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Propofol, but not sevorane, protects mitochondria and liver function after ischemia-reperfusion injury

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Background and aims: Patients undergoing liver transplantation may face several problems related to ischemia-reperfusion (IR) injury, which can compromise graft function. Clinical trials proved that volatile anaesthetics are better than propofol in the protection of myocardial cells after IR injury during heart surgery. However, there are no studies investigating the post-operative outcomes of liver function after hepatic IR. Propofol has shown antioxidant properties, but no studies focused on its effects on liver surgery. Thus, we designed the present study to compare sevoflurane versus propofol anesthesia in a rodent model of hepatic IR. Mitochondrial function was evaluated as a key factor in IR injury. Data were then confirmed in liver from a group of patients after liver surgery.

Methods: Sham-operated (S) and liver IR rats were randomly anaesthetised with intraperitoneal tiletamine/xylazine (S-CTRL and IR-CTRL), inhaled sevoflurane (S-SEVO and IR-SEVO) or intravenous propofol (S-PROP and IR-PROP). After surgery, rats were sacrificed and liver function tests (ALT and AST) were measured in the serum. Liver mitochondria were freshly isolated for measurement of bioenergetics parameters (oxygen uptake, membrane potential, respiratory complexes activity). Mitochondrial free radicals production was measured by evaluating H2O2 synthesis rate. Mitochondrial adducts formed by hydroxynonenal (HNE) and proteins were also measured.

Results: In the IR groups, ALT and AST levels were significantly lower in rats anaesthetised with propofol as compared to control and sevorane group. Moreover, oxygen uptake and respiratory activity from Complex I as well as membrane potential were severely impaired in IR-SEVO group but not in liver mitochondria isolated from IR-PROP. In addition, mitochondrial H2O2 synthesis rate and HNE-protein adducts were considerably lower in IR-PROP as compared to IR-CTRL and IR-SEVO. Very interestingly, liver tests and mitochondrial function were also preserved in patients after liver surgery.

Discussion: IR induces mitochondrial dysfunction that is not prevented by inhaled sevoflurane; propofol reduces liver damage and mitochondrial dysfunction by limiting mitochondrial free radicals production. The potential effect of propofol during liver surgery merits clinical investigation.

Modelling of the hepatic circulation by combining vascular corrosion casting and micro-CT imaging

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Introduction: Hepatic perfusion plays a crucial role in many liver-related research areas (e.g. living donor liver transplantation, machine perfusion preservation, cirrhosis). Nevertheless, liver perfusion remains relatively poorly understood, especially at the microcirculation level. It is thus essential to clarify the hepatic vascular morphology and hemodynamics. Therefore, we visualised the liver macro- towards microvasculature and performed computer simulations of the hepatic circulation.

Methods and results: Vascular corrosion casting was applied to a human liver (discarded for transplantation) by simultaneous injections of resin (Batson’s™#17, Polysciences, USA) in the hepatic artery and portal vein. Data on the liver macrovasculature were gathered by a high resolution (110 μm) in globo micro-CT scan. Consecutive samples of different orders of magnitude were dissected from the cast and imaged at increasing resolutions, the most detailed scan (resolution 2.6 μm) obtained from a sam-
ple of ± 0.134 mm³. Image processing (Mimics, Materialise, Belgium) allowed segmentations and 3D reconstructions up to the sinusoidal network (Figure 1).

These data were used to quantify branching topology and vessel features such as radii (up to 13 generations: range 13.2 to 0.08 mm; sinusoids: 6.63 μm) and lengths (range 74.4 to 0.74 mm). Sinusoidal porosity was found to be 0.15 ± 0.03. Various computational models (electrical network analogues, detailed 3D computational fluid dynamic models) were used to model pressure drops and flows throughout the liver (Figure 2; results of electrical liver model for natural blood flow and hypothermic machine perfusion). Microcirculatory flow simulations revealed anisotropic permeability characteristics within liver lobules (higher permeability parallel to the central vein; lower permeability in radial or circumferential directions).

**Conclusion:** Combining vascular corrosion casting and micro-CT imaging allows (i) to quantify the hepatic vascular anatomy up to the microcirculation level, and (ii) to model hepatic perfusion. This approach may lead to novel insights into liver microcirculation, that can be used to study normal and pathological liver perfusion in the future.

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### Xanthohumol suppresses hepatic inflammatory response to acute liver injury

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Liver cell injury induced by stress such as ischemia-reperfusion (I/R) or toxins triggers an inflammatory response, which leads to reactive oxygen species (ROS) formation. ROS play a major role in the mechanisms, which lead to hepatic inflammation and hepatocellular damage. Xanthohumol, the major prenylated chalcone found in hops, is known for its anti-inflammatory and ROS-scavenging properties.

**Aim:** The aim of this study was to investigate the effects of xanthohumol in two models of acute liver injury.

**Methods and results:** Xanthohumol was applied to BALB/c mice orally at a dose of approximately 1 mg/kg body weight for 5 days via food-supplementation. Control-mice received standard chow. Acute liver damage was induced either by injection of a single dose of carbon tetrachloride 72h prior to sample assessment or by clamping the vascular blood supply to the median and left lateral liver lobe for 1h (ischemic phase) followed by a 6h period of reperfusion. Histomorphology and serum levels of transaminases revealed considerable he-
patocellular necrosis in both models, which was accompanied by significantly enhanced hepatic expression of pro-inflammatory cytokines and elevated NFkappaB activity. While acute liver damage related GSH-depletion and induction of hepatic HMOX-1 expression were significantly reduced in xanthohumol-fed mice compared to control-mice, the degree of overall hepatocellular damage did not significantly differ between these groups. However, pro-inflammatory hepatic gene expression as well as I-kappaB-alpha degradation and subsequent induction of NFkappaB activity were almost completely blunted in xanthohumol-fed mice. 

Conclusions: Our data suggest that xanthohumol is able to counter hepatic oxidative stress in vivo, and more importantly, block the inflammatory response to acute liver damage, presumable at least in part via decreasing NFkappaB activity. Thus, this study indicates the potential of xanthohumol application to prevent adverse inflammatory responses to acute liver damage of various etiologies as after intoxication or surgically related I/R injury.

Post-transplantation metabolic syndrome: Is it only a therapeutic concern?

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Background and aims: Due to the improved survival after liver transplantation (LT), greater attention has been reserved to diseases occurring within the long term follow-up, such as Post-Transplantation Metabolic Syndrome (PTMS). Several predictors for PTMS have been identified: higher age at transplant, male gender, pre-LT metabolic derangements, the etiology of hepatopathy and immunosuppression. This syndrome contributes to increase the cardiovascular risk in transplanted patients. Aim of the study was

1. to evaluate the prevalence and the incidence of the Post-Transplant Metabolic Syndrome (PTMS);
2. to evaluate risk factors and predictors for its development;
3. to verify its influence on patients’ cardiovascular risk.

Methods: We enrolled 156 patients (mean age 58±9 years, 76% male) who underwent LT during the last twenty years. Mean follow-up was 67±50 months (range 6-114 months). Personal and clinical data were collected retrospectively for each patient; PTMS was diagnosed according to modified NCEP ATPIII criteria. Cardiovascular risk was calculated as suggested in www.iss.cuore.it.

Results: PTMS was present in 28% of the patients. All metabolic traits increased from pre-LT to post-LT period (arterial hypertension from 13 to 52%, diabetes mellitus from 17 to 30%, dyslipidemia from 8 to 58%); the prevalence of overweight/obesity did not change significantly. Diabetes mellitus represents the disturbance more contributing to diagnosis of PTMS (95%). Two independent predictive factors were identified, i.e. pre-OLT overweight/obesity ([OR]=8.2) and diabetes mellitus ([OR]=4.3). The prevalence of PTMS was higher in patients on Cyclosporine than in those on Tacrolimus (21% vs 38%, p=0.00). Cyclosporine showed a significant association with all metabolic derangements, except diabetes mellitus, for which a difference between Cyclosporine and Tacrolimus was not found. The majority of patients had a diagnosis of PTMS within the first two years after LT. Twenty-one percent of patients with PTMS showed an high (≥20%) cardiovascular risk (6% in those without PTMS). Cardiovascular events occurred in 6 patients (4% of total), the majority of them were males and belonged to the group of patients with PTMS.

Conclusions: A close follow-up and “tailoring” of immunosuppressive therapy is mandatory to prevent the development of PTMS mainly in patients overweight and diabetic before transplantation.

Role of kupffer cells in inflammasome activation following hepatic ischemia/reperfusion

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Background and aims: Inflammasome is a cytoplasmic multi-protein complex that mediates the activation of inflammatory caspases: caspase-1 can be activated by NOD-like receptor (NLR). Recent study implied that silencing of NLRP3 can protect the liver from I/R injury by reducing proinflammatory cytokines. Since Kupffer cells (KC), resident macrophages in liver, can provide the signals that regulate the hepatic response in inflammation, this study investigated the role of KC in activation of inflammasome and its signaling mechanism during hepatic I/R.

Methods: Male C57BL/6 mice underwent 70% hepatic ischemia for 60 min followed by reperfusion. To inhibit Kupffer cells, mice were pre-treated with gadolinium chloride (GdCl3, 20 mg/kg, i.v.) at 24 h prior to ischemia. Serum and tissues were collected at 1 and 6 h after reperfusion.
**Results:** Hepatic I/R markedly increased hepatocellular level of caspase-1 (p10) at 1 and 6 h after reperfusion. This was coincided with protein expression of inflammasome components, a caspase recruitment domain (ASC), NLRP3 and pro-caspase-1. Pretreatment with GdCl3 reduced elevation of active caspase-1 and inflammasome components. In I/R group, both pro- and active forms of interleukin (IL)-1β protein were increased, which were attenuated by GdCl3. We examined the molecular mechanisms required for inflammasome activation during hepatic I/R injury. Pannexin-1, a membrane channel, transduces purinergic receptor-mediated IL-1β maturation triggered by extracellular ATP. I/R induced the increase in the level of pannexin-1, and immunoprecipitation of liver lysates with pannexin-1 indicated that pannexin-1 associates with NLRP3 and caspase-1 (p10) after reperfusion. Inhibition of KC decreased interaction between pannexin-1 and inflammasome components. Serum and cytosolic double-stranded DNA (dsDNA) markedly increased in ischemic group, while GdCl3 attenuated dsDNA in serum and cytosol. Absent in melanoma 2 (AIM2) is one of the NLR family, which recognizes extranuclear dsDNA and directly recruits to ASC. We observed increased level of AIM2 after I/R challenge, and this increase was attenuated by pretreatment with GdCl3.

**Conclusion:** Our results suggest that KC are responsible for the activation of inflammasome by extracellular and intracellular danger signals following hepatic I/R.

**HCV receptor expression in transplanted liver before and after interferon-ribavirin therapy**

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**Background and aims:** Hepatitis C virus (HCV) infection is a dominant biological hazard for liver diseases. HCV entry into hepatocytes is a complex process determined by several proteins. Therefore, the understanding of mechanism might provide targets for therapeutic and preventive interventions. Our aim was to study expression of HCV receptors (claudin-1, claudin-6, occludin and CD81) in normal donor liver samples and in liver biopsies collected from liver transplanted (OLT) patients due to HCV cirrhosis before and after antiviral therapy following HCV recurrence.

**Patients and methods:** 28 patients were enrolled receiving combination of pegylated interferon/ribavirin (IFN/RIB) treatment for 12 months without interruption. 11 patients achieved end-of-therapy response (EOT). Out of these 11 patients HCV RNA was undetectable 6 months after the cessation of therapy (sustained virological response-SVR) in 6 cases. The other patients were non-responders. Protein and mRNA expression of HCV receptors were measured with immunohistochemistry and real-time RT-PCR.

**Results:** Pretreatment serum HCV titer was higher in SVR patients in comparison to non-responders. Knodell score decreased in all patients following antiviral therapy while HCV titer decreased significantly only in SVR. Claudin-1 and claudin-6 protein levels significantly increased while CD81 protein expression declined during the liver reinfection when compared with normal livers. Claudin-1 mRNA expression was similarly increased by reinfection, while claudin-6 mRNA expression decreased and CD81 mRNA remained unchanged. Claudin-6 protein expression was significantly higher at HCV recurrence in patients who later achieved SVR when compared with non-responders. IFN/RIB therapy caused significantly reduced expression of occludin and claudin-6 proteins in SVR patients. Claudin-6 expression correlated with HCV titer while occludin expression with Knodell score.

**Conclusions:** HCV recurrence is associated with increased protein expression of HCV receptors claudin-1 and -6 while CD-81 is decreased in comparison to normal liver. High HCV titer and increased claudin-6 protein expression at HCV recurrence might predict SVR. Successful interferon-ribavirin therapy induced decreased protein expression of HCV receptors claudin-6 and occludin.

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**Characterization of differentiated mesenchymal stem cells obtained from adipose tissue of immunodeficient mice**

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**Background:** Mesenchymal stem cells (MSCs) feature a multipotent differentiation potential. They differentiate into hepatocyte-like cells in vitro and in vivo. Therefore MSCs may be considered a new cell resource for the treatment of distinct liver diseases, e.g. the liver-based metabolic disease alpha-1-antitrypsin deficiency. Thus they may help to ameliorate the lack of donor organs for liver transplantation. The aim of this work was to isolate MSCs from adipose tissue of immunodeficient mice as well as to demonstrate and verify their differentiation potential.

**Methods:** MSCs were isolated from immunodeficient Pfp/Rag2-/- mice. They were cultured until a confluence of 90%. After a demethylation step defined growth- and differentiation media were applied to the cells. After 0, 7, 14, and 21 days the morphology of the cells was documented by microscopy. Mesenchymal (CD44, CD90, CD29) and haematopoetic (CD45, CD44, CD90, CD29) surface markers were detected by flow-cytometry. The gene expression of AFP as well as hepatocyte-specific markers like albumin, cytochrome P-450 type 3A11 (Cyp3A11) and microsomal triglyceride transfer protein (MTTP) were measured by sq-RT-PCR.

**Results:** The morphology of adult MSCs changed with increasing time of differentiation from a spindle-shaped into a polygonal morphology. Mesenchymal surface markers were expressed at each time point and haematopoetic markers were hardly detectable after 21d of differentiation. The relative gene expression of hepatic markers increased continuously and AFP was not expressed all over the culture period.

**Conclusion:** Adult MSCs derived from mouse adipose tissue can be differentiated into hepatocyte-like cells. After 21d of differentiation MSCs exhibited hepatocyte-like features in terms of morphology as well as liver-specific gene expression. The potential therapeutic benefit of MSCs may now be analyzed in a syngeneic mouse model of chronic alpha-1-antitrypsin deficiency.

**Novel ex-vivo perfusion system: Functional characteristics of human non-cirrhotic and cirrhotic liver sections mirror patients’ clinical parameters**


**Background and aims:** Evaluation of novel pharmaceutical components is usually performed in vitro or in animal models. Liver-related adverse effects extending to liver failure are a major cause for termination of clinical trials and comprise 32% of drug withdrawals. The present work aimed at elucidating baseline functionality of perfused liver tissue specimens in a closed-circuit system enabling ex-vivo partial human liver perfusion.

**Methods:** Sections of non-cirrhotic liver (NC; n=10; from patients with liver-metastasized neoplasms) and cirrhotic liver (CL; n=12; from patients with hepatitis C, primary biliary cirrhosis or ethanol toxicity) were characterized for 6h periods. General and liver-specific parameters, liver enzymes, overall (M65) and apoptotic (M30) cell-death markers, as well as indicators of phase-I/phase-II biotransformations were analyzed.

**Results:** The measured parameters resembled to a great extent (patho)physiological characteristics of patients with NC and CL. Mean urea and albumin productions as well as oxygen consumption were comparable between NC and CL. The mean courses of glucose release emphasized the reduced glucogen storage capability in CL, as they turned to consumption during the later time points. Furthermore, CL exhibited significantly stronger elevations of lactate, bile acids and the M30/M65 ratio, indicating a permanently higher rate of apoptotic cell death in CL. In contrast, NC tissue presented with significantly increased release of alanine aminotransferase, glutamate dehydrogenase and γ-glutamyl transferase in accordance with clinical observations. Phase-I transformations of phenacetin, midazolam and diclofenac occurred with higher rates in NC than in CL while metabolization of the respec-
tive phase-I to phase-II products was also processed faster in NC than in CL, both indicating superior hepatic functionality in NC.

**Conclusion:** The data presented here show that ex-vivo perfusion functionally maintains liver parenchyma for at least 6 h. Introducing this device for hepatologic studies and therapeutic modulation ex vivo may be most valuable and may allow for more reliable testing of novel drug candidates.

**Rejection is associated with matrix metalloproteinase-2 genotype chimerism after orthotopic liver transplantation**

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**Background:** Chimerism in transplantation medicine refers to the coexistence of cells of donor and recipient origin of which the clinical relevance remains largely unraveled. We used donor/recipient mismatches for matrix metalloproteinases (MMP) gene polymorphisms to study the presence of chimerism, in liver biopsies and in blood, to assess the relation with clinical complications after orthotopic liver transplantation (OLT).

**Methods:** MMP-2 and MMP-9 promoter polymorphism in donor and recipient were determined in 147 OLT patients, by DNA-HRMA and PCR-RFLP, respectively. The relationship of the MMP polymorphism mismatches in donor and recipient DNA with the development of ischemia/reperfusion (I/R) injury and rejection after OLT was evaluated. Liver biopsy specimens and peripheral blood samples, the latter for up to 12 years after OLT, were subsequently evaluated for the presence of chimerism also in relation to these complications.

**Results:** MMP polymorphism donor/recipient mismatches were found in 53.7% (MMP-2) and 35.5% (MMP-9) of the OLT patients, but no significant relation with I/R injury or rejection was observed. Chimerism in liver biopsy specimens was found to be present in 28.8% (MMP-2) and 16.2% (MMP-9) of the mismatch cases. Liver chimerism in MMP-2 was found to be significantly associated with rejection after OLT (41.2% versus 11.9% in the cases without chimerism, Chi-square 6.4, P=0.01). In addition, evidence of liver donor chimerism was found in peripheral blood samples of the recipients in a few cases, i.e., 6.3% (5/79) in the MMP-2 mismatches. MMP-9 donor chimerism in recipient blood was not observed.

**Conclusions:** Chimerism after liver transplantation can readily be found in liver biopsy specimens and in peripheral blood using MMP polymorphism donor/recipient mismatches. Liver chimerism in MMP-2 was found to be significantly associated with rejection after OLT. The exact functional implication of this MMP-2 mismatch with respect to expression and activity of this protease within the liver after OLT is subject to further study.

**Ectopic expression of murine CD47 minimizes macrophage rejection of human hepatocyte xenografts in immunodeficient mice**

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**Introduction:** Macrophages play an important role in the rejection of xenogeneic cells and therefore represent a major obstacle to generating chimeric mice with human xenografts that are useful tools for basic and preclinical medical research. The inhibitory SIRP-alpha receptor is a negative regulator of macrophage phagocytic activity and interacts in a species-specific fashion with its ligand CD47.

**Objective:** To facilitate the generation of human-mouse chimeric livers, we set out to investigate whether murine CD47 (mCd47), if expressed in human liver cells, can be used to downmodulate mouse macrophage activity against human cells.

**Design:** Murine Cd47 (mCd47) was lentivirally transduced into human liver cells for in vitro and in vivo experiments.

**Results:** Human HepG2 liver cells expressing mCd47 were less frequently contacted and phagocytosed by murine RAW264.7 macrophages in vitro than their mCd47-negative counterparts. In vivo, mCd47-positive human primary hepatocytes were selectively retained following engraftment in immunodeficient mice, leading to at least a doubling of liver repopulation efficiencies.

**Conclusion:** We conclude that ectopic expression of mCd47 results in increased chimerism levels, a finding that should have a profound impact on the generation of robust humanized small animal models. Moreover, dominance of
ectopically expressed Cd47 over endogenous human CD47 should also widen the spectrum of immunodeficient mouse strains suitable for humanization.

Histone deacetylase inhibitor alleviated liver ischemia reperfusion injury by heme oxygenase-1-mediated anti-inflammatory mechanism

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Background and aims: Acetylation is emerging as a crucial post-translational modification in controlling the expression of eukaryotic genes, which include some protective genes in antioxidant, anti-inflammatory and antiapoptotic actions. This study was designed to determine the in vivo effect and therapeutic potential of trichostatin A (TSA), a potent histone deacetylase (HDAC) inhibitor, in tissue inflammation and injury in a model of liver ischemia/reperfusion (I/R).

Methods: TSA-pretreated C57BL/6 mice were subjected to 70% liver ischemia followed by reperfusion for 24 h. The serum aminotransferases, caspase activities, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), mitogen-activated protein kinases (MAPKs) and NF-κB activation, heme oxygenase-1 (HO-1) expression and activity, and HDAC protein expression and activity were quantified.

Results: Compared with sham operations, HDAC activity and 11 HDAC family members were significantly expressed in the hepatic tissues of mice subjected to I/R. Pretreatment with TSA markedly inhibited HDAC activity, in agreement with this effect, TSA also ameliorated the hepatocellular damage and apoptosis, the levels of serum aminotransferases, caspase 3, 8, 9 activities, TNF-α and IL-6 productions, MAPKs and NF-κB activation. Interestingly, pretreatment with TSA markedly enhanced HO-1 expression and activity in I/R treated mice. Further, inhibition of HO-1 activity by ZnPP IX significantly reversed the protective effect of TSA on I/R-induced liver injury.

Conclusions: Our novel results indicate the key inflammation regulatory role of HDAC inhibitor in the pathophysiology of liver I/R injury, and provide a rational molecular target to HDAC as a novel therapeutic strategy to alleviate liver I/R injury.

Melatonin is a suitable therapeutic strategy to protect steatotic livers in major hepatectomy under ischemia-reperfusion: A role for ER stress and autophagy

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Antecedents: In clinical situations, major hepatectomy (HP) is usually performed under ischemia-reperfusion (I/R) to control bleeding during parenchymal dissection. Hepatic steatosis, a major risk factor for liver surgery, has been associated with increased complications and postoperative mortality following major liver resection. Steatotic livers show impaired regenerative response and reduced tolerance to hepatic I/R injury compared with non-steatotic. This was due, in part, to the exacerbated oxidative and endoplasmatic reticulum (ER) stress. Several studies demonstrated that ER stress inhibition reduced hepatic I/R injury and improved liver regeneration in steatotic livers after partial hepatectomy. ER stress was also correlated with a liver autophagy in obesity. Recent experimental and clinical data suggested that melatonin (ML), a potent immuno-modulator and antioxidant hormone, would decrease postoperative complications induced by major abdominal surgery. No data are reported concerning the ML benefits after major hepatectomy.

Aim: Here we examined the beneficial effects of melatonin administration to obese Zucker rats (30 to 60% liver steatosis) during partial hepatectomy under I/R on ER stress, liver regeneration including autophagy.

Experimental: Zucker rats (n=5 each group) were distributed as follows: Group 1 (Sham), Group 2 (PH+I/R): HP (70%) under 60 min of ischemia and Group 3 (HP+ML) same as Group 2, but treated with ML (10 mg/kg just before ischemia and also immediately after reperfusion respectively). Plasma and liver samples were collected at 24h reperfusion. We assessed liver injury (ALT/AST), ER stress (GRP78, pPERK, ATF4 and CHOP) as well as other factors associated with liver autophagy (Beclin-1 and ATG7). All of
them were correlated with liver regeneration (PCNA and phosphorylated JNKinase).

**Results:** ML administration significantly improved liver injury and decreased GRP78, pPERK, ATF4 and CHOP activation after HP+I/R (24hr reperfusion). This was consistent with an inhibition of liver autophagy parameters (Beclin-1 and ATG7) and increases in liver regeneration (PCNA and JNK phosphorylation) when compared with non ML-treated rats. These data demonstrated a close relationship between ER stress, autophagy and liver regeneration after major hepatectomy.

**Conclusion:** Our findings demonstrate that ML treatment is an effective therapeutic strategy for modulating liver ER stress and autophagy and thus to improve liver regeneration in major hepatectomy.

### Conventional and novel cardiovascular risk factors in liver transplant recipients (LTR)

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**Background and aims:** Cardiovascular events are increasing in LTR. Leukocyte and vascular adhesion molecules (CAMs) such as selectins, VCAM-1, and ICAM-1 play a critical role in the development of atherosclerosis. We investigated conventional and novel cardiovascular biomarkers (CB) in LTR.

**Methods:** 95 patients were submitted to liver transplant between August 2009 and July 2010, and followed-up by 1 year. 42 were consecutively included and compared to patients with biopsy proven NASH (n=19) and lean (BMI < 30) controls (n=10). Features of metabolic syndrome, glucose and lipid profile, HOMA-IR, cardiovascular biomarkers and inflammatory cytokines were determined.

**Results:** When compared to NASH patients, LTR had a significantly lower BMI (24.4 ± 4.32 vs 31.7 ± 4.35 - P < 0.001), age (P < 0.001), AST (P = 0.002), ALT (P < 0.001), fasting glucose (P < 0.001), fasting insulin (P =0.03), and HOMA-IR (2.65 [1.68 - 4.27] vs 5.02 [3.62 - 6.7] - P < 0.001). However, they did not differ regarding total cholesterol, HDL and LDL-cholesterol, triglycerides and blood pressure. Table shows CB results.

In LTR there were a significant correlation between ICAM1 and VCAM1 (P=0.03), and also among ICAM1 and e-selectin (P=0.02) and e-selectin and adiponectin (P=0.02). There was no correlation among CAMs and BMI, lipid or glucose profile. There was a significant inverse correlation among ICAM1, VCAM1 and IL-10 (P=0.02 and 0.03, respectively). CRP and PAI-1, conventional CB, were not increased in LTR.

**Conclusions:** After a short 1-year follow-up, LTR, even younger and lighter than NASH patients, and with no significant insulin resistance or CRP and PAI-1 elevation, had a similar increase of early CB (CAMs) like a notorious high risk NASH population. These results emphasize that LTR are under elevated risk of cardiovascular events and need to be screened early.

### A score predicting survival after retransplantation for hepatitis C virus cirrhosis

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**Background:** Hepatitis C virus (HCV)-induced cirrhosis is the leading indication for liver transplantation (OLT) in most Western countries. Virtually all recipients will develop an HCV recurrence and 20-30% progress to cirrhotic within 5 years after OLT. Re-OLT for HCV has shown worse results and many centres do not perform transplantations for such indications. The aim of this study was to design a score predicting outcome after re-OLT for HCV in order to improve patient selection.

**Patients and methods:** Patients with HCV undergoing a re-OLT and registered in the Scientific Registry of Transplant Recipients from 01.01.1990 to 31.01.2009 were included in the study. Survival was measured from the date of second OLT. Univariate analysis of various variables at 1st and 2nd OLT was performed by Cox

<table>
<thead>
<tr>
<th>Variable</th>
<th>NASH (n=19)</th>
<th>LTR (n=42)</th>
<th>Controls (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM1</td>
<td>1692.4±457.4</td>
<td>1820.6±443.9</td>
<td>1167.2±121.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICAM1</td>
<td>259.7±101</td>
<td>230.3±96.3</td>
<td>152.9±33.9</td>
<td>0.015</td>
</tr>
<tr>
<td>E-selectin</td>
<td>90.03 (69.5-137.1)</td>
<td>48.5 (36.0-70.9)</td>
<td>35.7 (28.4-47.04)</td>
<td>&lt;0.001</td>
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Table 1: Cardiovascular biomarkers results
and Log-rank tests, and variables with p< 0.15 were considered for a score assessment. Multivariate analysis was performed with a logistic regression, and the score was developed with an Akaike test, which provided a cross-population validation.

**Results:** A total of 1491 patients were included. Variables retained for the score were donor age (DnAge), pre-Tx serum creatinine (Creat), INR and pre-Tx serum albumin (Alb) at second OLT, recipient age (RecAge) at the first OLT, and the interval between 1st and 2nd OLT (Int).

The score = (1.01*DnAge + 1.27*logCreat + 0.88*logInt + 1.14*INR + 1.01*RecAge + 0.85*Alb +2)*20.

The score had a good accuracy, as the Receiver Operating Characteristic area under curve was 0.64. The score was split into three ranges including similar number of patients: Score I > 30, Score II 30-40, Score III > 40. At 3-year survivals were: Score I = 65%, Score II=48%, Score III=31% (Log-rank < 0.0001).

**Conclusion:** The proposed score can accurately identify HCV patients with good survival after re-OLT. We propose that only patients with score I can be considered for re-OLT.

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**Low accelerating dose individualised duration treatment regimen for recurrent HCV post liver transplantation**

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**Introduction:** Treatment with pegylated interferon and ribavirin is poorly tolerated post liver transplantation (LT) with significant side-effects. A low accelerating-dose regimen (LADR) has been used in patients pre-LT on the waiting list.

**Aim:** To retrospectively evaluate the efficacy of an individualised duration, LADR for the treatment of recurrent HCV post-LT.

**Method:** 28 patients were treated at our centre between April 2008 and June 2010. A LADR was used, with initiating antiviral dosages individualised by the treating physician. Treatment duration was determined by: patient tolerance, virological response, presence of advanced liver disease and previous treatment response. Treatment duration was extended beyond 48 weeks when a sustained virological response was felt to be less likely with a 48 week treatment duration.

**Results:** 15 patients (54%) had genotype 1 disease, 11 (39%) genotype 2/3 disease and 2 (7%) genotype 4. 7 (25%) had histologically advanced recurrence (F>3 ISHAK). Initiating doses of ribavrin varied between 200 and 1200 mg/day (mean dose 600 mg). Dose reduction of ribavrin was needed in most patients and EPO support in 61% (n=17). The mean duration of treatment was 42 weeks. 53% (n=15) discontinued treatment prior to the anticipated end of treatment date, 66% (n=10) of these demonstrated inadequate virological response and 33% (n=5) discontinued because of significant adverse events on treatment. 11 patients received treatment in excess of 48 weeks. The average treatment duration in this sub-group was 61 weeks. 63% (n=11) of the extended treatment subgroup discontinued treatment prior to 72 weeks.

The mean haemoglobin decrement in the first 8 weeks on treatment was 2.68 mg/dl. On average, the Hb nadir was seen at 23 weeks of treatment. 3 patients required a blood transfusion whilst on treatment. 11/28(39%) attained an SVR overall. In the extended treatment subgroup, 55% (n=6) attained an SVR.

**Conclusions:** Extending HCV treatment duration beyond 48 is feasible in the post-transplant population and may benefit more difficult to treat groups. Treatment initiation at low doses may help to moderate the onset of on-treatment anaemia and convert it into a late phenomenon on treatment, allowing for a more lengthy period of antiviral exposure.

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**Liver transplantation in patients with familial amyloid polyneuropathy: Comparison of different transthyretin mutations**


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**Introduction:** Liver transplantation (LT) is the only curative option for patients with familial amyloid polyneuropathy (FAP). A wide variety of mutations are known in FAP. Depending on the underlying mutation the outcome of patients may differ considerably.

**Patients:** Twenty-three patients with FAP (8 females, 15 males) underwent LT between 05/1998 and 07/2011. Transthyretin mutations included Val30Met (10 patients) and 10 other mutations.

**Symptoms:** In almost all patients symptoms of polyneuropathy were present. Cardiac symptoms differed considerably. Arrhythmia was present in all but 4 patients with Val30Met mu-
tation. 2 patients with Leu12Pro mutation suffered from severe seizures. 6/13 patients with non-Val30Met mutations presented cardiac symptoms.

**Treatment:** In 6/10 patients with Val30Met mutation a cardiac pacemaker was implanted before LT. In 3 patients with non-Val30Met mutations combined heart-liver transplantation was deemed required (impaired systolic function, severe arrhythmia during attempted LT). In the first patient this approach was performed simultaneously, in the 3 following patients LT was performed several weeks after cardiac transplantation with a clinical course being less complicated.

**Outcome:** 8 patients died after LT (5-year survival: 68%). 2 patients with Val30Met mutation being older than 60 years of age died 1 month, the other 1 year after LT even they had no or mild impairment of cardiac function. 2 patients of the combined heart-liver transplanted group died: One because of cachexia 10 months after transplantation, the second after 115 months due to urosepsis. In the group of sole liver transplanted, two carriers of the Leu12Pro mutation died with complications of grandmal seizures, and both patients with Gly47Glu died of cardiac arrest even though respective symptoms were totally absent before LT.

**Conclusions:** In younger patients with Val30Met mutation LT is the treatment of choice. It is consensus that LT should be performed as early as symptoms are recognised. The indication for implanting a pacemaker is questionable and obviously a defibrillator has to be preferred if required. In particular in patients with non-Val30Met mutations the indication of combined heart-liver transplantation depends on amyloid load of the heart and impaired systolic function. In general, indication for LT may be a problem in non-Val30Met.

**Follow-up of patients after liver transplantation using domino grafts**

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**Introduction:** A standardized follow up after domino liver transplantation (DLT) is lacking although de novo amyloidosis has been reported. Therefore, we implemented a special follow-up. The results and experiences of 12 years are reported herein.

**Patients and methods:** 20 patients underwent DLT since 09/98. The longest follow-up was nearly 12 years (median 68 months, range 4 - 142 months). After DLT patients were enrolled in a special protocol, beginning 3 months after transplantation. In addition to physical examination and blood tests, 5-day electrocardiogram, 24-hour blood pressure measurement, echocardiography, cardiac MRI, cardiac electrophysiological examinations, rectoscopy and extensive neurological examination were performed. This workup was repeated 3 years and 5 years after DLT and thereafter annually.

**Results:** 10/20 patients died after median 29 months (range 4 - 142 months), due to HCC recurrence (n=4), HCV recurrence (n=1), sepsis (n=1), pulmonary embolism (n=1), malnutrition (n=1), pneumonia (n=1) or cardiac arrest (n=1). Since the fatal cardiac complication occurred 3 years after transplantation, deposition of amyloid is unlikely. The follow-up of the surviving patients was 5-131 months. 1/10 deceased patients showed a definite onset of amyloidosis after DLT. After 4 years she developed isolated neurologic symptoms without any motor or autonomic signs, obviously caused by CNI. Immunosuppression was switched from CNI to a mTOR. A rectal biopsy at this time showed no amyloid. 3 years later neurologic symptoms deteriorated with progressive sensory loss in the lower limbs. One year later amyloid deposition was detectable in the gastrointestinal wall, reflecting de novo FAP 9 years after LT. This patient died after 142 months (12 years) because of malnutrition.

**Conclusion:** During our 12 years follow up period 1 patient of 20 domino transplanted patients developed de novo amyloidosis. After DLT the onset of symptoms is significantly earlier than in inherited patients. In the face of organ shortage, the use of domino grafts for elderly and well chosen patients, however, seems to be justified. Nevertheless, a close follow-up is deemed advisable in order to exclude a manifestation of the disease in the recipient of the domino graft and to learn more about the pathophysiology of amyloidosis.
Intravenous silibinin-therapy in patients with chronic Hepatitis C in the transplant setting

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Background: HCV reinfacts the graft in all patients unless HCV can be eradicated before orthotopic liver-transplantation (oLTX). Treatment with pegylated Interferon/Ribavirin (PEG/R) pre-oLTX is poorly tolerated. Intravenous Silibinin (Legalon SIL®, Rottapharm-Madaus; [iVSIL]) is a potent antiviral agent. This study evaluates the efficacy of different therapy strategies of iVSIL mono- and/or add-on-therapy in the transplant setting.

Patients/methods: Twelve patients (male:10; age:51.4±9.7; mean±SD) with HCV-related cirrhosis received iVSIL (20mg/kgBW/d) with or without PEG/R, either before oLTX (n=6) or at various time points after oLTX (n=6). In a compassionate use program their outcomes were evaluated.

Results: One of the 6 patients treated pre-oLTX was reported in detail (Beinhardt et al, J Hepat.2010). In 5 of these 6 patients HCV-RNA levels decreased (mean: 3.3±2.1log MIU/ml). One patient died of septic complications (last viral load: 474 IU/ml), 3 patients were treated for 21d. One patient (with agammaglobulinemia) did not respond. 2 were not transplanted yet due to lack of donor organ, they are still HCR-RNA negative. One patient received iVSIL after first oLTX and did not respond. This patient was listed for re-transplantation due to cholestatic hepatitis. On PEG/R he became HCV-RNA negative but had viral breakthrough after 8 months. After adding iVSIL HCV-RNA became undetectable again. He relapsed after end-of-treatment but his liver tests did not re-increase and he was taken off LTX-list.

4 patients received iVSIL before 2nd oLTX (in 3 patients SIL was started 3-12 months post-oLTX [SIL-treatment duration:8-28d]). 3 of them responded poorly (log16-drop after 8d:0.88±1.4 MU/ml), 2 of them died (GI-bleeding; septicemia). The 4th patient underwent re-oLTX after 8d iVSIL-monotherapy. At oLTX HCR-RNA decreased >5log, remaining detectable (<15 IU/ml) on continued iVSIL for 48 days when PEG/R was added. Despite HCV-RNA-negativity by addition of PEG/R, therapy had to be discontinued through to side-effects and the patient relapsed. In all patients receiving iVSIL bilirubin levels increased (range: 2.45-45.1 mg/dl).

Conclusion: Except for the increase of bilirubin iVSIL is well tolerated in the pre/peri-oLTX-setting and may be useful to prevent graft reinfection. Not all patients responded to iVSIL after oLTX, maybe due to immunosuppressive therapy. Further studies are needed to explore best time-point of iVSIL-application in the oLTX-setting.

Early and late indications of everolimus after liver transplantation

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Aim: Everolimus (Ever) is an mTor inhibitor with immunosuppressant indication on renal and cardiac transplantation. The objective of this study is to analyze the uses and management on liver transplantation (LT).

Material and methods: Since October 1988 to July 2011, 972 liver transplantations were performed in our center. Seventy-four (7,6%) have received Everolimus. Demographic characteristics of these patients, indication and timing of conversion, the evolution and mean follow-up after conversion, the adverse events and withdrawal rate have been analyzed.

Results: Mean age at time of conversion was 58 ± 10 years (r:27-74). The indications of conversion were: refractory rejection 22 (29,7%); HCC out of Milan criteria in explanted liver 13 (16,6%); HCC recurrence post-LT 6 (8,1%); “de novo” Tumor 13 (17,6%); post-LT renal insufficiency 7 (9,5%); neurotoxicity 9 (12,2%) and others 4 (5,4%). Mean time from LT to conversion was 26±42 months (r:0,5-160), median 6m. Mean follow-up post-conversion was 15 ± 14 (r:0,5-56), median12 months. At time of conversion, 19 patients suffered renal insufficiency, 25 arterial hypertension, 21 diabetes mellitus and 29 hyperlipidemia. Preconversion immunosuppressant regimen was based on: 69 Tacrolimus, 4 Cyclosporin and 1 MMF. Postconversion regimen was Tacrolimus + Ever 53; Cyclosporine + Ever 4; Ever ± MMF ± steroids 10; Ever ± steroids 7. Mean trough levels were around 3ng/ml. Out of the 74 patients, 51 (69%) resolved the cause of conversion. More than half of the patients with renal insufficiency and 7 out of 21 patients with diabetes mellitus ameliorated the basal status. The main adverse event was hyperlipidemia (42%). Thirteen patients withdrew the drug due to inefficiency (7) and resolution of adverse event (6).
**Conclusion:** Everolimus at low doses (trough levels around 3 ng/ml), in combination with Tacrolimus or Cyclosporin is a safe and efficient immunosuppressant with multiples indications in early and late post-LT period.

**Recipient’s vitamin D receptor genetic polymorphisms identify HCV positive liver transplanted patients at lower risk of graft fibrosis progression due to recurrent hepatitis C**

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**Background and aim:** Vitamin D receptor (VDR) genetic polymorphisms may confer susceptibility to immune-mediated liver diseases and vitamin D serum levels have been associated with poor antiviral response and worse fibrosis progression in chronic hepatitis C virus (HCV) infection. This study aimed to verify whether recipient’s VDR genetic polymorphisms might influence liver fibrosis progression due to recurrent HCV.

**Methods:** From 1996 to 2010 one hundred and one consecutive HCV positive liver transplanted recipients (72 males) from our Centre, with at least 6 months of follow-up, were included in the study. In each patient graft fibrosis, was assessed by means of annual per protocol or on demand liver biopsies and scored by Ishak. Genotypes for VDR polymorphic sites (FokI C>T, BsmI G>A, ApaI T>G, TaqI T>C) were assessed by RFLP.

**Results:** After a median follow-up of 81 months (range 6-198), 61 (60.4%) and 39 (38.6%) recipients reached an Ishak staging score ≥2 and ≥3 respectively; 20 (19.8%) developed cirrhosis (Ishak staging ≥5). Recipients carrying BsmI A/A and TaqI C/C genotypes reached a staging score ≥2 and ≥3 less frequently compared to those carrying the other genotypes (5/16 Vs 56/85, p=0.013 for BsmI; 5/15 Vs 56/86, p=0.025 for TaqI) for staging score ≥2 and (2/16 Vs 37/85, p=0.024 for BsmI; 2/15 Vs 37/86, p=0.042 for TaqI) for staging score ≥3. None of the recipients carrying these BsmI and TaqI genotypes developed cirrhosis (0/16 Vs 20/85, p=0.036 for BsmI; 0/15 Vs 20/86 p=0.037 for TaqI). No association was found between Apal or Fokl and fibrosis progression. By stepwise logistic regression analysis (donor and recipient age and gender, occurrence of rejection, biliary strictures, MELD score, cold ischemia time, type of immunosuppression, diabetes and VDR polymorphisms as covariates) the carriage of BsmI A/A genotype was confirmed as independent predictor of not reaching both Ishak staging score ≥2 (OR 0.212, p=0.014) and ≥3 (OR 0.154, p=0.027) while recurrent cirrhosis was independently predicted only by recipient gender.

**Conclusions:** The evaluation of recipient VDR genetic polymorphisms may represent a useful tool to identify patients at lower risk to develop more severe graft fibrosis progression due to recurrent HCV.

**Treatment with pegylated interferon and ribavirin during early acute phase of the hepatitis C recurrence vs late hepatitis C recurrence after liver transplantation**

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**Background:** Optimal interval to start antiviral treatment for hepatitis-C-virus (HCV) after liver transplantation (LT) is not known.

**Aim:** Retrospective comparison of the efficacy of early (acute-lobulillar-hepatitis) vs late (chronic-active-hepatitis) treatment of the HCV-recurrence with peg-interferon and ribavirin in 107 LT-recipients.

**Patients and methods:** HCV-LT patients treated for HCV-recurrence between 2001-2010 were included. Patients with non-1 genotype, HIV-coinfection, or colestatic recurrence were excluded. Patients were grouped according to the timing of treatment into early (ET) and differed treatment (DT) groups.

**Results:** Of 152 treated patients during the study period, 107 were included, of whom 53 (57%) completed treatment. Overall, 64 (60%) were assigned to group of ET, and 43 (40%) to group of DT. Median interval from LT to antiviral treatment was 3 (range 1-19) and 18
The effect of liver transplant on fatigue in patients with primary biliary cirrhosis

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Background: Liver transplantation (LT) is a recognized treatment for patients with end-stage primary biliary cirrhosis (PBC). PBC patients may also be transplanted for severe fatigue. The effect of LT on PBC-related fatigue is unclear. We undertook a prospective, longitudinal study to look at changes in measures of fatigue following LT.

Methods: The PBC-40 questionnaire was completed by 35 adult patients with PBC at the time of listing, at 6- and 12-months after LT. We used bilirubin, MELD and UKELD to assess liver function, and the PBC-40 to assess fatigue, before and after LT. Regression analysis was used to assess the relationship between liver function and fatigue. A two-way ANOVA was used to compare the variation of fatigue score before and after LT between patients with low-MELD (< 17) and high-MELD (≥17). The threshold of 17 was chosen because LT offers survival benefit when MELD ≥17.

Results: There was no correlation between MELD and fatigue before LT (r²=0.002; p=0.9). Fatigue score at 6- and 12-months following LT was substantially better than before LT (41.1 ± 10.8 vs 27.6 ± 9.4, pre-LT and 6-months post-LT, respectively, p<0.001). The improvement of fatigue was observed in both low-MELD and high-MELD patients; there was no difference between the two groups. However, it is noteworthy that 50% of the total cohort had moderate to severe fatigue 12-months after LT. Furthermore, in the low MELD group, for whom there was uncertain survival benefit from LT, 39% of patients had moderate to severe fatigue at 1 year after transplantation.

Conclusion: LT is associated with improvement in lethargy. However, a substantial proportion of patients continue to suffer from significant fatigue. LT should therefore be reserved for those with advanced disease.

Single operator peroral cholangioscopy in liver transplant recipients requiring evaluation of the biliary tract

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Background and aims: Anastomotic strictures (AS) after liver transplantation (LT) are commonly managed with endoscopic retrograde pancreatography (ERCP). A limitation of this technique is that it cannot provide direct visualization and tissue sampling of the bile duct. There is very limited information of the role of cholangioscopy in LT recipients that require ERCP. The aim of this prospective study was to describe both the cholangioscopic and histological findings of biliary complications after LT using a single operator cholangioscopy system (Spyglass Direct Visualization system).

Methods: We included adult (age >18 yr) deceased donor LT recipients with biliary complications referred for ERCP between 06/2009-06/2011. Patients were divided in Group 1: LT recipients with AS and Group 2: LT recipients with other biliary complications (CBD stones, bile leak). All patients underwent cholangioscopy with biopsies of the AS and native/graft bile duct with the Spyglass system. The main outcome measure was feasibility and success of the procedure.

Results: We included 16 patients: 12 in Group 1 and 4 in Group 2.
Regional body composition changes after liver transplantation

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Background and aims: Subjects that underwent liver transplantation (OLT) regained a quasi-normal look, normalized liver and kidney function and oral feeding. Unfortunately drugs normally used for immunosuppression can modify some metabolic pathways and share insulin resistance, overt diabetes or dyslipidemia. The aim of the study was to evaluate body composition changes in patients undergoing OLT and their possible relationship with therapy.

Methods: Twenty-nine patients (16 males and 13 females; mean age 52.8 years [SD ± 10], range 21-68) submitted to OLT were prospectively enrolled in the study. All patients had immunosuppression with tacrolimus and steroids. In all subjects body composition analysis was performed by a new dual-energy x-ray absorptiometry equipment (Lunar iDXA, GE Healthcare) after 1, 3, 6, 9 and 12 months from OLT. Fat mass (FM), non-bone lean mass (LM), bone mineral content (BMC) were assessed in a three compartment whole-body and regional model.

Results: Four out of 29 (13.8%) subjects showed diabetes before OLT, and 12/29 (41.3%) had it after surgery. Total and android FM/LM slightly decreased at 3 months, but then rose up with statistically significant differences between 12-month and baseline values (TFM/TLM, 1-mo: mean 0.44 [SD 0.16], 12-mo: 0.72 [0.25], χ²= 19.18, p= 0.001; AFM/ALM: 1-mo: 0.42 [SD 0.17], 12-mo: 0.87 [0.37], χ²=22.57, p< 0.001). Fraction of fat mass [FM% = FM/(FM+LM)] paralleled to FM/LM-ratios, increasing by approx. 35% from 1-mo to 12-mo (29.8 [7.82] to 40.8 [7.61] Kg, χ²=19.18, p=0.001). Subjects with weight gain at 3-months higher than 2% showed AFM/ALM three times higher than other subjects (Mann-Whitney U test, Z=-2.309; p=0.029). Insulin treatment did not significantly affect body composition, while steroid dosage was inversely associated to total and android FM/LM (Spearman’s rho=-0.326, p=0.009 and -0.472, p< 0.001, respectively).

Conclusions: Body composition assessment is essential in the understanding of physiopathology and metabolic-related disorders. DXA is a valid tool at this aim and confirms the data emerging from the old skinfolds assessments. Patients submitted to OLT showed significant changes in their body composition that might be related to different metabolic destinies (insulino- resistance, metabolic syndrome and cardiovascular risk).

Hepatic resection for hepatocellular carcinoma: Validation of simplified BCLC classification

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Aims: Our aim was to externally validate the capability of a simplified Barcelona Clinic Liver Cancer (s-BCLC) staging system (defined by only 2 groups: AA included BCLC A1+A2 classes with AFP < 20 ng/ml and AB included A1+A2 with AFP > 20 ng/ml plus A3 + A4 subgroups) in allocating patients to hepatic resection (HR) and the effect on survival (1).

Methods: We compared 132 patients (Training group: TG) with hepatocellular carcinoma
(HCC) submitted to HR in Milan with another group of 100 patients (Validation group: VG) in Creteil. All patients underwent US-guided HR (<3 segments) and then survival rates were evaluated on the basis of different staging systems (BCLC, s-BCLC, CLIP, Okuda, LCSGJ). Performance of prognostic systems was related to: 1) homogeneity within classification groups; 2) discriminatory ability; and 3) monotonicity of gradients shown in the association between stages and survival rates.

Results: Overall survival got worse from A1 to A4 BCLC stages (p=0.0271) in TG, as well as in VG (p=0.0044), with a more important overlapping of each curves. According s-BCLC classification, survival curves of TG (p=0.0001) and VG (p=0.0250) showed a definitive separation in two different staging groups. The s-BCLC provided the best predictive accuracy and it also presented the highest separability index and C-statistics in the TG. However, similar good relative performances were not confirmed in the VG. On the other hand, the discriminatory ability for death, measured by ROC curve areas, the s-BCLC staging system gave better results than the others. In any case, the overall absolute performances of all these staging systems were low. However, analyzing the prognostic effect of each stage system in all patients together using a Cox model, the only significant independent prognostic score was the s-BCLC.

Conclusion: Our study stressed the high value of BCLC system in staging of patients with HCC, but it probably may not be used to create stringent therapeutic guidelines above all for surgical patients. In a condition of low performance of actual staging systems, s-BCLC seems to obtain the best performance for candidates to HR.

References

An increased liver stiffness measurement one year after transplantation is very accurate at predicting clinical outcomes in hepatitis C recurrence

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Background and aims: Fibrosis stage and hepatic venous pressure gradient (HVPG) one year after liver transplantation (LT) identify HCV-infected LT recipients at high risk of graft loss. Although liver stiffness has been shown to correlate with liver fibrosis and HVPG, the potential ability of liver stiffness measurement (LSM) to predict clinical outcomes in the LT setting has never been investigated. Thus, our aim was to assess the value of LSM one year after LT to predict clinical outcomes in recurrent hepatitis C.

Methods: One-hundred and ninety-three consecutive hepatitis C-infected patients who underwent LT between 2004 and 2010 were included. LSM were obtained per protocol at several time points, including 12 months after LT. The development of clinical decompensations (ascites, hepatic encephalopathy, variceal bleeding) and graft loss (death or retransplantation) were prospectively recorded during a median follow-up of 44 months after LT (range 13-91).

Results: A LSM could be obtained one year after LT in 153 (79%) of the 193 patients. At this time point, 85 patients (55%) had a LSM < 8.7 kPa and the remaining 68 (45%) had a LSM ≥ 8.7 kPa. Among patients with LSM < 8.7 kPa, only 7 (8%) developed clinical decompensations and 7 (8%) lost their graft during follow-up, while among patients with LSM ≥8.7 kPa, 26 (38%) developed clinical decompensations and 23 (34%) lost their graft during follow-up (log-rank < 0.001 for both comparisons). The cause of graft loss was hepatitis C recurrence in 1 (14%) of 7 patients with LSM < 8.7 kPa and in 14 (61%) of 23 patients with LSM ≥8.7 kPa (p=0.03). The figures were similar when outcomes were assessed based on the presence of significant fibrosis or portal hypertension one year after LT.

Conclusions: LSM one year after LT is a reliable, safe and non invasive method to predict clinical outcomes in recurrent hepatitis C. A LSM higher than 8.7 kPa one year after LT accurately identifies those patients at higher risks of developing clinical decompensation and graft loss, and thus with a clear indication to receive antiviral therapy.

Antiviral therapy in recurrent hepatitis C: Advanced donor age and female recipient gender identify non responders at higher risk of graft loss

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Background and aims: Hepatitis C recurrence is the main problem of liver transplant (LT) programs in the Western world. There are few stu-
studies assessing the long-term effects of viral clearance on hepatitis C recurrence and particularly analyzing those variables associated with worse outcomes in non responder patients. The aim of our study was to assess the histological, hemodynamic, and clinical outcomes of antiviral therapy after transplantation, and to identify those individuals at high risk of graft loss in the absence of sustained virological response (SVR).

**Methods:** One-hundred and eighteen HCV-infected LT recipients who underwent antiviral therapy following transplantation were included. Liver hemodynamics and histology were assessed before therapy, upon completion of treatment, and 3 years after treatment interruption. Graft loss (death or retransplantation) and the occurrence of clinical decompensations were prospectively recorded, and baseline variables associated with graft loss in non responders were analyzed.

**Results:** Forty-three patients (36%) achieved SVR. Three years after treatment finalization, liver fibrosis and portal pressure improved or remained stable in 82% and 100% of patients who achieved SVR but worsened in 61% and 41% of non responders, respectively (p< 0.001). The 5-year cumulative probability of graft loss was 9% for patients who achieved SVR and 52% for non responders (p< 0.001). Among non responders, female recipient gender, old donor age (> 55 years) and advanced liver fibrosis were significantly associated with graft loss. Donor age and female recipient gender seemed to act synergistically: 100% of female recipients who received a liver from an old donor and 50% of female recipients who received a liver from a young donor lost their grafts, while the figures for male recipients were, respectively, 52% and 33% (p=0.004).

**Conclusions:** SVR leads to significant long-term improvements in liver fibrosis and portal pressure, which eventually result in improved graft survival. Among non responders to antiviral therapy, female gender and advanced donor age are associated with a very high risk of graft failure.

**Do children with end stage CF-related liver disease benefit from combined liver-pancreas transplant?**

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**Background and aim:** Liver disease is the second most important cause of death in cystic fibrosis (CF). Liver transplantation is the only effective treatment for CF related end stage liver disease. Over 85% of CF patients develop exocrine pancreatic insufficiency of which more than 40% develop CF related diabetes (CFRD). Exocrine and endocrine pancreas insufficiency is associated with poor growth, pulmonary decline and increased mortality. Only three cases of CF patients receiving combined liver pancreas transplantation (cLPTx) have been described in literature so far. Our aim was to evaluate the clinical outcome of cLPTx compared to isolated liver transplantation (iLTx) in children with CF related liver disease.

**Methods:** Through a multinational survey across North-America, Europe and Oceania, 4 centers were identified with experience in performing cLPTx who participated. We used a standardized form to obtain clinical data on patients who underwent iLTx or cLPTx in those centers. Pre-transplant and post-transplant information about height, weight and specific organ, i.e., lung, kidney, liver and pancreas function were obtained.

**Results:** A total of 8 patients with iLTx (75% male, median age at iLTx 12.5 years with range 0-16 years) and 8 patients with cLPTx (25% male, median age at cLPTx 15 years with range 12-22 years) were included. Pre-transplant parameters in terms of lung and kidney function, growth or body mass index (BMI) were similar in both groups. Endocrine pancreas insufficiency was diagnosed in 2/8 patients pre iLTx and 8/8 patients pre cLPTx. Median post-transplantation follow up was 19 months (range 3-114
Efficacy of tips for the prevention of total portal vein thrombosis in cirrhotic patients waiting for liver transplantation

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Introduction: Total portal vein thrombosis may complicate liver transplantation, increasing its technical difficulty, transfusion requirement and in some cases affecting survival after liver transplantation. TIPS could prevent total portal vein occlusion in patients with partial portal vein thrombosis.

Objective: To assess the efficacy of TIPS for the prevention of total portal vein occlusion in patients listed for liver transplantation.

Materials y methods: Clinical records of 15 consecutive patients with partial portal vein thrombosis, who underwent TIPS before liver transplantation, were analyzed. Control group consisted in 8 transplanted patients without TIPS, with partial portal vein thrombosis diagnosed before liver transplantation. Pretransplant characteristics were similar between groups. Portal vein patency at the surgery, transfusion requirements during transplantation and survival after liver transplantation were evaluated. Main complications have also been analyzed.

Results: Among the 15 patients of TIPS group the indications for TIPS were: prevention of total portal vein thrombosis before the transplantation in 8 patients, secondary prophylaxis of refractory gastrointestinal bleeding in 6 patients and refractory ascites in one patient. No relevant complications were observed after TIPS and all patients were transplanted. Median survival at 1 and 5 years after liver transplantation was similar between groups (TIPS-group 92 and 85% vs no-TIPS-group 100 and 75%, respectively; p ns). No differences in transfusion requirements and median duration of ischemia during surgery were observed between groups. However, in all of TIPS patients portal vein patency was observed at the time of surgery, while in 4 out of 8 patients (50%) without TIPS a total portal thrombosis was found (p =0.008).

Conclusion: Among patients with partial portal vein thrombosis TIPS could be performed in order to prevent total portal vein thrombosis.

De novo auto-immune hepatitis and HCV recurrence after liver transplantation: A challenging diagnosis and poor prognosis

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Aim: De novo autoimmune hepatitis (AIH) after liver transplantation (LT) in patients with HCV recurrence is a challenging diagnosis. Impact of immunosuppressive therapy for AIH (IS), consisting of steroids with azathioprine or mycophenolate mofetil, remains unknown after LT. The aim of this study was to determine clinical, serological, histological characteristics of patients with HCV recurrence and de novo AIH, and response to IS.

Methods: 24 liver biopsies (LB) performed between 2003-2010 in LT recipients with HCV recurrence were retrospectively evaluated by a senior pathologist. Plasma-cell infiltration, piecemeal necrosis, perivenular necrosis were blindly reviewed. Clinical, serological, therapy data were collected.

Results: Among 225 HCV recipients, 24 (11%) with histological autoimmune features were included. Gender was M/F 23/1, median age 54 years [27-66], median LT-LB interval 21 months [4.5-138]. According to histological revision, 11 (46%) patients had only HCV recurrence (HCV)...
Immunosuppression with sirolimus increases cardiovascular risk in liver transplant recipients

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Background and aims: Survival of liver transplant (LT) recipients increased dramatically in recent years and cardiovascular disease (CVD) emerged as an important cause of morbidity and mortality. We sought to identify predictors of CVD in LT recipients.

Methods: A random subset of adult patients undergoing first LT at the University of Miami between 01/2000 and 12/2010 and with follow-up > 6 months was evaluated. Statistical tests were used to examine predictors and odds of developing CVD; Kaplan-Meier curves and survival estimates were generated to examine overall survival by gender, ethnicity and CVD.

Results: 304 patients were included, 69% male, mean age 54±10 years, 87% White, transplanted mostly due to HCV (52%) or alcohol-related liver disease (23%). Fifteen patients had NASH. Before LT, 21.9% had been diagnosed with diabetes, 15.5% were hypertensive, 25.3% had a BMI ≥ 30 (mean BMI = 26.9, SD 4.9), 12.0% had hypercholesterolemia and 6.2% of patients were on statins. Post-LT, 21.6% of patients had a BMI ≥ 30 (mean BMI = 27, SD = 7.3, p<0.0001), 26.8% had diabetes (p<0.0001), 51.6% were hypertensive (p<0.0001), and 13.7% had hypercholesterolemia (p=0.11). During a mean follow-up of 5.3 years, 31 patients (10%) had CVD and 41 (13.5%) developed posttransplant metabolic syndrome (PTMS). Patients who developed PTMS had higher prevalence of CVD (29% vs. 11.7%, OR 3.08, p<0.05). There was no association between pre-LT biomarkers (including TB, uric acid and MELD) and CVD, neither did they predict development of PTMS. On univariate analysis age (OR 1.05;CI 1-1.09), nonalcoholic steatohepatitis etiology (OR 3.53;CI 1.05-11.8), PTMS (OR 3.08;CI 1.31-7.27), pretransplant CVD (OR 5.06;CI 1.61-15.9) and treatment with sirolimus (OR 3.97;CI 1.59-9.91) were associated with post-LT CVD. Sirolimus treatment remained as the only significant predictor of CVD on multivariate analysis (OR 3.66, CI 1.44-9.31). There were 78 (22.7%) deaths during the follow-up period. Sirolimus treatment was related to lower survival (log rank p=0.008) but CVD, NASH and PTMS did not predict increased mortality.

Conclusion: Sirolimus use may be associated with increased risk for CVD and death in LT recipients and careful selection of immunosuppression is needed until validated in larger studies.

Hepatocarcinoma in elderly patients: Study of functional hepatocellular regeneration

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Background and aims: More than 50% of liver tumors occur in patients aged 65 years or more. Hepatic resection remains the best treatment option. In elderly patients, assessment of functional liver regeneration capacity is crucial to minimize postoperative liver failure. We aimed to study functional hepatocellular rege-
generation, through scintigraphic quantification of Mebrofenin Hepatic Extraction Fraction (HEF), after partial heptatectomy, comparing elderly patients with younger ones.

**Methods:** 102 patients undergoing partial heptatectomy for primary or secondary hepatic lesions were retrospectively included and divided in two groups: Group A - 58 patients aged < 65 years (33 men, 53.9 ± 8.7 years), Group B - 44 patients aged ≥ 65 years (32 men, 71 ± 5 years). Groups were comparable in several aspects except for the presence of cirrhosis (more common in Group B, all patients Child-Pugh score A) and the initial diagnosis (Group B - Primary lesions, Group A - Metastases). The scintigraphic evaluation of Mebrofenin-HEF was performed before surgery, on the 5th and 30th day post-hepatectomy, evaluating the clearance time (T1/2 and Tmax).

**Results:** Mortality and morbidity were respectively 3.4% and 12.1% in Group A and 2.3% and 11.4% in Group B (ns). HEF values, T1/2 (min) and Tmax (min) showed no significant differences between the two groups: Group A (Preoperative: HEF = 99.2% ± 1.5%, T1/2 = 36.7 ± 21.3, Tmax = 15 ± 6. Day 5: HEF = 96.3% ± 10.8%, T1/2 = 76.4 ± 75.9, Tmax = 13.3 ± 4.9. Day 30: HEF = 98.4% ± 5.5%, T1/2 = 38.6 ± 7.7, Tmax = 12.8 ± 3.6) and Group B (Preoperative: HEF = 95.3% ± 13%, T1/2 = 38.1 ± 24.1; Tmax = 15.9 ± 4.9. Day 5: HEF = 98.4% ± 2.6%, T1/2 = 106.6 ± 131.7; Tmax = 15.1 ± 6.2. Day 30: HEF = 99% ± 2.1%, T1/2 = 40.5 ± 27; Tmax = 15.5 ± 6.7).

**Conclusions:** Our results suggest that functional hepatocellular regeneration is early, fast and similar between elderly and younger patients. Thus, age alone, does not appear to represent an absolute contraindication to hepatectomy.

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**Prognostic serum biomarkers for graft survival after liver transplantation in hepatitis C patients**


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**Background and aims:** Graft reinfection in liver transplanted patients with chronic hepatitis C (HCV) is almost universal, leading to severe fibrosis and graft loss in 25-35% of patients in the first five years after transplantation. As the currently available antiviral therapy is associated with severe side effects and rejection episodes, prognostic factors that can identify patients at risk for graft loss are urgently needed. We hypothesized that distinct immunological markers may predict the long-term outcome of graft hepatitis C.

**Methods:** Forty HCV patients that underwent liver transplantation in our centre between 2001 and 2006 were included in a retrospective-prospective pilot study. Serum samples obtained from clinically stable patients 6 months after transplantation were analysed. All patients were HCV-RNA positive, one cured HCV after IFN-Ribavirin therapy during the observation period and was excluded from the statistical analysis. 54 cytokines, chemokines and angiogenetic factors were measured in serum using multiplex technology (Bio-Plex System). Univariate Cox-analysis was performed considering various clinical and biochemical markers, parameters with p < 0.2 were included in a multivariate model. If two parameters were highly correlated (ρ > 0.8) the parameter with the larger p-value was excluded from multiple regression.

**Results:** Average follow-up time was 63 months (range 18-102). Nine patients suffered graft loss after a median of 34 months following transplantation (range 19-59). Serum HGF (p=0.15), G-CSF (p=0.034), follistatin (p=0.009), IL-16 (p=0.08) and donor age (p=0.05) were eligible for inclusion in the multivariate analysis, which revealed a statistically significant relationship of graft loss with low IL-16 and high follistatin levels (p-values 0.01 and 0.02 respectively). Furthermore we observed an association between outcome and donor age (average 52 years, range 25-76) but not recipient age (average 50 years, range 34-66). A model based on follistatin, IL-16 and donor age was able to predict graft loss with a positive and negative predictive value of 100%.

**Conclusions:** The identification of a distinct serum cytokine pattern could be useful to identify HCV liver transplanted patients that may urgently require antiviral therapy. Moreover, further investigation of the pathophysiological role of IL-16 and follistatin in the transplant setting could enable better understanding and management of graft hepatitis C.
Anti-HBV immunoprophylaxis in liver transplanted patients using subcutaneous administration of HBIG: preliminary results of an ongoing observational study

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**Background:** In Hepatitis B Virus (HBV) related liver transplant (LT) recipients the combined re-infection prophylaxis, antiviral agents plus hepatitis B immunoglobulines (HBIG) is critical to prevent HBV re-infection. Aim of this study is to evaluate the efficacy and safety of subcutaneous HBIG (Zutectra™) in LT recipients.

**Patients and methods:** This is a single center, investigator driven, prospective study. From January 2011 until March 2011, 137 adult LT recipients were enrolled. Inclusion criteria: at least one year from LT, anti-HBs titre >200 UI/ml, HBsAg and HBV-DNA negativity, and long-term HBIG immunoprophylaxis. Patients were switched to Zutectra™ within 4 weeks of the last HBIG administration. Zutectra™ was administered weekly at a dose of 500 UI if body weight ≤ 75 kg and 1000 UI if body weight > 75 kg. The anti-HBs titre was determined the day before the Zutectra™ administration, every two weeks during the first three months and monthly for the remaining three months of the study period (six months). Concurrent HBV antiviral agents was left unchanged.

**Results:** Among 137 cases, median age 55 years (34-78), 136 patients maintained a level of anti-HBs titre > 150 UI/ml; in only 1 case the anti-HBs titre was between 100 UI/ml and 150 UI/ml.

No patients (0/137) showed HBV reinfection throughout the complete study period. None of the patients asked to go back to previous i.v. immunoglobulins regimen and all of them showed a good compliance to self-administration. Only in 4 cases (2.9%) an adverse event (itch), not surely related to Zutectra administration, was observed. No clinically relevant changes in laboratory parameters, vital signs and physical condition were observed.

**Conclusion:** Zutectra™ administration in LT recipients showed a good effectiveness and safety.

Long-term outcome of liver transplantation for hepatitis B with anti-HBc positive grafts

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**Background:** Patients who undergo liver transplantation (LT) for hepatitis B virus (HBV) infection have been considered the most appropriate group to receive anti-HBc+ grafts. However, the only existing case-control study (Joya-Vázquez, 2002) showed that recipients of these grafts were 2.5 times more likely to develop HBV recurrence. Our aim was to evaluate the long-term LT outcome for hepatitis B with the use of anti-HBc+ grafts.

**Methods:** Between 1/1/1995 and 31/12/2010, 1618 LTs were performed at our center, of whom 153 (9.5%) were for hepatitis B.

**Results:** Of the 150 patients in whom donor HBV serology was available, 29 (19%) received an anti-HBc+ graft. 134 (89%) patients had cirrhosis, 27 (18.5%) and 10 (7%) had coexistent HDV and HCV infection, respectively, and 50 (33%) had HCC. 88 (59%) had received therapy with NUCs prior to LT and 32 (25%) were viremic at the time of LT. With a median follow-up of 5.5 years (range: 0.03-16 years), 11 (7.6%) of the 144 patients who had at least one post-LT HBV serology available developed hepatitis B (positivization of HBsAg) with a median time to re-infection of 1.8 years (range: 0.07-3.5 years). The cumulative probability of post-LT hepatitis B at 1, 5 and 10 years was 3.7%, 8.3%, and 8.3%, in recipients of anti-HBc+ grafts vs. 2.7%, 9.8%, and 9.8% in recipients of anti-HBc-grafts-(p =ns). In the multivariate analysis, pre-LT HBV-DNA positivity and acute rejection were independently associated with post-LT hepatitis B. 36 (24%) of the 150 patients died. The patient survival rates at 1, 5, and 10 years were 87%, 82%,and 58% in the anti-HBc+ group vs. 87%, 82%, and 74% in the anti-HBc- group (p=ns). In the multivariate analysis, age, HCV coinfection and chronic rejection were independently associated with survival. The presence of HCC was not associated with survival (p=0.31), although in this subgroup of patients, patients with recurrent HCC had lower survival rates (p< 0.0001) and an increased rate of post-LT hepatitis B (p=0.001).

**Conclusions:** In patients undergoing LT for HBV-related liver disease the use of anti-HBc+ grafts does not have a negative impact on the long-term LT outcome.
Exploring MELD (model for end stage liver disease) further
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Background and aims: The MELD score incorporates parameters of liver and kidney damage. Only certain patients with higher MELD scores require concurrent kidney transplant along with liver transplants. We hypothesize that post liver transplantation outcome is different for a given MELD score in patients with liver failure with and without concurrent kidney damage.

Methods: This was a retrospective analysis of the UNOS (United Network Organ Sharing - USA) database including all the patients undergoing liver transplants (n=21,023) from January 2003 to December 2010. We organized patients into 9 groups based on their MELD scores as follows: 6-15, 16-18, 19-21, 22-24, 25-27, 28-30, 31-33, 34-36 and 37-40. In each MELD group patients were further categorized into four categories as follows; 1) Creatinine >1 and Sodium <135 (n=5424), 2) Creatinine >1 and Sodium >135 (n=7221), 3) Creatinine <1 and Sodium <135 (n=3049), 4) Creatinine <1 and Sodium >135 (n=5329). Both patient and graft survival were evaluated.

Results: At three months post transplantation there was no difference in graft and patient survival at any given MELD score between patients with or without renal damage or transplant. At 12 and 24 months post transplantation, in patients with MELD score groups, 16-18, 20-24, 25-27, 31-33 and 34-36, patient survival was significantly higher in category 4 than in lower categories, being worst in Category 1, whereas there was no difference between categories in groups, 19-20, 28-30 and 37-40. Liver graft survival was better in category 4 over lower categories in groups, 16-18, 20-24 and 25-27. It was not significant in any groups with MELD score higher than 30.

Conclusion: In patients with a MELD score above 30 there was no impact of low Sodium or high Creatinine on the graft survival, while patient survival failed to show a consistent correlation pattern between the MELD score and high Creatinine or low Sodium.

Transjugular intrahepatic portosystemic shunts following liver transplantation can be associated with a good prognosis:
A single centre experience
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Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) is indicated in the management of portal vein thrombosis or stenosis, portal hypertension and for veno-occlusive disease in post-liver transplant (LT) patients. Previous series have reported 1 year mortality rates of 14-67%. A MELD score greater than 15 at the time of insertion may indicate a poor long term prognosis. We aimed to evaluate the safety of TIPS after LT at a UK tertiary referral centre.

Methods: We retrospectively analysed data from the Royal Free Hospital TIPS database between 1st January 1991 and the 31st January 2011. All patients who had undergone TIPS following LT were included.

Results: During the period studied 629 patients received a TIPS. In the same period 1192 liver transplant operations were performed. 10 TIPS were inserted into patients following LT for recurrent cirrhosis with refractory ascites (4), veno-occlusive disease (3) and portal vein thrombosis (3). The original indications for transplantation were PSC (3), PBC (3), Hepatitis C (1), Autoimmune (1), Primary Oxalosis (1) and Acute Liver Failure (1). We noted a median survival of 38 months. Survival at 1 and 5 years was 100% and 60% respectively. The median MELD at the time of TIPS insertion was 12 (range 7-19). No correlation between the MELD score at the time of TIPS insertion and survival was demonstrated (p=0.62).

Conclusions: These results suggest that TIPS can be performed safely after LT and that survi-

Figure 1: Survival post TIPS insertion
val rates better than those previously reported can be achieved. We suggest TIPS should be used in carefully selected candidates following LT as a definitive treatment for patients not suitable for re-transplant or as a bridge to re-transplantation. The alternative of re-transplantation should always be considered prior to TIPS insertion where indicated.

### Surgical resection is a good option for hepatocellular carcinoma with massive portal invasion

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Presence of portal venous tumor thrombus (PVTT) is one of the most ominous prognostic factors in patients with hepatocellular carcinoma (HCC). According to AASLD or EASL guidelines for HCC, only sorafenib is recommended in this setting with reported median survival time of 10.7 months (Llovet JM 2008 NEJM). However, in selected cases with good liver functional reserve, surgical resection may provide chance for cure. Our treatment strategy is:

1. Selective transarterial chemoembolization as an initial treatment,
2. Subsequent evaluation of liver functional reserve,
3. Anatomical resection of tumor bearing sector or hemiliver.

There are two surgical techniques to remove PVTT, conventional en bloc resection and the peeling off (PO) technique. The PO technique is less invasive in that PVTT is dissected from the portal venous wall and removed through the portal venotomy opening. Residual PVTTs intruding into tiny branches are meticulously extracted. Details of the operative technique will be presented with video. Between 1994 and 2008, 1,263 patients with HCC underwent liver resection at our institution. Of these, 74 patients, 14 patients survived more than five years including 5 patients without recurrence and 9 with recurrence promptly treated. In conclusion, liver resection with tumor thrombectomy provides chance of cure in patients with good liver function. Since tumor recurrence is common after resection, role of adjuvant chemotherapy is to be elucidated.

### The effect of an 'alcohol contract' on ethanol consumption after transplantation for alcoholic liver disease

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**Background and aim:** Recidivism after orthotopic liver transplantation (OLT) for alcoholic liver disease (ALD) remains a source of unease. Recidivism rates of 10-16% are reported with a low rate of alcohol-related graft loss (1,2). In 2005, the UK Transplant liver advisory group recommended an ‘alcohol contract’ in which ALD patients listed for OLT confirmed in writing their commitment to abstinence (3). Our aim was to measure the rates and consequences of post-OLT alcohol intake in a UK transplant program and assess the effect of the ‘alcohol contract’.

**Method:** Prospectively collected data was reviewed for 100 randomly selected patients transplanted for ALD – 32 patients transplanted since the ‘alcohol contract’ was implemented (Feb 2007) and 68 patients transplanted before.

**Results:** Overall (n=100; 62 male, median age 54), 37 patients reported some alcohol intake post-OLT. The proportion of patients returning to any alcohol was 35.3% before the ‘alcohol contract’ and 40.6% after (NS; p=0.66). For heavy drinking (>21 units [168g ethanol]/week) this was 16.2% and 15.6%, respectively (NS; p=0.66). Four patients underwent OLT despite pre-OLT liver histology consistent with active ALD. After OLT, one of these returned to heavy drinking; another denied drinking but had a positive blood alcohol. At explant, 10 patients had features of active ALD: 6 of these returned to drinking. Blood alcohol was measured in only 24 of 63 patients reporting abstinence. Two had positive tests; one of these subsequently disclosed heavy drinking. 23 patients died. Most deaths (87%) occurred in those (63%) who did not return to drinking.

**Conclusions:** Post-OLT recidivism is higher in our cohort than other published series but its
impact on post-transplant survival remained low. The introduction of an ‘alcohol contract’ may have value in improving public perception of transplanting ALD patients but is insufficient to alter rates of recidivism. Random blood alcohol testing is inadequate to detect post-transplant drinking. More robust abstinence support and better assessment measures might improve outcomes.

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Leaking umbilical hernia management in ascetic patients due to decompensated hepatic cirrhosis; safety and outcome of modified stone’s herniorrhaphy [MSH]

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Background and aim: Urgent repair of umbilical hernia in cirrhotic patients is indicated when complications developed. The evaluation of leaking umbilical hernia (LUH), complications and its management by Modified Stone’s Herniorrhaphy [MSH] in ascetic patients due to decompensated liver disease has been done. The new Technique of MSH by local lidocaine infiltration anaesthesia [LLIA] has been evaluated.

Methods: We have 10 years study of 168 LUH in ascetic hepatic patients. All cases have been evaluated and prepared by antibiotics, albumin, FFP and repeated sterile dressing of ulcerating skin preoperatively. The LLIA, intraoperative LVP, portal blood and lymph node biopsy have been done. Tripple Layers of suture repair have been done by our new technique of MSH as an emergency.

Results: The LUH patients were 108 males, 60 females and their ages were 28 to 62 years. They were between 6 and 271 months from transplantation. Overall sexual activity and conjugal satisfaction after liver transplantation in male and female patients

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Background: While good outcomes can be achieved after liver transplantation, only limited data is available on its impact on sexual activity. This is especially important considering that liver recipients have multiple risk factors for sexual dysfunction, including hormonal abnormalities, encephalopathy and, in some, a history of alcohol abuse. The aim of this study was to assess sexual function and conjugal satisfaction in patients prior to and after liver transplantation in comparison with healthy individuals.

Patients and methods: A cross-sectional cohort questionnaire assessment was performed in adult (≥ 18 years) recipients at the Geneva University Hospitals. Questionnaires included the International Index of Erectile Function (IIEF) for men or the Female Sexual Function Index (FSFI) for women. Conjugal satisfaction was assessed with the Locke-Wallace Marital Adjustment Test. Waitlist candidates and age-matched healthy individuals were used as controls.

Results: Questionnaires were sent to 242 patients and 136 replied (56.2%). They included 45 women and 91 men with a mean age of 57 ± 11 years. They were between 6 and 271 months from transplantation. Overall sexual
function improved after liver transplantation in both genders (male: $p=0.065$ and female: $p=0.072$). Similarly, the proportion of patients with severe dysfunction tended to be lower after vs. prior to transplantation (male: 18 vs. 42%, $p=0.09$, female: 40 vs. 77%, $p=0.61$). The level of post-transplant conjugal satisfaction is not affected in men, but significantly improved in women ($p=0.008$). Despite the observed improvements, liver recipients still demonstrated lower levels of sexual function than healthy individuals (male: $p<0.001$, female: $p=0.006$), but had similar conjugal satisfaction.

Conclusion: Liver transplant candidates have major sexual dysfunctions and problems with conjugal satisfaction, which improve after transplantation. After improvement, sexual function remains lower than in age-matched healthy individuals, and this topic requires specific management, especially considering that 76% of tested patients indicated that sexuality was important to them.

**Use of telaprevir plus PEG interferon/ribavirin for null responders post olt with advanced fibrosis/cholestatic hepatitis C**


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Aggressive recurrence of hepatitis C post OLT remains problematic with low SVR rates with PEGIFN/RBV (PR). There are limited data on treatment of HCV infection with DAA therapy plus PR post-OLT. Our aim was to review our experience with telaprevir addition to PR in treatment of aggressive hepatitis C in null responders to PR post OLT.

Methods: Adult patients who developed recurrent HCV infection following OLT with null response to PR for at least 12 weeks (< 2 log reduction) post-OLT received 4 week lead-in PEG-IFN alfa-2b (1.0 μg/kg/wk) plus RBV (600-1000 mg/day) followed by addition of telaprevir 750 q8. All patients who were not on cyclosporine modified (CYA) were converted to CYA from tacrolimus prior to initiation of HCV therapy. On the first day of TVR, patients received 25 mg CYA with trough levels titrated to 100 ng/ml. HCV RNA measured every 4 weeks by Cobas TaqMan HCV Test.

Results: Seven patients (3 M, 4 F), mean age 56 years, have been treated thus far, 4 patients have received 12 weeks of TVR after lead-in. Three were < 1 year post-OLT, 5 had cirrhosis and two bridging fibrosis. Treatment parameters are described in Table 1.

All patients required EPO, ¾ GSF, mean packed-blood-cell requirement was 10 U per pt during TVR treatment. One patient stopped at week 4 telaprevir for futility. Mild-moderate rash noted in all pts with no supra/sub-therapeutic CYA levels encountered.

Conclusions: Four week PR lead-in followed by telaprevir for 12 weeks can lead to significant clearance rates in null responders with advanced fibrosis though high rates of anemia/RBV dose reduction, and transfusion requirements were noted. CYA interactions were easily managed by CYA dose adjustment. Twelve week TVR treatment data will be available for 7 patients in 3/2012.

**Table 1: HCV RNA, RBV, CYA, Hgb weeks 0-16**

<table>
<thead>
<tr>
<th>Treatment week</th>
<th>log 10 HCV RNA (IU/ml)</th>
<th>HCV RNA undetectable</th>
<th>Mean CYA dose (mg/day)</th>
<th>Mean daily RBV (mg/kg)</th>
<th>Hgb (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.0</td>
<td>0/4</td>
<td>200</td>
<td>10.8</td>
<td>11.8</td>
</tr>
<tr>
<td>4</td>
<td>6.0</td>
<td>0/4</td>
<td>25</td>
<td>7.9</td>
<td>9.9</td>
</tr>
<tr>
<td>8</td>
<td>1.3</td>
<td>2/4</td>
<td>34</td>
<td>6.0</td>
<td>8.5</td>
</tr>
<tr>
<td>12</td>
<td>1.9</td>
<td>3/4</td>
<td>63</td>
<td>5.6</td>
<td>7.2</td>
</tr>
<tr>
<td>16</td>
<td>1.2</td>
<td>3/4</td>
<td>81</td>
<td>6.1</td>
<td>7.1</td>
</tr>
</tbody>
</table>

**Recurrence rate and cause of death in liver transplantation for primary sclerosing cholangitis: A 25 year experience**

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Primary sclerosing cholangitis (PSC) is an autoimmune disease that can progress to end-stage liver disease. PSC is an accepted indication for liver transplant (LT). The goal of this study was to determine long term recurrence rate and cause of death following LT in our PSC cohort. All patients transplanted for PSC between
The severity of hepatic ischaemia-reperfusion injury is associated with acute kidney injury following Donation after Brain Death liver transplantation

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1Liver Unit, Queen Elizabeth Hospital, 2NIHR Biomedical Research Unit and Centre for Research, University of Birmingham, Birmingham, UK

Donation after Cardiac Death liver transplant recipients have an increased frequency of acute kidney injury (AKI) during the immediate post-operative period. The prevalence of IBD in our cohort was 83% in the live cohort. This study confirms that in Atlantic Canada, liver transplantation is a successful treatment for PSC and cardiovascular death is relatively infrequent in our cohort.

Out-patient assessment for liver transplantation: A single centre experience

T.R. Lim1, M.J. Armstrong1, D.H. Houlihan1, K.H. Wong1, C. Cook2, A. Turner1, M. Perrin1, J. Cantrill1, P. Ashcroft1, D. Hughes1, C. Weijers1, A. Holt1

1Hepatology Unit, 2Finance Department, Queen Elizabeth Hospital Birmingham, Birmingham, UK

Background and aims: Assessment for liver transplantation (LT) traditionally requires admission to hospital. In 2010, the liver unit at the University Hospital Birmingham (UHB) launched the first UK-based out-patient assessment programme (OPA). This study aims to describe our experience, with specific focus on feasibility/efficacy, cost-effectiveness and patient satisfaction.

Methods: Patients undergoing elective LT assessment were retrospectively analysed bet-
ween June 2010-April 2011. Data collected included patient demographics/clinical features and LT assessment parameters. An extensive cost evaluation was performed on both in- and out-patient LT assessment, including clinical tests, staffing and hospital facilities utilised. Patient satisfaction questionnaires were collected prospectively from April 2011-Nov 2011.

**Results:** In total, 179 patients underwent LT assessment. 87/94 successfully completed OPA, with the remaining 7 converted to in-patient LT assessment (IPA) due to pre-existing co-morbidity (refractory ascites and hepatic encephalopathy). All patients referred for OPA were triaged 2 weeks prior to the assessment to ensure suitability. The remaining 92 patients successfully underwent IPA. Baseline demographics are described in table 1.

66/87 OPAs were listed for LT (median duration from OPA to listing 3 days [range 0-306]), of which 37/66 received a cadaveric graft. The reasons for OPAs not listed include: too early for LT (50.0%), contraindication to LT (42.9%) and patient refusal (7.1%). 53/92 IPAs were listed (mean duration 4 days [range 1-39]), of which 34/53 were transplanted. Reasons for IPAs not listed: contraindication to LT (48.2%), too early for LT (44.4%) and patient refusal (7.4%). A single IPA costs on average £14,441 versus £11,494 for an OPA. Overall satisfaction (mean score 9.6/10; 10=very satisfied, 1=very dissatisfied) and convenience (mean score 7.9/10) for patients undergoing OPA were high.

**Conclusions:** We describe for the first time that OPA is feasible, efficient and cost-effective. With increasing demand on hospital beds in the UK National Health Service, such a programme has the potential to reduce the burden on LT in-patient services.

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### Table 1: Patient demographics and clinical features

<table>
<thead>
<tr>
<th></th>
<th>Mean Age (±SD)</th>
<th>Male Sex (%)</th>
<th>Aetiology (Viral, Alcohol, HCC, Metabolic, Auto-immune/biliary, Other)</th>
<th>UKELD median [range]</th>
<th>Liver co-morbidities: Encephalopathy, Refractory Ascites, Variceal Bleeding</th>
<th>Other co-morbidities: Hypertension, Diabetes, Renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>52.3 (±1.3)</td>
<td>58.6</td>
<td>(n=6, 6, 26, 9, 30, 10)</td>
<td>51 [43-66]</td>
<td>n=23, 0, 14</td>
<td>n=10, 11, 1</td>
</tr>
<tr>
<td></td>
<td>55.0 (±0.9)</td>
<td>54.3</td>
<td>(n=11, 21, 12, 20, 13, 15)</td>
<td>53 [43-67]</td>
<td>n=40, 7, 8</td>
<td>n=3, 10, 4</td>
</tr>
</tbody>
</table>

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**The UN-SUSTAINABLE match in HCV liver transplant patients**


1Liver Transplant Center, “A.Gemelli”Hospital, Catholic University, Rome; 2Liver Transplant Center, “S. Giovanni Battista” Hospital, University of Turin, Turin; 3Liver Transplant Center, “S. Orsola” Hospital, University of Bologna, Bologna; 4Liver Transplant Center, IsMeTT-UPMC, Palermo; 5Liver Transplant Center, “Niguarda” Hospital, Milan; 6Liver Transplant Center, “Ospedali Riuniti”, Bergamo; 7Liver Transplant Center, University of Modena and Reggio Emilia, Modena; 8Liver Transplant Center, “S. Martina” Hospital, University of Genoa, Genoa; 9Liver Transplantation Center, IRCCS Foundation, “Maggiore” Hospital, Milan; 10Liver Transplant Center, “San Camillo-Forlanini” Hospital, Rome; 11Liver Transplant Center, “Umberto I” Hospital, Polytechnic University of Marche, Ancona; 12Liver Transplant Center, National Cancer Institute, IRCCS Foundation, Milan; 13Liver Transplant Center, University of Udine, Udine; 14Liver Transplant Center, “Umberto I” Hospital, “La Sapienza” University; 15Liver Transplant Center, “Tor Vergata” University Hospital, Rome; 16Liver Transplant Center, “G. Brotzu” University Hospital, Cagliari; 17Liver Transplant Center, Department of Emergency and Organ Transplant, University of Bari, Bari; 18Liver Transplant Center, Laparoscopic Hepatobiliary Surgical Unit, “A. Cardarelli” University Hospital; 19Liver Transplant Center, Hepatobiliary Surgical Unit, “A. Cardarelli” University Hospital, Naples; 20Liver Transplant Center, Department of Surgical and Gastroenterological Sciences, University of Padua, Padova; 21Epidemiology and
Biostatistics Unit, Institute of Hygiene, Catholic University, Rome, Italy

**Introduction:** Donor to Recipient (D2R) MATCH is a matter of debate in liver transplantation (LTx). D-MELD (Donor Age x biochemical MELD) has been identified as an effective formula to predict Patient Survival (PS) according to D2R-MATCH in United States and in Italy. To avoid resource wasting, LTx of pts with a 5yrsPS < 50% has been questioned.

**Methods:** As a subanalysis of the Italian D-MELD study, data obtained from 2355 HCV pts were evaluated using a training (2/3) and a validation set (1/3). D-MELD cutoffs were investigated using Kaplan Meier analyses. A web-site was implemented with a survival calculator (www.D-MELD.com, password “D-MELD123”).

**Results:** A cutoff able to predict the 5yrsPS < 50% was identified at the D-MELD=1750 (UN-SUSTAINABLE Match Cut-Off). 5yrsPS=44.2%, 95% CI 0.32-0.50 (training set); 5yrsPS=43.7%, 95% CI 0.28-0.49 (validation set).

We failed to identify a cutoff in HBV, HCC, Cholestatic Diseases.

**Discussion:** The UN-SUSTAINABLE match cut-off identifies a population with poor prognosis. The 5yrsPS=50% should be read as the minimal sustainable survival rate considering the competition within the waiting list. Using the 5yrsPS < 50% cut-off could be misleading because not evidence based. However it identifies a subgroup (equal to 7%) of HCV patients with a performance status below the currently defined minimal survival requirement. In case of donor to recipient high-risk match (D-MELD>1750) we suggest to change the allocation from an HCV to a non-HCV recipient, following the principle that the allocation of an organ with a high-risk should be shifted from a patient with a high-risk to another patients with a lower-risk, in order to balance the overall risk. However, elderly grafts can be safely transplanted in HCV patients if D-MELD is < 1750.

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Periportal sinusoidal fibrosis is an early marker of portal hypertension and significant fibrosis in hepatitis C recurrence after liver transplantation

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1Liver Unit, Hospital Clinic, CIBERehd, IDIBAPS, 2Pathology Unit, Hospital Clinic, CIBERehd, IDIBAPS, Barcelona, Spain

**Introduction:** Chronic HCV infection in liver transplant (LT) patients leads to cirrhosis in 30% of individuals only 5 years after LT. The presence of significant fibrosis (F≥ 2) or portal hypertension (HVPG≥ 6 mmHg) one year after LT identifies patients with an accelerated course. Sinusoidal fibrosis (SF) is an early expression of the fibrogenic process in response to liver injury. Its role in predicting an accelerated course of hepatitis C after LT has never been assessed.

**Aim:** Evaluate whether SF is a reliable and early marker to identify HCV-infected patients with an accelerated course of hepatitis C after LT.

**Methods:** 75 HCV-infected liver transplant patients were included. All patients underwent an early liver biopsy (2-6 months after LT), as well as an HVPG measurement and/or liver biopsy one year after LT. Patients with other diagnoses (acute rejection, biliar complications, pharmacological injury) were not considered for analysis. Samples were stained with Sirius Red and periportal SF was graded as mild, moderate or severe using a semi-quantitative scoring system. Results were correlated with the development of severe hepatitis C recurrence one year after LT (F≥ 2 and/or HVPG≥ 6 mmHg).

**Results:** SF was scored as mild in 50 samples (66%), moderate in 13 (17%) and severe in 10 (16%). One year after LT, the mean HVPG value in patients with moderate or severe SF was 10,1 mmHg (25th-75th quartiles 6,4 - 12,6) compared to 5,7 mmHg (25th-75th quartiles 3-7,5) in those with mild SF (p< 0,01). Portal hypertension (HVPG≥ 6 mmHg) and significant fibrosis (F≥ 2) one year after LT were detected in 86% and 76% of patients, respectively, in whom early SF was scored as moderate/severe (n= 19). The main factors related to the development of severe hepatitis C recurrence one year after LT (F≥ 2 and/or HVPG≥ 6 mmHg).

**Results:** SF was scored as mild in 50 samples (66%), moderate in 13 (17%) and severe in 10 (16%). One year after LT, the mean HVPG value in patients with moderate or severe SF was 10,1 mmHg (25th-75th quartiles 6,4 - 12,6) compared to 5,7 mmHg (25th-75th quartiles 3-7,5) in those with mild SF (p< 0,01). Portal hypertension (HVPG≥ 6 mmHg) and significant fibrosis (F≥ 2) one year after LT were detected in 86% and 76% of patients, respectively, in whom early SF was scored as moderate/severe (n= 19). The main factors related to the development of early SF were donor age (p< 0,01), AST (p=0,03), GGT (p< 0,01), bilirubine (p< 0,01)

<table>
<thead>
<tr>
<th></th>
<th>1 yr PS</th>
<th>2 yrs PS</th>
<th>3 yrs PS</th>
<th>4 yrs PS</th>
<th>5 yrs PS</th>
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<tr>
<td>Sustainable match</td>
<td>87 (85-89)</td>
<td>81 (78-84)</td>
<td>78 (75-81)</td>
<td>75 (71-78)</td>
<td>70 (87-74)</td>
</tr>
<tr>
<td>Un-sustainable match</td>
<td>76 (69-83)</td>
<td>63 (55-71)</td>
<td>58 (51-65)</td>
<td>52 (43-61)</td>
<td>44 (32-50)</td>
</tr>
</tbody>
</table>
Safety of intraoperative hemodialysis during liver transplantation: A 10-year experience

L. Matsuoka, W. Ananthapanyasut, M. Boyajian, S. Kang, A. Sedra, Y.S. Genyk, M.K. Nadim
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Background: Liver transplantation (LT) in patients with renal dysfunction is frequently complicated by major fluid excess, metabolic acidosis, electrolyte and coagulation abnormalities increasing the risks of operation. Intraoperative renal replacement therapy (RRT) is frequently required to combat these additional problems including large volume resuscitation and allow the surgery to proceed successfully. Continuous renal replacement therapy (CRRT) is frequently used in patients who are hemodynamically intolerant of hemodialysis (HD) however it requires continuous anticoagulation, associated with slower solute and volume removal and is an expensive mode of therapy compared to HD.

Aim: This is the first study examining the feasibility and safety of intraoperative hemodialysis (HD) during LT in a large patient cohort.

Methods: Retrospective, single center study of 175 patients who received intraoperative HD from 2001-2011, 59 of whom received a combined liver-kidney transplantation.

Results: Average age was 52.6 years. 131 (74.9%) patients were on RRT at the time of LT, 43.5% of whom were on CRRT, for a median of 11 days. For those patients not on RRT, the mean creatinine was 3.2 mg/dl. Median MELD was 38, 53% were in the ICU, 19% required mechanical ventilation and 50% of patients were on pressors at the time of LT. Mean intraoperative HD time was 442 minutes with lowest mean systolic pressure 81 mmHg during dialysis. Patients on average received 8L of colloids and crystalloids, 15 units of packed red blood cells and 12 units of fresh frozen plasma without any change in central venous pressure despite an average urine output of 479 cc. There was 1 (0.6%) intraoperative death and 2 (1.1%) deaths within the first 24 hours post LT. For patients who underwent LT alone, 58% patients required RRT within 72 hours of LT, for an average of 15 days. Dialysis dependency was 11% by 1 month and 3% by 3 months.

Conclusion: This is the first study to demonstrate that intraoperative HD can be performed safely, efficiently and with hemodynamic tolerability in a cohort of critically ill patients undergoing liver transplantation with low long-term dialysis dependency.

Systematic CT-scan on post-operative day 7 after liver transplantation decreases the rate of retransplantation for arterial complications

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1Centre Hepato-Biliaire, AP-HP - Hopital Paul Brousse, 2Unit 785, INSERM, Villejuif, 3Faculte de Medecine, Univ Paris-Sud, Le Kremlin-Bicêtre, France

Objective: Arterial thrombosis is a main cause of graft lost after liver transplant (LT). Objective of this study was to assess the incidence of systematic CT-scan on post-operative day (POD) 7 on the rate of retransplantation (ReLT).

Materials and methods: 232 consecutives patients transplanted in 1997-1999 (1st period) were compared to 250 transplanted in 2008-2010 (2nd period) in the same center. A clinical, biological and echodoppler control was daily performed from POD1 to POD7. An injected CT-Scan was realized only in case of abnormalities in 1st period and systematically on POD7 in 2nd period. Graft and donor features, risk factors of AT, incidence of arterial stenosis (AS) or thrombosis (AT), their treatments and their consequences in the 1st year after LT were compared in the two groups.

Results: The 2 groups (1st vs 2nd period) were different for donors’ ages and body mass index (age: 41±1 years vs 52±1 years; p=0.0001 - BMI: 23±4 vs 25±5; p=0.0001) and recipients’ ages (46±1 years vs 50±1 years; p=0.0004). In the 2nd period, the incidence of AS was significantly higher, 1/232(0.4%) vs 11/250(4%); p=0.006, and the incidence of AT at 1 year was lower but not significantly, 11/232(4.7%) vs 5/250(2%); p=0.2. Systematic POD7 injected CT-scan had significantly increased the radiological diagnosis of AS and/or AT (1st vs 2nd period): 7/12 (58%) vs 15/16 (94%); p=0.05 and decreased its diagnosis delay (3±2.5 months vs 1.1±0.3 months). In the 1st period, AS or AT treatments had been relT (n=5), arterial reconstruction (n=3), stent (n=1) or anticoagulation (n=3). In the 2nd pe-
Liver transplantation for overlap syndromes of autoimmune liver diseases

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Background and aims: The term overlap syndrome describes variant forms of autoimmune hepatitis (AIH) that present in combination with either characteristics of primary biliary cirrhosis (PBC), or primary sclerosing cholangitis (PSC). This study analyses the recurrence and other outcomes after liver transplantation in patients with overlap syndromes compared to patients transplanted for single autoimmune liver disease.

Methods: We evaluated 231 adult patients who received a liver transplant due to autoimmune liver diseases; including 103 with PBC, 84 with PSC, 32 with AIH, and 12 with overlap syndrome (7 AIH-PBC, and 5 AIH-PSC).

Results: The duration from diagnosis to liver transplantation was significantly shorter in patients with overlap syndromes than those with single autoimmune liver disease (35±11 vs. 101±11 months; P=0.009). Patients with overlap syndromes had a higher probability of recurrence than patients with a single autoimmune liver disease (5 years: 46 vs. 17%; 10 years 64 vs. 29%, P=0.008). Median time for recurrence in overlap syndrome was shorter when compared with patients with single autoimmune liver disease (61±23 vs. 183±12 months, P=0.008). Of the 7 patients with overlap syndrome AIH-PBC, 2 patients developed features of recurrent PBC, 1 of AIH, and the other of AIH-PBC overlap. Of the 5 patients with overlap syndrome AIH-PSC, 1 patient developed features of AIH, 1 PSC, and 1 overlap AIH-PSC. There were no differences in the frequency of graft loss and survival between patients with overlap syndromes and patients with either single autoimmune liver disease. Median graft-survival for overlap syndrome was 135±13 months, and 195±21 months in patients single autoimmune liver disease (P=0.5), and median patient-survival for overlap syndrome was 136±13 months, and 256±41 months in patients single autoimmune liver disease (P=0.6).

Conclusions: Patients with liver transplantation due to overlap syndrome-end stage liver disease may have disease recurrence as a single or combined autoimmune liver disease. In addition, these patients had an earlier onset and higher rate of recurrence when compared to those receiving liver transplantation for single autoimmune liver diseases. Despite this our study showed the overlap syndrome patients have similar survival post-liver transplant.

The clinical impact of preoperative estimation of remnant liver function using 99mTc-labelled galactosyl-human serum albumин liver scintigraphy

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Background and aim: The estimation of liver function preserved before hepatectomy is important to perform operation safely. The aim of this study is to assess the clinical value of preoperative estimation of remnant liver function using 99mTc-labelled galactosyl-human serum albumin liver scintigraphy and computed tomography.

Methods: One hundred and forty eight patients who had hepatic resection including lobectomy or partial resection were studied. Liver function was estimated by both liver single photon emission computed tomography (SPECT) and computed tomography (CT) scans using 99mTc-labelled diethylene triamine pentacetate galactosyl human serum albumin (GSA). Preoperative remnant liver function was calculated by hepatic regional GSA clearance using SPECT with fusion image of CT scan. Liver failure was defined as acites, total bilirubin (more than 3 mg/dl), or encephalopathy.

Results: Fifteen patients (10%) of 147 patients developed liver failure. All seven patients whose remnant liver function was less than 75 ml/min developed liver failure after hepatectomy. Regression analysis of clearance of remnant liver correlated with postoperative max total bilirubin with log approximation (R=0.76, P<0.01). Areas under the ROC curves for GSA clearance of remnant liver, whole liver, and LHL15 were 0.92, 0.62, and 0.58 respectively.

Conclusion: GSA clearance of remnant liver calculated using fusion images of SPECT and CT is useful in evaluating the risk of postoperative liver failure, which may contribute to the appropriate selection of operative procedure.
Liver disease and post-operative mortality in patients with colorectal cancer: A Danish nationwide cohort study

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Background and aims: The coexistence of chronic liver disease in patients undergoing colorectal cancer (CRC) surgery may pose a serious challenge since liver diseases are becoming more prevalent and may lead to increased mortality. However, knowledge on postoperative mortality after CRC surgery in patients with liver disease - particularly those with non-cirrhotic diseases - is limited. Such knowledge is needed to understand the prognostic effect of liver diseases and to optimize perioperative care.

Methods: Using individual-level linkage of Danish medical databases, we conducted a nationwide cohort study of all patients undergoing first-time CRC surgery from 1996 through 2009. Patients with any previous diagnosis of liver disease were categorized into two groups: those with liver cirrhosis and those with non-cirrhotic liver disease. Patients with no history of liver disease prior to CRC surgery were defined as the reference group. The Kaplan-Meier technique was used to estimate 30-day mortality for each patient group. We used a Cox regression model to compare 30-day mortality among CRC patients in each liver disease group to that in the reference group. Hazard ratios were used as measures of the relative risk (RR) of death, adjusting for gender, age, cancer stage, timing, comorbidities, surgery and alcoholism. Postoperative mortality and RRs were stratified by colon and rectal cancer.

Results: A total of 39,840 patients undergoing CRC surgery were included in the study. Of these, 369 (0.9%) had non-cirrhotic liver disease, and 158 (0.4%) had cirrhosis. Thirty-day mortality was 13.3% in patients with non-cirrhotic liver disease and 24.1% among patients with cirrhosis, compared to 8.7% in patients without liver disease. After adjustment, this corresponded to RRs of 1.49 (95% confidence interval CI: 1.12-1.98) for non-cirrhotic liver diseases, and 2.59 (95% CI: 1.86-3.61) for patients with liver cirrhosis. Similar results were obtained after stratifying patients by colon and rectal cancer.

Conclusions: Pre-existing liver disease was associated with markedly increased 30-day mortality following CRC surgery.

Endotoxemia management in liver transplant patients

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The presence of endotoxins, derived from Gram-negative bacteria, determine greater resistance to standard antibiotics therapy and facilitate rapid evolution to septic shock and multi-organ failure (MOF). Our principal end point was to use a new assay Test Endotoxin Activity Assay (tEAA) which has been developed to rapidly detect endotoxin activity (EA). Furthermore we aim to prove the validity and safety of removal of endotoxins using Polymyxin-B based hemoperfusion (PMX-DHP). Finally, survival, endotoxin activity and graft function were monitored at 30 days of follow up.

Material and methods: The criteria for inclusion in the study were the following findings: infection was suspected when patients had at least 2 of the 4 criteria of systemic inflammatory response syndrome (SIRS). Following these criteria, the tEAA was performed on 32 liver transplants. Fifteen recipients with EA>0.6 were enrolled in this study and received treatment to remove endotoxins (PMX-DHP). Each treatment was performed for two hours with a blood flow rate of 100 mL/min. All the patients were treated with PMX-DHP until an EA< 0.4 was found. None of the patients were in mechanical ventilatory support.

Results: Two PMX-DHP treatments were performed on 7 patients [median EA =0.69(0.62-0.76)], three treatments on 5 patients [median EA =0.85(0.77-0.92)] and four treatments on 3 patients [median EA =1.11(0.95-1.25)]. At the end of the endotoxin removal therapy, the median EA level was 0.33(0.23-0.4). The stabilisation of hemodynamic (p< 0.005) and inflammatory frameworks (p< 0.001) were immediately observed after the PMX-DHP. Microbiological findings showed the presence of Gram negative infections in 9 patients within 68.7±4.9h from enrolment. The remaining six patients had negative hemocultures. At 30 days of follow up all patients were alive with a good graft function and low level of endotoxin activity.

Conclusion: The EA assay could be considered a diagnostic test to detect infection early or may be used to clarify the role of endotoxin translocation and can help us to determine the
correct timing for intervention. Accordingly, larger multicenter clinical trials will be necessary to accurately assess the benefits of tEAA plus DHP-PMX for transplant patients with sepsis.

Simultaneous liver-kidney transplantation: A survey of US transplant centers

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Background: The introduction of MELD has led to an increase in simultaneous liver kidney (SLK) transplantation. As a result, consensus recommendations were published to help better define those patients who would benefit from a SLK transplantation. We conducted an on-line survey to determine the SLK practice patterns in the United States.

Methods: An on-line anonymous 20-questionnaire survey was sent to the Kidney Transplant Medical Directors at all transplant programs in the U.S that perform SLK.

Results: From the 88 centers that were surveyed, 57 centers completed the survey for a response rate of 64.8%. From the respondents, 27 (47.4%) performed between 5-10 SLK / year and 6 (10%) performed > 10 SLK / year. Definition of acute kidney injury (AKI) in patients with cirrhosis varied across centers with the majority (67%) defining AKI as an increase in creatinine by 50% from baseline. The majority of centers (73%) stated that they "always" use dialysis duration whereas only 30% of the centers use AKI duration for patients not on dialysis as a criteria for determining need for SLK. Dialysis duration of > 4 weeks was used by 31.6% of centers, >6 weeks duration by 36.8% and > 8 weeks duration by 31.5% of centers as a criteria for SLK. Kidney biopsy was performed "always" in only 3% of centers as a means for determining need for SLK. Glomerular filtration rate (GFR) was determined using the MDRD-4 equation by 47.8% of centers, whereas the MDRD-6 equation was used by 6.5%, iothalamate clearance by 10.9% and 24 hour creatinine clearance by 34.7% of centers to determine GFR. In patients with CKD, the GFR cut-off level also varied among centers with GFR < 40 ml/min used by 24.5% of centers, < 30 ml/min in 52.6% and < 25 ml/min in 19.2% of centers. Regional differences were also seen among the questions asked.

Summary: This survey demonstrates significant variation used in the criteria used for SLK among the centers with few centers following the current published recommendations and further emphasizes the need for developing evidence-based guidelines and uniformity in studying renal dysfunction in liver transplant candidates.

The receptor for advanced glycation end products (RAGE) axis in liver transplantation

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Background: Up-regulation of the multi-ligand receptor for advanced glycation end products (RAGE) is correlated with chronic vascular and metabolic disease. RAGE is also expressed in the liver, and RAGE blockade has been reported to mitigate the extent of liver injury. A soluble RAGE (sRAGE) circulates in the bloodstream and acting as decoy can contribute to the removal of circulating ligands. We investigated hepatic RAGE mRNA expression, plasma levels of RAGE ligand N(epsilon)-carboxymethyl-lysine (CML), and sRAGE in patients undergoing liver transplantation (LT) and in their deceased donors.

Methods: Twenty-four adult, consenting LT recipients of primary whole-size grafts were included (M:F = 20:4; mean age 52.7±9.2 years). The transcriptional expression of hepatic RAGE, and plasma CML and sRAGE levels were also evaluated in their deceased donors (mean age 60.4±17.9 years). In LT recipients CML and sRAGE levels were determined before surgery, and tested serially after graft reperfusion, 1, 7, 30 and 90 days post-transplantation.

Results: In LT recipients, pre-transplant hepatic RAGE mRNA levels were higher than in deceased donors (p< 0.01), inversely correlated with antithrombin III (β= -0.58, p= 0.013) and cholinesterase plasma levels (β= -0.717, p= 0.0018), and directly correlated with MELD scores, although this latter did not reach the level of statistical significance (β= 0.422, p= 0.063). Pre-transplant CML plasma levels, but not sRAGE, differed between LT recipients and their deceased donors (p< 0.05). At follow-up, recipients’ CML levels decreased immediately after graft reperfusion (p=0.0001) and returned progressively to basal pre-transplant levels during the follow-up period. Plasma levels of sRAGE did not change significantly soon after LT, while they decreased from day 7 (p = 0.0001) and remained constantly low during follow-up (p=0.02).
Conclusions: LT is associated with an unfavourable metabolic signature early on after surgical procedure. At transplantation, LT recipients show metabolic impairment as per up-regulated tissue RAGE expression and accumulation of toxic metabolites (CML). Circulating CML levels decrease after reperfusion and return to pre-transplant values rapidly thereafter. This, in conjunction with a dramatic decrease in sRAGE, might account for the metabolic complications associated with LT and their negative impact on graft and patients survival.

Development and validation of PeLTQL: A disease-specific questionnaire to measure health-related quality of life in paediatric liver transplant recipients

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Background and aims: Currently, no disease-targeted instrument is available for measuring health-related quality of life (HRQOL) in pediatric liver transplant (LTx) recipients. Using established tool development methodology (item generation, item reduction, questionnaire formatting, pretesting), a novel disease-specific HRQOL instrument entitled PeLTQL was developed by an international cohort of pediatric LTx recipients for pediatric LTx recipients. The specific aim of this study was to test the PeLTQL’s psychometric properties - reliability, sensibility, validity and responsiveness - for validation of this novel tool.

Methods: Construct validity was based on a priori hypotheses. Mean PeLTQL total scores (range, 0 [worst] to 130 [best]) were correlated with generic (PedsQL® generic, cognitive modules) and disease-specific (PedsQL® Transplant module), anxiety (SCARED) and Medication-Taking Behavior Tool (MTBT) instruments. Test-retest reliability was calculated by intraclass correlation coefficients (ICC). Internal consistency was tested using Cronbach’s α. PeLTQL sensibility was assessed by number of questions left blank and time to complete.

Results: N=123 (59% male) patients who underwent LTx in Canada (42%), USA (24%), Australia (19%), and United Kingdom (15%) for primary conditions of biliary atresia (30%), paediatric acute liver failure (12%), metabolic liver diseases (12%), liver tumour (8%), and other (18%) participated in this validity study. Median patient age at PeLTQL completion was 13.7 (range 8.1-18.0) years. The mean PeLTQL score was 97.99 ± 13.62 (range, 53 -126). Significant correlations were found between: mean PeLTQL vs PedsQL® Generic scores (0.63, p< 0.0001); mean PeLTQL vs PedsQL® Transplant module scores (0.71, p< 0.0001); mean PeLTQL vs SCARED scores (-0.50, p< 0.0001). Moderate correlation was found between mean PeLTQL vs MTBT scores (0.37, p< 0.0001). The mean PeLTQL score for the 8 patients who scored in the abnormal range for the CDI-S suggestive of depression (scores>=65) was significantly lower than those patients scoring in the normal range for CDI-S (78.1±16 versus 99.3±12, p< 0.0001). The ICC for PeLTQL was 0.85. Internal consistency was excellent with a Cronbach’s α of 0.85. 17/3198 (0.5%) PeLTQL questions were left blank. Self-administration time was less than 5 minutes.

Conclusions: The PeLTQL is a valid, reliable, and feasible HRQOL tool for children and adolescent LTx recipients.

High reticulocyte count predicts mortality and improves accuracy of UKELD in patients awaiting liver transplantation

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Background: The shortage of donor organs for liver transplantation (LT) makes it essential that organs are allocated to patients with greatest need. There has been increasing interest in haemoglobin as a predictor of LT outcomes. We investigated red cell parameters as predictors of survival after LT assessment.

Methods: Data on patients with end-stage liver disease assessed for LT between 2008 and 2010 at University Hospitals Birmingham, UK, were reviewed retrospectively. Kaplan-Meier and Cox regression analysis identified parameters predictive of death on the waiting list. To construct an updated UKELD model including high reticulocyte count (defined as >80), cases that had not received LT at 12 months were
randomly divided into two groups (2:1 ratio) to for model building and testing. Accuracy of the existing and new models was tested by calculation of c-statistics.

**Results:** Data were collected from 393 patients. Median age was 55 years (range 17-73), 60% were male. Median MELD was 14 (3-37) and median UKELD 56 (44-76). Median follow up was 18 (0-45) months. In total 144 (37%) underwent LT.

Abnormal reticulocyte count, seen in 120 patients (31%), was greatest predictor of death without LT (hazard ratio (HR) 3.1; 95% CI 1.7 - 5.6), compared to haemoglobin (HR 2.5; 1.3 - 4.5) and MCV (HR 0.6; 0.3 - 1.2). Abnormal reticulocyte count remained a significant predictor of death after adjustment for age, gender and diagnosis (p<0.001).

We used patients who had not had LT within 12 months of assessment to construct and validate an updated UKELD that incorporated abnormal reticulocyte count. Of these 267 patients, 129 had died and 138 were alive without LT. C-statistic for UKELD in this cohort was 0.75. Remodelling UKELD to include abnormal reticulocyte count (UKELD + 10.6[reticulocyte count > 80; yes = 1, No = 0]) improved predictive accuracy with a c-statistic of 0.79.

**Conclusion:** High reticulocyte count is associated with increased risk of death in patients awaiting LT. Remodeling UKELD to include high reticulocyte count significantly improved accuracy of predicting death on LT waiting list.

**Interleukin-2 receptor antagonists for liver transplant recipients:**

**Systematic review with meta-analyses and trial sequential analyses of randomised clinical trials**

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**Background:** The use of T-cell antibody induction therapy after liver transplantation has increased during the last decade. Currently 26% of liver transplant recipients receive induction therapy with antibodies. Interleukin-2 receptor antagonists (IL-2 RA) are the most commonly used T-cell antibodies for induction therapy in liver transplant recipients, however, the benefits and risks of IL-2 RA therapy are unclear.

**Objective:** To assess the benefits and risks of IL-2 RA in liver transplant recipients.

**Methods:** We conducted a systematic review with meta-analyses and trial sequential analyses of randomised trials following The Cochrane Handbook. We searched electronic databases (CHBG Controlled Trials Register, CENTRAL, MEDLINE, EMBASE, Science Citation Index, and the WHO International Clinical Trials Registry Platform) and bibliographies, and selected all randomised trials comparing IL-2 RA induction versus no intervention or placebo, and IL-2 RA versus corticosteroid (CS) induction.

**Results:** We identified 8 trials with 1336 patients comparing IL-2 RA versus no intervention. Mortality (Risk Ratio (RR) 0.69; 95% confidence interval (CI) 0.52-0.91; Heterogeneity
I^2=65%) and acute rejection (RR 0.75; 95% CI 0.59- 0.95; I^2=0%) were reduced in patients receiving IL-2 RA compared with no intervention, but the required information sizes were not reached when trial sequential analyses were applied and random errors cannot be excluded. No difference in infection and cancer incidence occurred when IL-2 RA were compared with no intervention.

We identified 5 trials with 1129 patients comparing IL-2 RA versus CS induction. None of the groups received maintenance CS. No significant differences in mortality and acute rejection were seen between these groups, however, diabetes (RR 0.33; 95% CI 0.17- 0.64; I^2=0%) and CMV infections (RR 0.49; 95% CI 0.30-0.81; I^2=27%) were less frequent with IL-2 RA induction compared with CS induction.

Conclusion: IL-2 RA seem to be superior to no intervention with regard to mortality and acute rejection. Furthermore, diabetes and CMV infections may be less common with IL-2 RA compared with CS induction in patients receiving no maintenance CS. Due to heterogeneity and risk of bias more trials are needed to confirm these findings.

Prospective assessment of liver fibrosis after liver transplantation in HIV/HCV coinfected patients: A useful tool assessing severe fibrosis on the liver graft

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Because fibrosis progression could be particularly rapid in HIV/HCV coinfected patients after liver transplantation (LT), an early detection of severe fibrosis is crucial. We prospectively assessed the stage of fibrosis of 15 HIV/HCV coinfected patients using liver biopsy, transient elastography, and serum markers after LT.

Patients and methods: From December 2007 to May 2010, 13 HIV/HCV coinfected patients (mean age 46.5 yrs ± 5.1 [36-57] with a mean MELD at inscription of 16.2 ± 11.7 [3-44]) underwent LT. A control group of 15 HCV monoinfected patients (mean age 58.4 yrs ± 9.4 [41-71], mean MELD score at inscription: 13.4±8.8 [3-39]) transplanted during the same period was also prospectively studied. Liver biopsies, liver stiffness (LS) and serum markers (Fibrotest, APRI, FIB-4) were analyzed at month, 6, 12, 18 and 24.

Results: Mean fibrosis scores in HIV/HCV coinfected and in HCV monoinfected patients are summarized in Table 1. Differences in LS in HIV/HCV coinfected and in HCV monoinfected patients are summarized in Table 1. Differences in LS in HIV/HCV coinfected patients were significant between M12 and M24 (p=0.015). Values of serum markers did not differ over time nor according to the type of co-

<table>
<thead>
<tr>
<th></th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
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<tbody>
<tr>
<td>Fibrosis (Metavir)</td>
<td>HIV+HCV+ / HIV-HCV+</td>
<td>HIV+HCV+ / HIV-HCV+</td>
<td>HIV+HCV+ / HIV-HCV+</td>
<td>HIV+HCV+ / HIV-HCV+</td>
</tr>
<tr>
<td>F≥2 n(%)</td>
<td>4(33) / 5(38)</td>
<td>4(36) / 6(50)</td>
<td>NA*</td>
<td>6(50) / 8(73)</td>
</tr>
<tr>
<td>LS (kPa)</td>
<td>8.01 ± 3.39 / 11.38 ± 7.24</td>
<td>7.53 ± 2.80 / 10.74 ± 7.08</td>
<td>14.6 ± 17.05 / 12.08 ± 5.62</td>
<td>14.45 ± 14.14 / 12.31 ± 6.55</td>
</tr>
<tr>
<td>Fibrotest</td>
<td>0.699±0.209 / 0.628±0.282</td>
<td>0.643±0.223 / 0.671±0.202</td>
<td>0.738±0.233 / 0.694±0.164</td>
<td>0.494±0.200 / 0.695±0.170</td>
</tr>
<tr>
<td>FIB-4</td>
<td>0.429±0.407 / 0.412±0.280</td>
<td>0.679±0.78 / 0.532±0.442</td>
<td>0.640±0.928 / 0.683±0.570</td>
<td>0.392±0.157 / 0.723±0.9203</td>
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NA = not available.
horts. Liver stiffness had the best diagnostic accuracy to identify patients with metavir score ≥ F2 (ROC curve = 0.944).

**Conclusions:** These results support the interest of transient elastography after liver transplantation to monitor HCV recurrence. Moreover, transient elastography identifies rapid fibrosers after LT in HIV/HCV coinfected patients.

**Monitoring blood eosinophils can predict response to corticosteroids in patients with acute cellular rejection after liver transplantation**

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**Background and aims:** Blood eosinophil count (BEC) is related to the occurrence and grade of acute cellular rejection (ACR) after liver transplantation. We aimed to evaluate the role of BEC in the prediction of treatment response and its clinical impact.

**Methods:** From 749 liver transplant patients available in our prospectively collected protocol biopsy database (1988-2011), ACR treatment with steroids (3 boluses of 1 gr methylprednisolone for 3 consecutive days) was needed in 263 cases which were included in the study. A second protocol biopsy was performed 6±2.1 days later to assess response to treatment. Rejection grade was defined according to Banff schema. BEC on the day of the second biopsy and ΔBEC between the first and second biopsy were evaluated as potential predictors of successful histological response (ie. when rejection grade improved from moderate or severe to mild or no rejection).

**Results:** Grade of ACR in the first biopsy was moderate in 162 cases (61.6%) and severe in 27 cases (10.3%). In the second biopsy, 109 patients (41.4%) showed improvement while 154 patients did not improve (131 remained unchanged and 23 worsened). BEC on the day of the second biopsy and ΔBEC between the first and the second biopsy were related to the likelihood of treatment response (p=0.003 and p=0.002 respectively) (figure 1). In the ROC curve, the AUC for ΔBEC was higher (65.4%). A ΔBEC rising higher than 0.3 x10⁹/L implied a high risk of no response to steroids (78.3%). Improvement in grade of ACR was also more frequent in patients who received 3 grams of steroids (102/221;46.2%) than in those who received a lower dose (7/42;16.7%) (p< 0.001); nevertheless this variable did not influence BEC (p=0.33). The multivariate analysis (including ΔBEC, steroids dose, immunosuppression protocol and liver function tests) identified ΔBEC as the only independent variable able to predict histological improvement of ACR after treatment with steroids (OR=2.58;CI=1.3-4.9;p=0.004).

**Conclusions:** Changes in BEC are associated with histological response to boluses of steroids to treat ACR. BEC monitoring can be a non invasive assessment tool in this setting.

**20-year protocol liver biopsies: Invasive but useful for the management of liver recipients**

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**Introduction:** Most liver transplant centres have discontinued the practice of protocol liver biopsies (LB), mainly because of the perceived lack of therapeutic benefit. This study aimed to examine the usefulness of 20-year LBs.
**Methods:** 10, 15 and 20-year protocol LBs from 147 patients surviving for >20 years were reviewed. 20-year biopsy findings were correlated with clinical data.

**Results:** 20-year-biopsy patients (N=91) and 20-year-non-biopsy patients (N=56) were similar in terms of transplant data, adverse events, and liver function tests (LFTs). 20-year LBs revealed a 90% prevalence of abnormalities, among which viral chronic hepatitis (VCH) was the most common (46%). Between 15 and 20 years, hepatic structural abnormalities were the only disorder to increase (p=0.008). An individual progression of abnormalities occurred in 56% of patients. At 20 years, the negative and positive predictive values (PV) of LFTs with respect to histological abnormalities were 95% and 18%, respectively; In VCH, Fibrotest and transient elastography displayed poor discriminative ability for fibrosis (80% and 81% discordance, respectively), but were satisfactory regarding significant fibrosis (negative PV of 77.7% and 80%, respectively); A decrease in immunosuppression was less frequent (14/91 versus 20/56, p=0.008) while an increase was more common (15/91 versus 2/56, p=0.017) in 20-year-biopsy patients than in non-biopsied patients. Antiviral therapy was administered in seven of the 20-year biopsied patients, but in none of the non-biopsied patients (p=0.04).

**Conclusion:** 20-year LBs provided important histological information on graft function that was available to a limited degree from LFTs and non-invasive markers. They exerted an impact on immunosuppressive and antiviral therapies.

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**Adult living donor liver transplantation – How efficient and safe is the donation?**

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**Background:** Adult to adult living donor (right lobe) liver transplantation (LDLT) is a modality to decrease the mortality rate on the waiting list (WL). Due to the cadaveric organ shortage, LDLT is a constantly growing part of orthotopic LT performed in our country. It raises various ethical, economic and health-related concerns from the donor standpoint.

**Aim:** We reviewed all LDLT performed in our center between January 2004 and October 2011. Basic demographic details were collected and various pre-operative parameters were obtained for the potential donors.

**Methods:** Clinical records of all (one hundred nineteen) subjects evaluated as potential donor were reviewed according to a step-wise evaluation protocol. Basic demographic details, various pre-operative parameters were obtained.

**Results:** A total number of 119 subjects were evaluated with the mean age at the time of surgery 34,9 years old, 58,82% of whom were women. 65,56% of the donors were biologically-related to the recipient. All donors had pre-operative imaging to define vascular and biliary anatomy and liver biopsy. Only 40 (33,61%) of the potential donors underwent surgery.

The non-exclusive reasons for rejection were: insufficient hepatic volume determined by CT volumetry (45%), positive hepatitis B serology (6,33%), severe dislipidemia (7,6 %), abnormal anatomy (5,07%); access to cadaveric hepatic graft (3,80%), socioeconomic reasons in 14,2 %, recipient contraindication (2,53%), pregnancy during evaluation (1,27%); one patient was identified with focal nodular hyperplasia and another one patient was found with tumoral hepatomegaly.

Liver biopsy was done in all potential donors with good right lobe hepatic volume and 6,27% were excluded due to abnormal histopathology (>20% steatosis).

Finally, 40 underwent surgery. Donor survival was 100% with seven days hospitalization rate in post-operative period.

**Conclusion:** LDLT can substantially provide significant contribution to the organ pool and thus reduce waiting-list morbidity and mortality. However suitable living donors are not easy to find. The donor evaluation process remains to be a large burden on the resources of our program.

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**The association of co-existent non-ischaemic cardiac disease with morbidity and mortality following liver transplantation**

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The risk stratification of potential liver transplant candidates with co-existent non-ischaemic cardiac disease (CD) is particularly challenging given the masking effect of the haemodynamic dysfunction of advanced portal hypertension. Whether such patients have altered outcomes following liver transplantation remains unknown. Our aim was, therefore, to exa-
mine the effects of mild and moderate non-ischaemic CD on post liver transplant morbidity and mortality.

**Methods:** Single-centre study of patients undergoing first liver transplantation for chronic liver disease. To determine the effects of mild CD, the routine assessment trans-thoracic echocardiography reports of 246 patients transplanted 01/2007-03/2010 were reviewed. To determine the effects of moderate CD, patients transplanted from 1994 to present were highlighted from a prospectively collected database.

**Results: Mild CD** 11.4%, 11.4%, 2.8%, and 0.8% of the 246 patients undergoing routine assessment echocardiography had left atrial dilatation, or mild mitral regurgitation, aortic regurgitation or aortic stenosis, respectively. After adjusting for confounding variables there was no association between left atrial dilatation (p=0.738) or mild mitral regurgitation (p=0.234) and a cardiac event post transplant. Similarly, there was no association between left atrial dilatation (p=0.146) or mild mitral regurgitation (p=0.157) and post transplant survival.

**Moderate CD** Ten patients were transplanted with moderate CD: aortic valve replacement (4), moderate valvular dysfunction (2), HOCM (2), moderate left ventricular failure (1), mitral valvuloplasty (1). Two of these patients underwent simultaneous valve replacement surgery. Of these 2 patients, 1 had a peri-operative cardiac event and both were alive at 1-year. For the remaining 8 patients who did not undergo intervention the cumulative incidence of a cardiac event by 1-year after transplantation was 68.7%, and the estimated 1-year survival was 46.7%. All 3 patients with a pre-existing aortic valve replacement that was not re-done had a cardiac complication: one patient developed bacterial endocarditis and awaits further valve replacement surgery, two died of cardiac failure at 90- and 200-days post transplant.

**Conclusions:** Chronic liver disease patients with co-existent moderate CD who receive a favourable cardiac risk assessment have greater than expected morbidity and mortality following liver transplantation. Our findings suggest that the severity of non-ischaemic CD is underestimated in this setting.

**Treatment by intraoperative microwave ablation (MCN) achieved 70% of 5-year survival rate for HCC within Milan criteria: MCN as an alternative to liver transplantation**

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**Background:** Recently, liver transplantation (LT) for hepatocellular carcinoma (HCC) have achieved a good outcome in patients who fulfilled the Conventional Milan Criteria (CMC; a single tumor ≤5 cm in diameter, or two to three tumors ≤3 cm in diameter). LT is now being used as a common treatment for HCC within CMC in many countries; however, LT is limited by an absolute shortage of deceased donor liver graft in Japan. Therefore, another treatment, which can achieve an excellent result comparable to LT, is needed.

We have used intraoperative loco-regional microwave ablation, named microwave coagulonecrotic therapy (MCN) as a part of treatment strategies of HCCs for more than 15 years. We evaluated the treatment outcomes of HCC within CMC and assessed whether MCN could be an alternative to LT.

**Methods:** Between July 1994 and December 2010, 2297 patients underwent hepatic surgery in our institute. 719 consecutive patients received MCN as their initial therapy for HCC. Of these, 470 patients met the Milan criteria. Three patients received living donor liver transplantation in their following courses and were excluded from this analysis. Of the remaining 467 patients, overall survival and recurrence free survival were prospectively evaluated.

**Results:** The 1-, 3-, 5-, 7- and 10-year survival rates of all patients who met CMC treated with MCN were 98.0%, 84.6%, 70.9%, 57.2% and 45.6% respectively. 5-year survival rate of 106 patients with a single HCC ≤2 cm in diameter was 95.0% and that of 377 patients who had ≤3 lesions ≤3 cm in diameter was 73.0%. Of 80 patients with a HCC larger than 3cm in diameter, 5-year survival rate was 65.8%.

Tumor recurrence occurred in 249 patients. Disease-free survival rates at 1-, 3-, 5-, 7- and 10-year, respectively in all patients were 89.9%, 53.0%, 38.0%, 27.1% and 22.6%. Repeated MCN were performed more than 2 times, if possible.

**Conclusions:** Our results showed that MCN achieved a good survival rate of HCC fulfilling the Milan criteria, comparable to that by LT. We consider that MCN could be used as an alternative treatment for HCC, in particular, in countries with scarcity of donor livers.
Reducing risk factors for skin cancer development following liver transplant – The need for more effective patient education and health promotion
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Background/aims: Sun exposure and immunosuppression are the main risk factors for skin cancer (SC) in organ transplant patients. Our primary aim was to audit the information given to liver transplant recipients (LTRs) with respect to the use of sun-protection and avoidance of sun-exposure.

Methods: 157 consecutive patients in our post-transplant clinic were surveyed by questionnaire. Information regarding underlying liver disease, immunosuppression and skin conditions developing after liver transplant (LT) was collected. The survey also asked whether patients had received education on skin, sun-exposure and SC. A subset of 51 patients provided added information on the use of sun-protection.

Results: The response rate was 76% (120/157). The mean responder age was 47.7 years (19-73). Numerous underlying liver diseases were identified with an average post transplant time of 5 years (0-24). Skin-types varied from Type I (Fair) to Type VI (Dark). After LT, 34.2% had been advised by their physician about their skin. Only 17.5% of patients had dermatology counseling. Recall regarding education on SC and sun-exposure after LT was 42.5% and 66.7%, respectively. Rates of received advice were largely equal in skin types I-III and IV-VI. Eighty-six percent of patients used mechanical sun-protection (i.e. hats/clothing). Sunscreen use in 51/120 patients was reported at 72.5%; 39.2% of the users applied sunscreen at the recommended sun protection factor (SPF) of >30; 25.5% used an SPF of 15-30; and 5.9% used an SPF of < 15. Sun-protection/sunscreen use was almost equal between skin types. Five patients (Skin-types I; I; IV; V; VI), developed squamous cell carcinoma with a mean of 9.8 years (3-19) post-transplant. Three of these (Skin types I; I; VI) either used no sunscreen or one with SPF < 15.

Conclusion: In our unit, LTRs are given information on sun-exposure and SC before/after transplantation – our pilot-project indicates poor recall on advice given. The use of sun-protection was good but the use of sunscreen (SPF >30) was poor, highlighting the need for better patient education. SC carries significant morbidity and even mortality, thus regular reinforce-ment of SC education should be considered after LT. Additionally, dermatology consultation may improve patient involvement and retention of information.

A model for dropout assessment of candidates with or without hepatocellular carcinoma on a common liver transplant waiting list
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Introduction: In many countries, the allocation of liver grafts is based on the Model of End-stage Liver Disease (MELD) score and the use of exception points for patients with hepatocellular carcinoma (HCC). With this strategy, HCC patients have easier access to transplantation than non-HCC ones. In addition, this system does not allow for a dynamic assessment, which would be required to picture the current use of local tumor treatment.

Aim: To design a model assessing the risk of dropout for patients with hepatocellular carcinoma on the liver transplant waiting list.

Methods: This study was based on the Scientific Registry of Transplant Recipients and included 5498 adult candidates of a liver transplantation for HCC and 43528 for non-HCC diagnoses. A proportional hazard competitive risk model was used.

Results: The risk of drop-out of HCC patients was independently predicted by MELD score, HCC size, HCC number and alpha fetoprotein (AFP). When combined in a model with age and diagnosis, these factors allowed for the extrapolation of the risk of drop-out. The C-index was 0.72 (95%CI: 0.69-0.79). While this model and MELD did not share compatible scales, a correlation between both models was computed according to the predicted risk of drop-out, and drop-out equivalent MELD (deMELD) points were calculated, where:

deMELD= -25+0.1*Age+1.6*MELD+1.6*Tumor-Size+1.3*LogAFP
+6.0 if Nb Tumors ≥2
+0 if Diag=HCV
-1 if Diag=HBC
+3 if Diag=Alcohol
+2 if Diag=NASH
+1 if Diag=Hemoc
+1 if Diag=Other

Conclusion: The proposed model, with the allocation of deMELD, has the potential to allow
for a dynamic and combined comparison of opportunities to receive a graft for HCC and non-HCC patients on a common waiting list.

Magnetic resonance elastography (MRE) can discriminate normal vs. abnormal liver biopsy in candidates for live liver donation

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Aim: Define liver shear stiffness values assessed by MRE that distinguish normal from abnormal biopsy, especially when steatosis >20%, in persons undergoing evaluation for live liver donation.

Methods: Patients undergoing pre-operative evaluation as live liver donors were included. Baseline clinical, laboratory, imaging, MRE and liver biopsy were performed. Using a pneumatic compression device, shear waves were propagated through the liver and imaged using modified phase contrast MR sequence displayed as an elastogram, from which hepatic shear stiffness in kilopascals (kPa) was measured and compared to biopsy results categorized as normal or abnormal (steatosis >5%, excess iron, fibrosis ≥1 and/or inflammation). Comparison between groups was done using Chi-square or Fisher's exact test for categorical variables and Wilcoxon test for continuous variables. Receiver operator characteristic (ROC) curves were calculated to assess diagnostic accuracy. Statistical significance was set at P< 0.05. IRB approval was obtained for the performance of these tests.

Results: 38 subjects (16 female), median age 40 years (interquartile range, IQR, 28-47) were included. Liver biopsy was normal in 27 and abnormal in 11. ROC curve for MRE defined optimal cutoff at 2.6 kPa (sensitivity 0.72, specificity 0.85, AUC 0.81) to distinguish these 2 groups. Hepatic steatosis >20% on biopsy is considered a contraindication for liver donation in our center; hence we also evaluated the diagnostic characteristics of MRE to distinguish this degree of steatosis: 8 persons had steatosis >20% and were not considered for donor hepatectomy. ROC curve for MRE defined optimal cutoff at 2.82 kPa (sensitivity 0.88, specificity 1, AUC 0.98) to distinguish those with this degree of steatosis on biopsy; and was a better discriminator than BMI or ALT.

Conclusions: Hepatic shear stiffness assessed by MRE, even in the absence of liver fibrosis, can be useful in differentiating normal from abnormal liver histology, and most importantly in patients under evaluation for live liver donation, can very accurately distinguish those with hepatic steatosis >20%, our institutional cutoff for donation. In the future MRE might provide sufficient information to make liver biopsy unnecessary in the donor evaluation process.

MELD-NA and survival benefit in liver transplantation

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There are currently no studies calculating the survival benefit of liver transplantation (LT) according to MELD-sodium (MELD-Na) score. Study group: consecutive adult patients with chronic end-stage liver disease entering the waiting list (WL) for primary LT (WL group = 337) and undergoing LT (LT group = 220) in the period 2006-2009. Two independent Cox regressions were created to measure the prognostic power of MELD-Na with respect to conventional MELD score both adjusted for age, sex, HCV aetiology, presence of liver cancer. Hazard ratios with 95% confidence intervals (CI) were then used to calculate the 3-year survival benefit of LT according to MELD and MELD-Na. WL model: MELD-Na predicted (HR = 1.12; 95% CI = 1.07-1.16; p< 0.01) slightly better than MELD score (HR = 1.11; 95% CI = 1.06-1.16; p< 0.01). LT model: both MELD-Na (HR = 1.03; 95% CI = 0.98-1.08; p>0.05) and MELD score (HR = 0.98; 95% CI = 0.93-1.04; p>0.05) had not correlation with survival. Both MELD and MELD-Na significantly predicted 3-year transplant benefit; the threshold value to define LT futile was 12 for MELD score and 14 for MELD-Na. Although MELD-Na significantly predicts 3-year transplant benefit, it doesn’t refine MELD prognostic performance on a mid-long-term perspective.
The assessment of GFR after orthotopic liver transplantation using Cystatin C and Creatinine-based equations

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Background: The measurement of kidney function after orthotopic liver transplantation (OLT) is still a clinical challenge. Cystatin C (CysC) has been proposed as more accurate marker of renal function than serum creatinine (sCr). Aim of this study was to evaluate sCr and CysC based equations including the CKD-EPI to determine renal function in liver transplant recipients.

Methods: CysC and sCr were measured in 49 patients 24 months after OLT. The glomerular filtration rate (GFR) was calculated using the MDRD 4, the Cockroft-Gault, Hoek, Larsson, and the CKD-EPI equations based on sCr and/or CysC. As reference method, inulin clearance (IC) was estimated. Bias, precision and accuracy of each equation were assessed and compared with respect to IC.

Results: Forty five percent had a GFR < 60mL/min/1.73 m² according to the IC. The Larsson, the Hoek and the CKD-EPI-CysC formula identified the highest percentage of patients with CKD correctly (88%, 88%, and 84% respectively). sCr based equations showed less bias than CysC based formulas with a similar precision. CysC based estimates had a higher accuracy within 10 and 30% of the standard.

Conclusion: All CysC-based equations were superior as compared to sCr-based equations in the assessment of renal function in patients after OLT.

One-year results of tenofovir and emtricitabine without immunoglobulin to prevent hepatitis B recurrence after liver transplantation

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Introduction: After orthotopic liver transplantation (OLT) for end-stage liver disease due to chronic hepatitis B, adequate prophylaxis for recurrence of hepatitis B virus (HBV) infection of the graft is mandatory.

Objective and aim: HBV prophylaxis in patients more than 6 months after OLT with a tenofovir and emtricitabine (TDF/FTC) combination tablet without hepatitis B immunoglobulin (HBIG).

Patients and methods: In 17 stable patients who received OLT for HBV related liver disease we changed HBV prophylaxis to TDF/FTC without HBIG. Post transplantation patients had received at least HBIG >6 months. At the time of medication conversion 15/17 patients were hepatitis B surface antigen (HBsAg) negative and 16/17 had undetectable HBV DNA. Before the year 2000 patients were treated with HBIG monotherapy, from then on a nucleos(t)ide analogue, mostly lamivudine (LVD), had been added to the treatment. Fourteen patients had been switched to LVD and adefovir (ADV) without HBIG at the end of 2006. In order to prevent resistance these 14 and the other three patients were converted to a combination of TDF and FTC in the course of 2010. We now present the results one year after this conversion to TDF/FTC.

Results: After one year follow-up 16/17 patients were alive, one died due to an unrelated cause. All 16 patients with undetectable HBV DNA remained HBV DNA negative. From the 15 HBsAg negative patients at the time of conversion to TDF/FTC, in one patient seroconversion to positive HBsAg occurred, without detectable HBV DNA. Liver biochemistry remained within the normal ranges and did not significantly change. There were no cases of drug discontinuation. No major side effects were reported.

Conclusion: After liver transplantation in chronic hepatitis B and after initial treatment including HBIG >6 months, one-year results of combined TDF/FTC without HBIG show that TDF/FTC adequately prevents HBV recurrence without major side effects.
Effect of antiviral therapy on cell mediated immunity in liver transplant recipients with HCV

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Background and aims: Cylex Immuknow assay (Cylex) is a test used to adjust immunosuppression (IS) drug levels. Whole blood is stimulated with phytohemagglutinin for 15-18 hours. CD4 cells are isolated, lysed, and the intracellular ATP is quantified. We previously reported that paradoxically, Cylex levels are decreased when pegylated interferon alpha (PEG-IFN) is introduced into liver transplant (LT) patients with hepatitis C (HCV). We hypothesized consequences may include more intercurrent infections but less allograft rejections than in those patients receiving interferon treatment.

Methods: We retrospectively reviewed LT recipients with HCV transplanted at our center between January 1st, 2006 and December 31st, 2007, including Cylex levels. The groups were compared using the Student’s t-test. To adjust for progressively decreasing IS, we analyzed the data by time post-LT for up to 4 years. At each time point, we reviewed patient records to document episodes of acute cellular rejection proven by liver biopsy or culture-proven infections.

Results: We reviewed 1148 samples from 118 patients transplanted for HCV. Cylex levels were significantly (p< 0.05) lower in recipients receiving PEG-IFN in each treatment year. With interferon, 3 out of 115 patients developed an infection in year one (p=0.79) and 3 out of 123 in year two (p=0.81). Without interferon, 4 out of 240 patients developed an infection in year two (p=0.20) and 3 out of 169 in year three (p=0.70). The impact of interferon on rejection episodes could not be determined due to an insufficient number of biopsies performed.

Conclusions: Cylex levels are significantly decreased in HCV infected liver transplant recipients receiving PEG-IFN. We did not find an increased incidence of infections between the two groups. We could not assess the incidence for allograft rejection as we did not have enough biopsies. Based on this data, there is no need to adjust the IS medications in patients with lower Cylex levels receiving PEG-IFN post-transplant.