high plasma levels pegylated Interferon-alpha only transiently induces interferon stimulated genes in the liver of patients with chronic hepatitis C

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Background: Pegylated interferon-α (pegIFN-α) has replaced conventional IFN-α in the treatment of chronic hepatitis C (CHC) because it is more effective. Due to the prolonged half-life of PegIFN-α high serum concentrations can be achieved during the entire one-week dosing interval. It is generally believed that the improved pharmacokinetic properties of pegIFN-α result in an improved antiviral efficacy because of a continuous induction of the antiviral IFN stimulated genes (ISGs). However, pharmacodynamics studies in mice have shown that IFN-α induced signalling becomes refractory within hours after injection of IFN-α and remains unresponsive to further stimulation. In the present study we investigated the pharmacodynamics of pegIFN-α in liver biopsies obtained at various time points during the first week of treatment.
Methods: 18 patients with CHC had a second liver biopsy 4h (n=6), 16h, 48h, 96h or 144h (all n=3) after the first injection of pegIFNα-2b. Additional 3 patients received pegIFNα-2a and were biopsied at 144h. To avoid non-response to IFN-α, we included only patients without ISG induction in the pre-treatment liver biopsy. The activation of Jak-STAT signalling was assessed by immunohistochemistry and Western blot using phospho-STAT1 specific antibodies. Gene expression analysis was performed using Affymetrix® Human Genome U133 Plus 2.0 arrays and Bioconductor packages of R statistical environment.
Results: Jak-STAT signalling was strongly activated only at the 4h time point. Gene expression analysis revealed a > 2-fold induction of 474 ISGs. Based on their expression values over time, 4 distinct gene clusters were identified: very early, early, intermediate and late ISGs. The ISGs in the very early and early cluster were transiently induced at 4h and 16h but didn't show prolonged upregulation or a second wave of induction. Comparison of pegIFNα-2a versus -2b at 144h time point showed no significant difference in the amount or extension of upregulated ISGs, despite the longer plasma half-life of pegIFNα-2a.
Conclusions: Despite persistent high serum concentrations, pegIFN-α induces only transient activation of Jak-STAT signalling and transient up-regulation of ISGs in the liver. The superior efficacy of pegIFN-α compared to conventional IFN-α cannot be explained by persistent signalling and ISG induction during the one-week dosing interval.

Establishment of HEV RNA Reverse Transcriptase PCR Assays for the Diagnosis of Acute and Chronic Hepatitis E 5

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Background and aim: Hepatitis E virus (HEV) infection has emerged as a cause of travel-related and autochthonous acute hepatitis as well as chronic hepatitis in immunosuppressed patients. While travel-related cases are caused primarily by infections with HEV of genotype 1 (HEV-1), autochthonous cases and chronic cases are due to genotype 3 (HEV-3), which is shared between humans and diverse animal species. The aim of this study was to establish HEV RNA detection assays for quantitative viral load testing and genotyping.

Methods: Viral RNA was purified from plasma or serum and converted to cDNA prior to (1) multiplex real-time PCR for HEV RNA quantification and (2) multiplex PCR coupled to DNA sequencing for HEV genotype determination. Real-time PCR was designed to match all known HEV genotypes available in Genbank while PCR was designed using conserved primers flanking a variable region of the HEV RNA.

Results: In a validation panel, the newly developed assays allowed for the reliable detection and genotyping of HEV-1 or HEV-3. Cases of travel-related and autochthonous acute hepatitis E as well as chronic hepatitis E in immunosuppressed patients have been identified using these assays and will be presented in detail. Anti-HEV antibodies were negative in three well-characterized patients with chronic hepatitis E after organ transplantation.

Conclusions: We developed and validated a quantitative HEV RNA detection assay that can now be offered on a routine basis (www.chuv.ch/imul/imu-collaborations-viral_hepatitis). Genotyping can also be offered on selected cases. HEV RNA detection is key in diagnosing chronic hepatitis E in immunosuppressed patients with unexplained transaminase elevations, as serology can be negative in these patients.

Deletion of TRAIL on NK cells is associated with excessive hepatic ischemia-reperfusion injury in mice 6

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Background: Ischemia-reperfusion injury (IRI) is a key factor that contributes to early and late dysfunction of liver grafts. We hypothesized that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a death ligand with high expression on NK cells significantly impacts IRI.

Methods: C57/BL6 wild-type and TRAIL knock-out mice (TRAIL-/-) were subjected to hepatic IRI. Adoptive transfer of wild-type and TRAIL-/- NK cells was performed into RAG2/common gamma null mice. Liver injury was assessed by hepatic neutrophil infiltration, alanine aminotransferase (ALT), aspartate transaminase (AST), hepatic neutrophil activation by myeloperoxidase (MPO) activity. NK cell subsets of the ischemic liver lobe were analysed by flow cytometry. NK cell cytotoxicity was performed in vitro studies.

Results: TRAIL-/- mice exhibit significantly more hepatic damage assessed by AST and ALT levels compared to wild-type mice. Adoptive transfer of TRAIL-/- NK cells to Rag2/common gamma-null mice was associated with significantly increased IRI compared to wild-type NK cells. Hepatic neutrophil activation was significantly increased in TRAIL-/- compared to wild-type mice. Staining for CD107a was significantly elevated in ischemic liver lobes of TRAIL-/- compared to wild-type mice. In vitro NK cell cytotoxicity to a Yac-1 cancer cell line was significantly increased in sorted TRAIL-/- NK cells compared to wild-type NK cells.

Conclusions: These results show that lack of TRAIL on NK cells is associated with an excessive liver injury in a murine model of hepatic IRI via the modulation of NK cell mediated cytotoxicity.

Impact of Glasgow-Blatchford Bleeding Score on Hospital Stay Duration of Patients with Upper GI Bleeding. 7

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Background: Upper gastrointestinal (UGI) bleeding is a frequent cause of hospitalization. Its severity may be assessed before endoscopy using the Glasgow-Blatchford bleeding score (GBS). It has been validated to identify patients who will need clinical intervention. The aim was to prospectively validate the GBS in patients admitted for UGI bleeding in the Geneva County and to use it for shortening the hospital stay in patients predicted at low risk of needing clinical intervention. Methods: Consecutive consenting patients with UGI bleeding were included between October 2009 and January 2012. A GBS of 0 was used to identify patients who would not need clinical intervention. In the first part of the study, UGI endoscopy was performed in all patients. In the second part of the study, patients with a GBS=0 were sent home with an appointment for an ambulatory UGI endoscopy. All patients had follow-up at 7 and 30 days. Need for clinical intervention was defined as performance of endoscopic haemostasis, blood transfusion or surgery. Results: 208 patients were included. (14 patients were lost to follow up including 5 deaths). GBS varied from 0 to 18, with 15 (14%) and 11 (11%) patients having a GBS=0 (first and second part of the study). Normal endoscopy was seen in 26% (GBS=0) vs 11% (GBS>0), $p<0.05$. Clinical intervention was needed in 1/26 (4%) vs. 120/182 (66%) patients with a GBS=0 vs. >0, $P<0.0001$. In the second vs. the first part of the study, hospital stay was shorter for patients with a GBS=0 (19 vs. 6 hours, $P<0.01$) while hospital stay did not significantly change for patients with a GBS>0 (7.8 vs. 8.6 days, part 1 vs part 2, respectively). No adverse event was observed in the patients sent home with a GBS=0 during the second part of the study. Conclusions: Among patients admitted with UGI bleeding, the GBS correctly predicted those who would need an intervention. Using the GBS allowed reducing duration and costs of management in patients predicted at low risk of needing a clinical intervention.

Molecular Determinants for Membrane Association of the Hepatitis C Virus NS2 Protease Domain 8

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Background: Hepatitis C virus (HCV) nonstructural protein 2 (NS2) plays essential roles in particle assembly and polyprotein processing. It harbors an N-terminal membrane domain comprising three putative transmembrane segments (amino acids [aa] 1-93) and a C-terminal cysteine protease domain (aa 94-217). Given that the latter has been predicted to be membrane-associated, we aimed to identify molecular determinants for membrane association of the NS2 protease domain.

Methods: A comprehensive panel of NS2 deletion constructs was analyzed by fluorescence microscopy, selective membrane extraction, and membrane flotation assays. Candidate aa residues involved in membrane association were substituted by site-directed mutagenesis.

Results: The NS2 protease domain alone was found to associate with membranes. Two N-terminal α-helices comprising aa 102-114 and aa 123-136 were found to mediate this association, with conserved hydrophobic and positively charged aa residues representing the key determinants. Interestingly, mutagenesis analyses revealed that electrostatic interactions involving a positively charged aa residue in α-helix aa 123-136 are required for membrane association. Mono- and bicistronic (i.e. NS2 cleavage-independent) HCV constructs were prepared to investigate the effect of these substitutions on RNA replication and infectious viral particle formation.

Conclusions: The NS2 protease domain itself harbors molecular determinants for membrane association within α-helices aa 102-114 and aa 123-136 which may contribute to proper positioning of the active site. These results provide new insights into the membrane topology and the poorly understood function of this essential viral protease.

Hepatitis C virus and the metabolic syndrome: cross talk between infected and uninfected cells

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Background and aims: Infection by the hepatitis C virus (HCV) induces several complex physiopathological changes leading, among others, to insulin resistance (IR). The mechanisms by which HCV alters glucose metabolism are still elusive: it has been shown that IR takes place in both liver and extra-hepatic organs, which are not infected by HCV. Our working hypothesis is that HCV-infected hepatocytes may induce uninfected cells to become insulin resistant *via* secretion of soluble effectors.
Methods: We co-cultured HCV-infected hepatoma cells with naive hepatoma cells as well as human skeletal muscle cells and adipocytes. Insulin signalling and metabolic responses of the uninfected cells were analyzed using several approaches.
Results: In uninfected cells, we found a common defect in the insulin signalling pathway: while insulin is still able to promote the phosphorylation of PKB and the majority of its targets, we observed a specific failing in the regulation of AS160 by the hormone. As AS160 is the main PKB's target involved in Glut4 translocation, we found, as expected, that glucose uptake was diminished in muscle and adipose cells co-cultured with HCV-infected cells. However, IR seems to be restricted to glucose metabolism since we did not find any alterations of insulin-regulated lipolysis or lipogenesis.
Conclusions: Our data suggest that HCV-infected cells are able to induce directly IR in uninfected cells, in particular in muscle and adipose cells. Importantly, IR seems to be restricted to glucose uptake which is in agreement with the observations made in HCV-infected patients.

Hepatic steatosis is an independent risk factor for surgical site infection

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Background: Elevated body mass index (BMI) and visceral fat are significant risk factors for postoperative complications. Hepatic steatosis is associated with visceral fat but may occur in the absence of elevated BMI. Aim of this study was to investigate the impact of hepatic steatosis on surgical site infection in patients undergoing liver and colorectal resection.

Methods: A total of 231 patients undergoing liver and colorectal resection with preoperative contrast-enhanced CT-scan and complete follow-up were investigated. As a surrogate parameter for hepatic steatosis, density of the liver parenchyma was measured in Hounsefield units (HU) in the portal-phase of the CT scans.

Results: The incidence of SSI in our study group according to the definitions of the Centers for Disease Control (CDC) was 37.2% (86/231). Among these patients, superficial or deep infections were described in 55.6% and organ-space infections in 44.4%. Demographic parameters including age, sex, and ASA-score were not significantly different between patients with and without SSI. Significantly higher median BMI was found in the SSI group compared to the No-SSI group (26.6 kg/m^2 (range 17.3-47 kg/m^2) vs. 24.15 kg/m^2 (15.9-40 kg/m^2); p< 0.001). Median operation time was significantly longer in the SSI group compared to the No-SSI group (300 min. (52-708 min.) vs. 240 min. (80-585 min.); p=0.006). Significant difference in median liver density was found in the SSI group (96.5 HU (43-156 HU) compared to the No-SSI group (108.75 HU (63-149 HU); p= 0.0009). Hepatic steatosis was found to be an independent risk factor in multivariate analysis for SSI (Odds ratio 3.68 (95% confidence intervals 1.02-13.37); p= 0.04).

Conclusion: Hepatic steatosis is an independent risk factor for SSI in patients undergoing visceral surgery and should be included in the preoperative risk assessment.

Genetic association analyses reveal a role for vitamin D insufficiency in hepatitis C virus-associated hepatocellular carcinoma development

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Background: Vitamin D insufficiency has been associated with the occurrence of various types of cancer, but causal relationships remain elusive.

Methods: Associations between the risk of HCV-related HCC development and *CYP2R1*, *GC*, and *DHCR7* genotypes, which are genetic determinants of reduced 25-OH-vitamin D_3 (25[OH]D_3) serum levels, were determined.

Results: A total of 5604 HCV-infected patients, 1279 with and 4325 without progression to HCC, were identified. The well-known association between 25(OH)D_3 serum levels and variations in *CYP2R1* (rs1993116, rs10741657), *GC* (rs2282679), and *DHCR7* (rs7944926, rs12785878) genotypes was also apparent in patients with chronic hepatitis C. The same genotypes of these single nucleotide polymorphisms (SNPs), which are associated with reduced 25(OH)D_3 serum levels, were significantly associated with HCV-associated HCC (P=0.07 [OR=1.13] for *CYP2R1*, P=0.007 [OR=1.56] for *GC*, P=0.003 [OR=1.42] for *DHCR7*; ORs for risk genotypes). In contrast, no association between these genetic variations and the outcome of antiviral therapy with pegylated interferon-α and ribavirin (P>0.2 for each SNP) or liver fibrosis progression rate (P>0.2 for each SNP) was observed, suggesting a specific influence of the genetic determinants of 25(OH)D_3 serum levels on hepatocarcinogenesis.

Conclusions: Our data suggest a relatively weak but functionally relevant role for vitamin D in the prevention of HCV-related HCC development. Controlled clinical trials to assess the benefit of vitamin D supplementation in HCV-infected patients with advanced liver fibrosis or cirrhosis are warranted.

Proliferative activity in CK7 positive cells and hepatocytes as well as macrophage expansion predict MELD score improvement in decompensated alcoholic liver disease (ALD)

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Background: Liver regeneration plays a key role in the prognosis of acute-on-chronic ALD. Both hepatic progenitor cell (HPC) and liver macrophages increase in response to acute liver injury, but the prognostic significance of these changes remains to be determined. We studied the expansion of both macrophage and proliferative HPC compartments on liver biopsies obtained from the bone marrow stem cell trial in ALD, and correlated with the outcome at 3 months. **Methods:** 58 patients with decompensated ALD (MELD 19) were included. Proliferative HPC were analyzed (immunohistochemistry) on liver biopsy performed at admission, by manual count of Ki67+/CK7+ and CK7-cells. Macrophage expansion was determined by CD68+ morphometric analysis. Cytokines and markers of regeneration were measured by immunoassays on serum and quantitative PCR on liver tissue. A ≥ 3 points decrease in MELD at 3 months defined the responders.

Results	Responders	Non responders	
CK7+/Ki67+ cells (HPC)	1.9±1.5	0.9±0.9	0.01
CK7-/Ki67+ cells (mature hepatocytes)	4.1±3.6	1.8±1.4	0.01
Liver macrophages (% of surface area)	4.4%	3.3%	0.05

Both hepatocyte growth factor and soluble TNF receptor serum levels were higher in responders. Liver PCR analysis showed that liver macrophagic expansion was associated with an increase in TWEAK receptor mRNA expression (p<0.05), known to stimulate HPC proliferation. **Conclusion:** This is the first study showing that markers of liver cell proliferation obtained on baseline liver biopsy predicts the clinical outcome at 3 months in patients with decompensated ALD. These data support the role of liver biopsy not only for diagnostic purposes but also to determine the short term prognosis.

Toll-Interacting Protein Modulates Gut Flora Composition, Epithelial Barrier Integrity and Susceptibility to Colitis 13

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Toll-like receptor (TLR) signals are key to maintaining host-microbial interactions. The Toll-interacting-protein (Tollip) is a ubiquitously-expressed inhibitor of inflammasome and TLR signaling. We hypothesized that Tollip might control gut homeostasis. Genetic ablation of Tollip did not lead to spontaneous colitis but had dramatic consequences on the intestinal expression of the α-defensin cryptidin 4 and the C-type lectin REGIIIβ. These changes were associated with intestinal dysbiosis and enhanced colonization by *segmented filamentous bacteria* - a key pro-inflammatory component of the microbiota. Tollip deficiency increased susceptibility to dextran sulfate sodium (DSS) colitis and aggravated chronic Th17-driven colitis in IL-10$^{-/-}$ mice. Flora depletion with antibiotics in Tollip$^{-/-}$ mice was not sufficient to restore DSS colitis susceptibility and deletion of Tollip in non-hematopoietic cells using bone-marrow chimeras was sufficient to increase susceptibility to DSS colitis. After DSS administration, we observed several epithelial defects in Tollip$^{-/-}$ mice including early tight junctions disruption, increased epithelial apoptosis, and increased intestinal permeability. Overall, our data show that Tollip significantly impacts intestinal homeostasis by controlling bacterial ecology and intestinal response to chemical and immunological stresses.

Identifying risk factors for central pontine and extrapontine myelinolysis after liver transplantation: a case-control study 15

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Background: central pontine and extrapontine myelinolysis (CPEPM) is a rare but potentially fatal complication after orthotopic liver transplantation (OLT). The aim of this study was to identify risk factors for clinical CPEPM after OLT and to assess patient outcome.

Methods: we reviewed the clinical data of 1378 patients who underwent OLT between 1987 and 2008 in Geneva, Switzerland and Edmonton, Canada. CPEPM diagnosis, based on neurological symptoms correlated with brain MRI, was made in 19 patients (1.4%). Each of them was compared with 2 control patients without clinical CPEPM matched by age, gender, date of OLT, and MELD score.

Results: 19 patients developed CPEPM (7F, mean age 52.1 ± 2 years, mean MELD score 26 ± 2.2. Indications for OLT were mainly alcoholic (47%) and HCV (21%) cirrhosis. Before OLT, INR values tended to be higher (p=0.059) in patients with CPEPM than in controls. The number of platelet units and fresh frozen plasma (FFP) transfused during surgery was significantly higher in cases of CPEPM (p=0.05 and p=0.047). Hemorrhagic complications after OLT were significantly more frequent in patients who developed CPEPM (p=0.049). After OLT, the values of Na were significantly higher in CPEPM (147.8 ±2 vs 143.2 ±0.8, p=0.002), with higher variations of Na before and after OLT (15.9 mmol/l±1.9 vs 11.1mmol/l±0.9, p=0.023). The first manifestations of CPEPM were observed 9.53 ±6.56 days after OLT (range 3-25 days). Mortality at one year of patients developing CPEPM was significantly higher (63% vs 13%, p<0.0001).

Conclusion: Our study shows that high MELD score patients undergoing OLT, receiving massive perfusions of Na-rich products, experiencing surgery related hemorrhagic complication and important fluctuations of serum Na, are at risk of developing CPEPM, a rare but often fatal neurological complication.

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Hemodynamic effects of bacterial intestinal colonization in normal and portal hypertensive mice

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Background
Gut-derived bacterial products and the resultant increase in inflammatory cytokines in the splanchnic and systemic circulation may contribute to the hemodynamic changes associated with portal hypertension (PHT).
We therefore hypothesized that in mice with PHT the absence of intestinal bacterial flora will be associated with an attenuated hyperdynamic circulatory syndrome.

Methods
We induced prehepatic PHT by partial ligation of the portal vein (PPVL) in mice with or without intestinal bacterial flora. After two and seven days we measured portal pressure (PP), systolic arterial blood pressure (SAP), mesenteric artery blood flow (MABF) and portosystemic shunts (PSS). Intestinal tissue, mesenteric lymph nodes and feces were collected for biochemical, microbiological and immunohistochemical studies. Data in groups of n=10 were compared using Mann-Whitney test.

Results
There were no differences in hemodynamic parameters between sham-operated mice with or without intestinal bacterial flora. In contrast, PPVL of germ-free mice led to alterations in several parameters as follows

	PPVL 2 days (acute PHT)			PPVL 7 days (chronic PHT)		
	germ-free	colonized	p value	germ-free	colonized	p value
PP mmHg	7.4	11.1	<0.05	8.2	10.4	<0.05
SAP mmHg	115	104	0.23	119	109	0.38
MABF mL/min	1.24	1.51	0.61	1.50	1.10	0.04
PSS %	0.4	2.6	0.28	0.9	14.8	<0.05
Spleen/BW%	0.29	0.31	<0.05	0.32	0.55	<0.05

Fecal albumin, a marker of intestinal mucosal permeability, was higher in germ-free compared to colonized mice 7 days after PPVL. In addition, intestinal submucosal blood vessels, identified by CD31 immunohistochemistry, were more abundant after PPVL.

Conclusions
Germ-free mice developed an attenuated portal hypertension in acute and chronic PPVL. This finding was associated with an increased intestinal permeability and a blood vessel proliferation in the intestinal submucosa.

IDENTIFICATION OF GPX8 AS A NOVEL CELLULAR SUBSTRATE OF THE HEPATITIS C VIRUS NS3-4A PROTEASE 16

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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 a prime target for antiviral intervention but also a key player in the persistence and pathogenesis of HCV. It cleaves and thereby inactivates two crucial adaptor proteins in viral RNA sensing and innate immunity (MAVS and TRIF) as well as a phosphatase involved in growth factor signaling (TC-PTP). The aim of this study was to identify novel cellular substrates of the NS3-4A protease and to investigate their role in the replication and pathogenesis of HCV.

Methods: Cell lines inducibly expressing the NS3-4A protease were analyzed in basal as well as interferon-α-stimulated states by stable isotopic labeling using amino acids in cell culture (SILAC) coupled with protein separation and mass spectrometry. Candidates fulfilling stringent criteria for potential substrates or products of the NS3-4A protease were further investigated in different experimental systems as well as in liver biopsies from patients with chronic hepatitis C.

Results: SILAC coupled with protein separation and mass spectrometry yielded > 5000 proteins of which 18 candidates were selected for further analyses. These allowed us to identify GPx8, a membrane-associated peroxidase involved in disulfide bond formation in the endoplasmic reticulum, as a novel cellular substrate of the HCV NS3-4A protease. Cleavage occurs at cysteine in position 11, removing the cytosolic tip of GPx8, and was observed in different experimental systems as well as in liver biopsies from patients with chronic hepatitis C. Further functional studies, involving overexpression and RNA silencing, revealed that GPx8 is a proviral factor involved in viral particle production but not in HCV entry or HCV RNA replication.

Conclusions: GPx8 is a proviral host factor cleaved by the HCV NS3-4A protease. Studies investigating the consequences of GPx8 cleavage for protein function are underway. The identification of novel cellular substrates of the HCV NS3-4A protease should yield new insights into the HCV life cycle and the pathogenesis of hepatitis C and may reveal novel targets for antiviral intervention.

REGULATION OF PATATINE-LIKE PHOSPOLIPASE DOMAIN-CONTAINING PROTEIN-3 (PNPLA3) EXPRESSION BY FATTY ACIDS AND ALCOHOL IN VITRO AND IN VIVO

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Background and Aims: Nonsynonymous sequence polymorphism I148M of PNPLA3 is associated with increased hepatic triglyceride content and liver fibrosis in chronic liver disease in humans. The present study aimed to investigate isolated and joint effects of fatty acids and mediators of alcohol toxicity on PNPLA3 expression in obese, insulin-resistant Zucker rats and lean littermates, and in Huh-7 cells stably transfected with wild type (WT) and mutant PNPLA3-I148M variant.

Methods: Obese Zucker rats and lean littermates were pair-fed with a Lieber-De Carli liquid diet containing 36% of total calories as ethanol for 12 weeks. Liver steatosis and fibrosis were quantified by Oil Red O morphometry and hydroxyproline levels, respectively. Huh-7 (WT and I148M variant) cells were treated with acetaldehyde (AA, 200μM), ethanol (EtOH, 50-200mM), H_2O_2 (10-100μM), and with fatty acids, such as: oleic, linoleic and arachidonic acids (100-400μM) alone or in combinations. PNPLA3 mRNA expression was measured by TaqMan PCR.

Results: PNPLA3 mRNA expression in obese Zucker rats was more than 5-fold induced compared to lean animals and correlated significantly with liver triglyceride content. Alcohol administration further upregulated PNPLA3 mRNA 2-fold in obese animals, but not in lean rats. Surprisingly, Huh-7 cells (neither WT nor PNPLA3-I148M) did not react to the treatment with oxidative stress markers (AA, EtOH and H_2O_2) in terms of PNPLA3 mRNA expression, however, fatty acids administration revealed a striking induction of PNPLA3 mRNA by polyunsaturated arachidonic (C20:4) and linoleic (C18:2) acids, whereas combination with monounsaturated oleic acid (C18:1) inhibited PNPLA3 expression by 50% in WT cells. In PNPLA3-I148M cells only linoleic acid showed a minor non-significant PNPLA3 upregulation by 25%. Interestingly, both cell lines synthesized triglycerides in lipid droplets to the same extend under the linoleic acid treat, whereas lipid hydrolysis or loss was significantly increased in Huh-7 WT cells after 24h.

Conclusions: Chronic alcohol feeding in obese, insulin-resistant rats exerts significant and synergistic effects on PNPLA3 mRNA expression, which correlated with triglyceride content. In vitro experiments suggest that PNPLA3 expression depends on the types of dietary fatty acids with polyunsaturated fatty acids inducing and monounsaturated fatty acids inhibiting PNPLA3 mRNA. I148M polymorphism of PNPLA3 leads to attenuation of lipolytic processes resulting in fat accumulation in the cell.

Early Results of the Swiss Multicentre Bypass Or Sleeve Study (SM-BOSS): a prospective randomized trial comparing Laparoscopic Sleeve Gastrectomy (LSG) and Laparoscopic Roux-Y-Gastric Bypass (LRYGB)

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Objective: LSG has been proposed as an effective operative alternative to the current standard procedure, the LRYGB. Prospective data comparing the two procedures are rare. Therefore, we performed a randomized clinical trial assessing the effectiveness and safety of the two operative techniques. Here we report on early results.

Methods: In all, 217 patients were recruited/randomized at 4 bariatric centres in Switzerland. In 107 patients a LSG was performed using a 35F bougie with suturing of the stapler line. In 110 patients a LRYGB was performed with a 150cm antecolic alimentary and a 50cm biliopancreatic limb and with a linear or circular stapled anastomosis. The mean BMI of all patients was 44 (35-61) kg/m^2, the mean age was 43 (19-65) years, and 73% were female.

Results: The two groups were equal in terms of BMI, age, gender, co-morbidities, and total length of hospitalisation. Mean operative time was less for LSG than in LRYGB (86 (40-300) min. versus 109 (40-300) min., p<0.002). The conversion rate was 0.9% in LSG versus 1.8% in LRYGB (n.s.). Total complications (<30 days) occurred more often in LRYGB (17.2%) than in LSG (8.4%, p<0.05). However, the difference in severe complications (Clavien-Dindo score >2) was not statistically significant (1.9 % for LSG versus 3.6% for LRYGB).

Conclusions: LSG can be performed faster with fewer total complications than can LRYGB but the difference in severe complications was not significant.

Inhibition of SIRT1 impairs growth and autophagy in HCC

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Objective: Autophagy is a metabolic process that degrades malfunctioning proteins and removes them to maintain cellular homeostasis. Therefore in HCC, autophagy reduces the efficacy of various anti-tumor therapies. Sirtuins are a highly conserved family of NAD+ dependant deacetylases that target the stability and activity of histone and non-histone proteins. SIRT1 positively regulates autophagy. Our preliminary data has shown that SIRT1 is highly expressed in HCC and inhibition of SIRT1 activity reduces HCC cell autophagy by improving the response to current anti-tumor treatment strategies.

Methods: SIRT1 was inhibited in HCC cell by using small molecule inhibitors. Autophagy was measured by changes in mRNA expression of autophagy-related (ATG) gene and additionally the conversion of LC3I to LC3II was monitored by Western blot. In a next step, HCC lines were treated with Rapamycin to induce autophagy alone and in combination with SIRT1 inhibition.

Results: Inhibition of SIRT1 lead to a decrease in ATG5 mRNA levels compared to DMSO treated controls. In all the HCC cells tested, HCC cells treated with Rapamycin induced LC3II conversion demonstrating that autophagy can be induced in these HCC cell lines. Rapamycin in combination with SIRT1 inhibition impaired LC3II conversion.

Conclusion: SIRT1 is highly expressed in HCC cells and its inhibition decreased basal and Rapamycin-induced markers of autophagy. Preliminary data support further studies for the clinical exploration of SIRT1 inhibitors in combination with Rapamycin for the treatment of HCC.

Better 6 months outcome for steroid refractory ulcerative colitis with infliximab rescue therapy compared to tacrolimus or ciclosporine: a SWISS IBD cohort retrospective analysis

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BACKGROUND: Ciclosporine (CsA), Tacrolimus (Tcl) and Infliximab (IFX) are effective rescue therapies in steroid-refractory ulcerative colitis (UC). Comparative studies are however missing. METHOD: This is the retrospective analysis of treatment outcome for oral Tcl (n=27, initially 0.05mg/Kg twice daily, aiming for serum trough levels of 5-10 ng/mL), intravenous CsA (n=23, 2mg/kg/daily and then oral CsA 5mg/kg/daily) and IFX (n=43, 5mg/kg intravenously at week 0, 2, 6 and then every 8 weeks) in patients with steroid refractory moderate to severe UC enrolled in the SWISS IBD cohort study. After successful rescue therapy with Tcl or CsA, thiopurine maintenance therapy or maintenance therapy with Tcl (in Tcl pretreated patients) was introduced. The endpoints analyzed steroid free remission rate (on the basis of modified Truelove-Witts severity index (MTWSI)) and number of colectomies after 6 months. RESULTS: At 6 months, 26% (7/27) of patients treated with Tcl remained in steroid free remission (MTWSI score ≤4) compared to 30 % (7/23) on CsA and 58% (27/41) of patients treated with IFX (Tcl & CsA vs IFX p= 0.018). Significant more patients had primary non response, loss of response or severe adverse events in the CsA cohort (61%, 14/23) compared to Tcl cohort (33.3 %, 9/27), and IFX cohort (30%, 13/43) (p= 0.037). Colectomy rate was significantly higher after CsA (17.4 %, 4/23) compared to Tcl (3.7 %, 1/27) or IFX (2.3 %, 1/43) (p= 0.047).CONCLUSION: After six month, rescue therapy with IFX had the lowest colectomy rate, significantly higher steroid free remission rate, and the lowest rate of non-response, loss of response and severe adverse events compared to CsA or Tcl rescue treatment.

Impact of genetic SLC28 transporter and ITPA variants on ribavirin serum level, hemoglobin drop and therapeutic response in patients with HCV infection

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Background: Treatment of chronic hepatitis C is evolving, and direct acting antivirals (DAAs) are now added to pegylated interferon-α (Peg-INF-α) and ribavirin (RBV) for the treatment of hepatitis C virus (HCV) genotype 1 infection. DAAs cause different side effects and can even worsen RBV induced hemolytic anemia. Therefore, identifying host genetic determinants of RBV bioavailability and therapeutic efficacy will remain crucial for individualized treatment. Recent data showed associations between RBV induced hemolytic anemia and genetic polymorphisms of concentrative nucleoside transporters such as CNT3 (*SLC28A3*) and inosine triphosphatase (*ITPA*). To analyze the association of genetic variants of *SLC28* transporters and *ITPA* with RBV induced hemolytic anemia and treatment outcome. **Methods:** In our study, 173 patients from the Swiss Hepatitis C Cohort Study and 22 patients from Swiss Association for the Study of the Liver study 24 (61% HCV genotype 1, 39% genotypes 2 or 3) were analyzed for *SLC28A2* single nucleotide polymorphism (SNP) rs11854484, *SLC28A3* rs56350726 and *SLC28A3* rs10868138 as well as *ITPA* SNPs rs1127354 and rs7270101. RBV serum levels during treatment were measured in 49 patients. **Results:** *SLC28A2* rs11854484 genotype TT was associated with significantly higher dosage- and body weight-adjusted RBV levels as compared to genotypes TC and CC (p=0.04 and p=0.02 at weeks 4 and 8, respectively). *ITPA* SNPs rs1127354 and rs7270101 were associated with hemolytic anemia both in genotype as well as in allelic analyses. *SLC28A3* rs56350726 genotype TT (vs. AT/AA, RR=2.1; 95% CI 1.1-4.1) as well as the T allele (vs. A; RR=1.8, 95% CI 1.1-3.2) were associated with increased SVR rates. The combined analysis of overall ITPA activity and *SLC28* variants together revealed no significant additive effects on either treatment-related anemia or SVR. **Conclusions:** The newly identified association between RBV serum levels and *SLC28A2* rs11854484 genotype as well as the replicated association of *ITPA* and *SLC28A3* genetic polymorphisms with RBV induced hemolytic anemia and treatment response underpin the need for further studies on host genetic determinants of RBV bioavailability and therapeutic efficacy for individualized treatment of chronic hepatitis C.

Intestinal inflammation induces alterations in enterohepatic Fgf15 signaling as well as changes in biliary and fecal bile acid profile

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Background: DSS-induced colitis is a well accepted and frequently used mouse model for inflammatory bowel disease in particular ulcerative colitis. Hepatic changes caused by intestinal inflammation are still poorly understood. Therefore alterations in bile acids metabolism and the enterohepatic circulation are in the focus of the current study. **Aims**: To study alterations in enterohepatic Fgf15 signaling and associated changes in hepatic bile acid metabolism and bile composition in bile and feces in murine colitis. **Methods**: Intestinal and hepatic target genes of Fgf15 pathway were quantified by RT-PCR in DSS-treated mice (7d, 2% DSS in drinking water) and control mice. Bile acid transporter expression was analyzed by RT-PCR and by western blotting. Fgf15 levels in serum were measured by ELISA. Biliary and fecal bile acid composition was differentiated by GC/MS analysis. **Results**: DSS-treated mice showed induction of Fxr expression in ileo-cecal region and correspondent higher concentration of Fgf15 in serum (180% vs. cntrl; $p<0.05$). In the liver, inhibition of bile acids synthesis could be observed by down-regulation of Cyp7a1 (40% vs. cntrl; $p<0.05$) that is regulated by Fgf15. In addition, expression of bile acid transporters such as Bsep, Ntcp, Mrp2, Mrp3 and Mrp4 were significantly down-regulated. Bile acid composition in bile was significantly different in treated mice with lower levels of hydrophilic bile acids including α- and ß-muricholic acid and taurodeoxycholic acid (20%, 20% and 50% vs. cntrl; $p<0.05$). In feces a trend towards lower levels of free BA was observed. **Conclusions**: Our results show for the first time a functionally relevant alteration in gut-liver interaction by activated Fgf15 signalling through Fxr activation in ileo-cecal region of DSS-treated mice. Alterations in biliary and fecal bile acid profiles are observed and need further investigation for understanding the underlying mechanism of Fxr activation in this context.

Generation of a murine hepatic angiosarcoma cell line and mouse tumor model

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Background: Angiosarcoma (AS) of the liver is a rare and highly aggressive tumor of endothelial origin with dismal prognosis. Studies of the molecular biology of angiosarcomas are limited since animal models are missing. Gaining insights into the molecular pathogenesis of this malignancy is crucial for developing new therapeutic strategies. We have previously shown that knockout of Notch1 in mice leads to vascular remodeling of the hepatic microcirculation and eventually results in spontaneous formation of hepatic angiosarcoma (Gastroenterology 2012). The aim of this study is to 1) establish and characterize a cell line from this murine angiosarcoma, 2) to identify the molecular pathogenesis and therapeutic targets and 3) to evaluate the role of antiangiogenics such as sorafenib in the treatment of angiosarcoma.
Methods: Notch1 KO mice developed hepatic AS 50 weeks after KO with 86% penetrance. Liver sinusoidal endothelial cells (LSEC) were isolated from three individual Notch1 KO mice harboring a macroscopic hepatic AS. Cell culture and passaging in LSEC-specific medium led to isolation of a malignant endothelial cell clones. Isolated AS cells were analyzed for endothelial-specific morphological and functional properties (*in vitro* capillary formation on Matrigel, expression of CD31 and VEGFR2). *In vivo* vascular casts and *in vitro* cellular ultrastructure were studied by scanning electron microscopy (SEM). Gene expression of AS LSEC in comparison to freshly isolated normal LSEC from control and Notch1 KO mice without AS was profiled with the Affymetrix® Mouse Gene 1.0 ST array. Expression levels were analyzed and further statistical processing was preformed by gene set enrichement analysis (GSEA). AS cells were subjected to capillary tube formation assay in the presence or absence of increasing sorafenib concentrations (0.1, 1 and 5 μM).
Results: AS LSEC retained specific endothelial properties such as tube formation activity, as well as expression of CD31 and VEGFR2. However, SEM analysis revealed dedifferentiated LSEC with numerous filopodia, loss of sieve plates, loss of fenestrae, and loss of contact inhibition. Intussusceptive angiogenesis and extensive vascular dedifferentiation were observed in vascular casts from angiosarcoma livers. Transcriptome analysis showed massive changes in gene expression identifying fibroblast growth factor receptors, transforming growth factor-beta 2, met proto-oncogene (MET) and vascular endothelial growth factor A (VEGFA) as potential drivers in malignant transformation of hepatic angiosarcoma. Moreover, GSEA revealed that six of the top 20 upregulated chemical and genetic perturbation gene sets were related to myc targets (FDR<0.25). Capillary tube formation ability of AS cells was significantly inhibited by sorafenib in a dose-dependent manner.
Conclusions: We identified Notch1 as LSEC tumor suppressor gene and key player of hepatic angiosarcoma development in our mouse model. Notch1 KO mice together with the isolated murine angiosarcoma cell lines provide a first and important *in vitro* and *in vivo* model to study endothelial pathobiology and allow to gain new insights in the molecular biology of angiosarcoma as well as to test novel therapeutic strategies.

Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, CRP, platelets, hemoglobin, and blood leukocytes

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Background and Aims: The correlation between noninvasive markers with endoscopic activity according to the modified Baron Index in patients with ulcerative colitis (UC) is unknown. We aimed to evaluate the correlation between endoscopic activity and fecal calprotectin (FC), C-reactive protein (CRP), hemoglobin, platelets, blood leukocytes, and the Lichtiger Index (clinical score).
Methods: UC patients undergoing complete colonoscopy were prospectively enrolled and scored clinically and endoscopically. Samples from feces and blood were analyzed in UC patients and controls.
Results: We enrolled 228 UC patients and 52 healthy controls. Endoscopic disease activity correlated best with FC (Spearman's rank correlation coefficient r = 0.821), followed by the Lichtiger Index (r = 0.682), CRP (r = 0.556), platelets (r = 0.488), blood leukocytes (r = 0.401), and hemoglobin (r = -0.388). FC was the only marker that could discriminate between different grades of endoscopic activity (grade 0, 16 [10-30] μg/g; grade 1, 35 [25-48] μg/g; grade 2, 102 [44-159] μg/g; grade 3, 235 [176-319] μg/g; grade 4, 611 [406-868] μg/g; P <0.001 for discriminating the different grades). FC with a cutoff of 57 μg/g had a sensitivity of 91% and a specificity of 90% to detect endoscopically active disease (modified Baron Index ≥ 2).
Conclusions: FC better correlated with endoscopic disease activity than clinical activity, CRP, platelets, hemoglobin, and blood leukocytes. The strong correlation with endoscopic disease activity suggests that FC represents a useful biomarker for noninvasive monitoring of disease activity in UC patients.

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Protein Phosphatase 2A negatively regulates Interferon-a signalling and modulates Hepatitis C viral replication

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Background: In response to viral infection, cells secrete interferons (IFNs) that bind cell surface receptors and activate the Jak-STAT pathway. Jak-STAT signalling is negatively regulated at different levels of the signalling cascade by several inhibitors like PIAS, SOCS, USP18 and PTPases. We have previously reported that protein phosphatase 2A (PP2A) is upregulated in HCV infection, and that IFN signalling is impaired in cells expressing a constitutive active form of PP2Ac (HA-PP2Ac). In the present work we further studied the role of PP2A in IFN-α signalling and in HCV replication.
Methods: Human hepatoma 7 (Huh7) cells were stably transfected with short hairpin siRNA against PP2Ac. Tyrosine phosphorylation of STAT1 (PY-STAT1) was investigated by Western blot. The expression of ISGs was quantified by RT-qPCR. Binding of STAT1 to m67 oligonucleotide probes was assessed with electrophoretic mobility shift assays. The STAT1-PP2Ac association was analysed by co-immunoprecipitation. PP2Ac was transiently silenced in Huh7.5.1 cells using lentiviral based silencing constructs. The role of PP2A for HCV replication was studied using the fully infectious HCV cell culture system. Cell extracts and cell culture supernatants were harvested at different time points and the extracellular infectivity, HCV RNA, and viral proteins were analyzed by titration, RT-qPCR and Western-blotting, respectively.
Results: We found decreased tyrosine phosphorylation of STAT1 upon IFN-α stimulation in PP2Ac overexpressing cells. The reduction of STAT1 activation resulted in a decreased binding of STAT1 to m67 probe. Consequently, we observed less induction of the ISGs upon IFN-α stimulation. Knockdown of PP2Ac resulted in enhanced STAT1 phosphorylation, STAT1-DNA association and ISGs induction. Inhibition of IFN-α signalling by PP2Ac resulted in an impaired antiviral efficacy against HCV, whereas silencing of PP2Ac enhanced the antiviral activity of IFN-α. Interestingly, we also noticed that over-expression of PP2Ac lead to increased HCV replication and that knockdown of PP2Ac reduced viral replication even in the absence of IFN-α.
Conclusion: Our results provide evidences that PP2A inhibits IFN-α signalling and therefore alters the IFN-α antiviral activity. Furthermore, PP2A influences HCV replication independent of IFN-α signalling.

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Renal biomarkers and prediction of acute renal failure in patients with cirrhosis and ascites

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Background: Renal failure is frequent in hospitalized patients with cirrhosis, with a strong prognostic value. Serum creatinine overestimates renal function, and renal biomarkers of acute renal failure (ARF) need to be assessed. Methods: This is a prospective, observational cohort study in 100 patients with cirrhosis and ascites admitted to hospital. ARF was diagnosed according to AKIN criteria (Acute Kidney Injury Network) with 3 stages of severity (*Kidney Int Suppl 2012; 2:8*).Plasma and urine levels of cystatin, NGAL and serum creatinine were measured within 24h of admission. Patients' follow-up was 30 days. Results: 77 patients are included to date (66% male, age 58 years), of whom 39 developed ARF (severity grade I, II, III: 51%, 31%, 18%). Table: univariate analysis (SD: standard deviation)

Variable	ARF (n=39)	No ARF (n=38)	P value
Infection	49%	21%	0.011
Creatinine (umol/l)(SD)	135 ± 93	64 ± 24	<0.001
Plasma NGAL (ng/ml) (SD)	89 ± 66	71 ± 77	<0.01
Urine NGAL/urine creat	7 [0.7-71]	4.4 [0.2-133]	0.02
Plasma cystatin (mg/l) (SD)	19 ± 0.7	1.2 ± 0.4	<0.001

Age, diabetes or chronic renal insufficiency were not related to ARF. In multivariate analysis, only cystatin (OR 15.2; 95% CI: 3.8-59.5, p< 0.001) was associated with ARF, with an AUC of 0.84 (0.7-0.93) for a cut-off of 1.3 mg/l, sensibility and specificity of 80% and 79%, respectively. Conclusions: this interim analysis suggests that the renal biomarker plasma cystatin is superior to creatinine and NGAL in the early prediction of ARF in patients with cirrhosis and ascites admitted to hospital.

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Treatment of Eosinophilic Esophagitis with the CRTH2-Antagonist OC000459: A Novel Therapeutic Principle

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BACKGROUND Eosinophilic esophagitis (EoE) is a Th2-type inflammatory disease of the esophagus, characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant inflammation. CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) is a receptor expressed by Th2 cells and eosinophils, which mediates chemotaxis and activation of these cells in response to prostaglandin D_2, a key prostanoid in allergic responses. OC000459 is a selective and orally bioavailable CRTH2 antagonist, which blocks the ability of PGD_2 to recruit and activate Th2 cells and eosinophils with proven efficacy in asthma. OC000459 is therefore expected to suppress tissue inflammation associated with EoE. The purpose of this study was to evaluate the efficacy and safety of an OC000459 monotherapy in adult patients with active EoE.

METHODS In this randomized, double-blind, placebo-controlled trial 26 adult patients (m/f = 22/4; mean age 41 yrs, range 22-69 yrs) with active (≥20 eos/hpf and symptoms), corticosteroid-dependent and/or -resistant EoE were treated either with 100 mg OC000459 (n=14) or placebo (n=12) twice daily for 8 weeks. Pre- and post-treatment disease-activity was assessed clinically, endoscopically, histologically and via biomarkers. The primary endpoint was the reduction of the esophageal eosinophil infiltration.

RESULTS After an 8-week treatment of active EoE with OC000459, the mean eosinophil number decreased from 114.7 to 74.2 eos/hpf, whereas under placebo, no reduction was observed (from 102.8 to 99.4 eos/hpf) (p=0.159). The effect of OC000459 was more pronounced in the proximal (64% reduction, p=0.131) than in the distal esophagus (16% reduction, p=0.667). The global assessment of disease activity decreased under OC000459 from 7.1 to 5.2 pts, whereas the reduction was less in the placebo group (from 6.7 to 5.8, p=0.424). The endoscopic appearance decreased under OC000459 from 6.3 to 5.5 and increased under placebo from 5.5 to 5.8 pts (p=0.118). In spite of these differences, the symptom score decreased in both OC000459 (from to 16.5 to 8.8 pts) and placebo (from 16.7 to 9.8 pts) groups equally (p=0.989). The treatment was well tolerated and no serious adverse events occurred.

CONCLUSIONS This study demonstrates that 1) treatment with the CRTH2-antagonist OC000459 may exert a moderate anti-inflammatory effect in a subgroup of adult patients with active EoE; 2) the effect is more pronounced in the proximal than in the distal esophagus and; 3) treatment with OC000459 is well tolerated.

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A MODEL FOR DROPOUT ASSESSMENT OF CANDIDATES WITH OR WITHOUT HEPATOCELLULAR CARCINOMA ON A COMMON LIVER TRANSPLANT WAITING LIST

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Background: Allocation of liver graft is based on the Model of End-stage Liver Disease (MELD) score and the use of exception points for patients with hepatocellular carcinoma (HCC). A more flexible model, better reflecting the risk of drop-out, would be welcome.
Methods: This study was based on the Scientific Registry of Transplant Recipients and included 5'498 adult candidates of a liver transplantation for HCC and 43'528 for non-HCC diagnoses. A proportional hazard competitive risk model was used.
Results: The risk of drop-out of HCC patients was independently predicted by MELD score, HCC size, HCC number and alpha fetoprotein (AFP). When combined in a model with age and diagnosis, these factors allowed for the extrapolation of the risk of drop-out. While this model and MELD did not share compatible scales, a correlation between both models was computed according to the predicted risk of drop-out, and drop-out equivalent MELD (deMELD) points were calculated.
Conclusion: The proposed model, with the allocation of deMELD, has the potential to allow for a dynamic and combined comparison of opportunities to receive a graft for HCC and non-HCC patients on a common waiting list.

Interferon-λ induces a sustained expression of interferon stimulated genes that are also upregulated in the liver of patients with chronic hepatitis C and poor response to IFNα-based therapy. 29

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Background
Hepatitis C virus (HCV) infection is the major cause of cirrhosis and liver cancer. To date, the standard therapy is limited to a combination of Pegylated interferon a (Peg-IFNa) and Ribavirin. However, only 44% and 72% for genotype 1 and 2/3 respectively, show a sustained virological response. We have previously reported that the non-response to IFNα-based therapy is linked to the degree of pre-activation of the IFN system. Indeed, patients with a high expression of interferon-stimulated genes (ISGs) prior treatment will poorly respond to the IFNα-based therapy. The molecular mechanism responsible for the elevated expression of pre-activation ISGs in these non-responder patients remains unclear. One plausible explanation would be that the maintenance of expression of these ISGs results from the activation of the IFNλ signaling since we have reported that IFNλ pathway is not refractory to further stimulation by IFNλ, contrary to IFNα. In the present work, we analyze the role of IFNλ signaling pathway in the pre-activation of ISGs.
Materials and Methods
IFNλ signaling was investigated in human primary hepatocytes (PHH), Huh7, and Huh7 overexpressing the IFNλ receptor chain IL28RA (Huh7R). The expression of ISGs was monitored by qPCR. Phosphorylation of STAT1 was measured by Western-blotting. Total RNA isolated from liver biopsies were used to analyze the correlation between IL28RA and ISGs.
Results
Analysis of PY-STAT1 in PHHs upon IFNα and λ stimulation reveals a weak response to IFNλ. We show that pre-stimulation of PHHs with IFNα induces an up-regulation of IL28RA leading to a stronger IFNλ response suggesting the importance of IL28RA expression level in IFNλ signaling pathway. Using Huh7 cells that overexpress IL28RA, we demonstrate that upon IFNλ stimulation the expression of pre-activated ISGs remains elevated up to 4 days. Contrary to IFNλ, IFNα was not able to maintain the expression of these pre-activated ISGs. Next, we perform a correlation study in liver biopsies and show a significant positive correlation between IL28RA and pre-activated ISGs.
Conclusion
These findings demonstrate that the IFNλ signaling pathway contributes to the elevated expression of the pre-activated ISGs in poor responders to IFNα-based therapy.

Long Diagnostic Delay In Crohn's Disease Is Associated With a Complicated Disease Course and Increased Operation Rate 30

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Background and Aims: The impact of diagnostic delay (a period from appearance of first symptoms to diagnosis) on the clinical course of Crohn's disease (CD) is unknown. We examined whether length of diagnostic delay affects disease outcome. **Methods:** Data from the Swiss IBD cohort study were analyzed. The frequencies of occurrence of bowel stenoses, internal fistulas, perianal fistulas, and CD-related surgery at distinct intervals after CD diagnosis (0 - < 2, 2 - < 6, ≥ 6 years) were compared for groups of patients with different length of diagnostic delay. **Results:** The data from a group of 200 CD patients with long diagnostic delay (> 24 months, 76th - 100th percentile) were compared to those from a group of 461 patients with a short diagnostic delay (within 9 months, 1st - 50th percentile). Treatment regimens did not differ between the two groups. Two years following diagnosis, patients with long diagnostic delay presented more frequently with bowel stenoses (25% *vs.* 13.1%, p = 0.044), internal fistulas (10% *vs.* 2%, p = 0.018), perianal fistulas (20% *vs.* 8.1%, p = 0.023) and more frequently underwent intestinal surgery (15% *vs.* 5.1%, p = 0.024) than patients with short diagnostic delay. Intestinal surgery was also more frequently performed ≥ 6 years after diagnosis in the group with long diagnostic delay (56.2% *vs.* 42.3%, p = 0.005) when compared to the group with short diagnostic delay. **Conclusions:** Long diagnostic delay is associated with worse outcome characterized by the development of increased bowel damage, necessitating more frequently operations in the years following CD diagnosis. Efforts should be undertaken to shorten the diagnostic delay.

Flights and Journeys to Regions ≥2000 Meters above Sea Level are associated with IBD Flares in the following 4 weeks 31

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Background: There is increasing experimental evidence that hypoxia induces inflammation in the gastrointestinal tract. Hypoxia-inducible transcription factor (HIF)-1α influences adaptive immunity and has been shown to induce barrier-protective genes in the case of experimentally-induced colitis. The clinical impact of hypoxia in patients with inflammatory bowel disease (IBD) is so far poorly investigated.

Aim: We wanted to evaluate if flights and journeys to regions ≥2000 meter above sea level are associated with the occurrence of flares in IBD patients in the 4 following weeks.

Methods: A questionnaire was completed by inpatients and outpatients of the IBD clinics of University hospital Zurich and Lausanne presenting with an IBD flare in the period from Sept 1st 2009 to August 31st 2010. Patients were inquired about their habits in the 4 weeks prior to the flare. Patients with a flare were matched with an IBD group in remission during the observation period (according to age, gender, smoking habits, and medication).

Results: A total of 103 IBD patients was included (43 Crohn's disease (CD), whereof 65% female, 60 ulcerative colitis, whereof 47% female, mean age 39.3±14.6 years for CD and 43.1±14.2 years for UC). Fifty-two patients with a flare were matched to 51 patients without flare. Patients with a flare had significantly more frequently had a flight and/or journey to regions ≥ 2000 meters above sea level in the observation period compared to the patients in remission (21/52 (40.4%) vs. 8/51 (15.7%), p=0.005). CD patients with a flare had significantly more frequently had a flight and/or journey to regions ≥ 2000 meters above sea level in the observation period compared to the CD patients in remission (8/21 (38.1%) vs. 2/22 (9.1%), p=0.024). A trend for more frequent flights and high-altitude journeys was observed in the UC patients (13/31 (41.9%) vs. 6/29 (20.7%), p=0.077). Mean flight duration was 5.8±4.3 hours. The groups were controlled for the following factors (always flare group cited first): age (37.6±13.4 vs. 45.5±14.6, p=0.0051), smoking (16/52 vs. 10/51, p=0.120), regular sports activities (32/52 vs. 33/51, p=0.739), treatment with antibiotics in the 4 weeks before flare (8/52 vs. 7/51, p=0.811), NSAID intake (12/52 vs. 7/51, p=0.221), frequency of chronic obstructive pulmonary disease (both groups 0) and oxygen therapy (both groups 0).

Conclusion: IBD patients with a flare had significantly more frequently had a flight and/or high-altitude journey within the four weeks prior to IBD flare compared to the group that was in remission. We conclude that flights and high-altitude stays are a risk factor for IBD flares.

Success rate, continence, and quality of life with a bioprosthetic plug for treating complex anal fistula 32

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Objective: Complex anal fistula continue to challenge surgeons and patients alike. Enthusiastic results from single centres in favor of a bioprosthetic plug (BP) were tempered by further studies. The present work prospectively assessed the success rate, continence, and quality of life following BP surgery in the context of a multicentre study.
Methods: Patients with complex anal fistula of cryptoglandular origin were prospectively included. Four colorectal surgeons participated. Patients were evaluated before surgery, at 10 days, 6 weeks, and 6 months. At each visit, clinical examination was performed and the Fecal Incontinence Score Index (FISI) and SF36 were completed.
Results: 47 patients (31 male, 16 female) were operated on between October 2006 and March 2009 for high transsphincteric fistula. Twenty (42.6%) fistula were branched or multiple. Seven patients (15%) had the BP as their first fistula surgery, while 40 patients (85%) had 2 - 4 prior fistula surgeries. Six patients (13%) had a redo BP surgery. Median operative time was 25 min. and median length of hospital stay was 1 day. Median follow-up was 7 months (range 4-34 months). Four patients (8.5%) extruded their BP within 10 days. Further 4 failed within 6 weeks and 11 more patients failed at 6 months, yielding a 6-month failure rate of 40.4%. Ultimately, a total of 24 patients (51.1%) failed the BP for a median time to recurrence of 9.4 months (95% CI 6.5 - 12.4 months), including 3 patients lost to follow-up. At 6 months of follow-up, the FISI incontinence score improved markedly from 18 to 12 (p=0.008). Six out of 8 quality of life components increased significantly (p<0.004). Accordingly, both quality of life summary scores physical (47.0 to 56.2, p=0.001) and mental (47.6 to 55.3, p=0.013) improved markedly.
Conclusion: The BP allows for a healing rate close to 50% in complex cryptoglandular fistula while improving fecal continence and quality of life. These results support the use of the BP as a first line therapy instead of more aggressive and potentially debilitating surgical options.

Red blood cell transfusions are associated with increased rebleeding in patients with nonvariceal upper gastrointestinal haemorrhage. G1

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BACKGROUND:
Acute upper gastrointestinal hemorrhage (UGIH) is one of the leading clinical indications for transfusion of Red Blood Cells (RBCs). There exists considerable practice variation and little evidence to guide effective use of transfusion of RBCs in the majority of patients who are not in shock. Studies in other critically unwell patients suggest associations between transfusion and adverse patient outcomes. The aim of this study is to determine the association between RBC transfusions administered within 24 hours following presentation to hospital in patients with non-variceal upper gastrointestinal bleeding (NVUGIB) and the clinical outcomes of rebleeding and mortality.
METHODS:
Observational study based on the Canadian Registry of patients with Upper Gastrointestinal Bleeding and Endoscopy (RUGBE). This study included 1869 randomly selected patients admitted to 21 hospitals between 1999 and 2002 with endoscopically confirmed NVUGIB. Transferred patients were then excluded, yielding 1677 patients for this analysis. Multivariate logistic regression models were used to examine the associations between RBC transfusion and patient outcomes.
RESULTS:
One thousand six-hundred and seventy-seven patients were included in the analysis (66.2 +/- 16.8 yrs, 61.7% male, 2.5 +/- 1.7 comorbid conditions, hemoglobin, 96.8 +/- 27.2 g/L). 53.7% of all patients received an RBC transfusion with a mean of 2.9 +/- 1.6 units of blood. 31.6% had haemodynamic instability at presentation. Endoscopy was performed within 24 h in 75.3%; 35.8% exhibited high risk stigmata of hemorrhage, while 35.2% underwent endoscopic therapy. Overall rebleeding (defined as continuous bleeding, rebleeding or surgery) and mortality rates were 17.9 % and 5.4%, respectively. After adjusting for potential confounders, transfusion of RBCs within 24 hours of presentation was significantly and independently associated with an increased risk of rebleeding (OR 1.8, 95% CI 1.2-2.8). No significant association was noted between transfusions of RBCs in the first 24 hours and death (OR 1.5, 95% CI 0.94-2.23).
CONCLUSIONS:
The findings of this observational study confirm an association between transfusion of RBCs in patients with NVUGIB and the subsequent risk of rebleeding, after appropriate adjustment for possible confounding. These results support the need for a prospective randomized trial comparing different blood transfusion strategies in patients with UGIH in order to inform safe, effective and judicious use of finite resources.

Fixed Rings and Strictures in Eosinophilic Esophagitis develop Due to Continuing Inflammation over Time G2

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Background and Aims: Two distinct endoscopic phenotypes of Eosinophilic Esophagitis (EoE) have been identified: the inflammatory (IP) and the stenosing (SP) phenotype. It is not known whether these EoE-associated phenotypes are reflective of different phases during disease course. We aimed to assess the phenotype at initial EoE presentation and diagnosis and to evaluate if SP increases over time.
Methods: Retrospective analysis of the Swiss EoE Database (SEED) extended by a review of patients charts, endoscopy and pathology records.
Results: Forty-four EoE patients were analyzed (33 males, mean age at index visit 41 ± 14 years, all Caucasians). Median follow-up time was 3.1 years (IQR 1-4, range 1-18 years). Median diagnostic delay was 5 years (IQR 2-16, range 0-34 years). At first diagnosis, 32% (14/44) of EoE patients had already presented with a stenosis. The mean diameter of the stenoses was 10 ± 2 mm, and the mean length was 2.8 ± 2.9 cm. Peak eosinophil count did not change over time (48 ± 39 eos/HPF at index visit vs. 59 ± 41 eos/HPF at end of follow-up, n=44). The risk of the presence of a stenosis at index visit was 0% for a disease duration of 0-4 years, 37% for a disease duration between 5-10 years and 67% for a disease duration >10 years (p = 0.0035, trend test).
Conclusions: The frequency of esophageal stenoses is proportional to the disease duration, whereas the inflammatory activity does not significantly change over time. Our findings underscore the necessity to reduce diagnostic delay in EoE and to control the underlying inflammatory processes to prevent esophageal remodeling.

Development of the First Disease Activity Index for Eosinophilic Esophagitis: Update on the EEsAI in 2012 G3

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Background and Aims: The international EEsAI study group is currently developing the first activity index (EEsAI) specific for Eosinophilic Esophagitis (EoE). Goal: To develop, evaluate and validate the EEsAI.
Methods: The development comprises three phases: 1. Selection of candidate items (completed); 2. Evaluation of the activity index in a first patient cohort (in progress, patient recruitment completed); and 3. Validation in a second EoE patient cohort. Focus group interviews with patients were used in phase 1 to generate patient reported outcomes (PRO) according to guidelines of regulatory authorities (FDA and EMA), whereas the section of biologic items was developed by Delphi rounds of international EoE experts from Europe and North America.
Results: The EEsAI has a modular composition to assess the following components of EoE activity: patient reported outcomes, endoscopic activity, histologic activity, laboratory activity, and quality of life (QoL). Definitions for all aspects of endoscopic and histologic appearance were established by consensus rounds among EoE experts. Symptom assessment tools were created that take into account different food consistencies as well as food avoidance and specific processing strategies. The EEsAI is currently evaluated in a cohort of adult EoE patients since March 2011 (patient recruitment completed).
Conclusions: The EEsAI standardizes outcome assessment in EoE trials. The collaboration with international EoE experts as well as following of the guidelines from regulatory authorities will lead to its wide applicability.

Small Bowel Bacterial Overgrowth is found in 71% of IBS Patients and associated Symptoms respond well to Rifaximin in a Phase IV Trial G4

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Background and Aims: The prevalence of small intestinal bowel bacterial overgrowth (SIBO) in patients with irritable bowel syndrome (IBS) ranges from 43% to 78% as determined by the lactulose hydrogen breath (LHBT) test. Although rifaximine, a non-absorbable antibiotic, has been able to decrease IBS symptoms in placebo-controlled randomized trials, these results were not repeated in phase IV studies. We aimed to assess the prevalence of SIBO in an IBS cohort and to evaluate the response to rifaximin.

Methods: IBS patients fulfilled Rome III criteria, had an absence of alarm symptoms, normal fecal calproectin, and normal endoscopic workup. They underwent lactulose hydrogen breath testing (LHBT) for SIBO diagnosis. Patients with SIBO were treated with rifaximine tablets for 14 days. Symptoms were assessed by questionnaires before rifaximin treatment and at week 6.

Results: Hundred-fifty IBS patients were enrolled (76% female, mean age 44 ± 16 years), of whom 106 (71%) were diagnosed with SIBO and consequently treated with rifaximine. Rifaximine treatment significantly reduced the following symptoms as assessed by the symptom questionnaire: bloating (5.5 ± 2.6 before *vs.* 3.6 ± 2.7 after treatment, p <0.001), flatulence (5 ± 2.7 *vs.* 4 ± 2.7, p = 0.015), diarrhea (2.9 ± 2.4 *vs.* 2 ± 2.4, p = 0.005), abdominal pain (4.8 ± 2.7 *vs.* 3.3 ± 2.5, p <0.001) and resulted in improved overall well-being (3.9 ± 2.4 *vs.* 2.7 ± 2.3, p <0.001). The LHBT was repeated 2-4 weeks after rifaximine treatment in 65/93 (70%) patients. Eradication of SIBO was documented in 85% of all patients (55/65).

Conclusions: The results of our phase IV trial indicate that a high proportion of IBS patients tested positive for SIBO. IBS symptoms were significantly diminished following a 2-week treatment with rifaximine.

Increased risk in first-degree relatives with colorectal cancer – is communication between physicians, colorectal-patients and first-degree relatives sufficient in (eastern) Switzerland? G5

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Background:
Colorectal cancer (CRC) contributes significantly to the global burden of cancer [1], and familial clustering of CRC is also common, an estimated proportion up to 5% of the population have a first-degree relative (FDR) with CRC [2, 3]. Those with one first-degree relative experience a 2-fold higher risk of CRC, those with two or more relatives, a 3-4-fold increased risk, independent of age at diagnosis [4]. The aim of our study is to analyze whether the communication between physicians and surgeons is sufficient in alerting CRC-patients and their FDR to undergo a screening colonoscopy ?

Methods:
We consulted in a retrospective single center cohort all index-patients aged 18-80 who underwent surgery for CRC between January 2004 and May 2010 (64 months) at Kantonsspital St. Gallen with a questionnaire. Patients with hereditary syndromes were excluded. After written approval by the index patients, we contacted their FDR (siblings and children) to fill out a questionnaire. We examined the rate of index patients and FDR who were educated about the higher CRC risk (with specification of the educator) and the rate of already realised screening colonoscopy by FDR. The study was approved by the local ethical committee.

Results:
The questionnaire return rates were 34.4% (134/390, median age 66.1, male 66,4%) and 69,7% (168/241, median age 43,5, male 50,6%) for index patients and their FDR (49 siblings and 119 children) respectively. 82.1% (110/134) of index patients were informed about the increased CRC risk of their FDR. 85.1% (143/168) of FDR were informed about their increased CRC risk, but 69% of all (respectively 40.8% of those aged > 50 y) did not undergo a screening colonoscopy. Figure 1 and 2 demonstrate the type of physician informing about raised risk.

Conclusions:
CRC patients and their FDR are well informed about the increased CRC risk of FDR. However, the majority of FDR do not undergo the recommended screening colonoscopy. Therefore further investigation is needed.

Figure 1: Information of index CRC-patients about raised CRC-risk for FDR (multiple answers permitted)

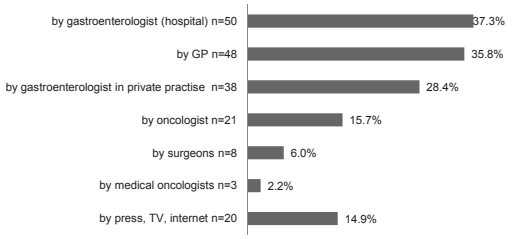
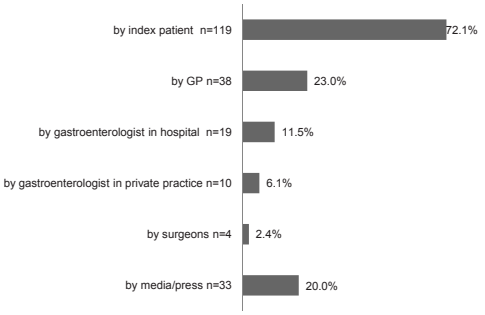


Figure 2: Information status of FDR about their increased risk of CRC



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G6

TITLE: Characteristics of Patients with Durable Use of Infliximab for ≥5 years

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ABSTRACT BODY:

Background: Anti-TNF antibodies are used successfully to maintain remission in patients with inflammatory bowel disease. About 40% of patients lose response within the first year of treatment, but little is known about the clinical characteristics of the patients who become long term users of this therapy.

Aim: The purpose of this study was to perform a descriptive analysis of Crohn's disease (CD) patients who received infliximab longterm and to develop prognosis factors to predict successful long term use of infliximab (LTUI).

Methods: Patients from Massachusetts General Hospital, Boston, exposed to infliximab (IFX), were identified through examination of infusion records. Data collection was based on the PRISM (Prospective Registry in IBD Study at MGH) database and complemented by a retrospective chart abstraction for each patient. We classified patients in order to compare long term users of IFX (≥5 years of treatment, LTUI), with 3 other groups of non LTUI: patients who were primary non responders (PNR), patients with secondary loss of response (LOR) and patients who stop due to adverse events (AE).

Results: We collected data on 348 CD patients (57% female), of whom 111 were identified as LTUI. In the comparison group were 138 CD patients (27 PNR, 39 LOR and 72 AE) included. Among LTUI, disease extension was 14% ileum, 30% colon, 56% ileocolonic. Additional locations were 6 % upper GI and 52% perianal. Penetrating disease behavior associated with perianal lesions (Montreal classification B3+P) was significantly higher in the LTUI (34% vs 22 %; p=0.04). Higher levels of education were observed in LTUI. Among the PNR and AE groups, the prevalence of active smokers was 15% in twice as frequent as among LTUI (p=0.04) and more people were older than 40 years (p=0.02). Thirty-five percent of LTUI required dose escalation to 10 mg/kg (vs 20% in comparison groups, p=0.1). Concomitant thiopurines were administered in a numerically but not statistically significant higher proportion in LTUI (30% vs 20%, p=0.2) whereas comparison groups included more patients with previous thiopurines AE (31% vs 20%, p=0.5).

Conclusion: A shorter duration of disease at time of first infusion and concomitant immunosuppressants seems to be good prognostic factors of long term success of IFX therapy. Age and smoking are associated with PNR and increased adverse events. These results need to be interpreted cautiously due to potential confounding by indication. Hence, patients with a high level of education, perianal and penetrating disease have higher rates of long term infliximab use.

Chronology of Extraintestinal Manifestations relative to IBD Diagnosis in the Swiss Inflammatory Bowel Disease Cohort G7

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Background and Aims: Due to a paucity of such data we aimed to assess the type and frequency of extraintestinal manifestations (EIM) in IBD patients and to evaluate their chronologic behavior.

Methods: Analysis of data from the Swiss Inflammatory Bowel Disease Cohort (SIBDCS) which collects data since 2005 on a large sample of IBD patients from hospitals and private practices across Switzerland.

Results: At total of 1,143 patients were analyzed (572 (50%) female, mean age 42.1 ± 14.4 years), 629 with Crohn's disease (CD), 501 with ulcerative colitis (UC), and 13 with indeterminate colitis (IC). Of these, 374 (32.7%) presented one to five EIM (65% with CD, 33% with UC, 2% with IC). Of those patients suffering from EIM, 41.7% presented two, 12.4% three, 5.3% four, and 3.2% five EIM during lifetime. The initial EIM presented with the following frequencies: peripheral arthritis (PA) 63.4%, ankylosing spondylitis (AS) 8.1%, primary sclerosing cholangitis (PSC) 6%, uveitis 5.7%, oral aphthosis 5.7%, erythema nodosum (EN) 5%, other 3.6%, pyoderma gangrenosum 1.8%, psoriasis 0.7%. In only 7.1% of cases, the EIM manifested before IBD diagnosis was made (median time 28 months before IBD diagnosis, IQR 7-60 months), in 92.9% EIM manifested after established IBD diagnosis (median 72 months, IQR 9-147 months).

Conclusions: EIM are a frequent problem in IBD patients. The vast majority of EIM manifest after IBD diagnosis has been established. Peripheral arthritis, ankylosing spondylitis, and PSC represent the most frequent first manifestations of an EIM.

Anti-TNF Therapy in the Swiss Inflammatory Bowel Disease Cohort G8

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Background: Anti-TNF 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 drug. We aimed to evaluate the frequency and reasons for anti-TNF switches.

Methods: Analysis of data from the Swiss Inflammatory Bowel Disease Cohort (SIBDCS). Eighty percent of included patients were recruited in hospitals and 20% from private practice.

Results: From 2,058 patients (1,172 with Crohn's disease (CD), 842 with ulcerative colitis (UC) and 44 with indeterminate colitis (IC)), 772 received at least one anti-TNF. Forty-eight % of patients with CD, 23% with UC, and 30% with IC were ever treated with an anti-TNF drug. There was no gender difference with respect to the frequency of anti-TNF treatment. A total of 584 patients (76%) were treated with one, 142 (18%) with two, and 46 (6%) with three anti-TNF (of which 32 were female). A total of 89% patients were treated with IFX, 28% ADA and 13% with CZP. Overall response rate (defined as drop in CDAI >100 points) to anti-TNF was 50%, with best response rates for the first used anti-TNF. Reasons to switch the anti-TNF were in 11% a primary non-response, in 38% a loss of response and in 36% anti-TNF side effects or intolerance (reasons for 15% of treatment failures not documented).

Conclusion: Anti-TNF drugs were used in half of the CD patients and in one quarter of UC patients. Anti-TNF drug switch due to insufficient response and/or side effects was necessary in one quarter of IBD patients. IFX was mainly used as first-line therapy. Best response rates were observed for the first used anti-TNF. Following analyses will identify risk median treatment duration as well as risk factors for anti-TNF switch.

Frequency and Type of Side Effects of Immunomodulating Medication in the Swiss Inflammatory Bowel Disease Cohort. G9

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Background and Aims: Most studies reporting on adverse effects (AE) of inflammatory bowel disease (IBD) therapy focus on single therapy. We aimed to assess the type and frequency of AE in IBD patients treated with single and multiple drug therapy.

Methods: Analysis of data from the Swiss Inflammatory Bowel Disease Cohort (SIBDCS). The following drug categories were analyzed: 5-ASA, azathioprine (Aza), 6-mercaptopurine (6-MP), Methotrexate (MTX), Anti-TNF (infliximab, adalimumab, certolizumab), cyclosporine, tacrolimus and steroids.

Results: A total of 1,961 patients were analyzed (977 female, mean age 42.1±14.4 years, 1,169 with Crohn's disease, 790 with ulcerative colitis, and 42 with indeterminate colitis. 318 (16.2%) patients were not treated with any of the above-mentioned drugs, while 650 (33.2%), 569 (29%) and 424 (21.6%) patients had one, two, and three or more drugs, respectively. 535 (32.6%) patients reported at least one side effect. We found a significant correlation between the number of drugs used by a patient and the frequency of side effects with 17.4% side effects for one drug, 29% for 2 drugs, and 60.6% for three or more drugs ($p<0.001$). The frequency of side effects for the different drug classes were as follows: 5-ASA (n=980) 10.8%, Aza/6-MP (n=636) 51.9% (pancreatitis in 9%, hepatitis in 2.7%), MTX (n=146) 42.5% (hepatitis in 2.7%), anti-TNF (n=255) 23.1%, cyclosporine (n=49) 10.2%, tacrolimus (n=5) 20%, steroids (systemic or topical, n=1,150) 9.6%.

Conclusion: IBD treatment is associated with a significant number of side effects. A direct correlation between the number of simultaneously used drugs and the frequency of AE was observed. Physicians should be vigilant for the occurrence of a variety of potential side effects in their IBD patients.

Experience with Golimumab as fourth anti-TNF-treatment in Patients with Crohn's Disease – a Case Series G10

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Background: Anti-TNF therapies play a crucial role in the treatment of Crohn's disease (CD). There are three anti-TNF antibodies available for the treatment of severe CD (adalimumab, certolizumab pegol, infliximab). Golimumab is a fourth anti-TNF antibody available for the treatment of rheumatoid arthritis, psoriasis arthritis and ancylosing spondylitis. We report our experience with golimumab in three CD patients with treatment refractory intestinal CD activity and spondarthropathy.

Methods: Three CD patients who were previously treated with all three currently available anti-TNFs suffered from severe intestinal activity with abdominal pain and diarrhea and spondarthropathy as documented by an experienced rheumatologist. Golimumab was given as indicated for ancylosing spondylitis with monthly s.c. injections of 50mg.

Results: A 25 year old female patient with severely active Crohn's colitis showed remission of intestinal activity and arthralgias, but had to stop golumimab due to mucocutaneous side effects as experienced with two other anti-TNFs. A 47 year old male patient with severely active CD showed clear response of arthralgias and intestinal activity to golimumab, which however was stopped due to persisting intestinal activity after 3 injections. A 39 year old male patient with severe Crohn's colitis showed some improvement of arthralgias but no intestinal response to golimumab which was stopped after 4 injections.

Conclusion: Our experience with "low dose" golimumab (50mg monthly s.c. without induction therapy) in this small case series shows mixed results for the use of golimumab as "rescue therapy" in CD patients with spondarthropathy and intestinal activity. Unfortunately, there are no clinical trials with golimumab for CD. Data from a large trial seem to support the use of golimumab induction therapy in ulcerative colitis, however with much larger doses than used in our patients (Sandborn et al., Gastroenterology 2012:142(Supplement1): p161: Abstract 943d).

First Explicit Criteria to Decide on the Appropriateness of Therapy of Ulcerative Colitis: the European Epatuc Panel. G11

V Pittet (1), JP Vader (1), JJ Gonvers (1), M Maillard (1), A Schoepfer (1), C Felley (1), C Mottet (1), P Michetti (1,2), F Froehlich (1,3). (1) CHUV & University of Lausanne, (2) Crohn's & Colitis Center, La Source, Lausanne, (3) University of Basel. Background: Ulcerative colitis (UC) is a chronic disease with a wide variety of treatment options many of which are not evidence based. Supplementing available guidelines, we developed explicit appropriateness (AP) criteria. Methods: 8 gastroenterologists, 2 surgeons and 2 general practitioners assessed the AP of therapy using the RAND AP Method. Assessment was based on an extensive literature review based on/supplementing the ECCO UC 2011 guidelines, combined with expert clinical judgment. Clinical indications were rated on a 9-point scale and re-rated at a two-day panel meeting. Ratings were aggregate into three categories: appropriate (A), uncertain (U) and inappropriate (I). Results: 718 clinical scenarios were rated, for 13 main clinical presentations: not refractory (n=64)/refractory (n=33) proctitis, mild to moderate left-sided (n=72)/extensive (n=48) colitis, severe colitis (n=36), steroid-dependant colitis (n=36), steroid-refractory colitis (n=55), acute pouchitis (n=96), maintenance of remission (n=248), colorectal cancer prevention (n=9) and fulminant colitis (n=9). Overall, 14% of indications were judged A, 18% U and 68% I. Conclusion: Explicit AP criteria for therapy of UC were developed that allow prospective assessment of treatment AP.

Is There a Relationship Between Information Concerns of Patients and Adherence to Therapy? Results from the Swiss IBD Cohort Study. G12

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Background: In spite of the relapsing nature of inflammatory bowel diseases (IBD), on average, 40% of IBD patients are non-adherent to treatments. On the other hand, they are often seeking information on their disease. The relationship between information seeking and adherence to treatment is poorly documented. The main aim of this study was to examine this association among IBD patients. Methods: Use of data from the Swiss IBD cohort study, collected through medical reports and patient self-reported questionnaires, and from a survey conducted to assess information sources and concerns. Crude and adjusted odds ratio (OR) for non-adherence to treatment, 95% CI, were calculated. Differences in the proportions of information sources and themes were compared between adherent and non-adherent patients. Results: The number of eligible patients was 488; 19% (N=92) were non-adherent to their drug treatment and 69% (N=335) were information seekers. Crude OR was 69% higher among information seekers compared to non-seekers (OR=1.69; 95%CI 0.99-2.87) and the OR=2.39 (95%CI 1.32-4.34) after adjustment for confounders (drug regimen, supplementation medicines use) and main risk factors. Family doctors were 15.2% more often consulted (p=0.019) among adherent-to-treatment patients, as were books and TV (+13.1%; p=0.048) while no difference in proportions was observed for sources like internet or gastroenterologists. Concerns linked to tips for disease management were 14.2% more often searched among non-adherent patients (p= 0.028). No difference was observed for the other concerns (research and development on IBD, therapies, basic information on the disease, patients' experiences sharing, miscellaneous). Conclusion: In Switzerland, IBD patients who did not adhere to their treatment were more often seeking information related to their disease than adherent patients. Management of symptoms and everyday life with the disease seemed to be the most pressing information concerns of patients. Results suggest that the family doctor plays an important role in the multidisciplinary care approach needed for IBD patients.

Posters Hepatology

Peribiliary gland dilatation in liver transplant recipients: preliminary results of a morphometric and clinical study. H1

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We studied the prevalence, histologic findings and clinical associations of peribiliary gland (PBG) dilatation, a poorly defined entity, in patients undergoing liver transplantation (LT) for cirrhosis. **Methods**: We measured the maximal diameter of PBG at the hilum using morphometric histologic analysis in explanted livers, and collected clinical, biochemical and radiological data at time of LT between 10.2006 to 10.2011. **Results**: 112/184 patients met the inclusion criteria. Preliminary data on 40 patients are presented (69% male; alcoholic cirrhosis: 57%; ascites: 62%; mean MELD score : 16). Patients with major PBG dilatation (35%) had more advanced liver disease and more severe hepatic encephalopathy (HE) as compared to those without this feature.

Table 1: Clinical characteristics of included patients

	No/mild PBG dilatation	Major PBG dilatation	p
n	26	14	
Age (years)	49.9 ± 2.1	55.7 + 1.2	0.11
MELD	12.3 ± 2	22.2 ± 2.7	**0.002**
Child-Pugh	8.4 ± 0.47	10.8 ± 0.69	**0.011**
Ascites	16 (57%)	10 (71%)	0.73
Grade 2-3 HE	5 (18%)	10 (71%)	**0.002**
Alk.Phosph (IU/L)	125 ± 11	118 ± 11	0.91
Bilirubin (umol/l)	83.3 ± 31	226 ± 61	**0.004**

Conclusion: Major PBG dilatation is not a rare finding in cirrhotic patients undergoing LT and it is associated with more advanced liver disease. Further studies should characterize this finding more fully.

Transient segmental hepatic ischemia following PTFE-covered TIPS implantation does not influence clinical outcome in cirrhotic patients H2

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Background: Use of PTFE-covered stents has dramatically decreased the incidence of TIPS dysfunction. However, segmental ischemia has been observed in cirrhotic patients. Aim: To evaluate the incidence of liver ischemia after TIPS, to assess the influence on clinical outcome and to evaluate its relationship with the distance between the hepatic vein end of the covered stent and inferior vena cava (DIVC). Methods: All patients treated with PTFE-covered TIPS were evaluated. Patients with hemodynamic instability or puncture of hepatic artery during procedure were excluded. Demographics, liver tests, MELD-score and Doppler findings were collected at baseline. After TIPS: changes in liver tests, DVCI, survival rates, incidence of hepatic encephalopathy (HE) and of liver failure (LF) were recorded. Hepatic ischemia (HI) was defined by a peak AST>200IU/L and doubling of baseline value; LF was defined as increase of ≥3 points on the MELD-score. Primary outcome was the survival rate; secondary outcomes were the incidence of post-TIPS LF and HE. Age, indication of TIPS, baseline AST and MELD-score, post-TIPS porto-hepatic gradient and DIVC were tested as predictors. Results: 99 patients were included (M/F:73/26; mean age: 60.9 years; alcoholics/non alcoholics 43/56; mean MELD:13.9). Indication for TIPS was refractory variceal hemorrhage (n=38); refractory ascites (n=49), preoperative (n=12). After TIPS, 41 patients developed HI, 47 patients HE of varying severity and 40 patients LF. Survival at 3 months and 1 year was 77 and 61%, respectively. DIVC was similar in the 2 groups (14.4 vs 14.3mm). Survival could not be predicted by any of the tested parameters except for the MELD-score. Indication of TIPS was an independent predictor of post-TIPS liver failure and HE. DIVC was predictor for post-TIPS HE for unknown reasons. HI could not be predicted by any of the studied parameters.
Conclusion: Our study confirms that hepatic ischemia may be associated with PTFE-covered TIPS implantation. However, this effect is transient and does not influence either post-TIPS survival or the incidence of HE or liver failure.

Futility rules in Telaprevir combination treatment H3

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Background: Futility rules for treatment with telaprevir (T) in combination with peginterferon/ribavirin (PR) are implemented to minimize potential evolution of T-resistant HCV variants in patients who are unlikely to benefit from therapy. Preliminary futility rules were established based on Phase 2 results and refined following Phase 3 studies. **Methods:** Retrospective data analyses were performed from ADVANCE, ILLUMINATE, and REALIZE (patients were assigned 12-week T/PR with either 12 or 36 additional weeks of PR (treatment-naïve, N=903) or 36 weeks of PR (treatment-experienced, N=266). We evaluated on-treatment HCV RNA levels and SVR in relation to the HCV RNA thresholds (>1000 IU/mL for treatment-naïve and or >100 IU/mL for treatment-experienced) and timepoints (Weeks 4, 12 for treatment-naïve and Weeks 4, 6, 8, and 12 for treatment-experienced) that were applied in the studies to identify patients unlikely to achieve SVR. A viral dynamic model of T/PR, developed based on data from Phase 3 studies, was used to simulate achievement of SVR with different futility rules. **Results:** At Week 4, 1.7% (14/844) treatment-naive patients, 0.7% (1/138) prior relapsers, no (0%, 0/46) prior partial responders, and 14% (10/70) prior null responders had HCV RNA levels >1000 IU/mL; none of these patients achieved an SVR with continued PR treatment (T was discontinued per protocol). 23/25 patients reached HCV RNA nadir at or prior to Week 4, typically at Week 2, with a subsequent increase in HCV RNA levels by Week 4. Among 16/844 treatment naïve patients and 7/254 treatment-experienced patients with HCV RNA levels between 100 - 1000 IU/mL at Week 4, 22% (5/23) achieved SVR with continued treatment. Modeling data confirmed patients with 100 -1000 IU/mL at Week 4 would benefit from continued T and PR treatment but patients with greater than 1000 IU/mL would not. **Conclusion:** A futility rule of greater than 1000 IU/mL at Week 4 identified and predicted treatment-naïve or -experienced patients unlikely to achieve an SVR, and prevented unnecessary exposure to T and PR in patients unlikely to benefit from further treatment. Additionally, 23/25 of these patients had reached HCV RNA nadir by Week 4 and were experiencing viral breakthrough.

Fibrosis quantification in alcoholic liver disease : a histological-hemodynamic study. H5

Nicolas Lanthier, Saskia Ditisheim, Sophie Clément, Nicolas Goossens, Laura-Rubbia-Brandt, Laurent Spahr , HUG Genève

Background: The relationship between portal pressure and architectural distortion in general, and fibrosis in particular, remains ill defined in patients with chronic liver diseases. We performed a morphometric analysis of fibrosis using a computer assisted method on liver biopsy specimens obtained during transjugular liver biopsy in 19 consecutive patients admitted for decompensated alcoholic liver disease. The hepatic venous pressure gradient (HVPG) was obtained in all patients. Liver biopsy was performed using a TJL 9F aspiration type needle (Cook), with a mean 2.5 passes. Mean fibrosis area (MFA) was expressed as the percentage of the total area of liver tissue specimen. Results: Patients characteristics are given in Table (median, range). Liver biopsy provided fragmented samples but were appropriate for a complete histological evaluation in all cases. Cirrhosis was diagnosed in all patients, but the number and thickness of fibrous septa were variable among cases.

n	19
Age (yrs)	55 [35-69]
Histological criteria for alcoholic steatohepatitis	10/19
HVPG (mmHg)	17 [4-23]
MFA (%)	11.5 [2-42]
Cirrhosis (%)	100
MELD score	18.5

MFA showed a weak correlation with portal pressure, as assessed by HVPG (r=0.29), and with the wedge hepatic pressure (r=0.21). Conclusions: In patients with decompensated alcoholic liver disease, fibrosis area measured by morphometry on liver biopsy specimens correlates poorly with portal pressure. We hypothesized that fragmentation of liver tissue in relation with the transvenous aspiration technique, the sampling variability, as well as the dynamic vascular component of portal hypertension overexpressed in alcoholic steatohepatitis may explain in part these results.

Bone marrow mononuclear cells infusion into the liver is associated with liver macrophage expansion in patients with decompensated alcoholic liver disease (ALD). H4

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Background In decompensated ALD, autologous transplantation of bone marrow mononuclear cells doesn't improve liver function at 3 months as compared to standard of care (Hepatology 2011, Abstract). We aim to analyze changes in hepatic progenitor cell (HPC) and macrophage compartments associated with this strategy. **Methods:** We examined liver biopsies obtained at baseline and at 4 weeks of follow-up in 58 patients. Both HPC and macrophage compartments were analyzed using immunohistochemistry for CK7 and CD68 and morphometric analysis. **Results:** Immunohistochemical staining for CK7 correlated with liver failure as assessed by the MELD score both at baseline (r=0.33; $p<0.05$) and at 4-week biopsies (r=0,61; p<0,01), in line with recently published data (Sancho-Bru, Hepatology 2012). Autologous transplantation procedure was not associated with changes in CK7 positive cells at 4-week follow-up biopsy. Table: (CD68 expressed in % of surface area)

Treatment Group	Baseline CD68 (%)	4-week CD68 (%)	P value
Bone marrow	3.7	5.4	0.01
Standard of care	4.2	4.6	NS

Further analyses of gene expression patterns are planned in order to determine whether those changes in the macrophage compartment are associated modifications in inflammatory or regenerative pathways. **Conclusion:** Total liver cell CK7 positivity correlates with the degree of liver failure in patients with ALD. Autologous mononuclear bone marrow cell infusion doesn't increase the number of HPC as compared to standard of care alone, but is associated with an expansion of the macrophage compartment. This is of particular interest, knowing the role of the micro-environment in HPC polarization.

Hyperferritinemia in patients with nonalcoholic fatty liver disease : transient elastometry values in 20 patients H6

Thao-Dahlia Cao, Nicolas Goossens, Saskia Ditisheim, Marc Girardin, Laurent Spahr HUG Genève

Serum ferritin (SFer) levels are frequently elevated in patients with nonalcoholic fatty liver disease (NAFLD), in relation with inflammation and/or increased iron stores. It has been shown that increased serum ferritin was associated with advanced liver fibrosis in these patients (Kowdley, Hepatology 2012 ; 55 :77-85). We studied transient elastometry (TE) values using Fibroscan in patients with NAFLD referred to our unit for hyperferritinemia, as defined by sFer > 1.5 upper limit of normal in the absence of HFE mutation. Methods : The data from 22 patients examined between 11.2011 to 4.2012 were reviewed, including available liver biopsy findings and MRI scans to quantify iron deposition. Results : Quality criteria of TE measurement were not met in 2 patients, leaving 20 patients for analysis. The XL probe was used in 4 patients. To date, 8 patients had a liver biopsy or a MRI scan for iron quantification performed. Table : patients characteristics (median values and range, mean ± SD)

Gender (M/F)	17/3
Age (yrs)	55 [36-70]
Obesity or overweight (%)	95%
HOMA score	3.2 [1.5-10.9]
Total cholesterol (mmol/l)	5.3 ± 2.2
ALT (U/L)	58 ± 52
GGT (U/L)	86 ± 58
SFer (ug/l)	716 [501-1575]
TE value (kPa)	5.8 [3.1-14]

All but 3 patients had TE values < 8 kPa. In the 4 patients with moderate/severe hepatic iron deposition (2 at histology, 2 at MRI), TE values were < 8 kPa. Conclusions : In this small group of patients with NAFLD and hyperferritinemia, the majority of TE values are within the normal range. The usefulness of TE to identify advanced fibrosis in this setting is therefore questionable and requires further studies.

H7

A comprehensive review of patterns of viral load decline in patients treated with telaprevir plus peginterferon and ribavirin

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Background: Viral load profiles in chronic hepatitis C virus (HCV) genotype 1-infected patients treated with peginterferon/ribavirin (PR) are characterized by heterogeneous HCV RNA kinetics ranging from rapid virologic response (RVR) to null response, which has implications for how early futility rules can be successfully applied. The introduction of direct-acting antivirals, such as Telaprevir (T), has dramatically changed the characteristics of viral load profiles and has enabled the use of earlier futility rules. In order to familiarize physicians with this new paradigm, we provide a comprehensive review of the most frequent profiles observed in patients treated with T and PR. **Methods:** HCV RNA profiles from 363 HCV genotype 1 treatment-naïve patients enrolled in the ADVANCE study, and 266 prior treatment-failure patients (including prior relapsers, partial responders and null responders) enrolled in the REALIZE study, were reviewed. All patients were assigned to receive 12 weeks of T with either 24 (T12PR24) or 48 weeks (T12PR48) of PR. **Results:** All patients, irrespective of baseline characteristics and/or prior-response to PR (relapse, partial response and null response), experienced a rapid decline in HCV RNA (> 2.0 $\log_{10}$) by Day 14, indicating that null response to T/PR is unlikely to occur. Subsequently, HCV RNA continued to decline to undetectable levels in patients with sustained virologic response (SVR), late virologic breakthrough (vBT; after Week 12, i.e. during the PR phase), or relapse. In patients with early vBT or meeting a futility rule before Week 12, HCV RNA usually never became undetectable and/or increased rapidly after reaching the nadir. **Conclusions:** HCV RNA profiles with T/PR are different from those with PR alone. It is important that clinicians understand these new HCV RNA profiles for proper application of futility rules. The HCV RNA dynamics allow for more stringent and earlier implementation of futility rules for patients who would not benefit from continued treatment.

H8

URSODEOXYCHOLIC ACID THERAPY FOR NON-ALCOHOLIC STEATOHEPATITIS (META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS)

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INTRODUCTION: Non-alcoholic steatohepatitis (NASH) is an emerging cause of chronic liver disease with the potential to advance to cirrhosis and hepatocellular carcinoma. Currently, there is no approved treatment for NASH. Ursodeoxycholic acid (UDCA) has cytoprotective properties that may be beneficial, but clinical investigations have conflicting results.

OBJECTIVE: This study aims to determine the efficacy of UDCA compared to placebo in improving liver biochemistries and histology among patients with NASH.

METHODOLOGY: A meta-analysis of randomized controlled trials retrieved through MEDLINE, Cochrane Library and PUBMED. Inclusion criteria consists of: patients at least 18 years old, with biopsy-proven NASH, and contain the following main outcome measures: rates of reduction in alanine and aspartate aminotransferase levels from baseline, and histological response on post-treatment biopsy.

RESULTS: Four studies were identified, randomizing 511 patients. In comparison with placebo, UDCA significantly decreased the ALT levels in patients with NASH (Mean difference -12.94 [95% CI: -25.64 - -0.24] P 0.05). Subset analysis comparing high-dose UDCA regimen to placebo demonstrated significant improvement in ALT values from baseline. Meanwhile, with standard-dose UDCA regimen, there was no significant reduction in ALT levels compared to placebo. Conversely, AST levels did not significantly decline with UDCA compared to placebo (Mean difference -5.42 [95% CI: -11.96 – 1.13] P 0.10), whether the standard dosage or high dosage of UDCA was used. On post-treatment biopsy, both the standard and high doses of UDCA have no statistical advantage over placebo in reducing hepatic steatosis (Mean difference -0.06 [95% CI: -0.20 – 0.07] P 0.38), inflammation (Mean difference -0.14 [95% CI -0.28 – 0] P 0.06) and fibrosis (Mean difference 0.05 [95% CI: -0.07 – 0.18] P 0.41).

CONCLUSION: UDCA has no significant effect on the liver histology of patients with NASH. It seems to be beneficial in decreasing the ALT levels, but not the AST levels in this population. The treatment effect on ALT values may be dose-related since on subgroup analysis, only high-dose UDCA, but not standard-dose UDCA, had significant benefit on ALT levels when compared to placebo. However, the implication of this biochemical response in liver-related morbidity and mortality is still unknown.

H9

Role of *CCR5* genetic polymorphisms in clinical outcomes of hepatitis C

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Background: The *CCR5* 32-base deletion (CCR5D32), which results into the expression of a non-functioning receptor, has been associated with HCV clearance and may influence fibrosis progression in hepatitis C. We assessed the link between CCR5D32 and clinical outcomes of HCV. **Methods:** Genomic DNA was isolated and analyzed by PCR to identify CCR5D32 in 1303 anti-HCV-positive persons (161 clearers and 1142 chronically infected, 1007 with a liver biopsy). **Results:** Overall, 200 (15.3%) were heterozygote and 16 (1.2%) homozygote for CCR5D32. HCV clearance (by univariate) was associated with male sex (OR 0.633, 95% CI 0.428-0.935, P=0.022), HCV acquisition by blood transfusion (OR 0.360, 95% CI 0.175-0.741, P=0.0056), polymorphisms at *IL28B rs12979860* (OR 0.482, 95% CI 0.277-0.839, P=0.0098) and *rs8099917* (OR 0.291, 95% CI 0.167-0.508, P=0.000014), but not with CCR5D32. However, CCR5D32 was associated with spontaneous HCV clearance when the 482 females only were considered, although the number of homozygotes was small (1/427 chronic vs 3/51 clearers) (OR 24.56, 95% CI 12.5-241.4, P=0.006). The CCR5D32 deletion was not associated with liver grading and staging scores, fibrosis progression rate, or therapy response. **Conclusions**: At variance with a previous report (Nattermann et al, 2011), suggesting that a non-functional CCR5 may hamper HCV clearance, CCR5D32 appeared to be associated with an increased spontaneous eradication in women (but not men). Given the small number of CCR5D32 homozygote persons, these data need further validation.

H10

Promotion of liver regeneration by natural killer cells in mice is dependent on extracellular ATP phosphohydrolysis

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Nucleotides, such as ATP, are released by cellular injury, bind to purinergic receptors expressed on hepatic parenchymal and non-parenchymal cells, and modulate cellular cross-talk. Liver resection and resulting cellular stress initiate such purinergic signaling responses between hepatocytes and innate immune cells, which regulate and ultimately drive liver regeneration. We have studied a murine model of partial hepatectomy using immunodeficient mice, to determine the effects of natural killer (NK) cell-mediated purinergic signaling on liver regeneration. We note firstly that liver NK cells undergo phenotypic changes post partial hepatectomy in vivo, with changes in expression of CD107a, CD27 and CD11b in keeping with increased cytotoxicity and a more immature phenotype. Hepatocellular proliferation is significantly decreased in Rag2/common gamma-null mice (lacking T, B and NK cells), when compared to wild-type and Rag1-null mice (lacking T and B cells but retaining NK cells). Extracellular ATP levels are elevated post partial hepatectomy and NK cell cytotoxicity is substantively increased in vivo in response to hydrolysis of extracellular ATP levels by apyrase (soluble NTPDase). Moreover, liver regeneration is significantly increased by the scavenging of extracellular ATP in wild-type mice and in Rag2/common gamma-null mice after adoptive transfer of NK cells. In vitro, NK cell cytotoxicity is inhibited by extracellular ATP in a manner dependent upon P2Y1, P2Y2 and P2X3 receptor activation.
Conclusion: We propose that hepatic NK cells are activated and cytotoxic post partial hepatectomy and support hepatocellular proliferation. NK cell cytotoxicity is, however, attenuated by hepatic release of extracellular ATP via the activation of specific P2 receptors. Clearance of extracellular ATP elevates NK cell cytotoxicity and boosts liver regeneration.

Hepatoprotective Properties of a Toll-like Receptor 5 Agonist H11

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Background and Aims: CBLB502, an agonist of Toll-like receptor 5, has been shown to have radioprotective activity in mouse and primate models. Here we investigate hepatoprotective effect of the compound in radioprotection of human hepatocytes and in an ischemia reperfusion model in rodents.
Methods Isolated human hepatocytes were exposed to 10Gy +/- 4ng/ml CBLB 502, cell viability and function was measured A rodent ischemia reperfusion model was also used to investigate the hepatoprotective effect off CBLB502 via ALT /AST and myeloperoxidase levels.
Results: Isolated human hepatocytes possess the TLR-5 receptor and CBLB502 activates nuclear factor-**ϰB** signaling. Irradiation of human hepatocytes with 10Gy caused no obvious effect on cell viability over the time course used (1-5 days post irradiation). However the ability to induce CYP3A4 was markedly reduced by the irradiation. Incubation of the hepatocytes with 4ng/ml CBLB502 30 minutes prior to irradiation significantly improved the ability to induce CYP3A4 ($p<0.05$) and returned it to the level of the unirradiated cells. Preliminary results show that CBLB502 provides beneficial influence on clinical symptoms of hepatic ischemia reperfusion injury in our mouse model by reduced serum transaminases ($p< 0.05$) and reduced myeloperoxidase activity reflecting reduced neutrophil infiltration ($p<0.0005$).
Conclusion: Activation of TLR-5 has a radioprotective effect in isolated human hepatocytes as shown by CYP3A4 induction, although viability was not affected possibly due to their lack of proliferation in culture. Ischemia-reperfusion (I/R) injury associated with hepatic resections and liver transplantation remains a serious complication in clinical practice, which could potentially be diminished by TLR-5 activation

Posters Surgery

Monitoring of c-reactive protein detects septic complications in laparoscopic colorectal surgery long ahead clinical signs S1

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Background: This work assessed the diagnostic accuracy of CRP level in the detection of septic complications after laparoscopic colorectal resection.
Methods: Patients were identified from a prospective database. Complications were graded according to the Dindo-Clavien classification. CRP was measured on postoperative days 2, 4, and 6. Multivariate and receiver operating curves analysis were performed.
Results: 355 patients were operated between 1998 and 2011 for diverticulosis (88.7%), neoplasia (6.8%), and inflammatory bowel disease (2%). Left, right, and total laparoscopic colectomies were performed in 316 (89%), 33 (9.3%), and 6 patients (1.7%). While complications occurred in 74 patients (36.6%), 51 patients (14.4%) suffered from a septic complication at a median of 6 days. Overall, CRP peaked on day 2. Yet, patients developing septic complications peaked again and worsened on day 6. A CRP above 56mg/l on postoperative day 4 had a sensitivity of 100% (95% CI 0.8-1) and a specificity of 49% (95% CI 0.4-0.6) for the development of septic complications in the absence of clinical signs. This translated into a remarkable diagnostic accuracy of 78% (95% CI 0.7-0.9).
Conclusions: Monitoring CRP level in laparoscopic colorectal resection demonstrated a high diagnostic accuracy for septic complications and preceded clinical signs by 2 days.

Implantation of prophylactic non-absorbable intraperitoneal mesh in patients with peritonitis is safe and feasible S2

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Background: Patients with peritonitis undergoing emergency laparotomy are at increased risk for postoperative open abdomen and incisional hernia. This study aimed to evaluate the outcome of prophylactic intraperitoneal mesh implantation compared with conventional abdominal wall closure in patients with peritonitis undergoing emergency laparotomy.
Methods: A matched case-control study was performed. To analyze a high risk population for incisional hernia formation, only patients with at least two of the following risk factors were included: male gender, body mass index (BMI) >25kg/m^2, malignant tumor, or previous abdominal incision. In 63 patients with peritonitis, a prophylactic non-absorbable mesh was implanted intraperitoneally between 2005 and 2010. These patients were compared with 70 patients with the same risk factors and peritonitis undergoing emergency laparotomy in one year (2008) who received conventional abdominal closure without mesh implantation.
Results: Demographic parameters including gender, age, BMI, grade of intraabdominal infection, and operative time were comparable between the two groups. Incidence of surgical site infections (SSI) was not different between groups (61.9% vs. 60.3%; p=0.603). Enterocutaneous fistula occurred in three patients in the mesh group (4.8%) and in two patients in the control group (2.9%; p=0.667). Incidence of incisional hernia was significantly lower in the mesh group (2 of 63 patients) compared with the control group (20 of 70 patients) (3.2% vs. 28.6%; p<0.001).
Conclusion: Prophylactic intraperitoneal mesh can be safely implanted in patients with peritonitis and significantly reduces the incidence of incisional hernia. The incidence of SSI and enterocutaneous fistula formation is comparable to conventional abdominal closure.

Implementation of Enhanced Recovery After Surgery (ERAS) in colorectal surgery is highly cost-effective S3

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Background Enhanced Recovery After Surgery (ERAS) pathways are known to reduce postoperative complications and to shorten hospital stay. This study evaluates whether the savings related to complications' reduction leading to diminished length of stay (LOS) outweigh the implementation's costs.

Methods The first 50 consecutive patients after implementation of ERAS (ERAS group) within a 6 months period were compared to 50 consecutive patients operated one year before its introduction (control group). Primary LOS, readmission within 30 days, complications, and total costs based on costs per day were compared.

Results Primary LOS was significantly shorter in the ERAS group compared to the control group: median 7 (interquartile range 5-12.25) days vs. 10 (7-18) days (P = 0.003). The total number of complications was reduced from 60 in the control group to 49 in the ERAS group (P = 0.64). Readmission rates were similar (n=2 in each group). The savings related to the reduction of LOS were 191'125 EUR. Investments required for the 50 first ERAS patients were 68'963 EUR. The overall cost saving therefore was 2'440 EUR per patient.

Conclusions The financial investment to introduce and maintain an ERAS program are non-negligible, however, ERAS is highly cost-effective even after a short-time period.

Effect of Preoperative Radio(chemo)therapy on Long-term Functional Outcome in Rectal Cancer Patients: A Systematic Review and Meta-analysis

S4

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Background: Preoperative radio(chemo)therapy (pR(C)T) significantly reduces the local recurrence risk, but may be associated with late adverse effects. To determine the effect of pR(C)T on long-term anorectal, sexual and urinary function, we performed a systematic review and meta-analysis.

Methods: Literature was systematically searched for studies reporting on long-term functional outcome after rectal cancer resection with pR(C)T. Only studies that reported anorectal, sexual, and/or urinary function after rectal cancer resection in TME-technique were eligible.

Results: Twenty-five studies including 6,548 patients were identified. Methodological quality of the eligible studies was low. The majority of studies reported higher rates of anorectal (14 of 18 studies) and male sexual dysfunction (9/10) after pR(C)T. Meta-analysis revealed that stool incontinence occurred more often in irradiated patients (risk ratio (RR=0.60 [95% CI: 0.49, 0.74], p<0.0001) and manometric results were significantly worse after pR(C)T (mean resting pressures -15.0 [95% CI: -29.3, -0.8], p=0.04), maximum squeeze pressures (-30.4 [95% CI: -39.3, 21.5], p<0.0001)). Meta-analysis of erectile dysfunction revealed no statistical significance (RR=1.41 [95% CI: 0.74, 2.72], p=0.30). Six of eight studies and meta-analysis demonstrated no negative effect of pR(C)T on urinary function (RR=1.05 [95% CI: 0.67, 1.65], p=0.82).

Conclusions: Although quality of studies on long-term functional outcome is limited, current evidence demonstrates that pR(C)T negatively affects anorectal and male sexual function after TME.

S5

Full mechanical bowel preparation is not necessary for primary rectal cancer surgery

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Objective: To assess postoperative complications in patients operated for primary rectal cancer undergoing either full mechanical bowel preparation (MBP) or rectal enema (RE).

Methods: Analysis of 50 consecutive patients each undergoing rectal resection with primary anastomosis and protective ileostomy at two different university teaching hospitals, whose rectal cancer management are comparable except for the preoperative bowel preparation (MBP in hospital A and RE in Hospital B). Prospective databases were retrospectively analyzed.

Results: A total of 100 patients were included. Patient demographics and cancer characteristics (level above anal verge, stage, neoadjuvant therapy) were comparable between the two groups. Anastomotic leakage occurred in 5.7% in the MBP vs. 8.5% in the RE group (p=0.703). Pelvic abscess (1.9% vs. 2.1%, p=0.990) and wound infection (5.7% vs. 14.9%, p=0.183) were also comparable. Extra-abdominal infections (7.5% vs. 12.8%,p=0.509) and non-infectious abdominal complications such as ileus and bleeding (15.1% and 25.5%, p=0.219) were not significantly different.

Conclusion: Postoperative infectious complications were not significantly increased in rectal cancer surgery patients undergoing bowel preparation with rectal enema only.

S6

Surgery for ischemic colitis: outcome and risk factors for mortality

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Background: Surgery for ischemic colitis is associated with high perioperative morbidity and mortality, but the risk factors for mortality and major surgical complications are unclear.

Methods: Retrospective single institution cohort study of all patients undergoing colorectal surgery because of histologically proven ischemic colitis between 2004 and 2010.

Results: Of the 100 patients included, in-hospital mortality was 54%; major surgical complications, defined as anastomotic leakage or rectal stump and stoma complications, occurred in 16%. In multivariable analysis, hospital death was more likely in patients with right-sided (odds ratio [OR] 3.8; 95% confidence interval [CI] 1.2, 12) or pan-colonic ischemia (OR 11; 95% CI 2.8, 39), both relative to left-sided ischemia, and after cardiac or aortic surgery (OR 2.4; 95% CI 0.82, 6.8), and less likely with increased preoperative pH-level (OR 0.40 per 0.1 increase; 95% CI 0.24, 0.66). Major surgical complications were associated with ischemic alterations at the resection margin of the histological specimen (OR 3.7; 95% CI 1.2, 11).

Conclusions: Colonic resection for ischemic colitis is associated with high in-hospital mortality, especially in right-sided and pan-colonic ischemia. In developing acidosis, early laparotomy should be considered. Since resection margins' affection seems to be underestimated upon surgery, resections should be carried out large enough within healthy tissue and second looks should be carried out liberally.

S7

Transabdominal percutaneous embolization of a pseudoaneurysm after pancreatic head resection

Styliani Mantziari, Francesco Doenz, Nicolas Demartines, Markus Schäfer

Background
Major postpancreatectomy hemorrhage (PPH) is a rare but serious complication with a reported incidence of 2-15% and mortality rates of 30%. The most frequent cause is an arterial pseudoaneurysm subsequently to a pancreatic leakage. Surgical treatment has been increasingly replaced during recent years by interventional radiology.

Aim of this study was to present a case of a bleeding pseudoaneurysm of the superior mesenteric artery (SMA) treated by transabdominal percutaneous embolization after failure of conventional interventional radiology methods.

Methods /case report
A 53-year-old male with a periampullary carcinoma of the pancreatic head underwent a pancreaticoduodenectomy with complete tumor resection. A pancreatico-jejunostomy was performed, whereby a very soft pancreatic texture was observed. At postoperative day 5, a pancreatic fistula was detected but was well drained by the intraoperatively inserted drains. Four days later, a first sentinel bleeding associated with a marked decrease of serum hemoglobin, acute abdominal pain, and a clinical deterioration occurred. Repeated contrast-enhanced computed tomography and transfemoral angiography finally showed a bleeding pseudoaneurysm originating from the SMA as well as a fibromuscular dysplasia of all major visceral arteries. Since the precise localization failed, several jejunal arterial branches and impaired arterial wall were present; no endovascular treatment was possible after two efforts. A final interventional attempt was made by transabdominal percutaneous puncture of the pseudoaneurysm and embolization by local thrombin application. The procedure was carried out using a Shiba 22g needle, guided under radiologic (CT) control, and 1ml (250 IU) of thrombin were injected directly into the pseudoaneurysm. Rebleeding occurred 24 hours later, and the transabdominal percutaneous procedure was repeated with half of the initial thrombin dose (120 IU). After this second intervention, no further bleeding occurred; and the patient was discharged at postoperative day 29 without further event.

Discussion
CT-guided percutaneous embolization is a novel approach, used successfully to stop bleeding from an arterial pseudoaneurysm. It may be kept in mind as "last interventional chance" before a challenging surgical approach with its increased morbidity and mortality becomes unavoidable.

Impact of preoperative risk factors on the severity of complications after esophagectomy for cancer S8

Styliani Mantziari, Nicolas Demartines, Henri Vuilleumier, Markus Schäfer

Background
Perioperative care of esophageal cancer has improved recently, but surgery is still associated with high morbidity rates Targeting reversible risk factors could be a promising approach to reduce postoperative complications and improve patient outcome. This study aimed to assess the role of several preoperative risk factors on the incidence and severity of postoperative complications.

Methods
A series of 95 patients who underwent esophagectomy for cancer from 2000-2011 were identified from our data base. Albumin, BMI, alcohol consumption, smoking, age, and ASA class were investigated as risk factors. Postoperative complications were graded according to a validated 5-point score system; minor complications included grades I-IIIA, major complications grades IIIB-V. Multiple regression analysis and ANOVA tests were used to analyze correlation between these risk factors and postoperative complications.

Results
There were 17 patients without complications (17%), 54 patients with minor (57%) and 25 patients with major complications (26%). Age, ASA classification and BMI were not correlated with the incidence and severity of complications. The positive predictive value (PPV) of a BMI <20 to identify patients with complications was 83% and the sensitivity was only 23%While mean albumin levels were similar in the groups with and without complications, preoperative albumin was significantly correlated to the occurrence of severe complications (p=0.04). The PPV of albumin levels <30d/l to identify patients with complications was 89%, the sensitivity and the negative predictive value (NPV) were 39% and 21%, respectively.
Active smoking was statistically significantly correlated to the occurrence of severe complications as all patients with severe complications were active smokers (p=0.0004). The PPV of active smoking to identify patients with complications was 87%, the sensitivity was 76%, and the NPV was 30%. Active alcohol consumption was not correlated to the incidence or to the severity of complications.

Conclusions
Patients with low albumin levels and active smoking are at increased risk to develop severe complications, whereas alcohol, BMI, ASA and age were of no particular importance. As a consequence, preoperative treatment of malnutrition and a strict non-smoking regimen are valuable targets to reduce patients' postoperative morbidity.

Hand-assisted laparoscopic nephrectomy in a donor with situs inversus totalis S9

B. Blaser, L. Di Mare, JP Venetz, N. Demartines and M. Matter

Objectives

Laparoscopic nephrectomy for renal transplantation has become a standard approach for living donors, because it improves donor outcomes, without compromising graft function. Since 2005, the hand-assisted laparoscopic nephrectomy technique is performed systematically in all patient. This video present the laparoscopic approach for removing the left kidney in a 48 year old woman with situs inversus totalis. It is known that situs inversus is a confusing anatomy especially by laparoscopy.

Methods

The patient was positioned in the right lateral decubitus position. A Pfannenstiel incision was performed to accommodate the hand device (Gelport) with direct pneumoperituneum creation. A 12-mm and a 10-mm ports were introduced in the left inferior quadrant and left superior quadrant, respectively. An additional 5mm port was placed in the epigastric region for liver retraction. The left parietocolic groove was opened and the ascending colon mobilized, allowing the exposure of the inferior vena cava and the "left" renal vein. The left (double) renal vein, a superior polar arterial two clips and transected. The kidney was released from its posterior bounds, the renal vein and artery were stapled. After delivery the kidney was placed in an ice bath, flushed (=warm ischemic time) and prepared for transplantation in the standardized manner.

Results

Despite situs inversus totalis, the preoperative investigations showed no contraindications for living donation. Duration for nephrectomy was 68 minutes and total operative time was 131 minutes. Warm ischemic time was 220 seconds and cold ischaemic time 80 minutes. We did not observed any surgery-related complications. The donor recovered uneventfully. A hospital stay of 9 days was explained by respiratory difficulties.

Conclusions

In our center, living donation is equally shared between right and left nephrectomies based on our own protocol. Therefore, the anatomical abnormality like the presented situs inversus totalis was not considered as a contraindication to live kidney donation. Provided the surgical team has the necessary experience, organ donation in situs inversus totalis is feasible and safe.

Titre : Hémorragies intraluminales post-opératoires après by pass gastrique coelioscopique: série rétrospective de 1467 cas avec revue de la littérature. S10

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Introduction:
Les hémorragies gastro-intestinales après by pass gastrique coelioscopique sont des complications rares mais grevées de conséquences potentiellement sévères. Les modalités de diagnostic et de prise en charge de cette affection ne sont pas standardisées.

Méthodes:
Revue rétrospective de notre expérience avec revue de la littérature.

Résultats:
En analysant notre expérience de 1467 by pass gastriques consécutifs, nous avons observé une hémorragie intraluminale post-opératoire chez 26 patients (1.8%). Les 5 patients ayant présenté une hémorragie à point de départ de l'estomac exclu ont été réopérés. Dans la majorité des 21 cas restants, l'origine du saignement est restée inconnue, sauf chez 2 patients avec un ulcère marginal et une patiente avec une hémorragie intraluminale active au niveau du pied de l'anse en Y documentée par angio-scanner. En cas d'hémorragie post-opératoire, notre protocole consiste en l'arrêt de tout traitement anticoagulant, remplacé par des bottes à compression intermittente et l'administration de hautes doses d'Etamsylate, avec transfusion de culots érythrocytaires si nécessaire. Seuls 2 p! atients (9.5%) ont nécessité une ré-exploration coelioscopique: un patient connu pour dysfibrinogénémie dont l'exploration s'est avérée négative et une patiente avec hémorragie active documentée par angio-scanner dont l'anastomose du pied de l'anse a pu être revisée avec succès. Parmi 16 séries de la littérature, 335 hémorragies post-opératoires sont décrites sur un total de 13'042 patients (2.6% - range 0.9-9.4%). 2 études ont évalué la prise en charge par endoscopie, avec un taux de succès de 83-85%, à condition que la source hémorragique se situe au niveau de l'anastomose gastro-jéjunale. L'exploration chirurgicale reste l'approche de choix en cas d'instabilité hémodynamique, mais la coeliscopie reste encore débattue dans ces cas, et la littérature actuelle ne permet pas de tirer de conclusions. La coeliscopie devrait être réservée aux centres à haut débit et expérimentés. L'angio-scanner permet le diagnostic et la localisation d'hémorragies intraluminales avec une sensibilité et une spécificité supérieure à 85%, mais sa valeur n'a pas été évaluée dans le contexte des hémorragies après by pass gastrique.

Conclusions: La majorité des hémorragies intraluminales après by pass gastrique peuvent être traitées conservativement, sauf celles dont la source se situe au niveau de l'estomac exclu. L' angio-scanner comme outil diagnostique précoce est un atout supplémentaire. En cas d'hémorragie persistante, ou en cas d'instabilité hémodynamique non contrôlée, une exploration coelioscopique est faisable et sûre dans les centres experts.

Posters Interdisciplinary

Quality Management and Structures of the Certified „Darmkrebszentrum" at the Kantonsspital Baden I1

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Background: „Darmkrebszentrum" is a network of specialists of different medical and care-giving disciplines from the out- and in-patient domain, where patients with colorectal cancer are treated integrated and in all stages of disease. Treatment is based on the published S3-guidelines of colorectal cancer.

Methods: The Department of Surgery at the Kantonsspital Baden (KSB) initiated in 07/2011 a project to implement a quality management system (DIN ISO 9001) and to fulfill the expert requirements of the German Society of Cancer (Onkozert, DKG).

Results: The "Darmkrebszentrum" of the KSB was certified on May 25th, 2011 and the one-year re-audit was passed successfully on May 7th, 2012. Processes for colorectal cancer patients from practitioners to outpatient clinic, hospital stay, diagnostic and therapeutic procedures, discussion in the interdisciplinary tumor-board and outpatient care were adjusted with partners of the network. Quality aims are yearly defined and checked. A clinical data registry has been established to monitor outcome quality. Process improvement and patient satisfaction were focused. The whole process of implemetation of such a cancer network will be presented.

Conclusions: The "Darmkrebszentrum" at the KSB represents the first certified Swiss Colorectal-Cancer-Center. Structures and processes improved significantly for patients and staff members. We aim to achieve a continuous improvement in the care of patients with colorectal cancer.

I2

Primary Sclerosing Cholangitis in the Swiss IBD Cohort Study: Prevalence, Patient Characteristics, and Disease Course

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Background and Aims: Primary sclerosing cholangitis (PSC) represents the most common hepatobiliary extraintestinal manifestation (EIM) in inflammatory bowel disease (IBD). We aimed to assess the prevalence of PSC in the Swiss IBD Cohort Study (SIBDCS) and to identify associated risk factors.

Methods: Data from the SIBDCS were analyzed. Patients with IBD and PSC were compared to patients with IBD but without PSC.

Results: Among 1,961 patients with IBD (1,119 Crohn's disease, CD; 800 ulcerative colitis, UC; 42 indeterminate colitis, IC), diagnosed between 1955 and 2010, 29 patients with PSC were identified (24 PSC-UC, 4 PSC-CD, 1 PSC-IC). The cumulative PSC prevalence was 3.0% in UC, 2.4% in IC and 0.4% in CD ($p < 0.001$ for PSC-UC vs. PSC-CD). PSC was significantly more prevalent in males as compared to females (risk ratio 2.59, $p = 0.016$). Mean age at PSC diagnosis was 30 years in males and 38 years in females. PSC was diagnosed either simultaneously with or after IBD. No specific risk factors in terms of family history, disease location or disease activity could be identified when comparing patients with UC with or without PSC. One patient with UC and PSC developed cholangiocarcinoma and was liver transplanted. Three other patients underwent liver transplantation because of recurrent bacterial cholangitis or liver failure.

Conclusions: PSC was more prevalent in patients with UC as compared to CD and showed a male predominance. No specific risk factors for PSC development could be identified in patients with UC. PSC was diagnosed either simultaneously with or after IBD.

I3

SPLENIC LYMPHANGIOMATOSIS IN A PATIENT WITH FACIAL CAVERNOUS HEMANGIOMATOSES AND PATENT DUCTUS ARTERIOSUS: A CASE REPORT

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INTRODUCTION and DESCRIPTION:
Splenic lymphangioma is a rare benign tumor, with about 240 cases reported worldwide since 1885 when it was first described by Fink. It is considered to be the result of a developmental anomaly in which obstruction or agenesis of lymphatic tissue results in lymphangiectasia. Splenic lymphangiomatosis is the presence of multiple cystic lesions of various sizes that replace all of the parenchyma. It may be a part of a diffuse lymphangiomatosis affecting multiple body parts. However, splenic lymphangiomatosis occurring with concomitant hemangiomatoses of another organ is extremely rare. Furthermore, there are no reports in the literature of its association with a congenital heart disease.

We present a case of a young adult female who came in with progressive abdominal enlargement and CT scan showing a huge abdominopelvic mass containing multiple cystic foci. Nine years prior to consult, she had incidental findings of splenomegaly and patent ductus arteriosus during pre-operative work-up for tumor debulking of an intraorbital cavernous hemangioma with intranasal extension.

DISCUSSION:
The patient initially underwent an abdominal CT scan with triple contrast, which revealed marked splenomegaly (28.1 x 24.7 x 16.1 cm) with multiple cystic foci, and resultant compression or displacement of the other abdominal organs. Complete blood count demonstrated mild anemia and thrombocytopenia Hematologic work-up done, including bone marrow biopsy, JAK-2 determination, and serum ferritin level, were negative for a primary hematologic problem. Chromosomal analysis was also normal. The patient subsequently underwent splenectomy, which revealed a grossly enlarged spleen, measuring 28 x 19 x 16 cms, with notable multiple lobulated cystic structures at the surface. There was no accessory spleen noted. Histologic examination revealed multiple, large cystic spaces that are lined with a single layer of endothelium and filled with proteinaceous fluid. This led to a diagnosis of splenic lymphangiomatosis.

Cystic lymphangioma is a very rare condition usually seen in children and commonly involving the neck and axilla. In adults, splenic lymphangioma has an asymptomatic course. Symptoms, such as abdominal pain, are commonly related to the size of the spleen. Surgical treatment is recommended to prevent recurrence, infection, rupture, and bleeding.

I4

Morbidity rate of reoperation in thyroid surgery: a different point of view

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Background: Goiter recurrence is a common problem following subtotal thyroid gland resection for multinodular goiter disease. The aim of the present study was to evaluate morbidity rate in relation to the side of initial and redo-surgery for recurrent disease.

Methods: A total of 1699 patients underwent consecutive thyroid gland surgery between1997 and 2010 at our institution. One hundred and eighteen patients (6.9%) underwent redo-surgery for recurrent disease after subtotal resection. One hundred and nine patients with complete follow-up were included in the present study.

Results: Recurrent disease was found in 79 patients (72.5%) in the ipsilateral lobe and in 30 patients (27.5%) in the contralateral lobe. The incidence of permanent recurrent laryngeal nerve palsy was significantly higher in patients undergoing redo-surgery on the ipsilateral lobe compared to patients undergoing initial operation (3.8% vs. 1.1%; p= 0.03), whereas no difference was found in patients with contralateral redo-surgery compared to patients undergoing initial operation (p= 1.0). Independent risk factors for contralateral recurrent disease were age at primary operation < 37 years (OR 4.86; 95% CI 1.58-15.01) and time to recurrence < 20 years (OR 6.53; 95% CI 2.23-19.01).

Conclusion: Morbidity rate for recurrent disease after subtotal resection was significantly higher for ipsilateral redo-surgery compared to initial surgery, whereas redo-surgery can performed safely on the contralateral lobe.Young age at primary operation and short time to recurrence are independent risk factors for contralateral recurrent disease.

I5

Brain mitochondrial respiration is specifically impaired in non-resuscitated murine sepsis

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Background: Early brain dysfunction is common in sepsis. We hypothesized the presence of impaired mitochondrial respiration in non-resuscitated sepsis.

Methods: Sixteen adult C57/BL6 mice were randomized to 18 hours of cecal ligation and puncture (CLP) and to a control group (n=8 each). At the end of the experiment, blood concentrations of tumor necrosis factor-alpha (TNF-alpha) and interleukin 6 (IL-6) were measured, and liver, heart and brain mitochondria were isolated. Mitochondrial state 3 and state 4 respiration were measured for respiratory chain complexes I and II, and state 3 for complex IV, using high-resolution respirometry. Alterations in mitochondrial structure were assessed by electron microscopy.

Results: All septic animals showed obvious deterioration of health condition. Systemic levels of TNF-alpha and IL-6 were significantly increased in the CLP group compared to controls (TNF-alpha p=0.008, IL-6 p=0.0003). CLP induced a reduction in brain mitochondrial complex-I-dependent respiration (state 3 p=0.01 and state 4 p=0.03). However, CLP was not associated with altered liver and heart mitochondrial complex I-, II- or IV-dependent respiration. Mitochondrial membrane disruption and altered cristae structures were visualized in brain but not in liver or myocardial mitochondria of CLP mice.

Conclusions: In this 18 hours non-resuscitated murine CLP model, ultrastructural damage specifically of brain mitochondria was accompanied by decreased cellular respiration. Liver and heart mitochondria were not affected.

The numbers refer to the pages of this supplement.