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Poster Abstracts

0005 REDUCED DOSE-ADAPTED MMF EXPOSURE UNDER PROTON PUMP INHIBITOR CO-MEDICATION IN STABLE HEART TRANSPLANT RECIPIENTS

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Background: Proton pump inhibitors (PPIs) are often prescribed for gastrointestinal discomfort after heart transplantation (HTX). This study investigates the impact of PPI use on mycophenolatic acid (MPA) pharmacokinetics in heart transplant recipients receiving mycophenolate mofetil (MMF) and a calcineurin inhibitor (tacrolimus [TAC]/cyclosporine A [CsA]) or mTOR inhibitor (sirolimus/everolimus).

Patients and methods: Abbreviated MPA-AUCs (area under the curve, 0, 30 and 120 minutes after morning intake) were obtained in 19 patients on a PPI (initial examination) and thereafter 1 month after PPI discontinuation (follow-up). Mean patient age was 58.2 ± 8.8 years and mean time post HTX was 2.3 ± 4.0 years (range 0.2−13.0 years).

Results: At initial examination mean daily MMF dose was 2.2 ± 0.8 g. MMF dose was kept unchanged for the duration of study (P = ns). Mean pre-dose (C0) MPA serum concentrations were insignificantly lower with PPI co-medication (2.5 ± 2.2 mg/l vs. 2.8 ± 1.7 mg/l, $P = 0.15$). Dose-adjusted abbreviated MPA-AUCs (adjusted to morning dose) were significantly lower during PPI therapy (45.2 ± 20.3 vs. 65.2 ± 38.8 mg*h/l*g [MMF], $P = 0.02$).

Conclusions: Patients with PPI co-medication during MMF therapy show significantly lower exposure to mycophenolic acid determined by dose-adjusted abbreviated MPA AUCs. While clinical relevance of this pharmacokinetic interaction was not determined in the present study, MPA drug monitoring by limited sampling strategies might be helpful during changes in antacid co-medication in patients on MMF.

0006 DONATION AFTER CARDIAC DEATH: DYNAMIC GRAFT RECONDITIONING DURING OR AFTER ISCHEMIC PRESERVATION?

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Background: The benefit of gaseous oxygenation during storage of liver grafts from donors after cardiac death should be investigated as applied either during the whole period of preservation or only for the last 2 hours prior to reperfusion.

Methods: Rat livers were explanted 30 minutes after cardiac arrest of the donor and cold-stored (CS) for 20 hours. Some grafts were subjected to venous systemic oxygen persufflation (VSOP) (1) either for 20 hours of only 2 hours subsequent to 18 hours of CS. Viability of the livers was assessed thereafter by warm reperfusion *in vitro*.

Results: Twenty hours VSOP and 18 hours CS+ 2 hours VSOP prevented mitochondrial protein breakdown of mtHSP70 and promoted a significant and approximately twofold increase in hepatic oxygen consumption, bile production and energetic recovery upon warm reperfusion. No differences were seen whether VSOP was performed for 20 hours or only 2 hours prior to reperfusion. Both techniques significantly abrogated parenchymal enzyme loss (ALT, AST) upon reperfusion compared to simple 20 hours CS. An increase in Perfusate levels of the mitochondrial enzyme GLDH was observed only in the 20 hours VSOP group.

Conclusion: Viability of DCD-liver grafts can still be augmented, similarly to continuous aerobic storage, by only endischemic reconditioning, both protocols preventing initial mitochondrial dysfunction and subsequent tissue injury.

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0009 ROLE OF THE CYP2D6 POOR METABOLIZER STATUS ON THE FIBROSIS PROGRESSION AFTER LIVER TRANSPLANTATION

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Background: CYP2D6 is part of the cytochrome P450 system, which catalyzes biotransformation of endogenous substrates and up to 20% of xenobiotics. Approximately 10% of the Caucasian population have two null alleles, resulting in a poor metabolizer (PM) status. Mostly allele 4 is responsible for the PM-status, which is suspected to be associated with an accelerated fibrosis progression in the non transplant hepatitis C population. Moreover, CYP2D6 has epitopes for LKM-1 autoantibodies not only in patients with autoimmune hepatitis type 2 but as well in 10% of HCV positive patients. Recurrent cirrhosis is accelerated after liver transplantation (LT) and occurs in HCV positive patients in up to 30% within 5 years after LT. Aim of the present study was to analyze the role of the CYP2D6 donor (liver) and recipient genotype for fibrosis progression after LT.

Methods: We determined CYP2D6-PM-genotypes in liver biopsies (donor) and peripheral blood (recipient) by fluorescence resonance energy transfer (FRET). Data were correlated with clinical parameters and risk factors for RC and fibrosis progression.

Results: We analyzed 411 liver transplantations, transplanted between 1997 and 2009. 123 heterozygous (±) and 22 homozygous (+/+) recipients for allele 4 were detected with an overall allele frequency of 20.32%. The allele frequency in HCV positive patients ($n = 98$) was 16.84% compared to 21.41% in HCV negative patients ($n = 313$; $P = 0.19$). Donor-allele frequencies, representing the normal population, were comparable with 17.99% ($P = 0.43$). Regarding the organ survival there were no genotype specific differences ($P = 0.89$). The liver-/donor- genotype did not correlate with the fibrosis progression. In contrast, recipients carrying the allele, showed a significant higher risk for an accelerated fibrosis progression compared to patients without PM genotypes ($P = 0.011$) in HCV positive ($P = 0.038$) as well as in HCV negative patients ($P = 0.033$).

Conclusion: The CYP2D6 allele 4-associated PM-status of the donor liver seems to have no influence on the fibrosis progression after LT. Recipients, carrying the allele, have an elevated risk for an accelerated fibrosis progression after LT. Immunological factors could be responsible for these findings.

0010 IMPACT OF IMMUNOSUPPRESSIVE THERAPY ON HEPATITIS C INFECTION AFTER RENAL TRANSPLANTATION

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Background: Among patients who had renal transplantation (NTx), hepatitis C virus (HCV) infection is a risk factor for graft loss and death caused by hepatic decompensation. Moreover, HCV has been implicated in the pathogenesis of glomerular diseases in native and transplanted kidneys. The aim of this study was to determine the effects of the calcineurin inhibitors cyclosporine A (CsA) and tacrolimus (Tac) on hepatitis C virus replication, inflammatory activity, development of liver fibrosis and long-term renal allograft function.

Subjects and methods: Seventy-one renal transplant recipients with HCV infection were enrolled. Patients received either CsA or Tac and were grouped according to the immunosuppressive treatment. Serum transaminases and viral kinetics were determined. Moreover, liver fibrosis was measured by non-invasive measurements using the FibroScan and renal allograft function was assessed biochemically.

Results: In the early period after transplantation, hepatitis C viral load and hepatic inflammatory activity were significantly lower in patients treated with Tac as compared to those treated with CsA. However, significance was lost after 3 months post NTx. Extent of liver fibrosis was similar in both treatment groups of HCV-infected patients as well as in a control group of non-HCV-infected renal transplant recipients. Renal function and glomerular filtration rate, as calculated by the MDRD formula, were significantly better in HCV infected patients receiving Tac.

Conclusions: The calciuneurin inhibitors CsA versus Tac showed no significant differences in HCV-infected patients after renal transplantation with respect to viral replication and development of liver fibrosis. However, function of the renal allograft is significantly better preserved in patients receiving tacrolimus.

0014 ABERRANT ACTIVATION OF COAGULATION IS INDEPENDENT OF XENOREACTIVE ANTIBODY TITER AND COMPLEMENT ACTIVATION IN EX VIVO PERFUSION OF PORCINE KIDNEYS

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Introduction: During pig-to-primate xenotransplantation aberrant activation of coagulation (AAC) can be observed causing disseminated intravascular coagulation (DIC). It is still controversial if AAC is an epiphenomenon of ongoing rejection or an independent pathomechanism. Thus, the aim of this study was to analyze the influence of xenoreactive antibodies (XRA) on AAC.

Methods: In an ex vivo perfusion system porcine kidneys ($n = 10$) were perfused with human blood. The experiments were performed in three different groups: perfusion with porcine blood (1), with human blood without pharmacological intervention (2) or addition of recombinant human activated protein C (rhAPC) (3). Donor sera were collected before start of perfusion and XRA titer

were detected by flowcytometry. Blood tissue samples were obtained after termination of perfusion.

Results: Perfusion in group 1 was not restricted. Analyses of blood and tissue samples revealed neither signs for AAC nor deposition of IgM/IgG and low XRA titer. Perfusion in group 2 was limited showing AAC and IgM/IgG deposits; XRA titer were high. Group 3 showed prolonged perfusion times without signs for AAC. However, strong IgM/IgG deposits were detected. XRA titer were high.

Conclusion: In this study we analyzed the effect of XRA on AAC. Xenogenic perfusion caused AAC in all experiments. However, C3a levels did not correlate with the grade of derangement. Addition of rhAPC abolished AAC despite high XRA titer. C3a levels were comparable to those of group 2. At least in this model AAC is not dependent on XRA titer or complement activation but on adequate anti-coagulative therapy.

0015 UW SOLUTION PRESERVES ORGAN QUALITY IN RENAL GRAFTS SIGNIFICANTLY BETTER THAN HTK SOLUTION AFTER PROLONGED COLD ISCHEMIA TIME: A COMPARATIVE EXPERIMENTAL STUDY

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Since conflicting data exist on the efficacy of the two most commonly used preservation solutions University of Wisconsin (UW) and Histidine-Tryptophan-Ketoglutarate (HTK), we conducted a comparative experimental study. Heat capacity of both solutions and renal temperature was measured. *In vitro* tubular cell viability was assessed directly after cold ischemia (CIT) by LDH release and ATP assessment. Rat kidneys were preserved for different periods of CIT. Serum creatinine was measured in recipients for 7 days. Tubular necrosis and apoptosis was studied one day after transplantation and both inflammatory markers and the number of ED-1 positive cells were assessed. Heat capacity revealed a significant difference between UW and HTK. Accordingly, renal temperature was significantly lower in UW. Tubular cells revealed an impaired viability (LDH-release and severe ATP depletion) in HTK. While a 100% animal survival was observed in recipients after prolonged CIT in UW, only 10% survived in the HTK group. Prolonged CIT was associated with severe tubular epithelial necrosis, DNA damage and renal inflammation only in the HTK group. KIM-1, IL6 and P-selectin were significantly increased in the HTK group. CIT correlated negatively with renal function in both UW and HTK group. In the UW group however, renal function recovered significantly faster. UW solution preserves organ quality significantly better than HTK solution. We speculate that superior heat capacity of UW and subsequently improved cooling and better cell viability of the graft might underlie these differences. Hence our data indicate that the use of HTK for renal allografts should be reconsidered.

0017 N-OCTANOYL-DOPAMINE IS MORE POTENT THAN DOPAMINE IN REDUCING INFLAMMATION AND IMPROVING RENAL FUNCTION IN ACUTE RENAL FAILURE

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We have previously demonstrated protective effects of dopamine (DA) in renal transplantation. Recently, we have developed a non-hemodynamic dopamine derivative, i.e. N-Octanoyl-Dopamine (NOD) that is more effective than DA to protect Human-Umbilical-Vein-Endothelial-Cells (HUVEC) against cold preservation injury. In the present study we tested if NOD has anti-inflammatory effects. Since warm reperfusion is considered as an inflammatory process, we compared the effect of DA and NOD on acute renal failure (ARF). HUVECs were stimulated with TNF-α in the absence or presence of various concentrations of NOD. Affymetrix Gene Expression Profiling, quantitative PCR, and westernblotting studies were performed *in vitro*. ARF rats were pretreated with an intravenous bolus of DA or NOD. Renal function and renal inflammation was assessed. The kidneys were harvested after 5 days. Gene expression profiling on cultured HUVECs revealed that a wide range of pro-inflammatory genes were down-regulated by NOD, e.g. adhesion molecules like VCAM and chemokines. This was most likely mediated via inhibition of NFkB. Hemeoxygenase-1 was strongly upregulated by NOD. In the ARF model NOD significantly improved renal function compared to both DA and saline controls. Immunohistochemistry revealed a reduced number of monocytes in both NOD and DA compared to controls. Our data demonstrate that NOD has potent anti-inflammatory effects. *In vivo* administration of NOD not only mitigates deterioration in renal function but also reduces renal inflammation in the setting of ischemia reperfusion. Since ARF is a genuine problem after ischemia, these data are of high clinical relevance to limit renal damage associated with ARF.

0018 RAPIDLY PROGRESSIVE HEPATIC ALVEOLAR ECHINOCOCCOSIS IN AN ABO-INCOMPATIBLE RENAL TRANSPLANT RECIPIENT

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We report on the case of an ABO-incompatible renal re-transplant recipient maintained on an intensified immunosuppressive regimen for recurrent cellular rejection episodes and transplant glomerulopathy who presented with rapidly growing hepatic tumors, radiologically suggestive of hemangiosarcoma. Upon resection and pathological work-up, the lesions revealed alveolar echinococcosis, an extremely rare but potentially life threatening parasitosis following solid organ transplantation. Usually infection with Echinococcus multilocularis remains asymptomatic for extended periods of time and can go unrecognized during a chronic phase of the disease that might last for years. In the case presented, we observed an atypically rapid growth pattern of Echinococcus multilocularis that might have been entailed by the extent of the immunosuppressive regimen which included repetitive anti-CD20 treatments. Retrospectively performed serological studies with enzyme-linked immunosorbent assays (ELISA) known to provide high sensitivity and specificity for the detection of Echinococcosis in the general population, yielded ambiguous results in our immunocompromised host, which could be in part explained by B-cell depletion and its effects on antibody production and indirect actions on cellular immunity. In conclusion this is the first report of hepatic alveolar echinococcosis in a renal transplant recipient. This case documents an altered clinical course of the parasitosis and the challenge of serological diagnostic tools under an intensified regimen of immunosuppressive agents, including rituximab.

0021 LISTING FOR TRANSPLANTATION IN PATIENTS WITH DILATED CARDIOMYOPATHY AND EVIDENCE OF BETA-1 ADRENOCEPTOR AUTOANTIBODIES CAN BE DELAYED BY IMMUNOADSORBTION THERAPY

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Background: With prolongation of waiting times for heart transplantation (HTx), improvement of therapies for heart failure is paramount. After long-term experience with immunoadsorbtion (IA) in patients with serum autoantibodies against β_1-adrenoceptors (β_1-AABs) we assessed its efficacy in HTx-candidates with dilated cardiomyopathy (DCM).

Methods: Cardiac function and survival without HTx or a ventricular assist device (VAD) were evaluated in β_1-AAB positive HTx candidates with DCM (LVEF <30%) who underwent IA between 7/1995−1/2005 (follow-up 5−14.5 years). For IA we used columns containing polyclonal anti-human immunoglobulin antibodies produced in sheep. A bioassay consisting of cell cultures of spontaneously beating neonatal rat cardiomyocytes was used for β_1-AAB measurements. Cardiac function was closely monitored after IA and regular β_1-AAB measurements were performed.

Results: One year post-IA follow-up was possible in 125 (94.7%) of 132 evaluated patients. The other 7 patients underwent HTx or VAD implantation ($n = 5$) or died ($n = 2$) before. After 12 months, the LV enddiastolic diameter (LVEDD) and LVEF in the 125 Tx/VAD-free survivors reached 69.4 ± 1 mm and 31.1 ± 0.9%, respectively, values which were better ($P < 0.05$) than those measured before IA (73.6 ± 0.8 mm and 23.6 ± 0.5%, respectively). The prevalence of responders to IA reached 69.5%. HTx/VAD-free survival after IA was reached at 5 years by 71.2% of the 132 evaluated patients. In the 92 responders IA, the 5 and 10 year HTx/VAD free survival reached 88.5% and 65.2%, respectively. There were no differences in HTx/VAD free survival with regard to the history length of the disease before IA. Therapeutic results of IA appeared not related either to patient's age and β_1-AABs serum levels or to LV size and EF before IA. Early reappearance of β_1-AABs was uncommon, but associated with rapid cardiac worsening.

Conclusions: Although the probability of regaining normal heart function after IA is low, in a high proportion of DCM patients with severe LV dysfunction and evidence of serum ß1-AABs, both unspecific and specific IA allows long-term stable cardiac improvement which provides not only an efficient bridge-to-transplant, but also can delay patients' HTx-listing for many years and some patients can even be spared from HTx.

0023 ECHOCARDIOGRAPHY CAN PREDICT SHORT-TERM COURSE OF RIGHT HEART FAILURE IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION REFERRED FOR TRANSPLANTATION

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Background: With prolongation of waiting times for transplantation (Tx), identification of patients with the need for Tx (lung or combined heart-lung Tx),

anticipation of clinical worsening and finding predictors of Tx-free outcome are major goals. We assessed the predictive value of echocardiography (ECHO), exercise testing, and NT-pro-BNP in Tx candidates with pulmonary arterial hypertension (PAH) to gain information useful in guiding Tx listing procedures.
Methods: We selected all consecutive Tx candidates with PAH, except those with systemic-to-pulmonary shunts, who were stable in WHO/NYHA class III at first evaluation performed between 1/2006 and 6/2007. Initially, after NT-proBNP measurements, patients underwent exercise testing and ECHO including tissue Doppler and strain imaging. All examinations were repeated at each further follow-up during the next 12 months. Parameters were tested for ability to predict Tx-free outcome.
Results: During the first year after initial evaluation, 17 (34.7%) of 49 Tx candidates showed clinical worsening despite maximum medical therapy and nine of them died. Only four survived without Tx. Comparing parameters obtained from these patients at first evaluation with those from the 32 patients who remained stable, we found no differences in systolic pulmonary arterial pressure (PAP_{syst}), right ventricular (RV) size and ejection fraction, right atrial size, tricuspid annulus plane excursion (TAPSE) or NT-proBNP plasma levels. However, those with subsequent worsening had initially lower RV wall motion peak velocities and higher systolic PAP_{syst} /stroke volume (PAP_{syst} /SV) ratios ($P < 0.05$). In unstable patients, strain imaging revealed higher early per late diastolic strain rate (SRE/SRA) ratios and higher RV longitudinal systolic dyssynchrony ($P < 0.05$). At certain cut-off values, the PAP_{syst} /SV and SRE/SRA ratios showed predictive values of between 83% and 90% for 1 year clinical stability.
Conclusions: In clinically stable Tx candidates with PAH, the PAP_{syst} /SV ratio and the RV longitudinal diastolic strain rate are predictive for the short-term (12 month) course of RV function and may provide valuable guidance in listing procedures for Tx.

0025 IMPACT OF MAINTENANCE IMMUNOSUPPRESSIVE REGIMENS - BALANCE BETWEEN GRAFT PROTECTIVE SUPPRESSION OF IMMUNE FUNCTIONS AND A NEAR PHYSIOLOGICAL IMMUNE RESPONSE

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Background and methods: Patient-tailored immunosuppressive therapy based on individual clinical risks as well as immunologic risk profiles may offer optimal benefits for the transplant recipient. To analyze effects of different maintenance regimens on clinically relevant immune parameters, we assessed CD4 helper activity, immunoglobulin-secreting cell (ISC) formation, neopterin, sCD30 and intracellular cytokine production in a prospective study in 77 renal transplant recipients treated with CsA/Aza, CsA/MMF, Tacr/Aza or Tacr/MMF at 2 years posttransplant.
Results: Tacr- compared to CsA-based immunosuppression provided an independent factor for better 2-year graft function (intention-to-treat analysis, $P = 0.014$) and was independently associated with increased IL-2 ($P < 0.0001$, CD4 cells; $P = 0.014$, CD8 cells) and CD4 cell IL-4 responses ($P = 0.046$; stepwise logistic regression) which reached nearly physiological levels in Tacr/Aza patients as compared to 25 healthy controls. Multivariate analysis showed MMF treatment to be an independent variable associated with suppression of CD4 cell IL-10 responses ($P = 0.008$), B cell IL-6R expression ($P < 0.0001$) and ISC formation ($P = 0.020$, SAC I; $P = 0.021$, PWM). The highest CD4 cell response of the B-cell factor IL-10 was observed on Tacr/Aza ($P = 0.005$) which coincided with early graft loss due to acute humoral rejection in three patients.
Conclusion: Our data suggest that Tacr/MMF had the most effective impact on graft protective Th2 responses (enhanced CD4 cell IL-4 by Tacr, decreased CD4 cell IL-10 responses by MMF) and suppression of B cell functions (MMF), whereas Tacr/Aza treatment was associated with nearly physiological IL-2 and IL-4 and stronger humoral responses which may reduce the risk of infectious disease complications.

0033 RISK FACTORS OF KIDNEY GRAFT SURVIVAL: THE IMPACT OF INTRA-OPERATIVE HIGH-DOSE INDUCTION WITH ATG-FRESENIUS AND IDENTIFICATION OF RELIABLE PROGNOSTIC FACTORS

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Aim: The intra-operative high-dose induction (HDI) with ATG-Fresenius (ATG-F: 9 mg/kg body weight) in addition to standard triple drug therapy (TDT) significantly improves the overall kidney graft survival (KGS). The aim of this study was to identify important risk factors influencing graft survival, to verify the impact of intra-operative HDI with ATG-F on these risk factors, and to identify reliable prognostic factors for long-term KGS.
Methods: All renal transplantations performed between January 1987 and December 1998 that involved TDT (azathioprine + steroids + cyclosporine) alone ($n = 208$) or in combination with an ATG-F high-dose induction (HDI, $n = 326$) were evaluated retrospectively. The following variables were included in the analysis: first vs. re-transplantations, HLA-mismatches, panel-reactive antibody (PRA) level, cold ischemia time, age, immediate vs. delayed post-transplant graft function, rejections, infections, and the serum levels of creatinine, CRP, T-cells, IL-6, IL-2R and IDO (anti-inflammatory acting enzyme Indoleamine 2,3-dioxygenase) at 3 post-transplant time points. According to KGS 3 risk groups were defined: high (≤1 year, $n = 86$), intermediate (>1−5 years, $n = 50$) or low (>5 years, $n = 398$).
Results: 1 Important risk factors for KGS were re-transplantations, pre-transplant sensitization and rejections (in particular vascular) requiring long-term treatment.
2 In 20.7% of the TDT-patients compared to 13.2 % of the ATG-F-patients KGS ≤1 year was observed (risk ratio: 1.64; $P = 0.016$).
3 Out of all parameters studied only low serum levels of IDO and to a lower extend of CRP within the first 3 post-transplant weeks were predictive for long-term KGS.
Conclusions: 1 Intra-operative HDI with ATG-F reduces the impact of risk factors on KGS.
2 Reasons for these results are a maximum intra-operative immunosuppression in combination with a pronounced immunomodulation by HDI with ATG-F.
3 The improvement in the early post-transplant period is significantly associated with better long-term KGS.

0034 ONCE-DAILY TAC EXTENDED-RELEASE FORMULATION: 1 YEAR-POST-CONVERSION IN STABLE PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS

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One daily formulations of immunosuppression might increase adherence and thereby graft survival. Till now there is no study about once daily use of Tacrolimus Extended-Release Formulation (Tac-ER) in children after pediatric kidney transplantation. In 11 stable pediatric kidney recipients, efficacy, safety and tolerability of a switch to Tac-ER were examined for 1 year. Compliance was examined by use of the BAASIS-Scale Interview and the comparison of intraindividual variability of Tac trough levels. Besides one patient with incompliance and repeated Tac trough levels of 0 ng/ml there were no acute rejections within observation time. The mean GFR was 56 ± 11 ml/min/1.73 m^2 at time of switch and 55 ± 11 ml/min/1.73 m^2 one year later (P = n.s.). There was no graft or patient loss. The mean intraindividual coefficient of variation of Tac trough levels was 0.27 ± 0.11 before the switch and 0.30 ± 0.19 one year later (P = n.s.). Tac dose was increased in 3/11 patients and decreased in 2/11 patients within the course of the study. Compliance as measured by BAASIS-Scale-Interview was good at all time points. Conversion to Tac-ER is safe and efficient in children after pediatric kidney transplantation.

0037 CUTANEOUS TUBERCULOSIS MIMICKING ERISYPELAS OF THE LOWER LEG IN A HEART TRANSPLANT RECIPIENT

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Question: Infectious diseases play a key role in the management of heart transplant recipients. However, tuberculosis infections in solid organ recipients are associated with an overall mortality of 31%. A rare manifestation of tuberculosis is a localized cutaneous affection. We report on a case with localized cutaneous tuberculosis of the lower left leg 9 months after orthotopic heart transplantation.
Methods: A 59-year-old male patient presented at our institution with an erythematous, doughy swelling of his left forefoot and pain in his upper ankle. The dermatology consultant's suspected diagnosis was erysipelas; symptoms did not improve after sequential therapy with ampicillin and clindamycin. Histology of skin biopsies revealed a granulomatous inflammation showing histiocytes and multinucleated giant cells. Polymerase chain reaction testing confirmed the presence of mycobacterium tuberculosis complex. Thus, the correct diagnosis was ''cutaneous manifestation of tuberculosis''. An extensive search for other tuberculoid foci was negative with respect to mycobacteriae.
Results: Specific treatment was started using isionazid, etambutol and pyrazinamide. In response to antituberculotic treatment, C-reactive protein levels normalized from >20 mg/l to <5 mg/l.
Conclusion: Cutaneous tuberculosis is a rare manifestation of mycobacteriosis in solid organ transplant recipients. In heart transplant recipients, any cellulites with concomitant efflorescence should lead to consideration of tuberculosis as a differential diagnosis. In dubious cases, skin biopsies with pathogen detection may lead to the correct diagnosis.

0038 REACHING THE ORIGINAL GFR OF A SINGLE KIDNEY AFTER LIVING DONOR TRANSPLANTATION: IMPACT OF DONOR AND RECIPIENT CHARACTERISTICS

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Background: The aim of the study was to analyze living donor (LD) and recipient's characteristics after kidney transplantation (KT) and their impact on reaching the original donated GFR of the kidney.

Methods: Two hundred and forty-two consecutive living donor kidney recipient/donor pairs from 1997–2007 were included. Pairs were comparable concerning HLA match, ischemia time, operative time, and induction immunosuppressive treatment. GFR of the transplanted kidney was evaluated by using creatinine-based estimation equations (MDRD2 formula) at 3, 10 and 180 days after KT.

Results: A total of 45.9% of recipients reached the original donated GFR already 3 days after LD KT and 64.9% 10 days after LD KT. Significant predictors for not reaching the transplanted GFR in the early posttransplant period were older age of the donor (mean 52 ± 9 vs. 49 ± 10 years, $P < 0.05$), a higher weight of the recipient (mean 74 ± 10.7 vs. 67 ± 12 kg, $P < 0.001$) and a higher recipients BMI (24.3 ± 3 vs. 23 ± 2.5 kg/m^2, $P < 0.01$), as well as the gender constellation of a male donation to a female recipient ($P < 0.01$). Adaptive hyperfiltration (GFR >60 ml/min) of the recipient after transplantation was a frequent finding.

Conclusions: The findings suggest that donor's age, recipient's weight, and the gender disparity of the donor-recipient pair should be considered as a criterion in the choice of donor and recipient pairs for successful short-term outcome in living donor renal transplantation. The problem of hyperfiltration in the early posttransplant period that may have a pivotal long-term prognostic impact deserves further exploration.

0039 INSUFFICIENCY OF THE CLASSICAL CDC-BASED CROSS MATCH TO DETECT DONOR-SPECIFIC ANTI-HLA ANTIBODIES UNDER CERTAIN CIRCUMSTANCES AS SHOWN BY CASE REPORTS REPRESENTING THREE GROUPS OF PATIENTS

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Background: Donor-specific anti-HLA antibodies represent the most prominent cause for hyper-acute and acute rejections. The complement-dependent cytotoxicity cross-match (CDC-CM) as the standard CM procedure strongly depends on the availability of vital donor lymphocytes. However, due to several diseases or pharmacological treatment of the recipients unexpected false-positive results may arise.

Methods: Due to the known diagnostic limits of the CDC-CM as a vitality assay we established the solid phase-based AMS-CM ELISA (GTI Diagnostics) to compare its outcome with that of the conventional CDC-CM.

Results: Case reports representing three groups of recipients for which the conventional CDC-CM is not applicable are shown.

1 Living kidney recipient without any anti-HLA antibodies exhibited a strong positive B-cell CM due to the treatment with the therapeutical monoclonal anti-CD 20 antibody Rituximab.

2 Prospective stem cell recipient suffering from juvenile myelo-monocytic leukemia exhibited a positive CDC-CM result after treatment with the cytostatic agent 6-mercaptopurine leading to the unspecific cell death of the donor lymphocytes.

3 HLA class II well-matched post-mortem kidney allograft which was offered to a patient without anti-HLA antibodies resulted in faint cross-match reactions with PBL and isolated T-cells, and a strong reaction with isolated B-cells. The underlying disease Lupus erythematosus characterized by the occurrence of immune complexes leads to an artifact by the binding of these complexes to B-cells.

Conclusion: These patients representing three groups which regularly occur during everyday diagnostics of tissue typing laboratories strengthen the urgent requirement for the acceptance of solid-phase-based CM procedures to complement the classical CDC assay.

0043 ADDITIONAL SOLID PHASE-BASED CROSS MATCH ASSAY FOR POST-MORTEM HEART AND LIVING KIDNEY TRANSPLANTATIONS TO PREDICT THE NEGATIVE INFLUENCE OF DONOR-SPECIFIC ANTI-HLA ANTIBODIES

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Background: Donor-specific anti-HLA antibodies (DSA) represent the most prominent cause for hyper-acute and acute rejections. The complement-dependent cytotoxicity cross-match (CDC-CM) as the standard CM procedure strongly depends on the availability of vital donor lymphocytes and, additionally, only identifies cytotoxic i.e. complement-activating antibodies (Ab).

1 For heart transplantation (HTX) a pre-transplant CM is not obligatory and difficult to perform within an acceptable cold ischemic time of about 6 hours. However, due to the impairing influence of preformed DSA as shown in many studies most transplant centres are interested in a retrospective detection to adapt the immune suppression or to reduce preformed DSA. For the retrospective analysis of preformed DSA the conventional CDC-CM as a vitality assay is often not applicable due to the highly reduced vitality of the donor cells.

2 For living kidney donations the CDC-CM on the one hand exhibited implausible positive results due to pre-transplant medical treatment and/or underlying diseases of the recipients and on the other hand generally fails to detect weak or non-cytotoxic anti-HLA Ab.

Methods: Due to these diagnostic limits of the CDC-CM as a vitality assay we established the solid phase-based AMS-CM ELISA (GTI Diagnostics) as a retrospective CM assay for HTX and prospective assay for living kidney donations.

Results: 1 Using the retrospective AMS-ELISA preformed DSA could be excluded in 17 out of 19 HTX recipients (90%). Two recipients exhibited DSA in the AMS-ELISA although their anti-HLA Ab-screening/-differentiation results in comparison to the donors' genotypes would not have pointed to anti-HLA Ab against the selected donor.

2 About 20% of all prospective living kidney donations exhibiting implausible CDC-CM results ($n = 44$) were validated by the AMS-ELISA. In 33 out of this 44 patients no DSA were detectable excluding an immunological contraindication for living donation. This demonstrates that the CDC-CM was characterised by false-positive results in 75% of the implausible cases.

Conclusion: The solid-phase based CM assay is a highly specific method to detect or exclude donor-specific anti-HLA class I and/or class II Ab for post-mortem HTX as well as for the living kidney transplantation both occurring frequently in the daily routine work.

0044 LOBSTER – LIVER OBSERVATIONAL STUDY TO ASSESS THE EFFECT OF CELLCEPT THERAPY ON CLINICAL OUTCOMES IN LIVER TRANSPLANT PATIENTS: INTERIM RESULTS AFTER 6 MONTHS

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Introduction: A host of clinical trials and registry analyses have provided evidence for the benefit of a MMF (CellCept®)-based therapy following liver transplantation (Tx) with respect to renal function and metabolic co-morbidities. However, little is known about the evolution of renal function under everyday clinical conditions where recipients may start MMF at various time points after Tx.

Methods: Non-intervenational study of patients who start MMF de novo or at any time point after liver Tx. In a pre-planned interim analysis of 200 patients the course of calculated GFR (abbreviated MDRD) over 6 months is measured. Reflecting the time after Tx, four strata were analyzed: MMF was started up to day 6 post Tx (A, $n = 107$), between day 7 and day 30 after Tx (B, $n = 26$), from day 31 to 1 year post Tx (C, $n = 36$) and >1 year after Tx (D, $n = 31$).

Results: Following liver Tx the best renal function was achieved in the first 30 days in all groups (median of highest GFR: 98, 97, 93 and 91 ml/min/1.73 m^2 in groups A-D). At start of MMF median GFR was 72 and 91 ml/min/1.73 m^2 in groups A and B and decreased to 60 and 74 ml/min/1.73 m^2 at 6 months, respectively. CNI levels were kept stable in group A. In group B Tac levels increased slightly, whereas CsA levels decreased. In groups C and D, GFR had dropped to 61 and 52 ml/min/1.73 m^2 at the time of MMF introduction. Interestingly, within the 6 months following the introduction of MMF, renal function recovered, as documented by an increase of median GFR to 66 ml/min/1.73 m^2 in group C and 61 ml/min/1.73 m^2 in group D. In parallel, CNI trough levels were reduced by 20–40% after the introduction of MMF, while MMF was administered at a mean daily dose of 1575 ± 538 mg (C) and 1733 ± 388 mg (D). Throughout the observation period, MMF therapy was well tolerated.

Conclusion: This interim data strikingly demonstrate that the natural attrition of renal function after liver Tx can be reversed by initiating a MMF-based regimen while reducing CNI between one and beyond 12 months post Tx. The initial decrease of GFR in groups A and B may reflect the lack of consistent reduction of CNI levels in the presence of MMF.

0046 CLINICAL OUTCOME OF HEPATITIS B VIRUS INFECTION IN PATIENTS RECEIVING HEMATOPOIETIC STEM CELL GRAFTS FROM IMMUNIZED DONORS*

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Background: After having shown that immune transfer can occur via hematopoietic stem cell transplantation and also after liver transplantation we implemented this knowledge in clinical patient care.

Methods: We here describe two patients who suffered from non-Hodgkin lymphoma or acute myeloid leukemia plus either acute or chronic hepatitis B (HBV) infection, respectively, prior to peripheral blood stem cell transplantation (PBSCT).

Results: In the patient with acute HBV infection occurring at month 6 prior to PBSCT, we actively immunized the HLA-identical sister 4 times (day 0, week 2, week 4, and month 5) using Bio-Hep-B, an HBV vaccine containing PreS1, PreS2 and S antigens and thereby obtained humoral and cellular HBV immunity prior to PBSCT (anti-HBs titer: 347 IU/L, HBV-specific stimulation index (SI): 8.5, and HBV-specific interferon-gamma ELISpot: 12 spots increment). The corresponding recipient was transplanted after HBV DNA became undetectable. He was followed up for 19 months and remained HBV DNA negative. At month 19 anti-HBs and HBV-specific cellular immunity was still measurable (1483 IU/L, SI of 4.8, and 8.5 spots increment) indicating that HBV infection was controlled by donor immunity. The patient with chronic HBV infection received a graft from an HLA-identical unrelated donor who had been immunized using a German standard HBV vaccine containing the S antigen (anti-HBs titer 265 647 IU/L). She was furthermore treated by antiviral drugs prior to and post transplantation. After PBSCT the patient cleared her chronic HBV infection and became HBV DNA negative. Furthermore, she displayed humoral and cellular HBV immunity at month 1 after transplantation (anti-HBs titer 588 497 IU/L, SI of 5.4, and 8 spots increment). At month 3 she was tested again and humoral HBV immunity further increased (anti-HBs 1 301 100 IU/L). Cellular HBV immunity, however, was undetectable at that time (SI of 1.0 and 2 spots increment). Most likely, after PBSCT HBs antigen had persisted outside the peripheral blood and ''boostered'' anti-HBs production.

Conclusion: The data demonstrate that in PBSCT recipients the reactivation of acute HBV infection could be prevented and chronic HBV infection could be cleared if donors were immunized against HBV.

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0047 HEPATITIS B VIRUS SPECIFIC IMMUNE TRANSFER IN AB0 INCOMPATIBLE LIVING DONOR LIVER TRANSPLANTATION*

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Background: In chronically hepatitis B virus comparable incidences in all groups and were rarelyHBV) infected recipients, reinfection of a transplanted liver remains a problem which may be overcome by adoptive transfer of HBV immunity from a vaccinated living donor. Previously, we showed that it is possible to transfer HBV immunity with the liver.

Methods: We here describe the long-term course of HBV immunity and of B cell numbers in an AB0 incompatible donor/recipient pair (both HBV negative). The donor was immunized four times against HBV with Sci-B-Vac in a short time immunization protocol. To overcome blood group incompatibility the recipient received rituximab prior to transplantation and several plasmapheresis.

Results: HBV immunity was observed in the donor prior to transplantation (anti-HBs titer: 9831 IU/L, HBV-specific stimulation index (SI): 32.5, and HBV-specific IFN-gamma ELISpot: 34 spots increment). At week 2 post transplantation the recipient displayed an anti-HBs titer of 10 IU/L which was likely due to antibodies in blood products given during the transplantation. Subsequent samples of this recipient were anti-HBs negative. In contrast, already 1 month after transplantation, the recipient showed an HBV-specific SI of 7.1. Again, positivity was observed at month 5 (SI of 3.1) and 6 (SI of 40). Further, a transfer of cellular immune responses was demonstrated by ELISpot at month 6 (22 spots increment). Starting at month 17 after transplantation, the recipient herself was vaccinated five times against HBV (months 17–39). Interestingly, anti-HBs remained undetectable. Cellular immunity, however, was observed prior to immunization of the recipient (SI of 5.9 and 8 spots increment) and increased thereafter (at month 41: SI of 15.9 and 15 spots increment). B cell numbers were below normal levels up to month 26 post transplantation and – although they reached normal levels at the time point of the last two immunizations – anti-HBs production after immunization had not been detectable.

Conclusion: Rituximab treatment led to long-term reduction of B cell numbers which most likely resulted in the absence of humoral immune responses against HBV despite repeated vaccinations.

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0048 PSYCHOSOCIAL IMPACT OF LIVE KIDNEY DONATION IN A SINGLE GERMAN TRANSPLANT CENTER

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Introduction: Since the frequency of postmortal organ donation is low in Germany thereby causing long waiting times, live kidney transplantation provides by far the best treatment option in end-stage renal disease.

Methods: In a single center study we analyzed physical and psycho-social health status in 106 living kidney donors of the Giessen Transplant Center (1993–2003) retrospectively. We examined general health with special emphasis on renal parameters. The standardized SF-36 questionnaire and 30 self-designed questions were used to test social, psychological and general health status.

Results: Sixty-nine of 106 (65%) kidney donors (5.3 ± 0.6 years after donation) were included in the study. The majority of 37 drop-outs were of foreign origin (23 of 28 (82%) versus 14 of 78 (18%) Germans; $P = 0.01 \times 10^{-8}$). Current renal function was well preserved (serum creatinine: 1.3 ± 0.2 mg/dl, creatinine clearance: 81 ± 10 ml/min, post-donation to pre-donation ratio of creatinine clearance: 0.73 ± 0.09). SF-36 data of the kidney donors showed higher scores concerning physical (54.3 ± 7.0 versus 49.3 ± 8.8; $P = 0.048$) and psychosocial health (53.8 ± 5.3 versus 50.7 ± 8.5; $P = 0.043$) than the average German population. In 13 of 69 (19%) donors financial problems occurred due to donation, mainly because travelling expenses were not reimbursed. No donor exercised his right to charge the recipients health insurance company with compensations for loss of earnings due to absence at work caused by pre-donation examinations. The donors saw themselves forced to organize their appointments by taking time off, in their leisure time or by using certificates of disability raised by their general practicioner.

Conclusion: Our data show that donors of foreign origin significantly more often rejected our call for study participation. This might be caused by poor understanding of the German language as well as a general scepticism regarding institutional facilities. It remains an open question, wether the necessary follow-up exams of foreign donors have been performed regularly. German kidney donors may experience financial and social disadvantage due to their donation. This is primarily caused by misinformation by health insurance companies, not completely informed patients and fear of job loss. It appears necessary to implement the rules of compensation given by the German transplant law and to protect against job loss by law in order not to compromise live kidney donation.

0051 EXCELLENT RENAL FUNCTION, PATIENT AND GRAFT SURVIVAL WITH LONG-TERM USE OF ONCE-DAILY PROLONGED-RELEASE TACROLIMUS IN KIDNEY TRANSPLANT RECIPIENTS

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Aim: Once-daily prolonged-release tacrolimus (Tacrolimus-QD) has shown similar efficacy and safety to the established twice-daily tacrolimus formulation in kidney transplantation. The aim of this prospective follow-up-study was to assess long-term efficacy, safety and effect on renal function of Tacrolimus-QD.

Methods: This was a multicenter, single-arm, open, prospective, additional 2-year follow-up of Tacrolimus-QD treatment in adult renal transplant recipients who had already participated in a Phase-III-study (12–03). Patients' original immunosuppressive regimen was maintained unless medical needs necessitated otherwise. Primary endpoints were patient-survival and graft-survival; secondary endpoints included adverse events (AEs), BPAR and renal function (Cockcroft-Gault).

Results: One hundred and ninety-one of 341 eligible kidney transplant recipients were enrolled into the follow-up-study. 163 (85.3%) patients completed the 2-year follow-up. 27 (14.1%) patients were withdrawn: due to AE (9), withdrawal of consent (4), pregnancy (3), prohibited medication (3), switch to regimen not containing Tacrolimus-QD (2), non-compliance (1), lost-to-follow-up (1), and other (4). Tacrolimus dosing and whole-blood trough-levels decreased slightly over the follow-up and amounted for 0.07 (±0.05) mg/kg and 6.9 (±2.2) ng/ml at 22–24 months, respectively.

Graft loss occurred in 5 (2.6%) patients (1 death, 2 chronic-allograft-dysfunction, 1 acute rejection, 1 ureter stenosis). Graft- and patient-survival was 97.4% and 99.3% during this 2-year follow-up (Kaplan–Meier). 1 BPAR-episode occurred, which was corticosteroid-sensitive and mild. Most commonly reported causally-related AEs were hypertension (8.9%), urinary tract infection (6.8%), tremor (6.3%) and non-insulin dependent diabetes mellitus (5.8%). Mean serum-creatinine (±SD) was 131.6 (±50.3) at Day1, decreasing to 126.7 μmol/L (±42.2) at the end of the follow-up. Mean creatinine-clearance (±SD) was 66.1 (±22.0) at Day1, increasing to 70.0 (±26.3 ml/min) at the end of the follow-up.

Conclusions: These results demonstrate that once-daily prolonged-release tacrolimus is efficacious and well tolerated in the long-term in de novo kidney transplant recipients without compromising renal function.

0052 RENAL FUNCTION AND SAFETY IN STABLE KIDNEY RECIPIENTS CONVERTED FROM TACROLIMUS TWICE DAILY TO A ONCE-DAILY FORMULATION

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Aim: Once-daily tacrolimus (TAC QD) may reduce post-transplant nonadherence and potentially prevent graft loss. This study assessed the renal function of stable adult kidney transplant-patients converted from twice-daily tacrolimus (TAC BD) to TAC QD.

Methods: In this multicenter, single-sequence crossover-study, clinically stable patients that were at least 12 months post-transplant and 12 weeks unchanged on Tac BD were converted to TAC QD on a 1:1 (mg:mg) basis after a 6 week run-in period (TAC BD-phase). The primary endpoint was change in steady-state creatinine-clearance (CrCl; Cockcroft-Gault) between TAC BD and TAC QD after 12 weeks.

Results: One hundred and eighteen patients completed the study; 91 patients had no major protocol deviations (Per-Protocol-Set). Mean daily dose was 0.06 mg/kg and 0.07 mg/kg at the end of TAC BD and TAC QD treatment phases. Mean trough level was 7.2 ng/ml before conversion, 6.3 ng/ml at Week1 and 7.0 ng/ml at Week 12. The majority of patients (82%) required either no or a single dose change post-conversion. Mean steady-state CrCl was 72.5 ml/min and 72.1 ml/min for TAC BD and QD, demonstrating non-inferiority of TAC QD (95%CI within 10%of TAC BD). Patient/graft survival was 100% and no BPAR episodes were reported. 22.2% and 25.0% patients had AEs during TAC BD and TAC QD-treatment; none led to dose modifications or withdrawals. During the 6-week TAC BD and 12-week TAC QD-phases, most frequently reported AEs were: infections (5.6% vs. 12.1%), metabolic disorders (4.0% vs. 2.6%), hypertension (0.8% vs. 4.3%), and respiratory disorders (3.2% vs. 0%).

Conclusions: Conversion of stable kidney transplant patients from TAC BD to a simplified TAC QD regimen is straightforward and does not adversely affect renal function or safety parameters.

0053 SIGNIFICANTLY BETTER FREEDOM FROM ACUTE REJECTION WITH TACROLIMUS VERSUS CYCLOSPORINE-BASED IMMUNOSUPPRESSION IN RENAL TRANSPLANT RECIPIENTS AT 7-YEAR FOLLOW-UP

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Aim: Six months after transplantation renal allograft recipients randomized to tacrolimus (TAC) experienced significantly less biopsy-confirmed acute rejection (BCAR) than patients randomized to cyclosporine-ME (CsA-ME) (20% vs. 37%; $P < 0.0001$) in combination with azathioprine and steroids. In this non-interventional study, data were collected to assess safety and late acute rejection for additional 7 years.

Methods: Observational data including immunosuppressive regimen, BCAR, patient- and graft-survival (Kaplan–Meier) and adverse events were collected from 6 months to 7 years after transplantation ($n = 237$ TAC and $n = 208$ CsA patients, 80% of the original intent-to-treat population) from 42/50 centers.

Results: Fewer TAC-patients than CsA-patients had switched primary immunosuppressant at 7 years (8% vs. 20%), and more Tac-patients than CsA-patients received monotherapy (18% vs. 4%). Late first acute rejections were confirmed in 6 TAC and 4 CsA patients resulting in BCAR-free estimates of 77% and 60% ($P < 0.0001$, Wilcoxon–Gehan-test) at 7 years. During follow-up, 32 TAC vs. 29 CsA grafts were lost and 28 TAC vs.22 CsA deaths occurred with Kaplan–Meier-estimates of 79% for graft-survival and 88% for patient-survival in both groups. Mean serum creatinine was 181 μmol/l (TAC) and 187 μmol/l (CsA). The incidence of malignancies was similar (11% vs. 8%) but cosmetic changes (2% vs. 14%), bone fractures (4% vs. 10%), and cardiovascular events (9% vs. 16%) were less with TAC. New-onset of insulin requirement was 2.1% (5/237 patients) with TAC and 1.4% (3/208 patients) with CsA. Serum–lipid parameters were similar but more CsA-patients required antihyperlipidemic medication (40% vs. 29%).

Conclusion: Longterm drug tolerance appeared to be superior with tacrolimus than cyclosporine. Significantly higher freedom from biopsy-confirmed acute rejection at 7 years was shown with tacrolimus over cyclosporine.

0056 COMBINED KIDNEY 5TH - HEART-TRANSPLANTATION: GOOD LONG-TERM RESULTS AFTER SEVERE ACUTE REJECTION AND INVASIVE ZYGOMYCOTA-PNEUMONIA: A CASE REPORT

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Purpose: History and three years outcome in a combined kidney 5th heart transplant recipient suffering from intermittend biopsy proven acute C4D positive renal and cardiac rejection ISHLT 2 R followed by an invasive Zygomycota pneumonia.

Patients and methods: A 46-year-old male, not immunized patient suffering from GoodPasture Syndrome with four preceeding renal graft losses and severe ischemic cardiomyopathy underwent combined kidney 5th heart transplant in 11/2006 at our center. The initial immunosuppression consisted of Alemtuzumab, Rituximab, steroids, followed by Tacrolimus plus MMF. A biopsy proven acute C4D-positive renal rejection requiring dialysis in the 2nd week was resolved by Rituximab plus plasmapheresis. An acute cardiac rejection (ISHLT 2 R, 11th week) was successfully treated by a steroid bolus. In week 12 post-transplant an invasive bilateral Zygomycota (Cunninghamella) pneumonia required surgical resection plus Posaconazole along with reduced immunosuppression. Long-term pulmonary recurrence of GoodPasture Syndrome at month 11, 19, 25, respectively, were treated with steroids.

Results: Early renal C4D positive rejection and the cardiac rejection ISHLT 2 R could be reversed with acceptable long-term functions of both grafts (creatinine level of 1.9 mg/ml, left-ventricular ejection fraction >50%). Fungal pneumonia improved by a right side lung resection plus Posaconazole over 6 months. Current immunosuppressive therapy comprises Tacrolimus (trough level 5 ng/ml), MMF (1 g/d), prednisone (5 mg/d).

Conclusion: A Zygomycota pneumonia following an extremely high dosed antirejective treatment was successfully treated by surgery, long-term Posaconazole and cautiously minimized immunosuppression in a combined kidney 5th heart transplant. The long-term heart and kidney function remained stable.

0059 IMPACT OF EVEROLIMUS ON PERICARDIAL AND PLEURAL EFFUSIONS IN DE NOVO HEART TRANSPLANT RECIPIENTS

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Introduction: Pericardial and pleural effusions occur frequently in heart transplant recipients (HTxR), are mostly easy to manage and do not compromise long-term outcome. However, an increased occurrence of severe pericardial effusions including cardiac tamponade as well as pleural effusions has been described for the mTOR-inhibitor sirolimus. Less data is available for the use of everolimus (EVR), a mTOR-inhibitor with a different pharmacokinetic profile.

Methods: A post-hoc analysis of the adverse event (AE) databases of three randomized multicenter studies in 1007 de novo HTxR was performed. HTxR received corticosteroids and either standard dose cyclosporine A (SD–CsA) with azathioprine (AZA, $n = 214$), mycophenolate mofetil (MMF, $n = 83$), EVR 1.5 mg/day ($n = 211$), EVR 3 mg/day ($n = 209$), TDM–EVR (C0 3–8 ng/ml, $n = 100$) or reduced dose CsA (RD–CsA) with TDM–EVR ($n = 190$; pooled from two studies). Pericardial and pleural effusion AEs up to Day 90 were analyzed.

Results: Baseline characteristics were balanced across the three studies. Comparable incidences of pericardial effusions were seen in the EVR cohorts and with MMF, but were numerically lower with AZA. Cardiac tamponade incidence was also comparable between the EVR and MMF cohorts but lower with AZA. Pericardial effusions reported as serious AE (SAE) were more frequent in the EVR groups than with AZA or MMF. The majority of pericardial effusions did not require drainage or hospitalization in the RD–CSA TDM–EVR, AZA and MMF groups. Most pericardial effusions occurred within 30 days post-Tx in all cohorts. Pleural effusion occurred with comparable incidences in all groups.

Conclusions: The results of our cross-study analysis showed that (i) the incidence of pleural effusions was comparable for all treatment groups, (ii) the incidences of pericardial effusion and cardiac tamponade were comparable for EVR and MMF but lower with AZA, and (iii) pericardial effusion SAEs were more common in EVR-treated HTxR. Close monitoring of HTxR receiving EVR during the first month post-Tx might be advisable to avoid pericardial effusions.

0060 MULTI-DRUG-DONOR PRECONDITIONING PROTECTS MARGINAL LIVER ORGANS AGAINST ISCHEMIA/ REPERFUSION INJURY

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Introduction: Drug preconditioning in heart beating brain-dead donors induce high bioavailability of pharmacological substances in liver cells at 37 °C. In an isolated liver perfusion model in the rat we demonstrated the effects of a short term multidrug pretreatment model in steatotic liver organs compared to non-steatotic livers.

Methods: A total of 24 Sprague Dawley rats were divided into three groups. In the preconditioning group (MDDP; $n = 8$) rats underwent the MDDP protocol before liver perfusion with 4 °C cold HTK solution. The Sham- and the SL (steatotic livers) -controls received 2.0 ml vehicle (0.9% NaCl) 30 minutes before liver perfusion with 4 °C cold HTK solution. Livers of animals of all groups were stored for 24 hours in 4 °C HTK solution. MDDP was initiated 30 minutes before starting the cold perfusion with HTK solution for organ harvesting by applying simvastatin, N-acetylcysteine, erythropoietin, pentoxyphylline, melatonin, glycine and DFO. After 24 hours cold storage, livers were reperfused for 60 minutes through the portal vein in a non-recirculating system. Perfusion was performed with freshly prepared Krebs Henseleit bi-

carbonate (KHB) buffer saturated with carbogen at a flow rate of 2 ml/min*g liver tissue using a pulsatile perfusion pump.

Results: The cellular and mitochondrial integrity in the SL-control were significantly lower during the whole reperfusion compared to Sham-controls ($P < 0.05$). MDDP treated SL significantly reduced the cellular and mitochondrial damage compared to SL-controls ($P < 0.05$). Liver enzymes were significantly increased in SL-controls after a period of 60min reperfusion periode compared to the Sham group ($P < 0.05$). The preconditioning of SL livers according to the MDDP protocol significantly reduced the hepatocellular damage ($P < 0.05$). The release of proinflammatory cytokines (TNF alfa, IL 6, IL 1) in SL-controls were significantly higher compared to the Sham group. The application of MDDP significantly reduced the proinflammatory reaction ($P < 0.05$).

Discussion: Twenty-four hours cold preserved marginal steatotic rat livers presented higher hepatocellular damage and an elevated release of cytokines, which were significantly reduced by the MDDP protocol. Taken together, short-term pharmacological preconditioning can be an effective, clinically applicable adjunct to improve organ preservation.

0061 AUTOLOGOUS TISSUE ENGINEERED HEART VALVE REPLACEMENT – THE CD133+ STEM CELL-PLUS-FIBRIN COMPOSITE BASED SPRAYED CELL SEEDING CONCEPT

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Objective: The development of biological heart valve prostheses with lifetime native-like performance and optimal graft integration is an ultimate goal of heart valve tissue-engineering. We describe a new principle for autologous graft coating based on a $CD133^+$ -stem-cells-plus-fibrin-complex (SC+F) processed from bone marrow and peripheral blood of one and the same patient.

Methods: $CD133^+$ -SC (1×10^6 cells/ml) from human bone marrow and autologous fibrin (20 mg/ml) were administered simultaneously via spray administration employing the novel Vivostat Co-Delivery System. During static cultivation, SC+F performance was monitored about 20 days after delivery, and it was compared to controls. FACS and immunohistochemistry analyses served for investigating cell differentiation. For dynamic testing SC+F-composite was sprayed on a decellularized porcine pulmonary valve and transferred to a bioreactor under pulsatile flow conditions for 7 days.

Results: Static cultivation of SC+F-composite induced significant improvements in stem cell proliferation as compared to controls. For dynamic testing, microscopic analyses on a smooth engineered heart valve surface detected homogenous distribution of stem cells. Ultrasonic analysis executed native-like valve performance. Applied $CD133^+$ stem cells differentiated into endothelial-like cells positive for CD31 and VEGFR2 and engrafted the valve. However, occasional delamination was observed.

Conclusion: SC+F serves as an excellent autologous matrix for intra-operative tissue-engineering of valve prostheses promising optimal *in vivo* host engraftment. However, stability remains an issue.

0063 LOCAL AND SYSTEMIC INFLAMMATORY RESPONSE AFTER IN-SITU SPLIT-LIVER PROCEDURE; CAN PRECONDITIONING STRATEGIES IMPROVE GRAFT QUALITY?

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Introduction: When vascular complications (VC) were identified after split-liver (SL) transplantation mostly urgent retransplantation is the only option to avoid lethal outcome. The systemic and local release of cytokines with endothelial activation in split-liver procedure could potentially impair microcirculation and play an important role in incidence of VC. The impact of SL-procedure on other organs like lungs is not sufficient evaluated. Despite the well-known proinflammatory effects of TNF-alpha, its role in the pathogenesis of lung injury after SL procedure remains unclear. The inflammatory response and impact of split-livers on liver and lung parenchyma were analyzed under pharmacological preconditioning interventions in a rat liver model.

Material and methods: Sprague-Dawley rats were randomized within three groups; Sham-group (non split liver) and two split liver groups (SL-Con and SL-HPP). Immediately after liver organ harvest, lung tissue was taken for further analysis of leukocyte invasion and cytokine parenchyma concentration. The Sham group and the SL-Con group received NaCl 0.9% before organ perfusion whereas the SL-HPP group was treated according to the Homburg preconditioning protocol. The first liver sample was taken directly after HTK perfusion, the second liver sample was taken after cold 8 hours conservation.

Results: HPP could nearly avoid the increase of TNF-alpha concentration within the plasma and significantly reduce the TNF-alpha levels and ICAM-1 expression in liver tissue compared to the SL-Con group. After 8h the TNF-alpha liver tissue concentration and ICAM-1 expression increased compared to Sham controls. HPP significantly reduced the release of TNF-alpha levels and ICAM-1 expression from liver tissue. The SL-Con group showed a markedly elevated number of transmigrated leukocytes after 0h (2.22 ± 0.44 per HPF) and 8 hours (2.16 ± 0.17 per HPF) conservation time. Pretreated livers according to the HPP with and without 8 hours cold ischemia were capable of abrogating the leukocyte transmigration. Hematoxylin–eosin-stained tissue sections showed an increase of vacuolization of hepatocytes after the split liver procedure when compared to sham controls after 0 and 8 hours cold preservation. HPP significantly reduced vacuolization if split-livers were not exposed for 8 hours cold conservation in HTK. The split procedure induced a significantly increase of TUNEL positive cells after 0 and 8 hours cold conservation in HTK solution. HPP reduced apoptosis after 0 and 8 hours cold conservation for nearly 10% compared to the saline treated SL-Con group. In lung parenchyma the SL-Con group showed a markedly elevated number of leukocytes invasion and cytokine concentration directly after liver flushing with 4 °C HTK. Again HPP significantly reduced leukocytes recruitment and cytokine concentration.

Discussion: In conclusion, we herein demonstrate that pretreatment of organ donors according to the Homburg preconditioning protocol exerts significant anti-imflammatory actions with reduced apoptosis and degeneration in split-livers. Also the inflammatory response in lung parenchyma was markedly reduced.

0064 IMPACT OF 6 DIFFERENT IMMUNOSUPPRESSIVE REGIMENS ON RATES OF CARDIAC ALLOGRAFT REJECTION

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Introduction: The use of immunosuppressive drugs in heart transplantation (HTx) requires balance of effective prevention of rejection and control of adverse drug effects. Acute rejections (AR) remain an important problem, especially within the first 90 days post HTx. Here, efficacy outcome of 6 different immunosuppressive regimens is analyzed. Methods: In a post-hoc analysis data of 1009 de novo HTx recipients (HTxR) from three randomized, multicenter studies (B253 $n = 634$; A2403 $n = 199$; A2411 $n = 176$) were reviewed. Immunosuppression included steroids and one of the following regimens: standard dose (sd) CsA+AZA ($n = 214$); sdCsA+MMF ($n = 84$), sdCsA+fixed-dose 3 mg everolimus (h-EVR, $n = 211$), sdCsA+ fixed-dose 1.5 mg EVR (l-EVR, $n = 209$), sdCsA+ tdmEVR (C0 3–8 ng/ml, $n = 100$), or reduced dose (rd) CsA+ tdmEVR ($n = 191$). C0 levels for CsA and EVR and daily doses for AZA and MMF were analyzed for relation to incidence of early and late acute rejections (per ISHLT grades 1R, 2R, 3R or 2R/3R pooled) at ≤90 days (d) and 91–180 d respectively. Results: HTxR had similar baseline characteristics. Incidences (%) of graft loss or death at Month (M) 6 were comparable across groups. Lowest AR rates at ≤90 d and 91–180 d post HTx were seen with sdCsA+ tdmEVR. However, HTxR with rdCsA showed less decline in renal function compared to baseline (Table 1). HTxR with AR 1R had lower CsA C0 exposure at time of AR compared to those without AR. In all EVR groups, patients with AR 1R had also lower EVR C0 at time of AR. Whereas CsA C0 levels were lower in all EVR-treated patients with AR 2/3R, the tdmEVR group had also lower EVR C0 exposure (Table 2).

Conclusions: Patients treated with sdCsA+ tdmEVR showed lowest AR rate at both ≤90 d and 91–180 d post HTx compared to all other immunosuppressive regimens analyzed. While further reduction of CsA resulted in a slightly higher AR rate compared to sdCsA+ tdmEVR, it also showed a better renal function at M6. In summary, the 6 immunosuppressive regimens showed different efficacy profiles, thus benefits need to be weighed to find the optimal treatment for individual patients.

0065 INFLUENCE OF 6 DIFFERENT IMMUNOSUPPRESSIVE REGIMENS ON NEW ONSET DIABETES MELLITUS IN CARDIAC TRANSPLANT RECIPIENTS

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Introduction: New onset diabetes mellitus (NODM) occurs in approximately 15% of patients after solid organ transplantation with a higher incidence seen in patients receiving CNI based immunosuppression. Thus, reduction of CNI while maintaining efficacy is a common objective of many clinical trials. However, there is a paucity of data evaluating the incidence of NODM following heart transplantation (HTx). Hence, we retrospectively evaluated the impact of 6 different immunosuppressive regimens (ISR) on glucose metabolism and the incidence of NODM in consideration of other risk factors such as ethnicity, BMI, smoker status, and concomitant medication.

Methods: One thousand seven HTx recipients (HTxR) from three randomized, multicenter trials received one of the following ISR: SD-CsA/AZA ($n = 214$); SD-CsA/MMF ($n = 83$); SD-CsA/h-EVR ($n = 211$); SD-CsA/l-EVR ($n = 209$); SD-CsA/TDM-EVR ($n = 100$); RD-CsA/TDM-EVR ($n = 190$; pooled from two studies) [SD = standard dose; RD = reduced dose; h-EVR = fixed-dose 3.0 mg/d; l-EVR = fixed-dose 1.5 mg/d; TDM-EVR = C0 3–8 ng/ml]. Evolution of blood glucose levels and incidence of NODM were analyzed from baseline (BL) up to Month (M) 6 and M12.

Results: Transplant-specific baseline (BL) characteristics and BMI were balanced across groups. More patients in the MMF and SD-CSA/TDM-EVR groups had pre-existing DM compared to the other groups. NODM became almost exclusively manifest within the first 6 months after HTx. At M6 and M12, SD-CsA with fixed-dose EVR showed highest incidence of NODM

compared to AZA, MMF, and TDM-EVR regimens (Table). Results of the multivariate analysis for identification of risk factors will be presented.

Conclusions: New onset diabetes mellitus is a known side effect of CNI-based immunosuppression. The combination of SD-CsA with AZA, MMF or different EVR exposures had different impact on glucose metabolism. Full dose CsA in combination with high exposure EVR showed highest blood glucose levels and highest incidence of NODM. Therapeutic Drug Monitoring of EVR exposure markedly improved glucose metabolism.

0067 THE FRAMINGHAM RISK SCORE: ESTIMATION OF CARDIOVASCULAR RISK IN 1007 HEART TRANSPLANTS RECIPIENTS

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Introduction: Models like the Framingham risk score (FRS) have been developed for estimating the risk of cardiovascular (CV) events in asymptomatic individuals based upon assessment of multiple variables. However, only few reports exist that applies FRS to heart transplant recipients (HTxR) and evaluate the impact of different immunosuppressive regimens (ISR) on the increase in risk for CV events.

Methods: HTxR (safety population, $n = 1007$) from three randomized, multicenter trials were exposed to one of the following ISR: SD-CsA/AZA ($n = 214$); SD-CsA/MMF ($n = 83$); SD-CsA/h-EVR ($n = 211$); SD-CsA/l-EVR ($n = 209$); SD-CsA/TDM-EVR ($n = 100$); RD-CsA/TDM-EVR (pooled from two studies; $n = 190$) [SD = standard dose; RD = reduced dose; h-EVR = fixed dose 3.0 mg/d; l-EVR = fixed dose 1.5 mg/d; TDM-EVR = C0 3–8 ng/ml]. Framingham Risk Score (FRS), a multivariate risk model including gender, age, total cholesterol, HDL cholesterol, systolic blood pressure, and smoking status, was applied to estimate 10-year risk of coronary heart disease (CHD; myocardial infarction, coronary death, angina) at 6 and 12 months post HTx. Patients in the SD-CsA/TDM-EVR group were only followed for 6 months.

Results: Whereas age, gender distribution and mean baseline (BL) BMI were comparable across groups, there were notable differences in incidence of smoking status and diabetes at baseline (Table 1). Assessment of FRS based 10-year risks by treatment and gender at month (M) 6 and M12 after HTx and changes from BL to M12 showed different risk profiles with the individual regimens. While SD-CsA in combination with AZA or fixed dose EVR showed higher 10-year risk and change in risk from BL to M12, TDM-EVR (C0 3–8 ng/ml) and MMF demonstrated lower changes over time. Lower values for 10-year risk were seen for female HTxR in all groups (Table 2). Detailed categorical analysis of single parameters will be presented.

Conclusion: Our analysis showed an increase in 10-year risk for CHD in male patients across all treatment groups. Individual treatment groups show different profiles when increase in 10-year CHD risk is assessed. The estimation of cardiovascular risk can support patient education as well as the decision of the transplant physician which ISR might be beneficial for an individual patient and when to initiate preventative strategies.

0068 FEASIBILITY OF ALISKIREN FOR TREATMENT OF REFRACTORY ARTERIAL HYPERTENSION IN HEART TRANSPLANT RECIPIENTS

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Purpose: Post-transplant hypertension is a complex disease and partially caused by immunosuppressant therapy. Insufficient treatment impairs prognosis, therefore treatment of post-transplant hypertension is a major issue. ACE inhibitors and angiotensin II receptor blockers are first choice treatment for most patients. Aliskiren is a potent direct renin antagonist and thus another anti-hypertensive drug interfering with the renin-angiotensin system. There are limited clinical data on the feasibility of treatment with aliskiren in immunosuppressed heart-transplant recipients.

Methods and materials: This is a retrospective analysis of 11 patients which have been treated with aliskiren for refractory HTN after HTx before safety warnings of the FDA emerged. Maintenance immunosuppression consisted MMF, steroids, and CsA (6 pts), Tac (3 pts) and/or Eve (4 pts). Concomittant medication comprises ARBs (9 pts) and ACEIs (4 pts).

Results: Aliskiren was administered for a median of 53 (range 12–67) weeks. Throughout the duration of aliskiren therapy, blood pressure levels improved at 1 month but subsequently increased again. No significant changes were observed in serum potassium or creatinine levels. Immunosuppressant trough levels remained stable. With doses up to 300 mg/d aliskiren had to be stopped in one patient due to hypotension after 16 weeks, no other limiting adverse effects (diarrhea, impairment of renal function, hyperkalemia, angioedema) occurred.

Conclusions: This study shows that administration of aliskiren in HTx recipients under immunosuppressant therapy with CNI or PSI is a feasible option in clinical routine. Antihypertensive treatment in this small number of patients did not show consistent efficacy beyond 1 month. No severe adverse effects occurred, renal function and immunosuppressive therapy were not altered.

0070 KIDNEY DYSFUNCTION AS A RISK OF SEVERE IR INJURY AFTER LIVER TRANSPLANTATION

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Background: Long-term kidney dysfunction occurs frequently after liver transplantation (LT) with detrimental impact on mortality and morbidity. The pathophysiology of acute and chronic kidney injury associated with LT is poorly understood. In this study, we tested the hypothesis that recipients or livers with severe IR injury develop long-term kidney dysfunction.

Method: Between January 2000 and December 2004, 577 adult patients underwent LT. After exclusion of retransplants and living donor transplants we included 316 decreased donor LT with available kidney function data (MDRD GFR) on pre- and up to 12 months post LT. We established three different groups based on liver enzymes ((AST+ALT)/2) on day 2: immediate LT function: below the 25th percentile (<285 U/l), average LT function: 25th–75th percentile (285–986 U/l), and delayed LT function: above the 75th percentile (>986 U/l). The number of patients with kidney function impairment at the time of transplant was similar in all three groups. All patients received daclizumab induction and were maintained on tacrolimus and/or mycophenolate.

Results: Chronic renal failure, assessed by a eGFR ≤30 ml/min suggested by Ojo et al. (NEJM 2003), was not different between the three groups at the time of transplantation (21%, 14.2%, 9.8%, $P = 0.06$) or after 12 months of transplantation (12.5%, 5.2%, 2.6%, $P = 0.06$), which is almost similar to the results by Ojo et al. Compared to pre-transplant kidney function, eGFR post-transplant was gradually increased post LT in groups 1 to 3 in One-way Anova analysis. This effect was maintained throughout 12 months follow-up. The effect of the hepatic IR-injury remained significant after adjusting for HCV-status, donor and recipient age and race ($P = 0.01$).

Conclusion: Our results show that recipients of liver transplants that are subjected to severe IR injury develop kidney dysfunction post LT. Strategies to prevent acute liver injury at the time of transplantation can preserve native kidney function after LT.

0071 SWITCH TO EVEROLIMUS FOR TACROLIMUS-INDUCED PANCOLITIS IN A HEART TRANSPLANT RECIPIENT: A CASE REPORT

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Background: Immunosuppressant agents have greatly increased graft and overall survival in heart transplant patients, but some of these agents (e.g. calcineurin inhibitors [CNI] and corticosteroids) can also induce adverse events that may contribute to cardiac allograft vasculopathy (CAV). Referring to this sometimes its necessary to change the immunosuppression therapy. Everolimus is an immunosuppressive agent belonging to the mTOR inhibitors, used in solid organ transplantation in order to prevent graft rejection.

Abstract: We report a 65-year-old male patient who presented under immunosuppression with tacrolimus (TAC) a cardiac allograft vasculopathy (Stage IV, Stanford classification) 5 years after heart transplantation. According to this TAC was switched to everolimus (EVER) to prevent progression of the CAV. After 10 days he developed pancolitis with all features of ulcerative colitis. An infectious or ischemic etiology was carefully excluded. The histology was consistent with ulcerative colitis. In addition to conservative therapy it was necessary to commence a parenteral nutrition. Considering the chronology, the disease was associated with change of immunosuppression therapy. After re-switch from EVER again to TAC the patient recovered and remained in a good state of health.

Conclusion: Main side effects of everolimus are hematological (leukopenia, neutropenia, lymphopenia, thrombocytopenia), metabolic (dyslipidaemia), renal (renal insufficiency), hepatic (elevation of liver enzymes, cholestasis). To the best of our knowledge, this is the first reported case in the literature on the Pancolitis as a side effect of Everolimus.

0073 COMBINATION OF CLOPIDOGREL AND EVEROLIMUS DRAMATICALLY REDUCED THE DEVELOPMENT OF TRANSPLANT ARTERIOSCLEROSIS

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Introduction: Our group has previously shown that platelet inhibition with clopidogrel reduced the formation of transplant arteriosclerosis (TxA). The aim of this study was to investigate whether a combination of cyclosporine or everolimus with clopidogrel has a beneficial effect on the development of TxA.

Methods: Fully allogeneic C57BL/6 ($H2^b$) donor aortas were transplanted into CBA ($H2^k$) recipients. Recipient mice were treated with cyclosporine (2 mg/kg/d) and everolimus (0.05 mg/kg/d) alone or in combination with clopidogrel

(1 mg/kg/d). Grafts were analysed by histology and morphometry and mRNA expression on days 14 and 30 after transplantation.

Results: In mice treated with clopidogrel alone, TxA was reduced as compared to untreated controls (intima proliferation 65% ± 8% vs. 79% ± 9% [control]/n = 5). Daily application of everolimus significantly reduced the development of TxA compared to untreated controls (intima proliferation of 48% ± 19% vs. 79% ± 9% [control], n = 5). Strikingly, combination of clopidogrel and everolimus almost completely abolished the formation of TxA (intima proliferation: 16% ± 12% vs. 79% ± 9% [control], n = 5). In contrast, daily application of cyclosporine alone did not reduce the development of TxA compared to controls (intima proliferation: 74% ± 8% vs. 79% ± 9% [control], n = 5). mRNA expression revealed reduced ICAM-1 and CD40L intra-graft expression after treatment with clopidogrel and everolimus.

Conclusion: These results demonstrate that combination of clopidogrel and everolimus can dramatically reduce the development of TxA in a mouse aortic allograft model.

0074 REDUCED TRANSPLANT ARTERIOSCLEROSIS AFTER TREATMENT WITH MMF AND MMF IN COMBINATION WITH GANCICLOVIR IN A MOUSE AORTIC TRANSPLANT MODEL

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Introduction: The aim of this study was to investigate whether Ganciclovir and Mycophenolate Mofetil (MMF), alone or in combination, have a beneficial effect on the development of transplant arteriosclerosis (TxA).

Methods: Fully allogeneic C57BL/6 ($H2^b$) donor aortas were transplanted into CBA ($H2^k$) recipients. Recipient mice were treated either with MMF (100 mg/kg or 300 mg/kg), Ganciclovir (10 mg/kg or 72 mg/kg) or a low-/high-dosed combination of both. After explantation on day 30, grafts underwent morphometrical, histological and immunohistochemical analysis. Furthermore, recipients' spleens were FACS-analysed with regard to the expression of regulatory T-cells (Tregs) and alloantibodies in the recipients' blood was quantified.

Results: Whereas Ganciclovir monotherapy did not influence TxA, MMF 300 mg/kg significantly reduced TxA-development compared to untreated controls (intima proliferation of 23% ± 8% vs. 68% ± 7% [control]). MMF 100 mg/kg did not show any effects on TxA, but combination of Ganciclovir and MMF- reduced TxA not only at high dose (intima proliferation of 24% ± 4%) but also at low dose (27% ± 2% vs. 68% ± 7% [control]). Alloantibody-levels were significantly decreased by high-dosed MMF (mean fluorescence of 722 ± 201 vs. 9507 ± 1808 [control]) as well as MMF and Ganciclovir-combination at either dosage (low dosage: 2049 ± 437; high dosage: 586 ± 105). Beneficial effects of CD4+ CD25+ Foxp3+ Tregs on TxA could not be detected.

Conclusion: Our results demonstrate a dose-dependent positive effect of MMF on the development of TxA and a synergistic effect of Ganciclovir in combination with MMF, which is mainly effective in modulating the humoral immunresponse.

0077 ROLE OF TEMPERATURE DURING GRAFT RECONDITIONING BY GASEOUS OXYGEN

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Background: The influence of temperature on the restorative capacity of gaseous oxygenation of cold stored livers should be investigated.

Methods: Rat livers were harvested and cold-stored (CS) in University of Wisconsin (UW) solution for 20 hours. Some grafts were subsequently subjected to venous systemic oxygen persufflation (VSOP) (1) for 90 minutes at varying temperatures (4 °C, 12 °C 18 °C or 22 °C).

Metabolic efficiency of the different reconditioning protocols was analyzed by restoration of tissue levels of ATP and the sum of energy-rich phosphates SEP (ATP+ADP+AMP) at the end of ischemia and after subsequent VSOP. Free-radical medicated side effects were monitored by tissue lipid peroxidation (LPO). Functional organ integrity was assessed by warm reperfusion *in vitro*.

Results: VSOP at 4° or 12°comparably increased tissue ATP and SEP without rising LPO. VSOP at 18° accelerated ATP recovery but also significantly induced LPO. VSOP at 22° was less effective than at 18°. Warm reperfusion after VSOP at 4° disclosed significantly lower enzyme release (ALT, LDH) and higher oxygen consumption compared with untreated livers, while after VSOP at 16 °C only oxygen consumption was improved albeit to a lesser extent than after VSOP at 4 °C.

Conclusion: Energetic recovery upon VSOP is not influenced by rising temperature to 12 °C, while 18° promoted concomitant free radical induced side effects. The extent of ATP replenishment prior to reperfusion is no independent denominator for ulterior organ integrity.

Reference: (1) Transplantation 1998; 65: 1262–1264.

0079 EXPRESSION OF PERIPHERAL NODE ADDRESSIN (PNAD) ON ENDOTHELIAL CELLS IN SKIN OF HUMAN HAND ALLOGRAFTS

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Background: Expression of peripheral node addressin (PNAd) in high endothelial venules can be found in tertiary lymphoid organs (TLO) of de novo lymphoid tissue in chronic autoimmunity and allograft rejection. To assess its role in hand transplantation we investigated expression of PNAd in skin biopsies of human hand allografts.

Methods: A total of 167 skin biopsies of 6 hand-or forearm transplant recipients were collected over a time-span of 10 years and assessed by HE-histology (graded as per Banff 2007 classification for CTAs) and immunohistochemistry using antibodies for PNAd (MECA-79), CD3, CD4, CD8, CD20, C4d, CD68, LFA-1, ICAM-1, E-selectin, P-selectin, VE-cadherin, HLA-DR, Psoriasin, IDO and Foxp3. Levels of PNAd expression was assessed semiquantitatively (% of PNAd+ vessels: 0,1,2,3 and PNAd staining intensity: 0, 1, 2, 3) and correlated with rejection grade, characterization of the infiltrate, expression of adhesion molecules and time after transplantation.

Results: Rejection ranged from grade 0 to IV (mean score: 0.79 ± 1.05). Upon rejection, expression of PNAd was increased in endothelial cells (grade 0: 0.24 ± 0.48 vs. all grades of rejection: 0.44 ± 0.62). Most often PNAd expression was only found in few vessels (1–10%). PNAd staining intensity was increased the higher the grade of rejection (grade 0: 0.38 ± 0.76; grade I: 0.41 ± 0.74; grade II: 0.67 ± 0.80; grade III: 0.73 ± 0.91; grade IV: 0.50 ± 0.58). Intense PNAd-staining was associated with more CD4+ and CD8+ infiltrating T-cells, but less B-cells and macrophages, compared to mild PNAd staining intensity (CD4+ cells 49.00% ± 29.89; CD8+ cells 31.00% ± 22.34; CD20+ B-cells 0.50% ± 1.54; CD68+ macrophages 0.57 ± 0.60 vs. CD4+ cells 37.35% ± 40.82; CD8+ cells 27.35% ± 35.93; CD20+ B-cells 0.94% ± 2.02; CD68+ macrophages 0.67 ± 0.66). Overall, PNAd expression correlated well with CD3+ cells (0.256) and CD20+ B-cells (0.279). Poor correlation was found for expression of adhesion molecules, IDO and Foxp3, except for LFA-1+ infiltrating cells (0.251). While PNAd expression was observed at all time-points after transplantation, staining intensity was enhanced late after transplantation (0.32 ± 0.69 vs. 0.46 ± 0.73).

Conclusion: PNAd expression in endothelial cells is increased in skin biopsies of human hand allografts indicating presence of TLO. Further analysis is warranted to clarify the role of PNAd in composite tissue allotransplantation.

0080 A SINGLE-CENTER-EXPERIENCE OF LIVER TRANSPLANTATION IN PATIENTS WITH ALCOHOL-TOXIC LIVER CIRRHOSIS: OUTCOME, ALCOHOL RECIDIVISM AND QUALITY OF LIFE

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Alcohol-toxic liver cirrhosis (ALC) is one of the main indications for liver transplantation (LTx). Aim of the study was to find out the risk factors for alcohol recidivism and to identify the outcome and quality-of-life of these patients.

Patients and methods: From March 2003 until July 2009**,** 226 patients underwent LTx (164 m) in our centre. In 120 of 226 patients (53%) liver cirrhosis was caused (sole/cofactor) by alcohol. Outcome and alcohol recidivism were assessed on patients' records, and interviews of general practitioners. All alive LTx patients (n = 152) received the SF-36 quality-of-life and a self-designed questionnaire (anonymous, return rate 69%).

Results: Mean follow-up after LTx was 31 ± 23 months. The 5-year-survival-rate after LTx in patients with ALC was significantly better compared to patients with other indications (78% vs. 64%; P = 0.016). 84% of patients with ALC and 80% with another indication for LTx survived the first 6-months post-operative period. The quality-of-life of both patients' groups (alcohol-tox. vs. others) was equal. Before LTx**,** 36% of patients with ALC had a moderate and 64% of patients' severe alcohol consumption. After LTx, severe alcohol recidivism was observed in 17 (16%) patients, while 4 (3.6%) of these patients developed a transplantat cirrhosis and died within 29 to 62 months. Patients with an alcohol abstinence time <3 months before LTx had a significant higher (P = 0.042) rate of alcohol recidivism in comparison to those >3 months.

Conclusions: ALC is a good indication for LTx and after careful selection of the patients the frequency of alcohol recidivism was <16%.

0082 DE NOVO CALCINEURININHIBITOR-FREE IMMUNOSUPPRESSION WITH SIROLIMUS AND MYCOPHENOLATE MOFETIL (MMF) AFTER HEART TRANSPLANTATION: 5-YEAR RESULTS

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Purpose: Despite improvements in immunosuppressive therapy chronic rejection, renal toxicity and malignancy are the major obstacles for long-term success after heart transplantation. Therefore we performed the worldwide first pilot-trial to evaluate the efficacy and safety of a de novo CNI-free immunosuppressive protocol.

Methods: Between May 2003 and April 2005, 15 de novo cardiac transplant recipients (10 male, 5 female, mean age 55.1 years, diagnosis 8 DCM/7 ICM) were assigned to receive sirolimus, MMF and steroids. Antilymphocyte induction was given for 5 days; steroids were withdrawn after 6 months. 6/15 patients received CMV-prophylaxis for high risk CMV-constellation (R-/D+).

Results: Survival at 1 and 5 years was 87.5% (one death caused by pulmonary adenocarcinoma). Freedom from biopsy-proven rejection was 71.3% at 1 year; 59.4% at 5 years. Freedom from angiographically detectable vasculopathy was 100% after 5 years and only one CMV-infection occurred.

Mean serum-creatinine was 1.43 ± 0.31 mg/dl prior to HTx, 1.29 ± 0.56 mg/dl at 1 year and 1.23 ± 0.53 mg/dl at 5 years. Cholesterol was 203 ± 32 at 1 year and 199 ± 40 at 5 years despite statins and hypertriglyceridemia (223 ± 97 mg/dl) persisted after 5 years. No new onset diabetes occurred. Surgical interventions for pericardial effusions were necessary in 5 patients.

Nine patients discontinued sirolimus treatment due to side effects (4 acute rejections, 3 delayed wound healing, 2 GI-toxicity).

Conclusions: De novo CNI-free immunosuppression after heart transplantation is less efficacious in prevention of acute rejection and has an inferior side effect profile. On the other hand CNI-free immunosuppression is possible and long-term results are favourable for survival, malignancy, renal function, CMV-infections and vasculopathy.

0084 CMV VALGANCICLOVIR PROPHYLAXIS VERSUS PREEMPTIVE THERAPY AFTER RENAL TRANSPLANTATION: ONE YEAR RESULTS OF A RANDOMIZED CLINICAL TRIAL

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Introduction: Prophylaxis and preemptive therapy are competitive approaches to prevent cytomegalovirus (CMV) infection after renal transplantation. Several prospective randomized studies show that in high risk (D+/R-) patients prophylaxis is the best option for preventing CMV, and to a lesser extend this is also true for D+/R+ patients. Within the last few years, evidence is growing that not only CMV disease but also asymptomatic (subclinical) active CMV infection correlates with increased long term morbidity, graft loss, diabetes, atherosclerosis and mortality following solid organ transplantation.

Methods: We performed a randomized clinical trial to determine if renal transplant recipients with a positive CMV serostatus had a higher rate of active CMV infection (i.e. CMV replication) and disease when treated preemptively for CMV infection, compared to recipients treated with primary prophylaxis; and whether this correlates with a higher rate of chronic graft alteration and long-term graft and patient survival. Prophylaxis consisted of 2×450 mg (900 mg) valganciclovir tablets/day adjusted for renal function for 100 days post-transplantation. Patients were monitored with a quantitative CMV PCR test (Cobas® Amplicor® CMV-Monitor) and positive patients (≥400 CMV DNA copies/ml) received four valganciclovir tablets 1800 mg/day adjusted for renal function followed by secondary prophylaxis with two valganciclovir tablets 900 mg/day for 28 days. Patients were to be followed for 5 years; initial 12 month data are presented in this abstract.

Results: Two hundred and ninety-six patients were analyzed (168 D+/R+ and 128 D-/R+), 146 to prophylaxis and 150 to pre-emptive therapy. At 12 months overall tolerability was good for both treatments. Episodes of acute graft rejection were more common with prophylaxis (18.5% vs. 12.0%, $P > 0.05$, prophylaxis versus preemptive therapy), but a significantly higher rate of rejection was only observed in the D-/R+ group (21.4% vs. 8.3%, $P = 0.042$, prophylaxis versus preemptive therapy), with no difference in the D±/R+ group (16.7% vs. 15.4%, $P > 0.05$, prophylaxis versus preemptive therapy). Active CMV infection was significantly higher with preemptive therapy (36.0% vs. 10.3%, $P < 0.0001$, preemptive therapy versus prophylaxis), and most CMV infection was seen for D+/R+ patients receiving preemptive therapy (51.3% versus 14.4%, $P < 0.0001$, preemptive therapy versus prophylaxis). Similarly, D+/R+ patients with preemptive therapy had the greatest rate of CMV disease (19.2% vs. 4.4%, $P = 0.003$, preemptive therapy versus prophylaxis). Renal function was similar for prophylaxis versus preemptive therapy. Graft loss occurred for more preemptive patients (4.7% vs. 2.7%, $P > 0.05$, preemptive therapy versus prophylaxis).

Conclusion: In conclusion, valganciclovir prophylaxis significantly reduces the incidence of CMV infection and disease, particularly for D+/R+ patients without reducing overall graft function. Hence, the antiviral effect of CMV prophylaxis may be dependent on the CMV status of the donor and routine prophylaxis for all D+/R+ patients should be considered. The ongoing follow-up will determine if additional long-term benefits for graft survival are observed for D+/R+ patients receiving prophylaxis.

0086 GENE TRANSFER MAXIMIZES MESENCHYMAL STEM CELL-BASED MYOCARDIAL SALVAGE AFTER ACUTE MYOCARDIAL INFARCTION

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Background: Mesenchymal stem cell (MSC)-based regenerative strategies were investigated to treat acute myocardial infarction (AMI) and improve LV function.

Methods and results: Murine AMI was induced by coronary ligation with subsequent injection of MSCs, HGF or VEGF, or MSCs +HGF/VEGF into the borderzone. LVEF was calculated using Micro-CT imaging after 6 months. HGF and VEGF protein injection (with or without concomitant MSC injection) significantly and similarly improved the LVEF and reduced scar size compared to the MSC group, suggesting that myocardial recovery was due to the cytokines rather than myocardial regeneration. To provide sustained paracrine effects, HGF or VEGF over-expressing MSCs were generated (MSC-HGF, MSC-VEGF). MSC-HGF and MSC-VEGF showed significantly increased in vitro proliferation and increased in vivo proliferation within the borderzone. Cytokine production correlated with MSC survival. MSC-HGF and MSC-VEGF-treated animals showed smaller scar sizes, increased peri-infarct vessel densities, and better preserved LV function when compared to MSCs transfected with empty vector.

Murine cardiomyocytes (CM) were exposed to hypoxic in vitro conditions. The LDH release was reduced, fewer CM were apoptotic, and Akt activity was increased if CM were maintained in conditioned medium obtained from MSC-HGF or MSC-VEGF cultures.

Conclusions: 1 Elevating the tissue levels of HGF and VEGF after AMI seems a promising reparative therapeutic approach.

2 HGF and VEGF are cardioprotective by increasing the tolerance of CM to ischemia, reducing CM apoptosis and increasing pro-survival Akt activation.

3 MSC-HGF and MSC-VEGF are a valuable source for increased cytokine production and maximize the beneficial effect of MSC-based repair strategies.

0087 LOCAL IMMUNOSUPPRESSION BY INHIBITION OF NFKB ACTIVATION USING INHALED TACROLIMUS

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Background: Local immunosuppression by inhalation is a novel strategy after lung transplantation. Here we investigate the feasibility of tacrolimus delivery via aerosol, assess its immunosuppressive efficacy, reveal possible mechanisms of action, and evaluate its airway toxicity on human airway epithelial cells.

Material and methods: Pharmacokinetic properties were compared and in vivo airway toxicity was assessed in rats. Full-thickness human airway epithelium (AE) was grown in vitro at air-liquid interface. Equal TAC doses (10−1000 ng) were either added to the bottom chamber (MED) or aerosolized for gas phase exposure (AER). AE TAC absorption, cell toxicity, and the interaction of TAC with NFkB activation were studied.

Results: SPECT imaging demonstrated a linear tracer accumulation within the lungs during TAC inhalation. TAC AER generated higher lung tissue levels, but 11-times lower blood levels. Airway histology and gene expression did not reveal drug toxicity after 3 weeks of treatment. In vitro AE exposed to TAC 10−1000 ng PO or AER maintained its pseudostratified morphology, did not show cell toxicity, and maintained its epithelial integrity with tight junction formation. TAC AER-treated AE absorbed the drug from their apical surface and generated lower-chamber TAC concentrations sufficient to suppress activated lymphocytes. TAC AER, better than TAC MED, prevented AE IFN-g, IL-10, IL-13, MCP-1, RANTES, and TNF-α up-regulation. TAC was found to inhibit airway epithelial cell NFkB activation.

Conclusions: TAC can easily and effectively be delivered into the lungs without causing airway toxicity and decreases inflammatory AE cytokine production via inhibition of NFkB activation.

0088 IMMUNOSUPPRESSIVE AGENTS DIFFERENTLY SUPPRESS T CELL SUBPOPULATIONS

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Purpose: The recent discovery of a CD4+ T cell subtype characterized by the secretion of interleukin IL-17 (Th-17 cells) had a major impact on our understanding of immune processes not readily explained by the Th-1/Th-2 paradigm. We investigated the efficacy of each member of the main immunosuppressive substance classes to specifically suppress activated lymphocyte subpopulations.

Methods: Heterotopic BN-Lew heart transplantations were performed. Six days after transplantation, spleens were recovered and splenocytes were isolated. Equal amounts of donor and recipient splenocytes were incubated for 24 hours at 37 °C. Unidirectional ELISPOT assays for Th-1 (IFNg), Th-2 (IL-4), Th-17 (IL17) and Treg subtypes (TGFβ) were performed to identify the frequency of activated T cell subsets. Drugs were added at concentrations which are considered therapeutic trough levels in patients: calcineurin-inhibitor (tacrolimus; 15 ng/ml), mTOR-inhibitor (rapamycin: 15 ng/ml), pyrimidine synthesis inhibitor (FK778: 120 ug/ml), purin synthesis inhibitor (MMF: 5 ug/ml), JAK3-inhibitor (R333: 3000 ng/ml), and Syk-inhibitor (R406: 3000 ng/ml). The *in vivo* situation was simulated by adding 10% albumin to the culture medium. The specific suppressive potency on the above T cell subsets was assessed for each drug.

Results: Total spot frequencies were 2731 ± 963 for untreated cells and were significantly decreased by tacrolimus (148 ± 66), rapamycin (1860 ± 701), FK778 (66 ± 100), MMF (751 ± 449), R333 (14 ± 14), and R406 (11 ± 9) ($P = 0.001$ for rapamycin vs untreated and $P < 0.001$ for all other treatment groups vs untreated). Tacrolimus decreased spot frequency of Th-1, Th-2 and Th-17 cells significantly to 3 ± 3%, 15 ± 12%, and 30 ± 18%, respectively compared to untreated cells ($P < 0.001$). However, no decreasing effect on TGFβ secreting cells was observed (102 ± 43%).

FK778 showed a significant decrease of all investigated subtypes (2 ± 4% Th-1, 2 ± 2% Th-2, 2 ± 2% Th-17, and 5 ± 4% TGFβ), similar to R333 and R406 (Th-1: 0% and 0%, Th-2: 5 ± 5% and 4 ± 4%, Th-17: 2 ± 2% and 4 ± 4%, and TGFβ producing cells 3 ± 3% and 4 ± 4%, respectively).

MMF was less potent than the above drugs, but still effective in decreasing Th-1 (35 ± 17%), Th-2 (17 ± 17%), and Th-17 cells (17 ± 17%) and also decreased Treg subtypes (11 ± 6%).

Rapamycin showed no significant suppressive potency on Th-1 (95 ± 33%) and Th-2 cells (77 ± 31%); however, Th-17 cells were suppressed significantly (53 ± 20%; $P < 0.001$), whereas TGFβ producing cells were only mildly effected (60 ± 26%).

Conclusion: FK778, R333, and R406 demonstrate the most potent but unselective effect on all investigated T cell subpopulations. MMF was also unselective, but far less potent. The suppressive effect of rapamycin was most potent on Th-17 cells, whereas the Th-1, Th-2, and TGFβ producing cell population seemed to be unaffected. Tacrolimus showed a selective, very potent effect on Th-1, Th-2, and Th17 without decreasing TGFβ.

0090 IDENTIFYING THE POTASSIUM CHANNEL KCA3.1 AS A NEW THERAPEUTIC TARGET TO PREVENT CHRONIC AIRWAY ALLOGRAFT REJECTION

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Background: Currently there is no effective therapy to prevent obliterative airway disease (OAD) which is the most common cause of morbidity and mortality after lung transplantations. The intermediate-conductance potassium channel KCa3.1 is upregulated in activated lymphocytes and proliferating fibroblast and vascular smooth muscle cells. Blockade of this channel therefore offers an attractive therapeutic target to prevent OAD. In this study we investigated the relevance of the KCa3.1 channel for OAD and examined the antiproliferative effects of the new KCa3.1 channel blocker TRAM34 after tracheal transplantation in a murine model.

Methods: Trachea from CBA donors were heterotopically transplanted in the greater omentum of C57Bl6 mice ($n = 6$ per group). Recipients were treated for 28 days with the KCa3.1 blocker TRAM-34 (120 mg/kg/d i.p.) or left untreated. KCa3.1$^{-/-}$ mice on C57Bl6-background were used as additional controls. Grafts were harvested and tracheal segments were processed for histological evaluation by computer morphometry determining degree of luminal obliteration and percentage of respiratory epithelium coverage.

Results: Since submucosal and epithelial tissues form the inner lining of the cartilage, the value for luminal obliteration in syngeneic tracheas obtained with this method corresponds to 13.2 ± 3.9%, whereas allogeneic grafts showed a mean obliteration of 92 ± 7% ($P < 0.001$). Luminal obliteration in the KCa3.1$^{-/-}$ group (60 ± 29%) was significant lower than in the allogeneic group ($P = 0.007$), which identifies the KCa3.1 channel as relevant target. The TRAM-34 treatment group showed an obliteration of 61 ± 28% ($P = 0.011$ vs. no medication). There was no significant difference between the TRAM-34 and the knockout group.

Conclusions: Our findings suggest that KCa3.1 channels are involved in the development of OAD and that KCa3.1 blockers hold promise to prevent OAD development.

0091 NON-VOLUME-LOADED HEART PROVIDES A MORE RELEVANT HETEROTOPIC TRANSPLANTATION MODEL

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Background: This study aimed to compare two techniques of heterotopic heart transplantations in rats. Our interest was focused on chronic allograft morphology, physiology, and immunology in the non-volume-loaded (NL) and volume-loaded (VL) model.

Methods: Heterotopic heart transplantations were performed in the PVG-to-ACI rat model and followed over 90 days. Graft morphology was assessed by weight, histology after 90 days, and echocardiography on days 15, 30, 45, 60, and 90. Heart physiology was investigated by analysis of pulse pressure and maximum dP/dt using Langendorff perfusion. We observed the immunological response through the development of chronic allograft vasculopathy.

Results: Ischemic time was significantly longer using the VL model compared to the NL model ($P < 0.001$). Echocardiography revealed no significant differences in posterior wall thickness between the groups. The VL donor heart showed significantly higher weight, decreased pulse pressure, and decreased maximum dP/dt. Histological analysis showed a significant amount of luminal obliteration in the allogeneic transplantation groups (31–37%), but no difference in luminal obliteration between the two models ($P = 0.61$). Remarkably, donor hearts in the VL model suffered from chronic myocardial ischemia, showing dilation and scarring on histology.

Conclusions: Due to model design, the VL model suffers from dilated cardiomyopathy after 90 days. Despite the NL model not pumping blood volume, it has a shorter ischemic time and comparable immunological results to the VL. We conclude the NL model to be the more clinically relevant model in chronic heart transplantation studies.

0093 EVEROLIMUS PLUS DOSAGE REDUCTION OF CYCLOSPORIN A IN CARDIAC TRANSPLANT RECIPIENTS WITH CHRONIC KIDNEY DISEASE: A TWO-YEAR FOLLOW-UP STUDY

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Background: The calcineurin inhibitor cyclosporine A (CSA) has nephrotoxic side effects. Methods: We switched 95 maintenance cardiac transplant (CTx) recipients with chronic kidney disease (CKD) stages 3–4 from CSA to everolimus (EVL). The CSA dosage was reduced by 50%. Kidney function, lipid metabolism, and cardiac function were investigated during a 2-year follow-up period and compared to CTx patients with CKD stages 2–3 who continued to receive CSA (CSA group; $n = 84$).

Results: Whereas 64 of the 95 patients received reduced CSA plus EVL during the entire follow-up period (ECN subgroup), 31 patients had to discontinue EVL (EDS subgroup) after 4.3 months (median) because of various clinically relevant adverse events. Glomerular filtration rate (estimated by MDRD formula) increased by 4.0 ml/min/1.73 m^2 in the ECN subgroup, but declined by 2.4 ml/min/1.73 m^2 and 9.0 ml/min/1.73 m^2 in the EDS subgroup and the CSA group, respectively.

Conclusion: EVL combined with low dose CSA had modest beneficial effects on kidney function in CTx patients with CKD stages 3–4. A significant percentage of patients had to stop EVL because of various adverse events.

0094 BENEFIT OF IMMUNSUPPRESSIVE THERAPY IN HEART TRANSPLANT RECEIPIENTS RECEIVING TACROLIMUS AND EVEROLIMUS COMPARED TO THE COMBINATION OF CICLOSPORIN A AND EVEROLIMUS

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Background: In cardiac transplant recipients with calcineurin inhibitor-induced chronic renal failure, mid-term efficacy and safety of an immunosuppressive regimen with everolimus (EVL) and tacrolimus (group T) compared to everolimus and cyclosporine A (CSA); syn.: group C are presently not known.

Methods: From January 2004 until December 2005, 95 maintenance cardiac transplant recipients with chronic renal failure were switched over from CSA and prednisolone or tacrolimus and mycophenolat mofetil to EVL comined with low dose cyclosporine or low dose tacrolimus. The CSA and tacrolimus dosages were reduced by 50%. Renal function, lipid metabolism, cardiac rejections, and mortality were investigated during a 1-year follow-up period. Group C ($n = 66$) received EVL under dosage reduction of CSA during the entire follow-up period. Group T ($n = 40$) received EVL under dosage reduction of CSA.

Results: During follow-up, creatinine decreased in group T (t0 2.0 mg/dl; t6 1.8 mg/dl) and slightly increased in Group C (t0 2.0 mg/dl; t6 1.8 mg/dl). Triglyceride levels and total cholesterin (improved by the intensified use of statins) levels increased in both gropus during the follow up perid with comparable values. In group T 25% of the patients compared to 29.3% in group C had to stop everolimus due to adverse events Mortality was 3% in group C and 0 in group T. Incidens of cardiac rejections was significantly lower in group T (14.9%) copared to group C.

Conclusions: EVL use in combination with low dose tacrolimus can protect kidney function in CTx patients with chronic renal failure in the medium term more efficient than in combination with cyclosporine. The risk of hypercholesterolemia can largely be avoided by an intensified use of statins in both groups. In group C more patients had to stop EVL exposure because of various adverse events compared to group T and rejection rate in group C was higher than in group T. We conlude that tacrolimus in combination with EVL may lead to more benefit than cyclosporine combined with EVL.

0096 GENDER AND WORRIES ABOUT THE FAMILY AS PREDICTORS OF OUTCOMES IN THE WAITING FOR A NEW HEART STUDY

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Background: We examined the role of gender and being worried about the family for the prognosis of patients awaiting heart transplantation (HTx).

Methods: A multi-site prospective study was conducted with 58 female and 260 male (51 ± 1 and 53 ± 5 years of age) HTx candidates newly waitlisted at 17 German-speaking hospitals. Baseline demographics and family worries (about the partner; about other family members) were assessed by questionnaires. Eurotransplant provided medical data and waitlist events. Using a competing risk approach, multivariate cause-specific Cox proportional hazard models were run to test the association of gender and family worries with time till the combined endpoint death and delisting due to clinical deterioration.

Results: During the follow-up (median: 338 days; range: 13 to 1394 days), 54 patients (13 women) died, 15 (5 women) were delisted due to clinical deterioration, 110 (17 women) received an urgent HTx, 41 (10 women) received elective HTx, and 31 (4 women) were delisted due to clinical improvement. Heart failure survival score, creatinine, age, medications, and family worries (excluding partner worries) did not differ by sex. Compared to women, men were more likely to be past smokers and reported more worries about their partner; they were more likely to be married and higher educated (all Ps < 0.05). After controlling for disease severity, age, and baseline differences, female gender was associated with a higher risk of death/deterioration (hazard ratio [HR] = 2.93; 95% confidence interval [CI] 1.53 to 5.54, $P < 0.01$); only worries about the partner interacted significantly with sex ($P < .05$), suggesting that worries about the partner had an adverse effect on death/clinical deterioration in women (HR = 1.44, 95% CI 0.97−2.12, $P < 0.07$), but not in men. Neither gender nor family worries predicted other events.

Conclusion: The worse survival of women, independent of age, disease severity and other confounders, may, in part, be influenced by worrying about their partner being overburdened.

0098 PATIENTS WITH 18-F-FDG NON-AVID HILAR CHOLANGIOCARCINOMA ON PET MAY ACHIEVE RECURRENCE-FREE LONG-TERM SURVIVAL AFTER LIVER TRANSPLANTATION

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Background: Liver transplantation for hilar cholangiocarcinoma (HC) is characterized by a high posttransplant recurrence rate. The aim of this trial was to assess the value of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) for predicting biological tumor behavior and outcome after liver transplantation (LT) in patients with otherwise unresectable hilar cholangiocarcinoma (HC).

Patients and methods: In 13 patients with surgically non-resectable type IV Klatskin tumor, ^{18}F-FDG-PET was performed before LT. FDG-uptake of the tumor was determined by semiquantitative assessment. PET+ status indicated patients with an increased pretransplant ^{18}F-FDG uptake, while PET-recipients had no increased preoperative ^{18}F-FDG uptake on PET. Pretransplant PET findings were correlated with histopathological tumor characteristics and patient outcome after LT.

Results: Eight patients demonstrated positive preoperative PET findings (61.5%), while five patients had no increased preoperative ^{18}F-FDG tumor uptake (38.5%) on PET. Seven PET+ liver recipients developed tumor recurrence, while five PET-patients were tumor-free alive after a median of 76 months post-LT and one PET+ patient died after one month due to liver allograft dysfunction (P = 0.001).

Of the five patients with regional lymph node involvement, four (80%) demonstrated positive pretransplant PET findings, and of the nine patients with perineural tumor invasion, eight (88.9%) demonstrated PET+ status pre-LT. The positive predictive value of PET+ status for indicating nodal invasion and perineural tumor involvement was 50% and 88.9%, respectively.

All seven patients with preoperative PET+ status (one PET+ patient excluded after in-hospital death) developed tumor recurrence, while five PET-recipients were still alive between 8 and 136 months post-LT (median: 76 months) without tumor relapse (P = 0.001;).

The two-year recurrence-free survival rate after LT was 100% in PET-patients and 28.6% in the PET+ population (log rank = 0.008).

Discussion: ^{18}F-FDG uptake on PET is an appropriate device for describing biological tumor behavior of HC. It should be used to identify patients with HC that may profit from liver transplantation.

0099 THE INFLUENCE OF HIGH-DOSE AND LOW-DOSE THERAPY WITH EVEROLIMUS IN HEART TRANSPLANT RECIPIENTS WITH CHRONIC RENAL FAILURE

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Introduction: The influence of dosage everolimus in combination with calcineurininhibitors in heart transplant recipients with chronic renal failure on the development of renal function and the safety referring to cardiac rejections is currently not known. Methods: A total number of 108 patients after orthotopic heart transplantation (between 1989 and 2004) developing chronic renal failure (Creatinine level ≥ 1.6 mg/dl) were included in our data analysis. Initial immunosppressive regime was: Cyclosporine A (reference range 110−190 ug/l; within the first year after HTX and 60−80 ug/l > 1 year after transplantation) and low dose prednisolon. Patients undergoing conversion to evrolimus between 1.1.2004−31.12.2004 received high dose therapy (HD) with everolimus (reference range of everolimus level: 5−8 ug/l). Patients undergoing conversion to evrolimus between 1.1.2005−30.06.2006 received low dose (LD) therapy with everolimus (reference range of everolimus level: 4−5 ug/l). Follow up interval: 1 year after conversion.

Results: Blood count values (leukocytes, erythrocytes and thrombocytes) did not differ significantly during the follw up intervall. Average value of renal parameters before conversion (low dose group): Creatinine 2.23 mg/dl and BUN 98.8 mg/dl. Creatinine decreased to 2.18 mg/dl and BUN decreased to 83.6 mg/dl 12 months after conversion. Average value of renal parameters before conversion (low dose group): Creatinine 2.0 mg/dl and BUN 93 mg/dl. Creatinine increased to 2.29 mg/dl and BUN increased to 96 mg/dl 12 months after conversion. The values of total cholesterin (inclusive HDL and LDL) and triglycerides did not differ significantly between both groups during the 1 year interval. Rejection rate was higher in the LD-group (15.7%) than in the LD-group (8.9%). Mortality rate was higher in the HD-group (3.6%) than in the LD-group (0). In the HD-group significant more patients (57.1%) developed adverse events than in the LD-group (33.3%).

Conclusion: We conclude that the compatibility to everolimus in the low dose group is better than in the high dose group especially referring the lower rate of adverse events in the low dose group. Furthermore development of kidney function is better in the LD-group than in HD-group. Otherwice rejection rate was higher in the LD-group than in the HD-group- but sufficiently treated by cortisone.

0100 DARK SIDE OF THE MOON: SUICIDE AFTER LVAD-IMPLANTATION AS A DESTINATION THERAPY

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Introduction: Left ventricular assist devices (LVAD) are increasingly used in patients with endstage heart failure as a destination therapy. Not all patients benefit durably from their improved quality of life under VAD-support. For some of them many psychological items might be a source of problems in their life far from normal. Depression and anxiety are well-documented in patients with end-stage heart failure and correlate with a higher risk of suicide.

Method: This case reports about a 69-year-old, depressive patient, who committed suicide by disconnecting his driveline almost three years after implantation of a LVAD. We provide a medical, psychological and psychiatric background of this unique case.

Result: The device itself might give depressive patients a new opportunity of committing suicide. The inhibition threshold seems to be dramatically decreased by an every day handling like changing the batteries or connecting/disconnecting the driveline of the controller in comparison to more rude suicidal attempts like hanging oneself or shooting oneself down.

Conclusions: This report highlights the importance of pre-implant psychological screenings, the need for regular and long-term psychological support for this vulnerable patient population, and the need for more research on the patients' views on "living with an LVAD" (qualitative research), together with research exploring risk profiles for depression/suicide. A debate about palliative care and end-of-life decisions after LVAD implantation as a destination therapy would be helpful as well.

0106 IMPACT OF 6 DIFFERENT IMMUNOSUPPRESSIVE REGIMEN ON EFFICACY AND RENAL FUNCTION AFTER CARDIAC TRANSPLANTATION

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Introduction: Achieving efficacy while maintaining safety is key after HTx. However, chronic kidney disease (CKD) is an increasing complication with substantial morbidity and mortality and seems to be related to immunosuppressive regimens (ISR) used. Lowering immunosuppression (IS) can be an

option to improve renal outcome but bears the risk of increasing acute rejections (AR). Here, we retrospectively analyzed the impact of 6 ISR on evolution of renal function (RFct) relative to efficacy outcome.

Methods: One thousand and nine HTxR (pooled ITT population) from three randomized, multicenter trials received one of the following ISR: SD-CsA/AZA ($n = 214$); SD-CsA/MMF ($n = 84$); SD-CsA/h-EVR ($n = 211$); SD-CsA/l-EVR ($n = 209$); SD-CsA/TDM-EVR ($n = 100$); RD-CsA/TDM-EVR ($n = 191$) [SD = standard dose; RD = reduced dose; h-EVR = 3.0 mg/d; l-EVR = 1.5 mg/d; TDM-EVR = C0 3–8 ng/ml]. Incidence and severity of AR and evolution of eGFR were analyzed. HTxR were also stratified according to CKD stages.

Results: HTxR had similar baseline (BL) characteristics. With EVR based IS more patients were free of AR and also less early AR occured than with MMF or AZA. The SD-CsA/TDM-EVR group showed the best efficacy profile. Comparing RFct, HTxR on RD-CsA/TDM-EVR showed the slowest decline in RFct (MDRD) from BL to M6 compared to the other ISR, but still showed a higher absolute change than HTxR treated with MMF or AZA (-7.8 vs. -4.9 and -6.5 ml/min). HTxR with BL GFR 30–59 ml/min showed less decline in RFct over time and less differences between the ISR compared to HTxR with better (60–89 ml/min) or good RFct at BL (>90 ml/min). (Table 1).

Conclusion: While controlling AR is the main goal of IS post HTx it is often accompanied by a rapid decline in RFct, therefore risks and benefits of different ISR need to be weighed. Best efficacy outcome was observed for SD-CsA/TDM-EVR. However, RFct was worse when EVR was combined with SD-CsA than with RD-CsA. EVR combined with CsA dose reduction resulted in improved renal outcome while providing better AR protection than AZA or MMF based ISR. HTxR with good RFct at time of HTx benefited most from CsA reduction.

0108 CASE TITLE: TOXOPLASMOSIS ENCEPHALITIS THREE MONTHS AFTER HEART TRANSPLANTATION

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Clinical question: Neurotoxoplasmosis after heart transplantation is a rare, but often fatal event. The lack of clinical awareness leads to difficulties in establishing a diagnosis and to start a sufficient therapy. Therefore it is highly important to focus on new diagnostic prospects and innovative treatment options.

Background: Compared to the world wide incidence, this severe complication is more likely in recipients living in Europe due to the overall high seroprevalence. Most often infection with Toxoplasma gondii could be caused by reactivation of seropositive recipients during immunosuppression or it could be transmitted with the transplanted organ to a seronegative recipient. Untreated, it leads to a high mortality up to 65% in heart transplant recipients.

Case summary: We present a 46-year-old woman who underwent heart transplantation because of arrhythmogenic right ventricular dysplasia. The patient was toxoplasma seronegative and received an allograft from seronegative donor. On a out clinic visit for a protocol biopsy 12 weeks after transplantation, she reported fatigue, headache and an impaired vision of her right eye, which had started to weeks earlier. The brain MR showed multiple lesions of variable size with a hyper intense signal on T1-weighted images sub cortical and in the brain stem. The spinal fluid PCR was positive for Toxoplasma Gondii. Specific therapy consisted of daraprime and sulfadiazine was administrated. After 2 month she was on a good way to full neurological recovery. In a control MR, 6 month later, all lesions decreased and perifocal edema formation was regressive under toxoplasmosis therapy.

Conclusion: Toxoplasmosis Infection should be considered in the differential diagnosis of focal neurological deficits and headache in heart transplant recipients. MR imagining as a non invasive method should established for early diagnosis, sufficient treatment and follow up instrument. Treatment with high daily doses of daraprime and sulfadiazine may be an effective therapy for this life threatening complication after heart transplantation.

0109 BIOPSY-INDUCED MITRAL REGURGITATION 13 YEARS AFTER ORTOTHOPIC HEART TRANSPLANTATION

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Clinical question: Does left heart biopsy as an uncommon procedure for diagnosis of allograft rejection lead to more fatal complications in contrast to right heart biopsy that presents the current gold standard for allograft rejection screening in heart transplant recipients?

Background: Endomyocardial biopsy represents the gold standard for diagnosis of allograft rejection following heart transplantation (HTx). It is a standardized invasive procedure mostly performed in the right ventricle (RV) with a low complication rate like tricuspid regurtation (TR). In contrast, left ventricular (LV) biopsy in HTx is only performed for convenience if a diagnostic procedure of the left heart is necessary.

Case summary: A 73-year-old male patient underwent orthotopic HTx in 1996. The clinical course post-transplant was uneventful besides an immunosuppressive drug induced nephrotoxicity leading to dialysis one year ago. Standard postoperative care included right ventricular biopsy on a regular basis over all years. Left heart angiography was necessary to evaluate the patient for renal transplantation 13 years after orthotopic heart transplantation. Therefore the routine biopsy was performed in the same procedure from the left apex. Initially, the procedure was uneventful and the patient was discharged from hospital after 2 days. Two weeks later the patient presented with dyspnea. Echocardiography revealed severe mitral regurgitation (MR) requiring mitral valve replacement. Intraoperatively a complete rupture of all primary chordae tendinae of the anterior mitral leaflet was found. The patient was discharged from hospital on the 20th postoperative day.

Conclusion: This is another case report from previously three similar reports showing that LV biopsy may lead to a severe complication like MR. In HTx recipients we recommend a RV biopsy as the gold standard for post transplant rejection screening and as a secondary invasive procedure if a left heart catherization is performed instead of including a biopsy in a left heart procedure.

0114 ESTIMATION OF MPA-AUC IN PATIENTS WITH TACROLIMUS TWICE DAILY AND AFTER CONVERSION TO ONCE DAILY ADMINISTRATION IN STABLE PATIENTS AFTER KIDNEY TRANSPLANTATION

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Introduction: Aim of the study was the estimation of mycophenolate mofetile (MMF) AUC before and after conversion to once daily tacrolimus. Safety and tolerability was also studied.

Methods: Single center study in patients after kidney transplantation with stable kidney function and immunosuppression the last 3 month before conversion. At time of conversion immunosuppressive doses and -levels and creatinine were estimated. MMF AUC was measured using the FDDC algorithm. 7–14 days after conversion the tacrolimus trough level was measured. Between 4–6 weeks after conversion trough level and MMF AUC was again measured. After 3 month tacrolimus dose- and level, MMF dose and creatinine were again estimated.

Results: Twenty-four patients were converted to once daily intake of tacrolimus. Mean age was 51 years; time after transplantation was 42 month. The mean tacrolimus dose was 4.8 mg/day, the trough level was 6.4 μg/l. The mean MMF dose was 1260 mg/day, the MMF AUC was 42 mg*h/l. The creatinine was 1.7 mg/dl. Sixteen patients tolerated the conversion without any complaints. Three patients reported loose bowels but stayed on the new medication.

Five patients were re-converted to twice daily intake of tacrolimus.

1 One patient described a loss of vision

2 One patient developed nausea and excessive perspiration

3 One patient reported high blood presure after first intake and discontinued the new medication at his own decision

4 One patient developed non specific gastrointestinal symptoms

5 One patient suffered from headache and dizziness

The tacrolimus dose (4.8 mg vs. 4.7 mg) and trough level (6.4 μg/l vs. 6.0 μg/l) were stable after conversion. No dose increase was necessary. Also the MMF AUC was stable (41.8 mg*h/l vs. 41.4 mg*h/l). Creatinine was stable. No rejection occured.

Conclusion: Conversion to once daily intake of tacrolimus is safe. The MMF AUC was stable.

0116 PHARMACODYNAMIC MONITORING OF MTOR-INHIBITOR BASED IMMUNOSUPPRESSION IN A CELL CULTURE MODEL: *ESTABLISHMENT OF A NOVEL ELISA TECHNIQUE FOR QUANTITATIVE ASSESSMENT OF PHOSPHO-P70 S6K*

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Background: Rapamycin is a critical dose drug with a low therapeutic index. Current pharmacokinetic monitoring may not correlate with the pharmacological effects of rapamycin on immune cells. Semiquantitative Western blot analysis has been used to investigate the immunosuppressive properties of rapamycin by assessing phosphorylation status at the Thr 389 site of the p70 S6 kinase (phospho-p70 S6K) a downstream effector of mTOR. A pharmacodynamic approach by quantitative assessment of phospho-p70 S6K via ELISA-technique might provide a novel and clinically feasible way to directly analyze the effects of rapamycin.

Methods: Phosphorylation status of p70 S6K was analysed in a cell culture model (Jurkat cells and PBMCs from buffy coats) before and after stimulation with the phorbol-ester PMA. Phospho-p70 S6K expression was measured by (i) semiquantitative Western blot analysis, recognizing both isoforms of S6 kinase1 (p70 S6K and p85 S6K) and (ii) a newly established ELISA based assay.

Results: Average levels of phospho-p70 S6K were increased after PMA-stimulation in Jurkat cells (unstimulated 4.18 vs. stimulated 7.65 U/100 μg protein) and in PBMCs (3.09 vs. 12.39 U/100 μg protein). We found an obviously dose-dependent down-regulation of phospho-p70 S6K induced by rapamycin in PMA-stimulated PBMCs ($n = 20$, $P < 0.05$), which was not statistically significant in unstimulated PBMCs.

Conclusions: Here we successfully established a novel ELISA-based method, which allowed reproducible quantitative measurement of phospho-

p70 S6K in an *in vitro* model. Large scale studies have now to demonstrate, that this ELISA assay is capable to optimize immunosuppressive therapy.

0119 SUSTAINED INHIBITION OF EPSILON PROTEIN KINASE C INHIBITS VASCULAR RESTENOSIS AFTER BALLOON INJURY AND STENTING

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Background: ϵPKC is involved in vascular smooth muscle cell (VSMC) activation, but little is known about its function in vascular pathology. We aimed at assessing the role of ϵPKC in the development of restenosis.
Methods and results: Rat models of aortic balloon injury with or without subsequent stenting were used. Rats were treated with the selective ϵPKC activator yeRACK, the selective ϵPKC inhibitor eV1-2, or saline. Both down-stream cascades of the PDGF receptor via ERK and Akt, respectively, were evaluated in vivo and in VSMC cultures.

Intimal hyperplasia with luminal obliteration developed in saline-treated balloon-injured rat aortas (20.3 ± 8.0%), and yeRACK significantly promoted neointima development (32.4 ± 4.9%, $P = 0.033$), whereas eV1-2 significantly inhibited luminal narrowing (9.2 ± 4.3%, $P = 0.039$). ϵPKC inhibition led to significantly reduced VSMC ERK phosphorylation *in vivo*, whereas Akt phosphorylation was not markedly affected. Neointimal proliferation *in vivo* and PDGF-induced VSMC proliferation/ migration *in vitro* were significantly inhibited by eV1-2. The inhibition of the PDGF pathway was mediated by inhibiting down-stream ERK and Akt phosphorylation. *In vitro*, eV1-2 showed inhibitory properties on EC proliferation, but that did not prevent reendothelialization *in vivo*. eV1-2 showed proapoptotic effects on VSMC *in vitro*. After stent implantation, luminal restenosis (quantified by optical coherence tomography imaging) was significantly reduced with eV1-2 (8.0 ± 2.0%) compared to saline (20.2 ± 9.8%, $P = 0.028$).
Conclusions: ϵPKC seems to be centrally involved in the development of neointimal hyperplasia. We suggest that ϵPKC inhibition may be mediated via inhibition of ERK and Akt activation. ϵPKC modulation may become a new therapeutic target against vascular restenosis.

0120 CONVERSION FROM A CALCINEURIN INHIBITOR TO EVEROLIMUS AFTER SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION (SPK)

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Background: The group of m-TOR inhibitors offers a immunosuppressive opportunity to avoid CNI toxicity and reduce the incidence of malignancy. Little is known about results after conversion to everolimus (EVL) in SPK recipients.
Methods: We describe our experience with nine patients after SPK converted to everolimus therapy. Patient- and graft survival, creatinine clearance and proteinuria as well as adverse events were analyzed after a mean follow up of 14 ± 4 months.
Results: Nine SPK recipients were switched from CsA ($n = 3$) or TAC ($n = 6$) to EVL at 52.2 ± 48.9 months after transplantation. Reasons for conversion were CNI toxicity ($n = 3$), CAN ($n = 3$), malignancy ($n = 2$) and CNI induced pain syndrome ($n = 1$). Targeted EVL trough levels were 8–10 ng/ml. Mean EVL trough level was 8.0 ng/ml and mean dosage was 1.75 mg BID after 12 months. Patients survival was 100%. EVL therapy was stopped in three cases (severe proteinuria ($n = 2$), gangrene ($n = 1$)). Seven out of nine patients showed improved kidney function after 12 months (GFR 37.1 ± 20.2 ml/min (0 months); GFR 45.2 ± 22.4 (12 months) $P = 0.46$. 2 patients lost their kidney graft function 3 and 8 months after conversion. Pancreas graft function was stable in all patients (HbA1c 5.3%, fasting glucose 86.5 (0 months); HbA1c 4.9%, fasting glucose 86.1 (12 months).
Conclusion: In our experience, conversion to EVL after SPK is feasible in the majority of cases. Pancreas graft function was stable in all patients. 77% of the cases were associated with an improvement in renal function.

0121 WILLINGNESS TO DONATE ORGANS AMONG MEDICAL STUDENTS PRIOR TO AND AFTER A LECTURE ABOUT ORGAN DONATION

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Introduction: By increasing the willingness to donate organs the persisting shortage of organs for transplantation could be minimized. An appropriate education of medical students early on could face the increasing shortage of organs and a positive attitude of medical students toward organ donation may have a positive impact on the attitudes of the general public.
Methods: During the summer semester 2009 and 2010 we conducted a voluntary survey concerning organ donation among medical students in the course of the main surgery lecture.
Results: The survey comprised 131 questionnaires. Eight per cent of the medical students received first information regarding organ donation during the lecture. At the beginning of the lecture there were 64 % of organ donor card carriers among the students. Additional 12 % imagined they might carry an organ donor card in the future. Thirty-two per cent of the students needed more information regarding organ donation. After the lecture only 12 % were still not willing to carry an organ donor card in the future. Eighteen per cent of the students needed further information. The attitude towards organ donation was influenced positively by the lecture in 37 % of the students, in 58 % there was no influence and 2 % were influenced negatively by the lecture.
Conclusion: Among medical students there are already a high number of carriers of an organ donor card compared to the general public. The majority (63 %) believes they are sufficiently informed and they are not influenced in their opinion through the lecture (58%). Well-directed interventions are needed to sensitize young adults to the topic of organ donation.

0124 IMPLANTATION OF BIOENGINEERED AV CONDUITS FOR TREATMENT OF COMPLETE AV BLOCK IN A LARGE ANIMAL MODEL

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Purpose: Atrio-ventricular block (AVB) is a significant problem for affected children. Treatment of choice is implantation of a pacemaker to ensure sufficient heart rate. The long-term performance of these devices in pediatric patients is often problematic. Problems can occur because pacemakers are unable to adjust to growth and repeated surgeries for battery replacement are necessary. Hence, a conductive biological alternative that is fully autologously derived would overcome these concerns and would greatly improve quality of life.
Methods: AV-conduits, containing autologously derived myoblast/ vascular smooth muscle cells (VSMC), were implanted in lambs 2 weeks after establishing complete AVB by interrupting His-bundle conduction using radio-frequency ablation at the base of the non-coronary cusp of the aortic valve. To ensure sufficient cardiac output due to extremely low ventricular escape rhythm (30 BPM) implantation of dual-chamber pacemaker devices with fixed leads was performed at the time of ablation. Respective electrophysiology studies were performed at 8 and 16 weeks after implantation to evaluate alternative AV conduction.
Results: AVB and pacemaker-dependency was successfully established in four immature lambs. Three animals received AV conduits containing either myoblasts or myoblast/ VSMC, 1 animal served as a control (dead cells). No alternative conduction was observed in control animal, whereas 1 out of 3 animals presented with alternative antegrade conduction indicated by surface ECG during intra-cardiac pacing.
Conclusion: This large animal study demonstrates an alternative treatment to conventional pacemaker implantation to treat complete AV block. Fabricated AV conduits containing autologous cells are capable to bridge AV groove and allow conductance.

0126 INFLUENCE OF MYCOFENOLATMOFETIL ON QUALITY OF LIFE DUE TO GASTROINTESTINAL SIDE EFFECTS FOLLOWING LIVER TRANSPLANTATION

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Purpose: Liver transplantation (LTx) is a well-established procedure for end stage liver diseases. Since long term survival rates are satisfactory, nowadays quality of life (QOL) gains increasing interest. Once postoperative surgical course was successful, QOL during maintenance therapy may depend on individualized immunosuppressive drug selection (IDS). We investigated QOL employing the EYPASCH questionnaire in de novo patients as well as under maintenance therapy with different combinations of immunosuppressive agents.
Method: We analyzed postoperative courses of $n = 420$ liver transplant recipients. Besides gastro-intestinal symptoms potentionally related to mycophenolat mofetil (MMF) treatment or IDS, general QOL was assessed using EYPASCH's QOL query form (group 1: day 1–180; 2: day 180–540; 3: >540 days post LTx).
Results: Gastrointestinal symptoms: 1. Cyclosporin (CSA) shows significantly better results ($P = 0.001$) compared to Prograf. 2. MMF combined with calcineurin inhibitors (CNI) significantly ($P = 0.032$) decreases QOL in group 3 but increases QOL in group 1. General QOL: (i) CSA shows significantly ($P = 0.002$) better QOL compared to Prograf. (ii) MMF increases QOL in group 1 and decreases QOL in group 3. (iii) CSA+ MMF significantly ($P = 0.002$) shows a better QOL than Tacrolimus (±MMF).
Conclusion: 1 CSA-based IDS significantly improved QOL in de novo patients as well as under maintenance therapy.

2 Gastrointestinal symptoms are related to MMF with significant decrease of QOL under maintenance therapy but increase in de novo immunosuppression.
3 MMF causes short-term inprovements but long-term decreases.
4 CSA+ MMF shows a higher QOL than Tacrolimus ±MMF.

0131 INTESTINAL REGENERATION AND RESIDUAL FUNCTION FOLLOWING RESCUE THERAPY FOR ACUTE CELLULAR REJECTION (ACR) AFTER RAT SMALL BOWEL TRANSPLANTATION

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Background: The small intestine is highly immunogenic and there is rising evidence that recurrent ACR episodes may trigger chronic rejection, having influence on the long term outcome. Therefore, the interest of this study is to investigate the process of recovery after rejection and to evaluate residual intestinal function and immunological priming after ACR.
Methods: Orthotopic allogeneic intestinal transplantation was performed in rats. Immunosuppression with Tacrolimus 2 mg/kg/day was started on POD1 (continuous immunosuppression group 1) or POD7 after manifestation of acute rejection. Animals were sacrificed on POD7; (group 2 – acute rejection, no treatment), POD14 (group 3, immunosuppression) and POD21 (group 4, immunosuppression) during the recovery process.
Results: Compared to group 2, group 4 revealed, not entirely, but steady improvement of severity on histological grading, accompanied by less leukocyte infiltration in the muscle layer (MPO-positive neutrophils, 73%; ED1-positive macrophages, 69%). mRNA expression in the muscle layer revealed a remarkable decrease in inflammatory cytokines (IL-6, TNFa) and macrophage activation (iNOs, MCP-1), while neural cell markers (S100b) and growth factors (VEGF) showed recovery. Contractility of muscle layer improved from 90% to 50% reduction, compared to an allogeneic group without rejection signs due to continuous immunosuppression from POD1 (group 1).
Conclusions: We established an experimental model to analyze the recovery and regeneration process after acute rejection. Recovery from acute rejection goes steady but slowly after starting immunosuppressive therapy. Time for complete physiological recovery of the muscle layer appears to take more than twice as long as compared to its biochemical and molecular recovery.

0132 SEVERE STENOSIS AND RIGHT VENTRICLE FISTULA OF THE LAD FOLLOWING RE-THORACOTOMY FOR HAEMOTHORAX AFTER HEART TRANSPLANTATION

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Introduction: We report the case of a 64-year-old male heart transplant (HTx) recipient who required a re-thoracotomy several hours after the operation due to a haemothorax. A bleeding of the left ventricle was found and sutured. The further clinical course was uneventful and the patient was discharged in stable condition from our institution 3 weeks after transplantation. After 3 months a routine echocardiography showed significant hypokinesia of the cardiac apex and a thrombus in the left ventricle. Coronary arteriography and thorax CT-scan showed severe stenosis of the sixth left anterior descending coronary artery (LAD) branch and a more distal located LAD fistula draining into the right ventricle.
Methods: Percutaneous coronary intervention (PCI) was performed using three stent-grafts. Two covered stents were placed into the LAD to close the fistula and one drug-eluting stent was placed into the stenotic LAD segment to revascularise the cardiac apex. Phenprocoumon was subsequently added to the medical regimen for lysis of the apical thrombus and prevention of further thrombotic events.
Results: Cardiac pump function significantly improved close to normal in the first weeks of follow-up. Since then no complications occurred and the patient has been successfully followed during the past 5 months.
Conclusions: Post-operative haemothorax after HTx often requires re-thoracotomy to evacuate the haematoma and localise the bleeding site. However, careful surgical manipulation on the new heart transplant is recommended to avoid complications such as severe coronary artery stenosis or even a coronary to ventricular fistula, which could both be treated by endovascular stent implantation.

0134 ANEMIA AND EPOETIN THERAPY IN RECIPIENTS OF RENAL TRANSPLANTS: A SINGLE CENTER SURVEY

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Introduction: The prevalence of post-transplant anemia (PTA) in the population of kidney allograft recipients amounts to 20–40%, and is precipitated by pre-existing comorbidities, pharmacological therapy (immunosuppressive, anti-hypertensive, anti-infective, etc.) and the declining excretory/endocrine renal function. In this retrospective survey, the clinical course of 229 kidney transplant recipients suffering from PTA, requiring prolonged epoetin (EPO)-treatment, is analyzed in depth.
Methods: Identifying 229 renal allograft recipients from the data base of the Kidney Transplant Outpatient Clinic at the Johann-Wolfgang-Goethe University Hospital in Frankfurt, who had been treated for anemia with EPO for at least 6 months in the time frame from 1998 to 2010. Demographic, peri-transplant, donor-related, and data on the clinical history up to one year post-transplant are being collected. Detailed information on immunosuppressive therapy, concomitant medication, rejection episodes, hematological parameters, cardiovascular events and GFR are collected from one year pre-EPO-treatment with a follow-up period of 24 months post-EPO-initiation.
Results: Currently, 200 patients have been analyzed; 114 were male, with a mean age of 47.6 ± 15.3 years at time of dialysis and 5.2 ± 4.5 years on dialysis. Reasons for kidney failure included glomerulonephritis (41.8%), idiopathic nephrosclerosis (26.9%), polycystic kidney disease (9.5%) and diabetic nephropathy (6.9%). Cold ischemia time was 799.8 ± 478.7 minutes, warm ischemia time was 45.2 ± 25.8 minutes Serum creatinine was 1.8 ± 0.77 mg/dl at discharge (donor: 0.99 ± 0.48 mg/dl). 19.5% of recipients experienced delayed graft function, following implantation. At the meeting, complete data on all 229 recipients undergoing at least 6 months of EPO-therapy will be presented. Special focus is directed toward the natural course of anemia in this population and the impact of EPO-treatment on hemoglobin levels and renal function.
Conclusion: The pathophysiological implication of PTA remains poorly understood, with conflicting data on the association of anemia with cardiovascular events and long term outcome. We will present extensive data on 229 recipients undergoing maintenance EPO therapy with focus on clinical course and renal function. These data will help clarify the role of EPO in the context of declining endocrine kidney allograft function and may form the rationale for a future prospective, randomized trial.

0135 IS ECMO SUPPORT USEFUL FOR GRAFT FAILURE AFTER HEART TRANSPLANTATION?

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Introduction: Graft failure after heart transplantation (HTX) is a dreaded complication. Extracorporeal membrane oxygenation (ECMO) is a therapeutic option for the transplanted heart to recover function or to treat underlying pathology. We reviewed our ECMO experience and outcome in HTX patients.
Methods: Retrospectively, we analyzed all HTX patients ($n = 221$) between 1997 and 2009 in our department and assessed the incidence of post-HTXTXHH ECMO-implantation, mortality rates (30 days, 1 year) as well as perioperative complications.
Results: ECMO was implanted in 26 patients (11.8%) with a mean-duration of ECMO-support of 4 days (four hours to 21 days). Cumulative mortality rates were 53.8% ($n = 14$) within 30 days and 76.9% in 1 year ($n = 20$). The six patients who survived the first year are still alive (maximum follow-up 9 years) except 1 patient who died after 3 years due to rejection. Causes of death were multiorgan failure ($n = 9$), sepsis ($n = 8$), lung failure ($n = 2$) and cerebral bleeding ($n = 2$). ECMO was implanted due to primary graft failure (PGF, $n = 12$), sepsis ($n = 5$), resuscitation ($n = 5$), rejection ($n = 2$) or right heart failure ($n = 2$). PGF-patients showed the highest recovery potential with a survival rate of 66.7% ($n = 9$) in the initial phase after ECMO-explantation. All patients who were transplanted due to an infected assist device ($n = 5$) and received an ECMO-implantation died within 10 days.
Conclusion: ECMO support for postoperative output failure offers a poor but acceptable perspective to patients with graft failure after HTX. The small fraction of patients surviving, appear to have a decent longterm prognosis.

0137 ADENOVIRAL TRANSFER IN THE LIVER: A NOVEL IN VIVO SIMULATION MODEL IN THE RAT

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Objective/Aim: Established *in vivo* models for adenoviral transfer are limited due to a restricted time period for application of pharmaceutical substances, problems in selective targeting of organs, and artificial lesions of the targeted organ because of the method itself. Therefore, we developed a liver circulation model to avoid these difficulties.
Material and methods: Male Lewis-(RT^1)-rats ($n = 8$) with a body weight of 120 g received median laparotomy under isoflurane anaesthesia. After exposition of the celiac trunk and the inferior vena cava the right renal vein was punctured. Next the abdominal aorta, the splenic artery, the left gastric artery, and the gastroduodenal artery were simultaneously clamped and intravenous infusion of methylene blue into the right renal vein was started.
Results: Due to the selective application of the agent into the liver we could demonstrate an obvious discoloration of the liver in this setting, whereas all other abdominal organs were not affected. Photometric extinction of cell suspensions of liver biopsies revealed a maximum concentration of methylene blue 30 minutes after injection (0.890–2.300 mM). As expected, no extinction was found in cell suspensions of other organs.
Conclusion: Our experimental setting represents a reproducible, reversible, and easily practicable model for selective *in vivo* application of pharmaceutical substances into the liver. Therefore, this approach enables the *in vivo* adenoviral transfer of cytoprotective agents or chemotherapeutic drugs selectively into the liver.

0139 EFFICACY AND SAFETY OF SUBCUTANEOUS HUMAN HBV - IMMUNOGLOBULIN (ZUTECTRA®) IN LIVER TRANSPLANTATION: AN OPEN, PROSPECTIVE, SINGLE-ARM PHASE III STUDY

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Background: Hepatitis B re-infection prophylaxis is crucial for long-term graft and recipient survival for transplanted patients and is administered routinely after liver transplantation for hepatitis B.
Objectives: Investigation of efficacy, safety, and feasibility of home-treatment of a novel human hepatitis B immunoglobulin BT088 (Zutectra®) after weekly subcutaneous application in liver transplanted patients.
Methods: Twenty-three patients (5 female, 18 male, median age 51 years) were enrolled and switched from monthly i.v. to weekly subcutaneous (sc) hepatitis B immunoglobulin administration. During a study period of 18 weeks (optional 24 weeks) anti-HBs levels, signs of re-infection, adverse events and feasibility of self-administration were studied. After 8 weeks of training on self-administration patients showing good compliance and stable antibody titres were allowed to start self-administration at home. The planned treatment period was 18 weeks; therapy was to continue for a further 6 weeks.
Results: All patients maintained a safety level of >100 U/l HBs-antibody concentrations as requested. Furthermore, mean linear serum anti-HBs levels of 350−400 IU/l were achieved at all times. No failure was noted and no re-infection occurred. A total of 135 treatment-emergent adverse events were observed. 10 events were assessed as related to study drug application (4 × injection site hematoma*, 3 × headache, 1 × abdominal pain, 1 × fatigue, 1 × hematuria). High numbers of self-administration (287 vs. 122 by staff) demonstrated general feasibility of sc administration.
Conclusion: Weekly subcutaneous administration of BT088 (Zutectra®) is effective, safe and presents an easy-to-apply treatment option for combined HBV re-infection prophylaxis in liver transplant patients.

0141 RENAL FUNCTION AND SAFETY POST-CONVERSION FROM TWICE-DAILY TO ONCE-DAILY TACROLIMUS: A MULTICENTER, CROSSOVER TRIAL IN LIVER TRANSPLANT RECIPIENTS

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Purpose: Tacrolimus once-daily (TAC-QD), a prolonged-release formulation, may facilitate improved adherence and survival compared with the established twice-daily formulation (TAC-BID). This study assessed renal function of stable adult liver transplant patients converted from TAC-BID to TAC-QD.
Methods: Liver transplant patients participating in this multicenter crossover trial completed a 6-week TAC-BID run-in-phase before converted to TAC-QD on a 1:1 mg:mg basis, remaining on TAC-QD for 12 weeks with minimal dose changes (adjusted if trough level-deviation >20% or if indicated). Primary endpoint: Change in creatinine-clearance (Cockcroft-Gault) between TAC-BID (Week-6 to Day-1) and TAC-QD (Week 6−12) at steady state. Approval was obtained from the local ethics committees and the EMEA (EudraCT-Nr: 2006-000936-28).
Results: Eighty patients (m/f: 58/22; age: 52.5 ± 10.3 years) were included in the Per-Protocol-Set. For both treatment phases, tacrolimus mean daily dose was 0.05 mg/kg. Mean tacrolimus trough levels were maintained within 6.2−7.7 ng/ml throughout the study. Eighty-six percent patients did not require a dose change and 51% received TAC-QD monotherapy. Mean creatinine-clearance was 85.7 and 85.5 ml/min for TAC-BID and QD, meeting the primary endpoint for non-inferiority (95%CI within 10%). Patient- and graft-survival were 100% and there were no acute rejection episodes. There were low rates of serious AEs/discontinuations due to AEs: TAC-BID (2.7% or 1.8%); 12-week TAC-QD (6.1% or 0%). Blood pressure improved significantly from Day-1 to Week 12: mean difference 2.0 mmHg ($P = 0.0084$). There were no significant changes in HbA1c, total bilirubin, and transaminases.
Conclusions: 1:1-conversion of stable liver recipients from TAC-BID to a simplified TAC-QD regimen is feasible and safe. Patients maintained stable renal function with improved blood pressure and without rejection.

0142 LIPIDOMIC PROFILING OF ISOLATED PANCREATIC ISLETS PREDICTS SURVIVAL *IN VITRO* AND *IN VIVO*

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Aim: Several lipid classes are known to be critically involved in apoptosis, inflammation and stress response, major pathogenic factors for pancreatic islets during organ procurement, storage, and isolation procedure. Besides optimized protocols in islet isolation and transplantation, the field is still lacking valid biomarkers that characterize the quality and predict the effectiveness of islets transplanted into type 1 diabetic patient's.

Here, we aimed at evaluating the sensitivity and predictive potential of lipidomics for rat and human islets, and correlate the *in vitro* results with islet function *in vivo*.
Methods: Rat and human islets were isolated according to standard protocols. Islets were cultured in CMRL with 10% FBS ± rotenone, a mitochondrial respiratory chain complex I inhibitor, or the proinflammatory cytokines TNF-α, IL-1β, and IFN-γ. Islets were washed with 150 mM ammonium acetate, and lipids were extracted with methyl-tert-butyl ether. Total lipid extracts were analyzed by direct infusion into LTQ Orbitrap XL mass spectrometer, and subsequently lipid species were identified and quantified by Lipid X software. Principal component analysis was performed using MarkerView software. Viability and function of isolated islets were tested *in vitro* using fluorescence microscopy and static incubation assay and *in vivo* by transplantation under the kidney capsule of diabetic NOD SCID mice.
Results: The shotgun lipidomics analysis showed that stress response of isolated rat and human islets is accompanied by increased levels of ceramides, decreased levels of diacylglycerols, and concurrently by the increased abundance of phosphatidylserin. The consistent alterations of the lipidomic profile significantly correlated with, and positively predicted, islet viability and function *in vitro* and *in vivo*.
Conclusion: We conclude that alterations of the lipidomic profile reflect various stress response pathways in a single multi-parametrical readout, thus representing a novel quality control assay with predictive value for pancreatic islets prior to transplantation.

0148 ASSESSMENT OF ENDOTHELIAL FUNCTION AND HEART FAILURE PARAMETERS IN HEART TRANSPLANT AND NON-TRANSPLANT PATIENTS

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Background: Flow-mediated vasodilatation (FMD), an indicator of endothelial function, is directly related to long-term survival. Terminal heart failure is characterized by very poor prognosis and depressed FMD. For these patients, heart transplantation is associated with improved life expectancy and quality of life. On the other hand, immunosuppression with calcineurin-inhibitors, i.e. cyclosporine or tacrolimus, as well as transplant vasculopathy (TVP) are known to induce endothelial dysfunction.

We aimed to examine endothelial function in a cohort of post-heart-transplant patients and patients with ischemic (ICM) or dilated (DCM) cardiomyopathy being candidates for transplantation.
Method: In an observational study, 73 patients, who are being followed in our institutional out-patient heart failure clinic, were examined using high-resolution ultrasound of the brachial artery for measurement of FMD and NMD (nitroglycerin-mediated vasodilatation) as well as classical clinical parameters.
Results: See table. Data expressed as mean value ±SD
Conclusion: Endothelial function assessed by FMD is ameliorated in patients after heart transplantation and normal left ventricular ejection fraction (LVEF) as compared to heart failure patients with optimal medical therapy. Although, clinical parameters like NYHA class, maximal oxygen uptake (VO_2max) and B-type natriuretic peptide (BNP) were not different between groups. In spite of still elevated BNP levels, low physical fitness, immunosuppressive therapy and risk of TVP, heart transplant patients show signs of preserved endothelial function.

0149 EARLY POSTTRANSPLANT HEPATIC VENOUS OUTFLOW OBSTRUCTION IN CHILDREN FOLLOWING SPLIT- OR LIVING RELATED LIVER GRAFTS: SUCCESSFUL APPLICATION OF PERCUTANEOUS BALLOON DILATATION

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Background: The development of new techniques such as living-donor and split-liver transplantation has increased the number of suitable grafts for small pediatric patients and consequently reduced the mortality rates and time spent on transplant waiting lists. Despite the progress achieved in overall outcome for these patients, there has been a relative increase in vascular complications following anastomoses of small vascular structures. Only limited data for the pediatric population is available indicating an incidence of hepatic venous outflow obstruction around 2% (Glanemann et al. 2000, Carnevale et al. 2008). The best approach to treatment of this complication is still debated.
Aim: Evaluation of safety and efficacy of balloon dilatation in 4 paediatric cases of venous outflow obstruction following split- or living-related liver transplantation.
Patients, material and methods: Retrospective analysis by chart review of 42 pediatric cases transplanted between 2005 and 05/2010. Venous outflow obstruction (VOO) is defined as stenosis of either the hepatic veins or the inferior vena cava (IVC).
Results: Forty-two pediatric liver transplantations were performed in 42 children, 17 by living-related donation (LRLT), 15 by post-mortem split-liver transplantation (SLT) and 10 whole-liver transplantations (WLT). Patient- and

graft survival are 100%. Postoperative thrombosis of portal vein or hepatic artery did not occur. In four cases VOO was diagnosed. The venous reconstruction in the four cases was performed as follows: three left lateral LRLT modified piggy-back anastomosis (i.e. E/S veno-caval anastomosis with triangular wide orifice at IVC) and in one extended right SLT with complete IVC replacement. Three to 40 days after LT the four patients developed increasing amounts of ascites (up to 500 ml/ kg body weight) in 3 cases or pleural effusion with tachypnoea in 1 case. Function of transplant parenchyma was normal in all cases. Primary investigations were performed by doppler ultrasound which demonstrated increase of flow velocity and/ or VOO stenosis and patency of portal vein and hepatic artery. Confirmatory studies were performed by angiography and showed stenoses of the hepatic vein anastomoses or of the IVC in 2 cases each. Interventions were performed 3–40 days after LT by percutaneous balloon angioplasty without stent-positioning in all 4 cases. A pressure gradient of 4–9 mm Hg was detectable in 3 cases. No complications related to the intervention occurred. Following the intervention, ascites and pleural effusion regressed completely in all 4 cases. Minor asymptomatic pleural effusion recurred 2.5 months after intervention in one case.

Conclusions: Pediatric patients symptomatic with significant postoperative ascites production and/or pleural effusion following LT should be evaluated for VOO. Balloon dilatation of VOO stenoses without stent placement early after LT is a safe and effective approach to treatment.

0150 MHC-BOUND PEPTIDES AS DETERMINANTS OF NATURAL HLA ANTIBODY SPECIFICITY

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HLA antibodies are thought to result exclusively from alloimmunizing events: transplantation, transfusion, and pregnancy. A recent publication by Morales et al. demonstrated that using Luminex bead-based assays, HLA antibodies can be detected in 63% of healthy, nonalloimmunized blood donors. These natural HLA antibodies are directed against infrequent HLA specificities and are hypothesized to be produced to cross-reactive epitopes derived from microorganisms, ingested proteins and allergens. A plausible specific epitope of these natural antibodies on the surface of HLA molecules cannot be determined in all instances. Moreover, the role of MHC-bound peptides in the recognition of HLA class I molecules by natural HLA antibodies has not been considered yet. We therefore analyzed case studies of frequently found natural antibodies directed against HLA-B*37:01 in respect of the involvement of MHC-bound peptides in determination of antibody specificity. We enrolled 13 patients all with a history of HLA-B*37:01-specific antibodies detected by Luminex. The cohort included 7 kidney and 2 lung transplant recipients as well as four patients with end-stage renal disease waiting for a transplant. Since the nine transplanted patients were immunized by alloantigens but the detected HLA-B*37:01 antibody was not related to the transplant and in 2 cases was even present before the transplantation we considered those antibodies as natural antibodies (expanded criterion). Collected sera were tested by flow cytometric crossmatch (FCXM) with HLA-B37-expressing vital T-lymphocytes. Luminex beads were treated with mild acid (MA) solution to elute the peptide from HLA antigens. MA treated beads were subsequently retested with patient sera containing natural antibodies. The reaction pattern of each serum was compared between regular and MA treated beads and an epitope mapping based on polymorphic single amino residues was carried out to predict the targeted epitope. FCXM was negative for all but one patient. The FCXM positive patient was alloimmunized by a kidney transplant more than 10 years prior to testing. The patient's serum revealed reactivity against intact HLA-B37 expressed on vital cells (true B37 antibody). Following MA treatment in 7 cases an increase in the reactivity of the antibodies against B37 was observed. MA treatment uncovered a buried, crypitic HLA-B*37:01-specific epitope. On the other hand in 6 cases the reaction was abolished after treating beads with MA solution indicating the direct involvement of the peptide in determination of antibody specificity. The MHC-bound peptide can act in two ways to impact the binding of natural antibodies. At first it can bury the antibody reactive site making the epitope inaccessible. However, due to the manufacturing process of Luminex beads and accompanied denaturation of antigens antibodies directed against these cryptic, buried epitopes can be found. The clinical relevance of these antibodies is equivocal. Secondly, the peptide itself exhibits the epitope a natural antibody is directed against. Thus, natural HLA antibodies in transplant patients may represent tissue-specific antibodies bearing clinical relevance.

0151 POLYMORPHISMS OF MANNOSE-BINDING LECTIN-2-GENE ARE ASSOCIATED TO HCV-INDUCED HEPATOCELLULAR CARCINOMA

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Background: Cancerogenesis is suspected to be partially determined by individual genetic background. Mannose-binding lectin-2 (MBL-2) is an important immunomodullatory factor, which had been proposed to be involved in complement activation and oncogenesis. Genetic polymorphisms of MBL-2 alter the protein functionality. Aim of our study was to determine the prevalence of the MBL-2-polymorphism (rs7096206) in HCV-induced hepatocellular carcinoma (HCC) based on histological analysis of explanted livers in patients undergoing liver transplantation and to describe its role in post-transplant-graft disease.

Methods: One hundred and sixty-four patients, who underwent liver transplantation for HCV-induced liver disease, were genotyped for MBL-2 by TaqMan Genotyping Assay. Sixty-two patients with histologically confirmed HCC were compared to 102 patients without HCC under the influence of same ethiologic agent. Furthermore, 594 post-transplant protocol liver biopsies were evaluated regarding graft fibrosis progression and median inflammation based on Desmet and Scheuer classification. Fibrosis stages, grades of inflammation, incidence of acute cellular rejection and antiviral treatment response were correlated to MBL-2-genotypes.

Results: No association of MBL-2-polymorphisms was observed regarding the incidence of acute cellular rejection ($P = 0.332$), antiviral treatment response ($P = 0.310$) and fibrosis progression ($P = 0.566$). Interestingly the prevalence of GG and GC- genotypes was significantly higher among patients with HCC compared to tumor-free explanted livers ($P = 0.002$; or 2.9; 1.5–5.6).

Conclusion: MBL-2-polymorphisms seem to be involved in the development of HCV-induced HCC. Surprisingly, they do not influence the course of post-transplant graft disease considering acute cellular rejection and fibrosis progression.

0153 RESECTION OF A RIGHT ATRIAL MASS IN A CARDIAC TRANSPLANT RECIPIENT USING A MINIMALLY-INVASIVE SURGICAL APPROACH

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Introduction: Intra-cardiac thrombus formation usually occurs in the left-sided cavities of the heart. We report the case of an initially unclear mass in the right atrium (RA) of a heart transplant recipient which was subsequently resected via a minimally-invasive surgical approach.

Case report: A 21-year-old male patient with hypertrophic non-obstructive cardiomyopathy underwent orthotopic heart transplantation. Routine follow-up documented adequate graft function. 19 months after transplantation, TTE revealed a round-shaped, pedunculated mass in the RA. This finding was confirmed by MRI (Fig.1). Differential diagnoses included atrial myxoma, thrombus and malignant tumor formation. As a first treatment, anticoagulation therapy with oral cumarins was initiated.

As neither regression nor growth of the atrial mass was observed during the following 6 months, decision was made for surgical extirpation with atrial myxoma being the most likely diagnosis. Surgical access was gained via a right antero-lateral minithoracotomy; cardiopulmonary bypass was established by cannulation of right-sided femoral vessels. A 5 mm endoscope was introduced. After intitiation of ventricular fibrillation, the RA was opened and the tumor excised. Atrial defect and atriotomy were closed, sinus rhythm restored and cardiopulmonary bypass terminated. Wounds were closed in standard fashion.

The patients postoperative course was completely uneventful with timely discharge on day 8 after surgery. Histopathological analysis of the specimen surprisingly yielded the diagnosis of partially calcified thrombus.

Conclusion: In summary, a minimally-invasive approach via right anterior mini-thoracotomy using videoscopic assistance allowed for uncomplicated RA thrombectomy, avoiding re-entry sternotomy with potential risk of cardiac injury. Due to the location of the tumor, aortic cross-clamping and cardioplegic arrest were not necessary. Surgery without definite preoperative diagnosis was justified considering the mobility of the tumor with the impending risk for embolization.

0155 ADAPTIVE AND MALADAPTIVE SIGNALING AFTER MTOR INHIBITION IS MODULATED BY HORMONAL STATUS IN FEMALE CARDIOMYOCYTES

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Introduction and aims: Proportion of renal and cardiac transplant recipients treated with mTOR inhibitors is rapidly increasing. Prevention of maladaptive myocardial hypertrophy post cardiac transplantation or faster regression of uremic myocardial hypertrophy after renal transplantation could broaden therapeutic options. Gonadal steroids are modulators of mTOR activation, yet not extensively studied. We sought to elucidate consequences of mTOR inhibition on hypertrophic signaling pathways in adaptive and maladaptive myocardial hypertrophy and influence of its modulation by ß-estradiol (E2) in the context of female cardiomyocyte.

Methods: Female HL-1 cardiomyocytes were treated with "physiologic" (IGF-1) and "pathologic" (ET-1) stimuli in the presence or absence of E2 or mTOR inhibitor rapamycin. Cell size was determined by immunocytochemistry and FACS-analysis. Signaling was assessed by immunoprecipitation with anti-mTOR polyconal antibodies and westernblotting using phospho-specific antibodies against Akt to monitor TORC2-activity, Erk and p70S6K to monitor TORC1-activity. Genomic changes were monitored by qRT-PCR.

Results: E2, IGF-1 and ET-1 induced phosphorylation of Akt and p70S6K. E2 reversed the increase in p70S6K-phosphorylation upon ET-1-stimulation,

whereas co-treatment of E2 with IGF-1 increased p70S6K-phosphorylation. mTOR-complex formation with raptor and rictor was increased by E2-cotreatment. ANP-mRNA-expression increased significantly with E2-cotreatment and most markedly with additional ET-1-stimulation. Rapamycin inhibited cardiomyocyte hypertrophy and p70S6K-phosphorylation by IGF-1 and ET-1 irrespective of E2-cotreatment, whereas positive feedback loop towards Akt-phosphorylation was differentially regulated by rapamycin dependent on the presence or absence of E2.

Conclusions: Rapamycin effectively inhibits female cardiomyocyte hypertrophy irrespective of the presence or absence of E2. However, E2 differentially modulates TORC1 and TORC2 activities dependent on the nature of the hypertrophic stimulus and rapamycin treatment. This could impact different cellular functions like cardiomyocyte contraction, apoptosis and autophagy. Evaluation of hormonal effects of mTOR inhibition is warranted in solid organ transplantation.

0156 THE IMPACT OF ACUTE KIDNEY INJURY ON MORTALITY AND MORBIDITY IN PATIENTS AFTER LIVER TRANSPLANTATION

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Background: Acute kidney injury (AKI) is now more and more recognized as a major determinant of mortality, especially in high risk patients on the ICU. Therefore, we have studied the impact of AKI on mortality and morbidity in patients after liver transplantation in the early postoperative phase.

Methods: A retrospective study was conducted from the data repository at the University Hospital Essen of patients who underwent liver transplantation. Patients, who developed AKI in the early postoperative phase (during the first ICU stay) were classified having AKI according to the criteria of the AKIN-Group (>0.3 mg/dl increase in serum creatinine in 48 hours) and the RIFLE classification (>0.5 mg/dl increase in serum creatinine in 7 days) or classified as renal replacement therapy (RRT) dependent AKI, if they received RRT in this period. Criteria for RRT dependance were potassium of >5.5 mmol/l or significant volume overload. Mortality (28 days and 1 year), duration of ICU stay and bleeding complications were assessed.

Results: We studied 162 adult patients, who received a liver transplantation during a 4 year period. According to the AKIN criteria 44 patients and according to the RIFLE criteria 42 patients developed AKI in the early postoperative phase without being RRT dependent. 50 of the patients developed RRT dependent AKI. Preoperative serum creatinine was significantly higher in patients developing RRT dependent AKI (Table 1, $P < 0.05$). Mortality was not different in patients developing AKI after liver transplantation, whereas mortality was considerable higher in patients with RRT dependent AKI (Table 1). Duration of ICU stay was significantly higher in patients developing RRT dependent AKI, whereas duration of ICU stay was not different in the other groups (Table 1, $P < 0.05$). Bleeding complications assessed by the use of erythrocytes transfusion (ET) were higher in patients developing RRT dependent AKI compared to patients with non RRT dependent AKI (Table 1, $P < 0.05$).

Conclusion: These data show that non RRT dependent AKI per se has no impact on mortality regardless of the classification used. In contrast RRT dependent AKI has a significant impact on mortality. Patients at risk for RRT dependent AKI have higher preoperative serum creatinine, longer ICU stay and require more ET. Thus preoperative serum creatinine is a strong predictor for RRT dependent AKI and should mandate protective renal therapy strategies.

0160 SURVIVAL OF MHC-DISPARATE SKIN GRAFTS IN RAT IS MODIFIED BY ADDITIONAL DIFFERENCES WITHIN THE NATURAL KILLER GENE COMPLEX (NKC)

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In rat, NKC maps on chromosome 4 and encodes cell surface expressed proteins with C-type lectin-like structure. They represent several gene families of NK-cell receptors in this species. In addition, the physiological ligands of some NKR-P1 receptors are encoded by this complex. Rat strains LEW and LEW.TO-NKC differ in their NKC-haplotypes. Using these strains as allograft recipients and the MHC-disparate strain LEW.1U as donor we have analyzed whether a genetic NKC-difference in multiple NKC-genes affects rejection in a MHC-mismatched setting of skin transplantation.

Results: NKC-disparate skin grafts (LEW -> LEW.TO-NKC) and syngeneic controls (LEW -> LEW) were not rejected. Interestingly, MHC- and NKC-disparate skin grafts (LEW.1U -> LEW.TO-NKC; $n = 10$) survived significantly longer (MST 14.2 ± 1.93 d) than solely MHC-disparate skin grafts (LEW.1U -> LEW; $n = 10$; MST 10.7 ± 1.49 d). Elimination of recipients NK-cells before transplantation ($n = 3$) in the MHC- and NKC-disparate setting using mAb HT30 (raised against NKR-P1A) resulted in skin graft survival of 12 days that was comparable to the combination mismatched only in the MHC.

Conclusion: Our data show the surprising result, that an additional NKC-difference can lead to a prolongation of graft survival of MHC-disparate skin grafts. The beneficial effect of NKC-disparity is partly abrogated by depletion of NK-cells in the recipient. A possible mechanism might be that donor derived antigen presenting cells of the graft are eliminated to some extent by NK-cells thus reducing the immunogenicity of the graft.

0162 DONOR HEARTS FROM PATIENTS WITH ACUTE PULMONARY EMBOLISM – A CONTRAINDICATION FOR HEART TRANSPLANTATION?

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Objective: To increase the cardiac donor pool, the criteria for acceptability has been expanded at many centers. The question transplanting hearts from donors with acute pulmonary embolism is discussed controversially. In the present study we report our experiences accepting donor heart from patients died because of acute pulmonary embolism.

Methods: In a 20-year period we have performed 1780 heart transplantations at our institution. In nine cases donor hearts were accepted from patients died because of hypoxia in acute pulmonary embolism.

The mean age of the nine donors (5 female, 4 male) was 35.2 years. All patients died because of hypoxia in acute pulmonary embolism (8 after resuscitation; 15–60 minutes). Protection of the hearts were performed using HTK solution.

The mean age of nine recipients (2 female, 7 male) was 52.2 years. Underlying desease was dilatative cardiomyopathy in five patients and ischemic cardiomyopathy in four cases. Two patients had VAD support before HTx (Thoratec $n = 2$; LVAD $n = 1$, BVAD $n = 1$).

Results: At least all patients underwent successful transplantation. Ischemia time and all transplantation related data did not differ from our overall data. Seven patients had triple immunosuppression (Cyclosporine, Azathioprine, Cortisone), two patients had double immunosuppression (Cyclosporine, Cortisone). Five patients died after a mean time of 4 years because of acute rejection ($n = 1$), renal insufficiency ($n = 1$), graftvasculopathy ($n = 1$), severe infection ($n = 1$) and neurological deficit ($n = 1$). Four patients are alive after a mean follow-up of 5.7 years after HTx.

Conclusions: In our experiences cardiac allografts from donors died because of acute pulmonary embolism can be transplanted successfully. Acute pulmonary embolism of the donor does not represent a contraindication for HTx. Acute right heart overload in this donor group seems not influence short- and long-term outcome after HTx.

0163 SUCCESSFUL BRIDGING TO HEART TRANSPLANTATION USING THE LEVITRONIX CENTRIMAG SYSTEM AND DURAHEART LVAD IN A PATIENT WITH RESUSCITATION RELATED LIVER INJURY

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Objective: Mortality rates from cardiogenic shock after acute myocardial infarction remain extremely high. Efforts have been made to develop ventricular assist devices capable of providing complete hemodynamic support in this situation. Mechanical circulatory assistance represents an evident problem when bleeding complications occur.

We report a very rare case of successful bridging to heart transplantation despite severe resuscitation related liver injury.

Methods: A 54-year-old male patient underwent failed PCI of LAD with consecutive prolonged resuscitation. A Levitronix Centrimag system was implanted via femoral vessels for rapid hemodynamic stabilization. An acute laparotomy was necessary because of severe injury of the left lobe of the liver. During laparotomy the abdominal cave was tamponated by multiple compresses. Three times re-laparotomy was necessary to achieve final hemostasis. After 4 weeks of Levitronix Centrimag support the system was switched to DuraHeart LVAD for long-term assistance as a bridge-to-transplant.

Result: Successful heart transplantation was performed after complete recovery and mobilization of the patient 320 days after the disastrous and hopeless initial situation.

Conclusion: The present case demonstrates that successful bridging to heart transplantation is possible even in cases of severe bleeding complications. Special attention is given to the thin line between bleeding complication and necessary anticoagulation because of mechanical circulatory assist.

0164 MONITORING OF ANTI-HLA AND ANTI-MICA ANTIBODIES IS NECESSARY IN PATIENTS WITH VENTRICULAR ASSIST DEVICE SUPPORT

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Objective: Patients that were bridged to transplantation with ventricular assist device (VAD) have a higher incidence for the development of antibodies directed against human-leukocyte-antigens (HLA) or against major-histocompatibility-complex-class I related chain A (MICA). HLA-antibodies and

MICA-antibodies have been associated with acute and chronic rejection leading to decreased survival after heart transplantation. Up to now, monitoring of these clinical relevant antibodies is not an established routine.

Methods: Sera of 15 patients who underwent VAD implantation were analyzed by Luminex-technology for anti-HLA and anti-MICA antibodies. Blood transfusion history, gender, age and panel reactive antibody (PRA) level before VAD implantation were reviewed.

Results: The mean age was 51.1 ± 11.6 years and the group consist of 12 men. The three women were pre-operatively HLA I or II positive. Regarding age, gender and number of received blood transfusions no significant differences were obtained between HLA/MICA-positive and HLA/MICA-negative patients. Seven of 15 patients (47%) showed anti-HLA and/or anti-MICA antibodies after VAD implantation, whereas three patients (20%) developed de novo antibodies against HLA class I, HLA class II and/or MICA antigens.

Conclusions: Patients with implanted VADs prior to transplantation have a higher risk to develop alloreactive antibodies because of the necessity of high amount of blood transfusion, but also due to the VAD itself. Due to increasing numbers of VAD implantations in consequence of missing donor hearts antibody monitoring and pre-operative intervention may be useful for better transplantation outcome.

0165 INCISIONAL HERNIAS FOLLOWING LIVER TRANSPLANTATION - IMPACT OF INCISION AND IMMUNOSUPPRESSION

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Introduction: Incisional hernias lead to a significant morbidity after liver transplantation and contribute to hospitalization. We evalutated the impact of different types of incisions and immunosuppression on the incidence of incisional hernias following liver transplantation.

Patients and methods: We prospectively monitored 98 patients following liver transplantation between 1998 and 2009 in terms of wound healing and occurance of incisional hernia. 66 patients had an incision following an inverse L, 32 patients the classic mercedes incision. Immunosuppressive protocol included tacrolimus, daclizumab, and 61 patients with steroids and 37 patients without.

Results: Overall, 37% of incisional hernias were found, 20% following an inverse L incision and 56% following the classic mercedes incision (p under 0.05). A significant reduction of hospital stay was observed (30 days after inverse L and 37 days after mercedes incision), as well as a reduction of time to mobilisation (8 days after inverse L versus 17 days after mercedes incision). Comparing patients with immunosuppression including steroids with those without steroids, there were significantly less patients suffering an incisional hernia without steroids ($P = 0.05$).

Conclusion: Inverse L incision compared to the classic mercedes incision lead to a significant reduction of hospitalization, time to mobilisation and incidence of incisional hernia. Thus inverse L incision should be considered as the incision of choice in liver transplantation. Steroid avoidance protects patients from developing incisional hernias.

0167 ANTIBODIES AGAINST MICA AND ANTI-HLA AFTER HEART TRANSPLANTATION ARE ASSOCIATED WITH CMV-INFECTION AND TRANSPLANT VASCULOPATHY

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Objective: The causes of transplant vasculopathy (TVP) after heart transplantation (HTx) are not solved completely, but comprise immunologic as well as non-immunologic factors. Evidence suggests that antibodies against HLA and major histocompatibility complex class I related chain A (MICA) play a key role in humoral response to alloantigens. We described the appearance and allocation of HLA and MICA antibodies after HTx in association with CMV-infection and TVP.

Methods: Sera of 116 HTx recipients were screened by Luminex-technology for anti-HLA and anti-MICA antibodies. For statistical analysis the gender, age, status of TVP (IVUS detection), CMV-infection (PCR positive) and time from HTx to beginning of the study was documented.

Results: Twenty-four percent ($n = 28$) of all recipients were positive for HLA and/or MICA antibodies. There was no significant difference in age and gender of recipients with positive or negative antibody status. CMV-infection was solely confirmed for HLA and/or MICA positive recipients, whereas 16.7% were positive for anti-MICA antibodies and 28.6% for anti-HLA antibodies. Furthermore, 50.0% of the recipients with TVP combined with positive antibody status were positive for MICA antibodies.

Conclusions: Our results showed that positive detection of MICA and HLA class I antibodies after HTx is related to a higher incidence for CMV-infection and TVP. Prospective studies have to show if post-transplant monitoring of HLA and / or MICA antibodies will serve as useful prognostic markers to identify for TVP and CMV-infection.

0168 TRANSCATHETER AORTIC VALVE IMPLANTATION LONG-TERM AFTER HEART TRANSPLANTATION

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Introduction/history of patient: Transcatheter aortic valve implantation (TAVI) has evolved into an established therapeutic option in high-risk surgical patients. Aortic stenosis occasionally occurs in the allograft long-term after heart transplantation. A 67-year-old male patient was referred to our institution with symptomatic allograft aortic stenosis 14 years after orthotopic heart transplantation for dilative cardiomyopathy. Comorbidities included cardiac allograft vasculopathy and poor left ventricular function. According to preoperative risk assessment (logistic EuroSCORE 29%) he was considered high-risk for standard surgery and therefore eligible for TAVI. Due to severe aortic calcifications and kinking of the iliac arteries a transapical approach was chosen.

Treatment: Transcatheter aortic valve implantation was carried out in a hybrid suite. Left anterolateral minithoracotomy was performed and a 26 mm Edwards Sapien valve was deployed antegrade in aortic position under rapid-pacing and fluoroscopic control. Valve performance was assessed by echocardiography and fluoroscopy. Effective orifice area increased from 0.6 to 3.1 cm2 and mean transvalvular gradient decreased from 23 to 6 mmHg. The patient could be discharged home 7 days after TAVI. At 6-month follow-up, the patient was doing well with excellent valve function.

Conclusions: Transapical TAVI for severe aortic stenosis can safely be applied in immunosuppressed heart transplant recipients with relevant comorbidities for whom standard surgery is not an option. With improving outcomes after transplantation, donor valve aortic stenosis might be anticipated to become more frequent in heart transplant recipients in the future. Additionally, due to the significant shortage of donor hearts, marginal organs may increasingly be accepted for transplantation. Patients with additional cardiac allograft vasculopathy and left ventricular dysfunction represent a particularly vulnerable high-risk cohort in whom transcatheter valve procedures may offer potential benefit after thorough risk-/benefit evaluation.

0173 KIDNEY TRANSPLANTATION WITH DONORS OVER THE EXPECTED LIFESPAN: A SINGLE CENTER ANALYSIS

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Background: Utilization of kidneys from donors ≥75 years of age is controversial and may lead to improved outcomes. The purpose of this study was to evaluate outcome of kidney transplantation (KT) involving these very expanded criteria donors.

Patients and methods: From 1/2001 to 11/2009 52 patients were transplanted with grafts from deceased donors ≥75 years. Donor and recipient data as well as intra- and postoperative variables were analyzed by uni- and multivariate regression analyses. Graft and patient survival were calculated using the Kaplan–Meier method.

Results: Forty-one single and 11 double KT were performed. Median recipient age was 66 years. Men/female ratio was 1.8/1. After a median follow-up of 30 months, 37/52 patients are alive with 29 functioning grafts (78%). Graft and patient survival rates at 3 and 5 years are 63%, 53% and 78%, 64%, respectively. Double-KT, Dindo-Clavien classification and primary graft function were significant predictors for graft survival by univariate analysis. The later two parameters reached multivariate significance. Co-Morbidity Index, primary graft function, hospital stay, rejection and re-KT were significant predictors for patient survival by univariate analysis. Co-Morbidity Index and re-KT reached multivariate significance. Cold ischemia time, single- and re-KT, reached significance as predictors of primary non function by general linear model forward analysis. Five-year graft survival for single and double KT was 41% and 82%, respectively, ($P = 0.0498$).

Conclusions: Excellent long term outcome of kidney transplantation from donors ≥75 years of age can be achieved in elderly recipients with low comorbidities only with double grafting and when retransplantations are avoided.

0177 THE INNSBRUCK HAND TRANSPLANT PROGRAM: A 10-YEAR REPORT

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We describe here the outcome after two bilateral hand, one bilateral forearm and one unilateral hand transplantation at 10/7/4 and 0.5 years after transplantation. Induction therapy with ATG ($n = 2$) or alemtuzumab ($n = 2$) was

followed by tacrolimus, prednisolon ± MMF ($n = 3$) or tacrolimus and MMF ($n = 1$) maintenance IS. Later, Prednisone was withdrawn ($n = 2$) and sirolimus/everolimus was added to the therapeutic regime under simultaneous withdrawal ($n = 1$) or dose reduction ($n = 1$) of tacrolimus ($n = 1$). MMF was discontinued in two patients. Steroids were entirely avoided in one and withdrawn in two patients. Range of motion reached up to 70% of normal with a grip strength of 2–10kg. Hand function correlated well with time after transplant and amputation level. Intrinsic hand muscle function recovery and discriminative sensation were observed after hand but not forearm transplantation. Complications included CMV infection, fungal infection, hypertension, hyperglycemia, transient creatinine increase and headache. Three, six, four, and one rejection episode were successfully treated with steroids, anti-CD25, anti-CD52 antibodies and/or intensified maintenance IS. Skin histology at current shows no or mild perivascular lymphocytic infiltrates without signs of progression. Vessels are patent without signs for luminal narrowing or intimal proliferation. The overall functional outcome and patient satisfaction after bilateral hand, bilateral forearm and unilateral hand transplantation are highly encouraging. All patients are now free of rejection with moderate levels of IS.

0179 FUNCTIONAL IMPACT OF RENAL ISCHEMIA-REPERFUSION INJURY IN THE ABSENCE OF INFLAMMATORY CELLS

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Purpose: Current immunosuppressive therapies in kidney transplantation act via the modulation of lymphocytes in particular. This study investigates the functional effects and regenerative capability of the kidney following renal ischemia-reperfusion based on a perfectly abolished inflammatory cell response.

Materials and methods: In immunodeficient mice strains, Balb/C nu/nu and Scid beige, unilateral warm ischemia was induced by vascular clamping of the kidney hilum for 40 min. Renal perfusion and tubular excretion function were examined using ^{99m}Tc-MAG3 scintigraphy 48 hours and 18 days post ischemia. Additional histological analysis was performed.

Results: In Balb/C nu/nu mice lacking T cells, ischemia-reperfusion injury led to substantial reduction of renal perfusion and function already early after injury. The follow-up examination on day 18 showed further decrease in renal blood flow and tubular function. Histologically, considerable tissue damage including tubular atrophy and necrosis, loss of brush borders, and abundant protein cylinders was found. In contrast, combined T cell, B cell, and NK cell deficient Scid beige mice were protected from ischemia-reperfusion injury. No significant decrease in renal blood flow was observed both 2 days and 18 days following ischemia. Tubular excretion function was decreased 2 days after ischemia, but showed significant recovery by day 18. In histological analysis, ischemic kidneys of Scid beige mice exhibited tubular dilatation and cytoplasmic degeneration as signs of hypoxia. Tissue viability was excellent with no signs of necrosis.

Conclusion: This model using immunodeficient mice strains examines and simulates the functional impact of renal ischemia-reperfusion injury in the absence of inflammatory cell response. While complete inhibition of inflammatory cells is difficult to achieve and may not be desired in terms of adverse effects, the present study allows for undisguised observation of the consequences of ischemic injury that are usually masked by the complex response and interaction of inflammatory cells. In the present study early impairment of renal blood flow strongly correlated with poor recovery and functional outcome. Our data suggest that the preservation of the renal vascularity shall be considered top priority. Meanwhile, efforts to reduce ischemic injury of the tubules may further facilitate renal recovery.

0181 THE FITNESS OF BONE MARROW DERIVED MESENCHYMAL STEM CELLS – AN ANALYSIS OF CARDIOVASCULAR PREDICTORS

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Objectives: Autologous cardiac transplantation of mesenchymal bone marrow stem cells (MSC) has shown promising effects for the treatment of ischemic and non-ischemic cardiomyopathy. However, it is disputable if heart failure patients who are suffering from cardiovascular co-morbidities are proper donors for autologous cell transplantation. In this study we evaluated cardiovascular risk factors and their impact on MSC fitness.

Methods: Bone marrow aspirates from cardiac surgery 51 patients were analyzed for MSC-frequency and cell-culture expansion potential. Fibroblastic colony-forming-units (CFU-F) were quantified for culture conditions applying different basic cell-culture media and autologous serum (AS) or fetal bovine serum (FBS). Multi- and univariate analysis were performed in order to identify the impact of cardiovascular risk factors on CFU-F numbers and MSCs were analyzed for phenotype and differentiation potential.

Results: Patients showed typical demographic parameters for elective cardiac surgery. Cells from expansion cultures showed MSC specific immunophenotype and displayed adipogenic, chondrogenic and osteogenic differentiation potential. CFU-F numbers were not significantly different when applying AS or FBS and different basic media, respectively. A high frequency of mononuclear cells in the bone marrow aspirates, diabetes mellitus, cortisone treatment, COPD or renal failure were significant determinants for higher CFU-F numbers.

Conclusions: Specific cardiovascular risk factors of potential patients for cardiac cell transplantation and their impact on MSC fitness could be determined. These results may help to establish a pre-cell transplantation patient profiling in order to identify those patients who would benefit from cardiac cell transplantation.

0182 KIR GENOTYPE DETERMINES NK-CELL PERFORMANCE AGAINST K562

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In myeloid leukaemia, stem cell grafts from donors with low number of stimulating killer cell immunoglobulin-like receptors seem to be beneficial. The relapse rate was reduced when patients received T-cell depleted grafts from donors with KIR haplotype A. We speculated that the ratio between stimulating and inhibitory KIRs influence the NK cell activity in individuals. To address this hypothesis we selected HLA matched blood donors and used isolated PBMC to assess their lytic activity against K562 target cells. Chromium release was performed with 5000 target cells and an effector/target ratio of 80:1. The calculated % specific lysis was normalized against an internal PBMC standard and the percentage of CD56+ cells in the respective samples. The mean specific lysis was 55.2% in KIR AA ($n = 5$), 41.7% in KIR AB ($n = 9$) and 30.0% in KIR BB ($n = 3$) individuals. In addition scattering of NK cell activity was lowest in KIR AA individuals.

0183 ONINVASIVE IN VIVO TRACKING OF MESENCHYMAL STEM CELLS BY MRI AND EVALUATION OF CELL THERAPEUTIC EFFECTS

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Introduction: Stem cell transplantation is emerging as a promising approach for the regeneration of infarcted myocardium. However, there is little known about the fate of the transplanted cells since the means for tracking transplanted cells and measuring their therapeutic effects in vivo are limited. The goal of this study is the in vivo analysis of stem cell transplantation into cryo-infarcted mice hearts by magnetic resonance imaging (MRI).

Methods: Murine mesenchymal stem cells (mMSC) were isolated from bone marrow. After expansion lineage specificity was confirmed *in vitro* by adipo-, chondro- and osteo-differentiation and FACS-analysis for CD44 and Sca-1. mMSC were labeled with paramagnetic microspheres (Ø 1 μm) and transplanted into the border zone of the infarcted myocardium subsequently after cryo-infarction. In vivo cell tracking and measurements of functional cardiac parameters were performed using a clinical 3T MRI-scanner (Philips Achieva) applying ECG-gated T2*-weighted imaging using a dedicated magnification coil for mice.

Results: Microspheres were phagocytosed by mMSC efficiently, without interfering with their proliferation and differentiation potential. A minimum of 50 000 transplanted mMSC could be clearly detected and co-localized by MRI up to 5 days after transplantation. Furthermore, compared to sham-controls, cell transplanted animals showed a significant improvement left ventricular function and reduction of the infarct scar 3 weeks postoperatively.

Conclusion: Transplantation of mesenchymal stem cells results in reduction of infarct size and improvement of left ventricular function. In addition, we could show that *in vivo* tracking of transplanted cells is feasible by MRI and opens new options to elucidate the mechanisms of cardiac cell therapy.

0184 DOSE PROPORTIONALITY OF MYCOPHENOLIC ACID IS LIMITED BY RENAL FUNCTION EARLY AFTER RENAL TRANSPLANTATION

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Background: Implementations of TDM as well as protocols with increased starting dose are concepts to improve adequate early mycophenolic acid (MPA) exposure. Both strategies relay on the presumed dose proportionality although this topic is understudied. In a recent pharmacokinetic study we investigated whether an intensified dosing regimen of enteric-coated mycophenolate sodium (EC-MPS) could achieve higher MPA exposure early post-transplantation versus a standard dosing regimen. In this sub-analysis we investigated the dose proportionality in the first week after transplantation.

Methods: De novo kidney transplant recipients ($n = 75$), treated with basiliximab induction and cyclosporine, were randomized to receive EC-MPS as either standard dosing (1440 mg/d; $n = 37$) or intensified dosing (days 0–14: 2880 mg/d; days 15–42: 2160 mg/d; followed by 1440 mg/d; $n = 38$). Full 12 hours pharmacokinetic profiles were taken to calculate AUC for total MPA, free MPA, AcMPAG and MPAG. Assessment of dose proportionality was performed by dose normalization of AUC and analysis of variance (ANOVA) on logtransformed data to test for differences between dosing regimens.

Results: Exposure to MPA was significantly higher on days 3 post-transplantation in the intensified versus standard group (45.0 15.5 vs. 32.6 18.7 mg/h*L, $P < 0.05$), but the log-transformed dose-normalized AUC was significantly lower (1.16 0.17 vs.1.28 0.22, $P < 0.05$) confirming the lack of dose proportionality. MPA-AUC on day 3 ($P = 0.027$) was significantly associated with CKD stage (based on estimated GFR calculated by Cockroft-Gault formula) in the intensified dose but not in the standard dose group. Excluding patients with severe impaired renal function from analysis resulted in dose proportionality for mycophenolic acid in the remaining patients (1.26 0.13 vs.1.27 0.19, ns).

Conclusion: Further studys have to investigate whether intensified dosing in patients with severe disturbed renal function can improve efficacy despite lower total MPA-AUC or if these patients even at higher risk for adverse events because of higher freeMPA- and AcMPAG-level.

0192 COMPARING AORTIC STIFFNESS IN KIDNEY TRANSPLANT RECIPIENTS AND PATIENTS WITH RESIDUAL RENAL FUNCTION

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Background: The poor cardiovascular survival of patients with renal insufficiency is ameliorated by transplantation. Carotid-femoral pulse wave velocity (PWV), a marker for aortic stiffness, is able to independently predict total and cardiovascular mortality. PWV is elevated in renal insufficiency. Consequently, PWV may adapt according to the amelioration of renal function after kidney transplantation.

Methods: In a cross-sectional setting PWV was determined in 40 renal transplant recipients (RTx) and compared to the PWV of 40 age and sex matched patients with comparable residual renal function (CKD) and 40 age and sex matched hemodialysis patients (HD). Factors involved in the prediction of PWV were characterized in these patients. Pairs of patients (RTx and CKD) were furthermore stratified according to duration of transplant follow-up, sex and median of age and median of blood pressure.

Results: RTx and CKD patients revealed comparable estimated GFR (RTx: 42.9 ± 18.4 versus CKD: 48.3 ± 29.1 ml/min/1.73 m^2) and protein-creatinine ratio (logPCR RTx: 2.33 ± 0.45 versus CKD: 2.39 ± 0.56) and PWV (RTx: 9.67 ± 1.91 and CKD: 9.72 ± 3.21 m/s). Aortic stiffness did not differ between 3–12 months and >12 months after transplantation as compared to matched CKD patients. The status of renal function (RTx, CKD, HD) did not predict PWV.

Discussion: Under the condition of matched age and sex different states of renal function are not associated with modified aortic stiffness.

0197 RISK FACTORS IN PEDIATRIC LIVER TRANSPLANTATION

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Purpose: Liver transplantation has become routine treatment for end stage liver disease in children. Herein, we aimed to identify risk factors affecting patient and graft survival.

Methods: Retrospective analysis of 75 (28.0% female) pediatric recipients receiving 87 liver transplants retrieved from 31 living and 56 cadaveric donors (1984–2009). Median age at the time of transplantation was 2.7 years (3 months to 16 years). Bilary atresia (42.7%), 1-antitrypsin deficiency (12.0%), M. Wilson (9.3%), cystic fibrosis (8.0%), and Aalagille Syndrome (6.7%) have been the most frequent causes of liver failure. For bilary reconstruction, hepatico-jejunostomy (61.4%), choledo-choledochostomy (32.0%), and cholecysto-jejunostomy (6.6%) have been carried out. Statistical analysis involved Kaplan–Maier method, log rank and Mann–Whitney *U*-test.

Results: One-, 5- and 10-year graft and patient survival was 76.6%, 75.0%, 66.0% and 87.1%, 85.7%, 72.7%, respectively. Twelve (16.0%) patients required re-transplantation for vascular complications (41.7%), acute or chronic rejection *U* test (41.7%) or due to primary non-function (16.6%). One patient received a 3rd-transplant after ocurrence of allograft cirrhosis 5.7 years after re-transplantation. Patient death occurred due to immunologic (18.8%) or non-immunologic allograft failure (37.5%), infectious complications (25.0%), hemorrhage (6.3%), brain edema (6.3%) and death during re-transplantation (6.3%). Bilary and vascular complications occurred in 17.3% and 18.6%, acute rejection in 17.3% of recipients, respectively. Preoperative recipient serum bilirubin >5 mg/dl ($P = 0.04$) and age <12 months ($P = 0.0004$) were identified as risk factors for allograft loss.

Conclusion: Excellent results can be achieved in pediatric recipients of liver allografts. Recipient age <12 months and serum bilirubin >5 mg/dl have to be considered as serious risk factors.

0198 ESTABLISHMENT OF THE AREAL DENSITY MEASUREMENT AS A PROCEDURE FOR DETERMINATION OF THE ISLET DOSIS AND ITS APPLICATION FOR ISLET TRANSPLANTATION

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Introduction: Precise quantification of islet mass as islet equivalent (IEQ) is a crucial part of quality control and adequate characterization/normalization of islet preparations in relation to good manufacturing pratice (GMP) criterions. So, a well defined dose and potency of the transplanted mass is very important. Because of an irregular form of islets the standard method which is based on manual analysis is often prone to operator-dependent variability and missing repeatabilty. Therefore, we developed a new method without sizing and counting individual islets. The aim of the study was the establisment and validation of this method, especially the finding of corrector factors between both methods and its practical application.

Material and Methods: Porcine Islets were isolated by continous digestions-filtration method and purified by density gradient centrifugation in a COBE 2991 cell seperator. After staining of the purified islets with dithizone they were repeatedly pictured under the microscope with random area selection (totally 168 pictures from 12 different islet preparations). The stained islets were analyzed by digital image analysis with the Adobe Photoshop program and IEQ number was determined by Conventional Analysis and Areal Density Measurement.

Results: There is a good linear relation with a correlation coefficient of 0.94 and a regression coefficient of 0.97 ± 0.03. The areal density measurement per picture was about 11 times faster than Conventional Analysis. The frequency distribution of islets in the distinct size classes could be found as a correctur between both mathematical different methods.Regarding islets smaller than 50 μm, IEQ number was approx. 12% too low using Conventional Analysis.

Discussion: Areal density measurement is a time-saving, objective and retrospective reproducible method for the assesment of transplanting islet mass. Failures and limitations of this method are found at an increased existance of large islets in the preparation (underestimation of the islet mass as IEQ because of missing correlation of areal density measurement with percental picture filling) such as of the age of the animals and the place of islets within the pancreas.

0199 HO-1 INDUCTION VIA NUTRACEUTICALS AMELIORATES RENAL ISCHEMIA REPERFUSION INJURY

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Introduction: HO-1 is an antioxidant enzyme acting beneficial in transplant related ischemia reperfusion Injury. Induction thereof is successful experimentally; however, the compounds being used so far cannot be administered to humans because of hepatotoxicity. Herein, we tested various nutraceuticals for their potential to induce HO-1 and prevent renal ischemia reperfusion injury.

Methods: Ten nutraceuticals known to induce HO-1 *in vitro* have been tested for their potential in vivo. HO-1 induction/expression has been assessed by PCR. Further, renal arteries of contralaterally nephrectomized Lewis rats have been clamped for 60 minutes 24 hours after oral administration of one of the nutraceuticals, in presence or absence of the HO-1 inhibitor SnPP at 10 mg/kg. Serum creatinine and urea have been measured at defined time points after reperfusion.

Results: Two of the nutraceuticals tested showed significant upregulation of HO-1 (N18519 11-fold, N791419 17-fold, $P < 0.0001$ for both). Forty-eight hours after reperfusion mean serum creatinine was 3.06 mg/dl (SD ± 0.86) in controls. Application of both, N18519 (serum creatinine 0.54 mg/dl ± 0.23) or N791419 (serum creatinine 0.53 mg/dl ± 0.06) dramatically reduced renal damage. When HO-1 activity was blocked by SnPP, the beneficial effect was reversed.

Conclusions: Nutraceuticals with the potential to induce HO-1 substantially should be considered for the prevention/treatment of transplant related ischemia reperfusion injury.

0201 CALCINEURIN-INHIBITOR-FREE THERAPIE WITH EVEROLIMUS AND MYCOPHENOLIC-ACID IN CARDIAC TRANSPLANT RECIPIENTS WITH CHRONIC KIDNEY DISEASE: EARLY FOLLOW UP

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Background: The calcineurin inhibitor cyclosporine A and tacrolimus (CSA, TAC) have nephrotoxic side effects. The calcineurin-inhibitor-free therapie with Everolimus and Mycophenolic-acid seems to be an efficient option to

avoid renal failure in Cardiac Transplant Recipients with Chronic Kidney Disease.

Methods: During 2007 and 2010 we switched 14 maintenance cardiac transplant (CTx) recipients with chronic kidney disease (CKD) stages 3–4 from dose-reduced calcineurin-inhibitor-therapy+ everolimus to everolimus (EVL)+ Mycophenolic-acid (MPA) such as Cellcept, Myfortic). Kidney function, lipid metabolism, and cardiac function were investigated.

Results: Eight patients received Everolimus in combination with MPA or Prednisolone and six patients received Sirolimus in combination with MPA or Prednisolone. Data analysis revealed an improvement of creatine and GFR. A significant alteration of blood count was not observed. One patient developed a massive herpes-zoster-infection. Cardiac rejections were not observed during the follow up.

Conclusion: EVL combined with MPA or prednisolone has moderate beneficial effects on kidney function in CTx patients with CKD stages 3–4. Cardiac rejections were not observed during the follow-up-intervall. Only a slight number of adverse event was observed.

0205 DONORS'ELIGIBILITY IN THE FRAME OF LIVING DONOR LIVER TRANSPLANTATION FROM THE PSYCHOSOMATIC PERSPECTIVE

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Objectives: Live donor transplantation offers an essential source of organs, but considerable time and effort is required to select eligible donors (Calder and Chang 2004). The protection of the donors from emotional harm is an important principle in the LDLT setting. The purpose of the psychosocial evaluation of candidates for living liver donation is to limit psychiatric risks after donation. Furthermore, donors effective evaluation constitute an important assumption for an adequate psychological support and counselling. The exclusion rate for psychosocial reasons ranged from 2% to 15% in transplant centers and might depend on whether transplant centers offer LDLT to their patients on a routine basis, on the information status, acceptance and cultural choices of the general public. Objective of the study was to analyse exclusion criteria.

Methods: Between January 2004 and January 2007, 161 donor candiates were admitted to psychosomatic evaluation.

Results: Considering the donor candidates, 19 donors (11.8%) were rejected after the psychosomatic interview as not eligible for LDLT, 142 donors (88.2%) were evaluated as eligible. The main reasons for exclusion were diagnoses according to ICD-10 ($n = 8$), conflict of ambivalence ($n = 4$), medical excuse ($n = 3$), no adequate coping skills ($n = 3$) and in one case the lacking capacity to comprehend the disclosed information. The excluded donors did not differ regarding gender ($P = .69$) or age ($P = .35$) from eligible candidates, but the excluded donor candidates obtained significantly more often psychiatric diagnoses according to ICD-10 ($P < .001$).

Conclusions: Mental disorders and feelings of ambivalence are frequent reasons for exclusion. Donor candidates with better psychosocial resources and mental stability are selected in the psychosomatic evaluation and this contributes to the good psychosocial outcome of living donors.

0206 SEX-SPECIFIC MODIFICATION OF THE RENAL CYP-EICOSANOID PROFILE LEADS TO ALTERATIONS IN TISSUE OXYGENATION AND INTRARENAL HEMODYNAMICS IN ISCHEMIC ACUTE KIDNEY INJURY

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Sexual dimorphism in renal injury is evident in clinical and experimental settings. However, the mechanisms of sex related differences remain undefined. Previously we found that blockade of the arachidonic acid (AA) metabolite 20-HETE conferred sex-specific protection in experimental acute kidney injury of rats. We hypothesized that females are protected against acute ischemic injury by changes in cytochrome P450 (CYP450) dependent AA metabolism resulting in a shift towards higher levels of vasodilatory and cytoprotective EETs. Renal injury was induced in uninephrectomized male and female rats through 45 minutes of left renal artery clamping. Groups were treated 5 minutes prior to ischemia with intrarenal injection of the specific EET-antagonist 14,15-EEZE or vehicle. Organs were harvested 2 days after reperfusion. Additionally, *in vivo* changes of renal hemodynamics and local tissue oxygenation were obtained by an ultra-sound flow probe and combined optical Laser-Doppler-flux- and pO_2-probes in renal cortex and outer medulla during ischemia and early reperfusion phase in male rats after vehicle treatment or blockade of 20-HETE with the inhibitor 6,15-20HEDE. Female rats developed less extensive functional and structural impairment and postischemic inflammatory response than male rats. 14,15-EEZE administration in female rats reversed the protective phenotype and caused a similar loss of renal function, tissue inflammation and tubular apoptosis as in male rats. Blockade of 20-HETE in males raised medullary erythrocyte flux and local pO_2 in renal cortex and medulla 2fold compared to vehicle treatment during early post-reperfusion period. Our results suggest that a distinct pattern of changes in the renal CYP-eicosanoid profile is responsible for sexual dimorphism during acute kidney injury. Alterations in intrarenal hemodynamics and local tissue oxygenation are possible underlying key mechanisms. Combined utility of 20-HETE-antagonists, EET-agonists, and sEH-inhibitors may offer new sex-adapted therapeutic strategies for ischemic acute renal failure.

0208 PSYCHOSOMATIC EVALUATION OF TRANSPLANT CANDIDATES: TRANSPLANT EVALUATION RATING SCALE OBJECTIFIES THE CLINICAL DECISION

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Objective: A high medical, psychosomatic, and ethical commitment is associated with the selection of eligible candidates for transplantation. A crucial topic in the psychosomatic evaluation is the psychosocial functioning and health behaviour of the transplant candidates.

Method: In 1116 liver transplant candidates who were interviewed prior to liver transplantation the level of psychosocial functioning was analysed with Transplant Evaluation Rating Scales' (TERS; Twillman et al. 1993; Johann & Lorenzen 1997).

Results: The prevalence of psychiatric disorders according to ICD-10 was 53.5% ($n = 598$), in further 393 patients (10.8%) personality disorders were diagnosed; impairment of the mental status in 285 (25.5%). The most frequent diagnoses were alcohol dependence ($n = 303$; 27%), followed by nicotine dependence (20%), adjustment disorders (3%) and depressive episodes (1.8%). The mean TERS-total score was M = 38.9 (SD=9.1). Regarding the subscales "actual psychiatric disorder, "social support and "quality of affect, women scored in comparison to male patients significantly higher and exhibit a significant lower level of psychosocial functioning ($P < .05$). Between age ($r=-0.08$; $P < .01$), education ($r=-0.16$; $P < .001$) and level of psychosocial functioning a negative correlation could be established. A total of 19% of transplant candidates were rejected because of psychosomatic reasons. A ROC-analysis revealed an optimal cut-off score for greater than M = 46.5 for TERS-total-score for rejected patients and 84 % of the patients could be classified correctly.

Conclusions: TERS allows a standardized evaluation of liver transplant candidates. Female gender, young age and patients with a lower educational level show an impaired psychosocial adaptation. These risk factors should be given special attention in the psychosomatic evaluation of liver transplant candidates.

0209 PERCUTANEOUS TRANSLUMINAL STENT ANGIOPLASTY AS TREATMENT OF PANCREAS TRANSPLANT ARTERY STENOSIS

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Background: Arterial stenosis of the vascular graft after pancreas transplantation is an uncommon cause of pancreas graft dysfunction and graft pancreatitis.

Methods: We report two male SPK-recipients (age 34 and 38 years) with a stenosis affecting the Y-graft of the pancreas transplant. In both cases stenosis was detected by MR angiography. In one case pancreas artery stenosis manifested on the 5th postoperative day because of acute graft pancreatitis affecting both arteries of the Y-graft. In case 2, insulin-dependent hyperglycemia appeared 5 months after SPK. Angiography of the pancreas vascular graft was performed followed by percutaneous transluminal stent-angioplasty in both cases.

Results: The method was technically feasible in both cases. No complications occurred after the interventions and pancreas grafts showed a good perfusion after stenting. Concerning antiplatelet therapy acetylsalicylic acid and clopidogrel were administered for 6 weeks. After a few days of hyperglycemia and the necessity of insulin substitution both patients showed decreasing glucose levels up to normoglycemia.

Conclusion: In our experience, percutaneous stent-angioplasty in cases of arterial stenosis affecting the pancreas vascular graft is a feasible and effective procedure.

0210 BRIDGE TO RECOVERY FOR ACUTE MYOCARDIAL FAILURE: SUPERIORITY OF PARACORPORAL COMPARED TO EXTRACORPORAL SUPPORT

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Objective: Retrospective analysis to evaluate efficacy of different mechanical ventricular assist systems used as bridge to recovery (BTR) in acute myocardial failure.

Methods: Between 01/2003 and 04/2010 45 patients required mechanical ventricular assist due to postcardiotomy failure ($n = 22$), acute myocarditis ($n = 9$), acute myocardial infarction ($n = 11$) and acute failure in pre-existing cardiomyopathy ($n = 3$). An extracorporal system was used in $n = 17$ (Gr.1: 8xbiatrial ECMO, 6xbiventricular BVS5000, 3xuniventricular Levitronix), a paracorporal biventricular system in $n = 28$ (Gr.2: 17xAB5000, 11xMedos HIA). Standardized anticoagulation was started immediately after implantation in Gr.1 and only after 12-24 hrs post implantation in Gr.2.

Results: Patient characteristics and distribution with regards to indication and pre-implant status were no different between groups 1 and 2. All patients left the OR with stable circulation and adequate cardiac index of >2.5l/m^2 (P = ns. between groups). Primary chest closure was possible in only 6% in Gr.1 vs. 72% in Gr.2. Post-implant transfusion requirements and rethoracotomy rates due to bleeding/tamponade were significantly higher in Gr.1 (10.8 ± 2.3 vs. 4.6 ± 1.8 units EK/FFP and 2.6 ± 2.3 vs.1.8 ± 1.1 rethoraces Gr.1 vs. Gr.2 respectively; $P < 0.05$). Duration of vasopressor support was 6.2 ± 4.5 days in Gr.1 and 2.3 ± 1.8 in Gr.2 (P = n.s). Successful myocardial recovery and system explant was achieved in 17.6% vs. 48%, survival and hospital discharge in 17.6% vs. 40% in Gr.1 vs Gr.2 respectively ($P < 0.05$). Duration of mechanical support was 19.9 ± 10 days in survivors vs. 10.8 ± 6 days in non-survivors ($P < 0.05$).

Conclusion: Use of paracorporal systems allowed a higher frequency of primary chest closure, less transfusions/rethoracotomies as well as superior myocardial recovery and survival.

0211 INTERLEUKIN-33 PROLONGS ALLOGRAFT FUNCTION FOLLOWING HEART TRANSPLANTATION IN MICE

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Background: IL-33 a member of the IL-1 family stimulates the generation of cells, cytokines, and immunoglobulins characteristic of a type 2 immune response. In this study, we demonstrate the effect of IL-33 on allograft function during chronic cardiac rejection in mice.

Material and methods: B6.C-H2bm12/KhEg hearts were transplanted into wild type MHC class II-mismatched C57BL/6J mice. IL-33 was administered i.p. daily. Cardiac allografts were harvested, graft infiltrating CD4+ T-cells were isolated and cytokine production was determined by ELISA. Isolated leukocyte populations were examined with flow cytometry. Further, immunhistochemical staining of cardiac allografts was performed.

Results: Allogeneic transplanted control animals showed complete allograft rejection within 22 days after transplantation, whereas allograft survival in animals treated with IL-33 was extended to 48 days. Under IL-33 treatment we observed a significant decrease in the production of pro-inflammatory IL-17A and increased levels of the Th2-cytokines. IL-33 treatment also resulted in changes in the lymphoid and myeloid compartment in both the cardiac allografts and the periphery. Flow cytometric analyses demonstrated a reduction of total $CD4^+$ T-cells with a significant increase in $CD4^+$ $Foxp3^+$ Tregs. Further, changes in the myeloid compartment were evident following IL-33 administration. A significant decrease in graft infiltrating $CD11b^{high}$ $Gr1^{high}$ granulocytes coinciding with a significant increase in $CD11b^{high}$ $Gr1^{intermediate}$ myeloid cells could be observed.

Conclusion: IL-33 treatment prolongs allograft survival after cardiac transplantation in mice. IL-33 induces changes in cytokine production of graft infiltrating cells and alters the composition of the lymphoid and myeloid compartment. Thus, IL-33 and its downstream effects need further evaluation as a possible therapeutic option for chronic allograft rejection.

0213 NONALCOHOLIC STEATOHEPATITIS AN INCREASING INDICATION FOR LIVER TRANSPLANTATIONEXPERIENCE OF THE UNIVERSITY HOSPITAL OF ESSEN

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Background and aims: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in western countries and considered to be a hepatic manifestation of the metabolic syndrome. The clinicopathologic spectrum ranges from simple steatosis through steatohepatitis (NASH) to end-stage liver disease (cirrhosis) and hepatocellular carcinoma. NASH cirrhosis is a consistently increasing indication for transplantation. This study aims to report our experience with patients who underwent liver transplantation due to NASH-related liver cirrhosis.

Methods: We retrospectively studied 364 consecutive liver transplants between October 2007 and May 2010. Twenty-four transplants were performed due to NASH. These patients' peri-operative course, short- and long-term outcomes were analyzed.

Results: Twenty-four cases were clinically and pathologically identified as NASH cirrhosis. There were 12 women and 12 men, ranging in age from 21 to 66 years (mean and median, 54.11 years and 54.84 years, respectively). The median MELD score was 26.5. The transplanted BMI ranged from 20.7 to 46.1 (mean and median, 30.63 and 29.6, respectively). 18 of the initial 24 patients are still alive. Four patients who died had remarkably increased BMI scores in mean of over 30.

Conclusion: First, a significant number of liver transplantations in our center were due to NASH. Second, liver transplantation in NASH patients is associated with a high mortality and postoperative complications, most likely due to associated obesity and metabolic syndrome. Improvement of obesity prior to LTx might lead to a better outcome in NASH patients with end stage liver disease.

0214 SAFETY STUDY OF MODIFIED HTK SOLUTION-FIRST RESULTS AFTER LIVERTRANSPLANTATION IN SWINE

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Introduction: A model of orthotopic liver transplantation in swine was developed to investigate an advanced reperfusion approach. We compared HTK solution with a modified HTK (HTK-N) solution.

Material and methods: We generated two study groups using 20 female swine of German Landrace breed with a donor median weight of 31.5 kg ($n = 10$) and a recipient median weight of 33 kg ($n = 10$). Group I ($n = 5$) was perfused by HTK-N solution and group II ($n = 5$) was perfused as control group by HTK solution. The grafts were perfused antegrade, additionally portal vein and bile duct were flushed backtable. Liver transplantation was performed orthotopic by removing the vena cava and without using veno-venous bypass. Seven days after transplantation the animals were mercy killed and an autopsy was performed.

Results: All 10 animals survived until study endpoint (7 days). The median cold ischemic time was 305 min and the median warm ischemic time 24 min. In trend the synthetic parameters TPZ and cholinesterase were in median higher in the HTK-N group at POD 7 (N-HTK: TPZ Median 120, HTK: TPZ Median 94) although there wasn't a significant difference between the two groups. Histology and further laboratory results are still under investigation, but will be presented.

Conclusion: HTK-N Solution seems to be by trend more effective than the usual HTK solution at 5 hours of cold ischemic time in swine. After this safety study in a large animal model further clinical studies seem to be justified.

0215 ANTITHROMBIN III INHIBITS MICROVASCULAR THROMBUS FORMATION UNDER IMMUNOSUPPRESSIVE THERAPY IN POSTISCHEMIC TISSUE *IN VIVO*

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Introduction: In the postoperative period following pancreas-kidney-transplantation, pancreatic venous thrombosis is one of the major complications leading to allograft dysfunction and loss. The ischemia-reperfusion(I/R)-injury and immunosuppressants, e.g. tacrolimus, have been implicated in the development of microvascular thrombosis. Several studies report a beneficial effect of antithrombin III-(ATIII)- and N-acetylcysteine-(NAC)-substitution on the I/R-injury. Aim of this study was to analyse their effect on thrombosis in post-ischemic tissue under therapy with Tacrolimus.

Materials/Methods: Using the skin-fold-chamber in C57BL/6J-mice, microvascular thrombus formation was induced photochemically and analyzed by intravital fluorescence microscopy. Control-animals without I/R received NaCl (10ml/kg/d ip; $n = 8$). Additionally, the influence of cold ischemia and reperfusion was examined. Those animals received NaCl (NaCl-I/R, $n = 7$) or tacrolimus (TAC-I/R, 10mg/kg ip, $n = 6$) and some additionally ATIII (250 IU/kg iv) or NAC (150 mg/kg ip) prior reperfusion (NaCl-I/R-AT: $n = 5$; NaCl-I/R-NAC: $n = 4$; TAC-I/R-AT: $n = 5$, TAC-I/R-NAC: $n = 4$).

Results: Microvascular thrombus formation was significantly accelerated in postischemic tissue compared to nonischemic tissue (arteriolar and venular occlusion: NaCl-I/R 451 ± 80s and 345 ± 39s vs. NaCl 888 ± 123s and 708 ± 141s, $P < 0.05$). Additional application of TAC enhanced thrombosis formation (arteriolar and venular occlusion: TAC-I/R 260 ± 45s and 209 ± 37s vs. NaCl-I/R, $P < 0.05$). Application of ATIII before reperfusion reduced thrombus formation in arterioles and significantly in venules in saline- and tacrolimus-treated animals whereas NAC had no effect (arteriolar and venular occlusion: NaCl-I/R-AT 718 ± 100s and 533 ± 82s vs. NaCl-I/R; TAC-I/R-AT 419 ± 55s and 421 ± 40s vs. TAC-I/R, $P < 0.05$ for venules).

Conclusion: The present results confirm the positive effect of ATIII- but not NAC-substitution prior reperfusion on thrombosis in post-ischemic tissue in vivo. Furthermore ATIII antagonizes the additional thrombogenic effect of tacrolimus.

0216 URINARY INTERLEUKIN- 6 IS INCREASED DURING REJECTION AFTER KIDNEY TRANSPLANTATION

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Background: Despite marked improvement in immunosuppressive therapy, acute rejection episodes are still a problem in the early post-transplant period. Successful antirejection treatment is dependent on early diagnosis and prompt treatment. Serum creatinine levels can take more than a day to accumulate to significant levels. In addition, there is an increasing number of patients taking anticoagulation (ASS, clopidogrel, phenprocoumon) who cannot be biopsied on a timely basis. Interleukin- 6 (IL-6) is a cytokine which is produced by infiltrating cells in the kidney. Its renal expression and urinary excretion has been shown to correlate with acute tubulointerstitial damage. We investigated whether an increase in urinary IL-6 levels predicted an acute rejection.

Methods: We prospectively measured IL-6 levels in urine of 100 patients after kidney transplantation. We investigated two cohorts, 21 consecutive new kidney transplant patients and patients from our outpatient clinic referred for graft dysfunction. Twenty healthy individuals were studied as controls. Urine samples were collected before performing renal biopsy. All new transplant patients received basic immunosuppressive therapy consisting of methylprednisolone, mycophenolic acid, cyclosporine or tacrolimus and induction with basiliximab.

Results: The mean IL-6 concentration in healthy individuals was 2 ± 4 pg/ml. In patients with borderline graft dysfunction the mean IL-6 concentration was 21.4 ± 1.8 pg/ml. Patients with acute rejection showed elevated levels of IL-6 which correlated with rejection severity (Banff Ia 23.9 ± 1.3 pg/ml; Banff Ib 15.3 ± 12.9 pg/ml ; Banff IIa-b, III 363 ± 303 pg/ml. After successful rejection treatment IL-6 concentrations returned towards baseline. In case of therapy resistant rejection ($n = 3$), elevated IL-6 concentrations persisted.

Conclusion: IL-6 in urine is of diagnostic and prognostic value for acute rejections. Elevated urinary IL-6 concentrations are found during episodes of acute rejection. Persisting elevations indicated therapy- resistant rejection, while successful rejection treatment reduced IL-6 concentrations to normal. Determination of urinary IL-6 might aid in the clinical management of patients who cannot be biopsied promptly. We found a negative correlation between the IL-6 concentration and rejection severity. Bacterial and viral infections are known to induce an increase of IL-6 in urine. IL- 6 in urine does allow very early diagnosis of rejection.

0218 LIVER TRANSPLANTATION FOR PRIMARY SCLEROSING CHOLANGITIS: AN ANALYSIS OF MEDICAL AND SURGICAL RISK FACTORS

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Background & Aims: Liver transplantation for primary sclerosing cholangitis (PSC) is the only treatment option with a proven benefit on patient survival. The aim of this study was to analyze risk factors affecting patient's and transplant's long term survival.

Methods: We performed a retrospective chart view of 159 patients who were transplanted for autoimmune liver diseases at three German transplantation centres from 1997 to 2010. A number of 75 patients transplanted for PSC were enrolled. As a control, 52 patients with PBC and 25 patients transplanted for autoimmune hepatitis were included. Kaplan Meier analyses and Cox regression were performed.

Results: The 5-year survival rate for patients transplanted for PSC was 81% as compared to PBC (79%) and AIH (71%). For split liver transplantation ($n = 20$; 84%) the 5-year survival was similar to full organ liver transplantation ($n = 46$; 81%). None of the patients with PSC who received duct-to-duct anastomoses died as compared to a 5-year survival of 65% for patients with choledochojejunostomy ($P = 0.05$). Patients treated with ursodeoxycholic acid post transplantation ($n = 42$; 5-year survival 91%) showed a tendency towards an improved survival as compared to patients without treatment ($n = 23$; 5-year survival 76%). The 5-year graft survival was 71% for PSC, 72% for PBC and 65% for AIH respectively. Duct-to-duct anastomosis was associated with enhanced transplant survival (86% vs. 66%). Recurrence of primary disease was diagnosed in 13% of patients with PSC not affecting patient or graft survival within the observation period.

Conclusions: The 5-year survival of patients transplanted for PSC was similar to that after transplantation for PBC. The type of bile duct anastomosis was identified as a factor that may affect patient and graft survival in patients with PSC.

0219 HOW CAN A 56 HOURS ANHEPATIC PERIOD AFTER FULMINANT GRAFT FAILURE BE BRIDGED TO RE-TRANSPLANTATION?

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Introduction: Fulminant liver failure (FHF), defined as the severe impairment of liver function resulting in coagulopathy and encephalopathy within 2 weeks of the onset of symptoms is associated with high morbidity and mortality. Orthotopic liver transplantation (OLT) is the only therapeutic option of proven benefit. The early postoperative outcome is highly influenced by intensive care treatment.

Case report: We here report a case of a patient with an anhepatic period of 56 hours in between two liver transplants. The patient underwent orthotopic liver transplantation (OLT) due to fulminant liver failure of unknown etiology. Post-transplant the patient developed heparine-induced thrombocytopenia (HIT) with consecutive portal vein thrombosis. This led to a progressive graft failure. Severe multiorgan dysfunction with hemodynamic dysbalance occurred due to the systemic response to excessive and sustained liver cell apoptosis. Hepatectomy and porto-caval shunt was performed as rescue therapy. Complex intensive care was administered including specific therapies of considerable complications (lactate acidosis, cerebral oedema, myocardial infarction, right heart failure) directly or indirectly associated with the end-stage liver failure and serious immunological problems (HIT II, anti-erythrocyte antibodies). The 56-hours lasting anhepatic period was bridged including a 37-hour period of artificial liver support. Finally the patient could be re-transplanted and complete restitution was obtained.

Conclusions: The reported case implicates the importance of sufficient treatment of numerous serious post-transplant complications in ICU to minimize mortality and morbidity. Nonetheless we were able to demonstrate that such treatment strategies effect the outcome positively even in the case of prolonged anhepatic conditions and several complications, including HIT.

0220 PELVIC RECONSTRUCTIVE SURGERIES FOR PELVIC ORGAN PROLAPSE IN FEMALE KIDNEY TRANSPLANT RECIPIENTS

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Purpose: Pelvic organ prolapse in female postmenopausal kidney transplant recipients may be complicated by adverse events affecting the graft function. We present our experience with pelvic reconstructive surgery in renal transplant recipients.

Material and Methods: Pelvic reconstructive surgery was performed in 16 female renal transplant recipients with pelvic organ prolapse with or without stress urinary incontinence. Intra- and postoperative data including medical and surgical history, POP-Q measurements, twenty-four hours PAD-count, quality of life measurements and graft outcome were recorded prospectively. Patients were followed for up to 12 months.

Results: Mean age at surgery was 58.3 ± 7.7 years (50−66 years), and the mean distance to renal transplantation was 54.2 ± 15.1 months (range; 38-123 months). A total of 12 anterior and 4 combined anterior/posterior colporrhaphy procedures were performed. Concomitant suburethral single incision transobturator sling procedure was performed in 8 women. There were no bladder and rectal injuries, no bleeding necessitating transfusion and no case of infections. Pelvic floor testing at follow-up of 12 months postoperatively showed only 4 patients (25%) with stage I vaginal wall prolapse. None of the patients had evidence of de-novo incontinence, synthetic sling infection, erosion or rejection. Further, all women reported an improvement in quality of life as measured by SF-36 questionnaire. Renal graft function remained stable in all patients.

Conclusions: Pelvic reconstructive surgery is feasible for management of pelvic organ prolapse in patients with kidney allograft being under immunosuppression. However, concern about impairment of graft function, infection and wound healing remain important.

0221 RIGHT-SIDED TRANSPERITONEAL HAND-ASSISTED LAPAROSCOPIC DONOR NEPHRECTOMY: IS THERE AN ISSUE WITH THE RENAL VESSELS?

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Objective: Short right renal vessels might complicate kidney transplantation causing traction and difficulties during anastomosis. Single-center prospective comparison of right- and left-sided transperitoneal hand-assisted laparoscopic donor nephrectomy is presented.

Patients and methods: Eighty-two living kidney donors underwent hand-assisted laparoscopic donor nephrectomy (HALDN) between 2003 and 2008. Right-sided HALDN was performed in 46 living kidney donors. The operative technique of right-sided HALDN was modified in order to obtain the maximum length of right renal vessels. Outcome data in donors including quality of life as well as graft outcome in recipients were collected prospectively.

Results: All procedures were completed laparoscopically with no conversion. Mean operative time was 127 min (vs. 138 min in left HALDN, P = 0.08). The mean warm ischemia time was 41 s (vs. 39 s in left HALDN, P = 0.23). There was no renal artery or vein thrombosis in any of the grafts. Mean blood loss was 81 ml (vs. 92 ml in left HALDN, P = 0.09). Hospital discharge was on an average of 3.6 days postoperative. Delayed graft function occurred in two recipients: one in the left group and the other in the right group. One-year graft survival rate was 95% in the left group versus 96.9% in the right group (P = 0.08). Further, no statistically significant difference in serum levels of creatinine was seen between the groups 1 year after the transplantation.
Conclusions: Right HALDN is technically safe and feasible and results in convenient extension of right renal vessels to full length with no increased incidence of vascular thrombosis.

0222 THE IMPACT OF HAND-ASSISTED LAPAROSCOPIC LIVING DONOR NEPHRECTOMY ON DONOR'S QUALITY OF LIFE, EMOTIONAL AND SOCIAL STATE

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Background: The laparoscopic donor nephrectomy has become the procedure of choice for living kidney donation in many centers. We report on donor-related quality of life (QoL) and social state after laparoscopic hand-assisted donor nephrectomy (HALDN) for living donation.
Patients and methods: Between 2003–2007, a total of 42 hand-assisted living donor nephrectomies had been performed at our institution. For evaluation of QoL, structured questionnaire has been mailed to the donors. The questionnaire was created at our center based on a combination of WHOQOL-BREF questionnaire and the 36-item health survey (SF-36) with slight modifications. The QoL scores were compared to data of German healthy population. Mean follow-up time was 2.45 years.
Results: The QoL scores were higher than those of the normal population in all domains. The higher quality of life in donors was independent of time since donation. When asked to rate their health at the time of the questionnaire, 91% rated it as good, very good, or excellent; 6% as fair and 3% as poor. When asked to rate pain around their scar, 91% rated it as mild or absent. 94% of the patients were likely to say they would donate again, if it were possible. For 6% of the patients was the overall experience very stressful.
Conclusions: Laparoscopic hand-assisted donor nephrectomy is safe and the QoL changes and risks after kidney donation are low and comparable to that of the healthy population. Further, HALDN has compared with open donor nephrectomy no negative impact on the transplanted graft function.

0224 POST-TRANSPLANT URINARY RETENTION DUE TO NEUROGENIC HYPOCONTRACTILE BLADDER: SUCCESSFUL IMPLANTATION OF SACRAL NEUROSTIMULATOR IN A KIDNEY TRANSPLANT RECIPIENT

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Impaired bladder emptying and urinary retention due to hypocontractile bladder negatively affect renal function in kidney transplant recipients. Conservative and medical treatment options might have short-term beneficial effects; however, in a substantial number of patients the effectiveness of these therapies is disappointing. Most of the patients end with intermittent self-catheterisation. We present a case of a 61-year-old male patient that presented with symptoms of voiding dysfunction 4 years after kidney transplantation. Sonographic assessment revealed a residual volume of 386 ml. After having a TUR-P procedure for suspected prostate hyperplasia, no change in postmictionary residual volume could be observed. An video-urodynamic evaluation showed a hypocontractile bladder with maximum P_{det} = 23 cmH_2O. Neurologic assessment showed two episodes of herniated vertebral discs in the past patient history. After failure of conservative treatment, indwelling catheterisation was necessary, which resulted in recurrent lower urinary tract infections sand two episodes of transplant PN. The patient was offered sacral neurostimulation (SNM) as a treatment option. During test stimulation, he experienced a striking improvement in voiding dysfunction with residual urinary volumes between 90–120 ml. He then underwent a one-stage implantation of a sacral neurostimulator (Medtronic®) without adverse events. In particular, no infections or rejections have occurred during the first 30 days after the implantation. The maintenance immunosuppression was not interrupted. After 9 months' follow-up, the sonographic residual bladder volume is averagely 75 ml. The results of this report suggest that sacral neurostimulator might be useful in treatment of voiding dysfunction in NTx patients in order to protect the transplant graft from recurrent urinary infections.

0225 SPONTANEOUS KIDNEY GRAFT RUPTURE CAUSED BY SEVERE PYELONEPHRITIS

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Background: Graft rupture is a rare event with only a few cases reported in the literature. We report a case of a 27-years old female with spontaneous covered graft rupture caused by severe pyelonephritis developing 8 days after kidney transplantation (KTX).
Methods: After uneventful living donor KTX using 49 years old graft, immunosuppressive regimen consisted of induction therapy with basiliximab in addition to tacrolimus, mycophenolate mofetil and steroids. Patient received a single-shot antibiotic therapy. Regular primary function with adequate diuresis was seen in the first postoperative days until kidney function suddenly failed with anuria and increasing creatinine at day 4. Duplex and magnetic resonance imaging showed regular perfusion. Kidney biopsy revealed no evidence for rejection, but pyelonephritis. Calculated antibiotic therapy with piperacillin/tazobactam was performed. Eight days after transplantation CT scan due to pain showed a lower pole hematoma. This was followed by immediate surgical revision. Intraoperatively, a covered graft rupture was detected and sutured successfully. The site of diagnostic kidney puncture was centimeters away and not the reason for rupture. Repeated histology demonstrated again fulminant pyelonephritis with significant swelling of the kidney.
Results: After detection of enterococcus faecium in urine, antibiotic therapy with gentamicin and meronem was performed. Within next 6 days renal function normalized. The patient was discharged at day 24 after an uneventful postoperative recovery. 6 month after transplantation serum creatinine is 1.4 mg/dl.
Conclusion: Severe pyleonephritis in KTX may result in life-threatening graft rupture and therefore should be treated consequently as in-patient with microbial sensitivity tested antibiotics.

0226 SUCCESSFUL CASPOFUNGIN THERAPY IN TWO LIVING-DONOR LIVER RECIPIENTS WITH INVASIVE PULMONARY ASPERGILLOSIS

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Invasive pulmonary aspergillosis is a severe complication after liver transplantation and associated with an extremly high mortality. We report on two living-donor liver transplant recipients developing invasive aspergillosis in the same time period.

Case 1: A 50-year old woman underwent rescue right-lobe living-donor liver transplantation (RL-LD-LTx) from her daughter for postoperative liver failure after resection of a liver tumor. The pretransplant course was complicated by aspiration and need for albumin-dialysis. Post transplant, the patient required hemodialysis for acute renal failure, prolonged mechinal ventilation for pneumonia and a reoperation for postoperative bleeding. On pod 7, the pneumonia exacerbated with bilobular manifestation. Diagnosis od probable invasive aspergillosis was recognized by slightly increased serum aspergillus titre 0.53 (norm <0.5). Antimycotic medication was converted from fluconazole prophylaxis to caspofungin therapy. Subsequently, the patient recovered and could be weaned off from mechinal ventiltion after 35 days. Initial immunosuppression consisting of cyclosporine and prednisolone was continued.

Case 2: A 26-year old female patient underwent RL-LD-LTx from her sister due to Budd-Chiari-syndrome. On pod 3, the patient developed pneumonia with bilateral infiltrates. Diagnosis of probable invasive aspergillosis was also recognized by increased systemic aspergillus titre 0.51. The anti-mycotic prophylaxis with fluconazole was switched to caspofungin and the patient was withdrawn from mechanical ventilation after 12 days. Immunosuppression was continued with cyclosporine and prednisolone. Frequent monitoring of aspergillus antigen and titre after LTx allowed early diagnosis and therapy of probable invasive aspergillosis. The conversion from fluconazole to caspofungin was effective in both patients after LD-LTx. Both patients are alive with excellent liver function after a follow-up of 12 months.

0230 HEPATITIS C LIVER TRANSPLANTATION RECIPIENTS WITH ABCG8 AND MDR1 POLYMORPHISMS HAVE A SIGNIFICANTLY HIGHER PREVALENCE OF ADVANCED FIBROSIS

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Background: Hepatitis C Virus (HCV) reinfection after liver transplantation (LT) has a critical influence on graft and patient survival. Hepatic insulin resistance increases expression of the ATP-binding cassette (ABC) transporter G8 implicated in the regulation of cholesterol metabolism as well as the severity of HCV infection. Expression of multidrug resistance (MDR)1 gene expression has been shown to be increased in activated hepatic stellate cells in chronic liver diseases.
Aim: To assess predictive factors of severe HCV recurrence after LT. Methods: We genotyped ABCG8 (C1199A and C1895T) and MDR1 (C3435T) in 165 LT recipients (46 with recurrent hepatitis C after LT, 119 controls transplanted for other liver diseases) by PCR-restriction fragment length polymorphism assay. Uni- and multivariate logistic regression analyses were used to identify predictors of severe HCV recurrence following LT.
Results: Analyses of single nucleotide polymorphisms (SNPs) revealed the following results: ABCG8 exon 8 C1199A (CC 69.1%, CA 29.7%, AA 1.2%), ABCG8 exon 13 C1895T (CC 46.1%, CT 44.2%, TT 9.7%), and MDR1 exon

26 C3435T (CC 22.4%, CT 40%, TT 37.6%). In the univariate analysis ABCG8 C1199C ($P = 0.006$), MDR1 T3435T ($P = 0.03$), presence of type 2 diabetes mellitus ($P = 0.01$), acute rejection episodes ($P = 0.002$), cytomegalovirus infection ($P = 0.005$), lower cholinesterase ($P = 0.0003$), higher direct bilirubin ($P = 0.03$) and aspartate aminotransferase ($P = 0.01$) were identified as predictors of severe HCV recurrence. Independent predictors of severe HCV recurrence included ABCG8 C1199C ($P = 0.01$), MDR1 T3435T ($P = 0.03$), presence of type 2 diabetes mellitus ($P = 0.03$).
Conclusions: HCV LT recipients with ABCG8 and MDR1 polymorphisms have a significantly higher prevalence of advanced fibrosis. Active screening of these mutations may help to predict and to manage severe HCV recurrence in LT recipients.

0231 DONOR AND RECIPIENT BODY MASS INDEX CORRELATE WITH INITIAL KIDNEY GRAFT FUNCTION

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Introduction: Obesity is a worldwide epidemic. The number of overweight renal transplant recipients and cadaveric donors is increasing. We investigated whether donor and/or recipient body mass index correlate with the occurrence of delayed graft function after kidney transplantation.
Patients and Methods: Retrospective analysis of 708 consecutive cadaveric kidney transplants between January 2003 and December 2009. Delayed graft function was defined as requirement for more than one dialysis post-transplant dialysis. Impact of body mass index, gender, age, re-transplant, cold ischemia and anastomosis time on the occurrence of delayed graft function were analyzed using uni- and multivariate analyses.
Results: DGF rate was 25.2%, 29.8%, 40.9% and 52.6% in recipients with a body mass index 30 kg/m2 respectively ($P = 0.0002$). Donor body mass index 30 kg/m2 resulted in a DGF rate of 22.5%, 31.0%, 37.3% and 51.2% ($P < 0.05$)

0232 IS CELL-FREE SOLUTION SUPERIOR TO BLOOD PERFUSION DURING EX-VIVO REPAIR OF DONOR LUNGS?

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Purpose: To evaluate whether ex-vivo reconditioning of donor lungs using cell-free solution (Steen-solution) is superior to erythrocyte-concentrate and Steen-solution.
Methods and Materials: Pig lungs were harvested after Perfadex perfusion (40 ml/kg), cannulated and connected to the basic circuit consisting of centrifugal blood-pump, heparin coated deoxigenator and tubing. Two study groups ($n = 6$ each: I=priming with erythrocyte-concentrate and Steen-solution 1:1, Hb5, 5 mg/dl; II=priming with Steen-Solution) were perfused for 6hrs according to standardized protocol. Perfusion started at 21 C to reach 37 C within 30 minutes, pressure-controlled ventilation started at 32 C ($FiO_2 = 0.5$). Ventilation, gas-exchange, hemodynamics were monitored pre-harvest and hourly during reperfusion. Pre- and post-reperfusion wet-dry ratios were performed, histology evaluated by a semiquantitative score.
Results: All lungs were perfused for 6hrs. Ingr. I two lungs failed transplantability, while only one lung in gr.II did not reach transplantability criteria at study end-point (PDI>3+ standard clinical donor criteria). Compared to gr.I, pulmonary vascular resistance was significantly lower during cell-free perfusion (groupII) after the second hour (736 ± 148 vs. 456 ± 130dynes; gr.I vs. gr.II) until study end-point (1120 ± 380 vs. 570 ± 194dynes). Both groups showed no significant changes in pulmonary compliance (43 ± 7 vs. 45 ± 6 ml/cmH_2O) and pulmonary oxygenation capacity (POC) (349 ± 68 vs. 364 ± 64 mmHg) throughout the study. Pulmonary deflation index (PDI) for macroscopic evaluation during disconnection from the respirator decreased during cell free perfusion until study-endpoint (2.2 ± 0.3 vs. 2.2 ± 0.4 after 30 minutes; 2.4 ± 0.6 vs. 1.4 ± 0.6 after 6hrs). Histology and wet-dry ratio confirmed these results.
Conclusion: Cell-free perfusion did not result in functional benefit of ex-vivo isolated lung perfusion according to gas-exchange and compliance but could significantly reduce PVR and edema formation.

0234 THE CAVAL ANASTOMOSIS TECHNIQUE DOES NOT INFLUENCE THE RENAL FUNCTION AFTER ORTHOTOPIC LIVER TRANSPLANTATION - A GERMAN SINGLE CENTER EXPERIENCE

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Introduction: The piggy-back (PB) technique is supposed to have beneficial on the renal function after orthotopic liver transplantation (OLT) compared to the standard technique (ST) with cross-clamping of the vena cava inferior and without using a veno-venous bypass. This might be explained by a preserved renal perfusion pressure using the PB technique. In this study we present the results of a german single center comparing both techniques of caval anastomosis and their effects on the renal function.
Methods: We performed a retrospective analysis of 71 patients who underwent OLT in the years 2008/09 at our centre. All patients received a full-size graft. Endpoints of our analysis were the creatinine level and the daily urine output after OLT.
Results: 46 patients (65 %) were transplanted using the ST, in 25 patients (35 %) the PB technique was performed. 12 patients in the ST group (26 %) and 6 patients in PB group (24 %) needed continuous renal replacement (CRRT) therapy prior OLT. In both groups, the serum creatinine of the patients without CRRT prior OLT reached its peak value on postoperative day (POD) 4 (ST: 130.5 mmol/l; PB: 134.5 mmol/l; no significant difference). The maximum serum creatinine in patients with CRRT showed also no significant difference between both groups (ST: 151.6 mmol/l; PB: 129.8 mmol/l). The daily urine output showed no significant difference between both groups, regardless of the need of CRRT prior OLT. Interestingly, the CRRT time of the PB treated patients was shorter compared to the ST treated patients if the patients were on CRRT before OLT (ST: 16.6 days; PB: 11.6 days). Patients who needed CRRT after OLT without being on dialysis before transplantation showed no difference between the groups concerning the length of CRRT treatment (ST: 23.1 days; 25.4 days).
Discussion: In the current literature, the PB technique seems to be superior compared to the ST regarding the renal function. Some authors describe the ST as independent risk factor for the development of acute renal failure post-OLT. Our results indicate that there is no difference between the technique of the cava anastomosis and the renal function. So, we use both techniques at our center without identifying the cava anastomosis technique as risk factor for the development of renal dysfunction.

0238 ARFI-BASED TISSUE ELASTICITY QUANTIFICATION AND KIDNEY GRAFT DYSFUNCTION: FIRST CLINICAL EXPERIENCES

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Background and Purpose: Acoustic Radiation Force Impulse Imaging (ARFI) is a new ultrasound-based technology (Siemens Acuson, S2000) for measuring tissue elasticity properties which is integrated into a high-end ultrasound machine. So far no experience has been reported with the evaluation of the new method in renal transplant follow-up. The purpose of this study was to evalue changes in ARFI-measurements between stable renal allografts and biopsy-proved transplant dysfunction.
Methods: We performed 16 serial ultrasound examinations in 8 renal transplant patients in a prospective study. Patients were first examined when presenting with stable allograft function for routine transplant kidney ultrasound. A second follow-up examination was done when patients presented for allograft biopsy and histologic evaluation of transplant dysfunction. All patiens were examined using ARFI-quantification (15 measurements/kidney). Resistive indices (RI) were also calculated on the basis of pulsed-wave Doppler ultrasound and transplant kidney size was measured based on B-mode ultrasound images. All biopsies underwent histological examination by a reference nephro-pathologist who was unaware of the results of the sonographic studies. Pathologic diagnoses were based on biopsy results, also regarding clinical and laboratory findings.Finally we calculated the changes of ARFI-quantification, resistive indices and kidney size on a percentaged basis at these defined times of asessment and compared the results with the final pathologic diagnosis.
Results: Histological results showed five cases of acute T-cell-mediated rejection, one case of calcineurin inhibitor toxicity and two cases of acute tubular necrosis. Calcineurin inhibitor toxicity and acute tubular necrosis were subsumed under other pathologies. Mean ARFI-values showed an average increase of more than 15% percent in transplants with histologically proved acute rejection whereas no increase was seen in transplants with other pathologies. Mean RI values showed no increase neither in the diagnostic group with acute rejection, nor in the group with other pathologies. Kidney size showed a mean absolute increase of 0.5 centimetres in allografts with acute rejection, whereas a mean decrease of only 0.17 centimetres was seen in the group with other pathologies.
Conclusion: As shown before in other studies, RI values and kidney size are of doubtful use in the evaluation of kidney allograft dysfunction. On the contrary, ARFI measurements are a new and promising parameter for evaluating the elasticity of kidney transplants in a follow-up condition. This new parameter might also gain clinical importance as an interesting complementary tool for making the diagnosis of kidney transplant rejection.

0240 POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE AFTER LIVER TRANSPLANTATION IN THE MELD-ERA

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Post-transplant lymphoproliferative disease (PTLD) is a well recognized phenomena after organ transplantation. Epstein-Barr-virus (EBV) and intensified

immunosuppression are associated with the pathogenesis of PTLD. Since the introduction of MELD, liver recipients often receive individualized and mimized immunosuppressive regimens. We therefore analyzed the incidence and type of PTLD in liver recipients at our centre since the introduction of MELD. In the time period from 16.12.2006 until the 31.12.2009 200 liver transplantation (LTx) in 175 patients were performed. The median age of the patients was 40.1 (0.2-75.1) years. In total, 3 out of the 175 patients developed PTLD including two high malignant B-cell lymphoma and one Hodgkin lymphoma. The time points of PTLD detection were 13, 20 and 31 months after LTx. Patient #1 is a 61 year old man liver transplanted due to cryptogenic liver cirrhosis. In a routine follow up control 13 months after transplantation he suffered from intense back pain. A subsequent MRI showed suspicious intramuscular lesions. Performed biopsies detected a centroblastic B-cell Lymphoma classified as a EBV-associated PTLD. Patient #2 is a 39 years old woman receiving orthotopic liver transplantation due to liver cirrhosis based on autoimmune hepatitis. The histology of her original organ detected a hepatocellular carcinoma in segment IV (pT1 pN0 G2 R0). 20 months after transplantation she presented herself in perfect condition in a routine follow up control, however the ultrasound control prompted to hypoechogenic mesenterial lesions. A CT-scan proved the finding and fine needle puncture biopsy led to the diagnosis of a diffuse large B-cell lymphoma without evidence for EBV-relation. Patient #3 is a 21 years old woman with autoimmune hepatitis, she received a living donor organ. 31 months after transplantation she developed abdominal discomfort. A consecutive ultrasound proved multiple intraabdomianl lesions. Histology, gained by surgery, exhibited a mixed cellularity classical Hodgkin lymphoma. 2 PTLD cases out of 3 the primary diagnosis before LTx was an autoimmune hepatitis. In our patient group the incidence of PTLD is 1.7%, in comparison from 3 up to 8% in the common literature.

0243 LIVER TRANSPLANTATION FOR POLYCYSTIC LIVER DISEASE. THE UNIVERSITY HOSPITAL ESSEN EXPERIENCE

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Objective: Polycystic liver disease (PLD), commonly associated with polycystic kidney disease, can result in massive hepatomegaly leading to abdominal distension, pain and debilitating symptoms. Hepatic failure is uncommon. Surgical interventions have been associated with significant morbidity and inconsistent long-term palliation. Liver transplantation (LTX) offers curative treatment, but its relevance as treatment modality is controversy, considering the absence of liver failure, organ shortage, perioperative risks and lifelong immunosuppression. The purpose of this study was to review our experience of LTX for PLD.

Material and Methods: Nineteen adults (16 females and 3 males) underwent LTX for diffuse PLD between 1992 and 2009. Mean age was 45 years. All of the patients had combined liver and kidney disease, but only eight required combined liver and kidney transplantation. Indications for transplantation were massive hepatomegaly, malnutrition, cholestasis and portal-hypertension. Eight patients underwent livermass reduction pre-LTX. Native liver weight was 6–15 Kg. Two patients received a right split liver graft.

Results: One patient who received a split liver graft died intraoperatively of bleeding due to massive portal-hypertension. Three patients died between 4th and 30th postoperative day due to sepsis and multiple-organ-failure. At present eleven patients are alive, relieved of symptoms and with good graft function (follow-up 6 months to 12 years).

Conclusions: Our experience demonstrates that PLD-patients with extensive hepatic involvement treated by LTX have good long-term prognosis and excellent symptoms relief. LTX might be considered in severe PLD-cases und must be balanced against the risks of LTX and lifelong commitment to immunosuppression, where conventional surgery is not a curative option.

0244 RESULTS OF KIDNEY TRANSPLANTATION AFTER RESCUE ALLOCATION

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Introduction: Rescue allocation (RA) applies to kidneys, which were refused by 5 transplant centers because of medical reasons. However these grafts may have acceptable function after transplantation (TX), so that the refusals were unjustified and a cascade effect could be seen. Aim of this study was to evaluate the function graft function after RA and to analyze if the TX of such kidneys is ethically justified.

Methods: The records of all subjects who received a RA-kidney from January 2000 until December 2009 were collected and analyzed retrospectively. Main outcomes were the graft function according to the serum creatinine and the graft survival.

Results: Sixteen kidneys were included. The time on waiting list before RA-kidney transplantation was 30 ± 26 month (range 0–72). Overall 108 refusals were documented, so each kidney was 6.8 ± 2.8 times refused before being offered to our center. The 1-year recipient survival rate was 100%. In 4 of the 16 (25%) allografts an episode of acute rejection was seen, 2 lost their function after 4 and 6 month. 1 kidney was explanted the first day after TX because of venous thrombosis. The mean follow up time was 37 month with a graft survival of 27 month and a 1 year survival rate of 77%. The creatinine values were after 1 month 2.3 ± 1.4 mg/dl, after 6 months 2.0 ± 1.3 mg/dl, after 12 month 2.3 ± 1.4 mg/dl and at study end 2.6 ± 1.4 mg/dl, for the non-rejected after 1 month 2.0 ± 1.0 mg/dl, 6 months 1.8 ± 0.9, 12 months 2.2 ± 1.6 mg/dl and at study end 2.04 ± 0.88 . The differences were not significant ($P \geq 0$, 05).

Conclusion: The graft function after rescue allocation transplantation is acceptable. Recipients with an estimated long time on the waiting list have a benefit of the early transplantation. Patients with immunological risk factors should not receive a rescue allocation kidney.

0245 INTERVENTIONAL THERAPY OF VENA CAVA INFERIOR THROMBOSIS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

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Introduction: Vascular complications involving the inferior vena cava (VCI) after orthotopic liver transplantation (OLT) are rare but potentially life-threatening. Patients with functional occlusion of the VCI may present with distinct edema of the lower extremities, renal insufficiency or even acute liver failure. Reported therapeutic options include angioplasty, reoperation and mandatory ReOLT.

Methods: We here report 2 cases of thrombosis of the VCI in the early postoperative course and their implications for the management of this rare complication in the future. Pat. 1: 54 y, male, OLT for primary sclerosing cholangitis. Pat. 2: 22 y, male, ReOLT for chronic Tx failure after 1st OLT 11 years before due to acute liver failure of unknown cause. Both patients showed above mentioned typical symptoms in the early postoperative course. Thrombosis of the VCI was diagnosed by dopplersonography and CT scan 16 and 28 days post OLT, respectively.

Results: In both cases mechanical catheter fragmentation and local thrombolysis (rTPA) were performed successfully 17 and 29 days postop, respectively. Anticoagulation was achieved with i.v. heparine followed by oral warfarin. Repeated follow up examinations (US, MRI, cavography and CT scan) showed no recurrence of VCI thrombosis.

Conclusions: Complications of the vena cava are infrequent after liver transplantation, but thrombosis of the inferior vena cava represents a serious, potentially life-threatening complication and requires early diagnostic and urgent treatment to avoid graft loss and other unfavorable outcomes. Distinct edema of the lower extremities combined with impaired renal function appearing after OLT may be symptoms of thrombotic occlusion of the inferior vena cava. Dopplersonography is a standard procedure after OLT, but it is up to the examiner to focus not only on arterial, portal and hepatic vein perfusion but also on the VCI perfusion especially in the presence of above mentioned symptoms. Because surgical revision of the VCI is difficult and associated with high morbidity and mortality interventional local thrombolysis and mechanical catheter fragmentation should be discussed as a less invasive alternative.

0249 ACTIVATION OF EXTRACELLULAR SIGNAL REGULATED KINASE PREDICTS OUTCOME IN CADAVERIC RENAL TRANSPLANTATION

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Introduction: Delayed graft function frequently occurs in cadaveric kidney transplantation resulting in decreased long term graft survival. Here we studied activation patterns of mitogen activated protein kinases (MAPK), known to be important mediators of cell death and survival during ischemia and reperfusion.

Methods: Kidney transplantation was done in Lewis rats ($n = 6$) after 12h of cold ischemia time (CIT). Grafts were collected at the end of CIT or 15 minutes after reperfusion. Biopsies of 30 consecutive human cadaveric kidney grafts (CIT 14 hours22 minutes ± 5 hours8 minutes) were taken at the same time-points. Western blot was done using antibodies directed against total and phosphorylated ERK, JNK and p38 MAPK and quantified using ImageJ. eGFR was calculated by MDRD 6. Delayed graft function was defined as the requirement for more than one dialysis.

Results: In rat kidneys, reperfusion was marked by a significant activation of ERK (7.4fold ± 3.5), JNK (3.0fold ± 0.8) and p38 (3.4fold ± 1.6). In human cadaveric kidney grafts a significant increase in ERK (8.3fold ± 6.4), JNK (3.3fold ± 1.8) but not p38 (1.3fold ± 1.2) activation was observed. ERK, but not JNK and p38 activation during reperfusion was associated with significantly lower rates of delayed graft function (27.2% vs. 83.3%, $P = 0.001$) and significantly higher eGFR three years after transplantation when compared to kidneys in which ERK activation was not seen (59.2 ± 26.3 vs. 45.4 ± 19.9 ml/min/1.73m^2, $P < 0.0001$).

Summary: MAPK activation occurs in kidney grafts upon reperfusion. Phosphorylation of ERK during reperfusion is a valuable predictor of kidney graft function, modulation thereof may improve outcome in kidney transplantation.

0251 LONG-TERM OUTCOMES AFTER ORTHOTOPIC LIVER TRANSPLANTATION IN HIV-INFECTED PATIENTS WITH END-STAGE LIVER DISEASE

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Objective: Orthotopic-liver-transplantation (OLT) is the best therapeutic option for end-stage-liver-disease (ESDL). Presence of Human-Immunodeficiency-Virus infection (HIV) used to be viewed as contraindication to transplantation. Advances in highly-active-antiretroviral-therapy (HAART), and effective management and prophylaxis of opportunistic infections, have changed the outcome of HIV-disease. ESLD is increasingly recognized as significant cause of morbidity and mortality among HIV-patients due to liver-related complications of co-infection with Hepatitis-B(HBV) and Hepatitis-C Virus(HCV). The purpose of our study is to describe the long-term outcomes and the management strategies of HIV positive patients with liver failure who undergo OLT.
Material and Methods: Eight HIV-infected patients (6 male, 2 female with age-range 35–61years) underwent OLT between 1996 and 2009. OLT indications were HCV(n = 5), HBV(n = 1), HCV/HBV/HDV-related cirrhosis(n = 1); one presented with acute-liver-failure. At OLT, CD4 cell-counts ranged from 113 to 621 cells/μl, and HIV viral-loads from <50 to 24000 copies / ml. Seven of eight patients were exposed to HAART before OLT. One patient with HBV-cirrhosis had a HCC in the explanded liver.
Results: Patients were followed-up between 1–136 months. Five died 1, 3, 10, 31 and 34 months after OLT due to sepsis and graft-failure respectively. Graft-failure causes were recurrent hepatic-artery thrombosis, HCV-associated hepatitis and chemotherapy-induced liver damage due to Hodgkin-disease. One survivor is relisted for OLT due to chronic HCV-disease but non-progredient HIV-infection. Two other survivors show stable liver function and non-progredient HIV-disease under HAART.
Conclusions: Outcome of OLT in HIV-infected patients and ESLD indicates that OLT is an acceptable therapeutic option in selected patients. Long-term survival can be achieved without HIV-disease progression under antiretroviral therapy.

0254 LIVER TRANSPLANTATION A NEW RISK FACTOR FOR INTESTINAL INTUSSUSCEPTIONS

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Background: Intestinal intussusception in adults is associated with chronic inflammatory bowel disease, coeliac disease, abdominal tumors or previous abdominal surgery but most often of unknown origin.
Aim: To evaluate circumstances and identify risk factors for intussusceptions.
Methods: All 65.928 abdominal ultrasound examinations performed at our tertiary medical center between January 2001 and June 2008 were analysed retrospectively for the diagnosis intussusceptions. After identifying individuals with sonographically proven intussusception we analyzed various patients' characteristics including age, gender and underlying disease as well as sonographic findings such as localization of the intussusception, absence or presence of ascites and lymph nodes.
Results: We identified 32 cases of intussusceptions (mean age 45 years (range 18 to 88); 18 patients were male). Twelve patients (38%) had a history of abdominal surgery including 8 patients who had undergone liver transplantation. A hepaticojejunostomy had been performed in 4 of the liver transplant recipients. Liver transplanted patients were significantly overrepresented in the intussusception group compared with the overall cohort of patients undergoing abdominal ultrasound examination (25% vs. 8%, Chi-Square-test, P = 0.0023).
Conclusions: In our retrospective study liver transplantation, in particular with hepaticojejunostomy, was identified as a major risk factor for intestinal intussusceptions. However, our analyses revealed that in addition to liver transplantation other abdominal surgeries with manipulation of the extrahepatic bilde ducts, particularly Whipple surgery, are associated with an increased risk for the development of intestinal intussusceptions.

0256 POLYOMAVIRUS BK VIRUS VIREMIA, BUT NOT THE INDIVIDUAL PLASMA VIRAL LOAD, IS SUGGESTIVE FOR BK NEPHROPATHY IN RENAL TRANSPLANT RECIPIENTS

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Background: In renal transplant recipients (RTR), reactivation of polyomavirus (BK) can lead to BK-nephropathy, associated with poor allograft graft survival. 30% of RTR are reported to develop BK viremia. But only between 1.1 and 10.3% of RTR biopsy-proven BK-nephropathy. A threshold of 5000 BK copies/ml plasma as viral load has been discussed to start reduction of immunosuppression in RTR with BK viremia to avoid BK nephropathy despite an increased risk for acute rejection.
Methods: RTR were screened routinely for BK viremia by RT-PcR every 3 months. In a retrospective observational study we analyzed the incidence of BK viremia and BK nephropathy as well as the individual viral load in our RTR patient cohort.
Results: Of 688 RTR, tested for BK viremia between 2007 and 2008. BK viremia was found in 67 RTR (9.7 %). The highest individual BK viral load ranged from 7 copies/ml to 17 million copies/ml [<1000 copies/ml (n = 29); 1000 < 10000 copies/ml (n = 16); >10000 copies/ml (n = 22)]. 43 RTR with BK viremia underwent renal graft biopsy. BK-nephropathy was proven in 7 biopsies (16.3 %), one biopsy was suggestive for BK nephropathy. The highest individual BK viral load in those 8 RTR ranged from 12 copies/ml to 1.25 million copies/ml (median 35320) with a copy number<5000/ ml in 4 RTR. In BK viremia positive, but BK nephropathy negative RTR the highest individual viral load ranged from 7 copies/ml to 17 million copies/ml (mean: 741190, median: 5280). In RTR with BK nephropathy individual viral load seemed of little predictive value for graft survival.
Conclusion: Even though the median BK viral load was higher in RTR with BK nephropathy, the individual viral load appeared of little predictive value for BK nephropathy or outcome. Thus BK viremia and clinical course rather than a BK virus load threshold should influence the decision on a patients immunosuppressive regiment.

0257 HIGH INTRAHEPATIC VIRAL LOADS OF HHV6 BUT NEITHER OF CMV NOR EBV ARE ASSOCIATED WITH DECREASED GRAFT SURVIVAL IN LIVER TRANSPLANT RECIPIENTS WITH GRAFT HEPATITIS

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While the influence of CMV infections on graft hepatitis in liver transplant recipients has been investigated in several studies, the role of HHV6 and EBV infections is not well defined in this context. We studied the possible association between intrahepatic levels of HHV-6, EBV and CMV and graft hepatitis, rejection and survival. One hundred and seventy liver transplant recipients who had been biopsied for graft hepatitis were studied. Inclusion criteria were twice above normal results for AST, ALT, bilirubin, AP or gamma-GT. Viral loads of CMV, EBV and HHV6 were determined in blood and liver samples by quantitative PCR. The median time of follow-up after liver biopsy was 23.8 months (range 0–56 months). At least one of these three viruses was detected in 75% of liver biopsies. HHV6 DNA, CMV DNA and EBV DNA were detected in 57%, 13% and 45% of liver samples. High intrahepatic HHV6 DNA levels (> 75% percentile copies/cell) but not CMV and EBV levels were associated with a significant lower graft survival (P = 0.014). Other factors associated with graft loss were HCV-infection, age, elevated AP, bilirubin and gamma-GT. Multivariate analysis confirmed the significance of high intrahepatic HH6 loads for decreased graft survival. As only high intrahepatic HHV6-DNA levels were associated with graft loss, our data may suggest that intrahepatic HHV6 reactivation contributes to graft hepatitis. In contrast, low intrahepatic levels of HHV6 loads are probably associated with HHV6 latency and do not influence graft survival.

0258 BLOODPRESSURE, CHOLESTEROL LEVELS AND RENAL FUNCTION AFTER A SWITCH FROM CYCLOSPORIN TO TACROLIMUS: A 24 MONTHS FOLLOW UP OF 54 RENAL TRANSPLANT RECIPIENTS

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Introduction: Today tacrolimus is considered to be superior to cyclosporine with respect to inducing less hypertension, less worsening of the lipid metabolism and potentially even comprising less nephrotoxicity. Nevertheless it is still unclear under which circumstances a switch from cyclosporine to tacrolimus is advisable.
Method: Three months to 18 years (mean 7) after renal transplantation 54 patients were switched from cyclosporine to tacrolimus. Thereafter, prospectively specified, blood pressure, blood pressure medication, lipid metabolism parameters, lipid-lowering medication and renal function were recorded in a follow up period of 24 months. Mean values finally were analysed using paired student t-Test.
Results: Blood pressure was significant lowered in the course of the study (mean baseline blood pressure 135.4/82.9 mmHg, average fall in systolic as and diastolic values 4 mmHg, P = 0.028). The number of antihypertensive drugs did not rise significantly (3.2 at baseline versus 3.4 at month 24, P = 0.068). There was a significant drop of cholesterol-levels (baseline mean 215.7 mg/dl, average drop 35 mg/dl, P = 0.001; LDL-level-reduction of 10.0 mg/dl, baseline 116.6 mg/dl, P = 0.05) accompanied by a non-significant increase in the rate of patients under lipid-lowering therapy (65% to 71%, P = 0.37). Renal function was stable with a trend to improvement at month 24 (increase of 0.03 mg/dl of reciprocal serum creatinine at the end of the study with a baseline average of 0.60 dl/mg, P = 0.29).
Discussion: From the point of view of hypertension and hypercholesterolemia a switch from cyclosporine to tacrolimus even years after transplantation may be favourable. More over renal function can be stabilized.

0264 ADVANCEMENT OF A BIOLOGICAL VENTRICULAR ASSIST DEVICE (BIO VAD®)

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Background: Engineered pouch-like heart muscle constructs can be applied as heart-embracing cardiac grafts *in vivo* and might be used as biological ventricular assist devices (BioVAD®). Implantation studies showed micro-gaps between the graft and native heart due to a shape mismatch. The incoherence can lead to electrical coupling problems and loss of support force. Here we developed a procedure to create BioVADs individually matched to the recipient heart.
Methods: A cast was created by embedding a rat heart in 2% agarose solution. The negative mold was used to generate an exact silicone rubber copy of the heart. We grew BioVADs from neonatal rat heart cells, collagen type I and serum-containing culture medium according to previously published techniques. Morphological analysis was performed by confocal laser scanning microscopy. Contractile function was assessed under isometric conditions.
Results: A dense network of connexin-43 interconnected cardiomyocytes and an endo-/epicardial surface lining composed of prolylhydroxylasepositive cells was obtained. The engineered tissue beat spontaneously and showed contractile properties of native heart muscle including positive inotropic responses to calcium and isoprenaline.
Conclusion: We have developed a novel casting technology to generate artificial cardiac tissue that is perfectly matched to the recipient heart and exhibits structural and functional properties of native myocardium. Transfer of this technique to the clinic could be done with a 3d printer.

0267 DEVELOPMENT OF A QUESTIONNAIRE ASSESSING MEDICATION ADHERENCE POST TRANSPLANTATION: COMPAD FRAGEBOGEN ZUR MEDIKAMENTENEINNAHME NACH TRANSPLANTATION

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Objective: Medication non-adherence is a major cause of organ dysfunction following transplantation. Reliable and feasible methods to detect and predict non-adherence are lacking. The aim of our study was to develop an evidence-based questionnaire to assess medication adherence in German-speaking transplant patients.
Methods: An expert panel of scientists as well as medical and psychological practitioners (COMPAD group) developed a questionnaire assessing empirically verified risk factors for non-adherence. A scale measuring barriers to medication adherence (Immunosuppressant Therapy Barrier Instrument, ITBS) was forward- and back-translated and incorporated into the questionnaire, which was then pre-tested in liver ($N = 30$) and kidney transplant ($N = 30$) recipients. Item analysis was performed in a sample of $N = 275$ kidney transplant recipients.
Results: The response rate for the pre-test sample was 81%, for the second sample 92%. There were no major concerns regarding acceptance, comprehensibility, or practicability of the questionnaire. Some items were revised according to the results of the analysis. Six items from the original ITBS were deleted following item analysis. The remaining six items showed a satisfying internal consistency (Cronbach's Alpha: 0.80). 6% of the patients reported that they had missed at least one dose of their immunosuppressive medication within the last 14 days. 10% disclosed smoking, and 37% reported experiencing medication-related side-effects.
Conclusions: The COMPAD patient questionnaire is a professionally developed, empirically-based, economic instrument to assess medication adherence in transplant recipients. Further testing will be necessary to assess the questionnaire's validity. A corresponding screening questionnaire for physicians to facilitate detection of non-adherence was also developed.

0268 ASSESSMENT OF DONOR-SPECIFIC ALLOREACTIVITY AND REGULATORY T-CELL FREQUENCY - SUITABILITY IN LIVING DONOR KIDNEY TRANSPLANTATION?

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Aim: To investigate the association of pre-transplant donor-specific alloreactivity and regulatory T-cells (T_{regs}) with acute rejection (AR) following kidney-Tx.
Methods: Pre-transplant blood samples were obtained from all patients ($n = 40$) to isolate peripheral blood mononuclear cells (PBMC). All patients received triple immunosuppression (CNI, MMF, steroids) and participated in the protocol-biopsy program. T-cell alloreactivity was assessed by proliferative responses using mixed lymphocyte culture (MLC): 1×10^5 PBMCs from graft recipients were stimulated with the identical number of irradiated PBMCs from organ donors and HLA matched 3rd-party controls (same number of mismatches as for donor/recipient constellation), respectively. Flow-cytometry was applied to determine the pre-transplant frequency of $CD4^+$ $CD25^+$ $CD127^{low}FoxP3^+$ T_{regs}.
Results: MLC was performed in 36 patients (no adequate 3rd-party in 4 cases). Patients with rejection-free Tx-courses (RF, $n = 21$) showed significantly lower proliferative responses to donor antigen compared to individuals suffering from biopsy-proven borderline findings (BL, $n = 9$) or AR ($n = 6$) (8.594 ± 1.131, 16.216 ± 3.307 and 23.137 ± 2.958 counts per minute, respectively). Intensity of alloreactivity was higher upon stimulation with 3rd-party antigen compared to donor antigen in the RF-group whereas lymphocytes of individuals with AR showed the inverse pattern. Flow-cytometry revealed comparable frequencies of $CD4^+$ $CD25^+$ $FoxP3^+$ T_{regs} for RF ($n = 23$; 5.0 ± 0.4%), BL ($n = 9$; 4.7 ± 0.7%) and AR ($n = 8$; 4.1 ± 0.4% of $CD4^+$ cells). However, within the $CD4^+$ $CD25^+$ $CD127^{low}$ subset a significantly higher expression of FoxP3 was observed in the RF-group compared to patients with AR (52.3 ± 3.2% vs. 40.2 ± 3.3%, $P = 0.038$).
Conclusions: Differences in pre-transplant alloreactivity and FoxP3-expression within the $CD4^+$ $CD25^+$ $CD127^{low}$ subpopulation exist between individuals with rejection-free Tx-courses and patients suffering from AR. Hence, assessment of these parameters might proof useful to further define the individual risk for acute graft rejection.

0273 IMPACT OF INCREASED SERUM FERRITIN CONCENTRATION PRIOR LIVER TRANSPLANTATION ON LONG-TERM SURVIVAL AFTER TRANSPLANTATION

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Introduction: Recently an impact of serum-ferritin (SF) on waiting-list-mortality of candidates for liver transplantation (OLT) was reported. However an elevated SF reflects not only an increased hepatic iron deposition, but also an iron accumulation in extrahepatic sites. Additionally a reduced outcome after OLT of patients with hepatic iron overload in their explanted livers has been described before. We therefore analyzed in a single-center retrospective study the impact of pre-transplant SF on outcome after OLT.
Methods: After exclusion of patients with fulminant liver failure, multiple organ transplantation, living-donor OLT and of 16 patients with a diagnosis of hemochromatosis, all adult patients receiving a first liver allograft between January 1st 2003 and March 30th 2008 were included. A Kaplan-Meier-Survival analysis was performed comparing (log-rank-test) patients with a SF greater/equal or lower than 365 μg/L.
Results: In 328 of 354 patients (92.7%) fulfilling the inclusion criteria, pre-transplant SF was available (61.3% men, mean age 48.8 + -10.9 years, mean calculated MELD 15.1 + -7.3). Major indications for OLT were alcoholic liver disease (20.7%), Hepatitis-C (18%), hepatocellular carcinoma (17.1%), primary sclerosing cholangitis (15.5%) and Hepatitis-B (12.2%). Patients with a SF >=365 μg/L had a worse 1year-survival (73.3% vs 81.1%, $P = 0.109$), a worse 3year survival (64.4% vs. 77.3%, $P = 0.017$) and a reduced overall-survival (61.1% vs. 74.4%, $P = 0.009$, mean follow-up 5.3years). There was no significant difference in overall graft survival.
Discussion: Our data suggest that patients with an elevated SF before OLT have a reduced long-term-survival. So far it is unclear if this impact on survival is a direct effect of an impaired iron homoeostasis, which would then have potential therapeutic consequences.

0274 TETRAHYDROBIOPTERIN (BH4) INCREASES KIDNEY INDOLEAMIN 2–3 DIOXYGENASE (IDO) AND ANELIORATES ISCHEMIA REPERFUSION INJURY

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Purpose: Indoleamin 2,3,dioxygenase (IDO) is a cytosolic enzyme that posses T-cell suppressive and antioxidant properties requiring BH4 as cofactor during its catalytic process. By consuming superoxide anion radicals (O_2*) as a substrate IDO initiates the formation of tryptophan metabolites which themselves act as potent radical scavengers. The role of IDO in IRI, however, is largely unknown.
Materials: Syngeneic Lewis rat kidneys were flushed and stored (120 minutes ± 30 minutes) in ice-cold (4°C) UW solution followed by orthotopic transplantation into bilaterally nephrectomized recipients. Both donors and recipients received BH4 (20mg/kg) prior to organ harvest and transplantation, respectively. Vector treated animals served as controls. Renal function (creatinine/urea), graft morphology (H&E), ROS formation (nitrotyrosine

immunostaining) and IDO activity (IDO immunostaining) was assessed at different timepoints after transplantation.

Results: Ischemia and reperfusion resulted in a significant impairment of kidney function ($P < 0.01$) and increased ROS formation as reflected by nitrotyrosine staining ($P < 0.01$). In parallel intragraft IDO activity was significantly decreased. However, BH4 treatment restored intragraft renal IDO activity after transplantation ($P < 0.05$). Furthermore, BH4 therapy of donor and recipient prior to transplantation significantly improved kidney function parameters and reduced morphologic damage and ROS formation as assessed by H&E and nityrosine-staining.

Conclusion: The present study provides direct evidence that BH4 supplementation maintains IDO activity and thereby protects transplanted kidneys from IRI.

0276 MOUSE HIND LIMB TRANSPLANTATION - A NEW COMPOSITE TISSUE ALLOTRANSPLANTATION (CTA) MODEL UTILIZING NON-SUTURE SUPERMICROSURGERY

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Purpose: Murine hind limb transplantation is an extremely demanding procedure. Since the mouse, however, would be a good model for the study of various CTA-related problems, we designed two new surgical techniques for orthotopic (ORT) and heterotopic (HET) hind limb transplantation.

Methods: BalbC hind limbs were transplanted to BalbC or C57BL6 recipients using a non-suture cuff technique and superfine microforceps for revascularisation. ORT: Donor femoral vessels were anastomosed to recipient femoral vessels, sciatic nerve was approximated end-to-end and osteosynthesis performed using an intramedullary rod. HET/cervical: Donor femoral vessels of a reduced size osteomyocutaneous CTA was anastomosed to recipient common carotid artery and external jugular vein without nerve approximation.

Results: Both (ORT/HET) procedures could be performed with a high success rate (80%). Donor operation lasted 100 ± 12 minutes and recipient operation 114 ± 27 minutes (ORT); 54 ± 16 minutes (HET). Complication rates in terms of bleeding, and thrombosis at the cuff side were comparable for both models. All syngeneic grafts survived long-term (>100 days). FK506 (2 mg/kg) and CTLA4-Ig, treatment was unable to prolong allograft survival (7.5 ± 0.53d and 7 ± 1.20d respectively) compared to untreated controls (6 ± 0.85d). However, high-dose FK506 (5 mg/kg) prolonged graft survival (>30d). H&E stains of HET-grafts showed muscular atrophy and normal skin whereas ORT-grafts revealed unaltered muscle, skin and bone histology. Functional evaluation of ORT grafts by means of walking track analysis and video gait kinematics revealed marked differences in terms of ankle range of motion and angular velocity in transplanted animals as compared to controls ($P < 0.01$).

Conclusion: The ORT hind limb tranplantat model seems to be best suited to study functional outcome and nerve regeneration in CTA. The technically less demanding HET/cervical model may be used to investigate basic immunology and ischemia reperfusion injury in reconstructive transplantation.

0281 EFFECT OF PROTEASOME INHIBITION BY BORTEZOMIB ON HLA-ANTIBODY TITERS AND SPECIFICITY IN SENSITIZED PATIENTS AWAITING RENAL ALLOGRAFT TRANSPLANTATION

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Rationale: Sensitization to human leukocyte antigen (HLA) prolongs waiting list time and reduces allograft survival in organ transplantation. Current antibody depleting strategies include B-cell directed therapy and extracorporeal techniques. Considerable interest has arisen from initial reports using the proteasome inhibitor bortezomib in antibody mediated rejection, in addition to standard therapy. Potential benefits include direct targeting of the antibody producing plasma cell and memory B-cells with alteration of donor specificity. We report bortezomib preconditioning in sensitized patients awaiting transplantation, providing first clinical data on dynamics and donor specificity of preformed HLA antibodies in response to bortezomib alone.

Methods: Two highly sensitized patients awaiting third kidney transplantation were treated with bortezomib (1.3 mg/kg bwt., days 1, 4, 8, 11). Time-course and levels of HLA antibody titers, as well as specificity to previous transplant antigens were monitored weekly by luminex.

Results: Bortezomib was well tolerated without side effects. In all patients, changes in IgG levels were small and no sustained reduction in HLA class I or II antibody titers was observed following bortezomib preconditioning over more than 100 days of follow-up. No differences among antibody responses to donor specific and non-donor specific antigens were oberserved.

Conclusion: Bortezomib preconditioning alone does not result in sustained reduction of HLA antibody titres in sensitized patients. Also, no change in specificity of antibody production was observed over a period of time clearly exceeding half-life of preformed IgG HLA antibodies. Hence, in a pretransplant setting, combination immunosuppressive strategies are required to obtain benefit from proteasome inhibition.

0282 EFFECTS OF DIFFERENT IMMUNOSUPPRESSIVE REGIMES ON LYMPHOCYTE SUBPOPULATIONS IN PERIPHERAL BLOOD AFTER ABO INCOMPATIBLE (ABO*I*) AND ABO COMPATIBLE (ABO*C*) KIDNEY TRANSPLANTATION (KTX) M.STRECKER, F. THAISS, B. NASHAN M. KOCH

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To increase the number of donor kidneys ABOi KTx has been established. The immunosuppressive (IS) regimen in Hamburg includes: low dose CNI, everolimus, steroids, praeoperative rituximab, immunoadsorbtion, basiliximab and thymoglobulin for induction. We analyzed lymphocyte subpopulations of peripheral blood in 10 ABOi patients by flow cytometry.15 ABOc transplanted patients receiving IS with basiliximab, CNI, MPA and steroids served as controls. FACS analyses were done before application of rituximab (ABOi only), prae IS, 1, 2, 4 and 12 weeks and 1 year after KTx. We quantified total lymphocytes, relative and absolute numbers of CD3+/CD4+/CD8+ T-lymphocytes, of T-regs (CD4+/FoxP3/CD25+) and of B-lymphocytes (CD19/CD20). Whereas prior IS lymphocyte counts in both groups were equal, numbers of CD3+/CD4+, CD3+/CD8+, CD4+/CD25b+ and CD4+/FoxP3+ T-lymphocytes in ABOi patients were clearly reduced 1 month post KTx. T-cells in ABOi patients were still reduced 1 year post OP (especially CD4+/FoxP3+-cells). CD19+/20+-cells were almost completely depleted (<1.3%) in 4/5 Patients 1 year after KTx, compared to 7.4% in ABOc patients. Considerable reduction of T-cells until 1 month post KTx is an effect of thymoglobulin induction. It needs to be determined if long term reduction of T-cells in ABOi group is caused by different maintenance IS or still due to thymoglobulin. A single application of rituximab (375 mg/m^2) leads to long term elimination of B-cells from peripheral blood for at least one year post KTx. Our results demonstrate a persistent long term modulation of lymphocyte subsets in peripheral blood with a new IS protocol used in ABOi KTx.

0283 1 YEAR FOLLOW UP OF ABOC AND ABOI LIVING RELATED KIDNEY TRANSPLANTATION: A CASE-CONTROL STUDY

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Due to increasing waiting time for deceased organ allografts and favorable long term results living-donor kidney transplantation has been globally adopted as the most effective therapy for patients with advanced kidney disease.

Methods: The aim of this retrospective case-control single center study was to compare an ABO compatible (ABOc) and an ABO incompatible (ABOi) transplanted group of patients by evaluating patient and graft survival, as well as renal function 1 year after transplantation. We defined both groups consisting of 8 patients by matching time point of transplantation, age, primary renal disease and number of retransplantations. Immunosuppressive therapy in the ABOc group consists of Basiliximab, calcineurin inhibitor(CNI), MMF/MPA and prednisone, in the ABOi group of Rituximab, Basiliximab and ATG induction, CNI, Everolimus and prednisone and immunoadsorption procedures and ivIg prior to transplantation.

Results: At time of discharge all grafts were functioning with a s-creatinine of 1.3 mg/dL in the ABOi group and 1.3 mg/dL in the ABOc group. One-year patient and graft survival did not significantly differ between both groups. The patient survival after one year was 100% in both groups with a 100% graft survival in the ABOi group and 7/8 grafts in the ABOc group. One patient lost his graft due to chronic dysfunction 11 month after Tx. The average creatinine at 1 year in the ABOi group was 1.7 mg/dL and in the ABOc group 1.4 mg/dL.

Conclusion: Patient and graft survival after one year were comparable between the groups using the different immunosuppressive regimens described. ABOi kidney transplantation with this newly described immunosuppressive protocol therefore is a safe and effective treatment in the long term follow-up for patients without the option of blood group compatible living kidney donation.

0284 SUBSETS OF CXCR3-EXPRESSING HUMAN CD4+ T CELLS EXERT IMMUNOREGULATORY FUNCTION

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$CD4^+$ $CD25^{hi}$ T regulatory cells (Tregs) play an important role in the suppression of immune responses to alloantigens and the development of transplantation tolerance. Recent studies have demonstrated that the expansion of this subset *in vivo* is associated the suppression of immune responses

to alloantigens, and that Tregs may modulate allograft rejection through selective migration into the graft. Several T cell chemoattractant chemokines including the CXCR3 ligands CXCL-9, -10 and 11 are expressed in allografts at early and late times post transplantation. In this study, we have identified a subset of circulating human FOXP3^{+} CD25^{hi} CD4^{+} T cells that express the peripheral chemokine receptor CXCR3 (~30–40%, $n = 20$). Furthermore, CXCR3 expression is induced on CXCR3^{neg} Tregs following mitogen-dependent activation (upto 40%, $n = 3$). *In vitro*, we find that CXCR3-depleted CD4+ responder cells exhibit significantly higher proliferation, as well as higher IFNg (2 to 3-fold) and IL-2 production (~5-fold) vs. undepleted cells in the MLR and in mitogen-induced assays. These findings indicate that this subset of circulating T cells are phenotypically and functional immunoregulatory. The majority of this subset was also found to co-express the Treg associated molecules CTLA4 or CD39. Additional characterization by four color FACS staining revealed that ~85% of CD25+ CXCR3+FOXP3+ Tregs co-express CD62Lhigh ($n = 5$), ~47% express CCR7 ($n = 5$), and ~61% co-express CCR5 ($n = 5$) likely enabling these cells to traffick to lymph nodes and the periphery. To evaluate the effect of immunosuppressants on peripheral homing Tregs, we first treated CD4+ T cells with anti-CD3/CD28 and rapamycin (1 or 10 ng/ml) or CsA (0.1 or 1 ug/ml). Rapamycin treatment resulted in an expansion of CD4+ CD25+ CXCR3+ FOXP3+ Tregs vs. untreated controls, or cells treated with CsA. Collectively, these studies indicate that functionally immunoregulatory CD4+ CD25+ FOXP3+ T cells express significant levels of CXCR3 and that CXCR3 is upregulated on CXCR3- Tregs after mitogen activation suggesting that CXCR3 may function to facilitate Treg trafficking at peripheral sites of inflammation. We further suggest that the selective expansion of peripheral homing CXCR3 populations of Tregs will optimize tolerance induction by enabling Treg homing into the graft.

0285 LOW DOSE ATG (THYMOGLOBULIN) INDUCTION FOR OLDER KIDNEY TRANSPLANT RECIPIENTS ("OLD FOR OLD''), SINGLE CENTRE EXPERIENCE OVER 4 YEARS

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There is increasing evidence that older kidney transplant recipients who receive an organ from an old donor (old for old or ESP transplantation in the Eurotransplant region) have a potent early immune response possibly leading to an increased number of rejection episodes. On the other hand risk of lymphoma due to induction therapy is small as residual life expectancy in this kidney transplant recipients is limited. Therefore we started in 2006 with an low dose ATG induction protocol for our older kidney transplant recipients. Here we present our preliminary data on graft function and patient survival in comparison to the patient of the same time period who were transplanted after living donation (LD) or the regular Eurotransplant allocation program (ETKAS). Between January 2006 and December 2009 we have done 306 kidney transplantations at our centre: 58 (19 %) ESP, 76 (25%) after LD transplantation and 172 (56 %) after ETKAS allocation. Seven of the LD transplantations have been AB0 incompatible. The induction protocol utilized 3.5 mg / kg body weight ATG divided in two doses on day 1 and 2, cyclosporine 3 mg/kg body weight per day, mycofenolat mofetil 1000 mg bid and methylprednisolon (500 mg - 250 mg - 125 mg, day 1–3, 20 mg qd subsequently reduced to 6 mg qd).

Conclusion: Old for old transplantation utilizing a low-dose ATG induction protocol is safe and successful regarding patient and graft survival and function at least in the short term follow up period.

0286 BONE METABOLISM AND FIBROBLAST GROWTH FACTOR 23 (FGF23) AFTER PEDIATRIC RENAL TRANSPLANTATION (PRT)

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Background: FGF23 is a circulating factor that regulates renal reabsorption of phosphate and inhibits calcitriol synthesis. After renal transplantation FGF23 seems to induce hypophosphatemia due to renal phosphorus wasting. Data on FGF23 in children, especially after PRT, are scarce, thus we performed a cross-sectional analysis in pediatric patients.

Methods: Intact FGF23 and other biochemical parameter of bone metabolism were analyzed in 62 children after PRT and 11 age matched controls. Estimated GFR (eGFR) of transplanted patients ranged from 15–204 ml/minutes/1.73 qm. Median time after transplantation was 40 months (range 5–135).

Results: Mean (±SE) Serum FGF23 and PTH levels after PRT were significantly increased compared to controls (FGF23: 142 ± 28 pg/ml vs. 43 ± 3 pg/ml, $P = 0.001$; PTH: 177 ± 39 ng/l vs. 74 ± 18 ng/l, $P = 0.003$). The increase of FGF23 was more prominent in transplanted children with an eGFR below 60 ml/minutes/1.73 qm compared to those with eGFR more than 60 ml/min/1.73qm (FGF23: 268 ± 64 pg/ml vs. 62 ± 4 pg/ml, $P < 0.001$). PRT patients showed a significant inverse correlation between serum FGF23 and eGFR (r = -0.45, $P < 0.0001$). Additionally serum FGF23 closely correlated with PTH levels (r = 0.69, $P < 0.0001$). No correlation between FGF23 and serum phosphate levels was found for all patients. 9 patients (14.5%) showed a persistent hypophosphatemia within the first months after PRT (14 ± 7 months) according to KDOQI-criteria. A correlation of phosphate levels and tubular phosphate reabsorption (TPR) was found (r = 0.78, $P = 0.012$). In contrast to PTH, FGF23 showed a borderline correlation with TPR (r=–0.66, $P = 0.53$).

Conclusions: These first data in children after PRT indicate a significant increase of FGF23, especially in patients with chronic allograft nephropathy (CAN). Further studies on the impact of FGF23 on hypophosphatemia in the early post operative period are necessary. Taken together, FGF23 seems to be a key regulator with dual effect on calcium-phosphate homeostasis after renal transplantation, both early after PRT and in CAN.

0287 CHIMERISM STUDIES AND APPLICATION OF INFLIXIMAB IN A LIVER RECIPIENT WITH ACUTE GRAFT-VERSUS-HOST DISEASE POST LIVER TRANSPLANTATION MASKED BY CMV ENTERITIS

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Introduction: Acute graft-versus-host disease (GVHD) is a rare complication after liver transplantation. Its correct diagnosis and proper treatment remains challenge.

Case report: A 60-year-old man (alcohol liver cirrhosis and hepatocellular carcinoma) was readmitted 3 months after liver transplantation in septic shock with florid watery diarrhea and obvious skin rash over the limbs and trunk. The colonoscopy and skin biopsy did not suggest GVHD. Cytomegalovirus (CMV) enteritis was confirmed by histology and PCR study. Beside broad-spectrum antibiotics and antimycotics due to bacteremia and viremia, the immnuosuppression therapy was maintained with prednisone (10 mg/day) alone. The progressive CMV enteritis and leucopenia under ganciclovir led to application of CMV-immunoglobulin and switch to foscavir from the 4th week. However, panenterocolitis persisted with progression to the small bowel at the 5th weeks. A bone marrow biopsy was performed. It showed a reactivation of CD3 positive T lymphocytes. In the FACS analysis of the peripheral blood, high portion of T lymphocytes, with 5–10% donor specific T-cells, was identified. These features were suggestive for the diagnosis of acute GVHD. From the 6th week after the admission, the immunosuppression was carried out with high dose of steroid and normal range of tacrolimus. No improvement was seen. Anti-TNF-alpha antibody (Infliximab 10 mg/kg body weight) was given at the 9th week. Forty-eight hours after the onset of infliximab therapy, we noted the disappearance of the skin rash and slight improvement of mucosa regeneration in the colonoscopy. However, the clinical course was complicated by angioinvasive pulmonary aspergillus with multi-organ failure, which led to the death at the 11th week after readmission.

Conclusion: Chimerism studies should be initiated early for diagnosis of GVHD. Recovery of GVHD-induced bowel damage following infliximab can be achieved.

0288 SUCCESSFUL COMBINED ATRIUM-LIVER TRANSPLANTATION FOR BUDD-CHIARI SYNDROME: CASE REPORT

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Introduction: We report a case of liver and partial atrium transplantation for a patient with Budd-Chiari syndrome (BCS), who underwent a hepatoatrial anastomosis with intend to resolve the hepatic venous outflow obstruction but developed acute liver failure. Case report Hepatic venous occlusion disease unknown aetiology led to BCS in a 17-year old woman. At the age of 20 she underwent a hepatoatrial shunt operation with partial liver resection and later on the inferior vena cava stenting. Despite of anticoagulation the hepatic vein thrombosed and the patient developed compensatory hypertrophy of segment 1. At the age of 46, she presented to us in an acute liver failure with occlusion of segment 1 hepatic veins in CT scan. Additionally polycythemia vera (PCV) was suspected. The patient was listed for liver transplantation as high urgency request. The organ procurement involved a liver and heart en-bloc harvesting. The transplantation was performed under hypothermia to 22 °C with extracorporeal circulation. The native liver, right atrium and partial inferior vena cava was removed under complete cardiopulmonary arrest. The implantation was uneventful. The initial liver function was good. A long ICU stay was necessary because of respiratory failure, catheter sepsis, fungal urinary tract infections and psychosis. Because of portal vein hyperperfusion syndrome due to splenomegaly she underwent a splenic artery embolisation on postoperative day (POD) 17. No clinical improvement was found. A splenectomy was then performed on POD 27. The further clinical course was uneventful. The patient was discharged on POM 4 in good general condition with Tacrolimus as immunosuppressant and hydroxycarbamide with aspirin for therapy of polycythemia vera. Conclusion Despite of successful atrium-liver transplantation in this complicated case, caution should be taken to performed hepatoatrial anastomosis for BCS. Early diagnosis of PCV and accordingly treatment might avoid transplantation.

0290 OUTCOME FOLLOWING EARLY AND LATE LIVER RETRANSPLANTATION IN CHILDREN

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Introduction: In case of acute or chronic liver graft failure retransplantation (re-LTX) remains the only option. However, due to the increasing organ shortage and the postulated inferior outcome following adult re-LTX this procedure is controversial. Up to date there are few data available regarding re-LTX in children.

Methods: We analyzed all pediatric LTX at our institution between 2000 and 2008 with special regard to re-LTX. Patients were divided early (≤30 days) and late (>30 days) re-LTX and compared to children with first LTX.

Results: Overall 332 children (median age 1.8 years, range 0–16 years, 171 male, 161 female) underwent LTX, thereof 265 patients primary LTX (80%) and 67 patients re-LTX (20%; first re-LTX $n = 51$, second re-LTX $n = 13$, third re-LTX $n = 3$). The re-LTX rate showed a clear increase over the years from 15% (2000) to 35% (2008). 28 children underwent early re-LTX (median 5 days after previous LTX, range 1–28 days) and 39 children underwent late re-LTX (median 2.3 years after previous LTX, range 0.3–15 years). Causes for early re-LTX were primary non function ($n = 18$) and vascular complications ($n = 12$), for late re-LTX chronic rejection ($n = 31$), vascular complications ($n = 4$) and other ($n = 4$). Patient survival was significantly worse for children undergoing early re-LTX compared to primary LTX and late re-LTX (Log Rank test P = 0.014 and P = 0.016, respectively). In contrast, patient survival for children with primary LTX and late re-LTX was comparable. 1- and 5-year patient survival rates were 99% and 93% for primary LTX, 100% and 97% for late re-LTX and 85% and 79% for early re-LTX. Also, graft survival was significant worse in children with early re-LTX compared to primary LTX and late re-LTX (Log Rank test P = 0.001 and P = 0.033, respectively), but comparable in primary LTX and late re-LTX. 1- and 5-year graft survival rates were 86%/76% (primary LTX), 90%/73% (late re-LTX) and 67%/43% (early re-LTX).

Conclusion: In our children we found an excellent and comparable graft and patient survival for primary LTX and late re-LTX, supporting liver retransplantation in case of liver graft failure. Early re-LTX showed an increased risk especially of early graft loss and patient death, however after the initial postoperative phase outcome remains comparable to primary LTX and late re-LTX.

0293 RAPID STEROID-TAPER AND DE-NOVO-LOW-DOSE-IMMUNOSUPPRESSION WITH TACROLIMUS AND EVEROLIMUS IN PATIENTS WITH SPK

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Introduction: We here report nine consecutive patients, who underwent simultaneous Pancreas-Kidney Transplantation (SPK) in 2009 and 2010 due to insulin dependent diabetes mellitus with diabetic nephropathy. The standard immunosuppressive regimes have different side effects which may deteriorate the outcome of these patients. For that reason we introduced a new immunosuppressive regime with rapid steroid taper and de-novo immunosuppression with low-dose Tarcolimus and Everolimus.

Patients: Nine consecutive patients with SPK received an induction therapy with Thymoglobulin (2 mg/kgBW), standard dose Basiliximab, low-dose Tacrolimus (target level 3–8 ng/ml) and Everolimus (target level 3–5 ng/ml) in combination with rapid steroid taper (stop within 8 days). In general patients received CMV prophylaxis for three months and PJ prophylaxis for 6 months.

Results: Nine patients underwent SPK and were treated with the above described regime. Two recipients received their 2nd SPK due to chronic graft failure respectively primary non-function/pancreatitis. One patient received preoperative Rituximab due to historic donor-specific antibodies (DSA) and positive cross-matches, the actual cross-match was negative. All patients had initial pancreas function, while one patient had a delayed graft function of the kidney. No BPAR was seen. All Patients were discharged with functioning grafts and are insulin free with good renal function (mean Creatinin 1.19 mg/dl ± 0.53 mg/dl) 30 to 356 days post transplant. All but one patient were tapered off steroids by day 8. Neither wound healing issues nor opportunistic infections were observed.

Conclusions: The immunosuppressive regime in a steroid free setting with low dose Tacrolimus and Everolimus in combination with induction therapy is assumed to be safe and effective.

0294 LIVER TRANSPLANTATION IN PATIENTS WITH LAB-MELD > 30: EXCELLENT RESULTS IN 54 PATIENTS AT UKT

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Background: Since its introduction in ET Area 2007, the MELD system showed dramatic side effects:

-only slight decrease of mortality on waiting list

-need of very high Lab-MELD score (actually 38 at UKT) to get organs via standard allocation

-Lab-MELD > 30 is associated with high rate of postop. Mortality (> 40% according to recent BQS data)

Aim: Single centre analysis of 54 patients with Lab-MELD Score > 30 undergoing LT at UKT.

Patientd & Methods: Retrospective analyses of 54 consecutive LT in pts with Lab-MELD ≥30 from Jan. 2007 to May 2010. Pts were divided in Group A (MELD 30–35) and B (MELD 36–40).

Results: The detailed results are repored in Table 1. Shortly: mainly young recipients, very sick (MELD mostly 35 and 40), receiving good livers (including Split-grafts (!)), requiring huge amounts of blood transfusions, long ICU- and hospital stay, BUT, very low early and late mortality rates (4% and 4% in Gr. A, 7.5% and 7.5% in Gr. B respectively).

Discussion: Through an accurate patients' selection and accurate perioperative management, excellent results can be reached in pts. with MELD scores > 30 too.

0295 IMMUNADSORPTION WITH PROTEIN A AND ORAL GALACTOSE THERAPY IN RECURRENT FOCAL SEGMENTAL GLOMERULOSCLEROSIS AFTER RENAL TRANSPLANTATION

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Introduction: We describe a case of a 41 - year - old patient with a proteinuria of 2.8 g/d one year after kidney transplantation (second transplant). Focal segmental glomerulosclerosis (FSGS) was the cause of end-stage-renal disease. The first kidney transplantation was performed in 2003 and was followed by graft loss after 5 years. A kidney biopsy showed recurrent focal segmental glomerulosclerosis. FSGS recurs after transplantation in about 30% and is associated with a circulating FS permeability factor (FSPF). This factor is supposed to consist of an anionic low molecular weight protein, which probably is inactivated by galactose.

Methods: We performed one plasmapheresis and six sessions of immunadsorption (IADS) with a reusable protein a column. In addition oral therapy with 15 g galactose twice a day was initiated.

Results: Proteinuria decreased from 2.8 g/day to 0.3 g/day. The level of serum creatinine remained constant during treatment. The IADS and the oral galactose therapy was well tolerated by our patient. We continued oral galactose as a remaining therapy with 15 g twice a day. Additional sessions of IADS can be performed in case of recurrence of a proteinuria.

Conclusion: IADS with a protein a column in combination with oral galactose therapy is an effective method to reduce proteinuria in recurrent FSGS after kidney transplantation. Probably the elimination of a circulating FS permeability factor plays an important role. We suggest to treat cases of relapsing FSGS following renal transplantation with a combination of IADS (with protein A column) and an oral galactose therapy.

0296 GENETICAL ANALYSIS OF THE BINDING SITES OF POLYCLONAL ANTITHYMOCYTE GLOBULINS (ATGS)

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Background: Polyclonal anti-thymocyte immunoglobulins (ATGs) are a group of immunosuppressive agents widely used in the prevention and treatment of acute rejection after organ transplantation, conditioning regimens for bone marrow transplantation as well as treatment for hematologic disorders. ATGs have been found to posses various mechanisms of action, mainly involving interaction and modulation of leukocytes, lymphocytes, and adhesion molecules. Although widely used, little about their exact composition is known. It was our aim to investigate putative binding partners of ATGs in an attempt to determine specific proteins and pathways of actions responsible for the above described effects.

Material and Methods: The whole ATG and the Fab fraction of the ATG probe were analyzed on four high-density protein MACROarray AS-40.000 (Protagen, Dortmund, Germany) which comprises 40.000 clones expressing recombinant proteins. Expression products for ATG and Fab were determined and the intersection of both samples was identified. Clones were cultivated and 5'-tag sequencing was performed. The obtained DNA sequences were translated into proteins. In addition, all proteins and protein fragments were immobilized onto customized UNIchips to validate specificity of ATG and Fab probe. Following the image analysis the mean signal intensity was determined for each protein feature and compared with the negative controls. Only those

proteins were considered as significant which had factor 2 higher signal intensities in comparison to control.
Results: ATG and Fab gave a very high background signal not observed for other immunoglobulin mixtures such as human serum. The negative control based on the secondary antibody led to a high number of detected proteins. In total, the clones detected on MACROarray AS-40000 by the ATG probe accounted for 480 expression products, while the Fab probe recognized 99 expression products respectively. The overlap for both probes consisted of 63 clones which were analyzed by DNA 5'-tag sequencing and translated into 60 proteins, which included TNF-alpha related proteins, different cadherins, caspases and other immunological active proteins.
Discussion: Despite the use of ATGs for over 30 years pre-, intra- and postoperatively in solid organ transplantation, the understanding of their exact composition still remains rudimentary. In this study we describe the binding partners of polyclonal ATGs. These findings may open up new perspectives regarding the potential use of ATGs for immunological modulation.

0297 MODULATION OF ADIPONECTIN, A CARDIOVASCULAR HORMONE, IN THE MYOCARDIUM OF PATIENTS WITH CHRONIC HEART FAILURE

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Introduction: Adiponectin is an anti-inflammatory fat-derived adipocytokine that plays a fundamental role in energy homeostasis. Recent data indicate the existence of a local cardiac adiponectin system, which may be modulated in chronic heart failure. Our aim was to determine whether CHF is associated with changes in expression and distribution of adiponectin and its receptors in human myocardium.
Material and Methods: Expression of adiponectin and its receptors (AdipoR1; AdipoR2) was assessed by means of real-time PCR and immunohistochemistry on myocardium of patients with CHF undergoing heart transplantation. All patients gave informed consent. Biopsies ($n = 40$) of the explanted hearts were obtained and divided according to the anatomical origin (Left & Right Ventricle, Atrium). A control group consisting of heart muscle biopsies ($n = 8$) from autopsies of heart-healthy subjects was designed. The results are expressed by mean + SEM.
Results: Expression of Adiponectin was significantly downregulated in myocardium of patients with CHF in comparison to the control group (2.9 + 1.2 vs. 3.5 + 0.5; $P < 0.05$). Expression of the Adiponectin receptors was significantly increased in the ventricles of patients presenting with CHF in comparison to the control hearts (AdipoR1: 7.5 + 0.9 vs. 2.25 + 0.83; AdipoR2: 6.5 + 0.9 vs. 1.75 + 0.4; $P < 0.05$).
Conclusions: These data indicate the existence of a local cardiac adiponectin system and its modulation in CHF. Expression of myocardial Adiponectin and its receptors is directly associated with myocardial function: CHF hearts exhibit an impaired adiponectin production and an -probably compensatory- increase in Adipo-R1, and AdipoR2 expression. Our data support the therapeutic potential of adiponectin signalling as a target for the treatment of heart failure.

0299 THYMOGLOBULIN INDUCTION IN LIVING DONOR KIDNEY TRANSPLANT RECIPIENTS

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Backround: The benefit versus safety of induction therapy in live-donor kidney transplant recipients is controversial.
Methods: This retrospective study assessed the efficacy and tolerability of a single-shot thymoglobulin induction (1.5mg/kg/BW) in 91 living donor kidney transplant recipients transplanted between 07/2002–12/2009 with an initial regimen of tacrolimus, mycophenolate mofetil and steroids. Patient- and graft survival, acute rejection incidence, delayed graft function rate and infectious complications as well as malignancies were evaluated.
Results: Analysis included 91 patients (53 related, 38 unrelated) with a mean age of 46.9 ± 13.3 years. 74(82%) recipients already started dialysis therapy before transplantation. Mean donor age was 48.4 ± 10.8 years. Induction therapy was well tolerated in all patients.1-year patient- and death censored graft survival were 97.8% and 95.6% and 97.8% / 93.4% after a mean follow up of 51.2 ± 29.4 months. Two Pat. died on postoperative day 2 and 43 (myocardial infarction $n = 1$, sepsis $n = 1$). Delayed graft function was observed in 6.6% of cases. Rejection rate after 1 year was 24.1%. Concerning rejection episodes, there was no statistically significant difference found between the related (17%) and the unrelated group (35%) ($P = 0.08$). Six patients lost their graft function (rejection $n = 1$, incompliance $n = 1$, venous graft thrombosis $n = 3$, recurrence of IgA nephropathy. The rates of CMV infection (8.8%), polyoma nephropathy (5.5%), malignancy (3%), and lymphoproliferative disorder (0%) were low.
Conclusion: In our experience, thymoglobulin is an effective and well tolerated option for the prevention of acute rejection in living donor kidney transplantation, resulting in good patient- and graft survival.

0300 HIGH INCIDENCE OF HEPARIN-INDUCED THROMBOCYTOPENIA IN LIVER-TRANSPLANT RECIPIENTS

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Aim: The factors associated with a high incidence (33%) of Heparin-induced Thrombocytopenia (HIT) in 48 consecutive patients who underwent liver transplantation at our institution between June 2007 and September 2009 were investigated.
Methods: In 16 of the 23 patients with suspected HIT the diagnosis could be confirmed by HIPA-assay. 37 clinical variables were retrospectively analyzed for their association with the development of HIT after liver transplantation using the Mann-Whitney U-test, the Student t-test or the χ^2-test where appropriate. Factors that were significantly correlated to the development of HIT in univariate analysis were included in a multivariate model and binary logistic regression analysis was performed. For the factor that was found to be an independent predictor of HIT in the multivariate model a cutoff was calculated using multiple χ^2-testing.
Results: Patient age ($P < 0.001$), underlying alcoholic liver cirrhosis ($P = 0.026$) and postoperative hospital stay ($P = 0.007$) were the only parameters significantly associated with the development of HIT in univariate analysis. When these factors were analyzed for their independent association with HIT-development, alcoholic liver cirrhosis and postoperative hospital stay turned out as epiphenomena of patient age, which was found to be the only independent predictor ($P = 0.028$) of perioperative HIT-development in patients undergoing liver transplantation. By multiple χ^2-testing a cutoff could be calculated, separating the patient population into a high- and low-risk group. Hereby patients younger than 60 years could be assigned to the low-risk group, while patients of 60 years and older had a higher risk of developing HIT.
Conclusion: The observed high incidence of perioperative HIT in liver-transplant candidates was not associated with factors that could be imagined to induce thrombocyte activation, like the use of blood products, cell-saver or perioperative hemodialysis. Only patient age could be identified as independent predictor of HIT-development in these patients.

0304 KIDNEY TRANSPLANTATION IN PREVIOUS HEART TRANSPLANTAT RECIPIENTS

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Backround: Chronic renal failure belongs to the most important comorbidities after heart transplantation, associated with increased morbidity. Pretransplant low cardiac output and toxicity of calcineurin inhibitors contribute relevantly to the development of end-stage renal disease.
Methods: Between 2004 and 2009 we performed 6 kidney after heart transplantations at our institution. In a retrospective study based on patients medical records following parameters were analyzed : age, cause of kidney failure, duration of hemodialysis, patient- and graft survival, graft function, postoperative hospital stay and complications.
Results: Patient- and graft survival were 100% after a mean follow up of 31.2 months. The mean length of time between heart and kidney transplant was 10.7 years. Postoperative hospital stay (median 30 days), blood creatinin level (median 132.6 μmol/l) representing graft function and occurence of complications were comparable with the results of patients who underwent kidney transplantation alone.
Conclusion: In our experience, kidney transplantation in patients with a prior heart transplantation results in good patient - and graft survival. The outcome is equivalent to the results of patients with kidney transplantation alone. However, good medical assessment and a stable cardiac function is necessary.

0305 DETECTION OF SIGNIFICANT CORONARY ARTERY STENOSIS WITH 64-SLICE MULTIDETECTOR ROW COMPUTED TOMOGRAPHY IN HEART TRANSPLANT RECIPIENTS

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Introduction: Transplant vasculopathy (TVP) is the leading cause of morbidity and mortality in late cardiac transplant patients. Currently TVP can only be detected using invasive modalities such as conventional coronary angiography (CCA) and intracoronary ultrasound (ICUS). Multidetector row computed tomography angiography (MDCT) is a well established non-invasive diagnostic tool to detect atherosclerotic changes within coronary vessels. The present study evaluates the clinical feasibility of cardiac MDCTA to detect significant coronary stenoses after heart transplantation (HTx).
Methods: Twenty-eight consecutive male HTx-recipients (mean age: 53 ± 13 years) 7.7 ± 4.1 years (range 3 months to 14 years) after heart transplantation scheduled for routine CCA additionally underwent 64-slice MDCTA (Sensation 64, Siemens Medical Soloutions, Forchheim, Germany,

standardized examination protocol). Stenosis graduation in CCA was performed with a quantitative coronary anlaysis (QCA) software tool (Quantcor.QCA; CAAS II, V.5.0, Pie Medical Imaging, Maastricht, Netherlands). Significant disease was defined as luminal diameter loss ≥50% or total vessel occlusion. The status for each coronary segment according to the AHA 15-segment model was documented and compared to the results of visually assessed MDCTA data.

Results: Two patients were excluded from further MDCTA analysis due to insufficient image quality. Out of 371 remaining coronary vessel segments evaluable by CCA, MDCTA was able to depict 302 (81.4%) in diagnostic image quality. On a segment based analysis, sensitivity, specificity, diagnostic accuracy (DA), negative predictive value (NPV), and positive predictive value (PPV) for detection of significant stenosis were calculated with 87.5%, 97.3%, 97.0%, 99.7%, and 46.7% respectively. Including all patients, specificity, DA, and PPV were reduced to 72.8%, 73.1%, and 6.1%, respectively. On a patient based evaluation, sensitivity, specificity, DA, NPV, PPV were 100%, 81%, 84.6%, 100% and 55.6% respectively with reduced specificity (73.9%), DA (78.6%), and PPV (45.6%) including all patients. Evaluation of stenosis degree by MDCTA showed systematic overestimation of 4.4%. A moderate to good agreement comparing both modalities was found (Pearson's correlation coefficient: 0.64).

Conclusion: Sixty-four-slice MDCTA offers the possibility to detect significant TVP in HTx patients with high NPV suggesting MDCTA being a reliable diagnostic tool for ruling out significant stenosis. Its clinical value in these particular patients needs further investigation.

0306 INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM - CHOLANGIOCARCINOMA-SEQUENCE IN A PATIENT WITH PRIMARY SCLEROSING CHOLANGITIS

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Intraductal papillary musinous neoplasm (IPMN) is a rare tumor entity of the biliary tract. We report on a patient with end-stage liver disease due to primary sclerosing cholangitis (PSC) developing an cholangiocarcinoma (CCA) after initial diagnosis of IPMN. A 46-year old female patient with PSC was evaluated for liver transplantation (LTx) after development of end-stage liver disease. The patient had a biliary stricture in the main left intrahepatic bile duct. Suspicion of an intrahepatic lesion was diagnosed by abdominal ultrasound. The lesion was punctured using endoscopic ultrasound. Diagnosis of IPMN was strongly implicated. The patient was followed up in abscence of a postmortal liver graft awaiting LTx. After 3 months, the patient developed progressive ascites. Paracentesis was performed and cytology of ascites showed CCA cells. Therefore, the patient underwent explorative laparotomy. Peritoneal carcinosis was verified histologically. The patient was withdrawn from the waiting list. Reports of an IPMN-CCA-sequence are extremely rare in the literature. Hitherto, this sequence has not been verified yet. Also, it is possible that CCA might mimic IPMN leading to misinterpretation or IPMN and CCA might occur coincidentally. Further research is required to clarify whether an IPMN-CCA-sequence exists.

0307 SUCCESSFUL LUNG RE-TRANSPLANTATION AFTER COMBINED LUNG-LIVER TRANSPLANTATION

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Purpose: Lung re-transplantation is an established treatment for end stage bronchiolitis obliterans syndrome (BOS) in young patients. A combined lung-liver transplantation has been performed in a few patients but there is no published case of a lung re-transplantation after combined lung-liver transplantation. In ISHLT registry there is only one documented case.

Case Report: We report the case of a 25-year-old lung and liver transplant recipient who developed respiratory failure due to a bronchiolitis obliterans syndrome (grade 4). He had been transplanted four years ago as a treatment for inborn multiple arteriovenous fistula. All conservative therapeutically procedures including extracorporeal photopheresis were performed to stabilize lung function but without any success. Liver function was unimpaired with normal transaminasis and ultrasonic findings. Due to the rapid progression of respiratory insufficiency a lung re-transplantation was the only option for this young patient. On October 5th 2009 the sequential bilateral double lung transplantation was perform as a redo procedure without any complications. The postoperative course was complicated by pneumonia (Klebsiella pneumonia). Furthermore, a plasmapheresis therapy was performed due to the presence of anti-HLA-A1 and A36 antibodies. The patient recovered completely from re-transplantation and postoperative complications and could be discharged on November 19th 2009.

Conclusion: Lung re-transplantation after combined lung-liver transplantation can be successfully performed. So it should considered as a therapeutically option in young patients after a combined transplantation with end stage BOS and stable liver function.

0308 A SIMPLE WAY TO AMELIORATE ISCHEMIA REPERFUSION INJURY WITH BILIRUBIN

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Introduction: In this study different ways of administration of bilirubin were tested. The best way was identified by assessing early mitogen activated protein kinase (MAPK) activation, graft function and apoptosis.

Methods: C57Bl/6 mouse hearts were transplanted heterotopically after 12 hours of cold ischemia. Grafts were rinsed with control solution, unconjugated bilirubin (UCB) or conjugated bilirubin ditaurate at 125 μM. Further, UCB (17.5 mg/kg) was administered i.p. to the donor and/or the recipient. Hearts were harvested at 15 minutes and 12 hours after reperfusion and probed for MAPKs and caspase 9. Serum creatin kinase MB (CK-MB) was assessed at 12 hours after reperfusion. Apoptosis rate was quantified with a TUNEL assay. Graft function was monitored by palpation.

Results: In control grafts, 15 minutes after reperfusion a significant increase in MAPK activation and after 12 hour an increase in caspase 9 cleavage was seen. Triple therapy (donor, graft, recipient) with UCB significantly inhibited MAPK activation. When only the graft was treated with UCB, MAPK activation was equally suppressed, what was not seen when bilirubin ditaurate was used. Treatment of only the donor less pronounced ($P < 0.05$) suppressed MAPK activation. 12 hour after reperfusion CK-MB levels were lower and functional score was better in the UCB rinsed grafts when compared to the control ($P < 0.05$). Further, UCB rinse resulted in a significant decrease of apoptotic cells and caspase 9 cleavage.

Conclusion: Rinsing mouse heart grafts prior to anastomosis with UCB prevents MAPK activation, improves outcome, decreases apoptosis rate and may be considered as a simple method to minimize ischemia reperfusion injury.

0309 SOLUBLE TFPI CAN INTERFERE WITH XENOGENIC ACTIVATION OF THE HUMAN COAGULATION SYSTEM AND PREVENTS COAGULOPATHY IN XENOPERFUSED KIDNEYS

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Introduction: Following pig to primate kidney transplantation xenogenic activation of the coagulation (XAC) system of the recipient eventually leading to organ dysfunction and disseminated intravascular coagulation (DIC) can be observed. Although there is no molecular incompatibility regarding the porcine Tissue Factor Pathway Inhibitor (TFPI) on the human coagulation, unlike thrombomodulin, the overexpression of TFPI or application of soluble TFPI (as done in this study) could improve regulation of coagulation.

Methods: Using an ex-vivo perfusion circuit based on C1-Inhibitor (C1-Inh) and low dose heparin mediated anticoagulation, we have analysed XAC following contact of human blood with porcine endothelium. Porcine kidneys were recovered following in situ cold perfusion with HTK organ preservation solution and were immediately connected to a perfusion circuit utilizing freshly drawn pooled human AB blood.

Results: Kidney survival during organ perfusion with human blood, CI-Inh, heparin but without any further pharmacological intervention was 126 ± 78 mintes. XAC was observed with significantly elevated concentrations of d Dimer, thrombin antithrombin complex (TAT). Pharmacological intervention with TFPI significantly reduced the increase in d Dimer and TAT and prolonged organ survival to 240 minutes (± 0). On histology, no signs of XAC were observed.

Conclusion: We conclude that soluble TFPI is able to inhibit XAC in this ex vivo perfusion model.

0312 ARE ADDITIONAL ANTIBODIES DETECTED BY LUMINEX SINGLE ANTIGEN TESTING CLINICALLY RELEVANT? A COLLABORATIVE TRANSPLANT STUDY REPORT

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Introduction: It is a matter of debate whether kidney transplant recipients with preformed donor-specific HLA antibodies (DSA) that are detectable only in the highly sensitive Luminex Single Antigen (LSA) assay are at an increased risk of graft loss and whether such transplants should therefore not be performed. We analyzed the clinical relevance of preformed LSA-detected DSA by studying retrospectively the presence of antibodies in patients with and without graft loss. All patients were negative in CDC and ELISA testing.

Methods: In the CTS serum study, out of 2310 patients who received a deceased donor kidney graft between 1996 and 2005 and whose pretransplant sera were negative in CDC as well as ELISA testing, 341 patients with complete 3-year follow up lost their graft within the first 3 years after transplantation. On 100 of these 341 transplants donor and recipient DNA was available for HLA-A,B,C,DR,DQ,DP typing which allowed the reliable

determination of antibody donor specificity. An additional 100 patients who were matched for the most relevant demographics and had no graft loss during the first 3 posttransplant years served as controls.

Results: When 1,000 MFI was used as cut-off for LSA positivity, 43% of patients with and 64% of patients without graft loss had preformed HLA class I antibodies, and 33% patients with and 53% of patients without graft loss had preformed HLA class II antibodies. The incidence of total DSA was also not higher in patients with graft loss than in patients without graft loss (class I: 7% vs 13%; class II: 4% vs 16%), even when DSA against HLA-A, -B, -DR, -DQA, -DQB, -DPA, or -DPB antigens were analyzed separately (for all loci P = n.s.). DSA against HLA-C was even higher in patients without graft loss than in patients with graft loss (P = 0.005). The incidence of strong DSA (MFI >3,000) detected only by LSA was low (for all loci between 0 and 2% in the group with and between 0 and 5% in the group without graft loss).

Conclusion: The incidence of DSA that go undetected in CDC and ELISA assays and are only detectable by LSA is not higher in patients with graft loss than in patients without graft loss. Our data suggest that under the currently practiced crossmatch procedures and immunosuppressive regimes exclusion of organ offers with HLA antigens as unacceptables based only on LSA antibody testing may not be justified.

0313 THE FIRST CASE OF SUCCESSFUL PEDIATRIC SMALL BOWEL TRANSPLANTATION IN GERMANY

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Introduction: Here we report the first case of pediatric small bowel transplantation in German.

Case report: The patient was a 4-year-old girl with total parenteral nutrition (TPN)-dependent short-bowel syndrome associated with aganglionosis of the entire intestine except for the first 15 cm of jejunum. She received a bowel graft that included jejunum up to transverse colon from a 6-year-old cadaveric donor. Blood types were ABO identical, cytotoxic cross matches were negative, cytomegalovirus statuses were negative-to-negative, Epstein-Barr virus (EBV) statuses were positive-to-negative. After removal of the patient own bowel, the implantation consisted of vascular anastomosis of superior mesenteric artery and vein and intestinal anastomosis of jejunum additionally with a loop ileostomy and an end colostomy. The cold ischemia time was 6 hour with warm ischemia time of 32 minutes. The intra- and postoperative courses were uneventful. The immunosuppressive regimen consisted of Basiliximab, tacrolimus and steroid. The graft surveillance was accomplished using zoom endoscopy and mucosal biopsy. Two months after transplantation, she was weaned from TPN, tolerating oral intake with a fully functioning graft. The enteral nutrition was partially supplemented by the feeding tube through the jejunostomy. The loop ileostomy was successfully reversed on the 10th month posttransplantation. The significant complications included 1) acute cellular rejection requiring steroid therapy on the 15th postoperative day, which was effective; 2) a post-transplant lymphoproliferative disorder (in the tonsils and the lung) at the 8th postoperative months. She underwent tonsillectomy and 4 cycles of Rituximab, which was effective. Thirteen months after transplantation the patient is in a good general condition with normal growth pattern.

Conclusion: Under the dedicated team work successful small bowel transplantation can be achieved in pediatric patients.

0314 AGONISTIC ANTIBODIES TO THE ANGIOTENSIN AT1-RECEPTOR AFTER KIDNEY TRANSPLANTATION

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Agonistic antibodies to G-protein coupled receptors form an alternate pathway of receptor activation, distinct from ligand interaction. AT1-receptor agonistic antibodies (AT1-RAA) have been described in the setting of preeclampsia, arterial hypertension and kidney transplantation. We report clinical course and histopathological findings of early antibody-mediated rejection (AMR) and malignant hypertension in a renal allograft recipient secondary to non-HLA AT1-RAA. A 48-yr. old patient underwent first kidney transplantation in a standard immunologic risk situation. Despite primary function, the patient became anuric on day 2 with loss of diastolic flow in the transplanted kidney. Renal biopsies revealed massive congestion of large vessels and glomeruli with progressive endothelialitis and atypical positive C4d staining, sparing peritubular capillaries. Plasmapheresis and a course of corticosteroids was initiated without improving renal function. Subsequently, malignant hypertension developed requiring i.v. antihypertensive therapy. No donor-specific HLA antibodies were detectable. In search of non-HLA antibodies, agonistic antibodies to the angiotensin AT1-receptor were detected. Within 48 hours upon initiation of AT1-receptor blockade by losartan, malignant hypertension and allograft perfusion normalised and the patient developed polyuria. Renal outcome at 9 months is excellent under continuous AT1-receptor blockade. Follow-up biopsy revealed no signs of AMR. In conclusion, non-HLA AT1-RAA are a rare cause of AMR in kidney transplantation. Underlying pathomechanisms include endothelial activation, interaction of recipient preformed AT1-RAA with naïve donor endothelium and altered AT1 receptor signalling. Both, functional hemodynamic and histopathological alterations are responsive to AT1-receptor blockade. Screening for AT1-RAA prior to transplantation could identify patients at risk for non-HLA AMR.

0315 LUNG EMBOLISM IN LONG TERM FOLLOW UP AFTER THORACIC ORGAN TRANSPLANTATION

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Purpose: Lung embolisms after heart and lung transplantation seamed to by a rare but serious complication and difficult differential diagnosis to acute rejection. Aim of the study is to detect the incidence and the helpful diagnostically procedures.

Methods/Materials: We analysed 138 consecutive patients (HTX n = 93, LTX n = 40, HLTX n = 5) in long term medical attendance (> 6 month) after thoracic organ transplantation from March 2007 to January 2009. All patients were analysed for episodes of lung embolism, clinical presentation, diagnostic procedures and outcome.

Results: We registered 5 cases with a severe lung embolism (incidence 1.98 %). All patients were admitted with dyspnoea (NYHA III n = 3, NYHA IV n = 2) under suspicion of an acute rejection. In each case acute rejection could ruled out by echocardiography and endomyocardial biopsy in heart transplant (HTX n = 3) or bronchoscopy and lung function in lung transplant (LTX n = 2) recipients. In echocardiography elevated pulmonary pressure was detected in only 2 patients without right ventricular exposure (mean PAP + CVP 44.4 mmHg). Significant D-Dimer was recognized in 2 cases (mean 650.8 μmol/l). Clinical signs for deep vein thrombosis were not detectable in any patient, nevertheless 3 patients showed deep vein thrombosis in duplex sonography. Lung embolism was revealed by CT angiography. All 5 patients received conservative therapy with anticoagulation and recovered form the event (mortality 0%).

Conclusion: Our analysis suggests that lung embolism must be considered as an underestimated and difficult differential diagnosis to acute rejection in patient's long term after thoracic organ transplantation. Only the performance of a CT angiography is effective to detect lung embolism so it should be considered earlier in the diagnostic process.

0316 MELATONIN IN LIVER RESECTION: FIRST CLINICAL EXPERIENCE

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Background: Experimental data suggest that melatonin, a potent immunomodulator and antioxidant, would decrease the inflammatory changes after major liver resection, thus positively influencing the postoperative course. This study was designed to assess the safety and tolerance of melatonin given preoperatively in an effort to evaluate its future possible benefits in living donor liver transplantation.

Material and Methods: A randomized controlled double blind single center pilot clinical trial on the safety and tolerance of preoperative melatonin application in patients undergoing major liver resection (PORTAL) [EudraCT number: 2006-005308-159] with two parallel study arms was performed. A total of 50 patients scheduled for major liver resection (≥3 segments) were randomized to receive a preoperative single dose of melatonin (50 mg/kg BW) dissolved in 250 ml milk. Controls were given the same amount of microcrystalline cellulose through the gastric tube right after the intubation for general anesthesia. Patients of both groups were comparable regarding demographics, operative procedures, and intraoperative data. Primary endpoints were safety and tolerance. Secondary endpoints were infectious and non-infectious complications.

Results: Melatonin was effectively absorbed with serum concentrations of 1142.8 ± 7.2 (Mean ± SEM) ng/ml in contrast to 0.3 ± 7.8 ng/ml in controls ($P < 0.0001$). Melatonin treatment resulted in lower postoperative transaminases over the study period ($P = 0.6$). There was no serious adverse event in patients after melatonin. Monitoring of laboratory data over the first 7 postoperative days confirmed the safety of the preoperative application of melatonin prior to major liver surgery. A total of 3 infectious complications occurred in either groups. Non-infectious complications occurred in 5 control patients (a total of 8 complications) vs. 3 melatonin patients (a total of 3 complications) ($P = 0.3$). There was a trend towards shorter ICU stay and total hospital stay after melatonin.

Conclusion: This study clearly demonstrates that a single preoperative enteral dose of melatonin is effectively absorbed and is safe and well tolerated in patients undergoing major liver surgery. A future phase III study will be performed to further assess the observed trends. If the clinical benefits of melatonin in liver surgery are documented, possible future applications may include living donor liver transplantation for both the donor and recipient.

0317 PRESERVATION OF RENAL FUNCTION AT SURGERY FOR PERSISTING HYPERPARATHYROIDISM AFTER RENAL TRANSPLANTATION

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Objective: Parathyroidectomy (PT) corrects tertiary hyperparathyroidism (tHPT) in renal graft patients, but can influence renal function. Different surgical procedures are compared for their effect on renal function and the efficacy to cure tHPT permanently.

Methods: A retrospective cohort study analyzed 83 patients with functioning renal grafts receiving PT for the first time. Group 1 received an incomplete PT, whereby entire parathyroid glands (PG) remained in situ ($n = 12$). Group 2 received an incomplete PT, whereby the most morphologically conserved PG was partially resected ($n = 22$). Group 3 received a complete PT with autotransplantation of PG tissue ($n = 49$). Primary endpoint is the postoperative change in glomerular filtration rate (GFR). Secondary endpoints are rates of re-dialysis, hypercalcemia and HPT within a follow-up period of five years.

Results: All groups had stable GFR one year before PT, but suffered an acute GFR decrease directly after PT. Renal graft biopsies were performed in 19 patients and revealed an infection or rejection episode in 5 cases only. Recovery of renal function was only observed in group 1, but not in groups 2 and 3 ($P < 0.001$). Seven patients (8.4%) needed re-dialysis (one in group 2, six in group 3). Hypercalcemia and tHPT were efficiently abrogated in 93% of patients without significant differences among the groups.

Conclusions: Incomplete PT preserving entire PG does not deteriorate renal graft function and corrects tHPT for long-term. Since the preservation of renal graft function is mandatory, renal graft patients with tHPT should be treated by less extensive PT.

0318 HEPATOCYTE PROGENITOR TRANSPLANTS AS A POTENTIAL SOURCE FOR TREATMENT OF INSULIN DEPENDENT DIABETES MELLITUS

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Background: Hepatocyte progenitors can differentiate at least in hepatocytes and cholangiocytes. Since subpopulations of cells isolated from developing rat livers share surface markers with cells of pancreatic origin and both organs are embryologically related, this study was designed to evaluate hepatocyte progenitors as a cell source for treatment of insulin dependent diabetes mellitus.

Methods: Cells were isolated from developing rat livers (Lewis-rats, embyonal days 14–20) using collagenase digestion and subsequent gradient centrifugation. Hematopoietic cells were depleted using MACS and hepatocyte progenitors were further MACS-sorted for the stem cell marker thy-1. To detect hepatic markers and the pancreatic differentiation marker pdx-1, qRT-PCR was performed. Moreover, cells were cultured using Williams E medium supplemented with FBS and growth factors with or without high glucose content (4.5 g/L). Cells were transplanted in streptozotocin-diabetic rats and blood glucose levels were monitored for 7 days.

Results: Both thy-1 positive and negative progenitors showed expression of hepatic markers on mRNA level. Expression of pdx-1 compared to adult hepatocytes and fetal pancreas on mRNA-level was 6-fold and 1-fold, respectively. Moreover, insulin secretion of hepatic progenitors after 3 days in high glucose culture media increased from 0.058 to 0.11 μg/L ($P < 0.05$) compared to cell culture in low glucose media ($P < 0.05$). While in vivo no significant decrease of blood glucose levels could be detected, all animals survived the procedure.

Conclusion: Progenitor cells isolated from developing rat liver show expression of pancreatic differentiation markers. Moreover, these cells can produce insulin as a response to high glucose in vitro. Transplantation of these cells is feasible. These and other cell candidates isolated from the liver might be an alternative to islet or pancreas transplantation and might be available as future treatment of insulin dependent diabetes mellitus.

0319 EVEROLIMUS ALLOWS EARLY CNI-REDUCTION AND LATE WITHDRAWAL IN HEART TRANSPLANT RECIPIENTS RESULTING IN IMPROVED RENAL FUNCTION

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Background: Nephrotoxicity is a common side effect of immunosuppressive protocols based on calcineurin-inhibitors (CNI). M-TOR-inhibitors like sirolimus have proven to be efficacious in preventing renal failure after heart transplantation (HTx). The combination Everolimus (EVL)/tacrolimus (Tac) as well as CNI-free immunosuppression with EVL has not been investigated after HTx. We evaluated the impact of CNI-reduction and withdrawal in EVL-based immunosuppression on renal function after HTx.

Methods: Between 2007 and 2009 sixteen patients (15 male, mean age 51.1 ± 16.7 years, 4.1 ± 4.8 years after HTx) were switched from Tac and mycophenolate mofetil (MMF) to an EVL-based immunosuppression for renal dysfunction. Patients were divided into two groups: patients within one year after HTx were switched to Tac/EVL (group1, $n = 6$) and patients longer than one year after HTx to EVL/MMF (group2, $n = 10$). Target trough levels were 3–5ng/ml for Tac, 1.5–4 μg/ml for MMF, and 4–10 ng/ml for EVL. Creatinine levels were measured up to 6 months after conversion.

Results: Renal function improved in all patients: baseline creatinine was 2.3 ± 0.6 mg/dl, 1.5 ± 0.2 mg/dl ($P = 0.04$) 3 months and 1.6 ± 0.3 mg/dl 6 months after conversion ($P = 0.06$). In group 1 baseline creatinine was 2.5 ± 0.3 mg/dl and 1.8 ± 0.1 mg/dl 6 months after conversion. In group 2 baseline creatinine was 2.3 ± 0.8 mg/dl mg/dl and 1.5 ± 0.3 mg/dl after 6 months. There were no acute rejection episodes. Due to adverse events, predominantly anaemia, pneumonia and edema, five patients were re-converted to the CNI-based immunosuppression.

Conclusion: EVL allows early CNI-reduction and late withdrawal after HTx resulting in improved renal function. Side effects are common and lead to a high reconversion rate.

0320 META-ANALYSIS OF INTERLEUKIN-2-RECEPTOR ANTAGONISTS FOR LIVER TRANSPLANT RECIPIENTS

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Background and objective: Interleukin 2 receptor antagonists (IL2Ra) are used as induction therapy for prophylaxis against acute rejection in liver transplant recipients. This study aims to systematically identify and summarize the effects of using an IL2Ra, as an addition to standard therapy.

Methods: MEDLINE (1966–November 2009), EMBASE (1980–November 2009) and the Transplant Library (1970–November 2009) were searched for trials in liver transplant recipients were IL2Ra was compared to placebo or no treatment. Titles and abstracts were independently screened by two reviewers and selected according to pre-specified quality criteria. For the final analysis only prospective, randomized, controlled trials were included with or without blinding.

Results: Fourteen trials including 2559 participants were included in the meta-analysis. Depending on co-medication three subgroups were identified: same co-medication in both groups, reduced or delayed calcineurin inhibitors (CNI) in experimental group, reduced corticosteroids in experimental group. Pooling estimates in fixed and random effects models, independently of subgroups, the incidence of acute rejection at 12 months or later (see figure) was significantly reduced in patients receiving IL2Ra (RR 0.81, 95%-CI 0.71 to 0.92) whereas the incidence of graft loss (RR 0.98, 95%-CI 0.72 to 1.33) and death (RR 0.86, 95%-CI 0.66 to 1.12) where not significantly different. Subgroup analyses show better renal function in patients with IL2Ra and reduced or delayed CNI compared to patients without IL2Ra and standard dose CNI.

Conclusion: The use of IL2Ra reduces the incidence of acute rejection independently of immunosuppressive co-medication but does not reduce graft loss or mortality. Additionally reducing calcineurin inhibitors may improve renal function without increase of adverse events.

0323 NATIVE URETER REIMPLANTATION - AN EFFECTIVE THERAPY FOR URINARY TRACT COMPLICATIONS FOLLOWING KIDNEY TRANSPLANTATION

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Introduction: Urological complications such as stricture of the ureter, urinary leakage, ureteral necrosis and vesico-ureteral reflux (VUR) are still a source of morbidity and mortality after kidney transplantation. Incidence is reported with 3–14% in recent studies. Secondary reimplantation of the native ureter is a good and safe surgical therapy to treat urinary tract complications after renal transplantation.

Materials and Methods: We performed a retrospective analysis of urinary tract complications in need of surgical therapy following kidney transplantation or combined kidney-pancreas transplantation performed between 01/2001 and 06/2009 at our transplant center. Of the 645 patients 25 were identified at our transplant center with re-surgery needed for postoperative urinary tract complications. In addition, one patient who had not been transplanted at our center, but received ureteral reconstruction at was included as well.

Results: Sixteen of 26 patients received implantation of the ipsilateral native ureter of which 10 for VUR, three for ureteric stricture, two for urinary leakage and one for ureteral necrosis. The native ureter reimplantation was successful in 14 of 16 patients (88%). Two patients needed to be re-operated and received a Boari flap.

Conclusion: In conclusion reimplantation of the native ureter is a promising option to treat ureter related urinary tract complications after kidney transplantation.

0324 INVASIVE PULMONARY ASPERGILOSIS SUCCESSFULLY TREATED WITH THE COMBINATION OF VORICONAZOLE AND MICAFUNGIN IN A HEART TRANSPLANT RECIPIENT

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Invasive aspergillosis (IA) is a common life-threatening infection in highly immunocompromised patients with mortality rates between 30% and 90%. Concerning the therapy of IA, the second-generation triazole voriconazole has replaced amphotericin B as first-line therapy. Due to the sub-optimal outcome with antifungal monotherapy either with azoles or amphotericin B combination antifungal therapy has become a point of interest. However, there is only scant information from controlled studies regarding antifungal combination therapy for the treatment of IA. On the other hand, some results of *in vitro* studies, animal models, and case reports suggest that antifungal combination therapy with azoles (e.g., voriconazole, posaconazole, and ravuconazole) and echinocandins (e.g., caspofungin, micafungin, and anidulafungin) may have additive activity against Aspergillus species. Herein, we report the case of a 45-year-old male patient who developed fever, progressive worsening of dyspnea and a mild productive cough without response to antibiotics 2 weeks after heart transplantation (HTx). The diagnosis of invasive pulmonary aspergillosis (IPA) was made on the basis of clinical, laboratory and radiographic findings. The patient was treated successfully with a combined antifungal therapy consisting of voriconazole and micafungin. At the 9-month follow-up the patient remained well with nearly resolved pulmonary findings on chest x-ray and CT of the chest (figure 1). This case report highlights (1) the importance of a high degree of clinical suspicion in order to enable curative treatment of invasive aspergillosis and (2) the convincing efficacy of newer antifungal drugs.

0325 THE RIGHT CHOICE FOR LAPAROSCOPIC DONOR NEPHRECTOMYTEN YEARS EXPERIENCE WITH 150 CASES

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Background: Usually left kidneys are preferred for laparoscopic donor nephrectomy if both are comparable regarding function and anatomy. A prospective study was conducted to analyze donor's and recipient's primary outcome and to compare long-term patient and graft survival depending on side of laparoscopic donor nephrectomy.

Patients and methods: The first laparoscopic donor nephrectomy (LDN) was performed at the University Hospital Lübeck (Germany) on July 7th 1999. In 2001 the LDN became the standard procedure for all living donations in our institution. Between July 1999 and October 2009 a total of 150 cases have been performed. In the first period of the study the left kidney (L-LDN) was preferred if equal function and anatomy were equal bilaterally. In the second period since 2005, right kidney (R_LDN) was preferred due to shorter operating time and comparable primary hospital outcome. Statistical analysis were done in SPSS Version 17.0 (Chi^2 -test, Kaplan-Meier, log-rank-test).

Results: The donor's age ranged from 24 to79 years (average 53), BMI from 17 to 34 (av. 25) and 59% were female for the entire group and did not differ for right or left-sided LDN. R-LDN was performed in 81 cases (54%) with a mean operating time of 190 minutes (96–400), respectively 232 minutes (143–400) for L-LDN (69 cases, $P < 0.0001$). Conversion rate was 4.7% (7/150) for the entire group, 3.7% right (3) and 5.8% left-sided (4), but did only occur in the earlier series (up to case-no. 61 in 2005), due to bleeding (4), obesity (2) and technical problems (1). No mortality was observed and donor-associated overall morbidity was 10.0% (hematoma (4), urinary tract infection (4), pneumonia (3), nerve irritation (2), mild pancreatitis (2)). Major complications reqiured laparoscopic revision in 2.7% due to bleeding (3 R-LDN, 1 L-LDN). Average postoperative length of hospital stay was 7.1 days for R-LDN, respectively 7.2 days for L-LDN. None of the donors developed renal insufficiency. Mean creatinine-level at discharge day was 100.7 μmol/l (63–148) for R-LDN vs. 102.6 μmol/l (67–150) for L-LDN (n.s.). The mean first warm ischemia time was 149 s vs. 178 s (R/L), mean cold ischemia time was 83 min vs. 79 min (R/L) and the mean second warm ischemia time was identically 31 min for right and left-sided anastomosis (n.s.). The initial function rate was 94% for each side. Two left grafts (1.3%) were lost before discharge due to renal artery occlusion (1) and severe vascular rejection (1). The mean recipient's creatinine-level at discharge day was 139 μmol/l (62–316) for R-LDN vs. 142 μmol/l (55–376) for L-LDN (n.s.). No Mortality was observed. There were no significant differences for patient survival at 1 yr (R-LDN: 99% vs. L-LDN: 99%) and 5 years (95% vs. 97%) and graft-survival at 1 year (97% vs. 97%) and 5 years (91% vs. 93%).

Conclusion: The right sided laparoscopic donor nephrectomy is a safe procedure with comparable outcome for donor and recipient. No special vascular reconstruction is needed for the venous anastomosis. Right LDN is faster, even after finalizing of the learning curve and therefore the preferred method in our institution.

0327 THE FIRST LAPAROSCOPIC DONOR NEPHRECTOMIES IN BANGLADESH - A FEASIBLE METHOD IN A DEVELOPING COUNTRY

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Background: The laparoscopic donor nephrectomy in living donation (LDN) for kidney transplantation (NTX) is a well accepted procedure in western countries. This enables the donor to profit of the laparoscopic method in general and may help to enlarge the donor pool. Bangladesh is a 3rd world country in wich only living related donation is possible.The cadaveric transplantation is not possible due to intensive care capacity and missing acceptance in the bengali population. So far only 2 centers (university hospital BSMMU, non-profit-organization Kidney foundation) in Dhaka were performing NTX with conventional donor nephrectomy via a lumbar access with resection the 11th rib. As kidney failure is a big problem in this country the need for safe methods with good acceptance for life donation is high. We report of a cooporation between a german and bengali university hospital, supported by german and bengali NGO's to improve the situation of living kidney donors bringing new technical input.

Method: Four donors were chosen by the local team and written consent was taken for the laparoscopic donor nephrectomy. This were all cases, in which donation was denied by the local team due to anatomical variation (multiple arteries).

Result: In cooporation with the local transplant-surgeons 3 laparoscopic (1 left, 2 right sided) donor nephrectomies were performed in 11/2007 in the kidney foundation and BSMMU in Dhaka. One donation was done in conventional technique because of shortage in availability of the laparoscopic tower. Operation time was comparable to operation time in our own institution. Donors were discharged after 7 days. No complications were seen perioperatively or in follow up until now on donor side. Three recipients had good initial function and are still alive with good creatinin level (mean 150 mikromol/l). One recipient lost organ function due to rejection in the first week and died 5 month after transplantation in a sepsis.

Conclusion: The laparoscopic donor nephrectomy is a feasible and safe method in a developing country.There is a huge need for technical input in poor countries and a strong will to share new technologies. Exchange programms for transplant surgeons and nephrologists from developing countries can help to overcome this deficiency.

0329 FURTHER ASSESSMENT OF IATP (CYLEX IMMUKNOW®) IN PEDIATRIC LIVER TRANSPLANTATION (LTX) AND HEALTHY CONTROLS

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Background: The optimization of immunosuppression after solid organ transplantation based on drug trough level measurement alone remains unsatisfactory. The side effects of Calcineurin-Inhibitors (CNIs) in particular are a limiting factor of long-time outcome and of quality of life. The assessment of cell-mediated immune response through measurement of intracellular ATP (iATP) production (Cylex®-ImmuKnow) could achieve an optimization of immunosuppression independent of drug dosages and of drug trough levels.

Methods: In a prospective trial, we investigated healthy subjects ($n = 31$, age<12 years $n = 15$, age>12 years $n = 16$) and children in a stable phase after liver transplantation ($n = 45$; <12 years $n = 39$, >12 years $n = 6$) as well as children with allograft rejection ($n = 4$) and with acute infection ($n = 3$). Twenty-four transplant patients received cyclosporine (CSA), 17 tacrolimus (TCL), 9 mycophenolate mofetil (MMF), and 1 everolimus (some patients received drug combinations). The reactivity of the immune system was measured as the rise of intracellular ATP (iATP) in CD4+ T-lymphocytes following PHA-stimulation (Cylex® ImmuKnow®).

Results: There was a non-significant trend towards a lower iATP in the older age subgroup of healthy subjects (median iATP 342 ng/ml vs. 399 ng/ml, $P = 0.128$). Event-free patients after LTX showed a lower iATP compared to healthy controls in the respective age subgroups (<12 years: median iATP 280 vs. 399 ng/ml, $P = 0.018$; >12 years: median iATP 240 vs. 342 ng/ml, $P = 0.097$) as well as in the whole group (median iATP 268 ng/ml vs. 385 ng/ml, $P = 0.007$). iATP concentrations in patients with clinically significant infections were in the low immune response range (median 181 vs. 268 ng/ml, $P = 0.148$). Patients with allograft rejection had significantly higher iATP concentrations as compared to the event-free group (median iATP 444 vs. 268 ng/ml, $P = 0.022$). No significant correlation between drug trough concentrations and iATP concentrations was found, neither for CSA ($r = 0.126$, $P = 0.600$) nor for TCL ($r = 0.397$, $P = 0.138$).

Conclusion: The age-related increase in iATP previously described by Hooper et al (1) was not confirmed in this study. The correlation of clinical events and corresponding iATP-levels confirms similar findings from the adult literature for the pediatric age group. The missing correlation of iATP to drug trough levels indicates that the ImmuKnow® assay provides independent information to guide immunosuppression in pediatric (liver) transplant patients.

Nevertheless the wide range of iATP levels in the event-free group suggests that serial iATP measurements are necessary to assess the individual constellation. Further investigations are necessary to validate and extend these findings.

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0330 VIRUS SAFETY AND XENOTRANSPLANTATION: STATE OF THE ART 2010

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Aim: To prevent transmission of porcine microorganisms in the result of xenotransplantation different measures should be undertaken. Whereas most of the potential zoonotic pathogens can be eliminated by designated pathogen-free breeding, porcine endogenous retroviruses (PERV) are integrated as proviruses in the genome of all pigs and can be released as infectious virus particles. PERV-A and PERV-B are present in all animals and they infect human cells. PERV-C are not present in all pigs and they infect only pig cells. Recombinant PERV-A/C, however, infect human cells and replicate at high titres.

Results: Highly sensitive and specific methods to characterise integrated proviruses as well as PERV expression at the level of mRNA and protein have been developed. These methods are used to analyse donor pigs as well as recipients of experimental and clinical xenotransplants. In addition, methods to detect antibodies as indication for PERV transmission have been developed. Several strategies have been developed to prevent PERV transmission. First of all, methods to screen for PERV-C in the genome were developed. These methods allow excluding such animals from further breeding. Second, methods to characterise the level of PERV expression in donor animals have been developed in order to select pigs with low expression of PERV. Third, PERV expression was successfully reduced in transgenic animals by RNA interference. Expression of shRNA in transgenic pigs was shown for more than two years.

Conclusion: Sensitive detection methods and numerous prevention strategies have been developed to minimize transmission of PERV.

0333 PDCA-BASED MICROSURGICAL TRAINING PROGRAM FOR RAT LIVER TRANSPLANTATION: AN EFFICIENT AND PRODUCTIVE WAY TO ACQUIRE MICROSURGICAL SKILLS

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Aim: We used a PDCA-based approach ensure a high efficiency of our microsurgical training program in respect to surgical quality and scientific output of the trainee during training period. Using this approach, we also want to reduce the number of procedures/animals needed to achieve predefined quality criteria for every training step.

Method and concept: The training program was divided into 5 phases: assessment of the surgical knowledge and skills, ex-vivo practice on surrogate models, basic microsurgical training including procedures such as vessel anastomosis and hepatectomy, productivity phase applying newly acquired skills within a formal experiment, and advanced microsurgical (= liver transplantation) training. Control of the learning process and the surgical process- and result-quality was based on the PDCA-cycle applying predefined objective and measurable quality criteria for the analysis of each surgical procedure. Predefined quality criteria included survival rate, operation time but also clinical chemistry, histological evaluation and the newly established molecular marker HMGB1. Consequent iterations of this Plan-Do-Check-Act cycles was requested from the trainee to facilitate constant improvement of surgical quality from one cycle to the next one. Transition from one training step to the next higher one was exclusively based on reaching all predefined quantitative and qualitative quality criteria.

Result: Four trainees were enrolled and four different procedures (corrosion casting, selective portal vein clamping, hemodynamic monitoring, and partial hepatectomy) were mastered. Two trainees completed the basic training phase and mastered the hepatectomy within 10 operations. All quality criteria were reached (100% SVR, ALT<1200U/L, BrdU-PI >10%, and lack of HMGB1 translocation, our newly established molecular marker for surgical handling quality). Another two trainees completed the advance training phase and mastered non-arterialized LTx within 30 and 60 LTxs, respectively, which is lower than reported elsewhere. They also reached the predefined quality criteria: anhepatic time <20 minutes, 100% 1w-SVR, no histomorphologic alteration at 1 week. All four candidates reached the productivity phase, in which they performed between 304 hepatectomies and contributed to 5 research projects.

Conclusion: The stepwise and PDCA-based training program increased the efficiency of LTx training, while the constant application and development of predefined quality criteria guaranteed and enhanced the quality of surgery.

0335 UROLOGICAL DE NOVO MALIGNANCIES AFTER KIDNEY TRANSPLANTATION -SINGLE CENTER EXPERIENCE

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Purpose: The development of de novo malignancies as a result of immunosuppression is a well-known complication after renal transplantation (RT). With increasing donor and recipient age the risk of posttransplant malignancy including genitourinary cancers is rising. Thus, especially urologists have an increasing likelihood to treat these patients. We report our experience with the management of urological de novo malignancies after RT.

Patients and Methods: Twenty-nine of 802 patients after RT between 1988 and 2009 developed urological de novo malignancies. Data were analyzed for tumor incidence, treatment, follow-up and possible factors contributing to tumor development.

Results: Patients suffered from RCC ($n = 12$, median 46.5 months after RT), TCC (bladder, $n = 6$; 35 months; renal pelvis, $n = 2$; 37.5 months), CaP ($n = 7$; 69 months), and seminoma ($n = 2$; 41.5 months). No treatment-related graft losses occured. 2 of 3 RCCs developing in the graft were removed using nephron-sparing surgery. There was no statistical difference between patients with and without posttransplant tumors with regard to age, gender, interval between first dialysis and transplantation, number of transplantations, ischemia time, rejection episodes or immunosuppression protocols.

Conclusions: Urological posttransplant malignancies are an increasing problem for urologists. A strict tumor screening before and after RT is mandatory. Standard urological treatment principles can be applied. Non-functioning native kidneys with suspicious lesions should be removed early. Radical pelvic surgery after RT and nephron-sparing procedures in the graft can be a challenge even for the experienced surgeon and require surgical versatility.

0337 FEASIBLE RELEVANCE OF DUFFY AND KIDD ANTIGENS FOR KIDNEY TRANSPLANTATION: ACUTE GRAFT LOSS AFTER THIRD KIDNEY TRANSPLANTATION DUE TO RED BLOOD CELL ANTIBODIES

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Introduction: There is no doubt that antibodies against Duffy and Kidd red blood cell antigens are clinically relevant in transfusion. Duffy (Fya/b) and Kidd (Jka/b) antigens are not only expressed on the surface of erythrocytes but also on other tissue e.g. kidney. Thus antierythrocyte antibodies are discussed to have an adverse effect on graft outcome after kidney transplantation.

Case reports: A 29 years old female patient with rapid-progressive glomerulonephritis due to pANCA positive vasulopathy was waiting for her third kidney transplantation. The patient lost her first two grafts early after transplantation due to acute rejection. Actually we found an anti-Fya (titer 1:4096) and anti-HLA-DR7 antibody against the second donor. Before next transplantation the patient was genotyped for blood group antigens (Kel*2; Jk*A; Fy*B). It has been decided to refuse Fy(a+) and HLA-DR7 antigen donors. The patient received a Duffy- and HLA-compatible organ (Kel*2; Jk*AB; Fy*B) after short waiting time. The crossmatch was negative. During inspection of the organ a thrombosis of the renal artery was observed. After thrombectomy the organ was reperfused sufficiently. There was no transplant function postoperative. Multiple, infarction in the kidney could be confirmed by angiography. Biopsy proven rejection (BANFF 4 IIa) was shown already 10 days post transplant. At that time a de novo donorspecific anti-Jkb antibody was detected in the patient serum for the first time. Transplantnephrectomy followed.

Discussion: Despite all measures of precaution the third transplantation was not successful. The early appearance of anti-Jkb antibody combined with poor organ quality was discussed as cause of graft failure. It was shown that Duffy antigen-receptor for chemokines (DARC) and Kidd antigens were up-regulated on peritubular capillaries during rejection and prolonged ischemia time.

Conclusion: Our case report indicates the feasible relevance of Duffy and Kidd antigens in kidney transplantation. Patients with rare phenotypes Fy(a-b+) and Jk(a+/b-) are naturally at higher risk to develop antibodies. Genotyping and subsequent antibody monitoring could be a benefit for theses recipients. In case of unclear graft failure antierythrocyte antibodies should be taken into consideration.

0338 OXIDATION OF HMGB1 IN EFFLUENT OF COLD PRESERVED LIVER GRAFTS CAUSED ATTENUATION OF THE PRO-INFLAMMATORY ACTIVITY

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HMGB1 is an evolutionarily conserved nuclear protein binding to chromatin which acts as inflammatory mediator when passively released by damaged cells or actively secreted by activated monocytes and macrophages. We demonstrated previously at HMGB1 is released into the effluent during prolonged cold saline preservation of liver grafts. We also demonstrated that transplantation of a cold-preserved liver graft did not interfere with spontaneous graft acceptance. We hypothesized that oxidation of HMGB1 during reoxygenation upon reperfusion of the liver graft would attenuate its pro-inflammatory potential. Using a bioassay with rat peritoneal macrophages we tested the inflammatory potential of the complete effluent. Expression of TNF-α, IL-6, CD80, CD86, CXL1, CCL2, CCL3 and CCL4 was taken as indicator for the pro-inflammatory potential. HMGB1 was purified from the effluent via immunoprecipitation. The protein was oxidized via pretreatment with H2O2 and tested in respect to its inflammatory potential using the macrophage bioassay. Addition of the effluent to the macrophage culture induced the expression of all inflammatory mediators. The pro-inflammatory activity was first observed when using effluent obtained after 4h of cold preservation. The "flow-through" depleted from HMGB1 had a significantly reduced inflammatory activity compared to the HMBG1 enriched fraction. Oxidation of the effluent also attenuated the expression of inflammatory cytokines. In conclusion, effluent obtained after prolonged cold storage induced synthesis of proinflammatory mediators in the macrophage bioassay. Oxidation of the HMGB1 using H2O2 reduced the pro-inflammatory potential. Reoxygenation during reperfusion might elicit exert the same effect and cause oxidized HMGB1 thereby reducing the inflammatory activity of the effluent.

0339 G-CSF ENHANCED THE LPS-INDUCED INFLAMMATORY RESPONSE AFTER RAT LIVER RESECTION VIA UPREGULATION OF LBP

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Introduction: Extended liver resection as needed for living liver donation may be complicated by the development of sepsis. Sepsis is attributed to increased levels of circulating LPS subsequent to portal hypertension and bacterial translocation. The LPS-induced inflammatory response is mediated via (LPS)-binding protein (LBP), a 60 KDa acute phase protein which is mainly produced by the liver. In the present study, we investigated the role of LBP, induced by GCSF, in mediating the inflammatory response in rats challenged with LPS in the setting of 70% partial hepatectomy (PHx).
Methods: Rats were divided into three groups: LPS group, G-CSF group, G-CSF+LPS group. NaCl group was set as a control in this project. To investigate the biological effects of each treatment model, liver damage, serum cytokine level, cytokine gene expression and histological alterations were analyzed.
Results: Hepatic damage after 70%PH, G-CSF pretreatment and LPS challenge was significantly enhanced as indicated by all parameters. All rats succumbed due to SIRS (high TNFa and IL6 levels) within 6h after PH, whereas LPS-challenge alone only caused the death of 4/6 rats, more than 6h after PHx. Hepatic damage as indicated by liver enzymes, neutrophil infiltration and confluent necrosis were most pronounced in rats subjected to combined treatment compared to rats subjected to LPS only treatment. GCSF treatment alone did not alter the clinical course after 70%PH. GCSF.treatment alone and in combination with LPS caused an early increase of serum LBP, which was not seen in the PH or PH+LPS group. However, cytokine production was only enhanced in case of simultaneous challenge with LPS, suggesting that LPS and LBP are needed for upregulation of cytokine expression.
Conclusion: GCSF-pretreatment did apparently not enhance LBP-levels to such a level, that the inflammatory response was attenuated as reported by others authors. In contrast, G-CSF enhanced the LPS-induced inflammatory response after PH through upregulation of LBP levels. We speculated that signal transduction may only occur if both molecules bind to TLR4 to from the active signal transducing complex.

0340 EFFECTS OF DONOR PRETREATMENT WITH DOPAMINE ON GRAFT FUNCTION AFTER HEART TRANSPLANTATION: DATA FROM A RANDOMIZED CONTROLLED TRIAL

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Background: Treatment of the deceased heart-beating donor with low-dose dopamine results in less dialysis requirement after kidney transplantation. This study investigates the development of all cardiac allografts from multi-organ donors that were enrolled in the randomized dopamine trial (clinicaltrials.gov Identifier: NCT00115115).
Methods: Between March 2004 and August 2007, 264 brain-dead donors were randomly assigned to receive or to not receive low-dose dopamine. Eligibility criteria included circulatory stability under low-dose norepinephrine. The present investigation was initiated under safety considerations and is nested in the multicenter randomized controlled trial on donor pretreatment with dopamine. We assessed the outcomes of 99 cardiac transplants performed at 22 European centers.
Results: Dopamine was infused for a median duration of 400 minutes [IQR 232 minutes]. Donors and recipients were very similar in demographic and clinical baseline characteristics. Fewer recipients of a pretreated graft required a cardiac assist device or hemofiltration immediately after transplantation [13 (26.5%) vs. 23 (46.0%), $P = 0.04$]. The beneficial effect was particularly enhanced when dopamine was applied to the donors until cross clamping. Circulatory parameters of the donors had no effect on the transplantation outcomes. Donor dopamine resulted in a significant survival benefit 3 years after heart transplantation [85.7% vs. 65.7%, $P = 0.02$]. Accordingly, treatment of 5 cardiac donors would rescue one heart allograft.
Conclusions: Treatment of brain-dead donors with low-dose dopamine at a dosage of 4 μg/kg/min is definitely not harmful for the cardiac allograft but appears to substantially improve patient and graft survival after heart transplantation.

0342 ESTABLISHMENT OF A DIETARY MODEL TO INDUCE HEPATIC STEATOSIS IN RAT LIVING LIVER DONORS

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Introduction: Hepatic steatosis is a contraindication for living liver transplantation because of the increased risk for the recipient as well as the donor in case of living related liver transplantation. Investigation of the underlying risks relies on the use of an adequate animal model. This study was designed to evaluate 3 different nutritional models of NAFLD in respect to the time course and intensity of fatty changes. We wanted to assess the impact on liver regeneration after 70% partial hepatectomy in Lew rats to identify the most suitable animal model.
Methods: Male LEW rats were fed with either "fatty liver" diet (FLD, low methionine-low choline diet ssniff Inc), modified methionine-choline deficient plus high fat diet (MCDD+HF) or methionine-choline deficient diet (MCDD) for 1, 2, 4 and 6 weeks. The rats were monitored daily in respect to their clinical condition. All rats were subjected to 70%PH at the end of feeding time and sacrificed 24h later. Microcirculation was assessed at both time points by OPS, and the extent of fatty changes by histology. Stress response was evaluated based on body and liver weight recovery as well as clinical chemistry and BrdU proliferation index.
Result: Rats subjected to the pure MCD diet lost about 25% of their body weight within the first 6 weeks of feeding whereas rats receiving MCD+HF, respectively FLD were gaining weight similar to rats receiving standard rat chow. Fatty changes were visible after 1 week of feeding when using MCD+HF and MCD, but not when using "fatty liver diet". These results were confirmed by histology showing almost no changes in the "fatty liver"-group, but abundant small and few large vacuoles in 50−100% of the hepatocytes in the two other groups. In the MCD-group we also observed single necrotic hepatocytes. PH was well tolerated by all rats although hepatic microcirculation was compromised as indicated by dilated as well as compressed sinusoids suggesting an inhomogenous perfusion. Liver weight recovery was most pronounced in MCD group, followed by FLD.
Conclusion: MCD+HF did induce substantial fatty changes within 1 week and was well tolerated, even when rats were subjected to surgical stress. Therefore, this model appears as a suitable model to study the risks for donor and recipient associated with living donation of liver with fatty changes.

0344 TRANSPLANTATION, SUPERSTITION AND ASTROLOGICAL MYTHOLOGY: HOW MOON PHASES INFLUENCE SHORT- AND LONG-TERM OUTCOME AFTER LIVING DONOR KIDNEY TRANSPLANTATION

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Background: The faith of superstitions is paradoxically increasing in modern society and can bring additional fear to patients who have to undergo major surgery. The astrological belief in the influence of celestial objects - and particularly the moon - on outcome of medical treatment is one of the most common ones. This study was designed to analyse the influence of "Moon Phases" on morbidity, mortality, graft and patient survival after living donor kidney transplantation.
Patients and Methods: The study population consisted of 278 patients who underwent living donor kidney transplantation between October 1994 and May 2009 at our institution. Data on intra- and postoperative complications, short- and long-term graft function and patient- and graft survival were retrieved from our prospective transplant database. All data sets were analyzed according to the four phases of the lunar cycle and multivariable confounder analysis was performed.

Results: Of the 278 patients 192 (69 %) were male, the median age was 42 [7–74] years with a follow-up was 8.2 [0.1–15.2] years. 17 (6 %), 127 (46 %), 22 (8 %) and 112 (40 %) patients were operated during the new, waxing, full and waning phases of the moon. Duration of the procedure and hospital stay (160 [65–345] minutes; 18 [1–65] days) did not differ between groups, neither did the surgical conplication- or relaparotomy rates (19.4 %; 18 %). Delayed graft function, rejection episodes, and long-term complications ocurred in 9.4 %, 20.1 %, and 9.7 % of patients, respectively, and were eaqually distributed between all groups. Patient and graft survival rates at 1, 5 and 10 years after transplantation were 98.9%, 93.9% and 92.4%, and 97.5%, 92.4% and 86.3%, respectively, and did not show any significant differences between phases of the lunar cycle. Therefore, no significant impact of the moon phases on intra- and postoperative complications, graft function and patient- and graft survival was observed.

Conclusion: Not surprisingly, the results of this study do not support any recommendations for scheduling patients for living donor kidney transplantation at any particular day of the lunar cycle. Thes results, however, might help transplant surgeons to quiet the minds of patients who are afraid of wrong timing surgery.

0345 SOLUBLE HLA-G AS AN INDICATOR FOR GRAFT REJECTION IN KIDNEY AND KIDNEY/PANCREAS TRANSPLANTATION SUPERIOR TO SOLUBLE CD30 LEVELS

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Soluble non-classical HLA-G molecules (sHLA-G) exert strong suppressive properties on natural killer cells and T-lymphocytes. Consequently, high levels of sHLA-G are found to favor graft acceptance after transplantation. Here we analyzed the clinical relevance of sHLA-G in comparison to sCD30, a well-established risk factor for kidney rejection. In total we analyzed by ELISA 511 plasma samples procured before (N = 62) and serially during the first 8 weeks after transplantation (N = 450) from 32 kidney- and 30 kidney/pancreas-transplanted patients. 76 healthy individuals served as controls. Pre-transplant sCD30 levels (U/ml) were significantly increased in patients (127 ± 23 vs. 57 ± 6; $P < 0.001$), whereas the sHLA-G levels (ng/ml) were in range in the healthy controls (18.2 ± 1.5 SEM vs. 22.9 ± 2.5 SEM). Importantly, pre-transplant sCD30 and sHLA-G levels did not differ between the two patients groups. Patients with biopsy proven rejection (N = 16) revealed significantly lower sHLA-G levels before (12.9 ± 1.8 vs. 20.1 ± 1.9; $P = 0.013$) and after transplantation ($P < 0.001$, two-way-ANOVA) than patients without rejection (N = 46). In contrast, sCD30 was increased before and post transplantation in patients with rejection ($P < 0.001$ two-way-ANOVA). Non-parametric determination analysis showed that pre-transplant levels of sHLA-G < 11.5 ng/ml (sensitivity: 68.6%; specificity: 82.2%; $P < 0.001$, positive likelihood ratio: 3.8) and sCD30 > 89.5 U/ml (sensitivity: 75.0%; specificity: 55.5%; $P = 0.051$; positive likelihood ratio: 1.6) were related to rejection. The combination of these two factors (sCD30 > 89 U/ml or sHLA-G < 11.5 ng/ml vs. the remaining) did not further increase the predictive value for graft rejection (sensitivity: 100%, specificity: 51.3%, $P < 0.001$; positive likelihood ratio: 2.0). Regarding antibody status, retransplantation, number of HLA mismatches, recipients' age and BMI, multivariate analysis showed that sHLA-G but not sCD30 is an independent risk factor for graft rejection. In conclusion, our results suggest that the prognostic relevance of pre-transplant sHLA-G levels is superior to soluble CD30 in kidney- and kidney/pancreas-transplantations to identify patients with increased risk of graft rejection.

0346 RELEVANCE OF NON-EXPRESSED HLA-CLASS I ALLELES FOUND IN TWO CASES OF BONE MARROW DONOR SEARCH

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In the bone marrow donor search process the recipient and the donor are matched at the high resolution level of HLA-typing. High resolution typing according to the current standards means, that the amino acid sequences of exon 2 and 3 for HLA-Class I (A/B/C-locus) or exon 2 for HLA-Class II (DRB1/DQB1 locus) of donor and recipient are identical and that non-expressed alleles (''Null-alleles'') were excluded. This can be achieved by molecular methods (preferably PCR-SSP), which are able to detect the known Null-alleles with specific probes even outside of exon 2 and 3 for HLA class I or exon 2 for HLA-Class II. The second option is serological HLA-typing by CDC, a method which, although it has been discontinued and found unnecessary by some laboratories, is still alive and good working. Here we present 2 cases, where Null-alleles were detected by serological typing. The donor search for the first patient was difficult due to rare HLA-haplotypes: HLA-A32, B70, Cw7 / A1, B51, Cw - (CDC) and HLA-A*32:01, B*15:18, C*07:04G, DRB1*11:03, DQB1*03:01 / HLA-A*01:01G, B*51:01G, C*15:02G, DRB1*04:02, DQB1*03:02 (molecular typing) and only donors with a minimum of one mismatch were identified. Confirmatory typing of the most suitable donor with a single A-locus mismatch (A*02 vs A*01) revealed identical alleles in the other loci. However, serological typing of the B-Locus showed repeatedly HLA-B70,-. Null-alleles had not been excluded by the laboratory, which performed the original high-res. typing of HLA Class I. High resolution typing of HLA-B*51 by PCR-SSP was performed additionally to PCR-SBT and revealed the presence of HLA-B*51:11N in the donor, which meant an additional mismatch to the recipient. A second Null-allele was found in a family donor search. The probable segregation of haplotypes suggested, that two out of four siblings were identical for HLA-A/B/C/DRB1/DQB1 to the patient (HLA-A*23:01G,*29:02; B*44:03,-; C*04:01G,*16:01; DRB1*07:01,-; DQB1*02:02,-). The pedigree primarily did not include a typing of the parents. However, the two siblings had a detectable Cw4 in HLA-typing by CDC, while the patient was Cw4 negative. High-resolution PCR-SSP for HLA-C confirmed HLA-C*04:09N for the patient and C*04:01 for the otherwise identical siblings. The presence of 2 haplotypes with HLA-A*23:01, B*44:03, DRB1*07:01, DQB1*02:02, one with C*04:01 and the other with C*04:09N in the same family seemed to be unlikely. However, the father, who was of advanced age, was finally available for typing and fortunately showed the presence of both haplotypes. These cases show, that the exclusion of residual Null-alleles by adequate methods is necessary. The Null-alleles HLA-B*51:11N and C*04:09N are both part of the nomenclature-based ''G-groups'' B*51:01G or C*04:01G and are not excluded by PCR-SBT of exon 2 and 3.

0348 FEASIBLE RELEVANCE OF DUFFY AND KIDD ANTIGENS FOR KIDNEY TRANSPLANTATION: ACUTE GRAFT LOSS AFTER THIRD KIDNEY TRANSPLANTATION DUE TO RED BLOOD CELL ANTIBODIES

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Discussion: Despite all measures of precaution the third transplantation was not successful. The early appearance of anti-Jkb antibody combined with poor organ quality was discussed as cause of graft failure. It was shown that Duffy antigen-receptor for chemokines (DARC) and Kidd antigens were up-regulated on peritubular capillaries during rejection and prolonged ischemia time.

Conclusion: Our case report indicates the feasible relevance of Duffy and Kidd antigens in kidney transplantation. Patients with rare phenotypes Fy(a-b+) and Jk(a+/b-) are naturally at higher risk to develop antibodies. Genotyping and subsequent antibody monitoring could be a benefit for theses recipients. In case of unclear graft failure antierythrocyte antibodies should be taken into consideration.

0350 PANCREAS AND ISLET TRANSPLANTATION - COMPETITIVE OR COMPLEMENTARY?

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In 2008 a Pancreas and Islet Transplantation Program has been established at the University of Dresden as collaboration between departments of surgery, diabetology, nephrology and urology. This allows an interdisciplinary comprehensive approach for the therapy of diabetic patients embedded in a vivid research environment. The indication for simultaneous pancreas/kidney-transplantation is clearly defined and the goldstandard in the treatment of type 1 diabetic patients with endstage-renal disease. However, the indication for islet transplantation or pancreas alone is less determined and often controversial. Either procedure is generally based on the indication ''brittle diabetes''. Another approach to islet transplantation is the ''bridging'' aspect for metabolically unstable patients with preserved kidney function until deterioration that will be followed by combined transplantation. Islet after kidney transplantation should be restricted to selected patients, e.g. reduced general condition. In our institution we have restricted islet transplantation to patients with severe metabolic lability and frequent hypoglycemic episodes not aiming primarily for insulin independence but improved glycemic control along with a protective effect on micro- and macrovascular complications. A crucial prerequisite for islet transplantation is a stable kidney function. Vascularized pancreas transplantation is performed in patients with good general condition

capable for a major surgical procedure with potential complications. Furthermore we assign patients for solid organ transplantation that are rather compliant with taking oral immunosuppressive medication than insulin therapy. Since 2008 a total of 5 islet transplants, 3 simultaneous pancreas/kidney-, 1 pancreas-transplant alone and 1 pancreas after kidney transplantation have been performed at our institution. All recipients achieved stable metabolic control (absence of hypoglycemic episodes, normal HbA1c) and a major improvement in quality of life. According to our therapeutic concept, islet patients stay on minimal exogenous insulin, assuming a protective effect on long term islet graft function. The vascularized transplanted patient (pancreoprive diabetes) is off insulin. The decision which patient should receive an islet or vascularized pancreas transplant is highly individual and driven by kidney function, metabolic regulation, general condition and patient compliance/ preference. An individualized treatment plan should be set up by an interdisciplinary board of transplant specialists clearly defining therapeutic goals and expectations for both, patient and physician.

0351 LEVELS OF SMICA, AS DETECTED BY A HIGHLY SENSITIVE LUMINEX ASSAY, HIGHLY ASSOCIATE WITH GRAFT REJECTION

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Introduction: MICA (MHC class I polypeptide-related sequence A) genes are a highly polymorphic lineage of non classical HLA-genes. They act as ligand for the activating NKG2D-receptor on natural killer (NK) cells. MICA-antibodies and sMICA (soluble form of the MICA-antigen) have been implicated in immunological processes in the transplantation setting as well as in autoimmune diseases and cancer.

Methods: We developed a highly sensitive Luminex assay for detection of sMICA. Detection threshold was approximately 5pg/ml, although lower target values can be extrapolated by the system. Our method is 10 times more sensitive than conventional ELISA assays. We tested 25 post transplant serum samples of two groups of solid organ recipients. Group 1: recipients with stable graft function ($n = 16$; serum samples deriving from post Tx days 2–745, median day 12); group 2: recipients with acute rejection (AR) or acute tubular necrosis (ATN) ($n = 9$; serum samples deriving from post Tx days 3–610, median day 8). DNA-samples of 15 transplant recipients were available and in these samples MICA typing was performed by an in house Sequence Based Typing-method which included testing for exons 2–5. As a control the serum sMICA levels were detected in a group of 75 healthy blood donors. Student t test as well as Chi square test were used for statistical evaluation.

Results: Results are summarized in table 1. The absolute sMICA levels were significantly higher in the serum of patients with AR/ATN (group 2) as compared to patients with stable graft function and healthy controls ($P = 0.036$ and 0.026 respectively). When using a positivity cutoff of 10 pg/ml separation power was even higher ($P = 0.042$ and $P < 0.001$, respectively). Comparison of sMICA levels in the stable graft and control groups did not reach statistical significance neither for absolute nor for positive/negative assignment ($P = 0.37$ and 0.79 respectively). The recipients with the highest levels of sMICA in both groups were carriers of MICA*008 (A5.1), which is not only the most frequent MICA allele, but also characterized by a stop codon in exon 5 leading to a truncated protein with defective membrane anchorage.

Discussion: We speculate that sMICA levels are influenced by two factors: Presence or absence of the A5.1 allele and presence or absence of disease activity (cell turnover). Larger studies are needed to assess the relationship between sMICA, MICA-genetics and rejection. As sMICA might have immunomodulatory effects due to the functional interactions with NK cells, assessment of sMICA levels may have implications for graft outcome prognosis as well as donor allocation.

0352 IMMUNOSUPPRESSANTS INDUCED CHANGES IN MICRO- AND MACROCIRCULATION: A PROSPECTIVE STUDY IN HEALTHY SUBJECTS AND PATIENTS AFTER KIDNEY TRANSPLANTATION USING INTRAVITAL MICROSCOPY, OXYGEN SPECTROSCOPY AND COLOUR-CODED ULTRASOUND

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Chronic allograft dysfunction after kidney transplantation is a multi-factorial pathophysiological entity. Several trials indicate a potential role of immunosuppressants (IS) per se in this context. Especially calcineurin inhibitors are known to reduce dose-dependently reduce renal blood flow by renal vascular vasoconstriction in animal models (Murray et al., Kidney Int, 1985). This study evaluates microcirculatory changes of cyclosporine (CyA), tacrolimus (Tac) and mycophenolat mofetil (MMF) in healthy volunteers and patients after kidney transplantation.

Methods: After approval of the University of Munich ethical committee $n = 18$ healthy volunteers and $n = 18$ patients 10–14 days after renal transplantation were assigned to receive CyA, Tac, and MMF ($n = 6$ per group). Exclusion criteria healthy subjects/ patients: chronic medication, hypertension, history of tumor/ >2 or i.v. anti-hypertensive drugs. Measurements (macrohemodynamics, intravital microscopy (OPS imaging, Cytoscan), tissue spectroscopy with laserdoppler flowmetry (O2C) and colour-coded ultrasound) were performed 30 min. before oral IS application, and 30, 60, 120, 180, and 240 min. after application under standardized conditions (20°C, dark room). Plasma concentrations of IS were measured as well as standard laboratory parameters. Microcirculatory analysis discriminated between arteriolar and venular flow. Vasoreactivity was quantified after 90s forearm ischemia. Resistive indices as well as arteriole-capsular distances were measured to quantify kidney perfusion.

Results: Patients receiving MMF (66.0 ± 0.4 ys.) were significantly older than patients receiving CyA and Tac (CyA: 49.5 ± 5.9; Tac: 43.7 ± 3.4; $P < 0.05$). Serum creatinine and BUN were higher in Tac patients compared to CyA and MMF (higher immunological risk transplants). Standard coagulation parameters, HLA mismatches, cold ischemia times, blood haemoglobin and hematocrit as well as leukocyte counts did not differ between groups. There were no differences in healthy volunteer subgroups in terms of age (mean age: 26.7 ys.), creatinine, BUN, INR, PT., D-Dimer, hemoglobin, hematocrit, platelet counts, and leukocyte counts ($P > 0.05$). IS plasma concentrations 120 minutes. after IS application were comparable between healthy volunteers and patients (about 1.100 ng/ml for CyA, 8 ng/ml for TAC, and 12–15 yg/ml for MMF). Mean arterial pressures and arterial oxygen saturations were not changed by IS application, and did not show significant discrepancies between groups. In healthy volunteers TAC induced a significant reduction in the number of perfused vessels 30 minutes. ($P < 0.01$) and 180min. ($P < 0.01$) in healthy subjects. A comparable trend was seen with CyA. In patients resistive indices in kidneys were significantly increased ($P = 0.005$) after CyA, whereas MMF and TAC application did not induce significant changes.

Conclusions: The combination of different devices allows non-invasive analysis of the microcirculation in healthy subjects and after kidney transplantation. We could not show an effect of IS on macrohemodynmics and oxygen saturation. CyA induced a distinctive microhemodynamic regulation that was not observed with MMF. This changes correlated with an increase in resistive index in the renal grafts. These non-invasive microcirculatory measurements could allow to quantify CNI toxicity in humans, and could be used to optimize immunosuppressant protocols.

0353 EVALUATION OF ORGAN DONOR CARD HOLDERS AMONG AN EMPLOYEE CLUSTER IN A MAJOR GERMAN CITY

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Introduction: In Germany each year, the lack of donor organs results in more than 1,000 patients dying while on the transplant waiting list. At the same time, there is an organ donor potential that is not being exploited. Objective of this study was to collect the rate of holders of organ donor cards among an employee cluster in a major German city.

Methods: In 2009, a survey was conducted among employees of a public institution in Essen, North Rhine-Westphalia, Germany, regarding the topic of organ donation. Gender, age and the ''indicator for organ donation willingness'' were stratified and analyzed according to the holding of organ donor cards.

Results: A total of 974 completely answered questionnaires were evaluated; 21.2% of the respondents had an organ donor card. A marginal statistically significant association between genders (*P*-value 0.0438) respectively age (*P*-value 0.0267) and possession of a donor card could be determined. A significant correlation (p-value <0.0049) between the ''indicator for organ donation willingness'' and possession of an organ donor card was observed.

Discussion: Based on current research, we consider an up-to-date, broader reaching, representative inquiry necessary for our society. Should this present similar results, then a special education campaign is necessary, which considers socio-cultural backgrounds and responds to the ''indicator for organ donation willingness'' that we analyzed. In doing so, one individual goal is the promotion of health and body awareness and thus an increase in the potential organ donor willingness associated with it.

Keywords: organ transplantation, organ donation willingness, organ donor card, indicator.