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Enhanced recovery pathways optimize health outcomes and resource utilization:

A meta-analysis of randomized controlled trials in colorectal surgery

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Objective: Provision of care to increasingly complex patients led to an exponential rise in costs. This situation is exacerbated by budgetary constraints, including the upcoming introduction of compensation schemes based on diagnosis-related groups. Enhanced recovery pathways (ERP) have been proposed as a means to reduce morbidity and improve effectiveness of care. Colorectal surgery is a prime example with high volumes of major procedures, significant morbidity, prolonged hospital stay, and unplanned readmission. We performed a systematic review and meta-analysis of the evidence supporting the implementation of ERP in clinical practice.

Methods: Original papers on ERP were critically reviewed by international contributors experienced in the development and implementation of ERP. Medline, Embase, and the Cochrane library were searched for randomized controlled trials comparing ERP to traditional care in colorectal surgery. A Bayesian random-effects meta-analysis was then performed. Primary endpoints were morbidity, length of stay, and readmission.

Results: Key components of ERP were identified, focusing on patient information, preservation of gastrointestinal function, minimizing organ dysfunction, active pain control, and promotion of patient's autonomy. Of 389 retrieved papers published up to June 2010, 6 randomized controlled trials were included in the meta-analysis for a total of 452 patients. These trials were performed in the UK (3), the USA, the Czech Republic, and Switzerland. For patients adhering to ERP, 30-day morbidity was halved (relative risk 0.52, 95% CrI 0.36, 0.73), while length of stay decreased by 2.5 days (95% CI -3.92, -1.11), and readmission was not increased (relative risk 0.59, 95% CrI 0.14, 1.43) when compared to patients undergoing traditional care.

Conclusion: Adherence to ERP achieves a reproducible improvement in the quality of care by enhancing recovery and safely reducing hospital stay in colorectal surgery, thereby optimizing utilization of health care resources. Hence, ERP can and should be routinely used in colorectal and other major gastrointestinal surgery, as they contribute to meeting the challenges of distressed healthcare systems.

2

Second and subsequent retranplants in Europe: are we justified to continue?

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Background: Multiple liver retransplantations (ReLT) are often associated with worse outcomes. Aim of this study was to evaluate trends in adults requiring ≥ 2 ReLT in Europe between 1980 and 2008.
Methods: Retrospective analysis was based on the prospective European Liver Transplant Registry (ELTR), including patients aged ≥16 years at primary liver transplantation (LT).
Results: 6397 patients required 7114 ReLT- 653 (10%) received a second, 62 (1%) a third ReLT. Second ReLT declined from 12% to 6% over the 28 years. While median recipient and donor age for first and subsequent ReLT increased between 1980 and 2000 (p<0.001), there was a parallel improvement in graft survival with 1-, 5- and 10-year rates for second ReLT increasing from 33%, 31% and 25% to 48% and 35% (10-year data not available yet) in the 2000s (p=0.05) and similar trends for third ReLT. Although overall actuarial survival following ReLT, especially multiple ReLT remain worse compared to primary LT, this trend is less obvious in the last two decades.
Similar to first ReLT, rejection accounted for 40% of second ReLT in the 1980's, decreasing to 11% in the 2000's (p< 0.001), while hepatic artery thrombosis (5%) and HCV recurrence (2%) increased substantially (31%, respectively 5%) from the 190's to 2000's. In the 1980's more patients received a first ReLT within 3months (71%, versus 51% in 2000's), with an opposite trend for second ReLT (p<0.001). Main causes of death were sepsis, vascular complications and primary non-function.
Conclusions: Multiple ReLT remain technically challenging. Fewer patients received ≥2 ReLT over the last three decades, owing to optimized patient selection, improved patient management and increased organ shortage. Despite improvements, outcome after multiple ReLT remains poor.

3

Poor Agreement among Expert Radiologists in Diagnosing Primary Liver Tumors by Magnetic Resonance Imaging in Non-Cirrhotic Patients: A Double blind International Multicenter Study

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ABSTRACT

Background: Differentiation of hepatocellular carcinoma (HCC) from hepatic adenoma (HA) and focal nodular hyperplasia (FNH) by magnetic resonance imaging (MRI) remains challenging in non-cirrhotic patients. The agreement between MRI and histo-pathological diagnosis remains unclear in this population.

Methods: Preoperative MRIs of 108 consecutive non-cirrhotic patients, who underwent liver resection for HCC (n=56), HA (n=24) and FNH (n=28), were collected from five high volume centers. Eight expert MRI radiologists from eight renowned hepato-biliary institutions in Europe, North America and New Zealand blindly reviewed all images. The agreement with the definitive histo-pathological diagnosis and inter-observer variability were evaluated by the Fliess' kappa test (excellent agreement >0.8). Radiologist' certainty of diagnosis (CoD) was assessed by a Visual Analogue Scale (VAS 1-10). Logistic regression analysis was performed to identify independent predictors for correct radiological tumor diagnosis.

Results: The radiologists correctly identified only 61% of the definitive histo-pathological diagnosis (moderate agreement with kappa= 0.43). Additionally, the inter-rater agreement among the radiologists was poor (kappa: 0.36). Radiologists' CoD significantly differed and the correlation of CoD among different radiologists was very poor (Intra-class Correlation Coefficient: 0.20), although radiologists with CoD ≥7 were 2.4 times more likely to predict the correct diagnosis compared with CoD <7 (p<0.001).

Conclusion: MRI diagnosis of primary liver tumors is strongly observer-dependent and does not predict the definitive tumor pathology. MRI cannot be considered as the standard guide for treatment of HCC, HA, and FNH in non-cirrhotic patients.

4

Calprotectin measurement in ascites: A new test for the rapid diagnosis of Spontaneous Bacterial Peritonitis

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Introduction: Spontaneous bacterial peritonitis (SBP) is diagnosed by the presence of ≥250 polymorph nuclear cells (PMN) per milliliter (ml) in ascitic fluid. This procedure is time-consuming and operator-dependent. Calprotectin is a protein in PMNs that is considered a valid marker of intestinal inflammation when measured in feces. We aimed to assess the role of calprotectin in acites for the diagnosis of SBP.
Methods: In 41 prospective patients with liver cirrhosis referred for paracentesis, the following investigations were performed: serum-ascites albumin gradient, ascitic PMN cell count (microscopic hand-count), bacterial cultures and cytological analysis. In addition, ascitic calprotectin was measured using an enzyme-linked immunosorbent assay (ELISA) and a point-of-care lateral flow assay (Quantum Blue®, QB, Bühlmann Laboratories, Switzerland). The QB is a quantitative bedside test that can be performed within minutes by the physician performing the paracentesis, independent of laboratory personnel.
Results: Ascitic calprotectin values measured by ELISA and QB correlated well with PMN cell count (Spearman rho=0.729, P<0.001 and rho=0.698, P<0.001, respectively) and had excellent correlation among them (rho=0.871, P<0.001). Calprotectin levels of patients with PMN ≥250/ml (N=6, 15%) were higher than in patients with PMN <250/ml (N=35, 85%) both with the ELISA (median 1.73µg/ml [95% confidence interval (CI) 1.3-3.0] against 0.1µg/ml [0.1-0.3], P<0.001) and with the QB (1.93µg/ml [1.8-3.3] against 0.3µg/ml [0.3-0.65], P=0.004). The area under the receiver operating characteristics curve to identify PMN ≥250/ml was 0.971 [0.85-0.99] for ELISA and 0.865 [0.69-0.96] for the QB. Both tests had similar accuracy (P=0.246).
Conclusion: Measurement of calprotectin in ascites might be a valuable surrogate marker for PMN cell count. Especially when used in conjunction with a point-of-care test, it might be highly valuable for the rapid diagnosis of SBP.

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) roles on HCV-associated steatosis and replication

5

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Background: The hepatitis C virus (HCV) perturbs the host lipid metabolism, often resulting in hepatic steatosis. In non-alcoholic fatty liver disease, the intrahepatic downregulation of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a critical mechanism leading to steatosis and its progression towards fibrosis and hepatocellular carcinoma. However, whether HCV infection triggers steatosis through PTEN-dependent mechanisms and whether PTEN is required for HCV replication is unknown. **Methods:** We first assessed the PTEN expression level in the liver of patients infected with HCV genotype 1 or 3, with or without steatosis. The role of PTEN in HCV-induced steatosis was further investigated *in vitro* using hepatoma cells transduced with the HCV core protein of genotype 1b or 3a. Finally, the effect of both overexpression and silencing of PTEN on HCV replication and viral particle secretion was assessed using both a subgenomic replicon and the genomic-length Jc1 construct. **Results:** Our data indicate that PTEN expression is downregulated at the post-transcriptional level both *in vitro* (50% of decrease) and in steatotic patients infected with genotype 3a. PTEN overexpression in HCV core 3a-expressing cells completely prevented hepatocytes from developing steatosis. Interestingly, while PTEN silencing had no effect on HCV replication, it induced a two-fold increase viral particle secretion. In a mirror experiment, overexpression of PTEN induced a 45% reduction of HCV virion excretion. **Conclusion:** In conclusion, PTEN downregulation is a critical event leading to the HCV genotype 3a-induced lipid accumulation in hepatocytes, and may modulate HCV virion secretion from infected hepatocytes.

Terlipressin improves liver regeneration in a small-for-size liver remnant mouse model

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Background: Small-for-size liver remnants post liver resection are associated with pre- and intrahepatic portal hypertension. The aim was to assess the effect of pharmacological reduction of portal pressure by terlipressin on liver regeneration.

Methods: Male C57/Bl6 mice were subjected to minor, standard and extended liver resection. Portal pressure and outcome was assessed after administration of terlipressin and compared to PBS.

Results: Portal pressure is significantly elevated after extended liver resection compared to standard and minor liver resection. Terlipressin administration is associated with a significant reduction of portal pressure post extended resection. Furthermore, liver regeneration was significantly increased with terlipressin compared to controls post 80% but not after 60% and 30% partial hepatectomy. Mortality was 0% for all groups.

Conclusions: Elevation of portal pressure depends on the extent of liver resection. Administration of terlipressin is associated with improved liver regeneration via reduction of elevated portal pressure.

Interferon Stimulated Gene Induction in Acute Hepatitis C is caused by Interferon gamma and does not impair Interferon alpha Signal Transduction

6

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Background: Therapy of chronic hepatitis C (CHC) with pegylated interferon alpha and ribavirin achieves a sustained virological response in approximately half of the patients. Non-response (NR) to treatment is associated with constitutively increased expression of IFN-stimulated genes in the liver already before therapy. In acute hepatitis C (AHC), therapy is much more effective, with SVR rates > 85%. In the present study, we analyzed liver biopsies of patients with AHC and CHC with the aim to elucidate the molecular mechanisms responsible for the different treatment response rates.

Methods: 8 patients with AHC were included and had a liver biopsy 2-5 months after infection with HCV. Gene expression analysis was performed using Affymetrix® Human Genome U133 Plus 2.0 arrays and Bioconductor packages of R statistical environment. The activation of STAT1 was assessed by immunohistochemistry using phospho-STAT1 specific antibodies. The inflammatory infiltrates were characterized using antibodies to CD3, CD4, CD8, CD20 and CD56. Reference gene expression profiles for IFNalpha and IFNgamma were generated by transcriptome analyses of primary human hepatocytes (PHH) treated with IFNalpha or IFNgamma.

Results: Hundreds of genes were differentially regulated in the liver of patients with AHC compared to un-infected control samples. Gene set enrichment analysis revealed an induction of classical IFN-stimulated genes (ISGs). However, there was only limited overlap with the set of genes dysregulated in patients with CHC with poor response to treatment. The gene expression profile of CHC samples matched to the set of IFNalpha induced genes in PHH, whereas AHC matched with IFNgamma induced genes. In AHC, but not in CHC, we found CD8 T-cell infiltrates co-localized with hepatocytes with nuclear pSTAT1 staining.
To obtain further insights into the mechanisms responsible for better treatment responses in AHC, we analysed the expression of negative regulators of IFNalpha signalling. There was no difference of SOCS1 or SOCS3 expression between AHC and CHC. However, USP18, an important negative regulator of IFNalpha signalling, was strongly induced in CHC NR, but not in AHC. The lack of USP18 up-regulation in AHC is consistent with the absence of a type I IFN response in AHC, because in PHH, USP18 was strongly induced by IFNalpha, but not by IFNgamma.

Conclusions: Gene expression in the liver of AHC patients significantly differs from CHC patients. In AHC ISGs are induced by IFNgamma produced by CD8 T-cells, while NR CHC patients show an IFNalpha gene expression profile. The lack of USP18 upregulation might explain the better treatment response in AHC patients.

Telaprevir in Combination with Peginterferon and Ribavirin in Genotype 1 HCV Treatment-Naïve Patients: Final Results of Phase 3 ADVANCE Study

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Background: The ADVANCE study is a 3-arm double-blind, randomized, placebo-controlled Phase 3 study assessing efficacy and safety of two telaprevir (TVR, T)-based response-guided regimens compared with peginterferon alfa-2a 180 µg/week and ribavirin 1000-1200 mg/day (PR) in treatment-naïve patients with chronic genotype 1 HCV infection.

Methods: Treatment arms were (a) T 750 mg q8h in combination with PR for 8 weeks, followed by additional weeks of PR; (b) T 750 mg q8h in combination with PR for 12 weeks, followed by additional weeks of PR; (c) PR for 48 weeks (control arm). Patients in T arms achieving an extended rapid viral response (eRVR, undetectable HCV RNA at weeks 4 and 12) received a total of 24 weeks of therapy while those who did not received a total of 48 weeks of therapy. Randomization was 1:1:1 and patients were stratified by HCV RNA (<800,000 IU/mL, ≥800,000 IU/mL), and genotype 1a vs. 1b. The primary endpoint was SVR (undetectable HCV RNA 24 weeks after last planned dose of treatment). The primary analysis was based on the Full Analysis (intention-to-treat) dataset. Safety is presented for TVR/Placebo duration phase.

Results: Of 1088 patients, 839 (77%) had HCV RNA ≥800,000 IU/mL, 631 (58%) were genotype 1a, 636 (58%) male, 94 (9%) black, 117 (11%) Latino/Hispanic, 231 (21%) had bridging fibrosis or compensated cirrhosis. The most common (>25%) AEs in the T arms were fatigue, pruritus, nausea, headache, anemia, rash, influenza-like illness, insomnia, pyrexia, and diarrhea. Discontinuation of treatment due to AEs occurred in 8% in T8PR, 7% in T12PR and 4% in PR48; due to rash occurred in 0.5%, 1.4% and 0.0% and due to anemia occurred in 3.3%, 0.8% and 0.6% in T8PR, T12PR and control arms, respectively.

Conclusions: A significantly greater proportion of patients achieved SVR with 12-week and 8-week telaprevir-based combination regimens (75% and 69%, respectively), compared with PR48 control arm (44%, *P*<0.0001). The safety and tolerability profile of telaprevir in the ADVANCE trial was consistent with the profile previously reported, with an improvement in treatment discontinuation rates due to adverse events, including rash and anemia. These final Phase 3 results confirm the clinical benefit previously reported in Phase 2.

Viral Response

	T8PR N=364	T12PR N=363	PR48 N=361
Patients achieving RVR, n (%)	242 (66)	246 (68)	34 (9)
Patients with HCV RNA undetectable at end of treatment (EOT), n (%)	295 (81)	314 (87)	229 (63)
Patients achieving SVR, n (%)	250 (69)*	271 (75)*	158 (44)
Difference in SVR rates, TVR arms vs control, % (95% CI)	25 (18-32)	31 (24-38)	NA
Patients with relapse†, n (%)	28 (9)	27 (9)	64 (28)

*P<0.0001, †Denominator is number of patients with HCV RNA undetectable at EOT

Abstract was presented at AASLD 2010

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Human intestinal and systemic adaptation of iron metabolism and transport to hypoxia in mountaineers after rapid ascent to 4559m

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Background: Human iron metabolism is closely regulated by erythropoiesis, oxygen homeostasis and intestinal iron absorption. The aim of this study was to characterize the adaptation of iron metabolism and transport to hypoxia under high altitude conditions in man at the levels of (**i**) intestinal iron uptake (**ii**) changes in systemic iron homeostasis in one comprehensive overview. **Methods:** 28 mountaineers (10 M/18 F, 44.0±2.6 y., BMI 23.7±0.6 kg/m^2) were studied. Duodenal biopsies were taken by unsedated nasal endoscopy from each volunteer at 490m in Zurich [ZH] at baseline and 2 [CM2] and 4 [CM4] days after rapid ascent to 4559m to Capanna Regina Margherita in the Alps. Blood samples were drawn in a fasting state at 8 a.m. on day 0 [ZH], 2 [CM2] and 4 [CM4]. RNA was extracted from intestinal biopsy specimens and mRNA expression levels of the divalent metal transporter I (DMT1) was measured by quantitative real time PCR (qPCR). Iron, ferritin, transferrin, transferrin saturation and CRP were quantified by standard autoanalyzer techniques. Plasma IL-6 and erythropoietin levels were measured using ELISA. Hepcidin levels were analyzed by mass-spectrometry. All data were correlated to clinical measurements including arterial oxygen saturation (SO_2). All data are given as mean ± SEM. Differences between ZH, CM2 and CM4 were calculated by a mixed effect linear model. **Results:** Arterial SO_2 was lower at high altitude (CM2 and CM4) than in Zürich (76±1 and 80±1 vs. 95±1 %, p<0.001). Erythropoietin increased under hypoxic conditions (72±6 and 30±3 vs. 6±1 mU/ml; p<0.001) followed by an erythropoietic response indicated by increased intestinal DMT1 expression (1007±282 and 941±249 vs. 137±165% compared to villin; p<0.001) and low serum iron only on CM4 (23±2 and 12±2 vs. 24±1 µmol/l, p<0.001). Serum ferritin also declined rapidly (108±7 and 96±6 vs.141±22µg/l, p<0.001). Plasma CRP and IL-6 increased on CM2 and CM4 for CRP and only on CM2 for IL-6 (CRP: 2.9±0.5 and 2.8±0.5 vs. 0.7±0.4 mg/l, p<0.001; IL-6: 2.7±0.5 and 1.5±0.5 vs. 0.9±0.3 ng/l, p<0.001). In line with a need for increased iron uptake, serum hepcidin levels decreased under high altitude conditions (1.25±0.1 and 0.5±0.1 vs. 4.5±0.25µg/l, p<0.001). **Conclusion:** This human healthy volunteer study showed for the first time that duodenal iron transport is rapidly upregulated together with decreased hepcidin under hypoxemic conditions to compensate increased iron consumption and mobilization of storage iron for enhanced erythropoiesis.

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Propofol sedation alone or in combination with pharyngeal lidocaine anesthesia for upper GI endoscopy – A randomized, double-blind, placebo-controlled non-inferiority trial

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Background: In patients undergoing upper EGD propofol is increasingly used without pharyngeal anesthesia (PA) due to its excellent sedative properties. It is unclear whether this practice is non-inferior in regard to ease of endoscopic intubation and patient comfort. It was the aim of our study to assess in patients with propofol sedation the relevance of local PA in respect of the ease of EGD performance.

Methods: We enrolled 300 consecutive adult patients undergoing elective EGD. All patients received PA with four squirts of lidocaine spray versus placebo spray immediately before propofol sedation. The number of gag reflexes (primary endpoint), number of intubation attempts, and degree of saliva during intubation were assessed by the endoscopists and staff.

Results: The mean rate of gaging in the pharyngeal anesthesia group was 0.27 (95% CI: 0.15; 0.38) compared to 0.76 (95% CI: 0.41; 1.10) with placebo (p=0.009). In adjusted logistic regression analysis the odds ratio for gaging for the pharyngeal anesthesia compared to the placebo group was 1.9 (95% CI: 1.03; 3.54). The number of intubation attempts and the degree of salivation was similar in both groups. Two patients in placebo group experienced oxygen desaturation in need of short mask ventilation.

Conclusion: Topical pharyngeal anesthesia reduces the gag reflex in patients sedated with propofol even though it does not seem to have an influence on the ease of the procedure and on patient or endoscopist satisfaction in adequately sedated patients.

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Morbidity in surgery: Impact of the 50-hour Workweek Limitation in Switzerland

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Background: Work-hour regulations for residency programs in Switzerland, including a 50-hour weekly limit, were set in on January 1, 2005. Patient safety was one of the major arguments for the implementation. As the effect of the restriction of residency work hours on patient care in Switzerland has not yet been evaluated on objective data, the aim of the present study was to assess its impact by comparing the patients' morbidity and mortality before (2001-2004) and after (2005-2008) the implementation.

Methods: Retrospective analysis of records of the Spitalzentrum Biel AG, a large referral center classified according to the Swiss Medical Association, collected in the database of the Association for Quality Assurance in Surgery (AQC), a prospective database of consecutive patients undergoing surgical procedures in Switzerland. A selection of 2686 patients with common surgeries, operated by residents, was performed.

Results: There were 1259 (46.9%) patients meeting our inclusion criteria who were admitted during the period *before* introduction of work-hour limitation and 1427 (53.1%) patients *after* introduction. The in-hospital mortality and postoperative surgical complication rate were significantly higher after the reform (p<0.05 and p<0.01, respectively). No significant differences could be found concerning intraoperative (p=0.61) and postoperative medical complication frequencies (p=0.08).

Conclusions: The work-hour limitation implemented in Switzerland was not associated with surgical patient safety measure improvement for common surgeries. Further research on a nationwide basis is needed to assess the value of the higher surgical complication and mortality rate.

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Large scale analysis of full-length Hepatitis C virus sequences links protective HLA class I alleles to clustered CD8 escape mutations

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Background: Several HLA alleles have been associated with spontaneous Hepatitis C virus (HCV) clearance. It is hypothesized that the impact of some CD8 escape mutations on viral replication may mediate immune control.
Methods: As a surrogate marker of CD8+ T-cell immune selection pressure we studied HLA class I-associated HCV sequence polymorphisms in full-length viral sequences from 405 HCV genotype 1a infected patients. The impact of selected HLA-associated polymorphisms upon viral replication capacity was tested using a subgenomic HCV replicon system.
Results: A total of 279 HLA-associated viral sequence polymorphisms (q<0.2) restricted by 52 HLA alleles were identified. Higher frequencies of these immune driven mutations were significantly associated with lower viral loads, with the strongest effects observed for HLA-B restricted mutations in NS5b (r=-0.19; p=0.002). Interestingly, 8 of 10 protective HLA alleles exhibited multiple clustered polymorphisms within individual epitopes, again most notably in NS5b, versus 0 of 7 hazardous HLA alleles. These clustered escape mutations were found to impair viral replication in vitro to a greater degree than single mutations selected in other CD8 epitopes.
Conclusion: This population-level analysis suggests that the selection of CTL escape mutations, including complex pathways of viral escape from immunodominant CD8+ T-cell responses targeting NS5b, might be a major determinant of viral control due to the inability of HCV to effectively escape from these responses.

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Adenocarcinomas of the upper third of the rectum and rectosigmoid junction might be treated as colon cancers

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Background: To investigate the survival of patients with cancers of the colon, the rectum and the region of the rectosigmoid junction before adoption of the technique of total mesorectal excison (TME).
Methods: From a 3-armed multicentric prospective randomized controlled trial on adjuvant short-term perioperative chemotherapy (5-FU and Mitomycin C for 7 days postoperative either systemically or via portal vein vs. surgery alone) for R0-resected colorectal cancer patients with stage I, II or III disease 726 patients were recruited from 1987 to 1993 (SAKK 40/87), and retrospectively divided into 3 groups: cancers of the lower two thirds of the rectum (defined as 0cm to 11cm distance from anal verge, Group A, n=205), of upper third of the rectum and rectosigmoideal junction (defined as >11cm to 20cm from anal verge, Group B, n=142) and of the colon (defined as > 20cm from anal verge, Group C, n=379). None of these patients received neo-adjuvant or adjuvant radiotherapy. The used short-term perioperative chemotherapy turned out to be ineffective.
Results: The five years overall survival (OS) rate was 0.6442 (95%CI: 0.5732 – 0.7065) in group A, 0.7919 (95%CI: 0.7144 - 0.8505) in group B and 0.7741 (95%CI: 0.7277- 0.8136) in group C. The five years disease-free survival (DFS) rate was 0.6315 (95%CI: 0.5605 - 0.6942) in group A, 0.7782 (95%CI: 0.6997 - 0.8385) in group B and 0.7588 (95%CI: 0.7116 - 0.7993) in group C. Compared with group C, patients in group A had a significantly worse OS (p<0.0001) and a worse DFS (p<0.0001); while patients in group B had a similar OS (p=0.6368) and DFS (p=0.7854).
Conclusions: Adenocarcinomas of the upper third of the rectum and rectosigmoideal junction might be treated as colon cancers. Even for surgeons being not familiar with total mesorectal excision, preoperative radiotherapy seems not to be justified for cancers higher than 11cm from anal verge.

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Synergistic effect of calcitriol and interferon-α on hepatitis C virus replication *in vitro*

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Background and aims: Vitamin D is an important modulator of numerous cellular processes, including innate and adaptive immune pathways. A recent large-scale genetic validation study performed within the framework of the Swiss Hepatitis C Cohort Study has demonstrated an association between the 1α-hydroxylase promoter single nucleotide polymorphism CYP27B1-1260 rs10877012 and sustained virologic response (SVR) after pegylated interferon-α (PEG-IFN-α) plus ribavirin treatment of chronic hepatitis C in patients with a poor-response *IL28B* genotype. This suggests an intrinsic role of vitamin D signaling in the response to treatment of chronic hepatitis C, especially in patients with limited sensitivity to IFN-α. In the present study, we investigated the effect of 1,25-$(OH)_2$ vitamin D3 (calcitriol) alone or in combination with IFN-α on the hepatitis C virus (HCV) life cycle *in vitro*.

Methods: Huh-7.5 cells harboring Con1- or JFH-1-derived HCV replicons or cell culture-derived HCV were exposed to 0.1-100 nM calcitriol ± 1-100 IU/ml IFN-α. The effect on HCV RNA replication and viral particle production was investigated by quantitative real-time PCR, immunoblot analyses, and infectivity titration analyses. The expression of interferon-stimulated genes (ISGs) and of calcitriol target genes was assessed by quantitative real-time PCR.

Results: Calcitriol had no relevant effect on the viability of Huh-7.5 cells. Calcitriol strongly induced and repressed the expression of the calcitriol target genes *CYP24A1* and *CCNC*, respectively, confirming that Huh-7.5 cells can respond to calcitriol signaling. Physiological doses of calcitriol did not significantly affect HCV RNA replication or infectious particle production *in vitro*, and calcitriol alone had no significant effect on the expression of several ISGs. However, calcitriol in combination with IFN-α substantially increased the expression of ISGs compared to IFN-α alone. In addition, calcitriol plus IFN-α synergistically inhibited HCV RNA replication.

Conclusions: Calcitriol at physiological concentrations and IFN-α act synergistically on the expression of ISGs and HCV RNA replication *in vitro*. Experiments exploring the underlying mechanisms are underway.

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PET-CT improves staging of intestinal-type adenocarcinoma of the esophagogastric junction and stomach - a prospective study

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Background: The accuracy of preoperative staging in patients with adenocarcinoma of the esophagogastric junction (AEG) and gastric cancer (GC) is low despite EUS and CT. PET-CT is a novel integrated imaging modality that could improve results with regard to N- and M-categories. Here, we prospectively assessed the sensitivity, specificity and accuracy of PET-CT compared to endoscopic ultrasound (EUS) and multidetecor spiral CT (MDCT) in preoperative N- and M-staging of patients with AEG and GC.
Patients and methods: Hundred-six consecutive patients with GC (n=45) or AEG (n=61) were prospectively evaluated. Systematic D2 or two-field lymphadenectomy (median: 31 nodes) was routinely performed (occasionally extended D2 or three-field LAD) with individual histopathological assessment of mediastinal (Japan Esophageal Society) and abdominal lymph node stations (Japanese Gastric Cancer Association). Preoperative staging results from EUS, MDCT and PET-CT were correlated to histopathological results.
Results: PET-CT showed the highest specificity (97%) and positive predictive value (95%) for the detection of lymph node metastases. The sensitivity however, is low (39%) resulting in an accuracy of 60%. In comparison, EUS was more sensitive (68%) but less specific (61%), MDCT displayed a specificity of 82% and a sensitivity of 43% with an accuracy of 58%. PET-CT performs poorly in diffuse type cancers, where primary tumors are significantly less positive compared to intestinal/mixed type tumors (62% vs. 85%, p=0.03). In patients with intestinal/mixed-type tumors PET-CT significantly facilitated the detection of extra-regional lymph node metastases (p=0.02) and distant metastases (p=0.03) compared to CT alone.
Conclusion: PET-CT does not improve overall accuracy of N-staging but improves specificity compared to EUS and MDCT in AEG and GC. In addition, the detection rate of extra-regional lymph node and systemic metastases is significantly higher in intestinal/mixed-type tumors. Therefore, we routinely perform PET-CT and EUS in patients with intestinal/mixed type but not diffuse type AEG and GC.

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Proteomic analysis of bile and pancreatic cyst fluid revealed promising sources of cancer biomarkers

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Background: Pancreas and biliary tract cancers have a very poor prognosis. Currently available diagnostic tools are plagued by a poor sensitivity and/or specificity. In this study, we used a proteomic approach to search for new biomarkers that could be used for determining the malignant potential of pancreatic and biliary tract lesions detected using clinical imaging.
Methods: Bile and cyst fluid from patients with malignant or benign diseases causing biliary stenosis or pancreatic cysts were subjected to qualitative and quantitative proteomics involving gel-based protein fractionation and LC-MS/MS analysis. Selected proteins were verified by immunoblot and/or immunohistochemistry.
Results: Proteomic analysis of bile and cyst fluids allowed the identification of a large number of proteins, including several cancer-associated proteins. Immunoblot verifications on bile samples indicated that CEACAM6 is a potential biomarker of malignant biliary stenosis. In pancreatic cyst fluid, olfactomedin-4 was detected only in the mucinous cystic lesions: mucinous cystadenomas and intraductal papillary mucinous neoplasm. Immunohistochemistry revealed that, in those lesions, olfactomedin-4 was expressed at the apical membrane of cystic cells, in contrast to other cyst types.
Conclusion: Our study demonstrated that bile and pancreatic cyst fluid are collecting cancer-associated proteins and represent extremely valuable sources of potential cancer biomarkers.

Characterization of response to toll-like receptor 9 agonist CpR-2252 in the mouse liver. 17

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Background: IMO-2125 is a toll-like receptor 9 (TLR9) agonist currently in phase I clinical development for the treatment of chronic hepatitis C. The aim of the present study was to compare the pharmacodynamic effects of CpR-2252, a closely related TLR9 agonist, and interferon (IFN)-α in the mouse liver.
Methods: We analyzed Jak-STAT pathway activation and induction of interferon-stimulated genes (ISGs) in the liver of wild-type and IFN-γ-deficient mouse strains after subcutaneous administration of CpR-2252.
Results: Injection of CpR-2252 produced a long-lasting activation of Jak-STAT pathway which, contrary to the response to IFN-α, was not reduced following repeated administration. Whole-transcriptome microarray analysis revealed that CpR-2252 induced broad transcriptional response in the mouse liver, including important upregulation of cytokine and chemoattractant genes. This sustained activation of antiviral response by CpR-2252 required endogenous IFN-γ production, as demonstrated by altered response patterns in the knock-out strain.
Conclusions: The lack of refractoriness to CpR-2252 combined with the long-lasting induction of ISGs hold promise for TLR9 agonists as treatment agents for chronic hepatitis C.

Is liver volume after portal vein embolisation worth more? A case-control study 18

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Background

Portal vein embolisation (PVE) is used before extensive hepatic resections to increase the volume of the future remnant liver within acceptable safety margins (conventionally 0.66% of the patient's weight). However, little is known about the impact of PVE on postoperative liver function. The aim of this study is to assess the impact of preoperative portal vein embolisation on immediate post-operative liver function following major hepatic resection, to validate/infirm the hypothesis that increase in volume is correlated to increased function.

Patients and methods

From a total of 68 patients undergoing PVE and right or extended right hepatectomy between 1999 and 2010 we excluded patients older than 70 years or with cirrhosis, and compared the remaining 28 patients (study group: PVE) to 17 donors of right liver grafts for adult-to-adult living donor transplantation (controls: LD). Statistical analysis was performed using the Student's t-test (demographics) and the two-way analysis of variance (laboratory values).

Results

Groups were similar for gender ($p > 0.1$), size ($p > 0.5$) and weight ($p > 0.06$). PVE patients were older than LD (58 vs. 41 years, $p < 0.0001$). The median weight of the resected liver was similar in PVE (760 g) and in LD (675 g) ($p > 0.07$). The calculated volume of the remnant liver (left liver or left lobe) was similar between two groups, 856 ml in PVE, 701 ml LD ($p > 0.1$), with similar residual volume/patient weight ratios (1.15% vs 1.10% respectively, $p > 0.5$). Analysis of the postoperative bilirubin levels showed significant lower values from day 1 to day 6 post surgery in PVE compared to the LD ($p < 0.0001$) [Fig.1]. Factor V levels showed significant higher values in the first two days after surgery in PVE when compared to LD group ($p < 0.0001$) [Fig.2].

Conclusion

Patients that underwent preoperative portal vein embolisation (in spite of older age and chemotherapy) show better remnant liver function than patient who underwent surgery alone. Our data suggest that current threshold figures for safe liver volumes in patients having undergone PVE may be too restrictive.

Telaprevir-based therapy in G1 HCV-infected patients with prior null response, partial response or relapse to peginterferon/ribavirin: REALIZE trial final results 19

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Background: This Phase 3 study evaluated telaprevir (T) in combination with pegylated-IFN alfa-2a (P) and ribavirin (R) in well-characterized G1 prior-PR treatment failure patients including prior PR non-responders (null and partial) and relapsers.
Methods: REALIZE was a randomized, international, multicentre, double-blind, placebo-controlled trial evaluating efficacy, safety and tolerability of T (750mg q8h) plus P (180µg/w) and R (1000–1200mg/d) compared with PR alone. The treatment arms (randomized 2:2:1, stratified by viral load and prior response) were: 12-weeks T/PR, followed by 36-weeks PR (T12PR48); 4-weeks PR followed by 12 weeks T/PR (T delayed start, DS), then 32-weeks PR (T12(DS)/PR48); 48-weeks PR (Pbo/PR48). The primary objective was efficacy of the T/PR arms in non-responders and relapsers. Secondary objectives included evaluation of T DS and efficacy in prior-null and -partial responders. HCV RNA was quantified using COBAS TaqMan® v2.0 assay (LLOQ=25IU/mL).
Results: 833 patients were screened, and 662 treated. 70% of patients were male, 93% Caucasian, 26% had cirrhosis, and 89% had baseline HCV RNA ≥800,000IU/mL.

	T12/PR48	T12(DS)/PR48	Pbo/PR48
	Relapsers		
%	N=145	N=141	N=68
SVR** (*P* value*)	83 <0.001	88 <0.001	24
	Prior PR Non-Responders		
	N=121	N=123	N=64
SVR ** (*P* value*)	41 <0.001	42 <0.001	9
	Partial-Responders		
	N=49	N=48	N=27
SVR ** (*P* value*)	59 <0.001	54 <0.001	15
	Prior PR Null-Responders (<2 log decline in HCV RNA at wk 12 of prior therapy)		
	N=72	N=75	N=37
SVR ** (*P* value*)	29 <0.001	33 <0.001	5

*In comparison to Pbo/PR48 **Assessed 24 weeks after planned treatment completion

AEs reported more frequently in T arms were rash, pruritus, diarrhea, anorectal disorders and anemia. 13% of T/PR patients had premature discontinuation (D/C) of T due to AEs: rash (4%) and anemia (3%) were the most common AEs leading to T D/C.
Conclusions: T/PR SVR was significantly superior to PR in all prior-treatment failure populations including null- and partial-responders. A telaprevir delayed start did not have a significant impact on SVR rates. Safety profile of T/PR was consistent with that observed in treatment naïve subjects.

SIMILAR SVR RATES IN IL28B CC, CT OR TT PRIOR RELAPSER, PARTIAL- OR NULL-RESPONDER PATIENTS TREATED WITH TELAPREVIR/PEGINTERFERON/RIBAVIRIN: RETROSPECTIVE ANALYSIS OF THE REALIZE STUDY 20

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BACKGROUND: IL28B polymorphisms are linked to differences in SVR rates in HCV treatment-naïve patients treated with pegylated interferon (P) and ribavirin (R). REALIZE is a Phase 3 study that compared the efficacy, safety and tolerability of telaprevir (T), with or without a Lead-in (LI), in combination with PR against PR alone in prior treatment-failure patients including relapsers, partial responders and null responders (NR). Both T/PR arms were superior to control in all three patient categories. The relationship between IL28B genotype and SVR was investigated retrospectively.

METHODS: 527/662 (80%) patients enrolled in REALIZE consented to genetic testing. This represented 72%, 76% and 98% of the total relapsers, partial responders, and NR, respectively. Genotype rs12979860 was determined using a TaqMan allelic discrimination assay validated against Sanger sequencing on 50 independent samples. This was a retrospective study based on patients who consented to genetic testing prior to the discovery of IL28B, thus, sample size was not based on formal statistical considerations.

RESULTS: Overall, 94% were Caucasian and 4% were Black. 18% of patients were IL28B CC, 61% CT and 21% TT. By prior response category, the highest proportion of IL28B TT patients was among prior NR (28%) while the highest frequency of CC patients occurred among prior relapsers (27%). The observed IL28B genotype frequencies indicate that the population was not in Hardy-Weinberg equilibrium (Chi^2=28, *P*<0.0001). IL28B genotypes were well balanced across all arms with exception of a higher frequency of TTs in the placebo arm. Since no differences were observed between the two Telaprevir arms, a pooled analysis is presented.

% SVR (n)	Overall Population		Prior Relapsers		Prior Partial Responders		Prior Null Responders	
	Pooled T12/PR48 Arms N=422	Pbo/PR48 Arm N=105	Pooled T12/PR48 Arms N=209	Pbo/PR48 Arm N=52	Pooled T12/PR48 Arms N=79	Pbo/PR48 Arm N=20	Pooled T12/PR48 Arms N=134	Pbo/PR48 Arm N=33
IL28B CC	79 (76)	29 (17)	88 (58)	33 (12)	63 (8)	20 (5)	0 (10)	NA (0)
IL28B CT	60 (266)	16(58)	86 (117)	20 (30)	58 (57)	20 (10)	29 (92)	6 (18)
IL28B TT	61 (80)	13 (30)	85 (34)	30 (10)	71 (14)	0 (5)	31 (32)	7 (15)

CONCLUSIONS: Differences in SVR rates among IL28B CC, CT and TT patients were only evident when the three patient subpopulations were pooled, however, SVR among CT and TT patients were still high. In this retrospective analysis, IL28B genotype did not contribute to outcome prediction in prior treatment-experienced patients treated with a telaprevir-based regimen and thus, may be of limited utility in this setting.

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Title

Do platelets play a role in remote ischemic preconditioning?

Name and Surname of Authors, Institutions, Addresses

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Background data

Major liver surgery often involves periods of ischemia followed by reperfusion. The injury caused by ischemia reperfusion (IR) can be significant, particularly for the diseased liver. Many experimental approaches have been undertaken to protect from IR injury, however only a few have been translated into clinical practice.
Of these, remote ischemic preconditioning (RIPC) appears to be the most promising strategy. Whilst resulting in levels of organ protection akin to direct ischemic preconditioning (IPC), RIPC is simple, non-invasive, and does not stress the target organ directly. In RIPC, blood flow is mechanically interrupted for repetitive periods in a remote body part, usually a limb. Presumably, the ischemic periods locally release factors that confer systemic protection in distant organs. However, the mechanisms underlying the mitigating effects of RIPC remain elusive.
Here, we assessed the level of RIPC-mediated protection from hepatic IR injury and investigated potential mechanisms of RIPC-action.

Methods

Lean livers (C57BL/6J mice), and macrosteatotic livers (B6.V-Lepob/J mice) were subjected to 70% partial ischemia-reperfusion injury. Before liver ischemia, mice were subjected to either transient occlusion of blood flow to a hind limb (four times five min., RIPC group) or remained untreated (control group). IR injury was assessed by serum ALT/AST and by the area of hepatic necrosis on histology. Hind limb muscle was examined for gene expression changes (*Hif1a, Nos3, Nos2, Vegf*). The role of platelets was investigated using mice with antiCD41-induced thrombocytopenia.

Results

RIPC significantly protected lean and steatotic livers from IR injury, as evinced by a marked reduction in both ALT/AST levels and the necrotic area (RIPC mean ALT 6770±1277 vs. Control mean ALT 11435±2320 ; RIPC mean AST5750±1788 vs Control mean AST 9.420±2.555). Of note, the protective effect was stronger for steatotic livers, which suffered from more IR injury than lean livers.
Intriguingly, however, depletion of platelets before preconditioning completely abolished the protective RIPC effect in both lean and steatotic mice.

Conclusions

This study demonstrates the ability of RIPC to efficiently protect from IR injury not only in lean, but also in macrosteatotic livers. Moreover, our results indicate a central role for platelets in the mechanisms underlying RIPC-mediated protection.

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Title

Trainee Satisfaction in Surgical Residency Programs: Modern management tools ensure trainee motivation and success.

Name and Surname of Authors, Institutions, Addresses

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* contributed equally

Objectives

To assess trainee satisfaction in surgical residency with a validated instrument and identify the contributing factors.

Background data

Currently, careers in surgery are deemed unattractive by medical students and ignored by many candidates with academic potential. New insights on the rational for such lack of interest are urgently needed. Job satisfaction is a central concept in organizational-and behavioural research, well understood by large companies such as Google, IBM and Toyota - it can be modified to assess trainee satisfaction in surgical residency.

Methods

A survey among 2039 surgical residents was conducted in three European countries analyzing satisfaction at work using the validated Global Job Satisfaction Instrument. Crucial factors covering different aspects of surgical residency where identified using the GJS-instrument combined with multiple logistic regression analysis.

Results

With an overall response rate of 23 %, we identified trainee dissatisfaction in as much as one third of residents. Factors affecting satisfaction related almost exclusively to training issues such as assignment of surgical procedures according to skills(OR4.2), training courses(OR2.7), availability of a structured training curriculum(OR2.4), bedside teaching and availability of morbidity-mortality conferences(OR2.3). A good working climate amongst residents(OR3.7) and the option for part time work(OR2.1) were also significant factors for trainee satisfaction. Increased working hours had a modest(OR0.98) -though cumulative-negative effect. Gender was not related to trainee satisfaction.

Conclusions

Validated measurement of trainee satisfaction –similar to job satisfaction assessment in the industry- is an efficient tool to identify shortcomings in surgical residency. Improvement of conceptual training structures and working conditions might facilitate recruitment, decrease drop-out and attract motivated candidates with possibly better quality of care.

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Title

Perforated left colonic diverticulitis with purulent or faecal peritonitis: Primary Anastomosis or Hartmann's Procedure? A Prospective Multicentre Randomized Controlled Trial

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Objectives

To evaluate the outcome after Hartmann's Procedure (HP) versus primary anastomosis with diverting ileostomy (PA) for perforated left-sided diverticulitis in a randomized controlled trial.

Background data

The surgical management of left sided colonic perforation with purulent or faecal peritonitis remains controversial. PA (with ileostomy) appears to be superior compared to HP, however results in the literature base on a significant selection bias. No randomized controlled trial has compared the two procedures.

Methods

62 patients with acute left-sided colonic perforation (Hinchey 3 and 4) from 4 centres were randomized to HP (n=30) and to PA (with diverting ileostomy, n=32) with a planned stoma reversal operation after 3 months in both strategies. Data were analysed on an intention to treat basis. The primary endpoint was the overall complication rate (according to the Clavien-Dindo classification) (NCT01233713).

Results

Patient demographics such as age, ASA score, Charlson index and the severity of peritonitis were equally distributed in both groups (Hinchey 3: 76% vs 75% and Hinchey 4: 24% vs 25%, for HP vs PA, respectively). The overall complication rate for both resection and stoma reversal operations were comparable (80% vs 84%, p= 0.813). While the outcome after the initial colon resection did not show any significant differences (mortality 9% vs 11% and morbidity 71%vs 71% in HP vs PA), the stoma reversal rate after PA with diverting ileostomy was higher (88% vs. 52%, p=0.005) with significantly lower rates of serious complications (Grade IIIa – IV: 0% vs 20%, p=0.046), shorter operating time (73min vs 183min, p<0.001), shorter hospital stay (6d vs 9d, p= 0.016), and lower in-hospital costs (16'711CHF vs 26'155 CHF).

Conclusions

This is the first RCT to report evidence that in patients with perforated diverticulitis primary anastomosis with diverting ileostomy should be preferred over Hartmann's Procedure.

Quantitating anti-TNF functionality to inform dosing and choice of therapy

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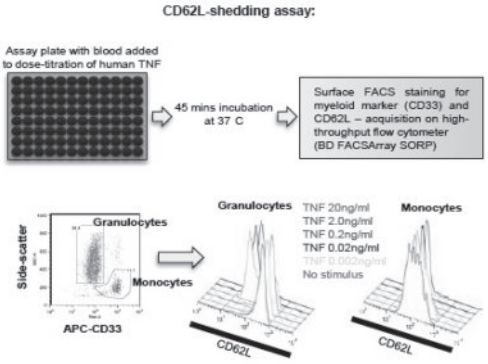
ABSTRACT BODY:
Background:
Biological therapy with TNF-blocking antibodies is now broadly applied in inflammatory bowel disease (IBD). Some disadvantages of treatment are high cost burden and therapy resistance. The latter carries the risk of delay of effective treatment and deterioration of the patients. Therefore simple tests that inform dosing and relevance of the treatment are urgently required.
Aim:
To evaluate a fast assay (FASTNF) that quantifies the extent of functional TNF blockade in IBD patients.

Methods:
TNF-stimulation of blood granulocytes triggers the enzymatic shedding of CD62L from the cell surface. Patient whole blood was therefore stimulated with a dose-titration of human TNF for 45mins at 37°C and median fluorescence intensity of CD62L on the surface of granulocytes was quantified by surface staining with specific antibodies (CD33, CD62L) and flow cytometry. Fitting 4-parameter logistic curves to these data permits the calculation of the TNF concentration required to give 50% granulocyte activation. Total anti-TNF antibody levels and anti-idiotype levels were quantified by direct ELISA. Measurements were carried out on a cohort of Crohn's disease and Ulcerative colitis patients being treated with TNF-blocking therapies from the Inselspital and Tiefenauspital, Bern, Switzerland.

Results:
Data from 55 IBD patients (25 F, mean age 41; range 20-60, 18 Ulcerative Colitis (UC), 34 Crohn's disease (CD), 3 controls). In all but two Infliximab-treated patients FASTNF revealed functional blocking of TNF activity despite ongoing disease whereas ELISA based measurements showed no above-background levels of anti-TNF antibodies in 8 patients. One patient displaying absence of TNF blockade (by FASTNF) despite Infliximab treatment, had measurable titres of anti-Infliximab antibodies indicating development of therapy resistance. No such antibodies were detected in the second FASTNF-negative patient suggesting increased dosing may be beneficial.

Conclusions:
Decreased sensitivity to TNF is observed in the majority of Infliximab-treated patients, but with a poor correlation to total Infliximab levels measured by ELISA indicating considerable variation in blockade sensitivity between patients. This method could detect the presence of TNF-blocking agents at up to 10-fold higher sensitivity that standard ELISA based-methods. When combined with direct measurement of antiidiotype
antibody responses in patient serum and the extent of clinical response, this technique could accurately distinguish patients who warrant higher dosing, patients with complete anti-idiotype blockade of anti-TNF efficacy, and patient who fail to respond due to TNF-independent pathology. The test can be further adapted to determine efficacy of further TNF-blocking agents in patients who have developed resistance to their current therapy.

Figure 1



Measurements carried out on a Inflammatory Bowel Disease cohort study with patients being treated with TNF-blocking agents from Inselspital and Tiefenauspital, Bern, Switzerland. TNF-stimulation of blood granulocytes triggers the enzymatic shedding of CD62L from the cell surface. Patient whole blood stimulated with a dose-titration of human TNF for 45mins at 37°C. Median fluorescence intensity of CD62L on the surface of granulocytes quantified by surface staining with specific antibodies (CD33, CD62L) and flow cytometry to give 50% granulocyte activation. Fitting 4-parameter logistic curves to these data permits the calculation of the TNF concentration required. Total anti-TNF antibody levels and anti-idiotype levels quantified by direct ELISA

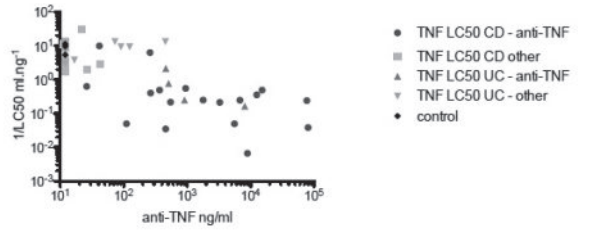


Figure 2: Sensitivity to TNF stimulation as indicated by TNF LC50 (Inverse Y axis) is a more sensitive indicator of anti-TNF treatment efficacy than plasma levels of the anti-TNF antibody levels in plasma (X axis).

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Notch1 and EphrinB2 are Downregulated in Patients with Nodular Regenerative Hyperplasia

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Background: Nodular regenerative hyperplasia (NRH) is a rare liver disease, which can be complicated by non-cirrhotic portal hypertension. The etiology and pathogenesis of NRH remain unknown. Clinical and experimental data suggest microcirculatory impairment and/or endothelial injury as possible causes of NRH. We have previously shown that knockout of the receptor Notch1 in liver sinusoidal endothelial cells induces NRH with portal hypertension through vascular remodelling and capillarization of the liver microvasculature (Hepatology 2005 and submitted). Molecular analysis in these NRH mice showed that the vascular changes are mediated through the endothelial ephrinB2/EphB4 pathway supporting the hypothesis that NRH is caused by an endotheliopathy at the level of the sinusoidal microcirculation.
Our aim is to analyze clinical, laboratory and molecular data of patients with NRH. Further, we want to assess whether the endothelial markers found in our NRH mouse model are also regulated in human NRH.

Methods: Patients with the histological diagnosis of NRH were identified by searching all entries between 1996-2011 in the liver biopsy database of the Institute of Pathology at the University Hospital Basel. All liver biopsies were reassessed and classified according to the nodularity grading score by Wanless (*Hepatology 1990*). Clinical and laboratory patient data were retrieved from their medical records. Associations between histological NRH severity and clinical/laboratory parameters were evaluated. mRNA expression of *Notch1,* its transcription factor *Hes1* and *ephrinB2* was measured in shock frozen liver biopsies from 14 NRH patients, who agreed to donate a second liver biopsy specimen for scientific purposes.

Results: 45 biopsies were identified with NRH on liver biopsy (27 male/18 female, mean age 46 (9-81)), including 32 with grade 1, 7 with grade 2 and 6 with grade 3. Grade 3 nodularity significantly correlated with increased CHILD and MELD scores (p=0.0034 and p=0.003) as well as the presence of portal hypertension: 3/6 (50%) with grade 3 vs. 2/39 (5.1%) with grade 1/2 (p=0.0126). mRNA analysis showed significant downregulation of *Notch1* (p=0.0005), *Hes1* (p=0.0194) and *ephrinB2* (p=0.0085) in NRH patients vs. controls.

Conclusions: In this largest NRH patient cohort reported to date we have shown for the first time that advanced grading correlates with presence of portal hypertension and impaired liver function. Downregulation of the endothelial signalling pathways Notch1, Hes1 and ephrinB2 supports the hypothesis that human NRH is caused by an endotheliopathy of the hepatic microcirculation.

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Appendicitis : should we stick to clinical diagnosis?

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Background:
Many surgeons still advocate that the diagnosis of appendicitis is mainly based on clinical findings. However, radiologic investigations such as CT scans and ultrasound are increasingly used in the diagnostic process. Yet the rate of negative appendectomies reach up to 12%. We analyzed preoperative investigations, surgical technique and their impact on patient's outcome.
Methods:
Prospective population-based analysis of all patients aged >16 years undergoing appendectomy for suspected appendicitis in 6 different Swiss hospitals covering a population of 500'000.
Results:
Over a 4 years period, 2560 appendectomies were performed. Median age of patients (47% female, 53% male) was 38 years (16-95). Ultrasound was performed in 64% of the patients, CT-scan in 14% and both examinations in 12%. In only 10% of patients, surgery was performed solely based on a clinical diagnosis. The overall median « door-to-scalpel » time was 5.8 hours (5min-175hours). The negative appendectomy rate in patients with no radiological investigation was 9.3%. This rate could be significantly lowered with a CT-scan (5.4%, p=0.008), but not with ultrasound (6.2%, p=0.54). Interestingly, this rate was significantly increased in patients presenting a Charlson index >3 (46.5% vs. 19.4%; p<0.001).
Laparoscopic appendectomy was performed in 78% of patients, mainly according to hospital policy. Laparoscopy decreased hospitalisation in perforated and in non-perforated appendicitis by one day, and shortened time off work by nearly 2 days (11.9 vs. 13.5 days).
Conclusions:
Indication to surgery, based solely on clinical findings, demonstrate a substantial rate of negative appendectomies. Patients with charlson index >3 are more likely to have a perforated appendicitis. Laparoscopic appendectomy decreased the reintervention rate and shortened time off-work.

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Title: The blood-based Septin9 test: Number of positive PCR replicates provides additional diagnostic value.

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Background: In Switzerland, about 1,600 people die of colorectal cancer (CRC) and 4,000 new cases are diagnosed each year, one of the highest incidences in Europe. The five-year survival rate for CRC exceeds 90% when diagnosed at an early stage and early detection is key in preventing CRC mortality. A new molecular diagnostic blood test for CRC based on ^{m}SEPT9 has been available as a CE-marked kit in Europe for over a year, with test results reported qualitatively as positive or negative. We examined whether the number of positive PCR replicates may add clinical value.

Methods: A prospective trial of the Septin9 test in CRC screening guideline-eligible individuals (PRESEPT) was reported previously. A total of 7,941 men (45%) and women (55%) with an average age of 60 years were prospectively enrolled at 22 sites in the U.S. and 10 sites in Germany. Briefly, subjects provided blood samples prior to bowel preparation for colonoscopy and the presence or absence of CRC or polyps was obtained from clinical record. Three independent labs, blinded to clinical status, used a real-time PCR assay for Septin9, initially in duplicate, but with a triplicate analyzed later, to assay plasma from all CRCs and a stratified random sample of other subjects. We evaluated the sensitivity, specificity, PPV and NPV of ^{m}SEPT9 according to the number of positive PCR replicates in order to test the hypothesis that this number might provide additional diagnostic value.

Results: The ^{m}SEPT9 triplicate test results from all available CRCs (n = 51) and a subset of subjects without disease (n = 910) were re-evaluated. Sensitivity for CRC at 1 of 3 PCR replicates positive was reported previously as 67% (95% CI: 47–78%) with a specificity of 88% (95% CI: 86–90%), yielding a PPV of 3.7% and an NPV of 99.8%. If 2 of 3 ^{m}SEPT9 PCR replicates were required for a positive call, the sensitivity for CRC detection fell to 43.1% with a specificity of 98%, yielding a PPV of 11.2% and an NPV of 99.6%. If 3 of 3 ^{m}SEPT9 PCR replicates were required, the sensitivity for CRC detection was only 31.4% but the specificity rose to 99%, yielding a PPV of 20.9% and an NPV of 99.5%.

Conclusions: An analysis of the emulated triplicate ^{m}SEPT9 results by number of positive PCR replicates shows that the PPV in patients having 3 of 3 positive replicates may be greater than 20%.

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Anti-TNF therapy and Pregnancy in Inflammatory Bowel Disease: A Prospective cohort study from the GETAID.

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Aim
The aim of this study was to assess the impact of treatments with anti-TNF on fetal development and pregnancy outcome in inflammatory bowel disease.
Patients and Methods
Pregnancies occurring during anti-TNF therapy or less than 3 months after withdrawal of it in patients with IBD followed in GETAID centres, were recorded from 01/01/2009 until 31/12/2010. Dosage and duration of exposure to anti-TNFs and associated treatments were recorded. Disease activity as well as maternal-fetal, obstetrical and neonatal complications were ascertained.
Results
130 pregnancies were recorded in 123 patients (98 CD, 23 UC, 2 IC) with median age of 29 years, of which 13/130 (10%) are still ongoing. 14/130 (11%) pregnancies were interrupted, mostly for miscarriages (8%), 103/117 (88%) were completed and resulted in 103 live births. At conception, 29/130 (22%) patients were in relapse and 101/130 (78%) in clinical remission. 23/101 (23%) patients in remission at the time of conception experienced flares during pregnancy. The anti-TNFs used were infliximab, adalimumab and certolizumab in 64%, 32% and 4%.Thiopurines were given in association in 22/130 (17%) cases (azathioprine=20, 6-mercaptopurine=2). Median duration of anti-TNF therapy at the time of conception was 63 weeks. Of the 103 completed pregnancies, anti-TNFs were preventively interrupted in 74/103 (72%) patients at the end of 2nd trimester and pursued until delivery in 22/103 (21%) patients. Completed pregnancies were uneventful in 74% (76/103) of cases, complicated in 26% (27/103) of cases: namely 20% premature deliveries (<37 GW) among live births, 4% metabolic complications, 1% maternal infections, one colectomy for severe UC. Among the 103 live births, 22/103 (7%) presented 29 neonatal complications, namely 20 (20%) hypotrophy (birth weight <2500g), 3 respiratory distress syndromes, 3 neonatal jaundices, 2 infections, 1 congenital malformation.
Conclusion
Our results support that one third of pregnancies exposed to anti-TNFs are complicated. These data are similar to those reported in historical IBD cohorts, suggesting an absence of excess risk linked to anti-TNFs. Based on the number of patients currently collected, the final results of our cohort which should include at least 116 births under anti-TNF will be available by September 2011.

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Autologous bone marrow stem cell transplantation (BMSCT) in decompensated alcoholic liver disease: interim analysis of a RCT

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Background: The short term prognosis of patients with decompensated alcoholic liver disease and steatohepatitis is poor. This RCT was designed to explore the role of BMSCT in the evolution of liver failure over a 3-month period after clinical decompensation. Patients/Methods: 58 patients (M/F: 34/24, mean age 54 yrs) with decompensated alcoholic cirrhosis (mean MELD 19) associated with alcoholic steatohepatitis (n=48) were randomized early after admission to receive standard medical therapy (SMT) alone (n=30) or in association with autologous BMSCT (n=28), that included a 5-day G-CSF-based mobilization therapy followed by bone marrow aspiration and stem cell isolation prior to reinfusion in the hepatic artery. The MELD score and clinical outcome were determined at 1, 2 and 3 months of follow-up. The primary endpoint was a decrease of ≥ 3 in the MELD score at 3 months. Results: Patients characteristics were similar at baseline. BMSCT could be administered in all but 2 patients. During FUp, 6 patients died (4 in SMT group). Adverse events were equally distributed in both groups, none related to BMSCT. FUp is not yet completed for all patients. Evolution of MELD was similar in both groups.(mean ± SEM, * p < 0.001 vs baseline)

	MELD baseline	MELD month 1	MELD month 2	MELD month 3
BMSCT	19 ± 0.8	15.8 ± 1.2*	13.7 ± 0.9*	13.7 ± 1.2*
SMT	18.6 ± 0.7	14.9 ± 1.1*	13.1 ± 1*	12.5 ± 1.1*

The primary endpoint was reached in 17/28 BMSCT patients, and 16/30 SMT patients (p=NS). Conclusions: in this group of patients with decompensated alcoholic liver disease, autologous BMSCT is well tolerated but doesn't improve liver function over a 3-month period as compared to SMT alone. Final data analysis is required to confirm these results.

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Neoadjuvant therapy of locally advanced esophageal cancer: Response evaluation by 18F-FDG-PET

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Background: Neoadjuvant radiochemotherapy for esophageal cancer is a widely accepted treatment. [18 F]-Fluorodeoxyglucose-positron emission tomography (FDG-PET) seems to be a helpful tool for response evaluation.The aim of this study was to assess the response after neoadjuvant therapy using FDG-PET and to correlate this with the histolopathologic response.

Methods: 40 patients with a locally advanced (T 3 or N+) carcinoma of the esophagus were included. 18F-FDG-PET was performed and standardized tumour uptake (SUV) measured before and three weeks after neoadjuvant radio- and/or chemotherapy. Decrease of SUV was correlated with final histology and regression grade according to Mandard.

Results: Mean tumour uptake SUV decreased significantly after neoadjuvant therapy (8.5 ± 0.8 vs. 3.7 ± 0.3). Mean decrease of tumour SUV for ypT0 (n=8) was 44.8 %, for ypT1 (n=4) 67.8%, for ypT2 (n=13) 55.1% and for ypT3 (n=15) 45.6% (n.s.). In addition no significance was seen if decrease of SUV was correlated with regression grade according to Mandard (TRG): TRG 1 (decrease SUV 42.8 %), TRG 2 (decrease SUV 59.8 %), TRG 3 (decrease SUV 36.7%) and TRG 4 (decrease SUV 58.3 %), TRG 5 (decrease SUV 45.3 %).

Conclusions: Response to treatment after neoadjuvant radiochemotherapy for esophageal cancer can be confirmed by 18F-FDG-PET. There was no correlation between decrease of SUV in restaging and the final tumour stage or regression grade.

Lifestyle Factors Modulating Promoter Methylation in Normal Colorectal Mucosa of Healthy Subjects

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Background Promoter hypermethylation is a prominent feature in colorectal cancer (CRC), modulated by biological factors such as age, gender and colonic location. We investigated the contribution of lifestyle factors on DNA methylation. **Methods** We measured promoter methylation levels of *hMLH1, MGMT* and *FOXF1* in each one biopsy of normal mucosa (NM) of the cecum (A) and sigmoid (B) colon in 546 healthy females and correlated the results with various lifestyle parameters assessed by a questionnaire. **Results** An age-dependent methylation increase was found in *hMLH1* (A: p<0.0001, B: p 0.01) and in *FOXF1* (B: p 0.001), but not in *MGMT*. Long-term aspirin use (≥ 2 years) was associated with declined *MGMT* methylation (A, B: p 0.005) and fewer hyperplastic polyps (HP) (B: OR 0.26, p 0.03). Heavy smoking (≥ 20 years) was associated with pronounced *MGMT* methylation (A: p 0.07) and an increased occurrence of serrated adenomas (OR 7.3, p 0.02) and HP (OR 2.8, p 0.001) in the left colon. **Conclusions** Our data confirm that DNA methylation in the NM varies with age in a gene-specific pattern. This phenomenon may be modulated by various lifestyle factors, such as aspirin use and smoking. Uncovering the pathophysiology of aberrant methylation is crucial to develop specific preventive strategies.

Systematic Assessment of Factors Influencing Preferences of Crohn's Disease Patients in Selecting an Anti-TNF agent (CHOOSE TNF TRIAL)

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Background and Aims: Infliximab (IFX), adalimumab (ADA) and certolizumab pegol (CZP) have similar efficacy for induction and maintenance of clinical response and remission in Crohn's disease (CD). Given the comparable nature of these drugs, patients' preferences may influence the choice of the product. Goal: to identify factors contributing to CD patients' decision in selecting one anti-TNF agent over the others.

Methods: A prospectdive survey was performed among anti-TNF-naïve CD patients. Prior to completion of a questionnaire, patients were provided with a description of the three anti-TNF agents focusing on indications, route of administration, side effects, and scientific evidence of efficacy and safety.

Results: One hundred patients (47f/53m, mean age 45±16yrs) completed the questionnaire. Disease location was ileal, colonic and ileocolonic in 33%, 40% and 27% of patients, respectively. Thirty-six percent preferred ADA as medication of choice, while 28% and 25% preferred CZP and IFX; 11% were undecided. Patients' decision in selecting an anti-TNF drug was influenced by the following factors: side effects (76%), physician's recommendation (66%), route of administration (54%), efficacy data (52%), time required for therapy administration (27%), recommendations by other CD patients (21%) and interactions with other medications (12%).

Conclusions: The majority of patients preferred anti-TNF medications that were administered by subcutaneous injection rather than by intravenous infusion. Side effect profile and physicians' recommendation are two major factors influencing the patients' selection of a specific anti-TNF drug. Patients' concerns about safety and lifestyle habits should be taken into account when prescribing anti-TNF drugs.

Clinical response to empiric PPI therapy predicts the results of reflux monitoring on PPI therapy

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Background: Currently most patients referred for reflux monitoring have been empirically treated with proton pump inhibitors (PPI). Reflux monitoring "on therapy" clarifies the relationship between persistent symptoms and reflux whereas monitoring "off therapy" is used to exclude GERD as the cause of reflux symptoms. While the decision whether to perform a study "on" or "off" therapy needs to be made at least 7 days prior to testing there are no criteria assisting this decision. **Aim:** Investigate whether clinical response to empiric PPI therapy can assist deciding whether impedance-pH monitoring should be performed "on" or "off" therapy.

Methods: Patients referred for reflux monitoring were asked to indicate if they had no, partial or complete symptom improvement during empiric PPI therapy. On PPI therapy esophageal acid exposure was considered abnormal if % time pH<4 was >1.6%, the total number of reflux monitoring was considered abnormal if >48 and symptom association was considered positive if the 5-min symptom index (SI) >50%.

Results: Among 117 patients undergoing reflux monitoring on therapy 48 (41%) reported no, 48 (41%) partial and 21 (18%) complete improvement while on PPI. Distal esophageal acid exposure (% time pH<4), total number of reflux episodes and proportion of patients with abnormal acid exposure, number of reflux episodes and positive symptom index (SI) are summarized in the table.

	no response (N=48)	partial response (N=48)	complete response (N=21)	p-value
% time pH<4 (total)	1.8 ± 0.4	4.2 ± 0.9	4.4 ± 0.9	0.038
Abnormal % time pH<4 (>1.6%)	13 (27%)	24 (50%)	13 (62%)	0.014
# reflux episodes (total)	39 ± 6	49 ± 6	65 ± 12	0.082
Abnormal # reflux episodes (>48)	11 (23%)	21 (44%)	12 (57%)	0.011
Positive SI (5-min)	4 (10%)	9 (24%)	9 (56%)	0.001

Continuous variables are presented as mean ± SEM, proportions as N (%)
p-value: Chi-square for proportions, ANOVA for continuous variables

Summary/Conclusions: Patients reporting no improvement from empiric PPI therapy are less likely to have abnormal reflux monitoring results on PPI therapy compared to patients with partial/complete response. Thus, in patients without symptomatic improvement, reflux monitoring should be performed "off therapy" with the aim of excluding reflux as cause of their symptom.

Single Port Transanal Surgery (SPTS): initial operative experience.

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Background: Transanal endoscopic microsurgery requires special equipment, laborious positioning of the patient facing the lesion and sphincter dilatation of more than 4cm. The aim of this study was to investigate safety and efficiency of single port transanal surgery (SPTS) for rectal tumors.

Methods: Consecutive patients undergoing SPTS using the SILS port (Covidien) and standard laparoscopic instruments.

Results: Ten patients (8 male) with a median age of 70.5yrs (42-87) underwent SPTS for tubulovillous adenoma (n=7) and T1(sm1) rectal cancer (n=3) located at a median of 7.5cm (5-12cm) from the anal verge. Patients were placed in the lithothomy position. The SILS port was easily inserted without need for dilatation of the anal sphincter. Median resection time was 25min (15-60) and the rectal defects were closed with single sutures in 65min (15-105). Two urinary tract infections (grade 2 complications) occurred. Patients were discharged after a median of 5 days (1-7). At median follow-up of 3 months (0.5-11), no incontinence was observed.

Conclusions: SPTS can be performed safely and efficiently with standard laparoscopic instruments. The SILS port does not require special anal dilatation and continence is not compromised.

G1

First experience in Switzerland with a non-sodium phosphate-based preparation for Colon capsule endoscopy. Marc Girardin, Florin Costea, Thai Nguyen-Tang, Jean-Marc Dumonceau. Gastroenterology and Hepatology Service, Geneva University Hospital.

Background: Colon capsule endoscopy is a recent diagnostic tool for colon examination (PillCam COLON 2, Given imaging®). As per colonoscopy, it needs colon cleansing before doing the procedure. The most frequently used and best established preparation contains sodium phosphate, an agent recently shown to be dangerous for kidneys. Aim: To evaluate the efficacy of a non-sodium phosphate-based preparation for colon capsule endoscopy. Methods: Nine control subjects had a liquid diet for one day, 2 liters of Moviprep® and Motilium® 1 hour after swallowing the capsule if it had not reached the small bowel. The capsule recorded colonic images at a rate of 32 images/sec. Colon cleanliness was analysed in 5 segments (caecum, ascending, transverse, descending and recto-sigmoid colon) using the validated Leighton's scale (1: very bad to 4: excellent preparation). Median Leighton's score and total time of grade 4 cleanliness were noted for each of the 5 segments. Bubble's amount was estimated as less or more than 10% of the colon surface. Results: Median age was 46 years, 8 subjects were males. One study failed due to capsule's malfunction (data weren't recorded) and two studies were incomplete (capsules not being eliminated during the recording time). A prokinetic was administered to 50% of the subjects. The capsules median excretion time was 5.5 hours. Median colon transit time was 1.5 hours. Median Leighton's score of colon cleanliness was 2.7 out of 4, corresponding to good (2.0 for the caecum, 2.5 for ascending colon, and 3.0 for transverse, descending and recto-sigmoid colon). During 23% of the colon transit time cleanliness was excellent (grade 4).The amount of bubbles was <10% of the colon surface. Conclusions: Colon preparation was well accepted by all the subjects. Globally, colon cleansing was good but it was rated as excellent in only 25% of the examination time. Failure to excrete a functioning capsule remains problematic for a significant number of patients.

G3

Systematic review of the Perforation Risk in Stenosing Eosinophilic Esophagitis: Dilation is much safer than initially reported

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Background and Aims: Dilation of stenosing Eosinophilic Esophagitis (EoE) is considered a high-risk procedure as perforation rates of up to 9% of patients have been reported. Goal: To systematically evaluate the dilation-associated perforation risk in stenosing EoE.

Methods: A systematic review of the literature was performed using pubmed and Embase. Keywords used were "eosinophilic esophagitis", "dilation", "perforation", and "complications".

Results: From 2002 to 2007 7 case series including 85 patients reported perforations in 5 patients (perforation rate 6%). The highest perforation rate was reported in a series of 36 patients documenting 3 perforations (9%). In 2010 and 2011 three large studies reporting on a total of 404 patients documented a perforation in 3 patients (0.74%). The perforation rate reported in small case series before 2010 was significantly higher compared to the rates since 2010 ($P < 0.001$). The overall perforation frequency is 8/489 patients (1.6%). A median of 3 endoscopic sessions with dilations were performed per patient, thereby leading to a perforation rate of 0.53% per endoscopy. Follow-up information on EoE patients with perforation was available in 6 studies, all patients could be managed conservatively, dilation-associated mortality was zero.

Conclusions: Dilation of stenosing EoE has a much lower perforation risk as reported in earlier case series. The perforation rate per endoscopy (0.53%) is much lower than the one reported for dilation of achalasia (2-4%). Taking into account the latest data, dilation of stenosing EoE can be regarded as a safe procedure.

G2

Macrophages from CD patients are defective in pro-repair function and produce low HGF levels

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Background: We previously reported that granulocyte-macrophage colony-stimulating factor (GM-CSF)-expanded myeloid cells can induce mucosal healing in a mouse model of acute colitis. Promotion of mucosal healing is becoming a major goal in the treatment of Crohn's disease. Our aim in this study is to investigate the pro-repair function of human myeloid cells comparing healthy donors (HD) with Crohn's disease patients (CD) and patients with ulcerative colitis (UC).

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples by Ficoll density gradient. Monocytic $CD14^+$ cells were positively selected and differentiated ex-vivo into macrophages (Mφ). The repair function of PBMCs, $CD14^+$ monocytic cells and macrophages was evaluated in an *in vitro* wound healing assay. Hepatocyte growth factor (HGF) concentration in the Mφ cultures supernatant was evaluated by enzyme-linked immunosorbent assay (ELISA).

Results: PBMCs and $CD14^+$ myeloid cells are not able to promote wound healing at any tested cell concentration. Mφ coming from HD and UC patients are able to induce wound healing and this capacity is mediated by HGF. Remarkably, CD Mφ are not able to promote wound healing and they produce lower levels of HGF compared to HD. Interestingly GM-CSF treatment of CD Mφ during their differentiation restores their pro-repair activity.

Conclusion: For the first time we brought evidence that CD Mφ, unlike HD and UC Mφ, are defective in promoting wound healing. Defective Mφ may contribute to the mucosal healing defects present in CD patients and to the subsequent chronic activation of the adaptive immune response.

G4

How do Swiss Gastroenterologists assess Activity of Inflammatory Bowel Disease in Daily Practice: by Clinical Indices, Endoscopic Activity, or Biomarkers?

Alain M. Schoepfer[1], Alex Straumann[2], Nadine Zahnd-Straumann[3], Stephan Vavricka[4], Christoph Beglinger[2]. [1]University Hospital Lausanne/CHUV, [2]University hospital Basel, [3]Abbott AG, Baar, [4]University Hospital Zurich

Background and Aims: There is an ongoing debate which is the most appropriate way to measure inflammatory bowel disease (IBD) activity (be it by clinical indices, endoscopy, or biomarkers). Accumulating evidence associates mucosal healing with a reduction in IBD-related surgery and hospitalizations. We aimed to investigate which outcome parameters are used in daily practice for IBD monitoring.

Methods: A questionnaire was sent in July 2010 to all board certified gastroenterologists in Switzerland to evaluate the assessment strategy of IBD activity, the items on which therapeutic decisions were based upon, and the kind of biomarkers used for monitoring IBD activity.

Results: Response rate was 57% (153/270). Mean physician's age was 50±9years, mean duration of gastroenterologic practice 14±8years, 52% of them were working in private practice and 48% in hospitals. Seventy-eight percent used clinical activity indices as gold standard for IBD activity assessment, followed by 15% choosing endoscopic activity, and 7% favouring biomarkers. Gastroenterologists based their therapeutic decisions in 70% on clinical activity indices, 24% on endoscopic activity, and 6% on biomarkers. Most frequently used biomarkers were C-reactive protein (94%), complete blood count (78%) and fecal calprotectin (74%).

Conclusions: In daily practice, most IBD patients are monitored based upon their clinical activity. Biomarkers are perceived as less important compared to clinical and endoscopic activity. Similar to activity assessment, also therapeutic decisions are mostly made on the basis of clinical activity indices. The upcoming scientific evidence on the impact of mucosal healing does not yet seem to influence the daily practice of gastroenterologists.

G5

Discriminating Irritable Bowel Syndrome from Inflammatory Bowel Disease: what is the Role of Biomarkers in Daily Practice?

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Background and Aims: Discriminating irritable bowel syndrome (IBS) from inflammatory bowel disease (IBD) can be a clinical challenge as symptoms can overlap. We and others have recently shown that fecal calprotectin (FC) is more accurate for discriminating IBS from IBD compared to C-reactive protein (CRP) and blood leukocytes. We aimed to assess which biomarkers are used by gastroenterologists in their daily practice for discriminating IBS from IBD.

Methods: A questionnaire was sent to all board certified gastroenterologists in Switzerland in July 2010.

Results: Response rate was 57% (153/270). Mean physician's age was 50±9years, mean duration of gastroenterologic practice 14±8years, 52% of them were working in private practice and 48% in hospitals. The following biomarkers were determined for discriminating IBS from IBD: CRP 100%, FC 79%, hematogram (red blood cells and leukocytes) 70%, iron status (ferritin, transferrin saturation) 59%, erythrocyte sedimentation rate 2.7%, protein electrophoresis 0.7%, and alpha-1 antitrypsin clearance 0.7%. There was a trend for using FC more often in private practice than in hospital (P = 0.08). Eighty-nine percent of gastroenterologists considered FC to be superior to CRP for discriminating IBS from IBD, 87% thought that patient's compliance for fecal sampling is high, and 51% judged the fee of USD 60 for a FC test as appropriate.

Conclusions: FC is widely used in clinical practice to discriminate IBS from IBD. In accordance with the scientific evidence, the majority of gastroenterologists consider FC to be more accurate than CRP for discriminating IBS from IBD.

G6

Iron Supplementation Therapy in a Large Swiss Cohort of Inflammatory Bowel Disease Patients: Shift from Oral to Intravenous Therapy over Time

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Background and Aims: The 2007 ECCO guidelines on anemia in inflammatory bowel disease (IBD) favour intravenous (iv) over oral (po) iron supplementation due to better effectiveness and tolerance. Application of guidelines in clinical practice may require time. We aimed to determine the percentage of IBD patients under iron supplementation therapy and its application mode over time in a large IBD cohort.

Methods: Helsana, a leading Swiss health insurance company provides coverage for approximately 18% of the Swiss population, corresponding to about 1.2 million enrollees. Patients with Crohn's disease (CD) and ulcerative colitis (UC) were identified by keyword search from the anonymised Helsana database.

Results: In total, 629 CD (61% female) and 403 UC (56% female) patients were identified, mean retrospective observation time was 20.4 months for CD and 13 months for UC patients. Of the entire study population, 29.3% were prescribed iron. Occurrence of iron prescription was 21.3% in males and 31.2% in females (odds ratio [OR] 1.69, 95%-confidence interval [CI] 1.26-2.28). The prescription of iv iron increased from 2006/2007 (48.8% with iv iron) to 2008/2009 (65.2% with iv iron) by a factor of 1.89.

Conclusions: One third of the IBD population was treated with iron supplementation. A gradual shift from oral to iv iron was observed over time in a large Swiss IBD cohort. This switch in prescription habits goes along with the implementation of the ECCO consensus guidelines on anemia in IBD.

G7

Non-anesthesiologist administered propofol sedation is standard practice for endoscopists in Switzerland: sedation and monitoring trends over 20 years

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Background and Study Aims: Sedation and monitoring practice for routine as well as for advanced endoscopic procedures is constantly changing. The aims of this nationwide survey were 1. to assess present practice among Swiss gastroenterologists, 2. to focus particularly on the use of non-anaesthesiologist administration of propofol (NAAP) and 3. to compare the results to similar data obtained in 1990 and in 2003, thus providing an overview spanning a period of 20 years.

Materials and Methods: A questionnaire (similar to those used in 1990 and 2003) was sent to all 279 Swiss gastroenterologists. The response rate was 78%. Data from 263,370 endoscopies performed during the previous 12 months were primarily analyzed.

esults: In 2010, sedation was used in 83% of esophagogastroduodenoscopies (EGDs) and colonoscopies (compared to 78% and 60% in 1990 and 2003 respectively). The sedative drug used most often was propofol with 158 (72%) endoscopists reporting its use without the assistance of an anaesthesiologist. The drugs were mostly administered by the endoscopy nurse, who was usually the only assistant present in 74% of the endoscopy suites, through an intravenous cannula. Overall sedation-related morbidity was 0.14% and the mortality rate was 0.0018%.

Conclusion: The use of sedation in gastrointestinal endoscopy has increased over the last 20 years. Since 2003 a distinct shift towards the preferred use of propofol can be observed, with the majority of Swiss gastroenterologists using it without the assistance of an anaesthesiologist. This change reflects a successful generalisation of NAAP from the hospital setting to private practice.

G8

How to Assess Histology in Eosinophilic Esophagitis: Standardization by the EEsAI Histopathology Questionnaire

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Background and Aims: The international EEsAI study group is currently developing the first activity index specific for Eosinophilic Esophagitis (EoE). So far histologic assessment in EoE is not standardized but urgently needed to harmonize histologic endpoints in clinical trials. Goal: To develop and evaluate the EEsAI histopathology questionnaire.

Methods: Based on multiple Delphi rounds with national and international (Europe and North America) EoE expert histopathologists and gastroenterologists, we have developed the EEsAI histopathology questionnaire.

Results: The EEsAI histopathology questionnaire takes into account the following items: number of eosinphils per high power field, pattern of inflammation, eosinophil abscesses, basal layer enlargement, and lamina propria fibrosis. Distinct definitions and categories for every item were established by agreement among experts. EoE expert pathologists had a median of 22 minutes to complete the questionnaire and judged it as well feasible. The histopathology questionnaire was piloted in 20 patients and is currently evaluated in a cohort of 150 adult EoE patients.

Conclusions: The EEsAI histopathology questionnaire is the first tool that assesses EoE severity according to clearly defined histologic criteria. These definitions, as well as their categories, established by international EoE expert pathologists, will standardize histologic EoE severity assessment and thereby facilitate the comparison of histologic outcome measures in clinical trials.

G9

Development of the First Disease Activity Index for Eosinophilic Esophagitis: Update on the EEsAI in 2011

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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; 2. Evaluation of the activity index in a first patient cohort; 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. 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 evaluated in a cohort of adult EoE patients since March 2011.

Conclusions: After successful validation, the EEsAI will allow to standardize outcome assessment in EoE trials which will likely lead to its wide applicability.

G10

The Visual Dysphagia Questionnaire: Evaluating the first Tool for Assessing Food Consistency-Dependent Dysphagia in Eosinophilic Esophagitis

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Background and Aims: The international EEsAI study group is currently developing the first activity index specific for Eosinophilic Esophagitis (EoE). None of the existing dysphagia questionnaires take into account the consistency of the ingested food that considerably impacts the symptom presentation. Goal: To develop and evaluate an EoE-specific questionnaire assessing dysphagia caused by foods of different consistencies.

Methods: Based on patient interviews and chart reviews, an expert panel (EEsAI study group) identified internationally-standardized food prototypes typically associated with EoE-related dysphagia. Food consistencies were correlated with EoE-related dysphagia, taking into account potential food avoidance and food processing. This Visual Dysphagia Questionnaire (VDQ) was piloted in 20 patients and is currently evaluated in a cohort of 150 adult EoE patients.

Results: The following 8 food consistency prototypes were identified: soft foods (pudding, jelly), grits, toast bread, French fries, dry rice, ground meat, raw fibrous foods (eg. apple, carrot), solid meat. Dysphagia was ranked on a 4-point Likert scale (0=no difficulties; 3= severe difficulties, food will not pass). First analysis demonstrated that severity of dysphagia is related to the eosinophil load and presence of esophageal strictures.

Conclusions: The VDQ is the first EoE-specific tool for assessing dysphagia caused by internationally-standardized foods of different consistencies. This instrument also addresses food avoidance behaviour and food processing habits. This tool performed well in a pilot study and is currently evaluated in a cohort of 150 adult EoE patients.

G11

A Sensitive Methylation Marker Panel that Discriminates Normal Mucosa from Colorectal Cancer with High Specificity

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Background Promoter hypermethylation is a prominent feature in colorectal cancer (CRC), but cancer-specificity has not been determined for many genes. We aimed to identify novel targets affected by cancer-specific aberrant methylation early in colorectal carcinogenesis. **Methods** By comparing methylation levels in tumor tissue, cancer-associated normal mucosa (CAM) and blood, we established 99% cancer-specific thresholds for seven gene promoters (*FOXF1, CA4, NPY1R, GREM1, IFITM1, hMLH1, MGMT*) and analysed these targets in 106 CRC patients and 31 healthy subjects. **Results** We identified *CA4*, *NPY1R* and *IFITM1* as novel targets of aberrant methylation in CRC. The most sensitive marker *FOXF1* was hypermethylated in 66% of all and in 91% of proximal tumors. The seven marker panel discriminated 87/106 (82%) of all and 30/32 (94%) of right-sided tumors from CAM with ≥ 99% specificity. The methylation frequency and levels of the analysed targets varied considerably in normal mucosa (NM) of healthy subjects. **Conclusions** The identification of a highly cancer-specific marker panel that covers the majority of CRC offers the possibility to monitor the methylation progress of relevant targets early in the colorectal carcinogenesis. Increasing methylation levels might have the potential to identify individuals at risk to develop CRC.

G12

Genome-Wide Profiling of Ageing Associated DNA Methylation in Healthy Population

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Background. Promoter methylation associated gene silencing at CpG sites is a prominent feature in colorectal cancer (CRC). Although, age is the main risk factor of CRC, interindividual methylation variations in normal ageing colorectal tissue are poorly characterized. Identifying their extent in the aging process is important for understanding fundamental dynamics of normal individual epigenomes and their contribution to CRC carcinogenesis. **Methods** We used illumina infinium HumanMethylation27 BeadChip to determine genome-scale DNA methylation in normal mucosa of 41 human donors of age 50 and 75. **Results** Methylation profile classes derived from unsupervised modeling were significantly associated with age (P<0.0001). In total, 653 age-associated differentially methylated CpGs (proximal: 491 CpGs; distal 162 CpGs) were identified. Among them, we found highly significant CpG island–dependent correlations; loci in CpG islands gained methylation with age, loci not in CpG islands lost methylation with age (P<0.001), and this pattern was consistent in both colon segments. Lastly, we found age-associated differentially methylated CpG sites where in physically proximity to genes involved in regulation of transcription. This suggests that specific age-related DNA methylation changes may have quite a broad impact on gene expression in the normal colon. **Conclusions** This work provides insight into epigenetic deregulation by age-related methylation alterations. Our data will be useful for future investigations towards understanding the role of aging associated methylation changes in colorectal tumorigenesis.

G13

Bloating and distension in functional GI disorders result from abdomino-phrenic muscle dyssynergia

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Introduction: During spontaneous bloating episodes, abdominal distension in patients with functional GI disorders results from caudo-ventral redistribution of the abdominal content without intra-abdominal volume increment. In response to experimental gas infusion into the colon, patients experience abdominal distension and show diaphragmatic contraction with abdominal wall muscle relaxation. We aimed to investigate the role of the abdomino-phrenic muscle coordination during spontaneous bloating and to elucidate its contribution to abdominal distension in patients with functional GI disorders.

Methods: In 8 patients (6 with IBS, 2 with Functional Bloating), electromyography (EMG) activity of the anterior wall - internal/external oblique, upper/lower rectus - (via four pairs of surface electrodes, n=8) and the diaphragm (via six ring electrodes over an esophageal tube, n=4) was recorded in erect and supine position during basal conditions and spontaneous bloating (perception grade >2). Abdominal girth was assessed by tape measure and perception was recorded by a graphic rating scale graded from 0 (no perception) to 6 (painful sensation).

Results: During bloating, girth increment (by 4.5±1.1cm, p=0.01) in erect position was accompanied by diaphragmatic contraction (by 23±7%, p=0.04) and relaxation of the internal oblique muscle (by 38±9%, p=0.02) with no significant EMG change of the external oblique (p=0.15), the upper rectus (p=0.40) and the lower rectus (p=0.15). In supine position, girth increased by 2.4±0.7cm (p=0.01) and the diaphragm contracted by 28±7% (p=0.04) while the internal oblique remained unchanged (+0.4±18%, p=0.37). Perception score was higher during bloating both in erect (by 3.2±0.6, p<0.01) and supine position (by 1.6±0.6, p=0.04).

Conclusion: Abdominal distension during spontaneous bloating is an active process driven by diaphragmatic contraction and paradoxical relaxation of the internal oblique muscle.

G14

Mean Corpuscular Volume (MCV) to monitor azathioprine and 6-mercaptopurine in Inflammatory Bowel Disease (IBD) patients.

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Background: Erythrocyte MCV might be used as an inexpensive marker to predict and optimize the efficacy and tolerability of thiopurine therapy in IBD patients. **Aim and methods**: Retrospective observational study aimed to assess the monitoring performances of MCV in patients under thiopurine treatment in the SIBDCS (at CHUV, Clinique la Source Lausanne[2], and Hôpital Neuchâtelois[3]). Inclusion criteria was >3 months AZA or 6-MP treatment. All available MCV and 6TG measurements, among others, were recorded. An IBD flare or event was defined as a composite outcome encompassing treatment change, colonoscopy, histology, CT scan or MRI reports showing active IBD lesions, occurrence of intestinal surgery and hospitalisation. Whether MCV measurements predicted efficacy of thiopurine treatment was investigated by assessing the statistical association between the occurrence of IBD flares/events, and the current or recent MCV values, taking into account the longitudinal aspect of data (nested case-control inspired analysis). **Results**: 140 patients (77 women), mean age 38 years (17-74), with Crohn's disease (n=104) or ulcerative colitis (n=36), mean disease duration 8 years (0.25-36), receiving either AZA (n=125, 54 with 6TG) or 6-MP (n=15) were included. The average probability of observing a flare during a visit was 9.7% (CI95 7.7%-12.3%). Across all visits, taking into account patient-specific variability, it appeared significantly influenced by the MCV, an increase by 10 fl being associated with an odds ratio for flare of 0.73 (CI95 0.55 – 0.97, p=0.03). AZA or 6-MP doses correlated with MCV (p<0.001), but not with the occurrence of flares. MCV correlated as well with 6TG levels (p=0.016), which also predicted flare occurrence (p=0.028). **Conclusions**: Under thiopurine treatment, the evolution of MCV is worth to be observed, as it could contribute to the prediction of the clinical course of IBD patients, in parallel with 6TG blood measurement. A longitudinal model taking into account further patients' characteristics along with MCV to predict the probability of flare recurrence is elaborated.

G15

Single-balloon colonoscopy: Success rate in patients with previous incomplete colonoscopy

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Background:
Infrequently cecal intubation is unsuccessful with standard colonoscopy. Extensive diverticulosis, prior abdominal surgery, female gender und low body mass index are risk factors for incomplete colonoscopy. The use of single-balloon overtube assisted colonoscopy in these situations is only little studied.

Methods:
We performed single-balloon overtube assisted colonoscopy in patients with previous incomplete colonoscopy because of technical reasons. We used the Olympus single-balloon enteroscope SIF-Q180 with overtube.

Results:
Between February 2008 and May 2011, 13 patients (8 females, 5 males; age distribution 38-78y, mean age 64y) were examined in single-balloon overtube assisted technique. The cecum was reached in 100%. There were no pathologic findings in two patients, six patients showed a marked diverticulosis. In five patients, there were one or several polyps found, all of which could be removed. There was one single mucosal defect as a consequence of a polypectomy, which was treated successfully (clipping, prophylactic antibiotics). There were no procedure-associated complications.

Conclusions:
Colonoscopy in single-balloon overtube assisted technique in patients with a previous incomplete standard colonoscopy, shows a very high success rate and is a safe method.

G16

Prospective Study of Contrast enhanced Ultrasound (CEUS) in active Crohn's disease

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Background
Specific vascular and bowel wall patterns are typical for Crohn's disease and have been described already 40 years ago in angiographic studies. We wanted to assess CEUS in active Crohn's disease with a special attention to these patterns.

Methods
We prospectively evaluated 26 inflamed ileum or colon segments in 24 patients. The disease activity was assessed colonoscopically by the endoscopic simplified disease activity score in Crohn's disease. CEUS was performed using an Acuson Sequoia 512 (Siemens) following the intravenous administration of 0.8-1.2 ml SonoVue®.

Results
The submucosal layer is typically rapidly contrasted and the dilated afferent vessels (vasa recta) lie closely together with partial spiral alterations (= **comb sign** which was seen in 20 of 26 inflamed bowel segments). The muscular layer is predominately spared and the subserosal layer is enhancing (= **zoning sign** which was seen in 23 of 26 inflamed bowel segments). Afferent vessels are distorted due to the fibrofatty proliferation in the mesentery. This was detected in 9 of 26 inflamed bowel segements.
Abscesses or mesenteritis were found in 12 bowel segements. Large and tiny fistulas were also easily detected using a high mechanical index in 3 patients.

Conclusions
In active Crohn's disease specific vascular and bowel wall patterns can be depicted. In addition, CEUS gives valuable information on abscess and fistulas. The information gained by CEUS could replace CT scan, MRI and capsule enteroscopy in many cases.

G17

Ischemic colitis: clinical presentation, localisation in relation to risk factors and long-term results

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Background: Ischemic colitis is commonly thought to occur most often in the left hemicolon, close to the splenic flexure due to insufficient blood supply near the Griffith's point. This study investigates the colorectal localisation pattern, the risk factors, and the long term outcome of histologically proven ischemic colitis.
Methods: 49 patients with colonoscopically assessed and histologically proven ischemic colitis were identified on behalf of the pathology database. Long-term results of 43 patients were evaluated retrospectively.
Results: In 27 patients (55%) more than one location was affected. We found 98 affected locations in 49 patients. The distribution of ischemic colitis in our group shows no significantly preferred location. In an exploratory analysis, cecum, ascending colon, and right flexure are affected significantly more often if non-steroidal anti inflammatory drugs intake is documented. No association between smoking, peripheral artery occlusive disease, coronary heart disease, diabetes, or malignant tumor and location of ischemic colitis was observed.
Conclusion: Ischemic colitis seems not to have a predisposing site of occurrence within the colorectum, especially the Griffith's point which was not afflicted significantly more often than other sites. Frequently, ischemic colitis afflicts more than one colonic location. In patients being treated with non-steroidal anti inflammatory drugs, ischemic colitis was observed significantly more often in the right hemicolon. Recurrences of ischemic colitis seem to be rare.

G18

Inflammatory Bowel Disease (IBD) in the elderly: first results from the adult Swiss IBD cohort study (aSIBDCS).

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Background and Aim. Limited data are available on IBD in the elderly. Baseline description of disease pattern and treatment of patients aged ≥60 years with Crohn's disease (CD≥60) or Ulcerative colitis (UC≥60). **Methods.** Retrospective study.

Results. Among the 1818 patients enrolled in the aSIBDCS 156 (8.6%) were CD≥60 and 110 (6.1%) UC≥60. Mean disease duration was 17 years (14 SD), 54% men, mean age 66 (6 SD) for CD≥60 and 14 (13); 59% men, mean age 69 (7 SD) for UC≥60; 50 (2.8%) were diagnosed ≥60 with CD (CDd≥60) and 44 with UC (2.4% UCd≥60).

Location	UC p<0.05						CD p<0.05					
in %	Proctitis		Left c.		Pan-c.		ileal		colic		ileo-colic	
< / ≥60	15	14	43	58	42	28	32	40	33	37	35	23

CD Behaviour in %	B1			B2			B3		
< / ≥ / d≥60	47	49	64	20	21	15	33	30	21

Treatment prescribed, in %, at enrollment, in CD vs UC < / ≥/ d≥60:

	o 5ASA			sys Steroid			o Bud			IM			aTNFα		
CD	16	17	22	12	10	18	8	7	12	52	47	46	29	12	12
UC	55	56	61	19	12	9	4	4	4	35	26	27	8	6	11

o = oral ; 5ASA = Mesalamine ; sys = systemic (oral + i.v.); IM = immunomodulator (azathioprine + 6-mercaptopurine + methotrexate); Bud = Budesonide; aTNFα =Anti TNF-alpha antibody.
In UC < / ≥ / d≥60, rectal 5-ASA was prescribed in 23%, 15%, 6,8%.

Conclusions: Pancolitis is less frequent in elderly UC patients. The CD phenotype is not associated with age. Therapeutic management is very similar in both age groups although anti TNF-alpha antibody treatments are less frequently prescribed in CD patients older than 60.

G19

Profile of anti-microbiota antibody responses in Crohn's disease and Ulcerative colitis

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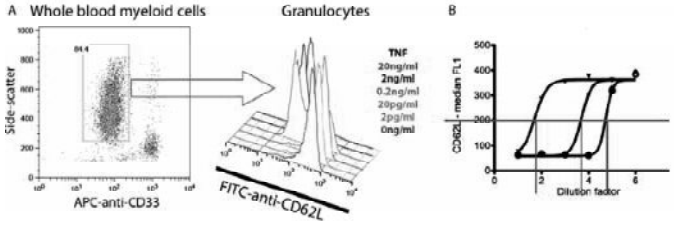
ABSTRACT BODY:
Background:
Crohn's disease and ulcerative colitis are both diseases which manifest as a failed mutualism with the intestinal microbiota, clearly demonstrated by the amelioration of symptoms on diversion of the fecal stream. In Crohn's disease, a large number of reports document the presence of elevated serum antibody responses specific for bacterial and yeast products. We have recently demonstrated in murine models that elevated anti-microbiota immunity is a common sequalae of innate immune deficiency. We therefore compared the spectrum of anti-microbiota immunity in patients with Crohn's disease or ulcerative colitis to functional measurements of innate immune functionality.

Methods:
Anti-microbiota immunity was quantified using a technique that we have developed based on high-affinity binding of serum antibodies to the surface of live bacteria (Figure 1). This binding is then quantified per bacterium by flow cytometry. By carrying out live bacterial staining with dose-titrations of plasma, titration curves can be plotted in a similar manner to classical ELISA titres. To functionally characterise innate immunity, concentrations of innate immune stimuli required to give 50% activation of granulocyte and monocyte CD62L-shedding and oxidative burst production were calculated for each patient. The IBD patient cohort was collected from the outpatient clinic of the Inselspital and Tiefenauspital in Bern and each patient diagnosis was re-confirmed.

Conclusions:
Crohn's disease patients show dramatically elevated IgG and IgA titres specific for gamma-proteobacteria, in particular Klebsiella pneumoniae (Figure 1) whilst Ulcerative colitis patients show highly elevated IgG titres specific for predominantly unculturable fecal bacteria. Innate immune sensitivity of patients varied considerably between individuals with up to 10000-fold differences in sensitivity to TLR1 ligands observed, but no obvious disease-associated trends (Figure 2). Further analysis of reactivity to bacterial species representative of the intestinal microbiota will reveal whether positive associations exist between innate immune sensitivity, anti-microbiota immunity and disease phenotype.



This assay is an extension of an assay developed by von Bernuth et al. Assay plates containing defined dose-titrations of agonists were produced on-bulk and stored at -80°C until required. On receiving a sample, an assay plate was thawed and whole blood pipetted into each well. The plate was incubated at 37°C for 45mins and then blood cells were stained for cell-surface CD62L and CD33 and analysed on the flow cytometer. Granulocyte and monocyte stimulation with TLR-agonists, NLR-agonists, cytokines and whole bacteria results in enzymatic cleavage of CD62L from the cell surface. . Representative raw data. Granulocytes and monocytes are identified based on CD33 expression and side-scatter. B. Median fluorescence intensities are analysed by fitting 4-parameter curves. Inflection points are used to calculate the concentration of ligand or agonist giving 50% decrease in CD62L MFI (LC50. Expressed as ng/ml).

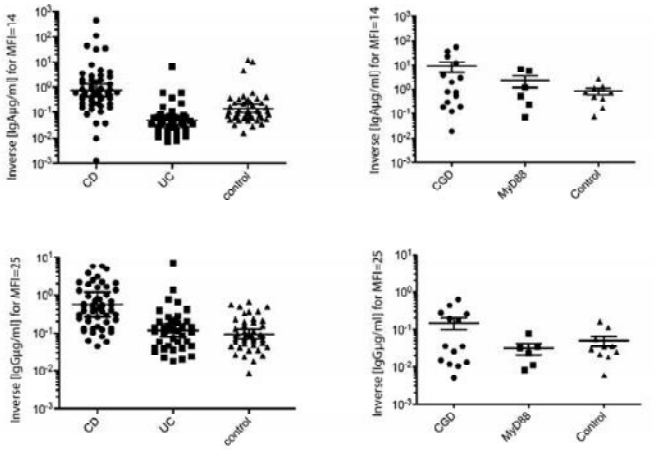


Figure 2: Elevated IgG and IgA titres specific for K. pneumoniae in Crohn's disease (CD) and Chronic granulomatous disease (CGD)

G20

Quantification of meal induced gastric secretion by MRI: Caloric emptying cannot be assessed by changes in gastric content volume

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Background and Motivation: Current methods to assess gastric secretion are invasive and may themselves influence the extent and the dynamics of gastric secretion. The distribution of gastric secretion and the formation of acid layers in the stomach after food intake are important parameters for the detailed understanding of gastroesophageal reflux disease. The aims of this study were 1) the non-invasive quantification of meal induced secretion using a purpose build chocolate test meal and 2) the analysis of the distribution of meal induced secretion and related meal dilution.

Methods: Six healthy fasted volunteers (4males, age: 22-45 years) were examined in right lateral position in a 1.5T whole body MRI System after ingestion of a viscous Swiss chocolate drink test meal (400ml, 450kcal, acid stable, low buffer capacity) containing Gadolinium-DOTA. Gastric content volumes (GCV), meal volumes (MV) and secretion volumes (SV) were assessed (GCV=MV+SV).

Results: The test meal continuously stimulated secretion with a linear net secretion volume increase of +1.1 +/- 0.7 ml/min. In contrast to secretion volumes, meal emptying and thus caloric emptying showed low inter-individual variation and a high caloric, linear emptying rate of - 2.7+/-0.6 kcal/min. Mixing of meal and secretion was heterogeneous and a secretion layer on top of the meal was observed at all times. After 100min gastric content volume (GCV) was 290+/-88 ml, of which a considerable amount was secretion (SV,178+/-80ml),resulting in a dilution of 60+/-12 %.

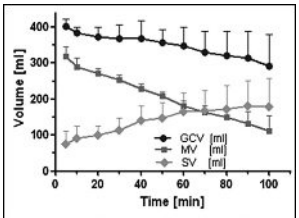

Fig. 1 Dynamics of gastric content volume (GCV), meal volume (MV) and secretion volume (SV). Displayed as mean ± SD.

Conclusion: The purpose-built Swiss chocolate test meal continuously stimulated gastric secretion, resulting in a meal dilution of 60 % after 100min. Despite the rapid linear meal emptying, the continuous stimulation of secretion led to a slower decrease of gastric content volume. Therefore, in the presence of secretion, caloric emptying can not be assessed by changes in gastric content volume. Accurate assessment of meal emptying requires measurement of gastric secretion.

Posters Hepatology

H1

Initial experience with the transjugular renal biopsy: safety and technical considerations.

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Background/Aim: Conventional percutaneous renal biopsy is a risky procedure in the presence of coagulopathy and/or important ascites. We report our initial experience using the transjugular route.

Patients/Methods: 6 patients were referred for a transjugular renal biopsy (TJRB) as part of a diagnostic work-up of renal parenchymal disease. The patients (M/F: 5/1, mean age 55 yrs) had a coexistent chronic liver (n=4), haematological (n=1) or immunological (n=1) disease, with coagulopathy (n=6) associated with ascites (n=2). The procedures were performed through a right jugular vein access, using the renal access and biopsy set (RABS-100; Cook) including a 19-gauge Quick-Core needle. All biopsies were obtained from the right kidney following catheterization of the right renal vein with a 6F multipurpose catheter. Results: The biopsy was unsuccessful in 1 patient (inability to access to the lower pole of the kidney). Specimens allowed a pathological diagnosis in 5 patients. There was one sub-capsular hematoma without associated symptoms.

	Technical success	Tissue acquisition	Histological findings	complications
1	Yes	Medulla	Acute tubular necrosis	None
2	Yes	Glomeruli/medulla	Tubulo-interstitial nephritis, normal glomeruli	None
3	Yes	Glomeruli/medulla	IgA glomerulonephritis	hematoma
4	Yes	Glomeruli/medulla	Glomerulosclerosis/amyloidosis	None
5	Yes	Glomeruli/medulla	IgA glomerulonephritis	None
6	No	-	-	-

Conclusions: In our initial experience, TJRB is feasible and appears as an alternative to the percutaneous approach. Caution is warranteed with regards to postprocedural complications.

H2

Functional Characterization of an NTPase Activity of the Hepatitis C Virus Nonstructural Protein 4B

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Background: Nonstructural protein 4B (NS4B) is the master organizer of hepatitis C virus (HCV) replication complex formation. It is a multispanning membrane protein that has been reported to possess NTPase activity. This enzymatic function has been poorly studied so far and its role in the HCV life cycle is unknown. The present work-in-progress aims at validating and functionally characterizing this activity and its role in the viral life cycle.

Methods: Bioinformatic analyses were performed to identify key residues for site-directed mutagenesis, both in the context of subgenomic replicons as well as recombinant viruses. Mutants were investigated with respect to RNA replication and infectious particle production. In parallel, expression and purification of recombinant wild-type and mutant NS4B proteins are being pursued to characterize enzymatic activity *in vitro*.

Results: Bioinformatic analyses revealed that predicted NTPase features are conserved only in HCV NS4B but not in NS4B from other *Flaviviridae* family members. Alanine substitutions were designed to target predicted key Walker A, B and C motifs. These substitutions affected RNA replication and infectious virus production to varying degrees. Optimization of recombinant protein production is in progress both in bacterial as well as mammalian expression systems.

Conclusions: These studies should yield new insights into the functions of this hitherto poorly characterized viral nonstructural protein and may reveal novel targets for antiviral intervention in the future.

H3

Elevated serum ferritin is an independent predictor of severe liver fibrosis, steatosis, and treatment failure in chronic hepatitis C

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Universities of Lausanne[1], Berne[3], Basel[5], Zürich[7] and Geneva[8], as well as Ospedale Moncucco Lugano[2], Kantonsspital St. Gallen[4] and Hôpital Neuchâtelois[8], Switzerland

Background: Infection with the hepatitis C virus (HCV) is associated with hepatic iron accumulation. We performed a comprehensive analysis of serum ferritin levels and of their genetic determinants in the pathogenesis and treatment of patients with chronic hepatitis C enrolled in the Swiss Hepatitis C Cohort Study (SCCS).

Methods: Serum ferritin levels at baseline of therapy with pegylated interferon-α (PEG-IFN-α) and ribavirin or before liver biopsy were correlated with clinical features of chronic HCV infection, including necroinflammatory activity (N=970), fibrosis (N=980), steatosis (N=886) and response to treatment (N=876). The association between high ferritin levels (> median) and the endpoints was assessed by logistic regression. In addition, a candidate gene analysis as well as a genome-wide association study (GWAS) of serum ferritin levels were performed.

Results: Serum ferritin > sex-specific median was one of the strongest pre-treatment predictors of failure to achieve SVR (P<0.0001, OR=0.46, 95% CI=0.34-0.60). This association remained highly significant in a multivariate analysis (P=0.0001, OR=0.32, 95% CI=0.18-0.57), with an odds ratio comparable to that of *IL28B* genotype, and persisted after adjustment for duration of infection. Additional independent predictors of nonresponse were viral load, HCV genotype, presence of diabetes, and liver fibrosis stage. Higher serum ferritin levels were also independently associated with severe liver fibrosis (P<0.0001, OR=2.67, 95% CI=1.66-4.28) and steatosis (*P*=0.0034, OR=2.34, 95% CI=1.33-4.12), but not with necroinflammatory activity (*P*=0.3). No significant genetic determinants of serum ferritin levels were identified.

Conclusions: Elevated serum ferritin levels are associated with advanced liver fibrosis, hepatic steatosis, and poor response to IFN-α-based therapy in chronic hepatitis C, independently from *IL28B* genotype.

H4

Evolution of liver biopsy findings at 4 weeks in patients with alcoholic liver disease in the bone marrow stem cell therapy trial

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In patients with alcoholic steatohepatitis (ASH), granulocyte macrophage colony stimulating factor (GCSF) is associated with increased tissue neutrophils and liver cell proliferation (*Hepatology 2008;48:221*). Histological changes at 4 weeks after GCSF + bone marrow stem cell transplantation (BMSCT) are unknown. Patients/Methods: we studied paired liver biopsies from 52 (26 in each treatment arm) of the 58 patients included in the BMSCT trial, obtained at baseline and 4 weeks after standard medical therapy (SMT) alone or associated with a 5-day course of GCSF followed by BMSCT. We performed a semi-quantitative scoring of steatosis *(< 33%*: 1; < *66%*: 2; > *66%*: 3) (*microvesicular steatosis present*: 1 point), inflammation (*portal* + *lobular* : max 4 points), fibrosis (max 4 points), hepatocyte ballooning (*few cells*: 1; *prominent*: 2), as well as the ductular reaction (DReaction) (*absent*: 0; *focal*: 1; *clusters < 50% of fields*: 2; > *50% of fields*: 3), being considered as a marker of liver cell proliferation, while blinded to patients' characteristics and treatment allocation. Results: There was no biopsy-related morbidity. A minority of patients resumed alcohol consumption: Results given as mean ± SEM, * p < 0.001; ** p < 0.05.

	BMSCT (0-4 wks)		**SMT** (0-4 wks)	
Steatosis	2.69±0.18	0.88±0.19*	2.6±0.21	0.5±0.1*
Inflammation	2.5±0.12	2.03±0.10	2.43±0.15	2.15±0.11
Ballooning	1.42±0.6	0.81±0.8**	1.54±0.7	0.9±0.8
Fibrosis	3.93±0.4	3.92±0.4	4	4
DReaction	1.65±0.7	1.65±0.6	1.5±0.6	1.35±0.7

Conclusions: In this group of patients with decompensated alcoholic liver disease, most of whom with ASH, there is a significant reduction in steatosis after 4 weeks independent of treatment allocation. Immunohistochemical studies will allow to better characterize cells within the ductular reaction.

H5

Combined Antiviral Therapy for Hepatitis C with Pegylated Interferon Alpha and Ribavirin is Not Less Effective in Elderly Patients

Pascal Frei[1], Anna Katharina Leucht[1], Ulrike Held[1], Reto Kofmehl[1], Monika Rau[1], Tilman Gerlach[2], Francesco Negro[3], Markus Heim[4], Darius Moradpour[5], Andreas Cerny[6], Jean-François Dufour[7], Beat Müllhaupt[1], Andreas Geier[1] and Swiss Hepatitis C Cohort Study Group

1) Zürich, USZ and Horton Zentrum; 2) St. Gallen; 3) Genf; 4) Basel; 5) Lausanne; 6) Lugano; 7) Bern

Background: The chance to achieve a sustained virological response (SVR) to antiviral hepatitis C therapy depends on viral and host characteristics. Age is frequently discussed as negative predictive host factor. However, elderly patients often show relevant fibrosis, making it difficult to interpret age as an independent predictive factor. Methods: From the framework of the Swiss hepatitis C cohort, we collected data from 67 hepatitis C patients 60 years or older who had been treated with PEG-interferon and ribavirin. 450 patients younger than 60 years served as control group. We analyzed host factors (age, gender, fibrosis, haemoglobin, depression, earlier hepatitis C treatment), viral factors (genotype, viral load) and treatment course (early virological response, end of treatment response, SVR). Generalised estimating equations (GEE) modelling was used for the primary end point (SVR), with young or old age as independent variable and gender, presence of cirrhosis, genotype, earlier treatment and viral load as confounders. SVR was analysed in young and elderly patients after matching for confounders. Additionally, classification tree analysis was done in elderlies using these confounders. Results: GEE model showed that age had no influence on achieving SVR (Odds ratio 0.91). Confounders influenced SVR as known (presence of cirrhosis, genotype 1/4, previous treatment and high viral load >600'000 IE/ml as negative predictive factors). SVR was not different in 59 elderly and 59 matched young patients (54.2% and 55.9%, respectively; p=0.795). The classification tree-derived best criterion for SVR in elderly patients was genotype. Only in genotype 1/4, further criteria were relevant (presence of cirrhosis and viral load <600'000 IE/ml in non-cirrhotic patients). Conclusions: In the SCCS cohort, age was not a relevant predictive factor for achieving SVR, when confounders were taken into account. Since life expectancy in Switzerland at age 60 is more than 22 years, hepatitis C therapy is reasonable in elderly patients with known relevant fibrosis or cirrhosis, because it improves survival in elderly patients above 60 years [Ikeda, Am J Med 2009].

H6

Hepatic Manifestations of Wilson Disease - CHUV Experience 2005-2010

Philippe Hiroz[1], Claudia Willheim[2], Anca T. Antonino[1], Joakim Delarive[1], Christopher Doerig[1], Christian Felley[1], Isabelle Pache[1], Paul Wiesel[1], Emiliano Giostra[3], Peter Ferenci[2] and Darius Moradpour[1]

[1]Div. of Gastroenterology and Hepatology, CHUV, University of Lausanne, CH-1011 Lausanne, [2]Dept. of Internal Medicine III, Gastroenterology and Hepatology, Medical University of Vienna, A-1090 Vienna, [3]Div. of Gastroenterology and Hepatology, HUG, University of Geneva, CH-1211 Geneva.

Background and aim: Wilson disease (WD) is an inherited disorder of hepatic copper excretion leading to toxic accumulation of copper in the liver as well as the brain, cornea, and other organs. The defect is due to mutations of the copper-transporting ATPase ATP7B. Here, we describe the adult cases of hepatic WD diagnosed at the CHUV between 2005 and 2010.

Methods: Clinical manifestions, results of diagnostic tests, and follow-up of adult patients with hepatic WD were recorded systematically.

Results: Seven new adult cases of hepatic WD were diagnosed in our center between 2005 and 2010. Three were women and 4 men, with a median age at diagnosis of 24 (range, 18-56) years. Three patients presented with acute liver failure (ALF), three with persistently elevated liver function tests, and one with advanced cirrhosis. None had neurological manifestations. Only one patient, presenting with ALF, had a Kayser-Fleischer corneal ring. Median ceruloplasmin levels at diagnosis were 0.13 (range, <0.03-0.30) g/l, median 24 h urinary copper excretion 6.3 (range, 0.4-62.0) μmol/24 h, and median hepatic copper concentration 591 (range, 284-1049) μg/g. At least one mutation in the *ATP7B* gene was identified in all patients. Allelic frequency of the common H1069Q mutation was 14%. Two patients presenting with ALF and the one with advanced cirrhosis underwent successful liver transplantation. One patient with ALF recovered under chelator therapy. D-penicillamine was used as first-line chelator treatment, with a switch to trientine due to adverse effects in 2 out of 4 patients under long-term treatment.

Conclusions: The clinical presentation of WD and the performance of diagnostic tests are variable. A high index of suspicion in clinically compatible situations is key, with a combination of tests allowing the diagnosis of WD.

H7

SUBANALYSES OF THE TELAPREVIR LEAD-IN ARM IN THE REALIZE STUDY: RESPONSE AT WEEK 4 IS NOT A SUBSTITUTE FOR PRIOR NULL RESPONSE CATEGORIZATION

Beat Müllhaupt[1], Graham.R. Foster[2], Stefan Zeuzem[3], Pietro Andreone[4], Stanislas Pol[5], EricJ. Lawitz[6], Moises Diago[7], Stuart Roberts[8] Paul J. Pockros[9], Zobair Younossi[10], Isabelle Lonjon-Domanec[11], Rolf Van Heeswijk[12], Sandra de Meyer[12], Maria Beumont[12] and Gaston Picchio[13].

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Introduction: On treatment, a poor therapeutic response to peginterferon(P)/ribavirin(R) is defined as a < 1 log10 decline in viral load at week 4. Null response (NR) to a current or prior course of PR is defined as a < 2 log10 decline in HCV RNA at week 12. The FDA adopted the week 12 NR definition in its recent draft guidance. The REALIZE study uniquely enrolled classically defined prior NR, partial responders and relapsers, and included an arm with a PR lead-in (L-I) phase. This design allows a comparison of on treatment response after 4 weeks of PR with prior response categories, including a comparison of 'null response', as well as the relationship between < or ≥1 log10 RNA decline and SVR in response to T/PR treatment.

Methods: Patients in the lead-in arm (N=240) received 4 weeks of PR followed by Telaprevir (T) 750 mg 8 hourly for 12 weeks combined with PR followed by 32 weeks of PR alone. Control patients (N=121) received 48 weeks of PR. All patients received pegylated interferon alfa-2a.

Results: 10% of prior relapsers and 31-40% of partial responders (shaded cells) had < 1 log10 decline in HCV RNA at week 4 in the control and L-I arm, respectively. SVR rates in the T L-I arm among prior relapsers and partial responders were higher (62% and 56%, respectively; combined SVR=58%) than in prior week 12 NR who experienced < 1 log10 decline in HCV RNA (15%). Although patients with ≥1 log10 response at end of the L-I phase had the highest SVR rates, SVR in T/PR patients with < 1log10 was considerably higher (62-15%) than control (0%).

			Results in REALIZE study				
	Prior response	N	% (n) Pts. with <1log at week 4	% SVR among pts. with <1log at week 4	% (n) Pts. with ≥1log at week 4	% SVR among pts. with ≥1log at week 4	% Overall SVR
Control Arm PR	Relapsers	61	10 (6)	0	90 (55)	27	24
	Partial Responders	26	31 (8)	0	69 (18)	22	15
	Null responders	34	68 (23)	0	32 (11)	18	5
Lead-in Arm T/PR	Relapsers	126	10 (13)	62	90 (113)	94	88
	Partial Responders	45	40 (18)	56	60 (27)	59	54
	Null responders	69	59 (41)	15	41 (28)	54	33

Abstract was presented at EASL 2011

Conclusions: Poor interferon responders on treatment (< 1 log10 decline in HCV RNA at week 4) are not the same as prior PR NR (< 2 log10 at week 12). SVR rates in T/PR patients were higher than control irrespective of their response (< or ≥1 log10) at the end of the L-I phase. Safety findings in the T arm were similar irrespective of week 4 response.

H8

THE PHARMACOKINETIC INTERACTION BETWEEN METHADONE AND THE INVESTIGATIONAL HCV PROTEASE INHIBITOR TELAPREVIR

Rolf van Heeswijk[1]*, Ann Vandevoorde[1], Peter Verboven[2], Griet Boogaerts[1], Els De Paepe[1], Rodica van Solingen-Ristea[1], and Maria Beumont[1]
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Background: A proportion of HCV-infected patients receive methadone maintenance therapy. We investigated the pharmacokinetic interaction between methadone and telaprevir, an investigational HCV NS3·4A protease inhibitor for the treatment of chronic HCV infection, and the effect on the pharmacodynamics of methadone.

Methods: This was an open-label, single-sequence clinical trial in HCV-negative volunteers on stable, individualized, methadone maintenance therapy. Telaprevir 750mg every 8 hours was coadministered with methadone for 7 days. Pharmacokinetic profiles of R- and S-methadone were measured over the 24-hour dosing interval on Day -1 (methadone alone, reference) and on Day 7 of telaprevir co-administration (test). The unbound fraction of R-methadone was measured in pre-dose plasma samples before and during telaprevir co-administration. All medications were taken with food. Least square means (LSMeans) and associated 90% confidence intervals (CIs) of treatment ratios (test/reference) were calculated based on log-transformed pharmacokinetic parameters. Symptoms of opioid withdrawal were evaluated throughout the study (questionnaires and pupillometry).

Results: Eighteen volunteers were enrolled; 2 discontinued prior to receiving telaprevir. Individual methadone dosages ranged from 40-120mg/day (median 85mg). The LSMeans ratio (90% CIs) of the Cmin, Cmax and AUC24h for R-methadone was, respectively, 0.69 (0.64-0.75), 0.71 (0.66-0.76) and 0.71 (0.66-0.76). The AUC ratio of S-/R-methadone was comparable before and during coadministration of telaprevir (0.90, 90% CIs 0.86-0.94), indicating lack of a stereo-specific effect. The unbound R-methadone was tested in 13 volunteers and increased from 7.92% to 9.98% during co-administration of telaprevir. The estimated median unbound Cmin of R-methadone, however, was comparable before (10.63ng/mL) and during co-administration of Telaprevir (10.45ng/mL). There were no discontinuations due to adverse events. During co-administration of telaprevir, fewer volunteers experienced withdrawal symptoms and the median resting pupil diameter was smaller, compared with treatment with methadone alone.

Conclusions: Although total exposure to R-methadone (active form) was reduced by approximately 30% during telaprevir co-administration, there was no indication of opioid withdrawal. This is consistent with the observation that unbound minimal concentrations of R-methadone were not affected by telaprevir. These findings suggest that no a-priori adjustment of the methadone is required when initiating telaprevir. However, clinical monitoring is recommended as individual dose modifications may be necessary.

H9

IL28B variants at marker *rs8099917* associated with poor HCV clearance protect against liver inflammation and fibrosis progression in patients infected with non-1 HCV genotypes

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University Hospitals of [1]Lausanne, [7]Geneva, [8]Berne, [9]Zurich, [11]Basel; [2]University of Lausanne; [3]SIB, Lausanne; [10]Canton Hospital, St Gallen; [12]Clinica Moncucco, Lugano; [13]Pourtalès Hospital, Neuchâtel; [14]Cantonal Institute of Microbiology, Bellinzona; [4]Université Descartes, [5]Pitié-Salpetrière Hospital, [6]Cochin Hospital, Paris, and Saint-Joseph Hospital, Marseille

Background & Aims: *IL28B* variants are associated with spontaneous and treatment-induced clearance of HCV, two processes requiring the host immune response activation. Liver inflammation is believed to mirror such activation, but its relationship with *IL28B* polymorphisms is unknown. **Methods:** We analyzed the association between *IL28B* variants and histology in 2335 HCV-infected Caucasian patients. Phenotypes included necroinflammatory activity (N=1098), fibrosis (N=1527), fibrosis progression rate (FPR, N=1312) and rate of HCC development (N=1915). **Results:** The rare G allele at *IL28B* marker *rs8099917* (previously shown to be at risk of treatment failure) was associated with lower activity (P=0.04) and lower fibrosis (P=0.02). Most striking associations were observed in patients infected with non-1 genotypes (P=0.003 for activity, P=0.001 for fibrosis and P=0.02 for FPR), where ORs of developing necroinflammation, fibrosis and rapid FPR for genotype GT or GG vs. TT were 0.48 (95% CI 0.30-0.78), 0.43 (0.26-0.70), and 0.56 (0.35-0.92). *IL28B* polymorphisms did not predict HCC development. **Conclusions:** In chronic hepatitis C, patients with *IL28B* variants at marker *rs8099917* associated with poor clearance have less liver inflammation and fibrosis progression, especially when infected with HCV non-1 genotypes.

H10

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

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[1]Department of Pathology and Immunology, University of Geneva, [2]Divisions of Clinical Pathology and of [3]Gastroenterology and Hepatology, University Hospital, Geneva

Backgrounds and aims - In humans, infection by the hepatitis C virus (HCV) induces several complex physiopathological changes leading, among others, to insulin resistance. 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 cause uninfected cells to become insulin resistant via secretion of soluble effectors.
Methods - We collected conditioned medium of HCV-infected hepatoma cells (ihCM). The effect of ihCM on naive hepatoma cells, adipocytes and myocytes metabolism was assessed by studying insulin signalling integrity, metabolic response upon insulin stimulation and secretion profile by a combination of real-time PCR and ELISA.
Results - We found that ihCMs impede the capacity of insulin to induce PKB phosphorylation (S473 and T308) and downstream effectors (AS160, GSK3β, FoxO1) in HepG2 cells and primary human adipocytes in a HCV genotype-specific manner. In addition, adipocytes cultured with ihCMs have an alteration of their endocrine function, characterized by an upregulation of cytokines (IL-8, RANTES).
Conclusions - Our data suggest that HCV-infected cells are able to induce insulin resistance in uninfected cells. The consequences of such defects in adipocytes metabolism have to be addressed but may additionally affect the metabolic responses of both infected and non-infected cells via a feed-forward mechanism.

H11

Liver Kidney Microsomal Type 1 Antibodies Are Associated With Reduced CYP2D6 Function in Patients with Chronic Hepatitis C Infection

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Background - Liver Kidney Microsomal type 1 (LKM-1) antibodies have been shown to decrease the CYP2D6 activity *in vitro*. We investigated whether LKM-1 antibodies might reduce CYP2D6 activity also *in vivo*. **Methods -** All anti-HCV-positive patients enrolled in the Swiss Hepatitis C Cohort Study (SCCS) with LKM-1 antibodies were assessed: ten were eligible and matched for anthropometric and clinical features with LKM-1-negative patients. Patients were genotyped for CYP2D6 variants to exclude individuals with a poor metabolizer genotype: all patients had a CYP2D6 extensive metabolizer genotype. CYP2D6 activity was measured using the dextromethorphan/dextrorphan (DEM/DOR) metabolic ratio to classify patients in four activity phenotypes (ultrarapid, extensive, intermediate and poor metabolizers). The concordance between real phenotype based on DEM/DOR ratio and predicted phenotype from genotype was examined in LKM-1 positive and negative patients. Groups were compared with respect to the DEM/DOR metabolic ratio. **Results -** The real phenotype was concordant with predicted CYP2D6 phenotype in 7 (70%) LKM-1 negative but in only 3 (30%) LKM-1 positive patients. The remaining cases presented a phenotype switch to an intermediate (six cases) or a poor (one case) metabolizer CYP2D6 phenotype. The median DEM/DOR ratio was six-fold higher in LKM-1 positive than in LKM-1 negative patients (0.096 vs. 0.016, p=0.004), indicating that CYP2D6 metabolic function was significantly reduced in the presence of LKM-1 antibodies. **Conclusions -** In most chronic hepatitis C patients with LKM-1 antibodies, the CYP2D6 metabolic activity was on average drastically reduced by 80%. The impact of LKM-1 antibodies on CYP2D6-mediated drug metabolism pathways warrants further studies.

H12

Searching for Novel Cellular Targets of the Hepatitis C Virus NS3-4A Protease

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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 ongoing study is to identify novel cellular targets of the NS3-4A protease.

Methods: Cell lines inducibly expressing the NS3-4A protease were established using a tetracycline-regulated gene expression system. Cells were analyzed in basal as well as interferon-α-stimulated states. Two-dimensional difference gel electrophoresis (2D-DIGE) and stable isotopic labeling using amino acids in cell culture (SILAC) proteomics analyses coupled with mass spectrometry were employed to search for cellular substrates of NS3-4A.

Results: A number of candidate cellular targets have been identified by these proteomics approaches. These are currently being validated by different experimental techniques. In parallel, we are in the process of further defining the determinants for substrate specificity of the NS3-4A protease.

Conclusions: The identification of novel cellular targets of the HCV NS3-4A protase should yield new insights into the pathogenesis of hepatitis C and may reveal novel targets for antiviral intervention.

Posters Surgery

S1

Laparoscopic gastric pouch and remnant resection in refractory anastomotic ulcers after Roux-Y Gastric Bypass

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Background: Anastomotic ulcers occur in 0.6 to 16 % after laparoscopic Roux-Y-Gastric Bypass (LRYGB). Initial therapy aims at eliminating medical risk factors and inhibition of gastric acid secretion. Although up to one third of these patients undergo a surgical revision, in 10% anastomotic ulcers still recur.

Methods: We report a case of an insidious marginal ulcer refractory to both medical therapy and surgical revision of the gastrojejunostomy, which was treated by a novel approach.

Results: In a 50 year male patient after LRYGB anastomotic ulcera kept recurring after medical treatment. After exclusion of underlying medical and surgical risk factors the gastrojejunostomy was revised. Nevertheless, ulcers recurred one month later. Finally, the gastric pouch as well as the gastric remnant were laparoscopically resected and a esophagojejunostomy with a Roux-Y reconstruction was performed (Figure1). This resulted in a sustained remission.

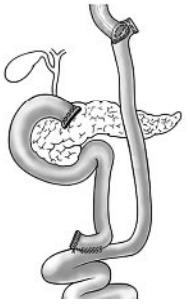

Figure 1

Conclusions: This innovative approach has proven to be effective in the management of a refractory anastomotic ulcer and might therefore represent a valuable option when simple revison of the gastrojejunostomy fails.

S2

Cervico-Mediastinales Emphysem nach STARR-Operation

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Einleitung:
Die STARR Prozedur (Stapled Transanal Rectal Resection) ist ein bewährter, transanaler Approach zur Behandlung verschiedener organischer Ursachen des Obstruktiven Defäkationssyndromes (ODS), wie u.a. der Intussuszeption und der Rektozele. Obwohl die Prozedur generell als gut verträglich gilt, sind in der Literatur lebensbedrohliche Komplikationen bis hin zu pelviner Sepsis und nekrotisierender Fasziitis beschrieben.

Fallpräsentation:
Eine 39-jährige anorektische Patientin (BMI 14,7 kg/m2) mit einer relevanten Hypalbuminämie von 22g/l (34-50g/l), Prä-Albumin 0.05g/l (0.2-0.4 g/l) wird wegen eines ODS, bei okkultem Rektumprolaps, mit einer STARR-Operation behandelt. Schon am 1. postop. Tag erfolgte die Entlassung gegen Verzichtschein. Notfallmässiger Wiedereintritt am 4. postop. Tag mit Fieber 38.1°C, ano-rektalen Schmerzen und erhöhtem CRP 85.2 mg/l (< 3.0mg/l). Computertomografisch findet sich ein retroperitoneales Emphysem vom kleinen Becken bis cervikal reichend. Proktoskopisch kann ein kleines Leck in der dorsalen Staplernaht gefunden werden.
Das schliesslich erfolgreiche Management beinhaltete eine Erweiterung des Lecks und die Einlage eines Endosponges, Nahrungskarenz und parenterale Ernährung, sowie eine antibiotische Therapie mit Tazobac®. Nach 14 Tagen konnte die Patientin in gutem Allgemeinzustand entlassen werden und zeigt 8 Wochen später eine normale Defäkation ohne okkulten Prolaps.

Konklusion:
Bei gegebener Indikation ist die STARR-Operation eine bewährte und gut verträgliche Methode in der Behandlung des ODS. Schwerwiegende Komplikationen sind bei besonderen Ausgangslagen möglich und verlangen nach spezieller Aufmerksamkeit und sicheren Lösungsstrategien.

S3

Sigmoido-rectal invagination : preliminary sign of colonic cancer ?

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Background : Intestinal intussuception in the adult is a rare occurrence (1 to 5 % of all intestinal occlusions). that is often associated with malignancy. It is generally associated with a causal lesion, allowing the peristaltic movements of the bowel to induce invagination. Causes are multiple and include : tumours, begnin and malignant, adhesions, Meckel's diverticulum, foreign bodies and endometriosis. A cause is found in 70-90% of cases. This case report illustrates a typical case operated in our unit, and demonstrates the use of correct clinical and oncological principles as applied to adult intestinal invagination.
Method: Female patient of 37 years of age, mother of two, no previous medical or surgical history. Following three weeks of lower abdominal and pelvic pain, followed by three days of diarrhoea, clinical anorexia without nausea or vomiting and two episodes of painful exoneration with hematochezia requiring manual reduction of what the patient describes as an « anal prolapsus ». She is seen electively by the gastroenterologist for colonoscopy,Family history for colon or other cancers was negative.On clinical examination patient was stable and apyretic. Slightly bloated abdomen with no signs of guarding or abdominal tenderness. Rectal examination revealed a large rectal mass of approx. 5 cm in diameter, extending towards the high rectum. Painless. At colonoscopy, important rectal mass of unknown origin with visual signs of mucosal necrosis.Hydro soluble contrast liquid enema was attempted, but did not obtain reduction of the suspected invagination nor provide adequate imagery.Intravenous contrasted abdominal spiral CT-scan revealed a sigmoido-rectal invagination over a distance of approx. 10 cm. with upstream dilation of the large bowel and ascitis. No evident sign of tumour.
Results:A midline laparotomy was performed, confirming sigmoido-rectal invagination. The starting point was on the highest point of the sigmoid loop and extended into the replenished rectum. To avoid the risk of extensive rectal resection, we opted for manual reduction which was easily obtained by gentle traction and manual pressure on the rectum. This confirmed a tumoral mass on the anti mesenteric verge of the sigmoidorectal junction as causal. The anti mesenteric colic serosae was retracted but not clearly invaded (T3).Oncological high anterior resection was done, with immediate side to end stapled sigmoido rectal anastomosis with protective loop ileostomy.Post operative course was uneventful. Patient was discharged on day 8.
Pathological analysis revealed a moderately differentiated colorectal adenocarcinoma without serosal perforation. Final TNM stage was: pT3 N0 (0/28) M0.Common immunohistochimic markers for colonic cancer were negative.
Conclusion : We present a fully iconographised typical presentation of intestinal invagination in the adult. We also review recent literature and compare to paediatric surgery attitudes.

S4

Single-port laparoscopic total proctocolectomy and ileal pouch-anal anastomosis (IPAA): a case-matched analysis.

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Aim: To describe our experience with Single-Port Laparoscopic Surgery (SPLS) for proctocolectomy and IPAA.

Material: Five consecutive SPLS patients were matched (1:2) to laparoscopic patients (LAP) using 4 trocars controlling for age, gender and BMI. SPLS were performed with the use of a 5mm camera and traditional laparoscopic instruments via a port placed at the planned ileostomy site.

Results: There was no conversion in the SPLS group and one conversion in the LAP group. There was no difference regarding age between SPLS and LAP (35 yrs vs. 34 yrs, p=0.7) or BMI (21.5 kg/m2 vs. 22.1 kg/m2, p=0.7). SPLS operations were shorter by 25 minutes (p=0.2). SPLS patients had less pain at POD#2 (VAS 0.6 vs. 3.7, p=0.01) with no difference in analgetic use (p=0.1). Interestingly, ileostomy output was higher in the SPLS group at POD#2 (1644 vs. 525ml, p=0.03) and POD#3 (1714 vs. 425ml, p=0.016). One small bowel obstruction occurred in each group (grade 1 and grade 3a) and one wound infection in LAP (grade 2). Hospital stay was comparable between the groups (7 vs. 10 days, p=0.1).

Conclusion: SPLS seems to be feasible and save for proctocolectomy and IPAA.

S5

Intraoperative complications of laparoscopic colorectal resections: Did we get better?

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Aim: To investigate the incidence of intra-operative complications in laparoscopic colorectal surgery over an 11 year period.

Materials and Methods: Analysis of 3'928 patients undergoing elective laparoscopic colorectal resection from 1995-2006 based on the prospective database of the Swiss Association of Laparoscopic and Thoracoscopic Surgery.

Results: Overall, 379 intra-operative complications occurred in 329 patients (8.4%). 163/379 (43%) were surgical and 216 (57%) were non-surgical complications. Surgical complications were organ lesions (n=63; incidence of 1.6%), bleeding (n=59; 1.5%), lesion by puncture (n=28; 0.7%) and intra-operative anastomotic leakage (n=13; 0.3%). Of note, 11% of intra-operative organ/puncture lesions requiring re-intervention were missed intra-operatively. Non-surgical complications were problems with equipment (n=12; 73.2%), anaesthetic problems (n=30; 0.8%) and various (n=59; 1.5%). Over time, the rate of intra-operative complications decreased, but not significantly (11.6% to 7.2%, p=0.07). However, the rate of intra-operative complications requiring conversion significantly decreased from 12.5% to 1.8% (p<0.001). Patients with an intra-operative complications had a significantly higher rate of postoperative local and general complications (41.2% and 32.9% vs. 18.0% and 17.2%, p<0.001 and p< 0.001, respectively).

Conclusions: Intra-operative complications in laparoscopic colorectal resections still occur in 8% of patients and are associated with an increased post-operative morbidity.

S6

Transanal endoscopic microsurgery for benign and malignant rectal lesions is a safe procedure for well selected patients. A 4-years experience of a single center.

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Transanal Endoscopic Microsurgery (TEM) is an effective surgical procedure for benign disease and early rectal cancer in selected patients. Aim of this study is to evaluate the indications, procedure, complications and outcome for patients who underwent TEM.

31 patients underwent TEM from 2006 to 2011, for benign adenoma (18), local rectal cancer (Tis) (4), invasive rectal cancer (2T1, 4T2, 1T3), and neuroendocrine tumors (2). The median distance from anal margin was 8 cm (4-13 cm), the median diameter of the lesion was 3.5cm (2-10 cm).

The median operative time was 56 min. (16-106 min.). No conversion was needed. The overall complication rate was 13%. Median postoperative stay was 3 days (1-21 days). Postoperatively, one patient presented local pain, and two patients intermittent diarrhea, symptoms resolved at three months. During long-term follow-up, benign local recurrence were noted in two patients. Two patients with invasive carcinoma underwent salvage low anterior resection. Local recurrence of carcinoma was found at 1 year in one patient.

In well selected patients, TEM is a safe treatment option for benign and early stage malignant lesions of the rectum. Since only few patients can be selected, surgical experience with TEM is mandatory to achieve good results.

S7

Predictability of complications after esophageal resection by means of the Amsterdam nomogram.

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Objective. Aim of this study is to externally validate the recently developed Amsterdam nomogram for the prediction of complications after esophagectomy.

Methods. We studied 43 consecutive patients who underwent esophagectomy for cancer from 2007 to 2010. The following six parameters were used to predict the incidence and severity of postoperative complications: age, myocardial infarction, stroke/TIA, FEV1, ECG changes, operative technique. Based on the calculated score patients were classified as low, intermediate and high risk.

Results. In our medium-volume center, morbidity rates were comparable to high-volume European centers. The nomogram presented a good calibration for outcome prediction in medium and high-risk patients. However, its discriminative ability did not reach statistical significance.

Conclusions. A valid prognostic system for complications after esophagectomy could guide decision-making concerning treatment modalities, surgical technique as well as need for preoperative intervention for patients identified as 'high risk'.

S8

Die Nuck'sche Zyste – seltene Differentialdiagnose bei weiblicher inguinaler Schwellung

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Background: Die Nuck'sche Zyste ist Folge eines persistierenden Processus vaginalis bei Frauen. Wie beim Mann, wo die Hydrocele resultiert, kommuniziert die häufigste Form nicht mit der Peritonealhöhle. Eine Nuck'sche Zyste ist aber über die gesamte Länge des Lig. rotundum möglich und in 1/3 der Fälle mit einer Inguinalhernie kombiniert.

Methods / Results: Bei einer 22-jährigen Patientin mit vor 4 Wochen nach dem Joggen erstmals bemerkter inguinaler, indolenter, nicht reponierbarer 3x2x1 cm grosser Schwellung links zeigte sich sonographisch eine mehrkammerige Zyste im Leistenkanal. Bei Verdacht auf Nuck'sche Zyste erfolgte deren Exzision über einen inguinalen Zugang. Da die mehrkammrige Zyste nur schlecht vom Lig. rotundum abgrenzbar war, musste dieses mitreseziert werden. Eine Inguinalhernie lag nicht vor. Bei erweitertem inneren Leistenring führten wir jedoch eine Netzeinlage analog Lichtenstein durch. Histologisch fand sich eine peritoneal ausgekleidete Zystenstruktur, mit glatten und quergestreiften Muskelanteilen, zahlreichen Gefässen und älterer Einblutung, vereinbar mit einer Nuck'schen Zyste.

Conclusion: Trotz ihrer Seltenheit ist die Nuck'sche Zyste bei weiblicher inguinaler Schwellung eine Differentialdiagnose zur Hernie, zu inguinalen Lymphknoten, Weichteiltumoren und Aneurysmen. Die Bildgebung mittels Ultraschall und ev. CT oder MRI dient dem Ausschluss von Differentialdiagnosen sowie der Bestimmung der genauen Lokalisation und Ausdehnung. Therapie der Wahl ist die vollständige Exzision, wobei dafür ev. die Resektion des Lig. rotundum nötig ist und die Versorgung einer allenfalls assoziierten Inguinalhernie.

S9

The "reversed" treatment approach for synchronous liver metastases and colorectal cancer. Feasability and first results

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Background: The « reversed treatment» approach inverts the treatment sequence of advanced synchronous colorectal liver metastases - i.e. the liver metastasis is treated first, followed by resection of the primary tumor. Chemotherapy is performed before and after liver surgery. We recently started to use a reversed treatment approach in selected patients. The aim of this study is to critically assess this new treatment modality.

Methods: Nine patients (7 male, 2 female, mean age 62 years) benefited from this new treatment between November 2008 and May 2010. The data were collected retrospectively.

Results: All patients responded to the neoadjuvant chemotherapy. The median number of liver metastases was 6 (range 1 - 22). The median size of the largest liver metastases was 4.3 cm (range 2.6 – 13 cm). Three patients had portal vein embolization prior to liver surgery. Two patients could not complete the treatment. One had to undergo emergency surgery for occluding colonic tumor. The second one showed liver recurrence before starting the adjuvant chemotherapy. The seven patients who completed the treatment are still alive after a median time of 27 months (range 17 – 37 months). Five of them had recurrence (1 rectal, 4 liver).

Conclusion: Based on our preliminary experiences, the reversed strategy shows encouraging results for the treatment of advanced synchronous colorectal liver metastases in well selected patients. The treatment was generally well tolerated and long term survival seems to be prolonged.

S10

"State of the art" in colonic resection for diverticulits: a worldwide survey of 232 colorectal centers.

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Background

Diverticulitis continues to be a source of significant morbidity worldwide. New strategies have been developed to treat diverticulitis. The objective was to evaluate the current practice worldwide regarding treatment of diverticultis.

Methods

A survey was sent to 285 colorectal centers worldwide, which focused on (a) treatment of the first episode of diverticultis, (b) timepoint of elective surgery for diverticulitis, (c) technique of resection and (d) the evidence for the applied technique.

Results

The overall response rate to the survey was 81%. Half of the centers performed more than 300 colonic resections per year. The diagnosis of diverticulitis was setted up by CT scan in 81% of the centers. Uncomplicated diverticulitis was treated conservatively in 80.5%, and complicated diverticulitis in 95.45% by laparoscopic lavage and drainage placement in 98.54%. Only 1.04% of the centers do usually recommended a colonic resection after the first episode of diverticulitis, 30.2% after the second episode. One third of the centers provided laparoscopic colonic resection with primary anastomosis for uncomplicated diverticulitis. The specimen measured median 26 (range 15-45) cm. Most of the centers recommended a colonoscopy after 6 (2-8) weeks for conservatively treated diverticulits. Two-fifths of centers used guidelines for their treatment regimes.

Conclusions

Treatment techniques for complicated and uncomplicated diverticulitis were comparable among different centers and continents. Laparoscopic techniques are commonly used for colonic resection. The standard treatment for the first episode of an uncomplicated diverticulits remained conservative and almost 70% of the centers performed colonic resection at the earliest after the third episode.

S11

Severe postoperative complications have detrimental effects on long-term survival after pancreas resection

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Background Modern pancreas surgery remains associated with an increased morbidity. While it is known that incomplete resection (R1/2) has a major impact on survival in cancer patients, the long-term effects of complications have not yet elucidated. This study assessed the role of complications on long-term survival after pancreas resection for malignant diseases.

Methods A consecutive series of 168 patients underwent pancreas resection (126 pancreaticoduodenectomy, 33 distal pancreatectomy, 9 others) for benign (n=51) and malignant (n=117) diseases at our institution from 2000 to 2008. Complications were graded according to its severity using a validated score on a 5-point scale. Mild complications were grade I/II, severe complications were grade III/IV.

Results Mortality after resection for cancer was 5.1%. There were 42%, 40% and 45% of patients in the malignant, R0 and R1/R2 group with at least one complication. In the overall group, patients with severe complications revealed a significant shortened median survival compared to those without complications (1.6 years vs. 5.0 years, p=0.033). There was a trend towards a shorter median survival in the malignant group of 1.4 years and 2.1 years for patients with severe complications and without complications (p=0.325).The median survival after R0 resection was not influenced by the occurrence and severity of complications, but patients with a R1/2 resection and severe complications showed a significantly worsened median survival of 0.8 years vs. 2.0 years without complications (p=0.013). Median survival in cancer patients without complication was similar in R0 and R1/2 resections (2.2 years vs. 2.0 years, p=0.39).

Conclusions Severe postoperative complications have a significant detrimental impact on long-term survival, particularly in patients with R1/2 resection. Once recovered from mild complications, survival is similar to those of patients without complications. Survival after resection without complications is not influenced by the R status.

S12

TEP or TAPP? Population-based analysis of prospective data on 4552 patients with endoscopic inguinal hernia repair

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Background: To compare outcome of total extra-peritoneal (TEP) versus transabdominal preperitoneal (TAPP) inguinal hernia repair in a large cohort study. **Methods:** Inclusion of all patients requiring unilateral TEP/TAPP from 1995-2006 based on prospective data of the Swiss Association of Laparoscopic and Thoracoscopic Surgery. **Results:** 3'457 patients underwent TEP, 1'095 TAPP. TEP resulted in more intraoperative (3.9 % vs. 2.0 %, p<0.01) and surgical postoperative complications (2.3 % vs. 0.8%, p<0.01), longer OR times (66 vs. 59 min p<0.001) and higher conversion rates (10% vs. 0.2%, p=0.011) than TAPP. **Conclusions:** On a population-based level, the TEP technique appears inferior in patients undergoing unilateral inguinal hernia repair.

S13

Long-term quality of life after Ivor-Lewis esophagectomy for esophageal and cardia cancer

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Background: Esophagectomy, remaining the standard of care for localized esophageal cancer, has a potentially high impact on physical, emotional, and social functions. Advantages in staging methods, (neo)adjuvant treatment options, and advanced surgical techniques have improved the outcome of esophageal cancer surgery leading to focus on postoperative quality of life. The aim of this study was to assess health-related quality of life (HRQOL) after esophageal cancer surgery.

Methods: We analyzed all patients who underwent an Ivor-Lewis esophagectomy for resectable esophageal and cardia cancer in our hospital from 1999 to 2008. HRQOL of eligible patients was then assessed using the German versions of the European Organization for Research and Treatment of Cancer (EORTC) HRQOL Questionnaire Core 30 (QLQ-C30) and QLQ-OES18.

Results: A total of 126 patients were operated in the surveyed 10-year period. At the time of analysis 34 patients (27%) were eligible for assessment, 85 patients (67%) had died, and 7 patients (6%) were lost to follow-up. 32 of the 34 eligible patients (94%) returned the questionnaires. The median observation interval since the operation was 47 (range 21-135) months. 26 patients (81%) judged their golbal health status and their quality of life as good to very good (5-7 on a 1-7 scale), corresponding a mean score of 76.3 of 100 (CI 95% 70.7-81.9). The mean scores of the functional scales were 84.2 (CI 95% 78.1-90.3) for physical functioning, 77.1 (CI 95% 67.7-86.4) for role functioning, 79.7 (CI 95% 71.4-88.0) for emotional functioning, 85.4 (CI 95% 77.8-93.0) for cognitive functioning, and 77.1 (CI 95% 68.1-86.1) for social functioning. The highest mean scores of the symptom scales were fatigue (37.8), diarrhea (25.0), and nausea (22.9). Mean scores of the esophagus-specific QLQ-OES18 symptom scales were 41.1 for reflux as a relevant postoperative symptom, 25.5 for eating problems, 17.4 for pain, and 10.1 for dysphagia.

Conclusions: After Ivor-Lewis esophagectomy for esophageal and cardia cancer 81% of the patients judged their quality of life as good to very good. Reflux symptoms and fatigue were the most relevant symptoms. Ivor-Lewis esophagectomy provides patients with esophageal and cardia cancer a generally good quality of life in the longterm.

S14

Laparoscopic Re-Sleeve Gastrectomy (LRSG) for Failed Open Biliopancreatic Diversion/Duodenal Switch (BPD-DS)

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BACKGROUND: Biliopancreatic diversion/duodenal switch (BPD-DS) combining malabsorption and restriction is considered the most effective procedure in bariatric surgery. However, weight regain after initial weight loss or insufficient weight loss is a challenging problem in the long-term. There is ongoing debate whether further restriction or malabsorption should be added to overcome this state.

METHODS: Six patients underwent LRSG for weight regain or insufficient weight loss (<50% of excess weight) after open BPD-DS associated with fundus-pouch or dilated gastric sleeve in upper gastrointestinal series.

RESULTS: All procedures were done laparoscopically. Mean initial body mass index (BMI) and mean excess body weight (EBW) were 45.3(34-52.9)kg/m^2 and 53.6(29.5-75.9)kg, respectively. The revision resulted in a mean BMI, percent of excess weight loss (%EWL), and percentage of excess BMI loss (%EBL) of 42.8kg/m^2, 24.3%, and 20% at 1 month; 39.6kg/m^2, 43.7%, and 41% at 3 months; and 36.4kg/m^2, 59.4%, and 56% at 6 months, respectively. There was no morbidity and mortality.

CONCLUSIONS: In this feasibility study we report six patients undergoing LRSG with weight regain after open BPD-DS. Restoration of restriction by LRSG is safe and effective in the short-term to obtain substantial weight loss.

Safety of Laparoscopic Sleeve Gastrectomy (LSG) for Patients with Excessive Perioperative Risk

S15

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Background: Even though morbidly obese patients with excessive concomitant disease carry a significantly increased perioperative risk, they may benefit most of a bariatric intervention due to resolution of those comorbidities.
Methods: Excessive perioperative risk was defined as Anesthesiologists physical status score (ASA)≥4, Revised Cardiac Index (RCI)≥3, Obstructive Sleep Apnea-Severity Index (OSA-SI)≥5 or Obesity Surgery Mortality Risk Score (OS-MRS)≥4. 30-day morbidity and mortality was studied prospectively.
Results: 54 patients (33 female) at median age 44y (range 18-69y) and median BMI 52.2kg/m^2 (38.9-77.5kg/m^2) underwent LSG with additional cholecystectomy performed in 25 patients (46.3%). 19 patients (35.2%) had a BMI≥60kg/m^2. 41 of the 54 patients (76.0%) had ASA≥4, 48 patients (88.9%) had RCI≥3 and/or OSA-SI≥5. Comorbidities were amongst others insulin-dependent T2DM (11 patients, 20.4%), history of pulmonary embolism (15 patients, 27.7%), severe neurological disease (13 patients, 24%). Median operating time was 120min (35-240min) with conversion to open surgery in 2 cases. Median hospital stay was 6 days (3-70d). There were a total of 22 complications in 12 patients (22.2%): leak (early 2, late 1), stenosis (1), pneumonia (3), cardiac complications (3) and successful reanimation after cardiac arrest (3), transient renal insufficiencies (4), epilepsy (1), wound infection (4). One patient (1.8%) died after the induction of anesthesia.
Conclusion: This prospective study shows LSG to be a safe procedure in patients with excessive perioperative risk. However, postoperative morbidity is considerable reflecting the severity of comorbidities.

Vaginal small bowel evisceration after hysterectomy

S16

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Background : vaginal evisceration of intestinal loops after hysterectomy has rarely been described since 1900. It happens rather in the early postoperative course, less frequently years later. Could we be threatened by increase of this complication with the generalisation of transvaginal NOTES ? We report herein a “classical” case.

Method : a 78-years old female patient complained of a sudden abdominal pain and sensation of a perineal mass. Clinical examination revealed evisceration of small bowel loops through the vagina. An abdominal hysterectomy had been performed thirty years ago for benign disease and a left hemicolectomy was realized in 2003 due to a dolichocolon with rectocele.

Results : Repair was done through laparotomy with reduction of the small bowel, closure of the vaginal defect with a running absorbable suture and omentoplasty. Recovery was uneventful.

Conclusion : vaginal evisceration is a rare event. It is observed essentially after hysterectomy in old patients, rarely in young patients.Repair of the vaginal defect is not standardized from simple suture to omentoplasty or use of a mesh.

Inkarzerierter Dünndarmprolaps peranal

S17

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Einleitung: Der Rektumprolaps ist für viele Betroffene eine invalidisierende Erkrankung, die zudem mit einem erheblichen Tabu behaftet ist. Viele Patientinnen werden wegen hohem Alter und Polymorbidität konservativ behandelt, obwohl chirurgische Optionen auch für solche Patienten zur Verfügung stehen. Nicht immer ist diese konservative Strategie die sicherste.

Fallbericht: Zuweisung einer 82-jährigen Patientin mit einem Dick- sowie Dünndarmprolaps peranal mit Blutabgang. Der Rektumprolaps war schon seit Jahren bekannt und symptomatisch. Der Dünndarm prolabierte durch einen Einriss des Douglas und des Rekums. Anlässlich einer notfallmässigen Laparotomie wurde der Dünndarm ins Abdomen reponiert und das rupturierte Rektum nach Hartmann reseziert. Der Dünndarm erholte sich bereits intraoperativ.

Konklusion: Wir postulieren, dass der Einriss des Rektums und des Douglas durch den chronischen Druck des Intestinums auf das prolabierte Rektum entstanden ist. Diese Komplikation hätte vermieden werden können, wenn der Rektumprolaps chirurgisch saniert worden wäre. Auch für Alte und Polymorbide Patienten existieren gut verträgliche und sichere Sanierungsoptionen.

A rare complication of a laparoscopic hysterectomy: Leiomyoma mimicking an incarcerated inguinal hernia

S18

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Background: Spilling of leiomyoma cells is a rare and unusual complication of laparoscopic surgery. Tumour development in the inguinal canal after laparoscopic gynaecological surgery should be kept in mind in the differential diagnosis of inguinal hernia and other uncommon pathologies.

Case: A 52-year-old woman was referred to our department by her gynaecologist because of the development of a right inguinal tumour. In April 2009 a laparoscopic total hysterectomy was performed because of severe menorraghia caused by leiomyomatosis. Three-and-a-half-months later, she discovered a right inguinal mass. An ultrasound (US), a CT Scan and a PET-CT were performed. An US-guided biopsy was inconclusive. At surgery seven months after hysterectomy, a vascularised inguinal tumor, situated towards the middle of the round ligament, was removed. Then, a Shouldice hernia repair was performed. She recovered uneventfully. Microscopy revealed typical features of a fibrotic, benign leiomyoma.

Conclusions: Migration and implantation of tumour cells is a rare complication of laparoscopic surgery for uterine myoma. Depending on the mechanism of spreading, tumour implantation can occur at various locations. Laparoscopic surgeons and gynaecologists should be aware of this possibility during the follow-up of patients undergoing such a procedure. Aberrant tumour implantation should be taken into consideration in the differential diagnosis of any pathology of the inguinal canal.

Metastatic neuroendocrine pancreatic tumors and liver metastasis. How much surgery is applicable?

S19

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Objective
Neuroendocrine tumours of the pancreas (PNET) are rare and have an incidence of less than 1 per 100'000 individuals. Patients with PNET are divided into an asymptomatic and a symptomatic group from peptide hormone secretion. Most PNET are metastatic at the time of diagnosis, and the liver is the most common site of metastasis. Surgical elimination of the tumor load should be achieved, but major liver surgery and pancreatic surgery are key physiological stressors, rarely combined. We aimed to analyzed how major liver surgery is tolerated in these patients.

Materials and Methods
Between 2002 and 2010 we performed a retrospective analysis of our prospective pancreas database. All the patients with histologically proven NET after pancreatic resection were included.

Results
Between 2002 and 2010 we resected 670 pancreatic tumors. 35 patients (5.2%) were diagnosed as having a PNET. 12 patients were female and 23 male. The median age was 58 years (range 31-85). In the preoperative CT scan 11 patients had synchronous liver metastasis. The tumors were mostly located in the head (18/35), 7/35 in the body and 10/35 in the tail of the pancreas. 14 cases were treated by a whipple procedure, 15 by a pancreatic tail resection, and five by sole enucleation of the tumor. One patient was treated by palliation only, because the tumor was technically not resectable. In eight cases a liver metastasis resection was performed as single-step procedure, in two cases as two-step procedure in one case liver resection was not possible due to the tumor extension. Histologically we found eight insulinomas, three glucagenomas, one gastrinomas, one VIPom and 22 nonfunctional PNET. The median hospital stay was 16 days (range 7-44 days). One patient died from cancer within 30 days, accounting for a mortality of 2.9%. The median follow-up was 38.5 months (range 2-89 months). Two patients died from cancer during the follow up.

Conclusion
Surgical resection of the primary PNET and the extensive liver metastasis is feasible. The single-step procedure should be attempted whenever possible. If the patient has an adverse medical condition increasing surgical risk, a two-step approach is preferred.

Acute Hepatitis associated with the use of natural product camu-camu.

S20

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Introduction: The use of complementary and alternative medicine is increasing. We present a case of liver injury probably related to the use of a dietary supplements containing camu-camu.
Case report: A 45 year-old previously healthy caucasian man was admitted at the end of september for pruritus, scleral icterus and dark urine. The patient reported, to have taken a spoon a day of a preparation containing camu-camu (myrciaria dubia) two months ago for a period of approximately 10 days. He took no other drugs and did not drink alcohol or use illicit substance. Laboratory studies revealed an elevated AST of 403 U/L, and ALT of 1185 U/L, alkaline phosphatase of 335 U/L, GGT of 300 U/L, and elevated total bilirubin of 142 μmol/L. His complete blood count was normal. Tests for viral, metabolic or autoimmune causes of liver injury were negative. Liver biopsy demonstrated centrilobular hepatocellular damage compatible with drug toxicity of not very recent origin. Clinical and laboratory signs of liver injury gradually improved and the patient was discharged.
Discussion: Myrciaria dubia, commonly known as camu-camu, is an amazonian fruit that offers very high content of vitamin C. It is used as a dietary supplement with antioxidant properties. To our knowledge this is the first report of liver injury probably related to use of camu-camu. Exclusion of other causes and the histological diagnosis compatible with drug toxicity render camu-camu as the cause of acute hepatitis most likely. Several scoring systems have been proposed to standartize such assessment. According to the CIOMS (Council for International Organizations of Medical Sciences) scale our case showed a probable causality (+6 points). In conclusion, the use of herbal drugs should always be considered in cases of liver injury. It is important to increase the awareness of both clinicians and patients about the potential dangers of herbal remedies in absence of reliable studies of clinical efficacy and benefit-risk assessment.

Successful downstaging of perianal Paget's disease using Imiquimod therapy before surgical excision

S21

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Background: Paget's disease of the perianal region, originating from apocrine glands, is a rare condition (< 200 cases in the literature). It presents with local exzema, itching and burning. The diagnosis is often delayed, although perianal Paget's disease can progress to an invasive carcinoma in 10 – 30% and is in some 42% associated with rectal carcinoma. The therapeutic gold standard is wide surgical excision. Problematic is a recurrence rate of > 30%. Other, even less satisfying therapeutic options include radiotherapy and local virostatic therapy.

Methods: A 79-years old lady presented with a history of perianal itching and burning for many years. The perianal skin showed an unspecific red exzema with white streaks and macerations that extended into the anal canal. The symptoms were only temporarily reduced by corticoid therapy. Peri- and intraanal biopsies demonstrated intraepithelial infiltration of pagetoid adenocarcinoma cells. A primary wide local excision would have involved the whole anal canal and approx. 8 cm around the anus with the associated morbidity risk. Therefore, a downstaging therapy with Imiquimod 5% (Aldara) three times per week was initiated prior to surgery.

Results: The local, neoadjuvant Imiquimod therapy was well tolerated, reduced symptoms as well as the extent of the local exzema immediately and sustained for 12 weeks.

Conclusion: Perianal Paget's disease is a rare entity and should always be considered in patients with prolonged perianal exzema. Local Imiquimod therapy is possible, can reduce the area involved by the illness and improve the success of complete surgical excision.

A salvage procedure for an accidentally twisted small bowel in orthotopic duodenal reconstruction after pylorus-preserving partial pancreatoduodenectomy

S22

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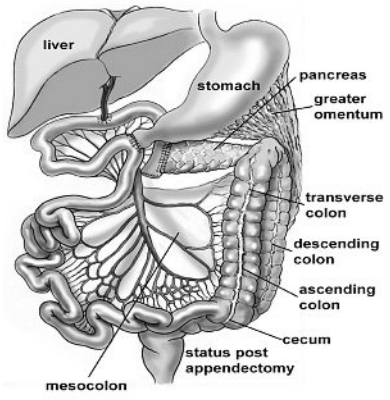
Abstract
A case of pylorus preserving Whipple procedure with an accidentally clockwisely 360°- rotated small bowel limb for orthotopic duodenal resconstruction is presented. A simplesalvage procedure is proposed.

Figure 1 showing the situs after the salvage procedure.



I1

Clinical characteristics of patients with idiopathic CT scan terminal ileitis: a case series of 32 patients. Sophie Restellini[1], Marc Girardin[2], Muriel Genevay-Infante[3], Laurent Kaiser[4], Antoine Hadengue[2]. [1]Internal Medicine Service, [2]Gastroenterology and Hepatology Service, [3]Clinical Pathology Service, [4]Infectious Diseases Service, Geneva University Hospital.

Background: Terminal ileitis (TI) on CT scan consists in a thickened terminal ileum with a contrast enhancement. It is frequently described on abdominal CT-scan performed in patients complaining of right lower quadrant acute abdominal pain. Causes of these TI can be inflammatory or infectious but remains unknown in a significant proportion of cases. **Aim & Methods:** To collect and describe clinical characteristics and outcome of patients admitted with a TI on CT scan. All patients with a TI and having also a colonoscopy between May 2007 and January 2011 were included. Patients with Crohn's disease were excluded. Demographical, clinical, biological, radiological as well as endoscopic characteristics were analyzed. **Results:** 37 patients were included. Stool analyses were performed in 25 patients (68%) and were positive in four (2 campylobacter jejuni, 1 mycobacterium tuberculosis and 1 chlamydia trachomatis). Yersinia serology done in 13 cases was positive in one. Thirty-two patients (87%) remained having a TI without identifiable cause. Median age was 33 years (16-90), 63% were female. The most common reported symptoms were abdominal pain (91%), diarrhea (38%), bloody stools (9%), and arthralgia (6%). Fever was present in 22%. Fifteen patients (41%) were smokers, one had a recent trip in a tropical country, 4 took NSAIDs and 2 antibiotics. Patients home were homogenously distributed throughout the canton of Geneva, a little bit more in area close to the lake or the river. Median CRP at admission was 86 mg/l. Twenty-two patients had endoscopic findings compatible with an ileitis (18 microscopically), whereas 10 had normal terminal ileum (14 microscopically). Most of them were treated with antibiotics. Clinical evolution was good (median CRP at day 10 drops to 9 mg/l) and 14 patients had a follow-up without any recurrence of symptoms. **Conclusions:** TI described on CT scan does not necessarily correspond to an inflammation of the intestine. TI with no identified cause is frequent in this series even if stool cultures and bacterial serology weren't systematic. The roles of proximity to water points and of infectious agents including viruses are under investigation and will be presented at the meeting.

I2

Small intestinal bacterial overgrowth is the most common cause of positive fructose breath tests in patients with unspecific abdominal symptoms.

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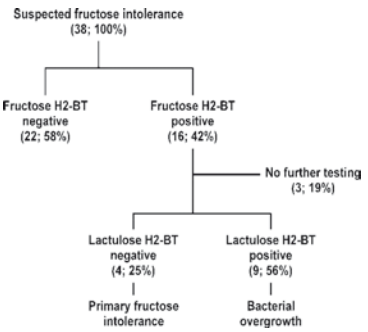
Background: Fructose intolerance is often considered among possible cause of unspecific abdominal symptoms. On the other hand fructose (and other sugar) malabsorbtion can be secondary to small intestinal bacterial overgrowth. Currently hydrogen breath tests (H2BT) are reliable non-invasive tests to diagnose sugar malabsorbtion and small intestinal bacterial overgrowth .

Aim: To assess the prevalence of primary vs. secondary (bacterial overgrowth) fructose intolerance in patients referred for fructose H2BT.

Methods: Data from 38 patients with diarrhea, abdominal pain or bloating referred for fructose intolerance testing were analyzed . All fructose breath test positive subjects underwent lactulose H2-breath test. During fructose and lactulose H2BT air samples were collected at baseline and in 30-min intervals for 180 min. The fructose H2BT was considered positive if the H2-concentration in at least 2 samples increased >20ppm over baseline at any time after oral ingestion of 25g fructose. The lactulose H2-BT was considered positive if the H2-concentation increased >20ppm over baseline 30-60 min after oral ingestion of 30g lactulose.



Results: Overall 16 (42%) referred patients had a positive fructose H2BT. Of these patients 9 (56%) had positive lactulose H2BT (i.e. secondary fructose intolerance) and 4 (25 %) had a negative lactulose H2BT (i.e. primary fructose intolerance).

Conclusion: Small intestinal bacterial overgrowth is the most common cause of fructose intolerance. Accordingly lactulose H2BT should be performed in patients with positive fructose H2BT as treatment of primary vs. secondary fructose intolerance warrant different approaches.

I3

Preoperative Indications for Complete Histopathologic Response after Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer

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Background: A more individualized treatment (wait-and-see-policy, local excision) in patients with complete clinical response after neoadjuvant chemoradiotherapy (CRT) for rectal cancer is under discussion. The present prospective study aims to show how accurate MRI, PET, endoscopy, and endorectal ultrasound are after CRT in patients with complete histopathologic response.
Methods: Between 2005 and 2010 in our department, 130 patients were re-staged four weeks after CRT with MRI, PET, rectoscopy, and endorectal ultrasound. Sensitivity, specificity, and accuracy for ypT0 ypN0 were calculated for each method and endoscopic findings were recorded.
Results: In all, 19% had a complete histopathologic response (ypT0 ypN0). Sensitivity, specificity, and accuracy for MRI were: 23%, 92%, 77%, respectively; for PET 56%, 75%, and 70% and for endorectal ultrasound, 24%, 94%, and 81%. In all patients with complete response endoscopy revealed either a scar or a very small ulcer.
Conclusion: Definition of a complete response in patients with locally advanced rectal cancer after CRT is difficult with all used clinical methods.

I4

Peritoneal carcinomatosis: Involvement of the Douglas pouch and tumor growth into the seminal vesicles

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Background: Radical cytoreduction in patients with peritoneal carcinomatosis often requires resection of the middle and upper rectum, together with a hysterectomy and adnexectomy in woman, for radical removal of tumor in Douglas' pouch. No details of such a technique and its risks for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) have been described in male patients. Here, we report on our experience in this particular phase of cytoreductive surgery.

Patients, Methods: From 1999 to 2011, a laparotomy was performed in 71 consecutive patients with peritoneal carcinomatosis, aiming at potentially curative surgery. CRS/HIPEC was offered to 62 patients, 24 males and 47 females.

Results: Involvement of Douglas' pouch by peritoneal carcinomatosis was observed in 27 patients and peritonectomy without rectum resection was performed in 10 patients (3 male, 7 female patients). Amongst eight men undergoing rectum resection for extensive invasion of Douglas' pouch, all tumor tissue was easily removed in five. In three, we observed tumor infiltration through and below the peritoneum in the perivesical space, macroscopically reaching the ductus deferens and the seminal vesicles. Out of these three patients, two had a signet ring cell carcinoma of the appendix with a high peritoneal cancer index.

Conclusion: Special attention should be given to possible invasion of seminal vesicles before surgery, especially in patients with signet ring cell carcinoma. When tumor infiltration is present or suspected during surgery, careful dissection of the prevesical ureter and bladder wall is mandatory. The prognostic significance of tumor invasion of the seminal vesicles in peritoneal carcinomatosis remains to be defined.

Prevalence of IgG4-related cholangitis in liver transplant recipients with an initial diagnosis of primary sclerosing cholangitis

I5

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Background : IgG4-associated cholangitis (IAC) is a recently described pathological entity displaying elevated serum IgG4 concentrations, characteristic histology, involvement of other organs and response to steroids. Since IAC shares clinical and radiological features with primary sclerosing cholangitis (PSC) differential diagnosis may prove difficult. We aimed to determine the prevalence of IAC in PSC patients receiving a liver transplant. Methods : Patients transplanted (n=7) or on the waiting list (n=5) for PSC were included. Liver transplant recipients for primary biliary cirrhosis (n=6) and alcoholic cirrhosis (n=11) served as controls. Serum IgG4 concentrations by the time of transplantation and 1 year post-transplant were determined by ELISA. Histology and immunohistochemistry for IgG4 on explanted livers and control biopsies (1 year post-transplant) were assessed by 2 experienced pathologists blinded to patient identity, serological and clinical data. Results : Two patients with an initial diagnosis of PSC met histological criteria for IAC. IgG4 serology, however, was negative. No recurrence was observed 1 year post-transplant. One additional PSC patient and two control patients displayed positive serology, but histology was negative. Conclusions : IAC is present in a significant proportion (2/11) of patients with an initial diagnosis of PSC. Serum IgG4 do not allow a reliable distinction between IAC and PSC. Hence, careful histological assessement including immunohistochemistry for IgG4 is primordial.

Effectiveness of ERCP-guided drainage and stent therapy for obstructive jaundice in hepatocellular carcinoma

I6

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Background: The management of obstructive jaundice secondary to hepatocellular carcinoma (HCC) remains controversial. We aimed to study whether endoscopic biliary drainage was feasible, safe and effective in this population.
Methods: We retrospectively studied patients at our institution with HCC and obstructive jaundice treated with endoscopic biliary stenting between October 2005 and May 2011.
Results: Six patients with HCC (5 men, 1 woman) had an endoscopic attempt at draining a HCC-related biliary obstruction. Median age was 60 years (range, 49-76); 4 patients had a cirrhosis (average MELD, 13; range 6-23). Biliary compression by HCC was at the level of the hepatic hilum in 5 patients (Bismuth types II, IIIB, IV and two indeterminate between type IIIB and IV) and at the level of the left hepatic duct in one patient. Endoscopic biliary stenting was successful in 5 patients (the stricture could not be crossed by a guidewire in one patient who had percutaneous biliary drainage). Median bilirubin at the time of the first ERCP, 7, and 14 days later was 295 (range 32-540), 110 and 147 µmol/L, respectively. Follow-up is available in 5 patients: 4 patients died (median survival after first ERCP, 84 [range 40-294] days). In the 5 patients with successful stent insertion, clinical success (bilirubin normalisation) was observed in 3 patients (clinical failure in one patient, missing follow-up in one patient). During follow-up, two patients had biliary events (one cholangitis related to stent obstruction and one hemobilia, both two months following ERCP), Three patients had a total of five ERCP during follow-up.
Conclusion: ERCP is feasible in patients with HCC-related biliary obstruction; clinical success was observed in 3/5 patients in our cohort. Larger samples of patients are required before definitive conclusion can be drawn.

Treatment of Acute Variceal Hemorrhage with Self-Expanding Metal Stents in Switzerland

I7

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Background: Today's standard therapy for acute variceal hemorrhage includes the combination of pharmacological and endoscopic therapy and short-term antibiotic prophylaxis. Balloon tamponade (BT) and emergency transjugular intrahepatic portosystemic shunt (TIPS) as salvage techniques have certain limitations. Since 2003, self-expanding metal stents (SEMS) have been used as a new treatment modality in acute variceal hemorrhage (Hubmann et al. 2006).

Methods: This case series (8 stents in 6 patients) reports the use of SX-ELLA Stent Danis (ELLA-CS, Hradec-Kralove, CR) in four different Swiss facilities in acute variceal hemorrhage.

Results: In 6 out of 8 cases the stent insertion was successful in stopping ongoing bleeding. Mean stenting time was 44 h. In one patient, rebleeding and in two patients stent dislocation to the stomach was observed. The survival at 30 days was 33%.

Conclusions: Self-expanding metal stents are an alternative to standard techniques in controlling variceal hemorrhage. Especially in hospitals with the lack of 24h endoscopic on-call service, SEMS might be very useful as a bridging measure to definitive therapy. Randomized trials are necessary for comparison to standard techniques.

Management of splenic artery aneurysms

I8

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Objective
Splenic artery aneurysms (SAA) are rare but nevertheless the third most common intra-abdominal aneurysms with a prevalence of up to 10%. They are potentially life-threatening. Mortality of the spontaneously ruptured SAA was up to 25% before we used routine CT-scan. SAA are mostly asymptomatic and detected incidentally. We aimed to analyze how modern management with CT scans and interventional radiology affects the treatment and outcome of these patients.

Methods
From 2005 to 2010 we performed a retrospective analysis of our database for SAA. The clinical presentation, diagnostic investigation, therapeutic intervention and outcome were analyzed.

Results
From 2005 to 2010 we diagnosed seven patients with a SAA. Four patients were female and three male. The median age was 60 years (range 53-70). The median ASA score was 3 (range 2-4). Two patients presented with hemorrhagic shock and had ruptured SAA in the CT scan. All the others had unspecific abdominal pain or a trauma and the SAA was detected incidentally in the CT scan, one of them showing a contained rupture. The contained rupture was successfully treated by coiling, the other ruptures by laparotomy, resection of the aneurysm and splectomy in one case, resection of the aneurysm and reconstruction of the artery in the other case. Both operations were associated with significant blood loss and the transfusion of eight and 17 red blood cells units respectively. The four unruptured aneurysms had a median diameter of 2.1cm (range 1-2.9). Coiling was used in two cases, stenting for the others. In one case the aneurysm was still perfused after stenting and there was a dissection of the celiac trunk. This was treated by laparotomy, en bloc resection of the aneurysm and pancreatic tail. No blood transfusion was needed. The media hospital stay for all the patients was 17 days (range 5-98). There was no mortality.

Conclusion
The use of multislice CT scan allows the quick and accurate detection of SAA as well as the incidental detection of asymptomatic SAA. Preemptive or therapeutic treatment by coiling or stenting is successful or leads to a controlled operative situation. Optimized treatment of SAA includes CT scan and interventional radiology.

Prospective Study to evaluate Contrast enhanced Ultrasound (CEUS) versus CT-Scan in preoperative Staging of Colon Cancer

I9

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Background: Contrast enhanced ultrasound (CEUS) greatly enhances ultrasound quality. We prospectively compared CEUS with CT-scanning in preoperative staging of colon cancer.

Methods: CEUS was performed with a Sequoia 512 (Siemens) after injection of 2 ml SonoVue® (Bracco Suisse) by the same physician. CT-scans were also assessed by only one radiologist. Both examinators were blinded for the other result. The results were prospectively compared with the intraoperative findings and the histological staging of the surgical specimen.

Results: 44 consecutive patients with colonic cancer were included in the study (med. age 75 y., 17 women and 27 men).

	CEUS (%)			CT-Scan (%)		
	T-Stage	N-Stage	M-Stage	T-Stage	N-Stage	M-Stage
Correct	66.7*	52.5	95.0	52.4*	52.3	94.9
Overstaged	11.9	32.5	0.0	7.1	45.5	2.6
Understaged	21.4	15.0	5.0	40.5	2.3	2.6

* p = 0.26

Conclusions: CEUS is at least as accurate as CT-scanning in preoperative staging of colonic cancer. They both have an excellent accuracy for the M-stage. However, they perform poorly in T- and N-staging.

I10

How to counter the problem of R1 resection in duodenopancreatectomy for pancreatic cancer?

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Background

Although duodenopancreatectomy has been standardized for many years, the pathological examination of the specimen was re-described in the last years. This was the consequence of methodical pathological studies finding up to 85% of R1 resections, mainly involving the posterior und medial resection margin. Evidently there is a need to perform standardized pathological exams of the specimens and to extend the surgical resection, where possible without risk for the patient.

Method and Result

In an instructive video we show the technique of duodenopancreatectomy with emphasis on the dorsal and medial resection margin. Furthermore we show the standardized pathological workup of the specimen, involving the reporting of all the resection margins.

Conclusions

To minimize R1 status at the posterior and medial resection margin, a close collaboration between pathologist and surgeon is crucial. Pathologists do a standardized workup of the resected specimen with staining of all the surfaces and systematic analysis of all the resection margins. Surgeons need to extend the resection of the pancreatic head to the superior mesenteric artery by dorsal dissection.

Surgical Treatment of Morbid Obesity in Patients with Bipolar and Other Psychiatric Disorders

I11

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Background: Bariatric surgery is the most effective treatment in terms of weight loss and resolution of comorbidities. Patients with psychological disorders are reported to have less optimal results and those with bipolar disorder, possibly worse.
Methods: A retrospective survey of clinical records to assess weight loss outcomes for morbidly obese patients, including those with bipolar disorders, other psychiatric conditions, and pstients without psychiatric diagnoses, was performed.
Results: For all three subgroups, the baseline mean BMI was more than 45kg/m^2 (*p=n.s*). At 6 and 12 months, BMI, excessive weight loss (EWL), and percent change in BMI were remarkably similar and not significantly different for those with bipolar disorder, other psychological conditions, and those without. The follow-up at 12 months also did not differ between the three psychiatric status subgroups.
Conclusions: In patients who undergo bariatric surgery, those with bipolar disorder have successful weight loss outcomes at 12 months that are not significantly different than those who have either other psychiatric diagnoses or no psychiatric disorder. Despite practices that suggest the contrary, well-managed morbidly obese bipolar patients should be considered as suitable candidates for bariatric surgery using established criteria for risk assessment.

The numbers refer to the pages of this supplement.

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