

POSTERS

KIDNEY

P001 KYNURENINE AS AN EARLY MARKER FOR COMPLICATIONS AFTER RENAL TRANSPLANTATION

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Aim: By this largest study as yet we want to clarify the suitability of Kynurenine (KYN) – the primary degradation product of the amino acid tryptophan – to detect post-transplant complications.

Methods: The KYN serum levels were quantitatively measured [$\mu\text{mol/l}$] in 4083 blood samples from 355 kidney transplant recipients. Statistics: ANOVA.

Results: (i) In recipients with immediately functioning grafts ($n = 212$), the KYN levels dropped down from pre-Tx 13.3 ± 5.9 to 5.8 ± 3.0 at post-Tx day 5 with subsequently further reduction (normal value: 2.7 ± 0.6). In recipients with delayed graft function, the reduction of the KYN levels started only after the last hemodialysis. (ii) The increase of the KYN levels in connection with ARs depended on the severity of ARs. In hemodialysis-free recipients the KYN levels increased within one week pre-AR to 6.0 ± 6.1 in steroid-sensitive ARs, to 12.9 ± 7.1 in steroid-resistant ARs and to 16.9 ± 9.1 in vascular rejections. (iii) All infections evaluated were associated with significantly elevated KYN levels already before the final diagnosis (5.7 ± 3.4 in asymptomatic CMV infection; 7.5 ± 4.4 in CMV disease; 8.3 ± 3.3 in pneumonia and 10.4 ± 6.5 in sepsis).

Conclusion: The KYN serum level is an additional reliable marker for detection of a broad spectrum of complications and for monitoring the efficacy of therapeutic measurements.

P002 SUCCESSFUL KIDNEY TRANSPLANTATION IN PATIENTS WITH AHUS UNDER PREEMPTIVE ECULIZUMAB THERAPY – A CASE SERIES OF FIVE PATIENTS

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Rationale: Recurrence of atypical hemolytic uremic syndrome (aHUS) is frequent after kidney transplantation, limiting transplant options for these patients. The reported incidence of 15–90% is largely dependent upon the underlying dysfunction of the complement system. The complement C5-inhibitor eculizumab effectively blocks terminal complement activation, thereby providing a specific therapeutic option.

Methods: Clinical and outcome data is reported from a case series of patients with a HUS, who successfully underwent kidney transplantation under preemptive eculizumab therapy at our University Hospital between 2010 and 2014.

Results: A series of 5 patients, among them 2 children, is presented. Four patients received living donor kidney transplantation, one patient was transplanted via regular waiting list. Eculizumab was given immediately prior to transplantation and after one week. Subsequent dosing intervals were two to four weeks. Outcome of these patients is excellent, with excellent allograft function and no recurrence of aHUS after a median follow-up of 30 [1–51] months.

Summary: Preemptive eculizumab therapy is effective in preventing recurrence of aHUS after kidney transplantation, thereby allowing access to transplantation for these patients, both, via living donor kidney transplantation or regular waiting list.

P003 WHO IS RESPONSIBLE FOR SURGICAL COMPLICATIONS AFTER KIDNEY TRANSPLANTATION? THE DONOR, THE PATIENT, THE IMMUNOSUPPRESSION OR THE SURGEON?

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We retrospectively analyzed risk factors for surgical complications (SC) in 405 patients transplanted between 2007 and 2012. We included patients from the ESP as well as highly sensitized and ABOi patients.

While cold ischemia time and donor age had no impact on SC, male gender, diabetes mellitus (DM) and postoperative dialysis were significant risk factors. Intense immunosuppression (IIS) with plasma exchange and B- and/or T-cell depletion caused significant more complications compared to standard IS (SIS). We could identify BMI > 30, DM as well as IIS as risk factors for wound healing disorders, but there was no difference in patients with SIS on mTOR inhibitors or MPA. No risk factors could be identified for lymphoceles or ureter complications but there was a significant impact of the surgeon performing the transplant ureter complications and severe complications (Clavien ≥ 3) in general.

We conclude that donor age or ischemia time were no risk factors for SC, but DGF increases the complication rate independent of donor or recipient age. Patients with DM, obesity and IIS are more likely to develop wound complications but the only identified risk factor for ureter complications is the surgeon performing the transplant leading to a significant impact of the surgeon on severe complications.

P004 ANGIOTENSIN TYPE 1 RECEPTOR ANTIBODIES: A POTENTIAL FACTOR IN TRANSPLANT GLOMERULOPATHY

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Transplant glomerulopathy (TG) is the most common cause of graft failure in kidney transplantation and is not necessary due to the presence of HLA antibodies. Angiotensin II type 1 receptor antibody (AT1RAb) and endothelin 1 type A antibody (ETARAb), two recently described non-HLA antibodies, are implicated as independent risk factor of acute vascular rejection in the absence of donor specific antibodies.

In a single centre retrospective study, we analysed from the ANZDATA registry, all of the TG patients, transplanted between 1980 and 2011, who met with TG Banff criteria. All were tested by a solid phase assay method for AT1RAb and ETAR and by Luminex single antigen for DSA.

Eight percent (141 patients) of the 1729 patients recorded along the period study met the TG biopsy proven criteria. More than 50% of this TG group had a value for AT1RAb and ETARAb >10 U/ml. Of the 89 TG patients tested for AT1RAb at transplantation, 38 were positive for AT1RAb. We showed a strong link between the value of AT1RAb and patient survival with a significant risk of death in the high value group (>17 U/ml). The presence of DSA did not correlate with AT1RAb and 8 of the 38 patients developed TG were positive for AT1RAb tested at transplantation without DSA or HLA antibodies, suggesting an independent role of AT1RAb in TG.

In conclusion, the prevalence of AT1RAb is high in this large cohort of TG and may be involved in the TG development independently of DSA.

P005 A PILOT STUDY IN KIDNEY TRANSPLANT RECIPIENTS TO ASSESS THE SUITABILITY OF ACTIVATED BZLF1 FOR THE MONITORING OF EBV-SPECIFIC CELLULAR IMMUNITY

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Objectives: In immunocompetent individuals, Epstein-Barr virus (EBV) infections are effectively controlled by cell-mediated immunity (CMI). Impairment of CMI by immunosuppressive therapy after transplantation occasionally causes EBV-reactivation which can be associated with serious clinical complications i.e. PTLD. The aim of the pilot study in renal transplant recipients was to evaluate the suitability of *activated (a)* BZLF1 to assess the functionality of BZLF1-reactive effector cells in the course of immunosuppressive treatment. Herein, (a)BZLF1 reveals the unique property to stimulate a broad spectrum of antigen-reactive effector cells.

Methods: We performed a two year prospective observational study in a cohort of 83 renal transplant recipients, of whom 92.8% revealed a positive EBV serostatus. Heparinized blood of patients was collected pre- and at different time points post transplantation. Functional BZLF1-reactive T cells were quantified applying (a) BZLF1 as stimulator antigen combined with the sensitive IFN- γ ELISpot. EBV load was determined in serum samples using quantitative PCR.

Results: Prior to transplantation, a significant (a)BZLF1-reactive CMI was detected in 60.9% of EBV-seropositive patients followed by a substantial decrease in the first three weeks post transplantation. In some patients, (a) BZLF1-reactive cells started to recover in month 6–18 reaching in part maximum levels exceeding even those observed prior to immunosuppression. Transient and weak, clinically inapparent EBV-reactivation was observed in 53% of the patients. Importantly, analysis of individual patient courses revealed that EBV-reactivations occurred preferentially at times with low numbers of (a) BZLF1-reactive effector cells.

Conclusion: Monitoring of functional (a)BZLF1-reactive CMI may be an interesting novel strategy to assess the risk for EBV-reactivation in immunocompromised transplant recipients.

P006 IMPACT OF ROUTINE USE OF URETERAL STENTS IN YOUNG AND OLD KIDNEY TRANSPLANT RECIPIENTS

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Background: Ureteral stents are commonly used in kidney transplantation, but data on their use in elderly recipients are scarce. We sought to evaluate the impact of routine ureteral stenting in kidney transplant recipients over 65 years (ESP; Eurotransplant Senior Program) compared to younger recipients under 65 years.

Methods: In this retrospective, single-center study, data of 1247 patients transplanted between 1 January 2000 and 21 December 2010 in Innsbruck were evaluated. Complication rates, shortterm and longterm outcome of 193 elderly patients and 1054 younger patients were investigated.

Results: Elderly recipients (median age: 68.17 \pm 2.75 years) had a lower patient (old vs. young: 5 years: 71.2% vs. 89.1%, 10 years: 50.6% vs. 79.2%, $P < 0.001$) and graft survival (old vs. young: 5 year: 65.9% vs. 79.6%, 10 years: 44.8% vs. 61.9%, $P < 0.001$) than younger patients (46.22 \pm 12.13 years; $P < 0.0001$). However, both groups showed a comparable graft survival censored for patient death with a functioning graft (10 year graft survival 72.5% vs. 75.6%, $P = n.s.$). Elderly recipients suffered more frequently from urological complications than younger patients (old vs. young 25.39% vs. 17.84%, $P = 0.015$). Next, ureteroneocystostomy techniques (Lich-Gregoire, LG, vs. Leadbetter-Politano, LP) were analysed. While there were no differences in elderly patients, the LG-technique was associated with a lower rate of ureteral stenosis in younger patients (LG vs. LP: 1.59% vs. 6.67%, $P = 0.007$).

Overall, patients with ureteral stents had fewer ureteral complications (stenosis: 8.33% vs. 2.13%, $P < 0.0001$; urine leakage: 1.44% vs. 0.24%, $P = 0.049$). When comparing the impact of stents in both age groups, the use of stents was associated with lower complication rates in younger patients, whereas elderly patients with a splint suffered more frequently from ureteral reflux. However, ureteroneocystostomy techniques or the routine use of stents did not impact on graft or patient survival.

Conclusion: Aged recipients had a lower patient and graft survival, yet graft survival censored for patient death was comparable between the groups. Routine ureteral stenting should be recommended as it was associated with lower complications rates without impacting on graft survival.

P007 NO ASSOCIATION BETWEEN TLR4 MUTATIONS D299G AND T399I AND GRAFT SURVIVAL IN MODERN ERA OF KIDNEY TRANSPLANTATION

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TLR4 displays a key player in innate immunity with a central role in fundamental processes in organ transplantation. Several studies showed conflicting results of genetic variations in TLR4 on transplant outcome, i.e. acute rejection episodes or graft survival.

Therefore we assess the impact of the two functional TLR4 polymorphisms (SNP) [D299G (s4986790), T399I (rs4986791)] on long-term graft survival as well as acute rejection episodes during the first year after kidney transplantation in 1992 donor-recipient pairs, randomly selected from the Collaborative Transplant Study.

Both TLR4- SNPs were in Hardy-Weinberg Equilibrium. According to acute rejection episodes there was no impact of both recipient or donor TLR4 SNPs. Furthermore, recipient as well as donor TLR4 T399I polymorphism showed no influence on graft survival. Interestingly, we found a trend for reduced graft survival in recipients bearing a TLR4 D299G mutated kidney. This trend was particularly driven by patients transplanted between 1989 and 1993, and could not be seen in patients transplanted thereafter.

In conclusion our data of a large cohort of kidney transplant recipients as well as their deceased donors show no impact of the TLR4 mutations on graft or patient survival in modern era of kidney transplantation.

P008 CORRELATION BETWEEN COLD ISCHEMIA TIME AND MONOKINE INDUCED BY IFN- γ (MIG) IN KIDNEY TRANSPLANTATION

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Introduction: In addition to other causes, the duration of cold ischemia is hold responsible for the extent of the ischemia-reperfusion injury of the graft. We investigated if there are parameters which are correlated with the cold ischemia time (CIT), and accordingly allow conclusions about the quality of the graft.

Materials and Methods: In 34 patients, who received a kidney transplant at our hospital, the pro-inflammatory urinary cytokines interleukin 6 (IL6), interleukin 8 (IL8) and the chemokine MIG were measured both before and after surgery. The CIT was <10 h in 20 patients (group 1) and longer than 10 h in 14 patients (group 2).

Results: The median values of the cytokine levels of the patients in group 2 (>10 h CIT) are higher than the ones in group 1 (<10 h CIT). The same conclusion applies the glomerular filtration rate, measured 3 months and 1 year following surgery.

These differences in the groups are only significant for MIG, measured in the first urine after transplantation ($P = 0.012$, Mann-Whitney U-Test). A significant positive correlation was detected between the duration of cold ischemia time and urinary MIG ($r = 0.449$, $P = 0.011$, Spearman rank correlation).

Conclusion: Urinary MIG is correlated with the duration of the CIT and could possibly help to provide information regarding the extent of ischemia-reperfusion injury.

P009 ACTIVATION OF INNATE IMMUNITY IN THE DONOR AND RELATION TO INDUCTION TREATMENT

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Microcirculatory changes, inflammation and scarring might be responsible for kidney failures. We hypothesized that investigating (early) inflammatory parameters like Kynurenine (Kyn), HMGB-1, IMPDH, CRP and C5b-9 could give predictive information about delayed graft function (DGF), rejection (AR) and long term survival (GS). Depleting anti-lymphocyte or-thymocyte polyclonal antibodies as induction treatment could have influence on this response and results.

Patients and Methods: In a consecutive group of patients transplanted between 10/1989 and 06/1992 ($n = 324$) treated either with quadruple drug induction (QDT, $n = 238$; ATG-F, CsA, AZA, MP) or triple drug (TDT, $n = 86$; CsA, AZA, MP) as immunosuppressive therapy.

Results: There was a significant difference between HMGB-1 in PF versus DGF. This was found even 14 days after transplantation (correlation HMGB-1 and DGF $r^2 = 0.718$) HMGB-1 in ATG-treated patients at week 1 after transplantation was decreased by 82% whereas elevated by 24% in TDT patients. With Kyn we differentiated two groups of patients, all with no surgical failures, no delayed graft function, no rejection episode and no CMV-reactivation within the first 2 months: Gr.I ($n = 52$) involved patients showing

Kyn levels $<4.0 \mu\text{mol/l}$, Gr.II ($n = 53$) $>5.0 \mu\text{mol/l}$ at day 21 and thereafter at least for 3 times. There was no statistic difference in demographic data between both groups. Gr. I showed 1/5/10 year graft survival of 100/89/71% vs. Gr.II with 87/54/31% ($P < 0.001$ at year 5 and 10, all data death censored). Kyn was already upregulated in the donor, without any predictive value for the outcome. CRP showed no predictive value and IMPDH was significantly higher in pretransplant probes.

Conclusion: Monitoring of Kyn is a novel non-invasive tool of immune monitoring with the potency of discrimination concerning long-term function. Results are supporting the idea of pretreatment to suppress innate immune reactions in the donor. These results were a proof of concept for preconditioning of donors.

We propose that the results are not independent but represent distinct injury: inflammation reflecting the cumulative burden of injury over time. "Silencing" inflammation and protection of scarring as an overreacting innate system might be responsible for good long term outcome.

P011 BLOOD GROUP RELATED WAITING TIME FOR A DECEASED DONOR KIDNEY IN SAXONY-ANHALT, GERMANY

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Purpose: In Germany the active waiting list for kidney transplant covers more than 8.000 patients. Expected waiting time for a new organ is one of the key issues for the patient influencing quality of life and survival. Eurotransplant official data suggest a median waiting time of 48 month, which can not be generalized due to various and possibly confounding allocation parameters. Purpose of this study was to analyze the influence of several parameters of the Eurotransplant allocation system (ETKAS) on individual waiting time.

Method: Retrospective cohort analysis of $n = 369$ transplant recipients at Saxony-Anhalt Renal Transplant Unit. Respectively, overall waiting time, blood-group related waiting time, European senior program (ESP), acceptable mismatch program (AM), living kidney donation (LKD), full house or high urgent allocation (OMM/HU) and other allocation parameters were evaluated. Descriptive statistical analysis was done with SPSS 17.0.

Results: Mean age was 52.2 ± 13.1 years, 65.3% were male, overall average waiting time was 53.9 ± 36.6 month. After adjustment for the above mentioned parameters (e.g exclusion of living kidney donations etc.), the average "censored" waiting time for a deceased donor kidney was 79.5 ± 28.1 month with longest waiting periods for blood group 0. Allocation to ESP reduced waiting time significantly. Subanalysis of blood group related waiting time, considering other ETKAS-parameters showed differences in waiting time from 32.5 ± 16.6 month for blood group AB versus 100.5 ± 21.1 month for blood group type 0.

Conclusion: Expected waiting time for a deceased donor kidney may vary according to individual situation and allocation parameters. Especially blood group related waiting time shows significant differences which may lead to disadvantages in recipient's morbidity, mortality and graft survival. Further investigation on outcomes should be performed. A different weighting of blood groups within our allocation system needs to be discussed.

P012 EARLY IDENTIFICATION OF A PATIENT WITH ACUTE CELLULAR REJECTION BY DETECTION OF PERFORMED ALLOREACTIVE T CELLS AGAINST THE DONOR

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Performed cellular alloreactivity may cause graft rejection although its determination is not implemented in clinical routine. We present the case of a 76-year-old female patient, where the flow-cytometric determination of performed T-cell alloreactivity against the donor helped in guiding anti-rejection therapy.

The patient had a negative crossmatch and did not show any panel-reactive antibodies. Diuresis started after transplantation but ceased shortly thereafter with concomitant rise in resistance indices. As cellular rejection was suspected, the patient received a three-day steroid pulse-therapy. As the clinical course did not improve and performed alloreactive CD4 (0.0435%) and CD8 T cells (0.2656%) against the donor were clearly detectable, therapy with antithymocyte globulin (ATG, 800 mg/5 days) was initiated. Although the biopsy during steroid pulse-therapy did not show evidence for acute rejection, diuresis rapidly increased after ATG-therapy, and serum creatinine decreased thereafter (2.04 mg/dl at discharge day 27; 1.27 mg/dl day 56). Histological analysis of a biopsy after 7 weeks only showed borderline changes.

In the absence of biopsy-proven evidence for acute rejection, performed alloreactive T cells led to an early initiation of steroid- and ATG-therapy. As the patient had no other risk factors for acute rejection, this case illustrated how performed alloreactivity may predict acute rejection after transplantation.

P013 IMMUNE MONITORING IN BK VIRUS NEPHROPATHY: HOW TO IDENTIFY RECIPIENTS AT THE HIGHEST RISK

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Quantification of BKV-load and BKV-specific immunity have been evaluated to monitor BKV-replication. Knowledge of risk factors, outcome, and immune markers, however, remains scarce.

We studied all kidney transplant recipients (KTRs) at our center between 2004 and 2012. 103 of 862 KTRs were diagnosed with BK viremia, among which 24 KTRs showed BKV-associated nephropathy. A control group of 598 KTRs was used for comparison. Samples were collected before, at +1, +2, +3 months posttransplantation. BKV-specific, CMV-specific, and alloreactive T-cells were measured using an interferon- γ Elispot assay. The extent of immunosuppression was quantified by lymphocyte subpopulations and cytokines.

Lymphocyte-depleting induction, CMV-reactivation and acute rejection increased the risk of early-onset BKV-replication, while sensitized KTRs were at risk of late-onset BKV-replication ($P < 0.05$). KTRs with early-onset BKV-replication showed a decline in BKV-specific T-cells from pre- to posttransplantation ($P < 0.001$). They showed lower CD3+, CD4+, CD8+ T-cells, and interferon- γ levels posttransplantation, but higher alloreactive T-cells ($P < 0.05$). KTRs with BKV-replication showed inferior allograft function ($P < 0.05$).

Our data suggest monitoring BKV-specific T-cells pre- and posttransplantation as a sensitive marker to identify KTRs at increased risk. Marked overimmunosuppression predisposes KTRs to a loss of protective BKV-specific immunity and early-onset BKV-replication. Increased alloreactive T-cells may contribute to inferior long-term allograft function.

P014 5-YEARS FOLLOW UP AFTER IMPLANTATION OF A SACRAL NEUROSTIMULATOR IN A KIDNEY TRANSPLANT RECIPIENT

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Purpose: Impaired bladder emptying due to a hypocontractile bladder negatively affects renal function in kidney transplant recipients.

Material and Methods: We present a case of a 65-year-old male patient who presented with symptoms of voiding dysfunction after kidney transplantation. The patient was followed 5 years. Statistical analysis was performed using SPSS 12.0.

Results: After successful kidney transplantation sonographic assessment revealed a residual urinary volume of 386 ml. An urodynamic evaluation showed a hypocontractile bladder. After failure of conservative treatment intermittent self-catheterisation was necessary, which resulted in recurrent lower urinary tract infections and two episodes of transplant pyelonephritis. The patient was offered sacral neurostimulation (SNM). During test stimulation, he reported a distinct improvement of the voiding dysfunction with residual urinary volumes of about 90–120 ml. He then underwent an implantation of a sacral neurostimulator without adverse events. The immuno-suppressive regime was not interrupted. During the following 5 years the bladder as well as the renal function remain stable with a residual volume decreased to 20 ml and a creatinine of about 100–110 $\mu\text{mol/l}$.

Conclusions: Sacral neurostimulation might be a useful treatment to protect the transplant graft in patients with kidney allograft and voiding dysfunction because of a hypocontractile bladder.

P015 ACOUSTIC RADIATION FORCE IMPULSE IMAGING (ARFI) AS A TOOL TO QUANTIFY TISSUE ELASTICITY IN RENAL ALLOGRAFT REJECTION

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Aim: Non-invasive diagnostics of renal allograft dysfunction includes today the use ultrasound parameters, such as the renal resistance index (RI). However, the gold standard for the diagnosis of transplant rejection remains the renal transplant biopsy. Acoustic Radiation Force Imaging (ARFI) -quantification is a novel ultrasound based method to measure tissue elasticity. Until today, only limited experience exists about the diagnostics value of this method in renal transplantation. Therefore, we studied ARFI measurements in comparison to renal resistance index at the time point of transplant biopsy for allograft dysfunction in renal transplant recipients.

Methods: ARFI was performed using "Virtual Touch tissue quantification" (Siemens Acuson S2000). ARFI was measured 5 times in the middle portion of the cortex after rest. Two RI values of different segmental arteries were obtained by color-coded duplex ultrasound. All ultrasound measurements were performed by one experienced operator (UE) at the time of transplant biopsy

(± 1 day), blinded to the histological result. The transplant biopsy was evaluated using the current Banff classification by an experienced pathologist. **Results:** We studied 58 renal transplant patients with a mean age of 53 ± 13 years (41 male). Transplant biopsy were performed in 26 patients during the first year post-transplant, in 32 patients after the first year. Histological categories according to the Banff categories (cat.) in relation to number of patients: cat. 1 (normal)-two, cat. 2 (Antibody-mediated rejection/AMR)-12, cat. 3 (Borderline changes)-12; cat. 4 (acute T-cell mediated rejection/ACR)-5; Cat. 5 (IFTA)-two, Cat.6 (other pathologies)-25. Cat. 6 was excluded from the current analysis due to heterogeneity of the pathologic diagnosis, cat.1 and 5 due to sparse patient cases. ARFI values were elevated in patients with AMR (2.4 ± 0.7 m/s) compared to patients with Borderline changes (2.0 ± 0.4 m/s), but did not differ from patients with ACR (2.2 ± 0.2 m/s). Especially patients experiencing AMR after the first year post-transplant showed elevated ARFI values (2.6 ± 0.6 m/s; $n = 10$). RI values were not different between all groups. Renal function showed a trend towards increased values in ACR.

Conclusions: ARFI as measure of tissue elasticity might be a valuable tool to identify risk patients by transplant ultrasound. Further analysis ARFI measurements in relation to renal allograft survival are needed to define the prognostic value for ARFI in renal transplantation.

P016

ALPHA-1-MICROGLOBULIN AND HAPTOGLOBIN AS BIOMARKERS FOR DETECTION OF ACUTE ALLOGRAFT REJECTION FOLLOWING KIDNEY TRANSPLANTATION

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Introduction: Early diagnosis of acute rejection and effective immunosuppressive therapy lead to improvement in graft survival following kidney transplantation. In this study, we aimed to establish a urinary protein profile suitable to distinguish between patients with rejection and stable graft function and to predict acute rejection based on postoperative collected urine samples. A further objective was to identify candidate proteins for the use as biomarkers in clinical practice.

Material and Methods: Urine samples of 116 kidney recipients were included. Rejection was proven by biopsy ($n = 58$) and stable transplant function was monitored for at least 2 years ($n = 58$). Postoperative urine samples were collected between 3rd and 10th day following transplantation. Urinary protein profiles were obtained by SELDI-TOF-MS. Protein identification and validation were performed using Multiplex-Fluorescence-2DE, Peptide Mass Fingerprinting and ELISA.

Results: A protein profile including 4 mass peaks differentiated acute rejection from stable transplants at the time point of rejection and at the postoperative state with 73% sensitivity and 88% specificity. Alpha-1-microglobulin (A1MG) and Haptoglobin (Hp) were identified as putative biomarkers. Protein levels were significantly higher in postoperative urine from patients with rejection (A1MG: $29.13 \mu\text{g/ml}$ vs. $22.06 \mu\text{g/ml}$, $P = 0.001$; Hp: 628.34 ng/ml vs. 248.57 ng/ml , $P = 0.003$). The combination of both proteins enabled the diagnosis of early rejection with 85% sensitivity and 80% specificity.

Conclusion: Protein profiling is suitable for non-invasive detection of rejection. A specific protein profile enables prediction of rejection in the immediate postoperative period. A1MG and Hp appear to be reliable rejection biomarkers.

P017

RELEVANCE OF URETERAL COMPLICATIONS IN KIDNEY TRANSPLANT PATIENTS

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Introduction: Ureteral complication may endanger the success of kidney transplantations.

Methods: We analyzed retrospectively whether the occurrence of such a complication led to an inferior outcome compared to transplant patients who had in this respect an uneventful transplantation.

Results: In our series of kidney transplants (total: 1218 patients) 50 patients underwent surgery for ureteral complications. The indications for the intervention were as follows: ureteral necrosis ($n = 5/10\%$), ureteral stenosis ($n = 26/52\%$), insufficiency of the ureteral anastomosis ($n = 11/22\%$), vesico-renal reflux ($n = 8/16\%$). Surgery for the complication was timed for ureteral necrosis

63.4 days (mean), for ureteral stenosis 367.16 days, for insufficiency 42.27 days and for vesico-renal reflux 718 days after the transplantation. Mean donor age was 53.18 years (28-72). Timing for surgery differed significantly and not surprisingly between correction of ureteral insufficiency/necrosis and correction of ureteral stenosis and vesico-renal reflux (t -test, $P < 0.05$). Creatinine levels within one year following successful correction of the underlying pathology were comparable to those of patients who had received a kidney without ureteral complications: ureteral necrosis: 1.85 mg/dl /ureteral stenosis: 2.53 mg/dl /ureteral insufficiency: 1.65 mg/dl /vesico-renal reflux: 2.43 mg/dl .

Discussion: The mean donor age in kidney transplants with ureteral complications showed no significant difference from kidneys without such drawbacks. The more favorable creatinine values following operations in ureteral necrosis and ureteral insufficiency in comparison to those in the later interventions because of other indications mirror the natural history of a kidney transplant. However, ureteral pathologies can be corrected without disadvantage to the transplant organ.

P018

TWO CASES OF ENTEROHEMORRHAGIC *ESCHERICHIA COLI* (EHEC) DETECTION IN SOLID-ORGAN TRANSPLANT RECIPIENTS

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We report two cases of EHEC detection in a male 55 year old patient after simultaneous pancreas-kidney transplantation in 2011 (patient A) and a male 60 year old patient after kidney transplantation in 2014 (patient B).

Prior transplant function was stable in both patients, they received our standard immunosuppression consisting of tacrolimus, prednisolone and mycophenolic acid.

Patient A had undergone cardio-pulmonary resuscitation in a peripheral hospital and was transferred to our transplantation unit suffering from severe sepsis of unknown origin. By means of a blood culture enterohemorrhagic *E. coli* was detected and stx1 gene was found encoding Shiga toxin 1. The Patient was treated on the ICU for 18 days undergoing continuous hemofiltration due to acute failure of the kidney transplant and combined antibiotic therapy including carbapenems, metronidazole and caspofungin. Sigmoidoscopy showed signs of a non-specific colitis. Restitutio ad integrum was achieved and the patient was dismissed with stable transplant function.

In patient B EHEC was detected accidentally in a fecal specimen that was taken due to mild diarrhea, apart from that the patient showed no clinical signs of sickness. All follow-up examinations did not detect EHEC again, defecation normalized spontaneously and no treatment was necessary.

Among the variety of microbiological agents causing severe infections in solid-organ transplant recipients EHEC has to be considered as well. The importance of the interdisciplinary collaboration between transplant center and microbiological institute is proved again.

P019

DIFFERENT WAYS OF PROTECTING A KIDNEY TRANSPLANT DURING AORTIC OR AORTOILIAC RECONSTRUCTION

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Introduction: If an aortic or aorto-iliac reconstruction is necessary in a patient who previously received a kidney transplant, there are different ways of preserving the perfusion of the graft during surgery. We present three different methods of how circulation to the transplanted kidney might be maintained.

Patient: The first patient had a high grade distal stenosis of the aorta and both common iliac and femoral arteries. The transplant kidney showed a deteriorating function. An aorto-bifemoral reconstruction with renal graft protection (temporary axillo-renal bypass) and later the implantation of the distal segment of the temporary bypass into the right branch of the bifemoral prosthesis was performed. After surgery the kidney function recovered and the patient had no more symptoms of claudication.

The second patient presented with a chronic Leriche syndrome. Further investigation revealed short-segment stenosis right above the aortic bifurcation. An aorto-biliac reconstruction with renal graft protection (temporary axillo-iliac bypass) was performed. Kidney function was well preserved and the patient was cured of his claudication.

The third patient underwent a repair of a suprarenal aortic aneurysm with a reinsection of the superior mesenteric artery and retrograde renal graft perfusion with a temporary axillo-femoral bypass. The intra- and postoperative kidney function was stable although the patient died on the second postoperative day due to a thrombosis of the first branch of superior mesenteric artery.

Discussion: If the expected ischemia of the graft exceeds time 30 min a temporary bypass procedure should be taken into consideration. Well-planned, in the hands of an experienced surgeon all of the methods seem to be effective.

P020 RENAL TRANSPLANTATION USING DONORS OLDER THAN 80 YEARS: A SINGLE-CENTER EXPERIENCE

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Background: Organ shortage has resulted in an increased use of older donors. We report the experience of our transplant center in the utilization of "very-old" (>80 years) donors in renal transplantation.

Methods: Between 2002 and 2013, 23 grafts from donors aged 80 years or older (mean age 83.4 ± 3.6 years, range 80–95 years) were used for 19

patients: 15 as single and 4 as double transplants (mean cold ischemic time 9.6 ± 2.9 h). Mean recipient age was 69.3 ± 3.7 years.

Results: Cumulative graft survival at 1, 3, and 5 years were 78%, 63%, and 42%, respectively. Patient survival was 100%, 93%, and 78% at the same time points. Eighteen grafts (95%) had posttransplant function with a mean serum-creatinine of 2.1 ± 0.7 at the time of discharge. The delayed graft function rate and one-year acute rejection rate were 42% and 26%. After a mean follow-up period of 38.8 ± 24.7 months, 16 (84%) patients were alive. 11 (58%) patients have a functioning graft with a mean serum creatinine of 2.3 ± 0.7 mg/dl. Two patients died with a functioning graft.

Conclusion: The results regarding graft survival and graft function are slightly worse than in our "old-for-old" program using donors aged 65–79 years, but still generally acceptable.

KIDNEY / PANCREAS

P023 THE ADRENAL GLAND AND PANCREATIC ISLETS: A BENEFICIAL ENDOCRINE ALLIANCE?

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A major limiting factor for long-term survival and function of islet transplants is in regard to the inappropriate microenvironment after intraportal transplantation. We aim to evaluate the microenvironment of the adrenal as a potentially beneficial transplantation site that promotes beta cell engraftment, survival, proliferation and long-term function as the adrenal offers extensive vascularization, anti-apoptotic and pro-proliferative effects of various signalling molecules and a local anti-inflammatory and immunosuppressive microenvironment.

For *in vitro* analysis of islet viability, function and reactive oxygen species (ROS) a co-culture system of adrenal cells and pancreatic islets was established. Pancreatic islets and adrenal cells were isolated from Wistar rats and co-cultured using inserts for up to 7 days and sequentially assayed for viability, insulin secretion and reactive oxygen species (ROS). The co-culture setting did not significantly impact on islet viability, insulin content and secretion and there is evidence that oxidative stress is markedly reduced in the presence of adrenal cells.

For *in vivo* studies, Streptozotocin induced diabetic NuNu-mice were used as islet recipients. For islet transplantation, the adrenal was exteriorized via retroperitoneal incision and 300 islets were injected through the upper pole of the gland or the kidney. Animals showed a fast decrease in blood glucose levels within the first days after transplantation in both groups, at around 10 days the curves between adrenal and kidney site drifted apart in favor of the adrenal site. Regardless of the transplantation site, islets showed a well preserved morphology and intense insulin staining. The intra-adrenally engrafted islets show higher vascularization compared to the kidney capsule control.

The preliminary work underlined the feasibility of islet transplantation into the adrenal with first promising results on the restoration of normoglycemia. The results achieved could prove the beneficial effect of the adrenal microenvironment on islet engraftment and function *in vitro* and *in vivo* and elucidate the underlying mechanisms in regards to promoting islet revascularization and protection from oxidative stress.

This novel concept might allow reducing the islet mass that is currently needed to reverse diabetes.

P024 PATIENT AND GRAFT SURVIVAL AFTER PANCREAS RETRANSPLANTATION: A RETROSPECTIVE ANALYSIS OF THE OUTCOME IN A SINGLE CENTER

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Introduction: Different complications can lead to the loss of the pancreas graft. Retransplantation may be a therapeutic option.

Methods: Between 1994 and 2014 in total 517 pancreas-Tx were performed with 39 s and third Re-PTX. Graft and patient survival rate were compared in the primary transplant and the retransplant group between 1996 and 2014. Causes of primary and secondary graft loss were analyzed.

Results: Graft loss following the first transplantation was caused by thrombosis (38.9%), chronic rejection (30.6%), severe pancreatitis (8.3%) and unknown reasons (22.2%). Reasons for pancreas graft loss after the second transplantation were thrombosis (9.5%), acute and chronic rejection (14.3%), severe pancreatitis (14.3%), sepsis with bleeding and death of the patient (57.1%) and unknown (4.8%). The median time until pancreas graft loss was 908 days. The median time between graft loss and retransplantation was 586 days. The median time between first and second transplantation was 1463 days. Total pancreas graft survival rate was 79.7%, 77.4%, and 73.2% after one, three and five years respectively in the comparison group. After second SPK the graft survival was 68.4%, 50%, 43.8% after one, three and five years and after second PAK 52.9%, 42.9% and 42.9% respectively. Total patient survival rate was 96.1%, 93.1%, and 91.2% after one, three and five years in our comparison group. After Re-PTx the patient survival rate was 80.6%, 72%, and 72% respectively. In total 13 patients died, 3 of them during the hospital stay after Re-Tx and 3 of them more than 8 years after Re-Tx. After the second transplantation 15 of 36 pancreas grafts are still working.

Conclusion: Although the results of second pancreas transplantation are inferior to the first transplant, pancreas retransplantation is a valuable option for patients with type I diabetes who lost their first graft especially with regard to spontaneous course of the disease.

P025 RECONSTITUTION OF HYPOGLYCEMIC COUNTERREGULATION AFTER ISLET TRANSPLANTATION

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Background: Long-standing type 1 diabetes (T1D) is associated with an absolute loss of endogenous insulin secretion and patients often exhibit defective glucose counterregulation and impaired hypoglycemia symptom recognition that substantially increase their risk for experiencing severe hypoglycemia.

In this project we sought to study the changes in counter-regulatory mechanisms and hypoglycemia symptoms in patients with type 1 diabetes and determine the effect of intrahepatic islet transplantation on glucose counter-regulation and hypoglycemia symptoms.

Methods: Patients with long-standing type 1 diabetes and severe hypoglycemia ($n = 9$) underwent induced hypoglycemic clamp while awaiting islet transplantation and every 6 months after intrahepatic single islet transplantation up to 2 years post transplantation. During induced hypoglycemia (≤ 3.0 mmol/l), plasma samples were taken for glucagon, insulin, pro-insulin, c-peptide, free fatty acids, cortisol, and catecholamines and autonomic symptoms were determined.

Results: Prior to transplantation, hypoglycemia induced basically no changes in glucagon or catecholamine levels indicating a highly defective counterregulatory system in patients awaiting islet transplantation due to severe metabolic lability. After islet transplantation all enrolled patients showed a restoration of endogenous insulin secretion and remarkable stabilization of blood glucose control. Comparison of pre- and post-transplant levels during hypoglycemia showed a substantial reconstitution of glucagonergic and adrenergic counter-regulation following islet transplantation.

Conclusion: The transplantation of isolated islets can restore β -cell secretory capacity, improve glucose counter-regulation, and return hypoglycemia awareness, thus alleviating severe hypoglycemia. This beneficial effect of islet transplantation is independent of achieving insulin independence.

A better understanding of the complex hormonal and autonomic defects in long-standing diabetes leading to severe hypoglycemia and symptom unawareness may not only be of general interest but moreover open up strategies for targeted treatment options bridging patients that await islet transplantation or even allow for an alternative treatment approach.

P026 EXTENDED INDICATIONS FOR ISLET AUTOTRANSPLANTATION – DRESDEN EXPERIENCE

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Objective: To assess metabolic outcomes of islet autotransplantation (IAT) in 12 patients undergoing pancreatic surgery for either benign or malignant disease.

Background: Traditionally islet autotransplantation is performed to improve glycemic control after extended pancreatectomy mainly in patients with chronic pancreatitis. Extending the indication for islet autotransplantation to patients with major complications following pancreas surgery for various reasons and to patients with pancreatic malignancies has been discussed controversially.

Methods: In addition to chronic pancreatitis, indications for islet autotransplantation were pancreatic anastomosis insufficiencies requiring completion pancreatectomy and distal/complete pancreatectomy for benign/borderline neoplasm of pancreatic body-neck including IPMN. Patients were followed metabolically by SMBG, glucose tolerance test and mixed meal test.

Results: 12 patients were autotransplanted with 150.000 ± 50.000 islet equivalents. The autotransplantation procedure was performed without complications. 2/12 patients died during hospital stay due to septic complications with functioning autografts. The remaining 10 patients showed good primary, 6 month and 1 year graft function with 50% of the patients off insulin. No graft failure was observed. HbA1c levels in all patients were normal after IAT. The mixed meal tolerance test showed similar results as the ivgt test with delayed c-peptide peak and slower return to baseline levels. No adverse events according to transfer of premalignant cells in to the liver was observed.

Conclusions: IAT results in a good glycemic control in all patients preventing overt pancreoprive diabetes with its complications. Although larger data and

controlled clinical trials are needed, our limited experience suggests that IAT indications can be possibly extended to selected patients with neoplasm.

P027 **SUCCESSFUL MULTIPLE PANCREAS
RETRANSPLANTATION IN COMBINATION TO RENAL
RETRANSPLANTATION: A SINGLE CENTER EXPERIENCE**

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Objective: Retrospective analysis of long term results regarding patient and graft survival, graft function and major complications in two patients after combined pancreas 4th-kidney 3rd and pancreas 3rd-kidney 2nd transplantation performed at our center.

Methods: Patient 1: A 47 years old woman underwent a combined pancreas 4th-kidney 3rd transplantation (after explantation of 2 previous kidney- and 2 pancreas-grafts). Patient 2: A 51 years old men underwent a combined pancreas 3rd-kidney 2nd transplantation (after explantation of the kidney graft).

The transplantations were performed due to standard techniques. The induction therapy consisted of Alemtuzumab and the maintenance immunosuppression of steroids, Tacrolimus, CellCept. Both patients are on permanent anticoagulation.

Results: No immunological complication occurred apart from one early reversible acute kidney rejection. Both patients are currently well within a stable pancreas and kidney function (mean serum creatinine 1.45 mg/dl, blood glucose 80 mg/dl). Leucopenia, thrombocytopenia, bacterial sepsis and chronic hepatitis C as major complications were controllable.

Conclusion: Good results can be achieved in multiple pancreas- retransplantations in combination to a simultaneous renal transplantation. An explantation of previously non functioning grafts could be favorable. An exact immunosuppression and careful monitoring basing on an excellent patients adhaerance would contribute to good long term results.

P029 **CD3-MEDIATED CONTRAST-ENHANCED SONOGRAPHY FOR
DIAGNOSIS OF ACUTE RENAL ALLOGRAFT REJECTION**

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Purpose: Here we evaluate contrast-enhanced ultrasonography targeting T-lymphocytes with anti-CD3 antibody labeled microbubbles for diagnosis and differentiation of acute renal allograft rejection in different rodent models of renal disease.

Methods: Uninephrectomized, allogeneically kidney transplanted rats [Lewis-Brown Norway (LBN) to Lewis, aTX] were intravenously injected with microbubbles conjugated to an anti-CD3 antibody. Ultrasound measurements of the transplanted as well as the native kidney were performed. Syngeneically transplanted kidneys (LBN to LBN, sTX), kidneys exposed to ischemia/reperfusion injury (IRI, 45 min warm ischemia), and kidneys subjected to acute cyclosporine A toxicity (CSA, 50 mg/kg for 2 days i.p.) served as controls. Post mortem histological evaluation of CD3 expression and quantitative real time PCR for KIM-1 were performed.

Results: Renal allografts demonstrating AR showed a significantly increased ultrasound signal (3.90 ± 0.50 A.U., $P < 0.05$, $n = 5-8$ in all groups) when compared to their native control kidneys (0.24 ± 0.12 A.U.).

Moreover, evaluation of signal intensities allowed a clear differentiation of AR from syngeneically transplanted kidneys without AR (1.31 ± 0.37 A.U.), kidneys with CSA toxicity (0.67 ± 0.27 A.U.) and kidneys with IRI (0.99 ± 0.28 A.U.). Finally, quantification of ultrasound signals correlated well with immunohistochemical analysis for CD3, but not with KIM-1 mRNA expression.

Conclusion: Contrast enhanced ultrasonography using anti-CD3-antibody labeled microbubbles is a non-invasive method to detect and differentiate AR from acute tubule necrosis and acute calcineurin inhibitor toxicity in different rat models of renal disease. Since in daily clinical medicine, sonography is easily available, fast, inexpensive and reproducible, this approach has significant potential for future application in patients.

INFECTIONS / COMPLICATIONS

P030 OUTCOMES AT 3 YEARS IN EBV+ EUROPEAN SUBPOPULATIONS FROM BENEFIT AND BENEFIT-EXT

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Background: The clinical profile of belatacept (bela) was demonstrated in two phase 3 studies; BENEFIT enrolled recipients of living donor or SCD kidneys, and BENEFIT-EXT enrolled recipients of ECD kidneys defined by UNOS criteria, anticipated CIT >24 h, or NHB donor. Each assessed a more (MI) and less intensive (LI) bela regimen vs. cyclosporine (CsA) in adult kidney transplant recipients. The bela LI regimen is approved for use in EBV+ recipients. Here we present *post hoc* analyses of 3-year outcomes in EBV+ patients (pts) in Europe (EU) from BENEFIT and BENEFIT EXT by donor type. **Methods:** EBV+ pts from EU were categorized by donor type: UNOS ECD in BENEFIT-EXT and deceased donors (DD, pooled from BENEFIT and BENEFIT-EXT). Endpoints evaluated at year 3 were death (D), graft loss (GL), cGFR, AR, and a composite endpoint (EP) of time to D, GL, or cGFR<30 ml/min/1.73 m².

Results: Among EU EBV+ patients in BENEFIT EXT, 67 MI, 69 LI, and 73 CsA received a UNOS ECD kidney. Of these, 54 (81%) MI, 60 (87%) LI, 59 (81%) CsA pts survived with a functioning graft; mean cGFR was 40 MI, 42 LI, 26 ml/min/1.73 m² CsA; AR was reported in 11 (16%) MI, 16 (23%) LI, 9 (12%) CsA pts. By 3 years, 26 MI, 21 LI, and 42 CsA pts met the composite EP.

Among EU EBV+ patients in the 2 studies 123 MI, 127 LI, and 118 CsA had a DD kidney. Of these, 107 (87%) MI, 116 (91%) LI, 102 (86%) CsA pts survived with a functioning graft; mean cGFR was 53 MI, 53 LI, 34 ml/min/1.73 m² CsA; AR was reported in 25 (20%) MI, 23 (18%) LI, 15 (13%) CsA pts. By 3 years, 30 MI, 25 LI, and 54 CsA pts met the composite EP.

The safety outcomes in the overall population of EBV+ pts were consistent to those of the ITT; the rates of serious adverse events in the cohorts presented here were similar between treatment arms.

Conclusions: Results of these analyses in EU EBV+ pts in BENEFIT and BENEFIT-EXT are consistent with those of the global ITT population and also demonstrate a lower rate of composite EP with both bela regimens vs. CsA.

P031 TREATMENT OF A SEVERE EARLY RECURRENT HCV INFECTION (GENOTYPE 1B) WITH SOFOSBUVIR, RIBAVIRIN AND SILIBININ: A CASE REPORT

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Introduction: A 53-year old female patient underwent liver transplantation (LT) for HCV-induced end-stage liver disease. 3 weeks following LT with good initial graft function using a Tacrolimus-based immunosuppressive regime, our patient developed severe HCV-recurrence with highly elevated aminotransferases and cholestasis. Viral load was 136.300.000 IU/ml, and recurrent hepatitis was confirmed histologically.

Methods: Due to imminent graft failure, Silibinin was administered intravenously as rescue therapy for 2 weeks (20 mg/kg of body weight), which resulted in a moderate decline of HCV copies to approximately 60.000.000 IU/ml. Treatment with the novel direct acting antiviral agent Sofosbuvir (400 mg od) in combination with Ribavirin (400 mg bid) was started.

Results: The combination of Sofosbuvir and Ribavirin resulted in a striking decline of HCV copies. Clinically, the patient improved markedly with resolution of HCV-related symptoms. Aminotransferases and cholestasis parameters normalized quickly. Sofosbuvir and Ribavirin showed no severe side effects or interaction with the immunosuppressive medication despite the early treatment period after LT. However, HCV viral load persisted at approximately 50 IU/ml.

Conclusion: Sofosbuvir and Ribavirin are applicable in the early course after LT and, in our case, resulted in good control of HCV replication with normalization of liver function. However, complete virus elimination was not achieved.

P034 INTRAVESICAL INSTILLATION OF COLISTIN AS A RESCUE APPROACH FOR THE TREATMENT OF A HIGHLY THERAPY-RESISTANT URINARY TRACT INFECTION WITH A MULTIRESTANT PSEUDOMONAS AERUGINOSA (4 MRGN) IN A KIDNEY TRANSPLANT RECIPIENT

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Background: Urinary tract infections are the most common infectious complications after kidney transplantation. Increasing resistance to broad-spectrum antibiotics is a growing problem in the treatment of infections especially in kidney transplant recipients. Frequently colistin, a very effective polymyxin antibiotic, remains the last-resort antibiotic for treating of bacteria involved in those potentially life-threatening events. However, systemic and especially prolonged use of colistin bears the risk of nephro- and neurotoxicity.

Results: We describe the medical case of a 73 year old female kidney transplant recipient with chronic graft failure (serum creatinine: 2.45 mg/dl). Four weeks after an episode of successfully treated urosepsis with *E. coli*, a recurrent transplant pyelonephritis and cystitis with a multiresistant *Pseudomonas aeruginosa* (classified as to 4 MRGN) was diagnosed. Antibiotic treatment with fosfomycin was already started at our outpatient clinic, but failed to eradicate the germ. A systemic therapy with the combination of colistimethate sodium, fosfomycin and meropenem was started after admission. Leukocyturia declined slightly, but urine cultures were still positive for *Pseudomonas* and resistance testing showed an increase in minimum inhibitory concentration for colistin and fosfomycin. Also, a preexisting diabetic polyneuropathy worsened dramatically during intravenous antibiotic therapy. Thus, we decided to deploy an intravesical treatment approach. Using a single-lumen urinary catheter we administered 100.000 IU of colistin in the subsequently blocked catheter over 90 min. This procedure was applied 3 times/day for 7 days. Additionally – to prevent endogenous reinfection – colistin sulfate was administered orally. Two days after completion the urine samples were sterile. Even 4 weeks after this phase the cultures were still sterile, with no signs of urinary tract infection.

Conclusion: Our case shows that urinary tract infections with multidrug-resistant *Pseudomonas* (susceptible to colistin only) can be successfully treated with intravesical instillation of colistin combined with selective decontamination of the bowel. Especially in kidney transplant recipients this could be a promising treatment option and should be considered in analogue situations.

P036 DIAGNOSIS AND MANAGEMENT OF POLYOMAVIRUS INFECTION AFTER PEDIATRIC KIDNEY TRANSPLANTATION

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Background: BK virus and John Cunningham virus (BKV an JCV) are viruses from the family of polyomaviridae. BKV-associated nephropathy is a severe complication after kidney transplantation. So far only little is known about relevance of JCV infections. We retrospectively analysed infections with BKV and JCV in a cohort of patients after pediatric kidney transplantation (pKTx).

Patients and Methods: 50 patients after pKTx in the age of 1–18 years were included, mean follow up was 4.9 years. In total 1764 BKV and 1689 JCV polymerase chain reaction (PCR)-measurements from urine and blood were analysed. Data on renal function, immunosuppressive and cidofovir treatment were recorded.

Results: 28/50 (56%) patients had evidence of polyomavirus infection. BKV-infections were more frequent than JCV-infections (BKV *n* = 16; BKV+JCV *n* = 9; JCV *n* = 3). Relevant viremia was only seen with BKV (14/25, 56%). Highest incidence of infections (*n* = 10) was during the first three months post transplant. Late infections (>3 months – ≤2 years after PKTx) were observed in eight and very late (>2 years) in ten patients. BKV copy number of >125.000 copies/ml urine was identified as prognostically relevant cut-off value for the development of a viremia (100% sensitivity, 93% specificity). Early reduction of immunosuppression was the main treatment approach, 12 patients received an additional 1–4 doses of cidofovir (0.5 mg/kg), which were well tolerated. Only one patient in our cohort developed BKV-associated nephropathy. Polyomavirus infection could not be identified as an independent risk factor worsening renal function. Treatment with tacrolimus and mycophenolate was not associated with a greater risk for BKV or JCV infection.

Conclusion: Polyomavirus-monitoring should be performed after pKTx, also during long-term follow up. We established a center-specific cut-off value for BKV copies from urine, which allows us to identify patients in which immunosuppression should possibly be reduced before viremia is developed.

P037 NOSOCOMIAL INFECTIONS IN A KIDNEY TRANSPLANTATION CENTER

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Introduction: Posttransplant bacterial infections are important because of their impact on patient and graft-outcomes. Therefore, efforts on preventing these infections are of great interest.

Material and Methods: In this surveillance study all hospital-acquired bacterial infections occurring during one year (2009) in a kidney transplantation center were analyzed and risk factors, such as age, gender, BMI, length of hospitalization and immunosuppression were investigated. Furthermore the microbiological spectrum of urinary tract infections (UTI) including the antibiotic resistance pattern was surveyed.

Results: 496 patients with 770 inpatient treatments were included in this study. 105 nosocomial infections occurred, whereas the infection rate among transplant recipients was higher than in non-transplant patients.

UTI were mostly diagnosed (63.8%, $n = 67$), followed by surgical site infections (15.2%, $n = 16$), pneumonia (12.4%, $n = 13$) and bloodstream infections (sepsis and catheter-associated bacteraemia) (8.5%, $n = 9$). 91% of UTI were associated with an indwelling urinary catheter. The most frequently isolated pathogens causing nosocomial UTI were *Escherichia coli* (37.8%), *Enterococcus* species (21.6%), *Enterobacter cloacae* (10.8%) and *Pseudomonas aeruginosa* (10.8%). High rates of bacterial resistance were detected for 3rd and 4th generation cephalosporins, fluorochinolones and co-trimoxazole. 100% of the isolated gram-negative bacteria showed carbapenem sensitivity.

Significant risk factors for the development of nosocomial infections were immunosuppression (especially immunosuppressive regimen with antithymocyte globulin) and BMI. Gender and age did not have a significant influence. The length of hospitalization was associated with higher rates of hospital acquired infections but also is extended by each infection in turn.

Conclusions: Reducing the time of long term catheterization (under surgical aspects as possible) and the duration of hospital treatment may prevent nosocomial infections in kidney transplant recipients.

P039 A COMPARATIVE ANALYSIS OF TWO ASSAY SYSTEMS FOR MONITORING CYTOMEGALOVIRUS-SPECIFIC CELLULAR IMMUNITY IN LUNG TRANSPLANT RECIPIENTS

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Objective: Monitoring the cellular immunity for Cytomegalovirus (CMV) in organ transplant recipients is a promising tool to support prevention strategies for posttransplant CMV infection or reactivation. Commercially available *in vitro* test systems differ substantially in their capacity to stimulate subpopulations of T-lymphocytes. We compared two assays for CMV immune monitoring in respect of their clinical practicability and significance.

Methods: Blood samples of 30 lung transplant recipients (LuTRs) were examined before transplantation and over a period of six months afterwards with T-Track[®] CMV (Lophius Biosciences GmbH, Regensburg) and QuantiFERON[®]-CMV (Cellestis GmbH, Darmstadt). The T-Track[®] CMV is based on ELISpot-technology, allowing quantification of interferon-gamma (IFN γ) secreting CD4+ and CD8+ T-cells after specific stimulation. Contrarily, the QuantiFERON[®]-CMV assay is restricted to detection of IFN γ secreted by CD8+ T-lymphocytes with ELISA. The data are evaluated in the context of transplant outcome and determination of viral load in plasma by qPCR.

Results and Conclusion: Both approaches provide similar results while exhibiting certain advantages and limitations. Early during immune suppressive therapy, QuantiFERON[®]-CMV generates often indeterminate results as depletion of T-cells is not taken into account. Although a comparatively large volume of blood is required, T-Track[®] CMV circumvents this drawback. In addition, T-Track[®] CMV reaches a higher sensitivity prior to LuTx and shortly after onset of immunosuppression.

ETHICS / PSYCHOSOMATICS

P040 SWITCH FROM HU TO VAD: PROBLEM-FOCUSED COPING AND PSYCHOTHERAPEUTIC INTERVENTIONS

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Introduction: Due to long HU-waiting time some patients have to be supported by VAD instead of heart transplantation. These patients have to deal with an addition surgical procedure, the loss of the HU-status, the emotional coping of disappointment and new challenges with the device.

Method: We present case reports of two patients with terminal heart failure who were listed for transplantation. The necessity for inotropes justified the HU status on the waiting list. The hemodynamic status deteriorated further, that finally a LVAD had to be implanted.

The patients reacted with acute stress disorder but differently according to their premorbid personality, decision making process and symptoms. A 34 year old man (DCM) suffered from severe fears of death and delirium in spite of his own decision pro VAD. A 45 year old male patient (DCM) described first a negative attitude against VAD and refused to accept the device. Consequently, specific psychotherapeutic treatments were installed in both cases.

Results: At first both patients described the disappointment about the loss of HU waiting time, the burden of an additional surgery, new future fears and finally, an emotional acceptance of a machine instead of a new heart and a sufficient quality of life on device. No further psychological complications occurred during the implantation and follow up processes.

Conclusion: Patients cope differently switching from HU waiting list to VAD program. Communication emphasizes on the life rescuing demand. Psychological treatment should be added to support individual coping styles. Further investigation (predictors, intervention) is needed.

P041 THE INFLUENCE OF THE SETTING ON ALCOHOL SELF-REPORTS: A COMPARISON OF THE SETTING OF LIVER TRANSPLANTATION AND REHABILITATION THERAPY

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Objective: For liver transplantation, patients with alcoholic liver disease are universally required to achieve a minimum of six months of sobriety prior to surgery. There is therefore a need to accurately measure the amount of alcohol consumption. Studies have found that self-report measures often underestimate the amount, as patients who abuse alcohol generally tend to minimize their drinking behavior. The present study investigates the influence of the setting on self-reported drinking behavior.

Methods: Patients prior to liver transplantation ($n = 40$) and patients in rehabilitation therapy ($n = 44$) were compared using the Munich Alcoholism Inventory, which consists of a self-report-scale and an expert-rating-scale.

Results: A significant difference in the MALT-self-report-scale and MALT-expert-rating-scale discrepancy was found between patients prior to liver transplantation and patients in rehabilitation therapy. Furthermore, patients in the rehabilitation therapy group reported higher alcoholism scores in the self-report questionnaire than patients prior to liver transplantation, but the groups did not differ in the expert evaluation value.

Conclusion: The transplantation setting seems to evoke minimizing in self-reports, in patients with alcohol abuse. Minimizing or denying alcohol consumption does not seem to be a specific characteristic of persons with alcohol abuse, as it is also caused by the circumstances. The results suggest the employment of biomarkers in addition to self-reports for a more precise appraisal of alcohol consumption and to relieve patients from the contradicting motivations of candor and self-protection.

P043 LONG TERM QUALITY OF LIFE AFTER COMBINED PANCREAS-KIDNEY TRANSPLANTATION

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Objective: In type I diabetics depending on dialysis there usually is a markedly decreased quality of life. There is only limited data on long term quality of life in patients after a simultaneous pancreas-kidney transplantation (PNTx).

Methods: The health related quality of life was measured with the Short Form Health Survey (SF 36) in 350 patients after PNTx. In a preliminary evaluation, the quality of life of 30 patients (17 m:13f) after successful PNTx and 30

patients on the waiting list (18 m:12f) were compared. The survey of the transplanted patients (mean duration of diabetes 29.38 ± 5.8 years) was conducted at a mean of 60 month after transplantation. The patients awaiting transplantation (mean duration of diabetes 28.97 ± 8.2 years) were listed for transplantation for a median of 622 days and were depending on dialysis for 1222 ± 899 days.

Results: Comparing the two groups there was a significant increase in physical functioning after PNTx ($P = 0.022$), general health perceptions ($P < 0.001$) as well as in mental health ($P = 0.007$). The psychological and social items showed a tendency towards improvement. There was no difference in emotional role functioning. The improvement of quality of life started being evident in the second year postoperatively. The subgroup analysis showed gender specific differences.

Conclusions: There is a significant increase in health related quality of life in patients after successful PNTx. This improvement usually is reached two years after transplantation.

P044 EVALUATION OF ADHERENCE TO TREATMENT AND COOPERATION IN PATIENTS PRIOR TO ORGAN TRANSPLANTATION – MORE THAN A FEELING?

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Adherence (compliance) to treatment and cooperation in the long term after organ transplantation is an important factor for a good long term outcome of organ transplantation. The evaluation of adherence as precondition for listing and organ allocation is required by the Transplantation Act and the Guidelines of the German Medical Association. Mostly factors as the patient's personality and psychopathology, patient's convictions on illness and treatment, acuteness and threat posed by the disease and factors of the patient-doctor-relationship are frequently named.

But yet there are neither clear and transparent criteria for the operationalization of adherence nor for a valid evaluation procedure for the prospective prediction of good and reliable adherence in long term treatment.

Reviewing the international literature (key words: adherence organ transplantation; compliance organ transplantation) since 1990 we tried to extract factors with a good reliability and will present a proposal for operationalization of adherence specially concerning the requirements of transplantation medicine which seems to be applicable in practice under the assumption that professional expertise is available.

We also will discuss the limits in evaluating prospective adherence and the impact on this factor as condition for organ allocation. The central point could be the question of classification the value of adherence as allocation factor in transplantation medicine under the condition of relevant uncertainty.

P045 THE CARE OF ORGAN DONORS – PERCEIVED STRESS OF MEDICAL PERSONNEL

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Objective: Little is known about the perceived emotional stress of hospital staff involved in the organ donation process. We have conducted a large survey to assess attitudes and experiences of hospital staff with organ donation, including emotional stress in relation to professional experience.

Methods: In 50 Bavarian hospitals, medical professionals, who are involved in the organ donation process, were asked to respond anonymously to a questionnaire. Responses were stratified for physicians and care staff and for the duration of professional experience (<5 years vs. >5 years).

Results: 2983 questionnaires could be evaluated. The majority of respondents in all four categories do not feel emotionally stressed by the donation process (range of mean values 53.4–69.7%). 24.4–31.3%, depending on the particular subgroup of the respondents, indicated a certain stress and 4.6–18.4% were uncertain. Medical personnel with more than 5 years of professional experience reported significantly less uncertainty.

Conclusion: A considerable number of medical professionals stated that they are emotionally affected by the donation process. Strategies to identify and cope with emotional stress may improve the attitudes towards organ donation among health care professionals with special focus on those, who are uncertain.

ORGAN DONATION / MARGINAL ORGANS

P046 LIVER FLUKE-INFESTED GRAFT USED FOR LIVING DONOR LIVER TRANSPLANTATION: CASE REPORT AND REVIEW OF THE LITERATURE

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Chlororchiasis is a cholangiopathy caused by foodborne trematode parasites, also known as liver flukes. *Clonorchiasis* is endemic in a wide geographical area extending from Eastern Europe to Southeast Asia. Infested hosts may remain asymptomatic for decades and consequently their liver can become available as graft.

We here report the first case in the Western world of living donor liver transplantation (LDLT) with an *Opisthorchis felineus*-infested graft and present a review of the literature.

A 6-month-old girl with decompensated secondary biliary cirrhosis underwent a LDLT with a left lateral graft infested with *Opisthorchis felineus*. After promptly diagnosis and adequate therapy both donor and recipient had an uneventful postoperative course and long term follow-up. To date 19 liver transplantations with liver flukes -infested grafts are reported in the literature. All of them occurred in Asian countries.

Liver grafts infested with liver flukes do not pose a contraindication to liver donation from deceased or living donors, provided that a correct timely fashion diagnosis and treatment are performed.

P047 WHO SHOULD RECEIVE THE TTR DOMINO LIVER?

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TTR-amyloidosis is caused by TTR variants, which are expressed and secreted by the liver. Therefore, liver transplantation was introduced as therapeutic option to prevent or to limit systemic disease progression in this fatal disease. Interestingly, the liver function is not affected by TTR variants. Organ scarcity is an international major concern resulting in increasing numbers of deaths on the waiting lists for organ transplantation. To extend the pool of donor livers, TTR livers are used for transplantation once the TTR-amyloidotic patient receives a donor liver. The so-called domino liver transplantation (DLT) is practised in many countries. In Germany domino liver transplantation was introduced in 1996. Since then 4–8 DLTs were performed each year. Domino livers were allocated on basis of the policy of the individual transplant center. In 2011 ET changed this policy without any scientific debate in Germany. Domino livers are now allocated according to the ET allocation rules, which utilize the MELD score since December 2006. Currently patients receive organ offers as liver transplant recipients once MELD is far beyond 30 points. 1-year mortality has reached around 30% after liver transplantation. The presentation will address pitfalls in the decision making regulations on allocation in the case of the gift of DLT.

P048 RESULTS OF LIVING DONOR KIDNEY TRANSPLANTATIONS FROM DONORS AGED MORE THAN 65 YEARS

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Introduction: The shortage of organs has led to more people receiving organs from living donors. Whether donor age in itself constitutes a limitation to living donation or not remains unclear.

Methods: The outcome of 22 living kidney transplantations (LKTx) from donors older than 65 years (average age 68.9 year), been performed in our center since 1997 was evaluated. The results were compared to the rest of our LKTx-cohort ($n = 164$) regarding this period.

Results: The mean ischemia-time of senior transplants was 203 min (range: 127–291 min) vs. 199 min (range: 115–329 min.) in the rest cohort (CG). The primary function and recipient survival rates in the senior group (SG) were as high as 95.5%. The donor mortality was zero percent. The mean creatinine value of the recipients of the SG at discharge was equal to that of the CG (1.6 mg/dl, range 0.8–3.5). The average postoperative hospital stay was 26 days (vs. 24 days in CG). The 1- and 3-year organ survival in the SG was

95.5% and 91% respectively (vs. 97.5% and 92.5% in the CG). There were no statistically significant differences observed between the two groups.

Conclusion: The LKTx eliminates the long wait time on the deceased donor waiting list. The operation can be timed for the optimal health of the recipient and for donor convenience. People older than 65 years can be safely considered as eligible for kidney living donation.

P052 ORGAN DONATION INFORMATION CAMPAIGN – WHAT IS LEADING TO SUCCESS?

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Introduction: The German transplantation system is in a crisis due to a lack of donor organs. One of the main approaches to increase organ donation rates are information campaigns. We raised the hypothesis: The willingness to sign a donor card rises by receiving information material due to the subsequent increase of specific knowledge.

Material and methods: We conducted an online survey. The hyperlink was distributed via Facebook groups and mailing lists of medical faculties in Germany. Five factual questions with different levels of difficulty were asked.

Results: A total of 2484 participants took part in our survey. Use of an online tool to conduct the survey and mode of distribution were associated with overrepresentation of academics, participants of the medical sector and younger participants. Putative organ acceptance rate was associated with specific knowledge score, but not with the general education level or with receiving information material. Holding a donor card was associated with specific knowledge, but not with the general education level. Receiving information material is not associated with an increase in specific knowledge, but with holding a donor card. Association between receiving information material of the health insurance funds and specific knowledge is very slight. However, receiving information material of the health insurance funds was correlated with holding an organ donor card. Reading the information material of the health insurance funds was also correlated with holding an organ donor card.

Discussion: Our study indicates a basic level of 46.9% organ donor card holders in our sample group. This is much more than in a representative previous study by Techniker Krankenkasse (21%). These different findings may be explained by the self-selection bias. It is possible that five factual questions were not sufficient to prove the effect of the information material on specific knowledge concerning organ donation.

Conclusions: The willingness to sign a donor card was higher in the group receiving information material. However, we did not observe that this effect was related to a subsequent increase of specific knowledge, but was apparently related to the combination of information and easy access to the organ donor card.

P053 HAND-ASSISTED LAPAROSCOPIC LIVING-DONOR NEPHRECTOMY VERSUS OPEN SURGERY: ARE DIFFERENCES IN EARLY GRAFT FUNCTION DETECTABLE?

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Introduction: It is suspected that in laparoscopic living-donor nephrectomy the perioperativ pneumoperitoneum may have adverse effects on the graft function.

We investigated whether differences between the two surgical methods are detectable based on renal function parameters.

Materials and Methods: Between 1999 and 2008, 60 patients received kidney transplantations from living donors. Laparoscopic hand-assisted nephrectomy was performed in 28 donors, and 32 underwent open living-donor nephrectomy. Biochemical markers of glomerular filtration rate (serum creatinine, serum cystatin C) and glomerular and tubular renal function (high and low molecular weight urinary proteins and enzymes) were determined up to one year after transplantation.

Results: Neither in the first days after transplantation, nor after one year, the glomerular filtration rates differed significantly between the two patient groups. This is also true for most of the urinary proteins. After a temporary rise during the first weeks after surgery, the urinary protein concentrations fall continuously to the normal level. Only the tubular marker protein β_2 -microglobulin and the urinary enzyme N-acetyl- β -D-glucosaminidase indicate a difference between the two surgical methods. This difference is not statistically significant.

Conclusion: Compared to open surgery, a significant adverse effect of the laparoscopy on the graft function was not detected based on the examined parameters.

P054 INTRODUCTION OF RETROPERITONEOSCOPIC DONOR NEPHRECTOMY IMPROVES OUTCOME AND ACCELERATES QUALITY OF LIFE RECOVERY IN LIVING KIDNEY DONORS

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Objectives: The major goal in living donation is to maximize donor safety while minimizing postoperative impairments. In 2011, we changed technique from open anterior mini-incision (MIDN) to retroperitoneoscopic donor nephrectomy (RPDN). We evaluated operation time, time to discharge, surgical complications, and health-related quality of life (QOL).

Methods: 38 MIDN and 45 RPDN donors were included. In a subsample ($N = 18$ MIDN; $N = 32$ RPDN), QOL was prospectively assessed with the WHOQOL Bref questionnaire.

Results: Age and BMI were not different between groups. Skin-to-skin time (169 vs. 116 min, $P < 0.001$) and hospitalisation (6.6 vs. 4.9 days, $P < 0.001$) were significantly shorter in RPDN. 10/38 (26%) MIDN patients and 6/45 (13%) RPDN patients developed postoperative complications ($P = 0.14$). Most complications were mild. No blood transfusions were necessary. While in MIDN, 3 of 5 QOL scales (physical: $P = 0.03$; psychological: $P = 0.03$; global: $P = 0.003$) were significantly reduced 3 months post donation compared to pre donation, no significant reduction was observed in RPDN. At 3 months, RPDN donors retrospectively reported significantly less pain ($P = 0.007$) and physical stress ($P = 0.05$) caused by the operation than MIDN donors.

Conclusion: We conclude that the change of procedure was safe for our patients, operation time and hospital stay were shortened, and QOL recovery was accelerated.

P055 LIVING KIDNEY DONATION: IMPORTANCE OF DONOR EDUCATION

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Background: The rising prevalence of end-stage renal disease and Germany's chronic organ shortage subsequently calls more people upon to consider living donation.

Methods: We performed a study on 312 living kidney donors at our transplant center in the last 15 years, and aimed to address the impact of donation on social determinants, mental and physical health. The questionnaire consisted of 5 questions about social, financial, and job-related consequences, and 12 questions about donation-related stress, and health changes.

Results: The response rate was 86.7%. Using a multivariate donation-related quality of living score, 51% of donors were in excellent health, while 34% reported of moderately, and 15% of severely compromised health. Severely compromised donors were more likely to be younger, unemployed (25%), or forced to change their job (16%; $P < 0.05$). Most donors would be willing to donate again (90%). However, siblings (16%), donors under 45 years (15%), and notably siblings under 45 years (37%), had negative attitudes towards donation ($P < 0.05$). While open-surgery correlated with compromised health, it didn't affect willingness to donate again.

Conclusions: For adequately informing potential donors, medical professionals must know possible long-term effects on physical and mental health in different subgroups. Reliable donor education is essential to improve society recognition of living donation.

LONG-TERM COMPLICATIONS

P059 SERUM CALCIFICATION PROPENSITY PREDICTS MORTALITY AFTER AENAL TRANSPLANTATION*U. Eisenberger¹, S. Farese², I. Bergmann², S. Benson³, A. Pasch²¹Nephrologie, Universitätsklinik Duisburg-Essen, Essen, Germany;²Nephrologie, Universitätsklinik Bern, Bern, Switzerland; ³Institut für med.

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Aim: Death with a functioning graft due to cardiovascular disease is the one of the most important issues in renal transplantation. Medial arterial calcification is accelerated in patients with chronic kidney disease and closely associated with arterial stiffness and mortality. Recently, we developed a novel *in vitro* blood test that provides an overall measure of calcification propensity by monitoring the maturation time (T 50) of calciprotein particles in serum. The current study elucidates clinical and hemodynamic factors influencing calcification propensity and analyses the value of T50 measurements for prediction of mortality after renal transplantation.

Method: We measured T50 in a prospective single centre cohort of 198 renal transplant patients with a follow-up of 5 years. Mean time after transplantation at study inclusion was on average 7 years. T 50 measurements were performed using a Nephelostar nephelometer (BMG Labtech, Offenurg, Germany) as previously described (Pasch et al. JASN 2012). Renal resistance index was measured by color-coded duplex ultrasound. All hemodynamic and laboratory measurements were performed at study inclusion.

Results: At baseline the major determinants for tertiles of T50 included higher serum phosphate ($P < 0.001$), lower transplant function ($P < 0.001$) and serum albumine ($P < 0.01$), higher HbA_{1c} ($P < 0.05$) and total cholesterol ($P < 0.01$), higher pulse pressure ($P < 0.05$), systolic blood pressure ($P < 0.05$) and renal resistance index ($P < 0.05$) as well as the use of Calcineurin inhibitors ($P = 0.02$).

In a multivariate analysis, increased serum calcification propensity was independently associated with higher serum phosphate ($P < 0.001$), lower serum albumine ($P < 0.005$), higher HbA_{1c} ($P < 0.05$), total cholesterol ($P < 0.05$) and interestingly with use of Calcineurin inhibitors ($P < 0.05$).

Mortality divided by tertiles of T50 is associated with highest calcification propensity corresponding to the lowest tertile of T50 (Kaplan-Meyer analysis, log rank $P = 0.01$). The lowest tertile of T50 revealed a more than 3 times increased relative risk for mortality compared to the highest tertile.

Conclusion: Our results suggest that serum T 50 measurement may be a valuable biomarker to evaluate cardiovascular risk in renal transplantation and might guide adjusted therapy in the future.

P060 NEW ONSET OF DIABETES AFTER TRANSPLANTATION IS ASSOCIATED WITH IMPROVED PATIENT SURVIVAL AFTER LIVER TRANSPLANTATION*F. Darstein¹, C. König¹, M. Hoppe-Lotichius², D. Grimm¹, K. Johanna¹, A. Zimmermann¹, J. Mittler², J. Schattenberg¹, M. Sprinzl¹, M.-A. Wörms¹, H. Lang², P. Galle¹, T. Zimmermann¹¹I. Medizinische Klinik, Universitätsmedizin Mainz, Mainz, Germany; ²Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsmedizin Mainz, Mainz, Germany

The influence of NODAT on survival of liver transplant recipients has not been clarified. Therefore, we evaluated the effect of NODAT on survival in LT recipients.

Data from 352 LT patients were analyzed. 97 patients with pretransplant diabetes mellitus were excluded, 255 patients without diabetes mellitus at time of transplantation were analyzed.

NODAT was diagnosed in 41 patients (16.1%). There was no difference in frequency of NODAT according to the etiology of liver cirrhosis. NODAT was associated with a higher body weight ($P = 0.004$) and BMI ($P = 0.002$) 5 years after LT, but not with weight gain ($P = 0.201$) or increase in BMI ($P = 0.335$) 5 years after LT. HbA_{1c} 5 years after LT was significantly higher in patients with NODAT ($P = 0.001$), but mean HbA_{1c} still remained lower than 6.5% (6.4 (±1.2)%). Patients with NODAT showed better survival rates (log rank: $P = 0.002$) compared to LT recipients without diabetes. This might be explained by recovery of metabolism in patients without complications after LT, while complications of NODAT will not appear during the relatively short postoperative time and observation period (mean follow up 6.08 (±2.67) years).

Conclusion: NODAT is frequently diagnosed in LT recipients and is associated with an improved 5 year survival after LT.

P061 LONG-TERM MORTALITY IN PATIENTS AFTER SIMULTANEOUS PANCREAS-KIDNEY-TRANSPLANTATION

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Background: Only few data exists about the reason of death in patients, who underwent a simultaneous pancreas-kidney-transplantation more than two years ago.

Methods: We reviewed 517 consecutive pancreas transplantations since June 1994, including 36 patients with two pancreas-transplantations and three patients with three pancreas-transplantations.

Results: From the 475 patients, who underwent at least one pancreas-transplantation, 26 patients died within the first two years after transplantation and 65 died during the long-term follow-up after the second year. Among the 65 patients there are 15 patients (23.1%), who died because of cardiac reasons, 13 patients (20%) who died due to sepsis and 8 patients (12.3%) who died of cancer. The reason of death is unknown in 19 patients (29.2%), as most of them died suddenly without being in a hospital.

Conclusion: Cardiac diseases and sepsis are the most common reasons of death in patients, who underwent a simultaneous pancreas-kidney transplantation more than two years ago. Regular cardiac checks and early treatment of infections in transplant centers seem to be very important in the long-term care of patients after transplantation.

P062 LENGTH OF TIME INTERVAL AFTER HEART TRANSPLANTATION AND PATTERN OF CARDIAC ALLOGRAFT VASCULOPATHY DETERMINED BY OPTICAL COHERENCE TOMOGRAPHY

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Objective: Assessment of possible differences in the pattern of cardiac allograft vasculopathy (CAV) evaluated by optical coherence tomography (OCT) in short- versus long-term cardiac transplant recipients (CTR)

Methods: Forty consecutive CTR underwent routine surveillance coronary angiography during 2013 in Munich University Clinic, twelve patients underwent OCT and were included in this study. Patients were divided into two groups according to the mean length of time interval after heart transplantation, <13.9 years ($n = 6$, group 1) and ≥13.9 years ($n = 6$, group 2). Primary outcomes of interest were intima and media thickness in OCT.

Results: The two groups had comparable baseline characteristics, except a significantly higher HbA_{1c} plasma level in group 2 (5.69 vs. 6.27%, $P = 0.01$). In 94.2% of all frames with distinct three layers intima hyperplasia could be diagnosed, defined as intima-media ratio >1. Significantly more frames with intima hyperplasia were detected in group 1 ($P = 0.048$). Mean intima thickness was similar in both groups while mean media thickness was significantly greater in group 2 (0.092 ± 0.04 vs. 0.101 ± 0.06; $P = 0.024$). Signs of atherosclerosis were present in all patients independently of the time since transplantation.

Conclusion: In long-term cardiac transplant recipients with CAV media hyperplasia develops in addition to intima hyperplasia.

LIVER

P064 PROTEIN BIOMARKERS FOR DIAGNOSIS AND PREDICTION OF ACUTE CELLULAR REJECTION AFTER LIVER TRANSPLANTATION

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The diagnosis of acute cellular rejection (ACR) after liver transplantation is based on histological analysis of biopsies because non-invasive biomarkers are not yet established for clinical routines. Here, we assessed the predictive and diagnostic value of CD44 and CXCL9 as serum biomarkers for ACR in the first six months after liver transplantation in a prospective study.

The protein levels were measured in 94 patients immediately prior to transplantation, at POD 1, 3, 7, and 14, and when biopsies were performed. ACR was confirmed histologically during episodes of graft dysfunction.

The CD44 serum protein levels were significantly lower at POD 1 in patients who experienced ACR in the follow-up compared with patients without ACR (p

Our results suggest that CD44 and CXCL9 may serve as biomarkers to identify liver allograft recipients at risk for ACR.

P065 PROTEIN BIOMARKERS IN BILE AS A DIAGNOSTIC TOOL AFTER LIVER TRANSPLANTATION

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Aim: Protein based biomarkers are emerging tools for diagnosis and prediction of allograft rejection. Identifying patients at lower risk of rejection could help to adjust immunosuppressive therapy and reduce long-term side effects which are crucial for long term outcome. The aim of our study was to investigate protein levels in the bile of liver transplantation (LTX) recipients in order to evaluate its usability for diagnostics of acute rejection.

Material and Methods: From August 2011 to December 2012, 120 patients received LTX at our institution. A total of 45 patients with external bile drainage and sufficient amount of bile for analysis were included in a prospective, non-interventional study. The study was approved by the local ethics committee and all participants gave their written informed consent. Bile samples were collected at consecutive time points after LTX (postoperative days/POD 1, 3, 5, 7) and when acute rejection was suspected. Primary endpoint of the study was histologically proven rejection within the first six months after transplantation. Patients were grouped into a *rejection group* (n = 25) and *control group* (n = 20). Protein levels were measured with ELISA.

Results: *Rejection* and *control group* showed no significant differences regarding Sex (male/female: 16/9 vs. 17/3; ns), BMI (26 vs. 27; ns), cold (519 vs. 551 min; ns) and warm ischemic time (48 vs. 51 min; ns), and labMELD score before LTX (19 vs. 16; ns). Only recipient age (50 vs. 56 years; P = 0.0349) and INR on the day before transplant (1.88 vs. 1.34; P = 0.0163) differed significantly between the groups.

CXCL9 as well as CD44 protein levels were significantly higher in bile of patients at time of acute rejection compared to controls (CXCL-9: P = 0.0067; CD44: P = 0.0043). CXCL9 did not show changes prior rejection, while CD44 was already increased on POD 1 and 5 in the *rejection group* (POD1: P < 0.0001; POD5: P = 0.0059). A significant higher level of CXCL9 in the *rejection group* was found on POD7 (P = 0.0087). IL-6 failed to distinguish between the groups (ns).

Conclusions: CXCL9 and CD44 in bile could be used as biomarkers to improve diagnosis after liver transplantation. Bile protein biomarkers could serve as prognostic markers to establish individualized immunosuppressive regimes and thereby reduce the long-term side effects of immunosuppression.

P068 PORTAL VEIN THROMBOSIS IN LIVER TRANSPLANTATION: A SINGLE CENTER ANALYSIS

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Introduction: Portal vein thrombosis (PVT) in liver transplantation remains a serious condition. An absolute contraindication in the earlier times, PVT can nowadays be successfully managed in the majority of pts. The aim of this study was to analyze our data for the incidence of PVTs prior to LTx, describe the operative techniques and compare the outcome to the LTx patients without PVT.

Methods: We retrospectively screened our liver transplant data for portal vein thrombosis and evaluated transplant variables, the underlying condition and the outcome. Budd-Chiari syndrome was excluded.

Results: We performed n = 277 liver transplants in n = 252 pts. from 2007 to 2012. A total of n = 33 PVTs (11.9%) was detected, which were mostly located in the main portal vein (34%). Underlying conditions were alcoholic (39.4%), HCV (24.2%), cryptogenic (9.1%), HBV (6.1%), drug related (6.1%), secondary biliary liver cirrhosis (3%), PSC (9.1%) and echinococcosis (3%). The majority of the PVTs were managed by venous thrombectomies (84.9%). In n = 3 (9.1%) patients we used a venous jump graft and n = 2 pts. (6.1%) received anastomosis to varix. 1-year-survival was similar to existing literature (76%) and showed no significant difference to survival of patients, who didn't suffer PVT (82%). PVT also had no significant effect on 1-year-graft survival (73% vs. 77%).

Conclusion: In our cohort of liver transplant patients we found a number of PVTs comparable to the existing literature. It remains a technically challenging situation. However, in most cases, PVT can be managed successfully.

P069 A PROSPECTIVE, RANDOMIZED TRIAL TO EVALUATE THE BENEFIT OF A SPONTANEOUS PORTO-CAVAL SHUNT IN CAVA-SPARING LIVER TRANSPLANTATION

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Background: A retrospective analysis of our liver transplant cohort has shown a reduction of I/R injury and superior graft survival rates in cava-sparing liver transplantation using a porto-caval shunt (PCS). In order to evaluate the benefit of a PCS during hepatectomy we propose a randomized controlled trial.

Methods: Patients receiving their first liver transplant are eligible. A cava-sparing liver transplant technique will be used in both arms. In the SHUNT group an extracorporeal PCS will be established during hepatectomy. Hepatectomy in the CONTROL group will be performed without a shunt. The primary endpoint is the peak ALT within the first 48 h after surgery. Secondary endpoints include patient- and graft survival as well as markers of I/R injury and liver function. Porto-venous and systemic endotoxin levels along with other immunological markers (e.g. IL-6) will be determined intraoperatively and in the early postoperative phase after transplantation to elucidate the mechanisms of the shunt. The calculated sample size to prove superiority of one of the arms is 60 per arm.

Conclusions: This investigator-initiated trial examines a technical/physiologic modification of a standard transplant technique. As industry sponsorship is unlikely, funding application for the trial is in review at the BMBF.

P070 FLUPIRTIN INDUCED LIVER TOXICITY: INDICATION FOR TRANSPLANTATION

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Background: The German Adverse drug reaction (ADR) database recently experienced an increase in reports on flupirtin induced liver injury (FILI; female: male ratio 4:1; 250% increase in 6 years). Clinical course with severe liver

injury has rarely been reported. We report two cases comparing clinical course, paraclinical findings, therapy and outcome.

Methods: Retrospective review of two Caucasian male patients with severe liver injury due to flupirtin intake. This included RUCAM (Roussel Uclaf Causality Assessment Method) score calculation and comparison of clinical presentation and histology.

Results: RUCAM score (8 and 10) was probable and highly probable. Both patients received flupirtin for pseudoradicular pain, and jaundice and malaise led to admission. Case 1: 48 year old otherwise healthy man, intake 400 mg daily for 90 days. Case 2: 42 year old male with polyarthritits, intake 300 mg daily for 45 days. Case 1 became severely encephalopathic (NH₃ 292 mg/dl) within 24 h and required urgent liver transplantation. Case 2 made an uneventful recovery under conservative therapy with steroids and intravenous N-acetylcysteine. Compared to case 1, alanine aminotransferase (ALT) levels on admission were >4-fold higher in case 2 (3528 U/l), whereas maximum total bilirubin was similar (21.4 and 19.3 mg/dl). Serological screening for viral hepatitis, autoimmune liver disease and infectious disease were negative. Explant histology in case 1 revealed panlobular necrosis and biopsy in case 2 bridging necrosis between portal fields.

Conclusion: Male cases in FILI are rarely reported and compared. In these two patients with severe FILI, there was no dose response pattern and the extent of ALT elevation was no predictor of outcome. Clinical deterioration is difficult to predict, but crucial for the indication of liver transplantation. Early liver biopsy in patients with suspected FILI provides additional diagnostic clues and potentially aids in outcome prediction and therapy.

P073 OCTOGENARIANS AS LIVER DONORS: A SOLUTION TO OVERCOME ORGAN SHORTAGE?

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Background: An increasing life expectancy and decreasing birth rates result in an aging population. This demographic shift suggests that older donors, including donors over 80 years, may help alleviate organ shortage in liver transplantation. The aim of this analysis was to determine the percentage of octogenarian donors in the Eurotransplant zone.

Methods: The percentage of octogenarian donors and median donor age were analyzed in the Eurotransplant Database from 2004 to 2013.

Results: 318 livers from octogenarian donors were transplanted during the observation period (total liver donors: 15 080). The percentage of octogenarians increased significantly (2004: 0.8%, 2006: 1.1%, 2008: 1.6%, 2010: 2.9%, 2012: 3.0%, 2013 3.0%) ($P < 0.001$, Chi-Square-Test). The median age of liver donors increased numerically within the last decade (2004: 46 years, 2008: 50 years, 2013: 53 years), but this change did not reach statistical significance ($P > 0.05$).

Conclusions: Although the demographic change is aggravating, octogenarians account for only 3% of all liver donors in the Eurotransplant allocation system. A detailed analysis to assess the short- and long-term survival of these grafts is in process. Facing an ageing society and the current critical organ shortage, those results may facilitate the acceptance of octogenarian donors thereby extending the donor pool.

P075 BENIGN INFLAMMATION DISTINGUISHES SUBCLINICAL FROM ACUTE CELLULAR REJECTION IN HUMAN LIVER ALLOGRAFTS

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Background and Methods: The subclinical rejection (SCR) of liver transplants constitutes a histological state of acute cellular rejection without any relevant biochemical abnormalities. In this prospective study we analysed the clinical course of 95 patients after liver transplantation being part of a protocol biopsy program (average follow up period of 21 months). Late SCR was a common event occurring in 32/95 patients. Furthermore protocol liver biopsies of 25 patients with SCR were stained for CD4, CD8, FOXP3 and DAPI with multicolour immunofluorescence and compared to patients with acute cellular rejection and normal protocol biopsies. In parallel PBMCs were analysed by FACs.

Results: Late SCR represents no risk factor for subsequent ACR, graft dysfunction, progressive liver fibrosis, graft loss or liver related death in our protocol biopsy program. This is despite the fact that liver biopsies of SCR and ACR are indistinguishable in terms of pathological diagnosis, size of portal

infiltrates and the density of T lymphocytes (CD4 & CD8) within the infiltrated areas. Immunophenotyping of the infiltrated portal areas revealed a possible explanation. CD4+ T cells increase significantly in both SCR and ACR with higher levels of inflammation (measured by the rejection activity index – RAI). CD8+ T cells, on the other hand, only correlate with RAI in ACR and do not increase in SCR. This causes a positive correlation of portal CD4+/CD8+ ratio with RAI in SCR and a negative correlation in ACR.

The portal infiltration of Treg (CD4⁺FOXP3⁺) increases with RAI in both SCR and ACR. The ratio of Treg to cytotoxic CD8⁺ T cells, the latter correlate with transaminases in ACR, only increases with RAI in SCR and remains steady in ACR. Compared to normal protocol biopsies without rejection Treg are significantly enriched in SCR and ratios of Treg to overall Tef, CD4⁺ and CD8⁺ cells are also significantly higher in SCR. These intra-graft changes are not paralleled in the blood.

Conclusion: Late SCR have a benign clinical course. Immunophenotyping shows the signs of successful regulation by Treg within the allograft. These patterns of T cell immunoregulation in portal infiltrates may contribute to the unimpaired clinical outcome of SCR after liver transplantation and may represent one aspect of the liver as an immunological privileged organ.

P076 EARLY INITIATION OF MARS® DIALYSIS IN AMANITA PHALLOIDES-INDUCED ACUTE LIVER FAILURE PREVENTS LIVER TRANSPLANTATION

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Amanita phalloides is the most relevant mushroom intoxication leading to acute liver failure (ALF). There are two principal groups of toxins, the amatoxins and the phallotoxins, both are small cyclic oligopeptides highly resistant to chemical and physical influences. The amatoxins are potent inhibitors of eukaryotic RNA polymerase II which causes transcription arrest affecting mainly metabolically highly active cells like hepatocytes and renal cells. The clinically most characteristic symptom is a 6–40 h long lag phase before onset of gastrointestinal symptoms and the rapid progression of acute liver failure leading to multi-organ failure and death within a week if left untreated. Extracorporeal albumin dialysis (ECAD) was reported to improve patient's outcome or facilitate bridging to transplantation. Out of nine intoxicated individuals from five independent families six patients were treated with ECAD using the MARS® system in our tertiary center, four of them were listed on admission for high urgency (HU) liver transplantation (OLT). In addition to standard medical treatment for *Amanita* intoxication we initiated ECAD once patients were admitted to our center. Overall 14 dialysis sessions were performed. All patients survived with full native liver recovery without the need for transplantation. ECAD was well tolerated; no severe adverse events were reported during treatment. Coagulopathy resolved within days in all patients, and acute kidney injury in all but one individual. In conclusion, ECAD is highly effective in treating intoxication with *Amanita phalloides*. Based on these experiences we suggest early initiation and repeated sessions depending on response to ECAD with the chance of avoiding OLT.

P077 GENOTYPES AND PHENOTYPES OF A LARGE GERMAN ATTR COHORT

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Transthyretin amyloidosis (ATTR) is the most frequent cause of autosomal-dominant hereditary systemic amyloidosis worldwide. The genotype of a German cohort ($n = 89$; 56 males; 33 females; age 51.4 ± 17 years) was studied. ATTR diagnosis was confirmed by DNA sequence analysis. 13 different genotypes were recorded in altogether 50 families/index patients. The highest frequency was observed for mutation p.V30M (53.9%) followed by p.G47A (25.8%). Mutations p.V30M and p.G47A were observed in 29 (58.0%) and 5 (10.0%) of the families, respectively. The remaining 11 genotypes (84.6% of all genotypes) were found in 18 patients (20.2%) from 16 families (32.0% of index patients). Within this latter group, p.L58H represented the largest single mutation with 3 families affected (6.0% of index patients). Pedigree analysis was performed in 4 families with mutation p.V30M, 3 families with p.G47A, and in one family each with mutation p.G53A, p.L58H and p.I107V. Whereas, a range of phenotypic expressions was observed, some unifying characteristics were noticed with individual genotypes. Onset of disease in patients having mutation p.V30M was observed relative late (>50 years) whereas onset in patients with p.G47A was earlier (<41 years). The highly progressive course of disease related to mutation p.G47A was demonstrated by the relative low time period between onset and fatal disease. Most patients died due to heart failure. One main phenomenon of this phenotype is the frequent involvement of failures in the autonomous nervous

system. To further analyze the phenotype of the ATTR patients on a cellular level, reprogramming of ATTR fibroblasts by induced pluripotent stem (iPS) cells has been performed. Such analyses, may offer molecular studies on pathogenesis as well as for prognosis of novel therapy. Taken together, we present data from a large cohort in Germany, including the local frequent mutation p.G47A.

P078 RISK OF POSTOPERATIVE INFECTIONS AFTER LTX RISES WITH MELD SCORE

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Aim: Identifying patients at higher risk of infection after liver transplantation could help to adjust treatment at large and anti-infective therapy and prophylaxis in particular. Known risk factors for postoperative infections after LTX are operation time, operation technique, blood volume replacement and episodes of acute rejection. Aim of this study was to evaluate and stratify the risk of postoperative infections after LTX. Although more critical ill patients receive liver transplantation (LTX) in the MELD era, a correlation between postoperative infections and MELD score has not yet been described.

Material and Methods: 748 consecutive liver transplantations after implementation of MELD score from December 2006 till December 2013 were included in a retrospective analysis. All transplantations were orthotopic liver transplantations from brain dead donors in adult recipients. Number of infections, infection-site and infectious agent during hospital stay after LTX were analyzed retrospectively and correlated to labMELD score resulting from lab values collected directly before transplantation. Statistical analysis was performed using Kruskal-Wallis-test and logistic regression analysis.

Results: At least one infection occurred in 166 of 748 cases during hospitalization after LTX. Pulmonary infections were the most common site of post-transplant infections ($n = 110$). Most infections were caused by enterobacteria. A higher MELD score correlated strongly with the risk of infection after LTX, the regression coefficient was highly significant (P -value

Conclusions: We identified MELD score as a strong predictor for infections after LTX. The risk of suffering from infection as well as number of infection rises with MELD score pre-transplant. Therefore, patients with high MELD score are at high risk for post-transplant infections. Subsequent analysis are necessary to identify risk factors for the location and type of infection to implement stratified measures for screening and prophylaxis.

P079 FINAL REPORT OF THE PROSPECTIVE-RANDOMIZED MULTICENTER TOP-STUDY: NO BENEFICIAL EFFECT OF AN EX VIVO TACROLIMUS RINSE IN EDC LIVER GRAFTS

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Background: Facing critical organ shortage the TOP-Study was initiated in November 2011 to reduce ischemia reperfusion injury (IRI) in extended donor criteria (EDC) liver grafts. Based on experimental data indicating protective effects of a Tacrolimus-Rinse on hepatic IRI, a prospective randomized multicenter-IIT was designed. Participating centers are Munich LMU, Berlin, Frankfurt, Heidelberg and Regensburg. Funding was received from Astellas.

Methods: Liver from donors exhibiting ≥ 2 EDC were flushed with Tacrolimus (20 ng/ml) in 1000 ml HTK (intervention) or with HTK before transplantation (control). Primary endpoint was the peak ALT level within 48 h following surgery, the observation period was 7 days. To analyze the effects of an organ-rinse in marginal liver grafts, study patients were compared to patients without a rinse treatment (placebo) utilizing the liver transplant data base of our hospital.

Results: 23 patients meeting the inclusion criteria had been enrolled in the trial until August 2013. An interim analysis revealed that tacrolimus rinse did not improve hepatic IRI indicated by similar maximum ALT levels in both groups: Tacrolimus-Rinse 768 vs. HTK-Rinse 610 (median, U/I, $P > 0.05$).

Conclusion: In contrast to experimental data, a tacrolimus Rinse is not advisable in EDC liver grafts. The rather low ALT levels in both groups may suggest beneficial effects of ex vivo organ rinsing prior to implantation.

P080 LONG-TERM GRAFT SURVIVAL AFTER PRIMARY LIVER TRANSPLANTATION IS INFLUENCED BY DONOR-RECIPIENT MATCHING ACCORDING TO EUROTRANSPLANT DONOR-RISK-INDEX AND LABMELD: A LARGE SINGLE CENTER EXPERIENCE

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Introduction: MELD-based liver allocation led to reduced graft and patient survival. Organ shortage has led to increased use of marginal donor organs. Detailed analyses of donor-recipient-matching according to labMELD and Eurotransplant Donor-Risk-Index (ET-DRI) and their impact on long-term graft-survival after liver transplantation (LT) are missing.

Methods: In a retrospective single-center study of 1727 adult primary LTs (median follow-up: 89 months) long-term graft-survival was assessed according to recipient labMELD-score and in regard to donor quality measured by ET-DRI (Kaplan-Meier-estimates, Log-rank).

Results: Mean labMELD and ET-DRI were $17(\pm 8.49)$ and $1.63(\pm 0.43)$. One-, ten- and 15-year graft-survival was 84.1%, 63.7% and 55.1%. Long-term graft-survival was not significantly influenced by labMELD ($P = 0.058$), but ET-DRI ($p35$) and ET-DRI (E1:1-1.2; E2: >1.2-1.4; E3: >1.4-2 and E4: >2) categories were defined. Matching those categories revealed significant influences of ET-DRI on long-term graft-survival in labMELD categories M1($p1.4$) causing markedly reduced long-term graft-survival. However, this marked difference was absent in patients of category M4 ($P = 0.172$). In these recipients 10-year graft survival was similar (E2:53.1%; E3:55.4%; E4:48.2%) for all donors with ET-DRI >1.2.

Conclusion: For recipients with labMELD ≤ 35 superior long-term graft-survival may among others be achievable with organs from donors with ET-DRI ≤ 1.4 . Although our data have to be analyzed in more detail, the usefulness of a reverse matching of high MELD and low DRI seems not to be supported by the present data.

P081 VARYING INFLUENCE OF THE EUROTRANSPLANT DONOR-RISK-INDEX ON LONG-TERM GRAFT SURVIVAL AFTER PRIMARY LIVER TRANSPLANTATION WITH A SPECIAL REGARD TO RECIPIENT PRIMARY DISEASE: A SINGLE CENTER EXPERIENCE OF 1767 CASES

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Introduction: Organ shortage has led to increased use of marginal donor organs. Recently the Eurotransplant Donor Risk Index (ET-DRI) was developed for estimation of graft outcome after Liver Transplantation (LT). Long-term data on ET-DRI and its impact on different indications for LT are missing.

Methods: In a retrospective single-center study of 1767 adult primary LTs (median follow-up: 88 months) long-term graft-survival was assessed according to indication and in regard to donor quality measured by ET-DRI (Kaplan-Meier-estimates, Log-rank).

Results: Mean ET-DRI in our cohort was $1.63(\pm 0.43)$. One-, ten- and 15-year graft survival was 83.5%, 63.3% and 54.8%. Long-term graft survival was significantly influenced by ET-DRI (p)

Conclusion: To achieve excellent long-term graft survival higher risk organs (ET-DRI > 1.4) should only be used restrictively for patients with CD/AIH or HCV. Their use in HCC, HBV, ALF and cryptogenic cirrhosis seems to be less problematic. If these results are confirmed in other analyses the ET-DRI may be a useful supportive tool in liver allocation.

P082 TRANSJUGULAR INTRAHEPATIC STENT SHUNT (TIPSS) PLACEMENT FOR SYMPTOMATIC PORTAL HYPERTENSION AFTER LIVER TRANSPLANTATION

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Aim: The aim of this analysis is the assessment of the benefit of TIPSS placement in liver transplant recipients with symptomatic portal hypertension.

Material and Methods: We analyzed data of 17 consecutive liver transplant recipients (male:female = 12:5; median age: 54 years; median time since transplant: 29 months) who underwent TIPSS procedure in our hospital between 2008 and 2014 retrospectively. TIPSS indication comprised re-cirrhosis of the graft and subsequent portal hypertension causing ascites and recurrent gastro-intestinal bleeding or intrahepatic portal vein obstruction, mainly in patients with hepatitis C re-infection ($n = 8$; other causes: recurrent PSC/PBC: $n = 3$, vascular causes: $n = 3$, chronic rejection: $n = 3$). Patients' state of health was assessed using the model of end-stage liver disease

(MELD) score. In 16 cases TIPSS could safely be placed in both patients with caval-replacement and piggy-back anastomosis of the V. cava.

Results: To our knowledge this is the largest case series of TIPSS placement after liver transplantation yet. The median labMELD score of patients at the time of intervention was 17 (range 8–24). The median atrial-portal gradient was 19 mmHg pre-interventionally and could significantly be reduced to a median of 7 mmHg in our patient collective, thus documenting technically successful TIPSS implantation. 4 patients were bridged to re-transplantation, 3 were listed and in 5 patients re-transplantation could be avoided. All TIPSS still in place were patent in patients alive at the time of analysis. No major, procedure-associated, complications occurred. Death within one year of TIPSS placement ($n = 7$) was associated with a significant higher MELD score (median = 20), whereas age, time since transplantation and height of the atrial-portal gradient did not show a significant impact.

Conclusion: TIPSS placement in liver transplant recipients is feasible and safe irrespective of the applied transplant technique, effectively reducing portal hypertension. Still, the indication should be carefully considered and individualized as patients with a higher MELD score do not seem to profit from TIPSS implantation as a rescue measure. The ideal time-point of application and its limitations have to be defined further.

P084 SUBNORMOTHERMIC EX VIVO LIVER PERFUSION IS A SAFE ALTERNATIVE TO COLD STORAGE FOR STANDARD QUALITY GRAFTS AND ALLOWS GRAFT ASSESSMENT DURING LIVER PRESERVATION

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Background: We developed a novel technique of subnormothermic *ex vivo* liver perfusion (SNEVLP) for the storage of liver grafts prior to transplantation. To test the safety of SNEVLP we compared it to a control group with minimal cold storage (CS) time.

Methods: Heart beating pig liver retrieval was performed and the liver grafts were either cold stored for 6 h (minimal injury) or preserved with a sequence of 2 h cold storage and 4 h SNEVLP (34 °C), followed by orthotopic liver transplantation. Liver function tests and histology were investigated.

Result: AST levels during SNEVLP remained stable within the normal range for pigs during *ex vivo* perfusion (42.2 ± 5.6 U/l) with stable bile production. SNEVLP vs. CS livers had a trend towards decreased AST (297.3 vs. 1396.0 U/l, $P = 0.104$) and alkaline phosphatase (131.3 vs. 194.7 U/l, $P = 0.115$) levels at day 2 after transplantation, as well as peak bilirubin levels (3.3 vs. 7.3 $\mu\text{mol/l}$, $P = 0.123$). Peak INR was similar between SNEVLP and CS groups after transplantation (1.07 vs. 1.27, $P = 0.408$). Histology revealed minimal necrosis at the end of follow-up in both groups.

Conclusion: SNEVLP allows assessment of graft injury and function during organ preservation and is associated with comparable outcome even to grafts with minimal CS time.

P085 LIVING VERSUS DECEASED DONOR LIVER TRANSPLANTATION PROVIDES COMPARABLE RECOVERY OF RENAL FUNCTION IN PATIENTS WITH HEPATORENAL SYNDROME: A MATCHED CASE-CONTROL STUDY

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Background: It is unclear if patients with chronic liver disease and hepatorenal syndrome (HRS) have similar outcome after deceased donor (DD) and living donor (LD) liver transplantation (LT).

Methods: 30 adult patients with HRS receiving a LDLT and 90 adult HRS patients receiving a full graft DDLT were compared using a match pair study design.

Results: LDLT vs DDLT of patients with HRS was associated with decreased peak AST levels (339 ± 214 vs. 953 ± 1253 U/l; $P = 0.0001$), and similar 7-day bilirubin (8.42 ± 7.89 vs. 6.95 ± 7.13 mg/dl; $P = 0.35$), and INR levels (1.93 ± 0.62 vs. 1.78 ± 0.78 ; $P = 0.314$). LDLT vs. DDLT had a decreased ICU (2 (1–39) vs. 4 (0–93) days; $P = 0.004$) and hospital stay (17 (4–313) vs. 26 (0–126) days; $P = 0.016$) and a similar incidence of overall postoperative complications (20% vs. 27%; $P = 0.62$). No significant difference was detected between LDLT and DDLT patients regarding graft survival at 1- (80% vs. 82%), at 3- (69% vs. 76%), and 5-years (65% vs. 76%; $P = 0.63$). The incidence of chronic kidney disease post-liver transplantation (10% vs. 6%; $P = 0.4$) was similar between both groups.

Conclusion: LDLT results in comparable long-term outcome when compared with DDLT in patients with HRS.

P087 RIGHT SIDED DIAPHRAGMATIC HERNIA AFTER PEDIATRIC LIVER TRANSPLANTATION: REPORT OF 2 CASES AND REVIEW OF THE LITERATURE

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Introduction and Aim: Diaphragmatic hernias (DH) are a rare but life threatening complication following pediatric segmental liver transplantation (LT).

Case Report: Herein we present two cases of right-sided DH after left-lateral LT in 2 paediatric recipients: a 19 month-old boy who developed an early DH 3 months after left lateral split LT because of Alagille syndrome and a 3 years old girl with a late DH, 18 months after left lateral LDLT because of biliary atresia.

Both children presented unspecific clinical manifestation such as respiratory distress, fever and general malaise. The small boy additionally showed signs of mechanical ileus. Although only the girl had increased inflammatory values, both children had elevated levels of lipase.

A chest X-ray and Ultrasound showed typical signs of right sided enterothorax.

Both children underwent urgent explorative laparotomy. Intraoperative a subtotal herniation of small bowel through a right sided enlarged diaphragmatic caval opening (maximal diameter 3.5 cm) was detected in both cases. After reposition of intestine in the abdominal cavity the diaphragmatic opening was closed with prolene running suture and a chest tube was inserted. The further postoperative course was uneventful.

Discussion: From the present 2 cases and review of the literature (to date 19 cases of right sided DH after segmental pediatric LT have been reported) we can conclude that: (1) it is a rare but potentially life threatening complication which can occur early as well as lately after LT (2) the clinical manifestation is insidious (3) lipase values can be elevated probably due to pancreatic venous congestion (3) chest-x-ray and US are sufficient and specific diagnostic tools (4) a urgent laparotomy with reposition of intestine in abdominal cavity and closure of diaphragmatic opening is the treatment of choice (5) possible risk factors reported in the literature are represented by segmental liver graft, surgical trauma, malnourishment, elevated intra-abdominal pressures, and immunosuppression with mTor-i.

BASIC SCIENCE

P089 FRAGMENTS OF AT1R AND ETAR-ANTIBODIES INDUCE COMPLEMENT-INDEPENDENT ENDOTHELIAL ACTIVATION*N. Zhu¹, A. Philippe¹, R. Catar¹, G. Riemekaster², D. Dragun¹¹Medizinische Klinik mit Schwerpunkt Nephrologie und internistische Intensivmedizin, Charité - Universitätsmedizin Berlin, Berlin, Germany;²Medizinische Klinik mit Schwerpunkt Rheumatologie und klinische Immunologie, Charité - Universitätsmedizin Berlin, Berlin, Germany

Autoantibodies of IgG1 and IgG3 subclasses simultaneously target the Angiotensin II type 1 receptor (AT1R) and Endothelin-1 type A receptor (ETAR) and induce severe autoimmune and transplant vasculopathy via activation of intracellular signaling. We aimed to generate model systems to evaluate complement independent mechanisms and intracellular signaling specifically induced by the autoimmune AT1R and ETAR activation.

Stable HEK293 cell lines expressing Flag tagged ETAR (F-ETAR+) or expressing His tagged AT1R (H-AT1R+) were generated by transfection followed by appropriate antibiotics selection. The clones expressing the highest level Flag-ETAR and His-AT1R were selected and verified by western blot and immunoprecipitation.

Natural receptor agonists Endothelin-1, Angiotensin II, specific pharmacologic antagonists (inverse agonists), and AT1R and ETAR-Abs positive IgG fraction (P-IgG) isolated from patients with renal transplant vasculopathy and/or scleroderma renal crisis were used to verify the functionality of the tagged receptors by means of ERK kinase activation. Stimulation of both stable HEK293 cell lines expressing individual tagged receptors with P-IgG and natural agonists induced an increase of ERK1/2 phosphorylation which could be blocked by respective antagonists. A stable cell line simultaneously expressing both tagged AT1R and ETAR (F-ETAR+-H-AT1R+) was generated next. Reliable activation of ERK in response to P-IgG and agonists was again detected. In order to better understand the activation of the receptors by P-IgG, IgG underwent pepsin digestion to produce the F(ab')₂ fragments without Fc fragments. F-ETAR+-H-AT1R+ were stimulated with total P-IgG or F(ab')₂ fragments, respectively. F(ab')₂ was significantly more biologically active than P-IgG (p

Our data indicate F(ab')₂ is the functional fragment of the autoantibodies which target ETA- and AT1 receptors and is responsible for their specific intracellular biological actions. We have moreover generated stable cell lines over-expressing biologically functional ETA and AT1 receptors for studies which will help to elucidate why antibodies targeting both receptors simultaneously occur in larger groups of patients.

P090 T-CELLS LICENCE IL-10⁺ REGULATORY B-CELLS TO PRODUCE GRANZYME B AND CONFER CYTOTOXIC CAPACITY TO REGULATORY B-BELLS*B. Wilde¹, S. Dolff¹, J.W. Cohen Tervaert², A. Kribben¹, O. Witzke¹¹Klinik für Nephrologie, Universitätsklinikum Essen, Universität Duisburg-Essen, Essen, Germany; ²Immunology, Maastricht University, Maastricht, The Netherlands

Objective: Regulatory B-cells (Breg) have recently been identified as a cell population with immunoregulatory capacity and play a role in solid organ transplantation by suppressing allograft rejection. Breg inhibit pro-inflammatory T-cell responses and promote Treg development. The exact mechanisms of Breg mediated T-cell inhibition are unknown. The aim of this study was to investigate possible mechanisms of Breg mediated immune regulation.

Methods: B-cells from 20 healthy blood donors were purified by magnetic bead isolation. Purified B-cells were then stimulated with CpG in presence of varying cytokines (without any exogenous cytokines, +IL-2, +IL-6, +IL-7, +IL-15, +IL-17A, +IFN γ). In some conditions, B-cells were co-cultured with autologous CD3⁺ T-cells. After 24–72 h of culture, B-cells were analyzed for IL-10, granzyme A/B (GrA, GrB) and perforin (Per) expression.

Results: CpG stimulation without any additional exogenous cytokines induced IL-10 production in B-cells (B-cells: %IL-10⁺ 14.4 \pm 1.2%). IL-10⁺ Breg and IL-10^{neg} B-cells did not produce GrA/GrB or Per. In contrast, CpG stimulation of B-cells in presence of IL-2, IL-15 or IFN γ induced an additional, separate GrB⁺IL-10^{neg} B-cell subset (B-cells: %GrB⁺ 7.2 \pm 0.8%, 7.0 \pm 0.9%, 5.1 \pm 1.5%). In these conditions, IL-10⁺ Breg were lacking GrA/GrB or Per. However, IL-10⁺ Breg acquired the ability to produce GrB upon coculture with autologous CD3⁺ T-cells (IL-10⁺ Breg: %GrB⁺ 35 \pm 9%).

Conclusion: Depending on the cytokine environment, a separate GrB producing B-cell population can be induced. GrB confers cytotoxic capacity to B-cells and may allow specific lysis of target immune cells. Thus, GrB⁺ B-cells can be regarded as an additional Breg subpopulation. IL-10⁺ Breg do not express GrA, GrB or Per. Interestingly, coculture with T-cells seems to licence IL-10⁺ Breg to produce GrB. Thus, autologous T-cells promote the development of IL-10⁺GrB⁺ Breg. These Breg may have a pivotal in establishing immune tolerance.

P091 THE COMBINATION OF EVEROLIMUS AND PIRFENIDONE SUPPRESSED THE DEVELOPMENT OF CHRONIC REJECTION AFTER RAT LUNG TRANSPLANTATION

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Aim: Chronic allograft rejection (CR) is the main risk factor after lung transplantation (LTx). The anti-inflammatory/anti-fibrotic properties of pirfenidone might reduce CR after experimental LTx alone or in combination with an inhibitor of mammalian target of rapamycin (everolimus).

Method: A rat model of left lung allo-transplantation (F344-to-WKY) was used to evaluate the anti-fibrotic effects of pirfenidone (InterMune, USA; 600 mg/kg/day; 0.85% in chow; day -3 to 60) alone (group 1; n = 8) or in combination with everolimus (Novartis, Swiss; 2.5 mg/kg/day; by gavage; day 7 to 60) (group 2; n = 8).

Results: Non-treated allografts showed severe acute (day 20, ISHLT A4/B2R) and chronic rejection (day 60, ISHLT C/D). Only the combination therapy reduced early acute rejection (ISHLT A3/B1R-B2R). Both treatment strategies significantly reduced chronic bronchiolar rejection (group 1, P \leq 0.05; group 2, P \leq 0.01). Additionally, group 2 demonstrated significantly less vascular damage (P \leq 0.01).

Conclusion: Early administration of pirfenidone in combination with everolimus retarded chronic rejection processes and might improve survival after experimental LTx.

P095 VARIABILITY OF INTRAHEPATIC VASCULAR ANATOMY IN RODENTS & THEIR SURGICAL IMPLICATIONS*C. Sanger¹, A. Schenk², L.O. Schwen^{2,3}, L. Wang², F. Gremse³, S. Zafarnia³, F. Kiessling³, W. Wei¹, B. Richter⁴, U. Dahmen¹¹Experimentelle Transplantationschirurgie, Klinik für Allgemein-, Viszeral- und Gefäßchirurgie, Universitätsklinikum Jena, Jena, Germany; ²Fraunhofer MEVIS, Bremen, Germany; ³RHTW Aachen, Aachen, Germany; ⁴Allgemein-, Viszeral- und Gefäßchirurgie, Universitätsklinikum Jena, Jena, Germany

Background: The need for precise experimental surgical procedures parallels the development of clinical hepatobiliary surgery rising. The intra-hepatic vascular anatomy in rodents, its variations and corresponding supplying and draining territories in respect to the lobar structure of the liver have not been described. We performed a detailed anatomical imaging study in rats and mice to allow for further refinement of experimental-surgical approaches.

Methods: LEWIS-Rats & C57Bl/6N-Mice were subjected to ex-vivo & in-vivo imaging using CT & MRI. Underlying vascular anatomy was reconstructed, analysed and used for volume-determination of the dependent territories.

Results: Variations in hepatic vascular anatomy were observed in terms of branching pattern and of distance of branches to each other. Most liver lobes have their own portal supply and their hepatic drainage. In contrast the paracaval liver is supplied by various branches from other lobar portal vein and drains directly into the vena cava. Surgically relevant variations were primarily observed in portal venous supply of right lobe and the distance between branching in left median and left lateral portal vein in rats, but not in mice.

Small differences of the volume were observed according to the vascular territory which is used for calculation.

Conclusions: It was demonstrated that lobar borders of the liver are not always matching territorial borders. Determination of small differences in liver volume during liver regeneration or in livers undergoing atrophy can only be detected when the liver lobe respectively the calculation of the liver lobe volume is anatomically defined. This is of importance for the development of surgical planning prior to experimental surgery.

P096 IMPAIRED LIVER REGENERATION IN MICE LACKING NUCLEAR FACTOR I-C*R. Fahrner¹, S. Edelmann², U. Settmacher¹, D. Stroka³, N. Mermode²¹Klinik für Allgemein-, Viszeral- und Gefäßchirurgie, Universitätsklinikum Jena, Jena, Germany; ²Institute of Biotechnology, University of Lausanne, Lausanne, Schweiz; ³Department of Clinical Research, University of Bern, Bern, Schweiz

Introduction: Knockout studies of Nuclear Factor I-C (NFI-C) revealed effects on skin wound healing and on the growth of its appendages. The aim of this study was to assess a possible role in liver regeneration following partial hepatectomy (PH).

Methods: NFI-C knockout and C57/Bl6 mice underwent 60% PH. Liver regeneration, gene and protein expression [e.g. transforming growth factor- β 1

(TGF- β 1), plasminogen activator inhibitor-1 (PAI-1), urokinase plasminogen activator (uPA)] were assessed at specific time points.

Results: NFI-C knockout mice revealed decreased number of proliferating hepatocytes at the peak of regeneration and a delayed liver regeneration process in comparison to controls. Gene and protein expression analysis revealed that TGF- β 1 and PAI-1 were overexpressed in NFI-C knockout mice. Knockout mice displayed a blunted increase in uPA activity, a PAI-1-regulated early liver regeneration event mediating the breakdown of the extracellular matrix (ECM), and they did not abrogate PAI-1 expression at later phases of liver regeneration. In knockout mice, the decrease of HGF signaling was indicated by lower phosphorylation levels of its receptor cMET.

Conclusion: NFI-C acts as a regulator of TGF- β 1 and PAI-1 expression following PH, leading to decreased PAI-1 secretion and to an increase of uPA signaling, thereby activating hepatocyte proliferation and liver regeneration.

P098 MULTIDRUG-PRECONDITIONING ALLEVIATES IMMUNE RESPONSE IN RAT KIDNEY GRAFTS

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Background: Reduced ischemia reperfusion-injury by multidrug-preconditioning inhibiting Crosstalk between ROS and Innate Immunity was evaluated in a rat kidney transplant model.

Materials and methods: 70 orthotopic, life-sustaining rat kidney transplants were performed using a fully mismatched allogeneic model (Lewis-Brown-Norway \times Lewis). Rats were randomly assigned to either therapy or vehicle group. Donors were preconditioned with oxidase inhibitors (Allopurinol, Diphenylethiodonium, Apocynin) and recipients received the radical scavenger Edaravone preoperatively and for 4 days after the operation. 6 h, 3, 7, 14 and 28 days after kidney transplantation biopsies and blood samples ($n = 7$ for each time point per group) were taken for analysis. Histological scoring of all tissue specimens was performed by two pathologists blinded to applied treatment. Expression of 84 genes relevant for innate immunity and adaptive immune response was studied by PCR-array.

Results: 28 day-survival was 100% vs. 71.4% (Therapy vs. Control). Histological scoring showed a lower ischemia-reperfusion injury at early time points [e.g. semiquantitative ATN-Score d3: 1.21 \pm 0.6 vs. 0 (Therapy vs. Control)] and a significantly lower cumulative Banff score (6 h, 3d, 7d, 28d, $P < 0.05$). PCR revealed significant regulation of >25 genes related to innate and adaptive immune response indicating an initially diminished innate immune response and a retarded activation of adaptive immunity.

Conclusion: Reduced damage during transplantation may lead to a lower activation of innate immunity and a delayed adaptive immune response.

P099 N-OCTANOYL DOPAMINE TREATMENT OF ENDOTHELIAL CELLS INDUCES THE UNFOLDED PROTEIN RESPONSE AND RESULTS IN HYPOMETABOLISM AND TOLERANCE TO HYPOTHERMIA

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Aim: Due to their hydrophobicity and redox properties, N-acyl dopamines (NADD) may affect oxidative protein folding and thereby induce the unfolded protein response (UPR) This was tested in the present study.

Methods: Genome wide gene expression profiling, confirmatory qPCR and reporter assays were employed on human umbilical vein endothelial cells (HUVEC) to validate induction of UPR target genes and UPR sensor activation. Intracellular ATP, apoptosis and thermotolerance were used as functional parameters to assess adaptation of HUVEC.

Results: NOD, but not dopamine dose dependently induces the UPR. This was also found for other synthetic NADD. Induction of the UPR was dependent on the redox activity of NADD and was not caused by selective activation of a particular UPR sensor. UPR induction did not result in cell apoptosis, yet NOD strongly impaired cell proliferation by attenuation of cells in the S-G2/M phase. Long-term treatment of HUVEC with low NOD concentration showed decreased intracellular ATP concentration paralleled with activation of AMPK. These cells were significantly more resistant to cold inflicted injury.

Conclusions: We provide for the first time evidence that NADD induce the UPR *in vitro*. It remains to be assessed if UPR induction is causally associated

with hypometabolism and thermotolerance. Further pharmacokinetic studies are warranted to address if the NADD concentrations used *in vitro* can be obtained *in vivo* and if this in turn shows therapeutic efficacy.

P100 N-OCTANOYL DOPAMINE IMPROVES VASCULAR BARRIER FUNCTION INDEPENDENT OF ITS CYTOPROTECTIVE PROPERTIES IN THE SETTING OF STATIC COLD PRESERVATION

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Aim: Static cold preservation (CP) severely impairs endothelial barrier function in solid organ allografts. Although N-octanoyl dopamine (NOD) treatment can prevent cell damage during CP, intercellular gap formation still occurs. We analyzed the effect of NOD treatment of EC in relation to barrier function.

Methods: Impedance was measured in NOD treated or untreated HUVEC during treatment and after CP and re-warming. Changes in F-actin and Paxillin (pax) staining were studied by immune-fluorescence and Western blotting.

Results: NOD strongly increased impedance when HUVEC were cultured at 37°C, paralleled by increased F-actin fibers, mostly associated with phosphorylated paxillin (pPax). This was completely abrogated in the presence of U0126 or Fasudil suggesting activation of p42/p44 and ROCK. Neither U0126 nor Fasudil impaired the propensity of NOD to protect EC against cold inflicted injury. While in untreated HUVEC subjected to CP impedance was strongly diminished, in NOD treated HUVEC impedance rapidly increased during re-warming. The expression of F-actin fibres and pPax increased in parallel to activation of p42/44. Phosphorylation of pax was strongly diminished in the presence of U0126. While inhibition of ROCK did not affect impedance; this was strongly abrogated in the presence of U0126.

Conclusions: NOD treatment of EC increase impedance suggesting improved endothelial barrier properties. This is mediated through the activation of ROCK and p42/44 and involves activation of focal adhesion contacts. During re-warming gap closure does not depend on ROCK activation but requires p42/p44.

P101 PERFUSION DISTURBANCES AND LOCAL INFARCTIONS AFTER EXPERIMENTAL KIDNEY TRANSPLANTATION CORRELATE WITH THE DURATION OF COLD ISCHEMIA TIME

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Background: Kidney transplantation in mice is challenging but offers good translational models to study mechanisms of disease. In this study allogeneic and isogenic kidney transplantation in combination with different cold ischemia times (CIT) was performed and analysed by functional magnetic resonance imaging (MRI) and histological evaluation.

Methods: For the model of acute rejection C57Bl/6 male donor kidneys were transplanted to Balb/C recipients and prolonged CIT (60 min) was used resulting in acute T-cell mediated rejection. As comparison isogenic kidney transplantation (ktx) was done. For chronic allograft rejection Balb/C donor kidneys were transplanted into C57Bl/6 recipients (CIT: 30 min). Warm ischemia time was 30 min in all surgeries. During transplantation the left recipient kidney was nephrectomized. After 3 weeks in the acute rejection model and 7 weeks in the chronic rejection model FACS analysis for infiltrating leukocytes and histology was evaluated (PAS stain) and immunostaining for fibrosis (Sirius red) and inflammation (leukocytes) was done. Functional MRI was performed repetitively and analysed for renal perfusion.

Results: Isogenic ktx histology revealed normal renal morphology 3 weeks after surgery and stable renal perfusion in functional MRI. Allogeneic ktx in the acute model resulted in acute rejection (Banff IIA, IIB, III) with severe inflammation. 75% of the allografts had local infarctions with vessel occlusion partially in areas of heavy inflammation suggesting that infarction was secondary to inflammation. Infarcted areas without any leukocyte are suggestive for surgical complications. Infarcts were characterized by MRI signal alterations and perfusion defects. Longitudinal functional MRI studies showed declining renal perfusion with ongoing rejection also when excluding areas of infarction. Perfusion defects occurred mainly after allogeneic kidney transplantation. Prolonged CIT enhances inflammation and the incidence of infarction (75% with 60 min CIT, 25% with 30 min CIT in the allogeneic model). In the direct vicinity of occluded vessels fibrosis was markedly enhanced.

Conclusion: The duration of cold ischemia time enhances the risk for partial infarction and accelerates rejection. Renal perfusion measurements by functional MRI correlate with rejection and offers non-invasive techniques to monitor inflammation and to assess graft pathologies.

P102 DONOR DDAVP MITIGATES INFLAMMATORY RESPONSE AFTER BRAIN DEATH, BUT HAS NO INFLUENCE ON GRAFT OUTCOME IN AN ALLOGENEIC KIDNEY TRANSPLANTATION MODEL IN RATS

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Introduction: Organs of brain dead donors are linked to compromised patient and graft survival. Hence interventions that counteract the negative effects of brain death and maintain organ quality are urgently needed. Retrospective studies suggest that donor desmopressin (DDAVP) treatment improves outcome after kidney transplantation. We hypothesized that DDAVP disarms the graft's endothelium from pro-inflammatory angiotensin-2 (ang-2) containing Weibel-Palade bodies (WPB) in the donor; resulting in a reduced WPB release at the time of reperfusion in the recipient.

Methods: The influence of DDAVP treatment on the expression of vasopressin-2 receptors (V2R) and adhesion molecules was tested in brain dead donor rats. Furthermore, renal function was evaluated in an allogeneic transplantation model of brain dead rats.

Results: WPB were released upon rewarming in a static cold preservation model of cultured endothelial cells, but V2R expression was only scarcely found on the renal vasculature and down-regulated in BD rats by DDAVP. Nevertheless, donor expression of VCAM-1 and ICAM-1 were significantly reduced in DDAVP donor rats, but these benefits neither improved renal function nor histology in our allogeneic renal transplant model.

Conclusion: Our results do not support the hypothesis that the beneficial effect of DDAVP treatment is caused by the release of WPB in renal donor grafts.

P103 ULTRASMALL PARTICLES OF IRON OXIDE ENHANCED MR-IMAGING OF ISCHEMIC ACUTE RENAL FAILURE AND CYCLOSPORINE NEPHROTOXICITY IN A RAT MODEL ON A CLINICAL 3T SCANNER

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Background: MRI is a promising tool to non-invasively visualize renal posttransplant diseases. To assess if MRI enhanced by ultrasmall particles of iron oxide (USPIO) P904 can detect ischemic acute kidney injury (IAKI) and cyclosporine nephrotoxicity (CyA) in a rat model.

Methods: Of 30 Lewis-rats were studied in three groups: Nine animals were subjected to 45 min unilateral ischemia (IAKI). Eleven animals received daily cyclosporine A (CyA, 15 mg/kg s.c.) under low-salt diet (<0.03% sodium) and 10 Controls received daily sterile oil (50 mg/ml s.c.) for 28 days. MRI was performed 36 h after injection of P904 (516 µmol/kg, Guerbet) on a 3T scanner (Siemens TimTrio), spatial resolution 0.3 × 0.3 × 1.0 mm³. Signal-to-noise measurements (SNR) were performed in the cortex, medulla and pylon, respectively. Histology was assessed as gold standard including Perl's Prussian blue staining to demonstrate iron (i.e. P904) and ED1-immunohistochemistry to detect rat macrophages.

Results: In the iAKI group a vast signal decay was seen mainly in the medulla. The SNR of the iAKI kidneys vs. Controls were: cortex 19.6 vs. 10.4, medulla 4.5 vs. 18.8, pylon 14.6 vs. 33.7 ($P < 0.0001$, respectively) In CyA kidneys we observed a moderate decrease of signal intensity without compartment-specific predominance: The respective SNR in the cortex were 11.0 vs. 10.4 (n.s.), medulla 15.3 vs. 18.8 ($P < 0.01$) and pylon 24.6 vs. 33.7 ($P < 0.0001$), CyA versus Controls, respectively. In kidneys with iAKI histology confirmed abundant Prussian blue- and ED1-positive macrophages predominantly in the outer medulla (ED1-labeling in iAKI versus Controls 49 vs. ≤1 cell(s) per field of view, $P < 0.0001$) in conjunction with typical changes of iAKI while being normal in the control group. Contrastingly, iron staining was completely negative in all compartments in CyA kidneys, whereas ED1-labeling detected moderate macrophage infiltration (CyA versus Controls: 20 vs. ≤1 cell(s), $P < 0.0001$) and light microscopy demonstrated the typical features of calcineurin inhibitor toxicity.

Conclusions: USPIO-enhanced MRI with the novel contrast agent P904 seems to be a suitable tool to detect iAKI with excellent correlation to histology.

In contrast, P904 alone fails to detect cyclosporine nephrotoxicity, probably due to its low-inflammatory histologic characteristics.

P104 IMPACT OF COLD ISCHEMIA ON THE AUTOREGULATION DURING NORMOTHERMIC EXTRACORPOREAL KIDNEY PERFUSION

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Objectives: The number of marginal organs for transplantation increased in the last recent years. The transplantation of marginal organs leads to a raised risk of graft failure and DGF. Normothermic extracorporeal kidney perfusion provides the chance to assess the organ quality before transplantation. However, existing parameters for vitality assessment are discussed controversial. For this purpose we discuss a novel approach based on the characterization of autoregulation.

Methods: Porcine kidneys ($n = 18$, cold static storage: 1–14 h) were normothermic and pressure controlled perfused with autologous oxygenated blood, conditioned with heparin, glucose and sodium-bicarbonate. After 1 h of kidney conditioning the arterial pressure during the perfusion was changed every 5 min by 2 mmHg in a range of 60 mmHg to 110 mmHg and flow characteristics were recorded.

Results: Three different flow characteristics (FC) were detected: FC1 – typical autoregulation ($n = 5$); FC2 – restricted autoregulation ($n = 6$); FC3 – no autoregulation ($n = 7$). Those could be assigned to the times of ischemia as following (FC-Q_{0.25}, median, Q_{0.75} in hh:mm:ss): FC1 – 01:05:02, 01:19:28, 01:52:00; FC2 – 02:51:38, 06:26:23, 08:09:13; FC3 – 08:12:17, 10:41:17, 13:00:52.

Conclusion: The results suggest that the autoregulatory behavior is highly correlated to the cold ischemia time. Accordingly, parameters describing autoregulation characteristics could be used as potential markers for kidney assessment during warm machine perfusion.

P106 RENAL TRANSPLANT RECIPIENTS LACK CIRCULATING CD19 + CD24^{hi}CD38^{hi} INTERLEUKIN-10 PRODUCING REGULATORY B-LYMPHOCYTES

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Recent studies demonstrated that CD19 + CD24^{hi}CD38^{hi} regulatory B-Lymphocytes (Breg) appear to suppress immune mechanisms by cell-cell contact or production of IL-10. Here, we analyzed peripherally circulating Bregs by flow cytometry in healthy subjects ($n = 18$) and renal transplant recipients receiving a calcineurin inhibitor (CNI) based immunosuppression (Tacrolimus $n = 35$, CsA $n = 11$).

The amount of B-cells among lymphocytes was reduced both in Tacrolimus (6.4%) and CsA (3.6%) treated patients compared to healthy subjects (9.5%). Among B-cells, a distinct subset of Bregs was found to be 4.9% in healthy subjects, 1.4% in TAC-patients and almost blunted in patients receiving CsA (1.1%). After mitogenic ex vivo stimulation with TLR9 agonist CpG, 4% of B-cells in healthy subjects and even fewer in CsA/TAC patients produced IL-10 (0.5% and 1.5%, respectively). Co-culture of positively isolated mitogen stimulated CD19 + B-cells of healthy subjects in presence of CsA (1, 10 and 100 ng/ml) or TAC (1, 5 and 10 ng/ml) confirmed these results. Interestingly, a low amount of peripherally circulating Breg correlated to a lower GFR ($r = 0.38$, $P < 0.05$). Furthermore, among patients exhibiting <1.0% of Bregs ($n = 29$) 38% patients developed a renal transplant rejection event.

Whether a low amount of Breg may precede allograft rejection needs to be confirmed in further studies.

THORACIC ORGANS

P107 A MULTI-CENTER, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP PHASE IV TRIAL INVESTIGATING THE OUTCOME ON RENAL FUNCTION, EFFICACY AND SAFETY OF CNI-REDUCTION OR ELIMINATION WITH EVEROLIMUS IN DE NOVO HEART TRANSPLANT RECIPIENTS: THE MANDELA STUDY DESIGN

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Background: There is growing evidence on the beneficial use of everolimus (EVR) in heart transplantation to support minimization or withdrawal of calcineurin inhibitor (CNI) therapy, mainly to spare renal function or avoid malignancy or to reduce progression of cardiac allograft vasculopathy. The MANDELA study (NCT00862979) aims to evaluate the benefit of either CNI-free or CNI-minimized EVR-based regimens after early conversion from standard treatment in de novo heart transplant recipients (HTxR).

Methods: MANDELA is a multi-center, randomized, controlled, open-label, 12 month study. Overall, 200 de novo HTxR (3 months post Tx) will be randomized (1:1) to receive either EVR (C0-h 5–10 ng/ml) + reduced CNI (TAC C0-h 3–8 ng/ml or CsA C0-h 50–150 ng/ml) + steroids (≤ 0.3 mg/kg) or to receive EVR (C0-h 5–10 ng/ml) + mycophenolic acid (EC-MPS max. 2880 mg/day or MMF max. 3 g/day) + steroids (≤ 0.3 mg/kg). The primary objective of MANDELA is to demonstrate superior renal function (assessed by eGFR, MDRD) 12 months post randomization in HTxR with a CNI-free regimen after tapering serum CNI-levels to the respective target ranges. Key secondary objectives include: non-inferior efficacy (composite endpoint of BPAR of ISHLT 1990 grade $\geq 3A$ /ISHLT 2004 grade $\geq 2R$, acute rejection, episodes of hemodynamic compromise, graft loss/re-transplant, death or loss to follow-up) and safety outcomes (infections, hypertension, hyperlipidemia, diabetes).

Results: So far 138 patients at nine German heart transplantation centers have been randomized in the MANDELA study until April 2014. Continuation of the study was well supported by a neutral data safety monitoring board.

Conclusion: The Mandela study might help to evaluate benefit on renal function of an EVR-based CNI-free regimen in HTxR after early conversion.

P108 IMPACT OF DONOR ORGAN QUALITY ON POSTOPERATIVE OUTCOME IN HIGH URGENCY RECIPIENTS – EXPERIENCE OF AN EUROTRANSPLANT CENTER

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Objectives: The lack of donors for heart transplantation (HTX) is increasing while at once the waiting list increases even greater. This leads to high urgency (HU) listing ("sickest first") of the recipients and need of acceptance of extended donor criteria (EDC) resulting in allocation of donor hearts to HU recipients in more than 90%. The purpose of our study was to investigate the impact of donor profile and pre-implantation factors on postoperative outcome in Eurotransplant (ET) HU recipients.

Methods: We retrospectively analyzed data of 50 consecutively performed HTX procedures in our institution (07/2010-08/2012). Data were collected from medical records and outcome were calculated for perioperative factors. Main outcome parameters included survival, intensive care unit (ICU) stay, graft injury characterized by postop creatine kinase (CK-MB)-release and postop catecholamine dosage.

Results: Of all recipients, 47 (94%) were HU (35 m,70%), mean age was 51.16 ± 1.81 years. Mean follow-up was 20.18 ± 1.46 month. 1-year survival was 84%; overall survival was 80%. Donor factors like age (48.23 ± 1.68 years), age ≥ 55 years ($n = 19; 45.8\%$), sex (16 m;32%), organ ischemic time (273 ± 7.29 min) and body surface donor/recipient index (1.01 ± 0.15), brain death-to-explant time (BD2Ex-t; 729.78 ± 42.88 min), cause of brain death (non-traumatic ICB ($n = 26.52\%$), traumatic ICB ($n = 10.20\%$), insult ($n = 9.18\%$), other ($n = 5.10\%$)) and postop CK-MB max (92.96 ± 5.85 U/l) did not show any association with the outcome measures. Early catecholamine therapy was need with a combination of nor-epinephrine (NE) and dobutamine (DBX) in 27 (54%), epinephrine+NE+DBX in 10 (20%), DBX+milrinone in 6 (12%) and other in 7 (14%) patients. Mean ICU stay (7.18 ± 1.31 days), ventilation time (50.5 ± 7.75 h), catecholamine dosage and CK-MB max was not influenced by BD2Ex-t, organ ischemic time, donor age or sex. Longer ICU-stay was associated with higher mortality ($P = 0.021$).

Conclusions: HU patients had a comparable survival as reported by the ISHLT. In our cohort, donor related factors did not have influence on the early and late outcome. Factors of success are more likely to be depending on recipient's condition rather than on the donor's. Our data support the use of

EDC donors in ET HU recipients. However, discussion about the principles of organ allocation focusing the ideal recipient and time remains even more crucial.

P109 RV INFARCTION, MANAGEMENT OF VSD REPAIR AND IMPLANTATION OF RVAD – A CASE REPORT

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Aim: We report on a 45-year-old male patient with a ventricular septum defect (VSD) following myocardial infarction due to acute occlusion of right coronary artery. This patient underwent repair of ventricular septum defect, implantation of right ventricular assist device (RVAD), successful weaning and explantation of the VAD.

Method & Result: On admission this patient was hemodynamically highly unstable following an acute proximal occlusion of the right coronary artery and a relevant ruptured ventricular septum. A percutaneous intervention of the RCA was unsuccessful. We performed a repair of the VSD through the apex of the left ventricle using cardiopulmonary bypass. The VSD was mainly apical but the myocardial infarction involved most of the anterior septum. After repair, weaning off from bypass with support of IABP and catecholamines was not successful due to massively impaired right ventricular function. A continuous flow pump (HeartWare[®] ventricular assist device) was implanted in a RA-PA position and weaning from bypass was possible. An epicardial lead was placed to the RV and attached to an implantable pacing device due to complete AV block. Two months later the patient was admitted to the emergency room with a thrombus that partially occluded the RVAD. Despite systemic thrombolytic therapy the pump completely stopped. The device was successfully explanted during an emergency operation. With stable hemodynamics, highly impaired right ventricular function and a small remnant VSD the patient was successfully heart transplanted within the next year.

Conclusions: Early repair of VSD during an unstable hemodynamic situation bears high risk for intra- and post operative lethal outcome. Implantation of HVAD for recovery or bridge is an adequate option for these patients.

P111 EFFECTS AND SIDE-EFFECTS OF IVABRADINE EARLY AFTER HEART TRANSPLANTATION: COMPARISON TO β -BLOCKERS

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Objective: After cardiac transplantation treatment of sinus tachycardia with β -blockers may significantly impair cardiac function, particularly regarding right ventricle. A favorable response to ivabradine after cardiac surgery was described in many studies. However, we wanted to evaluate effects and side-effects of ivabradine in the early period after heart transplantation (htx).

Methods: Between 10/2010 and 05/2014 44 patients underwent htx in our department. Ivabradine was administered in 23 patients immediately after htx (starting on POD 4-27), in addition to β -blockers in 6 patients. Of the other 21 patients, 11 received β -blockers due to sinus tachycardia.

Results: After ivabradine mean heart rate was reduced from 113.7 ± 15.2 bpm at baseline to 90.4 ± 11.0 bpm before hospital discharge ($P < 0.05$). Echocardiographic evaluation confirmed an improvement of cardiac function, correlating to substantial clinical advances. The heart rate reduction was less pronounced in patients with β -blockers ($P > 0.05$).

There were no substantial adverse effects in all patients with ivabradine. We did not detect relevant interactions with immunosuppressants, except from a distinct increase of mycophenolate mofetil blood levels.

Conclusions: We could demonstrate that patients with sinus tachycardia after htx can be successfully treated with ivabradine, even compared to β -blockers. Reducing the resting heart rate, it did not negatively influence cardiac contractility. Interactions with immunosuppressive medication or other adverse effects could not be detected.

P112 THE IMPACT OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATORS IN PATIENTS AFTER HEART TRANSPLANTATION WITH MULTIFACTORIAL ANEMIA WITH IMPAIRMENT OF RENAL FUNCTION

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Background: Multifactorial anemia with impairment of renal function (CRF) is a common problem after heart transplantation (HTX). Erythropoiesis – stimulating agents (ESAs) are commonly used to improve hemoglobin levels in patients with anemia due to CRF. With CERA (Continuous Erythropoietin Receptor Activator) a new therapeutic agent with a larger serum half time is available. However, data in patients after HTX are extremely limited. This study retrospectively evaluated the effects of anemia therapy with CERA versus conventional ESAs (Erythropoietin beta) in patients after HTX with anemia due to CRF.

Patients and methods: A total of 20 ESA naive heart transplant recipients with anemia due to CRF were included. All patients had baseline hemoglobin levels below 11 g/dl. 10 patients (mean age 53.4 ± 10.2 years, mean time post HTX 0.71 ± 0.73 years, 9 male/1 female) were included in the CERA group and 10 patients (mean age 60.3 ± 12.9 years, mean time post HTX 5.5 ± 5.2 years, 7 male/3 female) in the conventional ESA group (Erythropoietin beta). The primary endpoint was the change in hemoglobin level from baseline to month four, eight, and twelve month post initiation of either CERA or conventional ESAs. Hemoglobin target level was 12 g/dl.

Results: After 12 months of CERA and ESA therapy a statistically significant increase in mean hemoglobin levels was observed (CERA group: 9.0 ± 1.0 g/dl vs. 11.8 ± 1.9 g/dl, $P = 0.005$ vs. baseline, ESA group 9.2 ± 1.1 g/dl vs. 11.0 ± 2.2 g/dl, $P = 0.02$ vs baseline). In CERA patients, a continuous increase in mean hemoglobin levels was observed throughout the study period, whereas mean hemoglobin level was more fluctuant in conventional ESA patients. However, CERA and ESA therapy was well tolerated and no adverse events occurred during the study period. Patient self-assessment questionnaire revealed a lower pain level during the study period. Longer dosing intervals were advantageous as ease of dosing was more pronounced in CERA patients and the rate of missed doses was lower in CERA patients indicating a better adherence.

Conclusions: During the study period CERA corrected anemia and maintained sustained and stable control of mean hemoglobin levels. Our results underline the importance of optimized patient adherence by longer dosing intervals in this selected patient population with a multitude of comedications.

P113 REJECTION PROFILE IN PATIENTS AFTER HEART TRANSPLANTATION DEPENDING ON BASELINE CALCINEURIN INHIBITOR REGIMEN

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Background: The use of tacrolimus (TAC) in patients after heart transplantation (HTX) increased during the last years.

Aim: In this retrospective study we evaluated the effects of a TAC (conventional and extended release TAC) based immunosuppressive therapy regarding rejection profile in comparison to a Cyclosporine A (CSA) based regimen in patients after HTX.

Methods: The data of 233 patients who underwent HTX at the Heidelberg Heart Transplantation Center from May 1998 until November 2010 were retrospectively analyzed. Primary immunosuppressive therapy was changed from a CSA ($n = 114$) to a TAC ($n = 119$) based regimen in 2/2006 according to center routine. Follow-up period was two years post HTX. Primary end-point was time to first biopsy-proven rejection requiring therapy. In all patients routine follow-up at the Heidelberg HTX Center was mandatory.

Results: Risk factor analysis regarding time to first rejection episode showed no statistical significant differences regarding recipient age, donor age, recipient gender, donor gender, gender mismatch, ischemic time, and diagnosis leading to HTX between the two groups (all $P = ns$). Time to first biopsy proven rejection was significantly longer in the TAC group (intention to treat analysis (ITT), $n = 233$, log-rank-test $P < 0.0001$, per protocol analysis, $n = 150$, log-rank-test $P = 0.0003$). In patients who underwent a change of primary immunosuppression ($n = 49$), also a significant longer time to first biopsy proven rejection was found in the primary TAC subgroup (log-rank-test, $P = 0.0297$). Further subgroup analysis in the TAC subgroup showed a longer time to biopsy proven rejection under extended release TAC compared to conventional TAC, however the level of statistical significance was not met (ITT, log-rank analysis, $P = 0.1736$).

Conclusion: Our study demonstrated that a TAC based primary immunosuppressive therapy is superior to a CSA based immunosuppressive regimen in patients after HTX regarding time to first biopsy proven rejection.

P114 RISK FACTORS FOR ACUTE KIDNEY INJURY AFTER LUNG TRANSPLANTATION

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Background: Solid non-renal organ transplantations have an increased risk for acute kidney injury (AKI). Little is known about the peri-surgical risk factors for AKI. Identifying risk factors for AKI could help to modify the therapy towards reducing nephrotoxic medication. Therefore, we aimed to identify predictors to estimate the severity of AKI and to find new biomarkers for risk prediction.

Material and Methods: For risk factor identification we analysed 950 electronic patient files for type of surgery, blood transfusions, time on ICU, nephrotoxic medication and co-morbidities. AKI was defined according to the AKIN criteria into mild (AKIN-1), moderate (AKIN-2) and severe AKI (AKIN-3) based on by loss of eGFR, or increase of s-creatinine within the first 48 h after surgery. CART analysis for risk prediction was performed.

In addition, a prospective clinical trial to verify the risk factors was performed. Patient urine and blood samples were collected at different time points before and after surgery. Functional MRI (including 22 patients) was performed at day 12–16.

Results: AKI incidence was 50% after double lung-tx in the retrospective cohort (26% mild, 15% moderate, 9% severe). Relevant risk factors for aggravation of AKI was the transfusion of >2 red blood cells packages during surgery. Also pre-existing renal impairment increased the risk of AKI.

Prospectively, more than 50% of lung-tx patients developed AKI (36% mild, 32% moderate, 9% severe AKI). S-creatinine in AKI was 156 ± 70 vs. 80 ± 17 µmol/l without AKI, $P < 0.01$. NGAL elevation in urine correlated with AKI. By an antibody based microarray certain proteins could be identified which correlated with increased risk for AKI. Even prior to surgery certain proteins were expressed differently. In the functional MRI study renal perfusion in lung tx patients with AKI compared to healthy volunteers was significantly impaired (228 ± 64 vs. 329 ± 63 ml/(min*100 g), $P < 0.01$). Even patients without AKI showed decreased renal perfusion compared to healthy volunteers (258 ± 48 ml/(min*100 g). Renal perfusion impairment correlated significantly with AKI severity.

Conclusion: AKI is an important and frequent complication after lung-tx. The combination of new array biomarkers with advanced imaging techniques allows to estimate the severity of AKI and to identify new risk factors.

P115 OUTCOME AFTER ORTHOTOPIC HEART TRANSPLANT WITH NEED OF CONCOMITANT SECOND CARDIOPLEGIC CARDIAC ARREST

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Background: The outcome after orthotopic heart transplant (HTX) is most importantly dependent on a short cardiac arrest time. Here we present our single-center experience of patients who underwent HTX with need of a second cardioplegic cardiac arrest (CCA) due to intraoperative complication.

Methods: We analyzed perioperative and follow-up data of patients, who underwent HTX with need of concomitant secondary cardioplegic cardiac arrest between 1996 and 2014. Mean follow-up time was 63 ± 86 month (range 0–217).

Results: Nine patients (two female) with a mean age of 52 ± 14 years were identified who needed a concomitant second CCA due to intraoperative complications. Eight patients were in need of surgical intervention of the ascending aorta including overstitching or resection and replacement. One patient needed mitral valve reconstruction and mechanical aortic conduit. Average first cardiac arrest time was 263 ± 97 min (range 86–366) and second 117 ± 119 min (range 6–412). Actuarial survival displayed a 1-year and 5 years survival of 64 ± 17%. Six patients are currently still alive. Two patients died within hospital stay. One patient deceased after hospital discharge due to intra-cerebral bleeding. Two deceased patients received female and one male donor grafts. Mean donor age (seven female) was 47 ± 14 years.

Conclusion: Secondary cardioplegic cardiac arrest due to intraoperative complications after orthotopic heart transplant bears high mortality and morbidity risk, but can be performed with an acceptable short- and long-term survival.

P116 EVALUATION OF SHORT-TERM OUTCOME AFTER LUNG TRANSPLANTATION IN THE LUNG ALLOCATION SCORE ERA

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In December 2011, the Eurotransplant Foundation changed the allocation system for donor lungs from a model based on urgency and waiting time to the lung allocation score. The aim of the study was to investigate the effects of the lung allocation score implementation on the early outcome after lung transplantation in Germany.

We therefore retrospectively studied the outcome of the last 50 patients transplanted before and the first 50 patients transplanted after lung allocation score implementation.

Both patient groups compared in baseline characteristics at the time of transplantation. Postoperative hospital stays were comparable between the groups, i.e. 40.3 ± 26.8 and 40.3 ± 31.3 days ($P = 0.992$). Also, survival rates on intensive care, during entire hospital stay, at 90 days, 6 month and 1 year after transplant were comparable between the groups. The retrospectively calculated lung allocation scores of the patients transplanted under the old allocation system were not statistically significantly different from those after lung allocation score implementation, i.e. 46.5 ± 14.2 and 51.2 ± 17.4 ($P = 0.139$).

We demonstrate, that implementation of the lung allocation score in Germany had no negative effect on the early outcome after lung transplantation. Our data indicate that patients transplanted prior to implementation of the lung allocation score had a similar prospective transplant benefit.

P117 ISOLATED PERMANENT RIGHT VENTRICULAR ASSIST DEVICE IMPLANTATION WITH THE HEARTWARE HVAD- FIRST RESULTS FROM THE EUROMACS REGISTRY

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Objectives: Isolated right ventricular (RV) dysfunction with preserved LV function is difficult to treat and associated with high mortality. Temporary devices for right ventricular support (RVAD) are available and have been used for short-term right heart assistance. In some patients, RV function does not recover and long-term devices are needed. Recently, isolated RVAD implantation with a HeartWare HVAD device has been reported in patients with acute RV infarction and chronic graft failure. However, isolated implantation on the right side remains a rare occasion and still is an off-label use for this pump. To gather European data, we queried the EUROMACS database, in which procedures and outcomes data for patients receiving mechanical circulatory support are registered.

Methods: Until May 2014 data of eight patients (mean age 55.0 ± 17.3 years, 100% male) with an isolated HVAD for RV support were submitted to the EUROMACS registry. All patients were in INTERMACS classes 1–3. Device strategy was rescue therapy in seven patients (87.5%) and destination therapy in one patient (12.5%). Indications for RVAD placement were acute myocardial infarction in four (50.0%), failure to wean from cardiopulmonary bypass in two (25.0%), and post-cardiotomy RV failure in another two patients (25.0%). Intra- and postoperative results of the EUROMACS registry were analysed.

Results: Inflow cannulas were implanted into the right atrium (RA) in six patients (75.0%) and into the RV in two patients (25.0%). CPB was used in six patients (75.0%). Four patients (50.0%) survived the first 30 days. During follow-up, one patient died after 44 days due to multiorgan failure. In the surviving three patients, two patients were transplanted after 29 and 419 days and in one patient the device was explanted for pump thrombosis and recovered RV function.

Conclusion: In this very specific and sick patient cohort within the EUROMACS registry, isolated permanent RVAD implantation is a novel and promising rescue strategy.

IMMUNOLOGY AND HLA

P119 N FREQUENCY OF HLA- AND NON-HLA ANTIBODIES IN LIVER TRANSPLANTATION

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Introduction: Currently, only the blood group compatibility must be considered in a liver transplant in contrast to kidney and heart transplantations

In the period from May 2012 to February 2014 we examined sera from prospective liver recipients for the presence of HLA and non-HLA antibodies before and after liver transplantation.

Material and Methods: Sera from 265 patients who were sent to us in preparation for the planned liver transplantation, we tested the following methods:

1. Lymphocytotoxicity (CDC) – Detection of complement dependent HLA antibodies
2. Solid phase assay (Luminex) Detection of HLA and non-HLA antibodies
3. ELISA techniques for detection of HLA and non-HLA antibodies
4. ELISA techniques for the detection of auto-antibodies

During this period, 51 patients received one or two liver transplants ($n = 55$), where we also investigated the frequency of the above antibodies before and after transplantation.

Results: In the sera prior to transplantation, we were able to detect 52% ($n = 138$), antibodies against HLA class I in 23% ($n = 62$) against HLA-class II, in 37.7% ($n = 100$) against MICA and in 31.3% ($n = 83$), auto antibodies against angiotensin II receptor 1 (AT1R)/endothelin receptor (ETR).

The incidence of antibodies before and after transplantation (Tx) of 51 transplanted patients (55 transplants) was 20% before Tx ($n = 11$) and 52.7% after Tx ($n = 29$).

A more differentiated analysis of the tested antibodies after transplantation resulted in 36.4% ($n = 20$) donor-specific HLA antibodies in 16.4% ($n = 9$) donor-specific antibodies against HLA cross-reacting antigens; 23.6% ($n = 13$) against non donor-specific HLA antigens; in 12.7% ($n = 7$) auto antibodies against AT1R and ETR; in 5.4% ($n = 3$) antibodies against MICA.

Summary: Our studies show that in liver Tx immunological risks can be observed. Compared to frequency before and after Tx, more antibodies were tested after Tx in approximately 30%. One third of these antibodies were donor-specific! The negative influence of donor- and auto antibodies to the function of the graft must be controlled more frequently. Therefore regularly after Tx antibodies should be controlled.

P120 PREFORMED CELLULAR ALLOREACTIVITY IS ASSOCIATED WITH HUMAN LEUKOCYTE ANTIGEN MISMATCHES

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The risk of allograft dysfunction increases with increasing human-leukocyte-antigen-mismatch (HLA-MM) numbers. Although this may be mediated by preformed alloreactive T-cells, their association with HLA-MM and potential differences in healthy controls and dialysis-patients prior to transplantation are poorly characterised.

Whole-blood samples from 113 individuals (52 dialysis-patients and 61 healthy controls) were combined pairwise to determine alloreactive CD4 and CD8 T-cell frequencies using flow-cytometry (1502 tests in total, 681 from dialysis-patients, 821 from controls). Alloreactivity was associated with the number of HLA-MM.

Among the 1502 tests, a significant association was found between the frequency of alloreactive CD8 T-cells and the HLA-A/B/C-MM number ($P = 0.030$), and between respective CD4 T-cells with HLA-DR-MM number ($P < 0.0001$). Peak levels of alloreactive CD8 T-cells increased with HLA-A/B/C-MM numbers (0MM:0%; 1MM:0.041%; 2MM:2.752%; 3MM:4.118%; 4MM:7.001%; 5MM:8.549%; 6MM:6.864%), and CD4 T-cells with HLA-DR-

MM numbers (0MM:0.078%; 1MM:0.578%; 2MM:0.780%). Dialysis-patients showed higher alloreactive CD4 ($P = 0.015$) and CD8 T-cell levels ($P < 0.0001$) as compared to controls.

In conclusion, alloreactivity correlated with HLA-MM in the whole population but not on an individual level. This method may be used to explore whether the presence of alloreactive T-cells can serve as a more specific parameter to assess the risk of graft dysfunction as compared to HLA typing.

P121 STIMULATION OF PROTEIN-REACTIVE EFFECTOR CELLS BY ACTIVATED ANTIGENS: A NOVEL STRATEGY FOR MONITORING CELL MEDIATED IMMUNITY

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Suppression of cell mediated immunity (CMI) may cause serious clinical complications including microbial infections and reactivations. Thus, accurate quantification and monitoring of functional effectors of CMI may allow reliable prediction, detection and personalized treatment strategies. We have developed a novel methodology for the functional analysis of CMI based on the combined application of *activated* herpesvirus-derived stimulator antigens and the highly sensitive ELISpot technology. *Activated* proteins reveal the unique capacity to stimulate a broad spectrum of clinically relevant effector cells including T helper and cytotoxic T cells as well as NK and NKT cells. The *activation* of proteins mediates the translocation to the exogenous and endogenous processing pathway of APC for epitope-loading on MHC-I in addition to MHC-II molecules by cross-presentation. Stimulation of peripheral blood mononuclear cells (PBMC) with preselected *activated* CMV-proteins reveal a clinical sensitivity above 90% independent of the subject's HLA composition. Assay performance is highly reproducible with variability values less than 25% and a linear correlation between the amount of reactive cells and total PBMC counts. Thus, *activated* stimulator antigens in combination with ELISpot technology represent a promising strategy to assess the immune status of immunosuppressed patients.

P122 IGM- AND IGG-ANTIBODIES AGAINST HLA ARE ASSOCIATED WITH CHRONIC LUNG ALLOGRAFT DYSFUNCTION AFTER LUNG TRANSPLANTATION

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Introduction: The aim of our study was to investigate the clinical relevance of IgG- and IgM-antibodies (ab) against HLA on chronic lung allograft dysfunction (CLAD) in lung transplant recipients.

Methods: We performed a study of 120 lung transplant recipients transplanted between 2007 and 2011. Patient sera were investigated before and after transplantation. The sera were screened and specified by means of Luminex[®] and CDC for IgG- and IgM-ab. Outcome parameters were bronchiolitis obliterans syndrome (BOS) and survival.

Results: Preformed HLA-IgG-ab were detected in 19/120 (15.8%) and IgM-ab in 9/120 (7.5%). In 85% IgG-ab disappeared after transplantation, but all IgM-ab persisted. After transplantation 22 (18%) patients were positive for IgG-ab and 9 (7.5%) were positive for IgM-ab. The incidence of de novo IgG-DSA formation was 9/120 patients (7.5%). The development of BOS was seen in 5/9 (55%) IgG-DSA positive patients versus 17/111 (15%) IgG-DSA negative patients ($P < 0.01$). Death due to graft failure was observed in 25/120 (20.8%) patients; 8/25 patients were IgM-ab positive compared to 2/25 IgG-ab positive patients ($P < 0.01$).

Conclusion: According to our data we consider preformed IgM-ab and de novo IgG-DSA are a strong risk factor for CLAD in lung transplantation. Therefore regular pre- and post-transplant HLA-monitoring is essential.

IMMUNOSUPPRESSION

P123 CONVERSION FROM PROGRAF TO GENERIC TACROLIMUS IN GERMANY

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Introduction: Generic Tacrolimus HEXAL[®] was introduced in Germany in 2010. Despite overall exposure >287 000 patient-years worldwide and publications reporting >3000 transplant patients, clinical data in Germany is scarce. The present report retrospectively evaluates experience from two NHZM centers.

Methods: Of 18 stable patients (17 kidney/1 liver, mean age \pm SD 44 \pm 18 years) were switched from Prograf[®] to Tacrolimus HEXAL[®] on a mg:mg monitored basis at 69 \pm 71 months after transplant. Serum creatinine and tacrolimus trough levels were recorded up to 32 \pm 20 weeks post switch. Comparisons were based upon three visits post- versus three visits pre-conversion.

Results: Dose changes were not performed. The group mean tacrolimus dose remained unchanged vs. pre-conversion values. Similarly, trough levels 7.0 \pm 1.8 vs. 6.6 \pm 1.6 ng/ml ($P = 0.32$) and serum creatinine 1.8 \pm 0.7 vs. 1.8 \pm 0.6 mg/dl ($P = 0.37$) also remained stable. Some patients exhibited higher intra-patient variability in tacrolimus trough levels. This was unaffected by conversion and group mean variability was not significantly changed. Acute rejection was absent and conversion was well tolerated.

Conclusion: This initial experience confirms earlier reports that Tacrolimus HEXAL[®] has a similar therapeutic profile to Prograf[®]. Conversion is safe and feasible in a controlled setting under supervision from a transplant physician.

P125 USE OF PLASMA GCFDNA QUANTIFICATION TO GUIDE PERSONALIZED IMMUNOSUPPRESSION

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Objectives: A new graft-derived cell-free DNA (GcfDNA) method was used to monitor liver graft integrity in response to early post-transplant immunosuppression.

Methods: GcfDNA percent was measured as described (Beck et al. Clin Chem 2013). Total cfDNA was quantified by assays for single copy genes together with an artificial internal DNA standard in one droplet digital PCR. GcfDNA amount was calculated by multiplying GcfDNA (%) with total cfDNA (cp/mL); corrected for extraction efficiency of the internal standard. GcfDNA and trough blood tacrolimus were measured in 260 samples from 20 patients during 240 days post-transplant.

Results: There was good correlation ($r^2 = 0.66$; $P < 0.001$) between percent and amount GcfDNA, which is high after engraftment, rapidly declining during the first week. Subtherapeutic tacrolimus levels were associated with elevated GcfDNA percent and amount, with the latter showing better discrimination. Both, the cut-off value for GcfDNA and tacrolimus levels decreased with time post-transplant. Discrimination accuracy was 64% using GcfDNA amount versus tacrolimus with 3750 cp/ml and 7.8 μ g/l during week 2 post-surgery, 3000 cp/ml and 7.0 μ g/l (week 3 & 4) and 2000 cp/ml and 6.5 μ g/l thereafter.

Conclusion: Both GcfDNA expressions appear useful to identify the minimal needed tacrolimus concentrations, whereas the amount GcfDNA has advantage early after transplantation, given its higher dynamic range.

P126 OUTCOME ON RENAL FUNCTION OF AN EVEROLIMUS BASED THERAPY AFTER CALCINEURIN INHIBITOR WITHDRAWAL IN MAINTENANCE RENAL TRANSPLANT RECIPIENTS: 5 YEAR DATA OF THE APOLLO TRIAL

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Purpose: To study renal function, safety and efficacy of an Everolimus (EVR) based regimen after Calcineurin-Inhibitor (CNI) withdrawal in maintenance kidney allograft recipients.

Methods: In an open-label, randomized, controlled, multi-center study 93 patients on stable immunosuppressive therapy consisting of CNI (CsA or Tac), Enteric-Coated Mycophenolate Sodium (EC-MPS) with or without steroids were randomized to either continue CNI/EC-MPS or convert to an EVR/EC-MPS based regimen. After completion of the 12-months core study patients were included in an observational 4 year follow-up.

Results: 93 maintenance kidney Tx patients with a mean time of 6.4 years since the most recent transplantation (Tx) were randomized to either EVR ($n = 46$) or CNI ($n = 47$) treatment. 78 patients completed the 12-month core study and 67 (72%) attended the final 60-month study visit. Mean trough levels were 81 \pm 34 ng/ml in CsA, 5.2 \pm 1.9 ng/ml in Tac and 6.1 \pm 2.4 ng/ml in EVR treated patients. Mean time post-Tx at baseline was 82.6 months and 70.5 months in the EVR and CNI groups, respectively. At month 60, adjusted mean eGFR (Nankivell) was 63.0 (95% CI 57.8, 68.2) mL/min/1.73 m² in the EVR group versus 57.9 (95% CI 52.6, 63.1) mL/min/1.73 m² in the CNI group, a difference of 5.1 (95% CI -0.6, 10.8) mL/min/1.73 m² ($P = 0.076$). Among patients who remained on randomized study drug at month 60, mean eGFR (Nankivell) was 71.6 (95% CI 64.2, 79.0) mL/min/1.73 m² in EVR-treated patients ($n = 21$) versus 60.6 (95% CI 55.1, 66.1) mL/min/1.73 m² in CNI-treated patients ($n = 29$) (mean difference 11.0; 95% CI 3.6, 18.5 mL/min/1.73 m²; $P = 0.005$). No cases of BPAR occurred from randomization to month 60 in either group. Graft loss occurred in three EVR-treated patients and one CNI-treated patient. Graft loss occurred in three EVR-treated patients and one CNI-treated patient. Until month 60 one death had occurred in the EVR group, three deaths in the CNI group. No unexpected safety concerns were observed in either group.

Conclusion: The late conversion to an EVR/EC-MPS treatment in maintenance renal Tx patients after CNI withdrawal is safe and led to a sustained better renal function in EVR treated patients 5 years post Tx.

P127 POST HOC ANALYSIS OF ZEUS AND HERAKLES, TWO PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIALS: ONSET AND PROGRESSION OF DIABETES IN KIDNEY TRANSPLANT RECIPIENTS ON CYCLOSPORINE STANDARD OR CONVERTED TO CNI-FREE OR CNI-LOW EVEROLIMUS REGIMEN

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Purpose: To compare incidence of new-onset diabetes mellitus (DM) after transplantation (Tx) (NODAT) and progression of pre-existing DM in de novo kidney (K) allograft recipients after conversion to everolimus (EVR) based regimen and withdrawal or reduction of cyclosporine A (CsA) combined with EVR.

Methods: Post hoc analysis from ZEUS and HERAKLES, 12 months (Mo), prospective, open-label, multicenter, randomized (rdz) trials. De novo KTx pts received standard-exposure CsA + EC-MPS + steroids since Tx and were rdz to i) either continue CsA regimen or convert to ii) EVR/EC-MPS (at Mo4.5 post Tx in ZEUS, at Mo3 post Tx in HERAKLES) or to iii) a third rdz arm with reduced CNI+EVR regimen (HERAKLES). Post hoc analysis was done on NODAT development or DM progression.

Results: Results from ZEUS: 8% (25/300) of pts had DM at Tx, until Mo12 NODAT had developed in 8% (22/275) of non-DM pts (EVR 14/142, CsA 8/133); among these 22 pts 7% (20/275) had developed NODAT already at randomization (EVR 13/142, CsA 7/133). Incidence of NODAT after randomization was similar between groups ($P = 0.97$). Mean blood glucose change from randomization to Mo12 was similar in NODAT and DM subpopulation between EVR and CsA pts. eGFR (Nankivell, [ml/min]) was similar at randomization and significantly higher at Mo12 for EVR versus CsA pts within all subpopulations (NODAT: EVR +14.0(11.4) vs. CsA -9.2(15.9); pre-existing DM: EVR +5.5(5.9) vs. +0.7 (10.0) CsA). Results from HERAKLES: At Mo12 NODAT occurred in 6.8%(30/438) of all pts (EVR group 6.7%(10/149) vs. CsA group 8.3%(11/133) vs. reduced-CsA group 6.3%(9/143), thus the same incidence of NODAT was found between the 3 HERAKLES regimens ($P = 0.62$).

Conclusion: No difference in NODAT incidence or progression of DM after CNI withdrawal and conversion to EVR were found within 12 Mo post Tx by post hoc analysis of these two large randomized trials. The benefit on renal function of an early conversion to an EVR-based regimen was seen in the NODAT subpopulation similar to what was seen from total study population results.

P128 12-MONTH ATHENA STUDY: EVEROLIMUS VS. STANDARD REGIMEN IN *DE NOVO* RENAL TRANSPLANT RECIPIENTS

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Background: Post-kidney transplant (KTx) long-term and full dose/standard calcineurin inhibitor (CNI) use is associated with an increased risk for malignancies, cardiovascular disease, and renal failure. Previous studies have shown that everolimus (EVR) allowed further CNI reduction and therefore helps to preserve renal function without affecting efficacy. ATHENA study is designed to evaluate the renal function comparing EVR-based regimens with reduced CNI exposure (tacrolimus [TAC] or cyclosporine A [CsA]) versus a standard treatment protocol with mycophenolic acid (MPA) and TAC in *de novo* KTx (day 0) recipients (KTxR).

Methods: This is a 12-month (M), multi-center, open-label, prospective, randomised, parallel group study in KTxR (≥ 18 years) receiving renal allografts from deceased or living donors. Eligible patients will be randomized prior to Tx to one of the three treatment arms (1:1:1): TAC MPA+steroids ($n = 204$) or EVR+TAC+steroids ($n = 204$) or EVR+CsA+steroids ($n = 204$) all with basiliximab induction. Patients with thrombocytopenia or leukopenia, uncontrolled hypercholesterolemia or hypertriglyceridemia, ABO incompatible Tx will be excluded. The primary objective is to demonstrate non-inferiority in renal function (eGFR by Nankivell formula) in one of the EVR arms compared to the TAC MPA+steroids arm at M12 post-KTx. The key secondary objective is to assess the incidence of treatment failure (BPAR, graft loss or death) at M12 post-KTx. Other objectives are to evaluate GFR by different formulae, assess the incidence of efficacy endpoints (BPAR, graft loss and death), the incidence and severity of viral infections (CMV, BKV), the incidence and duration of delayed graft function, to evaluate left ventricular hypertrophy (by LV mass index), and to compare HLA- and non-HLA-antibody evolution.

Study status: The study recruitment is currently ongoing and 371 patients were enrolled in Germany and 66 in France. The preliminary results of this ongoing trial are expected in 2016.

Conclusion: ATHENA is the largest bi-national/German/French renal transplant study and the first study evaluating the non-inferiority of renal function as a primary objective in a *de novo* EVR-based immunosuppressive protocol.

P129 DIFFERENTIAL IMPACT OF BELATACEPT AND CYCLOSPORINE A ON CENTRAL AORTIC BLOOD PRESSURE AND ARTERIAL STIFFNESS AFTER RENAL TRANSPLANTATION

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Calcineurin inhibitors (CNI) are potent vasoconstrictors and induce an acceleration of arteriosclerosis, thus contributing to the cardiovascular risk after renal transplantation. The present study compares the impact of belatacept and cyclosporine A (CsA) on arterial stiffness and central aortic blood pressure. We performed a case-control study in 46 patients (23 on belatacept and 23 on CsA matched for age, body mass index, time after transplantation and time on dialysis prior to transplantation. Pulse wave analysis (SphygmoCor, AtCor[®]) was used to assess central aortic blood pressure, aortic augmentation pressure, and pulse wave velocity (PWV) as a marker of arterial stiffness. Assessment of vascular function was performed after a minimum of 20 months and a median follow-up of 81 months posttransplant. Peripheral systolic and diastolic blood pressure did not significantly differ in the two groups ($P > 0.05$ each). The central aortic augmentation pressure was higher in the CsA group (12.7 vs. 7.3 mmHg, $p = 0.048$). PWV as a measure of arterial stiffness did not differ in the two groups. Belatacept is not associated with a significant difference in arterial stiffness compared to CsA after a median of 81 months posttransplant. It is associated, however, with a lower aortic augmentation pressure, a strong independent cardiovascular risk factor.

P130 BALANCING EFFICACY AND RENAL FUNCTION PRESERVATION AFTER KIDNEY TRANSPLANTATION WITH EVEROLIMUS AND REDUCED CALCINEURIN INHIBITORS FOR BETTER GRAFT OUTCOMES: DESIGN OF THE TRANSFORM STUDY

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Introduction and Aims: Acute rejection and poor graft function at one year post renal transplantation are important predictors for graft failure. TRANSFORM, is a phase IV study that is designed to evaluate the impact of two immunosuppressive regimens [everolimus (EVR)-facilitated reduced (r) calcineurin inhibitor (CNI) exposure versus mycophenolic acid (MPA) plus standard (s) CNI exposure] on these clinically relevant outcomes in a novel single composite endpoint.

Methods: TRANSFORM (NCT01950819) is a 24 M, multicentre, open-label study randomising *de novo* RTxR 1:1 to EVR+rCNI or MPA+sCNI arm with basiliximab or antithymocyte globulin induction and steroids. Each arm will be further stratified by donor type (living donors, deceased standard criteria donors, or deceased expanded criteria donors) and CNI usage (cyclosporine or tacrolimus). At M12 the primary endpoint will be a composite of treated biopsy-proven acute rejection (tBPAR) rate or proportion of RTxR with estimated glomerular filtration rate < 50 ml/min/1.73 m² (eGFR; MDRD4). Key secondary endpoint will be composite efficacy failure rate (tBPAR, graft loss, or death). These endpoints will be also assessed at M24. In a subset of subjects, the incidence of donor-specific antibodies by treatment group in relation to acute rejection and development of chronic allograft nephropathy/interstitial fibrosis and tubular atrophy expression (renal protocol biopsy) will be explored. Patients completing 24 M of treatment will be eligible to participate in an extension study for a further 36 M with outcomes including eGFR, patient and graft survival, incidence of cardiovascular disease, malignancy, and infection analysed up to 5 years.

Results: TRANSFORM study will be conducted across 229 centres worldwide and approximately 2040 RTxR will be randomised. The study enrolment has started and first data are expected in 2017.

Conclusions: Using *de novo* CNI-reduction in an EVR-based regimen, the TRANSFORM study aims to address the unmet medical need of balancing immunologic efficacy and renal function preservation. As the largest clinical trial in RTx with extended follow-up to 5 years, TRANSFORM will provide critical data required to help improve long-term outcomes.

P132 EFFICACY AND SAFETY OF THREE DIFFERENT TREATMENT REGIMENS IN *DE NOVO* RENAL TRANSPLANT PATIENTS: MONTH 36 FOLLOW-UP RESULTS OF HERAKLES TRIAL

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Aim: To compare safety and efficacy of 3 different immunosuppressive (IS) regimens 3 years after renal transplantation (Tx).

Methods: Of 802 patients (pts) were included in this 1 year, prospective, open-label, randomized (rdz), controlled multi-center study. After induction therapy with basiliximab all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 months (Mo) post Tx 499pts were rdz 1:1:1 to either a) continue standard CsA(100–180 ng/ml)+EC-MPS ($n = 166$) (STD) or convert b) to a calcineurin inhibitor (CNI)-free regimen with everolimus (EVR)(5–10 ng/ml)+EC-MPS ($n = 171$) or c) to a CNI-low regimen with EVR(3–8 ng/ml) + reduced CsA(50–75 ng/ml) ($n = 162$). All pts continued on steroids. Mo36 follow-up(FU) visit was performed by 123(89%) STD, 130 (95%) CNI-free and 123(94%) CNI-low treated pts of the FU population (pop). **Results:** From rdz to Mo36 BPAR was reported in 19/151(13%)STD, 22/149 (15%)CNI-free and in 21/146(14%)CNI-low pts (ITT;p=ns). 3 deaths (2%) occurred in STD, 2(1%) in CNI-free and 5(3%) in the CNI-low group. 6(4%) graft losses were observed in the STD, 5(3%) in the CNI-free and 1(1%) in the CNI-low group. Composite failure (BPAR, death,graft loss,loss to FU) occurred in 27 (19%) STD, 28(20%) CNI-free, 33(23%) CNI-low treated pts. Premature discontinuation due to AEs occurred in 4/154(3%) of STD, 4/150(3%) of CNI-free and 1/147(1%) of CNI-low pts (safety-pop) from Mo12 to 36. Renal function (cGFR, Nankivell) was significantly improved by +7.0 ml/min/1.73 m² in favor of the CNI-free regimen at Mo36 (ITT; $P = 0.009$).

Conclusion: Mo36 results from HERAKLES show that IS regimens using EVR with low-dose or without CNI-exposure reflect an efficacious and safe therapeutic approach offering the opportunity for an individualized IS.

P133

COMPARISON OF SIROLIMUS AND EVEROLIMUS IN THEIR EFFECTS ON KIDNEY FUNCTION AND SURVIVAL IN HEART TRANSPLANT RECIPIENTS

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The mammalian target of rapamycin (mTOR) inhibitors sirolimus (SRL) and everolimus (EVL) are potent immunosuppressive agents, which allow reducing the dose of nephrotoxic calcineurin (CNI) inhibitors in solid organ transplant recipients. However, comparative data of the two mTOR inhibitors concerning

clinical outcome in heart transplant (HTx) recipients is scarce. We assessed 5-year mortality and kidney function in 212 maintenance HTx patients with poor kidney function (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m²), who were switched over to SRL (*n* = 64) or EVL (*n* = 148) between 2000 and 2007. In both groups, the CNI inhibitor dose was reduced by 50%.

Results: Baseline characteristics differed significantly between the two groups with respect to body mass index, age, duration on regular CNI inhibitor dose and year of SRL or EVL introduction (*P* = 0.013–2 (*P* = 0.012). Results did not differ between the SRL and EVL group (*P* = 0.911).

Conclusions: Data indicate that in HTx patients with poor kidney function, the introduction of both SRL and EVL plus CNI dosage reduction is able to maintain kidney function. Nevertheless, results also suggest that regarding 5-year survival EVL may be superior to SRL.