Tumor lymphocyte infiltration and prognosis in patients with hepatocellular carcinoma treated by liver transplantation

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ORALS

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BOS01-KIDNEY – ECD/DCD

BO01 RISK FACTORS AND CLINICAL OUTCOMES FOR DELAYED GRAFT FUNCTION IN DECEASED DONOR RENAL TRANSPLANTATION

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Backgroud: DGF is a well-known complication associated with increased risk of acute rejection and poor long-term graft survival, but the impact of DGF on post-transplant outcomes is not yet entirely clear. The purpose of this study was to analyze risk factors for DGF and determine its impact on the outcomes of deceased donor renal transplantation.
Methods: Between February 2000 and December 2011, we performed 195 deceased donor renal transplants. After exclusion of primary non-function grafts ($n = 4$), the study recipients were divided into two groups [group I: DGF ($n = 31$, 16.2%); group II: non-DGF ($n = 160$, 83.8%)].
Results: These donor-related variables showed significant differences: the comorbidities, Hypertension ($P = 0.042$), Diabetes ($P = 0.025$), and pre-retrieval serum creatinine ($P < 0.001$). But, there is no significant recipient-related factors. The significant transplant-related factor was positive of panel reactive antigen (PRA > 20%, $P = 0.008$). On multivariate analysis, only pre-retrieval serum creatinine level ($P < 0.001$, HR: 1.814) was independent risk factor for the development of DGF. The mean MDRD GFR level at 7 day, 1 month, and 6 month after transplantation was significantly lower in patients with DGF but MDRD GFR level at 1, 3, 7 and 10 years did not differ significantly. Between two groups, the incidence of AR and CMV infection were significantly different ($P = 0.039$ and $P = 0.032$, respectively). Graft survival at 1 and 5 year after transplantation were significantly lower among the DGF group namely, 83.7% vs. 97.3% and 79.1% vs. 90.6%, respectively ($P = 0.020$). Cox multivariate analysis of risk factors for graft survival identified theses independent risk factors: Nephron mass (Kw/Rw) index ($P = 0.018$, HR: 2.457), CMV infection ($P = 0.040$, HR: 0.017), AR episode ($P = 0.024$, HR: 0.144), surgical complication ($P = 0.040$, HR: 0.027).
Conclusion: In deceased donor renal transplantation, the independent risk factor for DGF was pre-retrieval serum creatinine level. Although there was significant difference in graft survival between two groups (DGF vs. Non-DGF), DGF was not an independent risk factor for graft survival in this study.

BO02 THE DGFS: A SIMPLE SCORING SYSTEM TO PREDICT DELAYED GRAFT FUNCTION AFTER KIDNEY TRANSPLANTATION

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Delayed graft function (DGF) is a common kidney transplantation complication known to impact short- and long-term graft outcomes. We explored the possibility to develop a simple tool that could predict the occurrence of DGF and could be helpful in current clinical practice. We built a score, tentatively called DGFS, from a French multicentric and prospective cohort of 1844 adult recipients of deceased donor kidney collected since 2007. Only the 5 following explicative variables (CIT, donor age and creatininemia, recipient BMI and induction immunosuppressive therapy) were independently associated with the risk of DGF in our model with a good predictive capacity (AUC at 0.73). DGFS calculation is facilitated by an application available on smartphones, tablets or computers at www.divat.fr/en/softwares. DGFS should allow the possibility to simply classify patients according to their DGF risk at the time of transplantation and to thus propose them management or therapeutics strategies.

BO03 RISK FACTORS FOR DELAYED GRAFT FUNCTION AND PRIMARY NON-FUNCTION IN KIDNEY TRANSPLANTS FROM DONATION AFTER CIRCULATORY DEATH DONORS

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Objectives: To evaluate the risk factors (RFs) for delayed graft function (DGF) and primary non-function (PNF) in kidney transplants (KTx) from donation after circulatory death (DCD) donors.
Methods: Retrospective single centre study for all consecutive adult DCD KTx performed between 04/2002 and 03/2011. For evaluating RFs for DGF, univariate analysis was supplemented by multivariate analysis. RFs for PNF were evaluated using univariate analysis. Median follow-up was 43 months. DGF was defined as need for dialysis during the 1st week of transplant.
Results: During the study period, 267 DCD KTx were performed. DGF was seen in 33 (12%), and PNF in 9 (3.3%) KTx until last follow-up (02/2013). Binary logistic regression analysis showed the following to be significant RFs for DGF: Donor age > 60 years ($P = 0.002$, OR 5.3, CI 1.8–15.3); donor terminal serum creatinine >120 ìM ($P = 0.01$, OR 4.4, CI 1.3–14.5); and pretransplant dialysis duration >3 years ($P = 0.02$, OR 1.9, CI 1.07–3.4). The following factors showed a trend as RFs for DGF (second warm ischaemia time >50 min, and donor history of cerebrovascular or cardiovascular disease). Univariate analysis of the PNF group showed the following to be significant RFs: donor history of hypertension (44% PNF group vs. 16% non-PNF group); and incidence of post-operative bleeding (22% PNF group vs. 3% non-PNF) (all $P < 0.02$). Small numbers precluded a multivariate analysis. Kaplan Meier analysis showed significantly greater graft survival in the DGF compared to the non-DGF group (87% DGF vs. 76% non-DGF group, at 5 years). There was no difference in the patient survival at 5 years (90% each). Kaplan-Meier analysis of the patient survival showed a significantly poor patient survival with PNF (44% in PNF group vs. 92% non-PNF at 5 years, $P < 0.00001$).
Conclusion: Following DCD kidney transplantation, the risk factors are different for DGF and PNF. Patient survival is adversely affected by PNF but not by DGF.

BO05 SERUM LIVER-TYPE FATTY ACID BINDING PROTEIN DURING THE EARLY POSTOPERATIVE PERIOD PREDICTS RECOVERY OF THE GRAFT FUNCTION AFTER KIDNEY TRANSPLANTATION FROM DONORS AFTER CARDIAC DEATH

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Purpose: The kidneys procured from donors after cardiac death (DCD) hold great potential to expand the donor pool but have not yet been fully utilized, in part because of the high incidence of delayed graft function (DGF). Although the urine liver-type fatty acid binding protein (L-FABP) level is newly developed early biomarker for renal injury after kidney transplantation (KTx), its utility is limited in cases with DGF because of the unavailability of a urine sample. This study evaluated the serum L-FABP level as a potential biomarker to predict the functional recovery of transplanted DCD kidneys.
Materials and Methods: Consecutive patients undergoing living-related (LD, $n = 39$), brain dead (BD, $n = 1$) or DCD ($n = 27$) KTx were retrospectively enrolled. Serum samples were collected serially before and after KTx. The serum L-FABP level was measured using the ELISA assay.
Results: In KTx with immediate function, serum L-FABP level decreased rapidly. In contrast, serum L-FABP decreased slowly in DGF and somewhat increase in DGF cases HD requiring longer than 1 week (DGF > 7 days). Analysis of receiver-operating-characteristic curves demonstrated that DGF can be predicted with 84 % sensitivity (SE) & 86 % specificity (SP) at a cut off of 9.0 ng/ml on postoperative day (POD) 1 (AUC 0.91) and 68 % SE & 90% SP at 6.0 ng/ml on POD 2 (AUC 0.85). Moreover, DGF > 7 days can be predicted 83% SE & 78% SP at 11.0 on POD 1(AUC 0.88) and 67 % SE & 78% SP at 6.5 on POD 2 (AUC 0.77). To evaluate the L-FABP levels as an indicator for

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recovery of renal function, we analyzed the correlation between L-FABP levels on early PODs and various clinical parameters on subsequent PODs by linear regression analyses. The duration of DGF and serum creatinine levels on POD 3 were found to be well correlated with the L-FABP levels on POD 1.
Conclusions: These data suggest that serial monitoring of the serum L-FABP levels may allow us to predict graft recovery and the need for HD after a KTx from a DCD.

BO06 EXCELLENT PERFORMANCE OF KIDNEYS FROM OCTOGENARIAN DONORS TRANSPLANTED AS DUAL KIDNEY TRANSPLANTATION (DKT)

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Introduction: DKT has allowed to optimize the results with very elderly donors, however the upper limit of age has not been defined yet. In this study, we retrospectively reviewed the results of DKT from octogenarian donors, performed in 2 Italian Centers.
Materials and Methods: Between 2006 and December 2012, 29 DKT were performed from donors >80 (group 1) (median age IQR 81 years, range 80–86): the majority were female (70%), hypertensive (73%) with cerebrovascular cause of death (80%), and mean s-creatinine was 83.6 20.2 μM. In all cases pretransplant biopsy was done with a mean Karpinski score of 4.68 ± 0.88. They all received immunosuppressive induction with antibodies (59% thymoglobulin, 41% anti-IL-2 R monoclonal) and maintenance was PSI- based in 13 cases, CNI-based in 5 cases and PSI + CNI in 11 patients. Renal function, DGF, incidence of acute rejection, surgical complications, patient and graft survival were compared with 106 DKT performed during the same period using donors 70–79 years old (group 2) (median age IQR 74 years, range 70–79). The recipients in both groups did not show significant differences in age, BMI, time on dialysis, time on waiting list, PRA levels and HLA mismatch.
Results: The one year graft survival was 97% in group 1 and 100% in group 2, with no deaths in both groups. No primary non function occurred in either groups and DGF was recorded in 4 patients (13.8%) in Group 1 and lasting a mean of 6.7 ± 4.3 days and in 24 patients (22%) in Group 2, lasting 7.3 ± 7.8 days (P = n.s.). The incidence of acute rejection in the first year after transplantation was 10.3% and 6.6% in Group 1 and 2, respectively (P = n.s.). Renal function was satisfactory in both groups: 3, 6 and 12 month serum creatinine were respectively 145 (IQR 114–170), 153 (IQR 122–186), 129 (IQR 105–106) μM (group 1) vs. 113 (IQR 95–142), 111 (IQR 91–144), 111 (IQR 89–137) μM in group 2 (P = 0.02, P = 0.003, p 0.16). Surgical complications included 2 lymphoceles (6.9).

BO07 APPLICATION OF EXPANDED CRITERIA DONORS IN RELATION TO OPTIMAL DONORS: MEDIUM-TERM RESULTS

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Background: The shortage in organs supply has required the use of expanded criteria donors (ECD) for kidney transplant. This study investigates the predictivity of Karpinski's histological score on 3-year graft function in renal transplant. Ex-post classification using Nyberg's score was carried out to assess the reliability of this clinical score and its applicability for organ allocation.
Methods: Four hundred and four organs from deceased donors (251 optimal, 156 marginal) were evaluated. The differences in creatinine levels and MDRD at transplant, 1, 2 and 3 years post-transplant between optimal and marginal donors were recorded. The effect of Karpinski's score classes (0–1, 2, 3, 4, dual transplant) on 3-years graft outcomes was analyzed. Renal function over time across Nyberg grades (A, B, C, D) was compared.
Results: Karpinski score 0–1 and 2 and double transplant had improved graft function compared to scores 3 and 4. Nyberg's score shows a good fit with medium-term outcome and Karpinski's scores, but a high Nyberg grade (C, D) fails to differentiate between allocable organs.
Conclusions: Our data demonstrate a correlation of histological damage at the time of transplant with 3 year graft function but we are unable to provide any supposition on the possible outcome of the discarded kidneys.

BO08 OUTCOMES OF RENAL TRANSPLANTATION WITH EXPANDED CRITERIA DECEASED DONORS: COMPARISON WITH STANDARD CRITERIA DECEASED DONORS

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Background: Our objective was to compare the clinical outcomes of expanded criteria (ECD) with concurrent standard criteria (SCD) deceased donors in adult renal transplantation.
Methods: Between February 2000 and December 2011, we performed 195 deceased donor renal transplants included 31 grafts (15.9%) from ECD and 164 grafts (84.1%) from SCD. Donor and recipient risk factors were separately analyzed and correlated with recipient graft function and survival (minimum 6-month follow-up).
Results: ECDs were older (56.8¡¾6.3 years), showed an increased incidence of hypertension, diabetes and cerebrovascular brain death, and had a higher pre-retrieval serum creatinine level compared with SCDs. ECD kidney recipients had a shorter waiting time (P = 0.019) but other baseline characteristics (age, gender, BMI, cause of ESRD, type of renal replacement therapy, number of antigen mismatch, positive of panel reactive antigen) were no significant difference from those of SCD kidney recipients. The mean MDRD GFR level at 1 month, 6 month, 1 and 3 year after transplantation was significantly lower in patients with ECDs but MDRD GFR level at 5, 10 years did not differ significantly (P = 0.134, 0.702). The incidence of acute rejection episodes, surgical complications and infectious complication did not differ significantly between two groups, but rate of delayed graft function (DGF) was higher in ECD kidney recipients (P = 0.007). Actual patient and graft survival rates were similar between groups with a mean follow-up of 43 months. There were no significant differences between two groups in graft survival (P = 0.111) and patient survival (P = 0.562).
Conclusion: Although intermediate term renal function was better in SCD kidney recipients, graft and patient survival of ECD kidney recipients were comparable to SCD kidney recipients. In conclusion, the utilization of renal grafts from ECDs is an acceptable offer to resolve the disparity of critical organ shortage.

BO09 COLD STORAGE FOLLOWED BY SHORT TERM HYPOTHERMIC MACHINE PERFUSION (HMP): A NEW CONCEPT FOR RECONDITIONING KIDNEYS FROM EXPANDED CRITERIA DONORS (ECD)?

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Introduction: In an animal model we showed that 2 h HMP after cold storage (CS) prior to transplantation is at least as effective as continuous HMP. In a first clinical study this concept is evaluated in ECD kidneys.
Methods: Between 10/11 and 12/12 in a single center prospective pilot study 30 distally procured and initially cold stored ECD kidneys received additional in house HMP (CS+HMP). Fifty-five kidneys from standard criteria donors (SCD) preserved by static CS only served as a control. Delayed graft function (DGF) was defined as the primary end point in this analysis. Standard donor and recipient data were compared by parametric and non-parametric analysis methods, where appropriate.
Results: Results are summarized in the table. One patient who received a SCD kidney developed primary non-function. Median in house MP-time was 6:44 h. Renal resistance after 15 min was 0.52 and 0.31 mmHg/ml/min at the end of HMP.
Conclusion: Outcome of ECD–CS stored kidneys may be notably improved by in house prior to implantation HMP. This concept should be further evaluated in a randomized clinical trial.

BO10 DOES ORGAN ALLOCATION OF DONATION AFTER CARDIAC DEATH PANCREATA AFFECT EQUITABLE KIDNEY TRANSPLANTATION?

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Introduction: Allocation of donation after cardiac death (DCD) pancreas and associated kidneys is currently a source of dispute in the UK. It is now mandatory for kidneys to travel with the respective pancreas to enable implantation of DCD pancreata as simultaneous pancreas kidney (SPK) transplants when possible. Some kidney only units (KTA) have postulated that

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this may unfairly bias their patients due to perceived 'loss of organs'. We assessed sources of DCD pancreata in our unit and correlated this with patient origin.

Methods: Retrospective analysis was performed of all DCD pancreas transplants since our programme's inception (SPK and pancreas alone (PA); 07/05 – present) The geographical origin of all DCD transplant allografts (local or zonal) and recipients was correlated to examine any potential mismatches in terms of equitable organ allocation for recipients.

Results: Two hundred and sixty-seven pancreas transplants (215 SPK, 80.5%; 52 PA, 19.5%) have been performed (27 [12.5%] DCD donors [17 SPK, 10 PA]). 7% of the SPK's are from DCD donors and 17.5% PA's ($P = 0.04$, Fisher's exact test.) Of the 17 DCD SPK's, 6 were implanted into local recipients (within our KTA catchment area) and 11 into imported recipients (zonal – outside our KTA area). We have used 10 DCD donors from our local area compared to only 7 imported DCD donors. Our current SPK waiting list (active [47] and suspended [56]) comprises of 30 (16 active) local recipients and 56 (31 active) imported recipients.

Conclusions: We currently implant more SPK's into imported recipients than organs received from outside region. Our centre is in debit regarding DCD organ usage, ultimately lessening the load on local waiting lists at KTA units. KTA unit's historical desire to keep both DCD kidneys also does our PA recipients a disservice, as they receive more DCD organs. Outcomes in DCD PA allografts, coupled with donor shortages mandates strict adherence to the current utilitarian allocation of kidneys with DCD pancreata.

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BOS02-MALIGNANCIES IN LIVER TRANSPLANTATION

BO11 DE NOVO MALIGNANCY IS THE MAJOR CAUSE OF DEATH IN PATIENTS TRANSPLANTED FOR ALCOHOLIC LIVER DISEASE

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Introduction: Alcoholic liver disease (ALD) is one of the most common indications for liver transplantation (LT). We analyzed determinants of long-term outcome.
Methods: Between 1994 and 2010, 204 pts underwent LT for ALD in our center.
Results: Baseline characteristics are presented in Table 1. Total group survival was 96% at 1 yr and 79% at 5 years. In 63 pts (33%) ALD was complicated by HCC at the time of LT. These ALD/HCC pts were older (61 $\pm$ 5 vs. 55 $\pm$ 8 years; $P = 0.010$), more frequently male (92% vs. 73%; $P = 0.003$) and had a worse post-LT outcome: 5 year survival with or without HCC was 61% and 87.5% ($P < 0.001$) respectively. Relapse of any alcohol use was present in 53 pts (27.5%) of the total group and 3/53 of these pts (6%) developed recurrence of end stage liver disease. Post-LT smoking (36% vs. 18%; $P = 0.008$), not having a life partner (36% vs. 20%; $P = 0.038$) and divorce in history (41% vs. 24%; $P = 0.048$) were more common in the alcohol relapse group compared with abstinent pts. Fifty pts developed a post-LT malignancy, of which recurrence of HCC (10/50 pts; 20%), oropharyngeal carcinoma (10/50 pts; 20%), lung carcinoma (6/50 pts; 12%), skin tumor (6/50 pts; 12%) and bladder/prostate carcinoma (5/50 pts; 10%) were the most common. Post-LT malignancy was the most frequent cause of death (in 58% of all deaths), followed by unknown cause (16%) and persistent alcohol use (12%). Post-LT malignancy was more prevalent in post-LT smokers compared with non-smokers (36% vs. 23%; $P = 0.08$), reaching significance in the subgroup of pts without HCC at LT (40% vs. 18%; $P = 0.011$).
Summary: Alcohol relapse is more frequent in post-LT smokers and in pts with poor social support. However, not recurrence of alcoholic liver disease, but de novo malignancy is the major determinant of mortality in pts transplanted for ALD and is more common in post-LT smokers. Studies that assess the cost-benefit of malignancy screening programs in pts after LT for ALD are required.

BO12 INTRAHEPATIC CHOLANGIOCARCINOMA OR MIXED HEPATOCELLULAR-CHOLANGIOCARCINOMA IN PATIENTS UNDERGOING LIVER TRANSPLANTATION. A SPANISH MATCHED COHORT MULTICENTER STUDY

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Background: Information on outcome of patients transplanted for HCC and diagnosed of HCC-CC or I-CC at pathology is limited.
Aim: Evaluate the outcome of patients with HCC-CC or I-CC on pathology after LT.
Methods: Multicenter matched cohort study 1:2. Study group: 42 patients diagnosed of HCC-CC or I-CC at pathology;control group: 84 diagnosed of HCC. I-CC subgroup: 27 patients-54 controls; HCC-CC subgroup: 15 patients-30 controls. Division according to preoperative tumor size and number: uninodular tumors $\leq$2 cm;multinodular or uninodular tumors >2 cm. Median follow-up: 51(3–142) months.
Results: One-, 3- and 5-year actuarial survival differed between study and control groups(83%,70%,60% vs. 99%,94%,89%, respectively, $P < 0.001$). Differences were found in 1-,3- and 5-year actuarial survival between the I-CC subgroup and their controls(78%,66%,51% vs. 100%,98%,93%, $P < 0.001$) but no differences were observed between the HCC-CC subgroup and their controls(93%,78%,78% vs. 97%,86%,86%, $P = 0.9$). Patients with uninodular tumors $\leq$2 cm in study and control groups had similar 1-,3- and 5-year survival (92%,83%,62% vs. 100%,80%,80%, $P = 0.4$). By contrast, patients in study group with multinodular or uninodular tumors >2 cm had worse 1-,3- and 5-year survival than their controls(80%,66%,61% vs. 99%,96%,90%, $P < 0.001$).
Conclusions: Patients with HCC-CC have similar survival to patients transplanted with HCC. Preoperative diagnosis of HCC-CC should not prompt the exclusion of these patients from transplant opt.

BO13 LIVER TRANSPLANTATION FOR INCIDENTAL CHOLANGIOCARCINOMA – TRULY A DILEMMA?

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Patients after liver transplantation (LTx) for cholangiocarcinoma (CC) have a poor prognosis without specific therapeutic strategies. Particularly patients with incidental cholangiocarcinoma might have the highest risk of disease recurrence, however sparse data on the long term course of unselected patients with CC undergoing LTx is available. Aim of the present study was the analysis of the post-transplant outcome of patients with CC in comparison to other malignancies (HCC, NEC) and benign indications.
Patients and Methods: Prospectively collected data of 625 patients after liver transplantation (1985–2007) were analyzed Long term courses of patients subpopulations with CC ($n = 19$) were compared with groups transplanted for HCC ($n = 128$), other malignancies (MALIGN, $n = 10$) and benign liver disease (NONMAL, $n = 468$). Investigated parameters were besides of survival biometric data, primary immunosuppression, perioperative complications and causes of death.
Results: In the different groups, patients age (394M/231F) ranged between 44.9 and 52.9. (n.s.). Primary immunosuppression was in all cases tacrolimus or Cyclosporin-based. 9/19 transplantations in CC patients were intended and revealed a hilar position, whereas 10 other patients showed a incidental CC with intrahepatic position. Between the groups with malignant indications no significant difference of 5- and 10 year survival was evidnet (36.8–43.7 – 20 [5y]; 25.3–25.3 – 0 [10y] for CC, HCC and MALIGN). Patients without malignancy had a significantly better survival 73.5 [5y]; 61.3 [10y]). Survival rates in CC patients with hilar and intrahepatic tumor location were identical, 6/19 deceased from tumor recurrence within 5 year after transplantation.
Conclusion: Incidental cholangiocarcinomas in liver transplantation are not necessarily associated with deleterious outcome. 36% of the CC-patients survived for 5 year without recurrence. The long term survival post transplantation of CC patients is comparable to unsele.

BO14 LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA USING DONOR GRAFTS FROM DONORS WITH A PAST HISTORY OF MALIGNANCY

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Background: Liver transplantation remains the only curative treatment option for patients with unresectable hepatocellular carcinoma (HCC). Despite persistent donor organ shortage and waitlist mortality, the use of donors with a past medical history of malignancy remains controversial because of the risk of potential tumor transmission. Malignancy after transplantation can occur in three different ways: de novo, recurrence of malignancy or donor-derived malignancy.
Methods: Objective of this study was to compare the occurrence of de novo, recurrent and donor-derived malignancies in patients who underwent liver transplantation for HCC using grafts from donors with a past history of malignancy.
Results: Over a 10-year period, 17 HCC patients underwent liver transplantation using grafts from donors with a past medical history of malignancy at our center. Seven different tumor sites were detected: genitourinary ($n = 8$), cerebral ($n = 2$), breast ($n = 2$), endocrine ($n = 2$), pulmonary ($n = 1$), skin ($n = 1$), blood ($n = 1$). Median follow-up was 327 [0-2005] days. Four patients died within 30 days after liver transplantation due to septic shock ($n = 2$), cardiac shock and primary non-function, respectively. Three patients developed recurrent HCC to the liver and three patients developed pulmonary metastases ($n = 2$) and osseous metastases. One patient was diagnosed with de-novo pancreatic adenocarcinoma (donor malignancy: mamma carcinoma). Six patients are alive and tumor-free.

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Conclusion: The use of organs from donors with a past medical history of malignancy provides patients with HCC timely access to liver transplantation and the risk of donor-derived malignancy seems to be small. The careful selection of donors as well as recipients remains mandatory and may expand the donor pool.

BO16 LIVING DONOR LIVER TRANSPLANTATION: DONOR SELECTION CRITERIA AND POST-OPERATIVE OUTCOME. A SINGLE CENTER EXPERIENCE WITH A TEN YEARS FOLLOW UP

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Background: Donor safety must be considered a priority in live liver transplantation (LDLT). The aim of this study is to evaluate the outcome of live liver donors in our center giving special attention to surgical complications and to their treatment.
Methods: Between March 2001 and March 2012, 80 live donors underwent right hepatectomy (5-6-7-8 segments). Median hepatic vein has always been left to the donors. Our retrospective study analysed the surgical outcome of donors and the complications classified according to Clavien classification modified for live liver donors.
Results: With a follow up of 63.2 ± 12.6 months our mortality is 0%. Two intraoperative complications are reported. All donors had complete recovery after donation. We had 22 complications in 17 donors (21.2%). Seven of these (8.7%) have been classified according to Clavien classification as major complications (grade 2b) but only in two cases donors underwent surgical treatment.
Discussion: LDLT has been accepted as a safe and feasible modality to treat ESLD in order to alleviate the shortage of cadaveric donors. The efficacy of this procedure for the recipients is comparable with DDLT results LDLT is associated to a quite high rate of complications with a discrepancy among data from different centers, partially solved with the Clavien classification of donor complications. We need an international register of LDLT in order to reach common classification criteria and a universal agreement on LDLT results.

BO18 RESULTS OF LIVER TRANSPLANTATION WITH DONORS OLDER THAN 70 YEARS: A CASE-CONTROL STUDY

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Background: Older donors are a growing part of the total pool but no definite consensus exists on the age limit for their acceptance.
Method/Material: Case-control unicenter study comparing outcomes of 72 orthotopic liver transplantations (OLTs) using donors older than 70 years versus 738 chronologically correlated OLTs performed with donors younger.
Results: No difference was observed in postoperative complications of rejection or renal insufficiency except for sepsis and mortality. Long-term survival was lower ($P = 0.001$) and these cases showed more blood requirements associated with prolonged cold ischemia ($P = 0.02$). Multivariate analysis revealed graft dysfunction, mortality, and reduced survival to be associated with donor weight and recipient MELD ($P < 0.05$). Interestingly, the mortality related to hepatitis C virus recurrence was not greater.
Conclusion: Septuagenarians 'livers can be used safely, but careful donor and recipient evaluation are required to avoid additional risk factors.

BO19 PRIMAY GRAFT DYSFUNCTION IN LIVING DONOR LIVER TRANSPLANTATION

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Background: Small-for-size syndrome does not necessarily caused only by small grafts in living donor liver transplantation (LDLT).
Methods: A total of 210 adult-to-adult LDLT grafts were studied.
Results: All of the grafts with early mortality ($n = 13$) caused by primary graft dysfunction had maximum total bilirubin levels >20 mg/dl after postoperative day 7 ($P < 0.001$). No other factors, including prothrombin time, ammonia and ascites output at the corresponding postoperative dates were not associated with early mortality. Thus, delayed functional hyperbilirubinemia of >20 mg/dl for >7 consecutive days occurring after postoperative day 7 was used to characterize primary graft dysfunction. This outcome showed high sensitivity (92.9%) and specificity (95.4%) for early mortality. Multivariate analysis showed that donor age >45 years ($P < 0.020$) and blood loss >10L ($P = 0.044$) were significant risk factors for delayed functional hyperbilirubinemia. The presence of both factors increased the incidence of early graft mortality by 5-fold ($P = 0.004$).
Conclusion: The term "primary graft dysfunction" represents more appropriately than so-called "small-for-size syndrome" for delayed functional hyperbilirubinemia in LDLT.

BO20 HIGH INCIDENCE OF COMPLICATIONS AFTER ABO-INCOMPATIBLE LIVING DONOR LIVER TRANSPLANTATION IN A LONG-TERM SINGLE CENTER EXPERIENCE

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Introduction: The survival rate in ABO-incompatible LDLT used to be much poorer than in ABO-compatible LDLT. The introduction of novel immunosuppressive regimens and apheresis has yielded excellent short-term results in ABO-incompatible LDLT. We present data regarding long-term results including complications of our series.
Methods: We experienced 13 cases of ABO-incompatible LDLT out of 152 cases from 1991 up to 2012. Namely, 6 infants, 5 children and 2 adults. An IgM or IgG titer of more than 16 was an indication for preoperative apheresis. Plasma exchange or double filtration plasmapheresis was performed for 3 consecutive days before Tx and the patients were administered azathiopurine or MMF 3 days before Tx followed by tacrolimus or cyclosporine, as well as methylprednisolone. Five patients were treated with rituximab and 2 patients had infusion therapy with prostaglandin E1 and methylprednisolone.
Results: Seven patients were subjected to preoperative apheresis. One patient who suffered rapidly progressing rejection died due to liver failure. Twelve out of the 13 cases have survived from the surgery, and they were followed from 1.5 to 18.6 years (mean 10.0). Eight patients experienced acute rejection and of them, 6 patients experienced steroid-resistant rejection that was treated with deoxyspergualin and apheresis. Three patients who were administered rituximab did not suffer severe rejection nor adverse effects. Nine late complications were occurred in 6 cases from 0.5 to 11.5 years, but 6 cases had no long-term complications. The long-term complications included biliary stenosis in 3 cases, PTLD in 2 cases, NODAT in 1 case, portal occlusion in 1 case, intestinal bleeding in 1 case, recurrence of HBV in 1 case. One case was dead due to HCC recurrence, but other 11 cases are in good conditions at present.
Conclusion: Although the high incidence of late complications after ABO-incompatible LDLT, the patients survival were secured.

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BOS03-PANCREAS TRANSPLANTATION – CLINICAL ASPECTS

BO21 125 CASES OF DUODENODUODENOSTOMY IN PANCREAS TRANSPLANTATION: A SINGLE-CENTER EXPERIENCE OF AN ALTERNATIVE ENTERIC DRAINAGE

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Backround: Different technical procedures have been developed successfully to perform exocrine drainage in pancreas transplantation (PT).
Methods: Out of 241 PT(217 SPK) performed between 2002 and 2012, Duodenoduodenostomy (DD) was performed in 125 patients, and Duodenojejunostomy (DJ) was performed in 116 patients. We compared our experience with these two types of enteric drainage, focused on graft- and patient survival as well as postoperative complications.
Results: Cumulative patient survival (DD versus DJ) was 96% vs. 96.5% after 1 year and 95% vs. 92% after 3 years ($P = 0.62$). Pancreas transplant survival after 1 and 3 years was 83% and 82% in DD-group and 78% and 73% in DJ-group without significant difference ($P = 0.20$). There were 13/125(10%) cases of pancreas graft loss in the DD-group and 21/116(18.1%) in the DJ-group ($P = 0.08$). Relaparotomy rate was slightly higher in the DJ group (48.2% vs. 41.6%, $P = 0.09$).
Conclusion: DD is a feasible and safe technique in PT.

BO22 SYSTEMATIC ANALYSIS OF MORPHOLOGICAL ALTERATIONS OF PANCREAS ALLOGRAFT AFTER CLINICAL TRANSPLANTATION

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Background: Pancreas can undergo substantial morphological changes post-transplant including tissue atrophy and vascular narrowing. Here, we present a prospective analysis of alterations in pancreatic morphology (APM) by means of CT in patients undergoing pancreas transplantation (PT).
Methods and Materials: The methodology and reliability of pancreas-CT (PCT) has previously been described (Lundqvist et al. 2012). Overall, 21 patients were enrolled after PT. PCT was performed at baseline (2 weeks), 1- and 2-year post-transplant, respectively. Data are expressed as median with ranging scale. Differences in pancreatic volume for each patient were tested by Wilcoxon rank test.
Results: The median pancreatic volume at baseline and 1-year were 98 cm^3 (48, 137) and 56 cm^3 (29, 94), respectively ($P < 0.0001$). The median difference of volume reduction was – 39 cm^3 (–86, 5). In 11 patients (52%), 2-year surveillance was available. Here, the median PV at baseline, 1 year and 2 year were 103 cm^3 (48, 125), 54 cm^3 (29, 94) and 47 cm^3 (19, 71), respectively (baseline vs. 1 year: $P < 0.002$; baseline vs. 2 year: $P < 0.0038$; 1 year vs. 2 year: $P = 0.07$). In accordance with the shrinkage of pancreatic volume, both the splenic and the mesenteric superior artery were shown to undergo a distinct narrowing.
Conclusion: Pancreas allograft seems to undergo substantial and consistent APM. This phenomenon needs to be further characterized in order to evaluate its significance for outcome and its potential confounding effect on the consistency of rejection surveillance based on either duodenal-graft or pancreatic tissue biopsy. A multifactorial analysis of the current cohort is being performed to pinpoint events affecting APM.

BO23 TOWARD 100% PANCREAS GRAFT SURVIVAL BY CHANGING THE STRATEGY OF ORGAN ACCEPTANCE AND SURGICAL PROCEDURE: THE UKT EXPERIENCE

Paolo Girotti, Silvio Nadalin
University Hospital

Background: The actual pancreas graft survival rates in Germany are quite poor (i.e. around 65% at 1 year). Similar results were observed also at our Centre until December 2009. In our opinion main factors influencing such results are: unreliability of P-PASS Score alone, technique and expertise of harvesting surgeon, logistic and implantation technique Aim Single centre retrospective analysis of results of PxTx at UKT, after changing strategy of organ acceptance and surgical procedure.
Patients and Methods: Retrospective analysis of 53 pancreas transplantations at UKT, divided in 2 periods: 2004–2009 ($n = 39$), 2010–2012 ($n = 17$). The new strategy since 2010 was characterized of: a- Accurate donor selection based not only on P-PASS score but also on the medical history (i.e. trauma mechanism) and the amount of transfusion of blood products b- Acceptance of organs retrieved only by experienced pancreas transplant senior surgeons c- Optimal logistic (i.e. acceptance only in case of shipping time <5 h) d- Two surgical teams working parallel at bench and at recipient e- Modified Boggi'S implantation technique (graft retroperitoneal with systemic endocrine drainage in IVC).
Results: During the first period was detected an high rate of graft lost (up to 60%). Furthermore the overall short term post-operative morbidity was 39.4%. Since 2010 we could reach 100% overall patient survival and 92.8% overall graft survival rates (1 graft loss). Overall short term post-operative morbidity was 28.6% (Complications III and IV Dindo-Clavien Classification) with re-operation in only 2 cases 2 cases was carry out a re-operation. Median Hospital stay and ICU stay were 20 and 3 days respectively.
Conclusion: The new strategy of hyper selected pancreas graft acceptance and modified graft implantation technique allowed us to reach graft survival rates near to 100%.

BO24 RISK ASSESSMENT IN PANCREAS TRANSPLANTATION: UTILISATION OF THE WATERLOW SCORE

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Introduction: Pre-operative scoring systems to assess risk and inform patient choice are valuable but have not been validated in Simultaneous Pancreas Kidney (SPK) transplantation. The Waterlow Scoring system, initially developed to assess patients for decubitus ulcer risk, may have utility as a surrogate marker to predict outcome in pancreas transplantation.
Methods: A prospective analysis of SPK recipients at a single unit was performed (11/2011–01/2013). Waterlow scores were collected for all patients (incorporating scores for age, gender, body mass index, nutritional state and tissue quality). These were correlated with other prospectively collected risk scores (Multiple Organ Dysfunction Score, P-POSSUM, Charlson Score, Revised Cardiac Risk Index and ASA) for each recipient. These scores were correlated to Intensive Care, High Dependency Unit and total length of hospital stay, which are important surrogate markers of patient progression and outcome. Potential confounding factors in donors and recipients were calculated.
Results: Thirty-two SPK recipients were analysed (18 female, 14 male; mean age 42.5 (range 27–62); 2 excluded – early graft loss; no late losses, no mortalities). The cohort had no statistical difference in any confounding factor. The Waterlow score had a high correlation to total hospital stay for all patients ($P = 0.0006$; Spearman Correlation). None of the other scoring systems had any correlation on analysis.
Conclusions: Outcome prediction in SPK transplantation is notoriously difficult. Systems designed for emergency surgery are used, with limited applicability in a transplant cohort. The Waterlow Score, with known applications in general surgery appears to have suitability in transplantation. It is traditionally stratified into risk categories, but for SPK recipients, where all are at least high risk, there appears to be a strong correlation between length of stay and absolute score and it is therefore a useful surrogate marker of outcome.

BO25 INTRAVENOUS OR SUBCUTANEOUS OCTREOTIDE FOR PANCREATIC GRAFT FISTULA?

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Institute of Transplantation

Aim: Pancreatic exocrine leaks after pancreas transplantation constitute a major source of morbidity and mortality. We use octreotide as part of a multimodal strategy to treat pancreatic graft fistulas (PGF). Our aim was to evaluate the use of either high dose (IV) or low dose octreotide (SC) in management of PGF and graft outcome.
Methods: We retrospectively analysed 59 patients (Male 48% mean age 42 range 30–51 years) who underwent PT in a single centre during a 13 year period. Patients with and without PGF were compared along with those that received either IV (1200–2400 μgm/24 h) or SC (200–1500 μgm/24 h) octreotide to control their fistula.
Results: Fifteen patients developed a pancreatic leak (25%). The majority presented with either graft pancreatitis or intra-abdominal sepsis (80%). Eight patients were treated with high-dose and 7 with low-dose octreotide. PGF patients demonstrated a prolonged hospital stay (median PGF 21 days vs. no PGF 13 days, $P = 0.04$) but demonstrated no difference between those treated with high or low dose octreotide (21 vs. 22 days). Those with leaks had more re-operations (leak 86% vs. no leak 13.6%, $P = 0.035$) however there was no difference between high or low dose octreotide groups (87.5% vs. 85.7%). Those with leaks had more radiological interventions (leak 80% vs. no leak 18%, $P = 0.04$) but again no obvious difference between high or low dose octreotide groups (75% vs. 85%). Furthermore, there was a trend towards lower rates of 1 year graft survival between patients with PGF and those without (73% vs. 82%, $P = 0.5$).

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Conclusion: PGF after pancreatic transplantation remains a source of considerable morbidity, prolonging hospital stay and may reduce 1 year pancreatic graft survival. Treatment with different doses of octreotide does not appear to change the clinical course of a PGF.

BO26 PANCREAS RETRANSPLANTATION – A 10 YEAR EXPERIENCE

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Oxford Transplant Centre

Background: Pancreas Transplantation (PTx) is an effective treatment for type 1 diabetics, with nephropathy or severe hypoglycaemic unawareness. However, graft attrition rates remain high. Up-to-date, data on the outcome of pancreas reTx is scarce.
Methods: March 2002 to January 2013, 582 PTxs were performed in the Oxford Transplant Centre, of which 17 were reTx in 16 previously transplanted patients [first Tx included 11 simultaneous pancreas kindey Tx(SPK), 4 pancreas Tx alone(PTA), 2 pancreas after kidney Tx(PAK)]. The Immunosuppression Protocol included Alemtuzumab induction with Tacrolimus & Mycophenolate mofetil for the entire study group. Mean recipient age at reTx was 41 years and the mean interval between Txs was 2.6 years. The study also evaluated the effect of pancreas reTx on kidney graft function and the overall patient survival. The cause of first and second pancreas graft failure was considered.
Results: ReTx pancreas graft survival was 53% and 33% for the first and fifth year, respectively, compared to 74% and 44% respectively, for the general PTx population. In the reTx patients, second graft survival was superior compared to the first graft (31% and 0% for first and fifth year, respectively). First and reTx were comparable for Donor factors. After reTx, 17% of patients underwent relaparotomy, 66% of which resulted in pancreatectomy. 50% of graft failure occurred due to graft thrombosis within 2 months post reTx, while immune rejection was the cause of the remaining graft failures occurring at median 238 days (IQR 138d-355d). Kidney graft survival was 100% at 5 years. Patient survival at the time of analysis was 88%.
Conclusion: Pancreas reTx appears to be a reasonable option for patients whose first graft was lost. Survival of the second graft was significantly higher compared to the first PTx. Although the graft survival rate was lower compared to the registry results, it does not affect the longevity of the kidney graft or patient survival.

BO27 OUTCOME OF PATIENTS UNDERGOING SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANT ASSESSMENT IN SCOTLAND

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Background: The national transplant programme was established in Scotland (5 million people) in 2002. We set to investigate the assessment process and the long-term outcome of all patients who were considered for simultaneous pancreas kidney (SPK) transplantation.
Methods: All patients assessed for pancreas transplantation between 2002 and 2011 were included in this analysis. Socio-demographic data, renal and diabetes complications as well as comorbidity at the time of assessment were collected by linking the records of the Scottish pancreas transplantation unit and the Scottish Renal Registry (SRR). The long-term outcome analysis was carried out according to the outcome of assessment (list for SPK, list for kidney transplant [KTx] or not listed [NoTx]) on an intention to treat basis.
Results: Three hundred and nine patients were assessed: 277 (89%) SPK, 18 (6%) pancreas after kidney and 16 (5%) pancreas transplant alone. Of those assessed for SPK, 162 (58.5%) were listed for an SPK. Of 115 patients assessed but not listed for SPK, 51 were listed for a kidney transplant alone. Median follow-up from the time of assessment was comparable (SPK (5 years), KTx (6 years), NoTx[5 years]). One and 5 year survival following assessment was significantly higher ($P < 0.0001$, log-rank test) in those listed for SPK (95% and 89%) compared to those subsequently listed for kidney transplant (96% and 65%) and those not listed (87% and 59%). Although survival was higher in those listed for kidney transplant compared to those not listed, this was not significant ($P < 0.16$, log-rank test).
Conclusions: Long-term survival in patients listed for simultaneous pancreas kidney is significantly higher than patients subsequently listed for kidney transplant alone or patients who remain on dialysis. This long-term survival benefit is not seen in those listed for kidney transplant alone.

BO28 REVISITING BLADDER DRAINAGE IN PANCREAS TRANSPLANTATION ALONE: A SINGLE CENTRE EXPERIENCE

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Introduction: The role for bladder drainage (BD) in pancreas transplantation is still controversially discussed. While easy monitoring of the kidney contributes to excellent results in simultaneous pancreas kidney transplantation, pancreas transplantation alone (PTA) is still hampered by an up to 20% graft loss within the first year post transplantation. Herein we report our recent experience with enteric and with bladder drained PTA.
Material/Methods: Between February 2010 and September 2012 34 consecutive PTA were performed. Re-transplantations were not included. All but 1 patient suffered from type I diabetes. Immunosuppression was based on Campath induction and TAC/MFF maintenance therapy. In 17 grafts exocrine drainage consisted in enteric drainage (ED), the other 17 underwent exocrine BD.
Results: Median follow-up was 23 months (range 0 – 33) for the ED group and 12 months (1 – 19) for the BD group. Except donor BMI ($P = 0.02$), donor and recipient demographics were not significantly different. 1 year graft survival in the ED group was 64.7%, with 4 losses due to acute rejection, and 2 losses due to intraabdominal sepsis. In the BD group, 1 year graft survival was 100% ($P = 0.01$). In the BD group, 7 patients experienced 9 episodes of urinary amylase dropping more than 50%. These episodes correlated with either acute rejections confirmed by duodenal biopsies or with partial thromboses of the main graft vessels. Following methylprednisolone or heparin treatment, respectively, urinary amylase levels recovered back to their baselines. Hospital readmissions (8/17 ED vs. 11/17 BD; P = ns) were higher in the BD group, without however reaching statistical significance. Three BD patients necessitated conversion to ED.
Conclusion: So far, BD resulted in significantly better 1 year graft survival compared to ED PTA. Close monitoring of the graft by urinary amylase with early detection of (non)immunological complications might be a crucial factor.

BO29 IS REINNERVATION OF THE PANCREAS AFTER TRANSPLANTATION IMPORTANT?

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During the last years significant improvement of the pancreatic transplantation results was achieved. There are few reports about functional status of pancreatic grafts several years after transplantation. Few reports mention significant functional decrease and morphological sclerosis of the graft. The question of nervous connection reconstruction was discussed but never applied in clinics.
Aim: In order to improve the pancreatic transplantation late results, to study the human and animal anatomy of the local pancreas innervation, to create models of the neuroreflector isolation (NRI) of the pancreas and reinnervation and the methods of the surgical directed reinnervation (SDR) of different pancreatic grafts, to evaluate their spontaneous and directed reinnervation. Materials and methods Anatomy: 22 human cadaver pancreas, adult 8 dogs, 9 cats, and 8 Lewis rats. Surgery, physiology, histology: 27 dogs, 28 cats, 94 Lewis rats 94. Neurophysiogical investigation of nervous conductivity between pancreas and CNS used to tested NRI and SDR. Load tests with glucose adrenalin insulin, amylase lipase determination were performed to evaluate the influence NRI and SDR on pancreatic functions. The samples were collected at 0, 30, 60, 90, 120 and 180 min at 1 week, 1 and 3 months after the operations.
Results: 1. Anatomical studies have shown the theoretical feasibility of surgical reconstruction of the continuity of nervous plexus responsible for pancreas transplant/graft innervations in animals as well as in humans. 2. Models of pancreatic tail NRI and surgical reconstitution of the interrupted nervous pathways SDR were created and successfully tested in cats, dogs and rats. 3. Electrophysiological studies performed in the cat models of NRI and NRI+SDR of the pancreas tail have proved the efficiency of the proposed SDR 4. NRI or transplantation of the pancreas leads to an exaggerated reaction to usual stimulations, that may cause of the functional exhaustion of the graft in late delays. 5. SDR shortens the period of NRI of the graft, contributes to a quick restoration of its normal function and prevents its late degradation, as confirmed by relatively early normalization of its histological structure in rat model but also in dogs.
Conclusion: The SDR is a simple surgical technique, easily and quickly performed after the graft surgical revascularization without any complication and its functional and morphological effects were shown to be positive. So SDR may be recommended to be used in human pancreas transplantation.
Acknowledgment: To Professors JP. Squiffle and Lamotte (UCL).

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BO30

LIVING DONOR PANCREAS TRANSPLANTATION – SINGLE CENTER EXPERIENCE OF 16 CASES

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Background: Living donor pancreas transplantation (LDPT) is not so popular due to high technical failure rate and elevated chance of donor morbidity including development of diabetes. However advantages of LDPT include shorter waiting time especially in patients waiting simultaneous pancreas and renal transplantation, lower probability of rejection, and chance of pre-conditioning in sensitized condition.
Methods: From October 1992 to December 2012, we have performed 16 living donor PT (6 PTA, 10 SPK) including one ABO incompatible patient. We retrospectively reviewed our clinical cases.
Results: All the donors have been studied extensively by endocrinologist. Mean donor age was 42.5 year old (9.6) with mean BMI 21.9 (2.5). Relation of donors was parents in 6, siblings in 5 and spouse in 5. Mean recipient age was 30.9 year old (8.6), with type I DM 14 patients, and mean BMI 20.3 (1.7). Overall patient survival was 100%. Graft survivals at 1, 3, and 5 year were 90%, 77.7% and 77.7% respectively in SPK recipients, and 50%, 33.3% and 16.7% in PTA recipients. Causes of graft failure in SPK were one thrombosis, and one rejection, while in PTA those were 2 noncompliance, one thrombosis, one reflux pancreatitis, and one chronic rejection. According to pancreatic exocrine drainage, one out of 8 grafts survived in bradder drained group while all the grafts survived in enteric drained group. Minor pancreatic juice leak was the most common complication (5/16) in donors. Most of donors were normoglycemic, however in 2 donors diabetes developed that was treated with oral hypoglycemic agent.
Conclusions: In living donor pancreas transplantation, the donor surgical risk is acceptable. The surgical procedure of LDPT seems to be justified is SPK recipient with enteric drainage. However we considering the poor graft survival in PTA in our small series, LDPT in PTA recipient should be performed cautiously.

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BOS04-ISLET TRANSPLANTATION

BO33 TRANSPLANTATION OF FETAL KIDNEY PROGENITOR CELLS IN TREATMENT OF CHRONIC RENAL INSUFFICIENCY: RESULTS OF PILOT STUDY

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Background: Until lately, basic paradigm of nephrology was that kidneys are not capable to regenerate, but restoration function of kidney occurs exclusively due to hypertrophy of undamaged nephrons. Today we are aware that renal tissues are like neural cells, restores due to division of adult stem cells which are located in renal parenchyme. Tissues of fetal kidney consistof all cellular elements in developmental stages, which have potential to replace, damaged (injured) renal structures in adults.
Objectives: Analysis of effectiveness of fetal kidney progenitor cells (FKPC) transplantation in chronic renal insufficiency.
Methods/Materials: Transplantation of FKPCwas performed in 20 patients with chronic renal failure. All patients were in hemodialysis and had normal potassium level in blood plasma. Concentration of creatinine in blood plasma fluctuated from 280 to 560 μM. FKPC were introduced once intravenously. After FKPC transplantation patients were under observation for 1 year. Monthly performed control of creatinine level in blood and urine, weekly – concentration of potassium in blood plasma.
Results: Results of the pilot study evidences that in cases of sustaining not less than 50% of renal parenchyme the transplantation of fetal stem cells (performed on the background of hemodialysis!) in chronic renal insufficiency reduces the level of creatinine in blood plasma, increases glomerular filtration rate, normalize the capability of kidney to concentrate urea. In 40% of patients renal functions restores, that allows to eliminate from further hemodialysis.
Conclusion: For studying safety and effectiveness of fetal kidney progenitor cells transplantation in chronic renal insufficiency it is appropriate to conduct multi-center clinical trial.

BO34 TLR4 BLOCKADE ENHANCES ISLET ENGRAFTMENT AND INDUCES INDEFINITE ISLET ALLOGRAFT SURVIVAL

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The aim of the present study was to assess the role of Toll-like-receptor 4 (TLR4) in mediating the immune response to allogeneic pancreatic islets. *In vitro* experiments were conducted in murine and human models using anti-TLR4 monoclonal antibodies (mAb). We assessed the impact of TLR4 blockade on â-cell apoptosis and T-cell proliferation in mixed islet-lymphocyte cultures. *In vivo*, we used both a syngeneic (B6-to-B6) marginal mass islet transplant model to assess the impact of TLR4 blockade on islet engraftment, and a DBA1-to-B6 allogeneic model. *In vitro* TLR4 blockade decreases LPS-mediated â-cell apoptosis ($P = 0.014$) and T-cell proliferation against islets (human 79 ± 2% $P < 0.0001$; murine 67 ± 16% $P = 0.004$). *In vivo*, marginal mass syngeneic islet transplantation resulted in 100% recipients reversing diabetes in a median time of 7 days, as compared to 75% in 20.5 days in controls. Anti-TLR4 treatment of both islets and recipients led to indefinite allogeneic graft survival (>100 days) in 63% of animals ($P = 0.02$ vs. controls). In conclusion, TLR4 blockade leads to a significant improvement of syngeneic marginal mass islet engraftment and allogeneic islet graft survival. A mechanism of graft accommodation with concurrent inhibition of donor-specific immune memory is likely to be involved.

BO35 NLRP3 INFLAMMASOME IN HUMAN ISLETS

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NRLP3 inflammasome is a protein complex playing an important role in innate immunity. This complex is activated in response to infections, inflammation and autoimmune processes and is involved in the maturation of IL1β by the cleavage of caspase-1. A deregulation of the inflammasome increases seric level of IL1β and contributes to the pathogenesis of inflammatory and autoimmune diseases such as type I diabetes, by inducing the immune cell recruitment in islets, altering insulin secretion and leading to pancreatic beta cell destruction. The transplantation of pancreatic islets is a promising therapy in the type I diabetes treatment but the function of transplanted pancreatic islets declines over time. The objectives of this preliminary study are to determine the expression and activity of inflammasome in human islets. Human islets were stimulated with LPS for 4 h and/or ATP for 30 min in the presence or absence of glyburide, an inflammasome inhibitor. IL1β secretion was quantified by ELISA assay in supernatants. Protein and gene expression of inflammasome components were studied by western blot and real time PCR. NLRP3 and IL1β gene expression are significantly increased in islets in response to LPS and LPS plus ATP treatment. This augmentation is prevented by glyburide. Interestingly, only LPS plus ATP treatment induces the cleavage of caspase-1, indispensable to the maturation and secretion of IL1β. Glyburide prevents the cleavage of caspase-1 and blocks the IL1β secretion. These preliminary results show that inflammasome is expressed and active in human islets in response to LPS plus ATP. To block the secretion of IL1β, by inhibiting the inflammasome, could be a potential therapeutic target to prevent the islet graft loss of function.

BO36 BETA CELL PROLIFERATION IN TRANSPLANTED ISLETS OVER TIME

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Aim: Beta-cell replication is thought to play a significant role in maintaining pancreatic beta-cell mass. Nevertheless, it is still unknown whether a similar role could be accounted to cell replication in transplanted islets. The aim of this study was to determine the beta cell replication rate in islets after their transplantation over time.
Methods: Rat islets were transplanted under the kidney capsule of SCID mice. Mice were randomly allocated into experimental groups (1, 3, 8, 15, 22 and 29 days post-transplantation) and BrdU was added to drinking water. Cell replication was determined by BrdU incorporation or Ki67 staining and apoptosis by TUNEL staining. Graft vascularization was determined by von Willebrand factor immunostaining.
Results: At 8 days post-transplantation, 5.95 ± 1.11 % beta cells incorporated BrdU in the islet graft. Between 15 and 29 days post-transplantation, this percentage gradually decreased to become stable around 1.5% of proliferating beta-cell. However apoptotic rates were very low in islet grafts at the different time points. In the early period of graft implantation (1, 3 and 7 days post-transplantation) a low proliferation rate was observed at 1 day post-transplantation (0.84 ± 0.17%) followed by an increase until 3 days to reach the same value that the proliferation rate observed at 7 days after transplantation. Computer quantification (Metamorph software), showed that vascularisation gradually increased overtime to reach a plateau at 3 weeks after transplantation. We also observed that beta cell proliferation was inversely correlated to vascular density in the islets. Our data suggest that beta cell proliferation plays an important role in engraftment and maintenance of beta cell mass and so islet graft function, especially in the first days post-transplantation until partial or total restoration of vasculature has been performed, and within moment after implantation associated with a high high release of pro-inflammatory cytokines.

BO38 GLP-1 ANALOGUE MODULATES APTOSIS AND TISSULAR FACTOR IN RIN-M5F IN RESPONSE TO MICROPARTICLES: IMPLICATION FOR ISLETS TRANSPLANTATION

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Background: IBMIR (Instant Blood Mediated Inflammatory Reaction) follows islet transplantation and is characterized by cytokine secretion and tissue factor (TF) expression at islet vicinity. Microparticles (MPs) are plasma membrane fragments shed from stressed cells that act as cellular effectors. Islet cytoprotection by incretinomimetics was reported. Protective effects of Liraglutide on î² cell dysfunction mediated by MPs, were assessed in oxidative and inflammatory cell stress models.
Methods and material: Rat î²cells, Rin-m5f, were stimulated by 100î¼M H2O2 or 50 U/ml IL-1î² combined to 1000 U/ml TNF-i±. Generated MPs were isolated and applied to naive Rin-m5f for 24 h. Effects of 1î¼M [Liraglutide] on insulin secretion, apoptosis by hypodiploÃ¯d DNA quantification, MP release and TF activity by ELISA ($n = 9$) were measured. Cell membrane integration of fluoreseent MPs was probed.
Results: A significant decrease in oxidative stress-induced apoptosis (10% vs. 18%) and restored insulin secretion (oxidative stress: +55%, cytokinic stress: +25%) revealed direct protection by [Liraglutide]. Indirect protection of î² cells occured through reduced MP shedding (oxidative: −25%, $P = 0.006$; cytokinic −18%, $P = 0.01$) and by counteracting the MP-driven decrease in insulin secretion. By fluorescence probing, 50% of Rin-m5f integrated MPs and integration was not modified by [Liraglutide]. [Liraglutide] reduced oxidative and

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cytokinic TF-induced activity with a significant decrease at Rin-m5f (oxidative: −18%; cytokinic: −17%) and MP surfaces (respectively: −31%; −15%).
Conclusion: [Liraglutide] shows a multiple protective effect on i² cell survival targetting apoptosis, insulin secretion and TF activity. Furthermore, [Liraglutide] limits the deleterious message conveyed by MPs. Our data bring new hints on the mechanisms of cytoprotection by [Liraglutide] in islet transplantation and particularly during IBMIR. This work received financial support from Novo Nordisk.

BO39 CORRECTION OF DIABETES BY SYNGENIC MINIMAL MASS ISLET TRANSPLANTATION INTO THE SMALL INTESTINAL SUBMUCOSA

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Background: Transplantation of mature islets into portal vein has been most effective thus far, although attrition of transplanted islets constitutes a major limitation, and alternative approaches are required. We analyzed mechanisms by which pancreratic islets engrafted, vascularized and functioned over the long-term in the small intestinal submucosa. This permitted evaluation of whether transplantation of semi-pure preparation of minimal islet number was sufficient for glycemic control in rats with streptozotocin (STZ)-induced hyperglycemia.
Methods: Animal groups were established to determine engraftment, survival and function of 350 islets transplanted into either intestinal segments or portal vein over up to 1 year. Islet reorganization, vascularization and function were analyzed by histological analysis, RT-PCR analysis, as well as by glycemic control.
Results: Transplantation of syngeneic islets in marginal numbers successfully restored normoglycemia in diabetic rats. None of the diabetic rats achieved normoglycemia after intraportal transplantation. Transplantation of semi-pure islet preparation did not impair their engraftment, vascularization and function. Islets were morphologically intact and expressed insulin as well as glucagon over the 1 year. Expression of angiogenic genes permitted revascularization of transplanted islets. We identified expression of transcription factors required for maintenance of beta cells, i.e., Pdx1 and Pax6.
Conclusions: These studies demonstrated that marginal mass of transplanted islets was sufficient to restore euglycemia in STZ-treated rats. These superior results were obtained despite use of an impure preparation of islets in animals with small intestinal segment compared with animals with intraportal islet transplantation. Our findings will help advance new horizons for cell therapy in patients with diabetes.

BO40 PREVENTION OF EARLY GRAFT LOSS BY PROLIFERATOR-ACTIVATED RECEPTOR-AGONIST, PIOGLITAZONOE, IN CANINE ISLET AUTOTRANSPLANTATION

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Background: Approximately 50% of islet grafts are destroyed within 72 h after pancreatic islet transplantation (PITx) due to non-specific inflammatory responses. Previously, we reported that inhibition of NF-[kappa]B activation shortly after PITx prevents graft loss in mice. A Proliferator-activated receptor (PPAR)-[gamma] agonist exerts anti-inflammatory effect via NF-[kappa]B inhibition. The effect of PPAR-[gamma] agonist on islet graft loss was examined in a canine auto-PITx model.
Methods/Materials: Diabetes was induced in beagle dogs by a total pancreatectomy. Islets isolated from the extracted pancreas were auto-transplanted into the liver through the portal vein. To determine the marginal islet number, 500, 1000 or 2000 IEQ/kg islets were transplanted (n = 5–7). A PPAR-[gamma] agonist, pioglitazone (PIO), was given p.o. 1 h before and twice daily thereafter for 3 days (n = 7). Fasting blood glucose level (FBGL) was monitored daily. An intravenous glucose tolerance test (IVGTT) was performed on day 14 after PITx.
Results: Following PITx with 500, 1000 or 2000 IEQ/kg islets, FBGL normalized in 0% (0/6), 42.9% (3/7), 80% (4/5) of islet recipients, respectively. PITx with 1000 IEQ/kg islets was defined as marginal (Control). Treatment with PIO at 5 mg/kg improved the normal glycemic rate to 71.4% (5/7, P = 0.32). When PIO was given at 10 mg/kg, FBGL normalized in all PITx animals (7/7, p [lt]0.05) (Fig. 1). The calculated BGL-AUC 0-120 after IVGTT in the control, PIO 5 mg/kg and PIO 10 mg/kg groups was 34758[plusmn]4315, 27778[plusmn]5509 (P = 0.34) and 18949[plusmn]553 mg*min/dl (p[lt]0.01), respectively.
Conclusion: A PPAR-[gamma] agonist, PIO prevents early islet graft loss and maintains normoglycemia in canine PITx.

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BOS05-DONATION/RETRIEVAL

BO41 NATIONWIDE SYSTEM OF DONOR HOSPITAL TRANSPLANT COORDINATORS, CREATED BY NATIONAL TRANSPLANT ORGANIZATION IMPROVES GLOBAL DONATION RATES, BUT IT IS EFFECTIVE ONLY IN A HALF OF HOSPITALS

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Coordinators in the number of 218 trained professionals (134 doctors and 84 nurses) are employed by Poltransplant in 200 hospitals (ca 50% of total number of hospitals with potential of donation). This resulted, after 21 months of work, compared to 21 month period prior to their employment in changes of the following hospital donation indicators: * increasing the number of reported potential deceased donors by 27% * Increasing the number of actual deceased organ donors by 24% * increasing the percentage of multiorgan donation from 54% to 56% * increasing the number of transplanted organs by 20% * increasing the percentage of family refusals to donation from 8.5% to 9.3% * reducing the rate of utilized organs per actual donor from 2.65 to 2.57 The desired effect of the employment of hospital donor coordinators to improve organ procurement rates was reached in 102 (51%) hospitals; in this group there were hospitals where there was no pre-employment donations and they took place after the employment, where the number of donations has increased or remained the previous level. In 98 (49%) hospitals had no procurements before or after the employment of coordinators, were before hiring them, but there was no after or the number of actual donors has decreased. Pronounced effect was observed in hospitals: * located in regions with low baseline rate of donation (59%) * academic hospitals (63%) and multi-profile hospitals in large cities (77%) * hospitals, where a team of two coordinators was set up (67%) * hospitals for adults (52%) * hospitals, where doctors were assigned coordinators (55%) The annual formal analysis of activity of donor hospital coordinators gives to national transplant organization a rational basis for their employment taking into account the characteristics of hospitals and the characteristics of hospital coordination team.

BO42 THE EFFECT OF THE β-HUMAN CHORIONIC GONADOTROPIN-RELATED PEPTIDE (AQGV) ON A BRAIN DEATH MODEL

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Introduction: AQGV previously described by Khan et al has been utilized as an anti-inflammatory molecule. This new molecule showed promising results in septic and shock inflammatory models. Brain death (BD) is an inflammatory condition, which is deleterious for organ quality in transplantation. Therefore, we aim to assess the effect of AQGV in a brain death rat model.
Methods: BD was induced in rats by inflating a subdurally placed balloon catheter. Animals were treated with PBS or AQGV (30 mg/kg) 1 h before BD. After 4 h of BD, serum, kidneys and livers were collected. Sham-operated rats treated with PBS or AQGV served as controls. Tissue gene expression was measured by Real Time qPCR. Tissue protein expression was detected by immunohistochemical analyses.
Results: After the BD period, plasma levels of IL-6, creatinine, AST, ALT and LDH were not significantly reduced after AQGV treatment. Polymorphonuclear influx in liver and kidney tissue were not reduced. Relative expression of inflammatory genes (IL-6, TNF-a, MCP-1 and C3) were not significantly down-regulated in liver and kidney.
Discussion: Pre-treatment with AQGV in this model did not show any anti-inflammatory effects. However, this could be attributed to timing or dosing. We postulate that AQGV could exert anti-inflammatory effects when administered after brain death induction based on the chemical properties. Recents *in-vitro* results suggest that AQGV treatment after BD reduces inflammatory cytokines. More research needs to be conducted to understand the potential effects of AQGV in the BD setting.

BO43 ESTABLISHING A NOVEL FELLOWSHIP TRAINING PROGRAM IN DONOR MANAGEMENT

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In 2012 an Organ Donor Physician Fellowship Training Program, the first training program of its kind in Canada, was initiated at the University of Alberta, an active multi-organ transplant center performing over 250 solid organ transplants annually. The purpose of the program was to train physicians in effective identification, management and allocation of multi-system organ and tissue donors. The curriculum was developed in consultation with local and national experts and stakeholders. Specific educational domains of the training program included: (i) identification and management of multi-system organ donors and interfacing with critical care professionals, (ii) coordination and logistics of organ and tissue donation within a geographically dispersed catchment area as directed by donation coordinators, (iii) ethical approaches to clinical and research matters applicable to both heart-beating and non-heart beating (DCD) donors, (iv) introduction of existing and emerging techniques of ex-vivo donor organ perfusion, assessment and repair and (v) involvement in ongoing quality improvement, benchmarking and public and health care worker awareness activities related to missed opportunities for organ donation. It is expected that introduction and successful implementation of this program will act as an impetus to formalize a speciality certification in organ and tissue donation in Canada.

BO44 EXPANDING THE LIVING DONOR POOL, "FIRST ACT": ANALYSIS OF THE CAUSES OF EXCLUSION OF POTENTIAL KIDNEY DONORS

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Background: The evaluation of a potential living kidney donor (LKD) determines in most studies the exclusion of not less than 50% of candidates (1,2,3). The aim of this study was to analyse the reasons for exclusion of potential LKD referred to our centre.
Methods: We retrospectively analysed anamnestic and clinical data of all potential LKDs who were evaluated at our center over 7 years, between January 2005 to March 2012. Data were obtained by review of an electronic transplant database.
Results: Seventy-nine (50 female, 29 male) candidates entered the assessment program, 24 (30.3%) successfully donated, comprising 22 related and 2 unrelated donors, 45 (56.9%) were excluded, 10 (12.6%) were actively undergoing evaluation. Reasons for exclusion were medical in 14 (31%), non medical in 18 (40%), positive cross-match in 8 (17.7%), pregnancy in 2 (4.4%), other in 3 (6.6%). Of the 14 donors excluded for medical reasons, 75.8% were excluded because of diabetes, cardiovascular disease, hypertension, obesity, while 21.5% for inadequate renal function, malignancy, liver disease. Of the 18 (40%) excluded for non-medical reasons 6 (33.3%) were excluded because the intended recipient received a deceased donor transplant before the evaluation could be completed, 5 (27.7%) because the recipient was no longer a candidate for transplantation, 5 (27.7%) because of donor withdrawal, 2 (11.1%) for other reasons.
Conclusions: Positive cross-match and deceased donor transplantation during the evaluation process were the two most common reasons for LKD exclusion. The evaluation of potential LKDs is time consuming and requires a remarkable amount of human and material resources. A dedicated pathway for the diagnostic work-up of LKD may speed-up the evaluation process and improve the efficiency of the system, ABO incompatible and paired exchange donation may contribute to increase the yield of donor organs.

BO45 GENDER DIFFERENCES IN EXPECTATIONS OF INTERPERSONAL BENEFIT FOLLOWING LIVING KIDNEY DONATION

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Background: In the United States, women are more likely to volunteer for and undergo living donation (LD). We have developed and validated a measured designed to assess the expectancies of living donors. In this study, we examine whether there are gender differences in the interpersonal benefits derived from the donation experience.
Methods: Adults (N = 102) completed the 42-item Living Donation Expectancies Questionnaire (LDEQ) pre-donation and 1 year post-donation. We calculated difference scores for the Interpersonal Benefits (IB) scale and classified donors based on whether their pre-LD IB expectations were not met, met, or exceeded 1 year following donation.
Results: The IB expectancies of women pre-LD did not differ significantly from those of men. However, women had significantly higher mean IB scaled

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scores at 1 year post ($P < 0.05$) compared to men. Also, women were more likely than men to report exceeding their pre-LD IB expectations 1 year post-LD ($P < 0.01$). Compared to men, women were more likely to exceed their pre-LD expectations on being seen as heroic, being respected and admired by family and friends, having more compassion and understanding from family members, and having an improved relationship with family members.
Conclusion: Women may derive more interpersonal benefit from LD than men. Further research is needed to better understand factors that may account for this gender difference. The LDEQ is a useful tool for assessing the pre-LD expectancies of donors as well as the degree to which their donation experiences match these expectancies.

BO46 THE INFLUENCE OF TRANSPLANT PROCUREMENT MANAGEMENT (TPM) TRAINING PROGRAM IN ORGAN AND TISSUE DONATION AND TRANSPLANTATION

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Background: Training on organ donation/ transplantation (D&T) is relevant for transplantation improvement. TPM has been providing training on organ D&T in compliance with the agreed professional requirements.
Methods: Considering that micro level change practices can have macro level influences, a survey was developed assessing the impact of training on development of policies, practice, career choices, leadership, and knowledge dissemination. Thus a new type of evaluation was designed focusing on how different groups perceive training benefits. It was translated into five languages (Spanish, English, Italian, French, and Portuguese). Individuals who participated in TPM training courses were sent a recruitment letter and link to an online survey. Additionally, links were posted on Facebook and handed out at organ donation meetings and congresses. Potential participants and key individuals were asked to forward the link to individuals active in D&T. Respondents were required to rate on a scale of 1–5 (1- no influence and 5- a great deal of influence) the influence of trainings on 12 items to answer the following Research question: What is the perceived influence of specialized training programs on career, collaboration, and skills in D&T?. Institutional review boards at the University of Barcelona and Purdue University (USA) approved the study.
Results: Of 1102 participants agreed to take the survey, 87% reported participating in a TPM course, out of which 95% selected TPM courses as most influential. Specifically, 98% reported influence on knowledge (score 4.45/5), 93% on technical (4.15) and communication (4.14) skills, 89% on attitude toward D&T (4.08), 92% on motivation to work (4.23), 91% on desire to innovate (3.98), 87% and 79% on ability to change D&T practices (3.85) and policies (3.51), respectively.
Conclusion: Participation in TPM training courses has positive perceived benefits.

BO47 TRAINING 'COMMUNIATION ABOUT DONATION' SUCCESFUL IN THE NETHERLANDS: EMBEDDED IN MORE THAN 50% OF ALL HOSPITALS

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Introduction: To facilitate professionals in discussing donation with relatives of a potential donor, the European Donor Hospital Education Program (EDHEP) was developed a long time ago. University hospitals organized the training a number of times a year. After many years of experience in the Netherlands and evaluation of the EDHEP results, we updated the training into 'Communication about Donation' (CaD). Main objective was to train many professionals in an accessible manner. Therefore, this training is now organized in local hospitals and reduced to a maximum of 4 h. To meet the latest educational insights the training resulted in 'blended-learning'; an e-learning module and a practical training. We then tried to stimulate hospitals to adapt the training.
Methods: The training was first implemented in 2008 in a pilot setting in five hospitals and afterwards psychologists were trained, according to a Train the Trainer (TtT) module, to become a qualified trainer. With financial help of the Ministry of Health we offered hospitals the first CaD training free of charge, in the hope of enthusiasm and implementation in their local training programme. In order to monitor satisfaction of the participants, a questionnaire was completed after each training.
Results: From 2008 to 2012 the number of participating hospitals increased from 5 to 42. In total 115 psychologists participated the TtT. In total, approximately 3000 medical professionals are trained in 263 CaD training courses. Medical professionals highly appreciate the CaD training with an average score of 8 on a range of 1–10.
Conclusion: What started as a small initiative to facilitate professionals in discussing donation with relatives, the CaD training now plays a prominent role in more than half of the Dutch hospitals. The training is highly accessible as it is organized in local hospitals, therefore the number of participating professionals is huge. We hope that our initiative will inspire other countries.

BO48 DIFFERENT SURGICAL STRATEGIES FOR THE MANAGEMENT OF HEPATIC VEINS ANOMALIES DURING LAPAROSCOPIC LEFT LIVER SECTIONECTOMY FOR PEDIATRIC LIVING RELATED LIVER TRANSPLANTATION

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Background: Laparoscopic left lateral sectionectomy (LLLS) is more and more adopted and has been proposed as the gold standard for pediatric living donor liver transplantation (LDLT). We described surgical tips for approach to donors with left hepatic vein (LHV) variations.
Materials and Methods: Between May 2010 and August 2012 we performed 8 consecutive LLLS. Five donors presented LHV anomalies: (a) common trunk draining the middle (MHV) and the LHVs into the inferior vena cava (IVC) ($n = 1$); (b) branch of the hepatic vein draining the segment 4 ($n = 1$); (c) communicating trunk between the LHV and MHV ($n = 1$); (d) separate confluence of segment 2 and 3 hepatic veins into the MHV ($n = 1$); (e) 2 LHVs that draining into the IVC ($n = 1$).
Results: For conventional LHV anatomy, the vein was encircled using a cotton tape with an extraparenchymal approach. In anomalies (a), (d) and (e) the complete isolation and encirclement of the LHV was achieved only at the end of parenchymal transection. When sectioning of the LHV with staplers the cotton tape was pulled up and towards the left, like in a hanging maneuver. In cases (b) and (c) the hepatic vein trunk crossing the transection plane were identified and sectioned during the transection of the liver. On the back-table, in (a), (d) and (e) we ended up in having two hepatic vein ostia, and a direct venoplasty was performed in order to obtain a common ostium. No donor caval complications were experienced. In (b) we evidenced transient hypertransaminasemia related to liver congestion of segment 4. No recipient hepatic outflow or arterial complications were experienced. In (d) recipient developed portal vein thrombosis. No differences in terms of recipients liver function assays or surgical recovery were revealed. All of the donors and recipients were discharged and are alive and well.
Conclusion: The venous outflow requirements apply as well when anatomic anomalies are present in the setting of minimally-invasive approaches for pediatric LDLT.

BO49 NOT ALL POTENTIAL TISSUE DONORS INDENTIFIED, A STUDY IN THREE HOSPITALS

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Backgrounds: Nowadays, the demand for tissue transplantation is increasing. In order to optimize donor recruitment, the potential of tissue donors has to be evaluated.
Method: We conducted a cohort study in three Dutch hospitals in 2011. The potential of eligible tissue donors found, based on medical records in three Dutch hospitals is compared to the physician's judgement written on the Donation form.
Results: In total 1342 patient records were analysed. From these records, the donation officers considered 484 patients as a potential tissue donor (36.1%). Despite the absence of contraindication, the physician did not appropriate recognise eligible tissue donors in 123 of the 484 records.
Conclusions: Physicians lack of knowledge of tissue donation was the main obstacle. A higher percentage of tissue donors in the three Dutch hospitals should be feasible.

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BO50

EVALUATION OF DONOR CRITERIA FOR SUCCESSFUL LUNG TRANSPLANTATION

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DSO

Background: There are no standardized acceptance criteria for donor lungs. Therefore, we evaluated the different criteria usually used for acceptance donor lungs.

Methods: We analyzed donor factors from 458 donors in the DSO Region Bavaria between 2006–2012. In the first group lungs were transplanted (n = 261). In the second group lungs were not accepted for transplantation (n = 197). We analyzed the following factors: gender, age, breathingtime, blood-gas-analysis (BGA), radiology, bronchoscopy findings, history of lung diseases and antiobiotic treatment.

Results: Acceptance of lungs in the younger age group (younger than 50 years) was much higher (198/305), compared to lungs from older donors (older than 50 years), (63/153). Lungs with donor age over 50ys had four times higher no acceptance. Acceptance of lungs was significantly decreased with pathological BGA (OR 7.44) or pathological bronchoscopy (OR 3.61). Medical history of lung diseases, radiology findings or gender were of minor importance. Breathingtime and antibiotic treatment had no statistically significant influence.

Conclusion

Due to the shortage of donor organs more lungs with extended criteria are accepted by experienced transplant-centers. More data are needed to develop reliable acceptance criteria.

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BOS06-IMMUNOBIOLOGY/BASIC SCIENCE

BO51 DONOR BRAIN DEATH RESULTS IN DIFFERENTIALLY MODULATED IMMUNE ACTIVATION IN SOLID ORGANS

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Background: Brain death (BD) and its complex pathophysiological changes have been shown to significantly influence graft quality. However, detailed information regarding immune activation of distinct lymphocyte subsets in the periphery and especially in BD donor organs is missing.
Material and Methods: C57BL/6 mice underwent BD induction and were followed for 3 h under continuous ventilation. Ventilated mice (sham group SH) as well as naive mice served as controls ($n = 6$/group). Cells were isolated from blood, spleen and solid organs including heart, kidney and liver.
Results: By flow cytometry, a strong down regulation of CD3+ T cells in all tissues as a consequence of BD was observed and CD3+ CD4+ CD25+ FOXP3+ T regulatory cells were significantly induced in peripheral blood and spleen derived from BD donors compared with controls ($P < 0.01$, respectively). Whereas naive CD3+ CD44-CD62Ldim T cells were significantly induced in the periphery, kidney and liver, CD3+ CD44bright CD62L effector memory T cells were clearly down regulated. Both CD19 + CD220 mature B cells and CD19 + CD220- immature B cells were significantly induced in kidney and liver ($P < 0.05$ versus SH and control), whereas plasma cells were increased in spleen only. Interestingly, we detected the highest level of MHC class II+ mDCs in the kidney ($P < 0.05$ versus spleen, lymphnodes and liver) which was significantly diminished due to BD (<0.05, repectively). Strikingly, NK cell receptors including NKG2D and NKp46 were highly induced indicating an activation of NK cells as a consequence of BD. By studying gene expression markers including TNFa, IFNg, ICAM-1 and IL-1ß were strongly induced following BD, showing the highest expression especially in the liver. Conclusion: Our results gain novel insights into the pathophysiology of BD revealing significant differences between various organs and the periphery. This indicates distinct mechanisms of activation which needs consideration for future treatment strategies.

BO52 THE IMMUNOGENICITY OF PLURIPOTENT STEM CELLS AND THEIR DERIVATIVES

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Transplantation of cells or tissue derived from human pluripotent cells (i.e. hES cells, iPS cells) from a genetically unrelated donor would give rise to an immune response mediated by T- and NK cells. NK cells are of special interest because human pluripotent stem cells do not express MHC class I, making them excellent targets for NK cells. In addition, NK cells proved less susceptible to immunosuppression compared T or B cells, at least according to *in vivo* studies in solid organ transplantation. Besides, NK cells could also be an excellent tool for eliminating residual pluripotent stem cells from *in vitro* derived progenitors, mature cells or tissue. Therefore, we have analyzed the expression of ligands of receptors involved in the immune reaction, like MHC class I, MHC class II, MICA A/B, ULBP, HLA-G and HLA-E and the co-activators CD80, CD86, CD40 before and after induction of pro-inflamatory cytokines on the surface of hES cells, three iPS lines; From these pluripotent cell lines, neural progenitor have been derived and modelization of brain have be generated *in vitro*. Cytotoxity of NK cells and T against hES cells, iPS or their derivatives including tissue generated *in vitro*) have tested by direct killing assay and expression of CD107 (marker of NK- and T-cell degranulation) and cytokine secretion by NK- and T cells (Elisa, multiplex luminex technology and IFN-ä capture assay) have been analysed. Our results demonstrated a large heterogeneity between pluripotent stem cells when expression of ligands of receptors involved in the immune reaction have been analyzed. More interestingly, this heterogeneity is also evident when each cell lines is cultured and tested after several passages. The killing activity of T cells is reduced due to the low expression of MHC class I at the cell surface of pluripotent stem cells. In contrast the NK cells activity is stronger with pluripotent stem cells and their derivatives.

BO53 INTERLEUKIN-7 RECEPTOR BLOCKADE BY MONOCLONAL ANTIBODY TO IL-7RINDUCES ISLET ALLOGRAFT TOLERANCE AND LONG-TERM SKIN ALLOGRAFT SURVIVAL THROUGH INHIBITION OF T CELL RECONSTITUTION

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Using a pancreatic islet allograft model in which Balb/c mice previously rendered diabetic by streptozotocin received islets from C57BL/6 donors, we show that anti-IL-7Rα mAb given every other day from 3 weeks before graft to 4 weeks post-graft induced graft tolerance with graft survival >180 days compared to 21 days in untreated mice, ($P < 0.001$). This treatment decreased T and B cell numbers but the islet graft as well as and the abrogation of both cellular and humoral alloimmune responses were maintained despite treatment cessation and lymphocyte recovery. In a stringent skin allograft model using the same strain combination, IL-7R blockade given after T cell depletion by anti-CD4 and anti-CD8 mAbs doubled graft survival to 58 days vs 30 days with depletion alone ($P < 0.0001$), and when low-dose tacrolimus was added, two-third of mice accepted skin graft for at least 90 days. The principal mechanisms of action of IL-7R blockade following T cell depletion included: (i) inhibition of lymphocyte reconstitution resulting in 3–10-fold reduction in the absolute number of B cells, T cells, CD4+, CD8+ T cells, and CD44hiCD62Llo memory T cells, (ii) 2-fold increase in CD4+ FoxP3+ Treg frequency, (iii) abrogation of both cellular and humoral alloimmune responses as shown by IFNγ Elispot, MLR-3H thymidine and DSA measurement (iv) inhibition of skin graft leukocyte infiltrate, (v) diminution of intragraft expression of TH1, TH2, and TH17 cytokines, chemokines, and chemokine receptors (all $P < 0.05$ compared to depletion alone). Interestingly, a 5-week treatment with anti-IL-7Rα mAb did not decrease cellular and humoral anti-viral immune response in mice previously infected with an adenovirus vector. Taken together, we demonstrate for the first time that IL-7R blockade has strong tolerizing effect and synergizes with other immunosuppressants to induce long-tem graft survival even in a stringent allograft model and therefore might be a clinically relevant therapy in transplantation.

BO54 MESENCHYMAL STEM CELLS CONTROL ALLO-REACTIVE CD8+ CD28- T-CELLS THAT ARE UNAFFECTED BY BELATACEPT TREATMENT

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Introduction: CD28/B7 co-stimulation blockade with belatacept prevents allo-reactivity in kidney transplant patients. Cells lacking CD28 are not susceptible to belatacept treatment. As CD8+ CD28- T-cells have cytotoxic and pathogenic properties, we investigated whether immunosuppressive mesenchymal stem cells (MSC) are effective in controlling CD8 + CD28- T cells.
Methods: MSC were isolated from perirenal adipose tissue of kidney donors. Mixed lymphocytes reactions (MLR; 7-days) with PBMC from healthy blood donors were used to mimic allo-reactivity. Flow cytometric analyses were performed.
Results: Belatacept (1 μg/ml) and MSC (1:10) reduced effector cell proliferation by 37% and 43%, respectively. The combination of both inhibited proliferation by 60%. While belatacept did not affect the proliferation of CD8+ CD28- T-cells (43% dividing cells in MLR, 44% in MLR with belatacept), MSC reduced the percentage of CD8 + CD28- T-cells in the proliferating cell fraction by 44%. The same effect was observed when MSC were separated from the MLR in a transwell system. Allogeneic stimulation of PBMC depleted of CD28-T-cells did not result in the generation of CD28- T-cells suggesting that MSC control pre-existing and not newly induced CD28- T-cells.
Conclusion: Allo-reactive CD8+ CD28- T cells that remain unaffected by belatacept treatment are reduced by MSC in a cell-cell-contact independent manner. MSC are superior to belatacept in controlling the whole alloreactive T cell population.

BO55 MESENCHYMAL STEM CELL-DERIVED FACTORS PROMOTE LIVER REGENERATION BUT DO NOT PROTECT AGAINST ISCHEMIA REPERFUSION INJURY

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Mesenchymal stem cells (MSC) and their secreted factors represent a potential new therapeutic strategy to stimulate liver regeneration in living-donor liver

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transplantation to prevent small-for-size syndrome. Our previous data show increased liver weight gain and hepatocyte proliferation in mice treated with MSC-derived factors after partial hepatectomy (PH). In this study we investigate if these factors protect against ischemia and reperfusion injury (IRI), alone or combined with PH. In the IRI alone model, C57BL/6 mice underwent IRI by clamping the median and left lateral liver lobes for 90 min. In the IRI+PH model, mice underwent 60 min. of IRI after which a 50% PH was performed, leaving only ischemic tissue. All mice were treated immediately after surgery with serum-free concentrated conditioned culture medium of liver-derived MSC (MSC-CM) or with concentrated unconditioned medium (UM) as vehicle control. The IRI mice were sacrificed after 6 or 24 h. to investigate effects on transaminases and hepatocyte damage. The IRI+PH mice were sacrificed after 48 h. to also investigate hepatocyte proliferation. In the IRI model, serum ALT and AST levels after 6 and 24 h. showed no differences between the MSC-CM and UM group. Similar, in the IRI+PH model, ALT and AST levels were not significantly different between both groups. In this combined model, however, significant reduction in tissue damage after MSC-CM treatment was observed, accompanied by reduced inflammatory cell infiltration. Average damage score in this group was 0.63 vs 1.40 in the UM group ($P = 0.04$). This was furthermore accompanied by a significant increase in hepatocyte proliferation in the MSC-CM group compared to the UM group (13.5% vs. 5.0% BrdU-positive nuclei, $P = 0.002$). Conclusion: This study shows that MSC-derived factors do not protect against early effects of IRI, but significantly stimulate hepatocyte proliferation and improve liver regeneration after liver resection, despite combined IRI.

BO56 EVALUATION OF ESSENTIAL ROLE PLAYED BY NOD1 AND NOD2 PATTERN RECOGNITION RECEPTORS IN T CELL RESPONSES TO ALLOANTIGENS

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Introduction: The nucleotide-binding oligomerization domain (NOD)- like receptors are intracytoplasmic pattern recognition receptors (PRRs) that upon activation by peptidoglycans, or endogenous danger signals, trigger an inflammatory response leading to the activation of NF-(kappa)B and MAPK's, cytokine secretion, and apoptosis. The role of these intracellular innate immune receptors has not yet been clarified in transplantation models.
Study Plan: The hypothesis of our study was that activation of NOD-dependent signaling pathways play a key role in early T cell activation in response to alloantigen and blockade of NOD signaling would ameliorate T cell activation. To determine our hypothesis, we isolated APCs and T cells from WT (H-2b), NOD1& 2 (both H-2b) doubly deficient mice (NOD1/2-/-) and tested an extensive range of ex vivo allogeneic responses.
Results: Our data show that the blockade of NOD1 and 2 markedly inhibits T cell proliferation to alloantigen, but that the inhibition was distinct between CD4 and CD8 T cells. The NOD-deficient T cells were rapidly activated (based on a panel of activation markers and analysis of cytokine production), upon stimulation with allogeneic DCs. But, within a few days of activation the NOD-deficient cells underwent cellular death. In CD8+ T cells there was a markedly increased rate of cellular death, compared to CD4+ T cells, and this was accompanied by a dramatic increase in pro-apoptotic signaling. T regulatory cells were completely unaffected by the NOD deficiency.
Conclusions: Our data demonstrate a unique, and highly important, role for the intracytoplasmic PRRs, NOD1& 2, as regulators of T cell survival. In response to stimulation with alloantigen, the NOD-deficient T cells, particularly CD8 T cells, underwent initial rapid activation followed by death. Data to date suggest that the functional defect in NOD-deficient T cells is due to enhanced antigen-induced apoptotic signaling upon stimulation with alloantigen.

BO57 GENERATION OF HLA-SPECIFIC HUMANISED MICE USING BONE MARROW-DERIVED HAEMATOPIETIC STEM CELLS FROM CADAVERIC ORGAN DONORS

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Introduction: 'Humanised' mice are an invaluable tool in the study of the immune response to adult and stem cell-derived tissues. Bone marrow (BM) from cadaveric organ donors represents a potentially abundant source of haematopoietic stem cells (HSCs) for the generation of humanised mice. Cells and tissues can also be harvested from syngeneic and allogeneic cadaveric donors for immunological challenge, as well as for the generation of induced pluripotent stem cells. We therefore examined the potential of cadaveric BM-derived HSCs for the generation of a humanised mouse model to investigate human alloimmunity.
Methods: BM was aspirated from the vertebrae of human cadaveric donors and the mononuclear fraction was separated using Ficoll gradient and cryopreserved at −180 °C in 10% DMSO + 90% FCS. After thawing, live CD34+ HSCs were isolated using magnetic beads and adoptively transferred into sub-lethally irradiated immunodeficient NOD/SCID/IL2rγ-/- mice (NSG; 1–5 × 105 cells/animal). Engraftment with human CD45+ cells was assessed by flow cytometric analysis of weekly peripheral blood samples. Skin, splenocytes and mesenteric blood vessels from the same donors were also cryopreserved.
Results: BM was successfully aspirated (22–150 ml/donor) from 5 DCD and 6 DBD cadaveric donors (age 35–81 years). The percentage CD45+ viability after BM harvest was >90%, of which 0.8–1.4% were CD34+ HSCs. Post -thaw viability of the CD45+ fraction was 69.0–79.8%. NSG mice ($n = 12$) were successfully reconstituted with human CD45 + cells with on average 78.1% B cells (CD19+), 12.5% CD4 T cells and 1.6% CD8 T cells in peripheral blood and up to 91% chimerism in the BM at 10 weeks.
Conclusion: BM-derived HSCs survive circulatory arrest for several hours and maintain their engraftment potential in immunodeficient mice. This model enables the generation of HLA-specific humanised mice, using a readily available source of HSCs, to investigate the human immune response to alloantigens.

BO58 PRIMARY CYTOMEGALOVIRUS INFECTION AFFECTS THE T-CELL DIFFERENTIATION STATUS AFTER KIDNEY TRANSPLANTATION

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Background: Cytomegalovirus (CMV)-infection has profound effects, associated with premature ageing, on the T-cell compartment. Premature aged T cells increase the risk for infection and atherosclerosis. We studied the impact of CMV on T-cell ageing parameters in CMV- kidney transplant (kTx) recipients, who received a kidney from a CMV+ donor (D+/R-).
Methods: Thymic output was measured by T-cell receptor excision circle (TREC) content and percentage of CD31 + naïve T cells. The proliferative history by relative telomere length (RTL) and differentiation status by immunophenotyping in D+/R- patients ($n = 31$, all received valgancyclovir 6 months after kTx) before kTx, and 3, 6 and 12 months afterwards and we compared outcomes with D-/R- recipients ($n = 47$).
Results: All D+/R- patients had detectable anti-CMV IgG titers 12 months after kTx. No differences in the TREC content, percentage of CD31 + naï ve T cells or RTL were found. Twelve months afterwards, a significant increase was observed in EMRA CD8 + T-cell numbers ($P = 0.01$) and percentage CD4 + CD28null ($P = 0.03$) and CD8 + CD28null ($P = 0.01$) memory T cells compared to D-/R- recipients. Conclusion: Under immunosuppressive conditions, primary CMV-infection in D+/R- kTx recipients does not affect thymic output or RTL but substantially affects the T-cell differentiation. (This study was financially supported by the Dutch Kidney Foundation [KSPB.10.12])

BO59 NAKED CASPASE-3 SIRNA AMPLIFIES INFLAMMATION VIA TLR AND PKR SIGNALING IN A PORCINE RENAL AUTO-TRANSPLANTATION MODEL

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Background: Small interfering RNA (siRNA) has the potential to elicit innate immune responses and trigger interferon responses like long, double-stranded RNA. In our previous study, naked caspase-3 siRNA infused into the renal artery during cold preservation was effective, but did not protect the auto-transplant kidneys in a porcine model, with increased inflammation and apoptosis. Therefore, there is a warranty to further elucidate whether the siRNA activates innate immune responses and which signaling pathways are involved. Materials and Methods

The left kidney was retrieved from mini pigs and infused by University of Wisconsin solution with/without 0.3 mg caspase-3 siRNA into the renal artery with the renal artery and vein clamped for 24-h cold storage. After right nephrectomy, the left kidney was auto-transplanted into the right for 48-h without siRNA systemic treatment. The protein expression was detected by western blotting, while the mRNA expression was detection by qPCR.
Results: The protein level of toll like receptor (TLR)-3 and TLR-7, as well as their main adapters, TRIF and MyD88, was up-regulated by the siRNA in the auto-transplant kidneys. Furthermore, the mRNA level of inflammatory transcription factors, NF-κB and c-Jun, was also increased, which resulted in the enhanced mRNA expression of pro-inflammatory cytokines, including IL-1β and IL-6, TNF-α and interferon (IFN)-α, β and γ. The protein of PKR, an non-TLR RNA sensor, was also up-regulated by the siRNA, but RIG-1 was not affected.
Conclusion: Naked caspase-3 siRNA administered into the kidney activated TLR- and PKR-mediated innate immune responses, and then amplified inflammation, which provided valuable evidence to guide future pre-clinic studies.

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SERUM STABILIZED NAKED CASPASE-3 SIRNA PROTECTS TRANSPLANT KIDNEYS IN A PORCINE AUTO-TRANSPLANTATION MODEL

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Background: Caspase-3 associated with apoptosis and inflammation plays a key role in ischemia reperfusion injury. The naked caspase-3 small interfering RNA (siRNA) was effective in the cold preservation and ex vivo hemoreperfusion of the kidney, but its *in vivo* effects need to be further evaluated. Hence, a novel version of naked caspase-3 siRNA with super serum stability was applied in a porcine kidney auto-transplantation model.
Materials and Methods: The left kidney was retrieved from mini pigs and infused by University of Wisconsin solution with/without 0.3 mg caspase-3/negative siRNA (Ambion *In vivo* siRNAs, $n = 5$) into the renal artery with the renal artery and vein clamped for 24-h cold storage (CS). After the right nephrectomy, the left kidney was auto-transplanted into the right for 2 weeks with an intravenous injection of 0.9 mg siRNA 1-h before reperfusion. All animal work was performed under the regulation layout by Chinese animal welfare authority.
Results: The expression of caspase-3 mRNA was down-regulated in both the post-CS and post-transplant kidneys preserved by caspase-3 siRNA, while the caspase-3 precursor was reduced in the post-CS kidneys and 17 kD active subunit was inhibited in the post-transplant kidneys respectively. The level of IL-1β mRNA, apoptotic cells and myeloperoxidase+ cells, was all decreased in the post-CS and post-transplant kidneys. In addition, HMGB-1 protein was decreased only in the post-transplant kidneys, but no significant changes were revealed in TLR-3 and TLR-7 between the groups. Moreover, renal tissue damage was ameliorated by caspase-3 siRNA, with better renal function.
Conclusion: The serum stabilized naked caspase-3 siRNA administered locally and systemically protected transplant kidneys via altering apoptosis, inflammation and immunity responses. Using this novel caspase-3 siRNA in a large animal kidney auto-transplantation model for 2 weeks provides invaluable data for future human clinical trials.

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BOS07-ETHICS/LAW/PSYCHOSOCIAL/PUBLIC POLICY

BO61 EVALUATION OF PROTOCOL ADHERENCE IN A HOME-BASED EDUCATIONAL INTERVENTION

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Background: We investigated the relationship between protocol adherence of health educators and the efficacy of a protocolized home-based educational intervention. The intervention was aimed at supporting well-informed decision making for end-stage renal patients on the deceased donor waitlist and their social network.
Methods: The health educators held tailored, group educational meetings in the homes of 63 patients. A Treatment Adherence Measure (TAM: scale 1–5) questionnaire was completed by patients after receiving the education (TAM1) and 2) was administered by an independent researcher by telephone (TAM2). TAM1 was also completed by 88 invitees.
Results: TAM1 results show that the health educators received high scores on the content (4.4) as well as the process (4.5) of the intervention from patients. The invitees also evaluated the intervention positively: content (4.6) and process (4.7). TAM2 scores showed similarly positive results: professionalism (4.8), communication skills (4.7), accessibility (4.8), and goal achieved (4.7). Using regression analyses, higher evaluation of the intervention on TAM2 was related to higher knowledge at the end of the intervention ($\hat{a} = 6.94$, CI95% [1.67–12.22], $P = 0.012$).
Conclusions: When implementing a protocolized educational intervention, treatment adherence can be a predictor of patients' response to intervention.

BO62 CAN WE OPTIMIZE THE ORGAN PROCUREMENT TRAVEL PRACTICES IN FRANCE?

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Background: For historical reasons, the rule in France is that each transplant team performs its organ procurements, no matter the donor hospital location. This results in many travels by car or plane and entails a risk for the teams. In October 2006, two young surgeons were killed in an airplane crash. The aim of the study is to describe in details the current practices and to determine models of improvement.
Methods/Materials: The charts of all deceased donors in whom one organ at least has been procured in 2011 in France were included in the study. The following parameters were analyzed: distance between donor and recipient hospitals, teams performing the procurement and the transplant, transportation modalities, costs of transportation, salaries of procurement teams, costs of organ shipments. We recalculated the same parameters, applying two different organization models, the "organ-share model" (OSM), in which transplant teams of a same organ trust each other for procurement, the closest travelling to the donor hospital, and the "level-share model" (LSM), in which a single team (the closest one) procures all the organs of a given level (thoracic or abdominal).
Results: In 2011 in France, 3651 teams travelled 1 359 499 km across the country (3.5 times the distance earth-moon), generating 240 tons-equivalent CO2, using 2765 cars and 886 fixed-wing airplanes, on 1 119 different routes. The costs were 19 821 000 €. The OSM would allow to reduce the distances by 29% and the costs by 21% but would not result in a reduction of the number of teams involved. The LSM would allow to reduce the number of teams by 38%, the distances by 69% and the costs by 52%.
Conclusion: The OSM is relatively easy to apply but would results in an unfair repartition of the procurement duties between small and large teams. The current training conditions of procurement surgeons do no allow applying the LSM model. However, the major savings generated by this model would allow to fund the three

BO64 PATIENTS' VIEWS ON THE KIDNEY ALLOCATION SYSTEM IN UK

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Background: The aim of this study was to assess patients' views, understanding and priorities on how kidneys are allocated on the deceased donor list in UK.
Methods: A two-part questionnaire was sent to 1221 patients awaiting kidney transplantation in UK after ethics approval (Ref 10/H083/61). Part-1 assessed patients' knowledge and priorities and Part-2 assessed patients' understanding and agreement after reading the UK kidney allocation guidelines.
Results: Of 410 patients responded (34%). The main issues patients think should be taken into consideration are the degree of tissue matching between recipient and kidney (84%), the time spent on the waiting list (76%), the likelihood the patient will die soon (74%), whether the patient will take their medication after transplantation (75%) and if they have a rare tissue type (69%). The ability to pay (76%), contribution to society (54%) and patient's ethnic origin (56%) were issues that most did not think should be part of the guidelines. 9% thought the ability to pay for a kidney is part of the allocation system. Moreover, 32% thought that patient contribution to kidney failure is part of the allocation system and 52% thought that it should be part of it. After reading the enclosed guidelines, there was an increase in understanding of the system from 39% to 84% saying that they mostly or completely understand the guidelines now. Finally, 81% said they mostly or completely agree with the current guidelines.
Conclusion: Patients were aware of some aspects of the current UK allocation system but seemed incompletely informed with respect to other aspects. When provided with the appropriate information the majority agree with the prioritization criteria. We deduce that provision of more information as well as greater patient involvement should increase understanding of the system and help with management of expectations for patients on the transplant waiting list.

BO65 PUBLIC ATTITUDES TO ORGAN DONATION IN AN EMERGING ECONOMY

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Background: South Africa is a unique emerging economy in which to study public attitudes to organ transplantation. With both developed and developing world characteristics and significant diversity in population, South Africa is comparable to many other countries. Published literature suggests that public attitudes towards organ donation in South Africa are generally positive. However, there has been a decline in the actual number of transplants taking place annually which is not consistent with expressed positive attitudes. Objectives: The main objective was to assess the attitudes of a representative sample of the South African metropolitan population toward organ donation and how these might affect transplant numbers.
Methods: A structured, interviewer administered questionnaire was utilised to measure attitudes amongst a study population of 1048 adults in five major metropolitan areas of South Africa. Field work was undertaken by supervised field workers. Written informed consent was obtained from all participants. Ethics clearance was obtained from three affiliated institutional IRB's.
Results: Of the study sample, eighty nine percent (89%) of respondents had heard of organ donation and 77% indicated they would accept an organ transplant if necessary. Seventy percent (70%) of respondents specified they would be willing to donate their own organs after death while 67% expressed willingness to donate a relative's organs after death. Participants were more positive about kidney donation than any other organ.
Conclusion: Public attitudes toward organ donation are generally positive amongst the study population. Recommendations include the need for cultural and linguistic sensitivity in educational and advertising campaigns.

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BO66 REGULATION, REGULATION, REGULATION: IT'S FUNCTION AND THREAT TO VITAL TRANSPLANT RESEARCH

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Transplant research is under threat from excessive Regulation. In the UK the Human Tissue Act 2004 introduced a system of licensing for transplantation research that, by separating it from the transplantation process (then exempt from licensing), has damaged this vital activity by a combination of inflexible interpretation of the Act and fear of criminal liability on the part of researchers. Similar difficulties have been encountered across Europe. Now, following the EU Directive (2010) on standards of quality and safety of human organs intended for transplantation, new UK Regulations to implement it have been published. Initial draft Regulations imposed on the whole transplantation process a licensing system similar to that for research, with criminal sanctions for breaches. This went beyond what is required by the Directive and was considered by many likely to have an inhibitory effect similar to that already seen in research. Following a public consultation process, the Department of Health (DH), as a result of the overwhelming view of respondents that the proposed licensing system was unnecessary, decriminalised all sanctions under the final regulations, with the sole exception of operating without a licence. While this does not eliminate the negative effect of licensing, it does suggest an awareness by the DH that excessive Regulation unnecessarily harms the transplantation process. This paper examines the function of Regulation in this domain, and highlights an opportunity for the Human Tissue Authority (the UK Regulatory body for both the new licences and research licences under the Act of 2004) to end the current illogical and harmful separation of transplantation and transplantation research by ensuring that all centres licensed for organ donation, retrieval, and transplantation are also fully licensed for related research. A successful British approach may provide a useful precedent for other European jurisdictions.

BO67 PREVALENCE OF PSYCHOLOGICAL ILLNESS IN LONG-TERM RENAL TRANSPLANT PATIENTS

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Background: A high prevalence of psychological illness, in particular anxiety and depression, in patients with chronic kidney disease (CKD) is well documented. However its prevalence in long-term kidney transplant patients (LKT) is less clear. Morbidity and mortality in LKT remains high compared to age-matched non-CKD populations and so LKT may be a susceptible group. The Hospital Anxiety and Depression Self-Assessment Scale (HADS) questionnaire assesses the role of emotional factors in clinical practice and sets criteria for referral to a specialist psychologist.
Methods: We analysed GFR measurements and assessed completed HADS questionnaires on 335 LKT (>8 years post transplant) seen between 2010–2012. We offered referral to a specialist renal psychologist to all patients who met HADS score criteria for this.
Results: Mean GFR was 45 mL/min (range 15–122). Of 335 (100%) completed the HADS questionnaire. 54(16%) patients reported being seen previously by a counsellor, psychologist or psychiatrist. 29(9%) patients met HADS criteria for referral to our renal psychology service. Increased symptom burden was reported in this group. Of these 6(21%) were subsequently referred to our local mental healthcare team. A broad range of conditions ranging from anxiety ($n = 6$), depression ($n = 12$), sexual/relationship difficulties ($n = 4$), bereavement disorder ($n = 2$), obsessive compulsive disorder ($n = 1$), work related stress ($n = 3$), and psychosis ($n = 1$) have since been formally diagnosed.
Conclusion: The majority of our LKT have stage 3 CKD. There is an increased prevalence of psychological illness, particularly anxiety and depression, in our LKT. In our experience HADS is a simple yet reliable tool for identifying LKT who require further psychological assessment and support. Further work to identify and understand reasons underpinning this increased prevalence is required. Symptom burden may be a contributory factor.

BO68 HOW YOUNG IS TOO YOUNG TO BE A LIVING DONOR?

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In several Canadian provinces 16 year olds can legally consent to living organ donation. Reservations about accepting young living donors (YLD) include concerns about their ability to appreciate the potential risks and benefits of donation surgery, and the ethical acceptability of taking organs from young people. Parts of the brain associated with judgment continue to develop into the mid-20s. It is challenging to determine how to evaluate the judgment of potential YLDs. The LD evaluation needs to address personal values influencing decision-making at different stages in the life-cycle. This presentation will address the evaluation of YLD autonomy and voluntariness, the informed consent process, donor motivation and expectations, and judgment of risks and benefits. The influence of family support and peer relationships on YLDs' decisions to donate will be explored. We contend that there are compelling ethical reasons to offer living donation to carefully selected young people and propose that living donor programs develop policies and procedures to evaluate YLDs that recognize that young people vary in maturity, dependence/independence, life experiences and personal development.

BO69 A NOVEL USE OF THE MDT TEAM TO INCREASE AWARENESS OF RENAL FAILURE AND TRANSPLANTATION AND THEIR IMPLICATIONS IN MEDICAL STUDENTS

Paul Herbert
Imperial College Healthcare Trust

Background: An awareness of renal failure and its implications is an important part of medical training. We noted a knowledge gap existed amongst medical students, especially relating to transplantation, and endeavoured to investigate and rectify this.
Methods: An online questionnaire was sent to all final year medical students at our institution to establish awareness and attitudes towards transplantation. After reviewing this to raise awareness we ran an educational interactive session with an MDT team for all first year medical students, focussing on the clinical, psycho-social, ethical and practical issues surrounding transplantation. The team included an expert renal patient, renal psychologist, GP and transplant surgeon. In addition part of a recent documentary on a transplant was screened. Feedback from the session was analysed, looking for key words and themes, and we then ran focus groups looking at longer term impact 9 months later.
Results: We received 161 complete responses to the questionnaire. Only 15% had seen a renal transplant, 30% had had exposure or would get exposure to transplantation by the end of their training issues surrounding renal failure via our MDT session. After this education session 330 feedback forms were returned. They showed greatly increased awareness of the difficulties of renal failure and the positive effect of transplantation (95%). The results from the focus groups were analysed using thematic analysis and showed good understanding of the holistic impact of renal failure and the benefits of transplantation, suggesting good retention and impact. Interestingly a theme of the importance of team working also emerged from the data.
Conclusions: The results of our initial survey suggested low exposure to renal transplantation at our medical school by the final year.

BO70 QUALITY OF LIFE, PSYCHOSOCIAL WELL-BEING AND SATISFACTION OF KIDNEY LIVING DONORS- RESULTS FROM A EUROPEAN MULTICENTRE RETROSPECTIVE STUDY (ELIPSY)

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Introduction: European Living Donor Psychosocial Follow-Up (ELIPSY) is a multicenter study, co-funded by EAHC and conducted in six different centres examining the psychosocial outcome and the impact of donation process on kidney living donors (KLDs). Objective To assess thoroughly a retrospective study the long term impact of donation and the impact of recipient outcome on KLDs.
Methods: Of 278 KLDs were assessed up to five years after donation. The donors completed a post-operative questionnaire containing psychometric tests (HADS, PHQ, SOC, SF-36, ACSA, life events and ELSA), and specific questions regarding satisfaction, decision to donate and donor-recipient relationship. Each transplant centre adapted the methodology to its characteristics and resources.
Results: KLDs quality of life as indicated by SF-36, scores within the normal range compared to the general population. The donors' ability to manage major life events and daily hassles (Sense of coherence) was the most consistent factor.
Conclusions: Results are discussed in terms of differences in the evaluation of follow-up practices and the legitimacy for KLDs. A consistent ability to manage or improve life stressors is fundamental for good psychosocial outcome on KLDS.

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BOS08-TOLERANCE

BO71 NATURAL TREGS CONTROL THE DONOR-SPECIFIC CYTOTOXIC T-CELL RESPONSE LONG AFTER TRANSPLANTATION

Nicole van Besouw, Ronella de Kuiper, Mariska Klepper, Michiel Betjes, Willem Weimar, Carla Baan
Erasmus MC

Introduction: CD4 + CD25highCD127- are potent regulators of cytokine production and proliferation of alloreactive T-cells. Although donor-specific cytotoxic T-cells (CTL) destroy the allograft, the influence of regulatory T-cells (Tregs) on their cytotoxicy is unknown. Therefore, we questioned whether the donor-specific CTL response is controlled by Tregs.
Methods: We assessed the involvement of Tregs both by depleting them from patients' PBMCs (n = 12: 4.7 ± 1.2 years after renal transplantation) as well as by reconstitution experiments. PBMCs were incubated with irradiated donor or 3rd-party cells in the presence of IL2, IL7 and IL15 to obtain optimal numbers of effector memory CTLs. After 7 days of culture, a cell mediated lympholysis assay (CML) was performed.
Results: Donor-specific hyporesponsiveness compared to 3rd-party response was found (P = 0.003). A clear role for donor-specific Tregs in 9/12 patients was found by depletion and coculture experiments. Reconstitution of Tregs to CD25- effector T cells (1:10), showed a significantly decreased donor-reactive CML (56% inhibition, P = 0.006). The potency to inhibit 3rd-party reactivity was comparable. We found that most of the CD4 + CD127-FoxP3+ Tregs expressed Helios, the marker of natural Tregs (nTregs: mean±SD; 68%±4.1). Only 5%±2.3 nTregs were capable to produce IFN-γ, while 28%±13 of the induced Tregs (Helios-) produced IFN-γ.
Conclusion: Functional nTregs circulate long after transplantation to control donor-specific CTL responses.

BO72 COMPLETE DONOR-SPECIFIC NONRESPONSIVENESS: DOES IT EXIST LONG AFTER TRANSPLANTATION?

Nicole van Besouw, Joke Zuijderwijk, Ronella de Kuiper, Michiel Betjes, Willem Weimar, Carla Baan
Erasmus MC

Background: In earlier studies, we observed that the majority of patients did not have the capacity to proliferate to (76%) or lyse (62%) donor cells long after transplantation. The maintenance of memory cells is dependent on their capacity to respond to the homeostatic cytokines IL7 and IL15. Therefore, we questioned whether these cytokines can increase the donor-specific response long after transplantation.
Methods: We assessed the frequency of cytotoxic T-lymphocytes (CTLf) and IFN-γ producing cells (pc) in the absence and presence of IL7 and IL15. Thereafter, cell mediated lympholysis (CML) and Elispot assays in the presence of cytokines were performed long (4 years ±1.5) after renal transplantation.
Results: Donor-specific CTLf (P = 0.004) and IFN-γ pc (P = 0.01) significantly increased in the presence compared to the absence of cytokines. Nonresponsiveness (<10/105 IFN-γ pc, <10 CTL/106 PBMC) was seen in 29% of patients in the absence and 6% in the presence of cytokines by Elispot, and 46% versus 23% by CTLpf. This was confirmed by CML: 31% of patients did not react to donor cells (<10% lysis) in the presence of cytokines. All patients reacted to third-party cells in the assays.
Conclusion: Donor-specific nonresponsiveness can be abrogated by homeostatic cytokines, resulting in increased sensitivity of donor-reactive assays in long term transplant recipients.

BO73 POTENTIAL ADJUNCTS FOR THYMIC REJUVENATION

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Background: An involuted thymus can be rejuvenated when transplanted into a juvenile host. This rejuvenation promotes thymopoiesis, which is considered vital in the induction of central tolerance.
Methods: We conducted a literature search on PubMed using the keywords "thymic rejuvenation" and collated all articles till 2001. We also analysed any relevant references in these articles.
Results: The agents/techniques used to demonstrate thymic rejuvenation include zinc, arginine, IL-7, growth hormone (GH), ghrelin, melatonin, lutenising hormone releasing hormone (LHRH) agonists and even surgical castration of both genders. Two studies involved humans, 1 used the swine model and the rest involved murines.

In humans, the NCT00275262 trial administered LHRH agonist (Lupron) to patients after bone marrow transplantation for haematological malignancy. They developed significantly raised TRECs (T-cell excision circles) at 9 months compared to placebo. In swine, thymic rejuvenation was demonstrated post-Lupron treatment within 2 months lasting up to 6 months. There was an increase in the cortex/medulla ratio and T-cell excision circles (TREC) levels however, there was no concrete increased thymic release of CD45RA+CD4 + T-cells. In aged mice, the individual supplementation of zinc, melatonin, GH and IL-7 restored normal T-cell levels. One group administered either Lupron or performed surgical castration and found similarly increased thymic weight and T-regulatory cell levels.
Conclusion: There is a lack of translational studies from murines to large animals. Multiple agents/techniques can rejuvenate the thymus in mice however the similarity via both medical and surgical methods indicates a role for sex steroid levels in tolerance induction. The role of Lupron should be investigated in solid organ transplantation.

BO75 FETAL STEM/PROGENITOR CELLS INDUCED IMMUNE TOLERANCE TO ALLOGENEIC TISSUES IN EXPERIMENTS

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Background: The molecular origin of graft rejection is an interaction between T-lymphocytes receptors and molecules of MHC (HLA). In transplantation currently used such methods for prevention of transplant rejection: immune suppression, non-reactivity induction through a direct change of the cytokine regulation of immune response, modulation between type 1 and 2 T-lymphocytes generation and antibodies against CD3 + cells, etc. We studied possibility of allogeneic tissue engraftment while simultaneous transplantation fetal stem/progenitor cells (FSP/Cs).
Methods/Materials: Rats of 550 in number were used. FSP/Cs isolated from rats' fetuses according to original method (Patent Ukraine Invention ¹ UA 72796). FSP/Cs (5–8 × 106/ml) introduced intravenously. Spleen transplantation was done in pairs: control (½ of allogeneic spleen + 0.9% sodium chloride) & experimental (½ of allogeneic spleen + FSP/Cs) animals. After the median laparotomy in both anaesthetized rats, were removed ½ of the spleen and then, they were decapsulated and stitched in created pouch of the recipient's omentum. Same design (pair's transplantation) was performed in skin flaps grafting. Caspase-3, -8 activity were identified in thymus, bone marrow, spleen and lymph nodes. To estimate FSP/Cs in immune system organs staining of FSP/Cs membranes was done by PKH 67 (Sigma).
Results: Re-laparotomy was carried out after 1, 2, 6 and 12 months that revealed spleen engraftment only in those rats received FSP/Cs, and likewise in skin transplants. After tag-PKH-67-FSP/Cs introduction marked cells appear in thymus, lymph nodes, spleen and bone marrow. Analysis of an apoptotic cells showed that apoptosis intensity in thymus and bone marrow of animals those received FSP/Cs was much higher compared to the control data.
Conclusion: The results of our biological experiments evidences about the possibility of inducing tolerance to allogeneic tissues with the help of FSP/Cs (Patent Ukraine Invention ¹ UA 72310).

BO76 SUCCESSFUL TREATMENT OF RENAL FAILURE CAUSED BY MULTIPLE MYELOMA WITH HLA-IDENTICAL LIVING KIDNEY AND BONE MARROW TRANSPLANTATION

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By a 45 year-old man with ESRD multiple myeloma (MM) and κ light-chain nephropathy was diagnosed. Cytostatic treatment lead to partial remission, so autologous peripheral stem cell transplantation (SCT) was carried out leading to complete remission, however the patient remained anuric. The patient's HLA-identical brother offered living donation, thus peripheral stem cells were collected and cryopreserved. Kidney transplantation was carried out with tacrolimus + sirolimus + methylprednisolone. With a well functioning kidney graft, yet in the incipient relapse phase of MM, allogeneic SCT was performed after total body irradiation. Severe oropharyngeal infections, diarrhea, sepsis, and renal failure occurred. Fearing acute renal rejection, steroid shot therapy was given, kidney function was gradually restored. Then, steroid-responsive acute graft-versus-host disease (aGVHD; grade II, predominantly bowel) was diagnosed in the background of diarrhea, which returned once. Later on left subclavian vein thrombosis (central venous catheter) and sepsis occured. Recovering from these the patient enjoys good health, has stable kidney

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function and normal protein excretion. Steroid was tapered, than stopped. Bone marrow biopsy revealed full-donor type normocellular hemopoiesis. Because of chimerism, gradual discontinuation of immunusuppresion was planned. Sirolimus was stopped. At present, with a minimal trough level of tacrolimus (planned to be discontinued as well) there are no signs of complications and the latest bone marrow biopsy showed still complete remission. HLA-identical combined kidney and bone marrow transplantation from a living donor in MM with ESRD may offer not only complete remission and good renal function, but also a new life and good health without any immunosuppression. Our case is unique, because this combined transplantation is rarely possible and reported, furthermore the management strategy we used has not been published before.

BO77 INDUCTION THERAPY AND MOLECULAR MARKERS OF REJECTION/TOLERANCE IN KIDNEY TRANSPLANTATION

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Background: Induction therapy has been shown to improve the outcome of kidney transplantation but little is known about involved mechanisms.
Methods: The expression of 11 genes associated with tolerance/rejection and lymphocyte subpopulations were monitored in the blood of 60 transplant recipients during one year. Patients received CNI+MMF+steroids and induction with rATG ($n = 24$), basiliximab ($n = 17$) or no induction ($n = 21$).
Results: Compared to basiliximab and no induction, rATG group had CD247, FOXP3, GZMB, PRF1 transcripts lower that reflected depletion and slow repopulation of T and NK cells (all $P < 0.0001$). Tolerance associated transcripts of MAN1A1 was higher ($P < 0.0001$) and TOAG-1 ($P < 0.01$) lower in rATG group compared to other groups.
Conclusion: rATG induction was associated with profound decrease of effector T cell-related transcripts while induced some of tolerance associated genes. Basiliximab induction lacks tolerogenic potential. Supported by GACR No. P301/11/1568.

BO78 INTRA-GRAFT EVENTS ASSOCIATED WITH GRAFT ACCEPTANCE "THE ACCEPTANCE REACTION" IN DA TO PVG RAT LIVER TRANSPLANTATION

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Background: A major goal of organ transplantation has been an induction of the donor-specific tolerance. In the rat combination DA to PVG, liver graft has donor-specific tolerance. The present study clarified the intra-graft events associated with graft tolerance in liver grafts.
Methods /Materials: Orthotopic liver transplantation was performed from DA (RT1a) to PVG (RT1c) rats without immunosspression (tolerance group; mean survival >100 days) or from DA (RT1a) to Lewis (RT1 l) (rejection group; mean survival 11 days). We studied pathological characteristics and cytokines milieu in liver grafts in the DA-to-PVG and DA-to Lewis rat transplantation.
Results: Donor-specific tolerance was confirmed by skin transplantation. In DA liver grafted into PVG, T-cell infiltrate by day 7 with acute cellular rejection. However, the features of rejection resolved by day 21 with mild cellular infiltration, and grafts were survived more than 100 days with tolerance. The infiltrates in accepting grafts at day 7 differed from that in rejecting grafts in certain features, including less infiltration by CD3 + T cells, less T-cell proliferation (PCNA+), less degree of cellular rejection in portal areas and lobules, and less levels of Th1 (IL-12, IFN-ƒÁ, TNF-ƒ¿) and Th2 (IL-4, IL-10) cytokines. In addition, many Foxp3 + Treg cells were evident in accepting grafts compared to rejecting grafts, indicating that high frequency of Treg cells was noted in infiltrating cells in accepting grafts. In addition, long lasting apoptosis of graft infiltrating T-cells occurred, which may have contributed the limitation of the immune response.
Conclusion: The development of tolerance of liver graft is characterized pathologically by the progressively diminished infiltrating cell proliferation and cell-mediated graft cell injury (T cell anergy), as well as persistence of infiltrating cell apotosis (T cell deletion). In addition, Treg cells were also involved in the development of transplant tolerance.

BO79 THE USE OF RITUXIMAB IN ABO-INCOMPATIBLE TRANSPLANTATION RESULTS IN DECREASED MEMORY RESPONSES AND LOWERED INFLAMMATORY CYTOKINES

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Background: ABO incompatible (ABOi) transplantation is one strategy to increase the donor renal transplant pool. In this context, B cells are important due to their actions as antigen presenting cells (APCs) as well as playing an integral part in the humoral immune response. Rituximab has been used to deplete B cells in ABOi transplantation, but little is known about the effect this has on the T cell mediated response. This study aims to characterise the effects of Rituximab on the response to common antigens and cytokine expression.
Methods/Materials: ABOi renal transplant recipients were given standard immunosuppression +/- Rituximab 2-4 weeks pre-transplant. Memory responses of PBMCs to common antigens (whole/extract*Candida albicans* and CMV surface proteins), using proliferation (Thymidine incorporation) and cytokine production as readouts, were tested throughout the next year.
Results: Rituximab administration significantly depleted CD20 + B cells but after one year, there was evidence of CD20 + B cell reconstitution. B cell depletion resulted in significantly diminished memory responses, as measured by proliferation in response to *C. albicans* for all time points (one-way ANOVA, $P < 0.05$, table 1). TNFα, IFN-γ and IL-10, were also diminished following B cell depletion (Table 1, $n = 5$). Both TNFα and IL-10 secretion recovered in line with B cell reconstitution whereas IFN-γ responses remained reduced across all time points (Table 1).
Conclusion: B cell depletion using an immunosuppression regime containing Rituximab results in inhibited memory T cell responses. This may indicate that Rituximab-containing regimes can affect cellular, as well as humoral immune responses. This has important implications for all transplant recipients and may help to explain the mechanisms of action of Rituximab in preventing or treating rejection. Table 1 Memory response against *C. albicans*. Numbers show fold increase over Media alone (mean ± SD) ($n = 5$)

BO80 PRELIMINARY DATA OF CONTROLLED RANDOMIZED STUDY (EVER TWIST) ON TOLERANCE INDUCTION

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According to Calne's "window of opportunity for immunologic engagement" concept to favor tolerance, we have designed a prospective, randomized, open-label clinical trial in which de novo renal transplant recipients will be randomized according to: (a) new immunosuppressive protocol (group A) that after induction with methylprednisolone (M) and Thymoglobulin (ATG) dosage immunosuppression is interrupted for 72 h. and resumed with Tacrolimus (low-dose)+Everolimus+Mycophenolate sodium (MPS) + M; (b) standard arm (group B) induction with ATG and maintenance with Tacrolimus+MPS+M. Up to the present we have recruited 33 patients (14 males and 6 females): 7 in the group A and 6 in the group B. On enrolment blood samples were collected before the transplant (BAS) and at 6 month after kidney transplantation (Tx 6mo). The frequency of CD4 + CD25high and CD127- T-cells was determined by Fluorescence Activated Cell Sorter (FACS) analysis. Immunological data are reported, absolute number (n) and percentage (%) in this table like average SD: These preliminary data suggest that after 6 months, CD4 + CD25high-CD127-, in patients of group A, at six month are significantly increased when compared to the BAS, while T-reg cells are suppressed by standard immunosuppressive therapy (group B). These results suggest that sperimental immunosuppressive protocol *in vivo* may improve peripheral tolerance in kidney transplant recipients.

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MONDAY, SEPTEMBER 09, 2013
OS01-KIDNEY I

O001 DONOR TRANSMITTED CANCER IN KIDNEY RECIPIENTS: UK EXPERIENCE

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Donor origin cancer [DOC] in kidney recipients may be transmitted with the graft (donor-transmitted cancer, DTC) or develop subsequently from the graft (donor-derived cancer, DDC). Recipients of kidney allograft with DOC (2001–2010), were identified from the UK Transplant Registry and database search at transplant centres of 21 029 transplants, 14 recipients developed DOC from 12 donors (0.07%): 2 were DDC and 12, DTC. Of the 12 DTC, 6 were renal cell ca; 4, lung ca and 2, lymphoma. Ten recipients with DTC had surgery. Five-year survival was 83% and 93% respectively for recipients with and without DTC ($p = 0.08$). None of the donors resulting in cancer transmission was known to have cancer at the time of donation. The risk of cancer transmission was significantly associated with donor age ≥50 years (OR = 5.1) and DCD donors (OR = 3.8). We conclude that the risk of cancer transmission is low, but cannot be eliminated. As donors get older and DCD donation increases, the risk is likely to increase.

O002 RISK FACTORS FOR DEATH FROM MALIGNANCY AFTER KIDNEY TRANSPLANTATION IN ENGLAND – AN OBSERVATIONAL COHORT STUDY

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Background: Deaths from malignancy are rising among kidney transplant populations. The aim of this study was to determine risk factors for death from malignancy post kidney transplantation in England over the last decade.
Methods: We used data from Hospital Episode Statistics (HES) to select all kidney transplant procedures performed in England between April 2001 and March 2012 (HES is an administrative data warehouse containing admissions to all National Health Service hospitals). Patient demographic data was collected including age, gender, donor type (living or deceased), ethnicity, transplant year, allograft failure, medical co-morbidities (e.g. diabetes, cardiovascular disease, cerebrovascular disease, cancer) and area socio-economic deprivation (Index of Multiple Deprivation [2010]). Data linkage analysis was performed with the Office for National Statistics (ONS) to identify all deaths occurring amongst this study cohort. The primary outcome measure was death secondary to malignancy, with Cox proportional hazard models performed to identify independent factors associated with malignancy-related mortality ($p < 0.05$ considered significant).
Results: HES data was available for 19 688 kidney transplant procedures, although exclusions for missing data resulted in 19 103 for final analysis. Median follow up for this study cohort was 4.4 years (interquartile range 2.2–7.3 years). 2085 deaths occurred amongst the study cohort, of which 376 (18.0%) were due to malignancy (42 deaths from malignancy occurred within the first year post-transplant). The three most common malignancies post-transplantation were lymphoma ($n = 69$), lung ($n = 66$) and renal ($n = 37$). Risk of malignancy-related death increased with age; <50 (0.8%), 50–59 (2.5%), 60–69 (4.8%), 70–79 (6.5%) and over 80 (9.1%). However death from lymphoma (the most common cancer) was significantly more common as the cause of malignancy-related death in younger versus older age brackets compared to other malignancies; <50 (39.4%), 50–59 (15.4%), 60–69 (10.1%), 70–79 (5.3%) and over 80 (0.0%), $p < 0.001$. Recipients with pre-transplantation history of cancer had a higher risk of post-transplantation death from malignancy compared to those without any previous history (17.6% vs. 1.9%, $p < 0.001$). South Asian recipients had lower risk of death from malignancy versus other ethnic groups (1.3% vs. 2.0% respectively, $p = 0.024$). Live-donor versus deceased-donor kidney transplantation was associated with lower risk of malignancy-related death (1.1% vs. 2.4% respectively, $p < 0.001$). On Cox proportional hazard models only increased age, pre-transplant history of malignancy and deceased-donor kidney transplantation were independently associated with risk for post-transplantation death from malignancy (all $p < 0.05$).
Conclusion: Malignancy as a cause of death post kidney transplantation is common and associated with expected (age, pre-transplant history of malignancy) and unexpected (deceased-donor kidney transplantation) independent risk factors.

O003 PROLONGED DELAYED GRAFT FUNCTION IS ASSOCIATED WITH INFERIOR PATIENT AND KIDNEY ALLOGRAFT SURVIVALS

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Background: The incidence of delayed graft function (DGF) is variable according to donor/recipients demographics. It is still unclear the influence of DGF on clinical outcomes after renal transplantation. This study investigated the influence of DGF and its duration on patient and kidney allograft survivals.
Methods/Materials: This retrospective analysis evaluated the impact of DGF and duration of DGF on 1-year graft and patient survivals of all deceased donor kidney transplants performed between 1998 and 2008 in a single center ($n = 1412$). DGF was defined as the need for dialysis during the first week after transplantation and duration of DGF was computed up from the day of transplantation to the last dialysis section.
Results: The population was composed predominantly by men (54.9%), Caucasian (49.5%), with a mean age of 41.1 years. The mean donor age was 36.9 years with 16.6% expanded criteria donors and mean cold ischemia time of 23.1 h. The incidence of DGF was 57.3%. Patient survival was 94.2% and there were no differences between patients with or without DGF. Overall graft survival was 88.2% and patients who presented DGF had inferior graft survival (83.1 vs. 95.7%, $p < 0.001$). Importantly, inferior patient and graft survival were observed only in patients whose DGF lasted more than 15 days.
Conclusion: In this cohort of kidney transplant recipients with high incidence of DGF 1-year graft and patient survivals were significantly inferior only among those with prolonged DGF of more than 15 days.

O004 SCREENING FOR COLORECTAL CANCER IN RENAL TRANSPLANT PATIENTS: ADDITIONAL MEASURES ARE NOT REQUIRED IN THE CONTEXT OF A NATIONAL SCREENING PROGRAMME

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Background: Immunosuppression associated with haemodialysis (HD) and renal transplantation (RT) is linked to an increased risk of colorectal cancer (CRC), leading to suggestions for targetted bowel screening following RT. The aim was to assess the incidence of CRC in HD and RT patients and their uptake of the faecal occult blood test (FOBt) Scottish Bowel Screening Programme (SBoSP).
Methods: A cohort observational study of 1239 patients with ESRD was undertaken. Data was cross-linked with the NHS GG&C prospectively maintained SBoSP database.
Results: Of 782 patients underwent RT (median age 44.5 years) and 457 patients were on HD (median age 64.2 years). At median follow-up of 5.4 years post-RT (range: 0.1–11.9), five patients (0.5%) had been diagnosed with CRC. All diagnoses of CRC predated RT. Five HD patients (1.1%) had a diagnosis of CRC; 3 (60%) after starting HD. Of the 782 RT patients, 89 (11.4%) had functioning renal transplant, were aged 50–74 years old and residing in NHS GG&C during the first round of the SBoSP. Two hundred and twenty-three HD patients (49%) were eligible. One hundred and twenty-five of the eligible HD patients (56%) would have been fit for colonoscopy. Of these, only 71 patients (32%) participated in screening. Three patients (7.5%) tested positive on FOBt, one of whom (33%) attended for colonoscopy where a highly dysplastic polyp was found. All of the 89 RT patients were fit for colonoscopy. Forty-six (51.7%) participated in screening. One (2.2%) patient tested positive on FOBt and subsequently attended for colonoscopy where adenomata were detected. The participation rate (51.7% vs. 51.7%, $p = 0.990$) and positivity rate (2.2% vs. 3.0%, $p = 0.749$) in RT patients were similar to the general population.
Conclusions: The increased risk of CRC in immunosuppressed patient was not seen in our population. In those eligible to take part in the SBoSP, participation and positivity rates were similar to the general population. There is no role for CRC screening in RT patients within the context of a national screening programme.

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O005 IS HIGHER CO-MORBIDITY THE EXPLANATION FOR THE INCREASED MORTALITY IN "NEVER TRANSPLANTED" WAITING LIST PATIENTS COMPARED TO RENAL TRANSPLANTED PATIENTS?

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Background: Due to organ shortage, some waiting-list patients never achieve transplantation. The aim of the present study was to describe the co-morbidity, mortality and causes of dead, among patients on the waiting-list compared to transplanted patients.
Methods/Materials: Data from Danish Nephrology Registry and Scandiatransplant were merged. Charlson Comorbidity Index (CCI) scores were derived from the National Danish Admissions Registry, which records all discharge diagnoses. Study period: 1.1.95–31.12.11. Patients were divided into three groups: Waiting list group (WL) i.e. never transplanted, transplanted with deceased donor (DDTx) and transplanted with a living donor (LDTx). Only patients waiting for or receiving their first renal transplant were included.
Results: WL patients were significantly older with a higher CCI score compared to DDTx and LDTx patients (Table 1). WL patients had significantly increased mortality, especially due to cardiovascular diseases. In a multivariate regression analysis comparing WL to DDTx hazard ratio was: 3.32 (2.81–3.82, $p < 0.001$).
Conclusions: Renal waiting list patients never transplanted are older and have more co-mobidity. However, even after statistical correction for this, these patients had a considerably higher mortality than transplanted patients.

O006 EXPRESSION OF MIR-142-5P IN PERIPHERAL BLOOD MONONUCLEAR CELLS FROM RENAL TRANSPLANT PATIENTS WITH CHRONIC ANTIBODY-MEDIATED REJECTION

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Background: In renal transplantation, the unresponsiveness of patients undergoing chronic antibody mediated rejection (CAMR) to classical treatment stress on the need for accurate biomarkers to improve its diagnosis. We aim to determine whether microRNA expression patterns may be associated with a diagnosis of CAMR.
Methods/Materials: We performed expression profiling of miRNAs in peripheral blood mononuclear cells (PBMC) of kidney transplant recipients with CAMR or stable graft function. Our results were validated on independent samples from kidney transplanted recipients with CAMR, stable graft function, acute rejection and non-transplanted patients with renal failure.
Results: Among 257 expressed miRNAs, 10 miRNAs associated with CAMR were selected. Among them, miR-142-5p was increased in PBMC and biopsies of patients with CAMR as well as in a rodent model of CAMR. A ROC curve analysis performed on independent samples showed that miR-142-5p is a potential biomarker of CAMR allowing a very good discrimination of the patients with CAMR ($AUC = 0.74$; $p = 0.0056$). The lack of modulation of miR-142-5p in PBMC of patients with renal failure, suggests that its over-expression in CAMR was associated with immunological disorders rather than renal dysfunction. Moreover, its expression was decreased in PHA-activated blood cells and was not modulated in PBMC from patients with acute rejection, excluding a non-specific T cell activation expression. The absence of modulation of this miRNA in immunosuppressed patients suggests that its expression was not influenced by treatment.
Conclusion: Altogether, these data suggest that miR-142-5p could be used as a biomarker in CAMR and these finding may improve our understanding of chronic rejection mechanisms.

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OS02-KIDNEY II

O007 EXCELLENT LONG-TERM OUTCOME OF ABO-INCOMPATIBLE LIVING KIDNEY TRANSPLANTATION IN LAST DECADE-MARKED REDUCTION OF CHRONIC ANTIBODY MEDIATED REJECTION

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Introduction: In this retrospective single center study, we analyzed the long-term graft survival of ABO-incompatible living donor kidney transplant for over 10 years by comparing with ABO-compatible living kidney transplantation (ABO-CLKT) as control.
Methods: Six hundred and forty-one patients who underwent living kidney transplantation at our institution between January 2001 and August 2012 were enrolled in this retrospective study. One hundred and eighty-one patients underwent ABO-ILKT and 460 patients underwent ABO-CLKT. All recipients had been treated with tacrolimus, mycophenolate mofetil and methylprednisolone for basic immunosuppression. In the induction phase, basiliximab was administered to most of the recipients. ABO-ILKT recipients underwent 0–5 pretransplant sessions of double filtration plasmapheresis (DFPP) and were treated by either splenectomy 53/181 (29%) or by low dose (200 mg/person) rituximab injection 138/181 (76%) as a preconditioning treatment. Thirty-eight (174/461) percent of ABO-CLKT recipients received rituximab injections for positive donor specific anti-HLA antibody (DSA) with three sessions of DFPP.
Results: The 5-year graft survival rates were 95.3% and 93.2% in the ABO-ILKT and ABO-CLKT, respectively. The 10-year graft survival rates were 95.3% and 85.9% in the ABO-ILKT and ABO-CLKT, respectively. The incidence of C-AMR after 6 months post surgery were 8%, and 16% in the ABO-ILKT and ABO-CLKT groups, respectively. The ABO-CLKT patients had a significantly higher incidence of chronic antibody-mediated rejection. The incidence of DSA was lower in ABO-ILKT compared to ABO-CLKT recipients.
Conclusions: The ABO-ILKT patients had excellent long-term outcomes and a significantly lower incidence of C-AMR, compared with the ABO-CLKT group. The significantly higher incidence of C-AMR in the ABO-CLKT recipients was caused by higher DSA production than in the ABO-ILKT recipients.

O008 AB0-INCOMPATIBLE LIVING KIDNEY TRANSPLANTATION WITH USING A DESENSITISATION PROTOCOL – SINGLE CENTER EXPERIENCE

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Background: Permanent shortage of organ donors in Germany forces the transplant centers to new solutions to expand the donor pool. Since 30 years living kidney transplantation is the main focus at the University Clinic Freiburg, 550 LKTx were performed and in 2004 the first successful AB0-incompatbile LKTx was realized.
Method: Between 2004 and 2012 315 LKTx were performed, there from 231 (73%) AB0c-renal transplantations and 84 (27%) AB0i-renal transplantations using a specific desensitisation protocol consisting of Rituximab®, antigen-specific immunoadsorption (Glycosorb®), IL2-R-Antibody and conventional triple-therapy with Tacrolimus, MMF, corticosteroids. 78 AB0i-recipients were compared with 195 AB0c-recipients with the same initial and maintenance immunosupressive therapy based on IL2-R antibody, Tacrolimus, MMF and corticosteroids. Concerning follow up −12 months, first transplantation and maintenance immunosuppressive therapy there were 61 AB0i and 55 AB0c recipients.The age of recipient AB0i 46 ± 11 years and 48 ± 12 years in AB0c, donor age in AB0i 51 ± 9 years and 51 ± 10 years. There were 12 (20%) preemptive transplantation in AB0i group and 16 (29%) in AB0c group. Number of HLA mismatches was also comparable 3, 9, ± 1, 3 in AB0i and 3, 5, ± 1, 6 in AB0c patients.
Results: The comparison of both groups showed no statistically significant differences in graft survival rates at 1 and 3 years post-transplant (AB0i = patient survival, 98% graft survival 95%; AB0c = patient survival, 93% graft survival 98%). Also T-Cell mediated as Antibody mediated rejections in both group were not statistically different. There are no significant differences in bacterial and viral infections after transplantation in both groups of recipients.
Conclusion: The outcome of ABOi-LKTx has significantly improved in the modern immunosuppressive era with patient- and graft survival. ABOi-LKTx is by now a safe standard option for LKTx-recipients who have only ABOi-donor-candidates.

O009 RISK FACTORS ASSOCIATED WITH ANTIBODY-MEDIATED REJECTION IN ABO INCOMPATIBLE KIDNEY TRANSPLANTATION

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Background: ABO incompatible transplantation (ABOi Tx) has excellent 1 year graft survival rates. However, there is some evidence of an increase in antibody-mediated rejection (AMR) when compared with compatible transplants. The aim of this study was to determine the risk factors associated with the development of AMR after ABOi Tx, in order to aid in stratifying risk.
Methods/Materials: Eighty-two living-donor ABOi recipients have been included. Pre-transplant antibody removal was performed if baseline AB IgG titre was above 1/8. Donor specific HLA antibodies (DSA) were identified at baseline using the single antigen bead assay. Univariate and multivariate analysis was performed to identify which factors were related to the risk of AMR (2009 Banff classification).
Results: Mean age was 45 ± 15 years, mean time on dialysis 28 ± 37 months, and median CRF 50%. 16% were found to have baseline DSA. Seventy-nine percent had at least one session of pre-transplant antibody removal. Basiliximab, Rituximab/Basiliximab and Campath were used as induction treatment in 13%, 78% and 9% of patients, respectively. All patients received tacrolimus, MMF and steroids. Routine post-transplant antibody removal was performed in 9%. Five year patient and death-censored graft survivals were 91% and 88%, respectively. The incidence of AMR was 29% at 1 year. AMR was associated with graft loss ($p = 0.003$). Only two independent risk factors for AMR were identified: recipient blood group O (OR = 3.8, $p = 0.04$) and baseline DSA (OR = 10.3, $p = 0.04$). Baseline, pre-transplant and post-transplant levels haemagluttinin titres were not predictive of AMR. Finally, baseline DSA was also associated with graft loss ($p = 0.002$).
Conclusion: Post-transplant AB antibody titre monitoring may not be necessary, and routine post-transplant antibody removal is not needed for decreasing the risk of AMR. The major risk factor associated with AMR after ABOi Tx is the presence of preformed DSA. Alternative strategies may be indicated in these patients.

O010 PROTOCOL BIOPSIES IN ABO-INCOMPATIBLE VERSUS ABO-COMPATIBLE LIVING DONOR KIDNEY TRANSPLANT RECIPIENTS

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Introduction: Short and medium term ABO-incompatible (ABO-i) kidney transplant results are comparable with ABO-compatible (ABO-c) kidney transplants (KT). Protocol biopsies (PKB) of ABO-I kidneys show positivity for C4d without evidence of antibody-mediated rejection (AMR), but little is known about the histologic progression.
Objective: To compare the histological parameters of PKB at 3 and 12 months after ABO-c and ABO-i KT and analyze the clinical outcome at 1 year.
Methods: Prospective observational study. Between June 2009 and December 2011 152 consecutive living-donor KT were performed: 128 ABO-c and 24 ABO-i. Desensitization Protocol ABO-i: Conditioning with rituximab, plasma exchange (PE) or immunoadsorption (IA) and immunoglobulins iv. Two PE or IA were performed after KT. We analyzed age, sex, PRA, donor-specific antibodies and renal complications after KT. Indication biopsies were performed if patient showed deterioration of renal function.
Results: At 3 and 12 months PKB were offered to all patients and performed in 89/17 ABO-c/ABO-i patients. Fifty-nine adequate biopsy samples were obtained (≥10 glomeruli and arteries ≥2) to perform complete Banff score: ABO-c /ABO-i 48/11. There were no differences in the clinical characteristics of donor/recipient between groups. At 1 year ABO-c/ABO-i creatinine was 1.36 (1.14–1.63) vs. 1.2 (1.3–1.5) mg/dl (pNS), proteinuria 209 (120–412) vs. 208 (132–290) mg/24 h (pNS). Clinical biopsy-proven and treated acute rejection during the first year ABO-c/ABO-i: cellular rejection 12.6%/8.4% (pNS), AMR 3.9%/8.3% (pNS), Borderline 3.1%/12.5% ($p = 0.004$). In PKB there were no differences between groups except C4d positivity in the ABO-I group at 3 months and 1 year ($p < 0.001$).
Conclusion: ABO-i renal allografts show a higher incidence of borderline clinical rejection during the first year. Moreover, diffuse C4d+ staining in the absence of clinical antibody mediated-rejection was observed.

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O012

DROP-OUTS IN ABO-INCOMPATIBLE (ABOI) LIVING-DONOR RENAL TRANSPLANTATION MAY BE PREVENTED – A SINGLE CENTER EXPERIENCE

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Background: ABOi living-donor renal transplantation using a single dose of rituximab and blood-group specific immunoadsorption (IA) for desensitization, has become an established treatment modality to increase the donor pool and lower patient mortality. However, 10–20% of patients are high responders and doe not reach the target anti-ABO titers enabling successful ABOi transplantation.

Methods: We retrospectively analyzed 30 patients who were desensitized for ABOi living-donor renal transplantation (rituximab 375 mg/m^2, basiliximab (ATG $n = 1$), tacrolimus/mycophenolic acid/ tacrolimus/prednisolone, IA and IVIG).

Results: Donor-specific anti-ABOi titers were 1:128 before desensitization (median; >1:128: 33% of patients). All patients reached the target of 1:8 pretransplant, using repeated administration of rituximab in high-responder patients (2, 3 and 4 rituximab infusions, respectively). One patient could not be transplanted because of a posterior reversible encephalopathy syndrome. Twenty-nine of the 30 patients were successfully transplanted (1-year graft survival 95%, serum creatinine at discharge 1.5 $\pm$ 0.1 mg/dl, 1.8 $\pm$ 0.2 mg/dl at last follow-up [25 $\pm$ 3 months]). The number of pre transplant IA treatments was significantly related to the pretreatment anti-ABOi titers ($r = 0.80$, $p < 0.0005$) as was the number of rituximab infusions ($r = 0.82$, $p < 0.0005$). In a randomized prospective trial of ABOi compared to blood group compatible renal transplants, preliminary data of our study indicate an increased risk of BK viremia after rituximab treatment (7/20 (35%) vs. 3/36 (8%), $p = 0.025$). Repeated rituximab infusions, however, did not increase the risk of BK viremia compared with a single infusion ($p = 0.470$).

Conclusion: Our data suggest that repeated rituximab infusions in high-responder patients may enable successful ABOi LD renal transplantation without increasing the risk of BK viremia.

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OS03- INFECTIONS IN LIVER TRANSPLANTION

O013 RELATIONSHIP BETWEEN LIVER GRAFT STEATOSIS, VIRAL RECURRENCE AND POST-LIVER TRANSPLANTATION SURVIVAL IN HEPATITIS C VIRUS POSITIVE RECIPIENTS

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Background: The use of steatotic grafts is increasing to expand the donor pool, but results in HCV-positive recipients remain controversial. We analyzed the effect of graft steatosis on overall outcomes and viral recurrence after liver transplantation (LT) in HCV-positive recipients.
Methods: We evaluated 1021 LTs performed in our center from 10/2002 to 12/2010. Recipients were divided in HCV-negative (n = 586, 57%) and HCV-positive (n = 435, 43%). A blind reassessment of the intraoperative biopsies was performed by a single expert pathologist, and liver graft macrovesicular steatosis was categorized in: absent (n = 509), <10% (n = 317), between 10% and 30% (n = 166), >30% (n = 29).
Results: A strong association was seen between graft steatosis and early allograft dysfunction (p = 0.0001). Viral recurrence was not significantly related to steatosis, neither for timing nor for gravity. Graft survival was significantly worsened by steatosis>30% in overall (p = 0.0424) and in HCV-positive (p = 0.0012) population, while no differences were observed for patient survival. In Cox-model, steatosis >30%, donor age >60 years and recipient HCV-positivity had a strong influence on graft early function and long-term survival.
Conclusions: Association between factors which have a negative impact on graft outcomes should be avoided. Therefore, use of grafts with steatosis >30% is not advisable in HCV-positive recipients.

O014 ANTIVIRAL TREATMENT FOR HEPATITIS B VIRUS RECURRENCE FOLLOWING LIVER TRANSPLANTATION

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Background: The purpose of this study was to identify the factors associated with the recurrence of hepatitis B virus (HBV) following liver transplantation (LT) for HBV-related disease and to recognize the outcome of treatment for HBV recurrence with oral nucleos(t)ide analogues.
Methods/Materials: A total of 667 liver transplantations were done for HBsAg-positive adult patients in our institute from 1996 to 2010. HBV prophylaxis was done by hepatits B immunoglobulin (HBIG) monotherapy or HBIG and entecavir combination therapy. The medical records of 553 LT recipients included in this study were retrospectively analyzed.
Results: There were 63 cases (11.4%) of HBV recurrences during a median follow-up of 51 months. The median time to HBV recurrence was 22 months. A preoperative HBV DNA load of more than 105 IU/ml, HBIG monotherapy and hepatocellular carcinoma in the explant liver were independent risk factors for HBV recurrence following LT in multivariate analysis. Patients with HBV recurrence had significantly reduced survival compared to those who remained HBsAg-negative. Patient survival at 10 years was 54.2% for HBV recurrent patients and 95.1% for patients without HBV recurrence. Among patients with HBV recurrence, HBsAg seroclearance was achieved after antiviral therapy in 23 patients (35.4%), but HBsAg seroclearance did not affect survival in these patients after the recurrence of HBV (p = 0.14). The recurrence of HBV led to deterioration of graft function and graft failure in nine cases. There were six cases of graft failure due to HBV recurrence.
Conclusion: The recurrence of HBV following LT resulted in reduced survival compared to patients remaining HBsAg-negative. Thus, HBV recurrence following LT should be prevented with a strict management policy to lower pretransplant HBV viremia and an active post-transplant HBV prophylaxis regimen consisting of HBIG and an antiviral nucleos(t)ide analogue.

O015 JAK INHIBITOR TOFACITINIB INTERFERES WITH INTERFERON-MEDIATED INHIBITION OF HEPATITIS C REPLICATION

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Background: With end stage liver disease due to chronic hepatitis C virus (HCV) infection being a leading indication for liver transplantation, management and treatment of recurrent disease still remains a major clinical challenge. As immunosuppressants may contribute to the aggravated course of recurrence and resistance to antiviral therapy, there is an urgent need to improve immunosuppression in HCV infected recipients. Tofacitinib, a JAK3 inhibitor, was developed as a new class of immunosuppression for use in organ transplantation. The aim of our study is to investigate the effect of tofacitinib on HCV replication and antiviral activity of interferon-α (IFN-α).
Method: The Huh7 hepatoma cell line stably transfected with the non-structural coding sequence of HCV coupled to a luciferase reporter (Huh7-ET) was used as a HCV replication model. Huh7 cells, stably transfected with a luciferase gene controlled by an interferon response element (Huh7-ISRE-luc), were used to investigate effects of tofacitinib on IFN-α signal transduction.
Results: Though selected for JAK3 inhibition, tofacitinib completely inhibited the JAK1 mediated IFN-α receptor signalling in a dose dependent manner. At the highest dose of tofacitinib (1000 ng/ml), complete inhibition of IFN-α stimulated luciferase activity in Huh7-ISRE-luc was observed and 100 ng/ml tofacitinib reduced luciferase by 50%. Treatment of Huh7-ET cells with 10 U/ml IFN-α inhibits HCV replication, but this IFN-α mediated inhibition was fully abrogated by tofacitinib in a dose dependent way. Moreover, tofacitinib treatment abolished the induction of anti-viral interferon stimulated genes.
Conclusion: Although tofacitinib was developed as a specific inhibitor of JAK3, our study shows that tofacitinib effectively inhibits IFN-α stimulated JAK1 signalling and interferes with IFN-α mediated inhibition of HCV. These observations may explain the higher incidence of viral infections found in patients treated with tofacitinib.

O016 HEPATITIS C RECURRENCE AFTER LIVER TRANSPLANTATION: MAINTENANCE THERAPY WITH PEGYLATED INTERFERON IN NONRESPONDERS TO STANDARD THERAPY SLOWS THE DISEASE PROGRESSION AND IMPROVES SURVIVAL

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Background: Long-term maintenance therapy with low-dose pegylated interferon (PegIFN) in HCV-infected liver transplant (LT) recipients has been scarcely evaluated. We aimed to evaluate the clinical effect of long-term PegIFN in recurrent hepatitis C patients without virological response but with biochemical response (BR) to standard antiviral therapy.
Methods: One hundred and thirty-nine patients with a severe hepatitis C recurrence were considered. Among them, 89 patients received antiviral therapy with PegIFN and ribavirin and were divided into three groups: (i) patients who achieved a sustained virological response (SVR, n = 23); (ii) non virological responders to therapy (NR, n = 47); and (iii) non virological responders who achieved a BR and received maintenance therapy with Peg-IFN (NR-M, n = 19). Patients in the NR-M group were treated with Peg-IFN alfa-2b 50 μg/week for a median time of 20 months (range 2–45). BR was defined as a decrease ≥75% or normalization in transaminases levels during standard therapy.
Results: In patients who achieved SVR the hepatic venous pressure gradient (HVPG) improved or remained stable in 95% of cases and graft survival 5 years after treatment was 100%. HVPG improved or remained stable 3 years after completing antiviral therapy in 82% of patients in the NR-M group compared to only 31% of patients in the NR group (p = 0.003). Graft survival 5 years after antiviral therapy was 59% in the NR-M group versus 40% in the NR group (p = 0.012). One patient developed a *de novo* autoimmune hepatitis during maintenance therapy; other adverse events included asthenia and neutropenia.
Conclusion: Long-term maintenance therapy with PegIFN in HCV-infected LT recipients not responding to standard therapy who achieve a BR is associated with a stabilization in recurrent disease and a significant increase in survival; thus, it may be a bridging strategy for patients while awaiting new direct antiviral agents.

O017 LIVER DONOR RIBAVIRIN TRANSPORTER GENE POLYMORPHISM INFLUENCES VIRAL KINETICS AND REPRESENTS A NOVEL PRETREATMENT PREDICTOR OF VIROLOGIC RESPONSE IN LIVER TRANSPLANTED PATIENTS WITH HEPATITIS C VIRUS RECURRENCE: A PROOF OF CONCEPT

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Background and Aims: Ribavirin (RBV) is a synthetic guanosine analogue that has proven to be necessary for maximing sustained virological response (SVR) rate in HCV patients also in the post transplant setting. Most of RBV

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proposed anti viral mechanisms require RBV import into cells via the equilibrative nucleoside transporter 1 (ENT-1) and A the inhibition of ENT1-mediated ribavirin uptake significantly attenuated its A the antiviral activity. The aim of our study was to determine whether donor hepatic ENT-1 could influence the probability of treatment response compared with other baseline and host genetic factors.

Patients and Methods: LT patients with HCV recurrence treated with RBV and pegylated interferon (PEG-IFN) for 48 weeks were studied for the following polymorphism (SNP): rs12979860 for Il28B gene, and rs760370 for ENT1 gene. A sample of donor liver tissue was snap frozen at the time of transplantation (before reperfusion). Ribavirin plasma levels were evalutated by high pressure liquid chromatography (HPLC).

Results: Thirty-two patients were treated with PEG-IFN and RBV for 48 weeks. The main baseline characteristics of the patients are shown in IL-28B polymorphism distribution was omogeneus across the ENT-1 variants. Achievement of RVR and SVR was more frequent among ENT-1 GG carriers than in AA/AG (figure 1). No difference between AA versus AG carriers was found. In GG patients the decline in HCV- RNA during the first weeks of therapy was significantly higher than in AA/AG carriers. The liver donor ENT-1 polymorfism did not correlate with RBV plasma concentrations. Indipendent predictors for SVR were liver ENT-1 GG genotype and RBV concentrarion >2 ng/ml.

Conclusions: Subjects with a donor hepatic polymorfism GG at rs760370 showed an higher SVR than the AA/AG carried. It seems reasonable that both the Ribavirin intra-hepatic via ENT-1 concentration and Ribavirin plasma concentration indipently contribute to virological response.

O018 RESULTS OF LIVER TRANSPLANTATION IN THE TREATMENT OF HEPATIC ALVEOLAR ECHINOCOCCOSIS

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Background: Alveolar echinococcosis (AE) is a rare disease caused by the Echinococcus multilocularis larvae growing in the liver. This observation suggests that liver transplantation (LTx) may be indicated when other therapies become ineffective and no extrahepatic lesions are founded. The purpose of this study was to assess the value and timing of LTx in the treatment of AE of the liver.

Material and Methods: A retrospective study was carried out, including all cases of LTx for AE performed in our Department between 2000 and 2012. There were 20 cases AE (14M, 6F) in middle age of 42 $\pm$ 8.2. In 16 cases (80%) LTx was a priori decided to be the method of management due to the advancement of the disease preventing radical surgery. In four cases (20%) prior surgery led to the LTx (one extensive liver resection, one unresectable alveococcosis recurrency within the liver and two cases of diagnostic laparoscopy). Ten classical and 10 piggy-back LTx from cadaveric donor were performed. All of the patients received additionally albendazol, prior to and after LTx – mean period 2 years.

Results: Complications were observed in six cases (30%) – wound infection in four cases, pneumonia in one and in one transient renal failure requiring dialysotherapy. Two patients (10%) died within the 1st post-LTx year – 1 due to sepsis leading to multiorgan failure. Second patient died 7 months after LTx due to sepsis after small bowel resection in the course of mechanical occlusion. In group of five patients appeared immunological exponents of infection recurrence in ELISA test, without changes in imaging examinations, after average 24 $\pm$ 12 months. Actuarial survival rate after LTx was 90% at 1 year, 85% at 5, and 75% at 10 year.

Conclusion: Echinococcosis multilocularis of the liver in late stage can be considered as one of the indications of LTx, especially when other therapies are scarce and ineffective. In those cases LTx may be an appropriate option of radical treatment with excellent long term survival.

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OS04-ALLORECOGNITION

O019 T-CELL HELP DETERMINES MODE OF ALLOANTIBODY-MEDIATED REJECTION

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Introduction: What determines kinetics of humoral rejection remains unclear; here we examine the role of CD4 T cell help.
Methods: BALB/c hearts were transplanted into T cell-deficient (TCR−/−) or control Rag2−/− BL/6 recipients. T cell help was provided by transfer of either 105 or 103 TCR-transgenic TCR75 CD4 T cells that recognise donor MHC class I H2-Kd antigen as processed peptide via the indirect pathway.
Results: TCR−/− recipients reconstituted with 105 TCR75 T cells rejected BALB/c hearts acutely (Median Survial Time [MST] 9 days, $n = 10$), with high anti-Kd alloantibody titres (Fig. 1). While this antibody production was associated with a splenic Germinal Centre (GC) reaction, GC responses were not detectable until after rejection, suggesting that strong extrafollicular responses driven by high helper T cell numbers are sufficient to mediate acute humoral rejection. Reconstitution with 103 CD4 T cells produced lower alloantibody titres, which increased gradually, with the development of progressive allograft vasculopathy and eventual graft failure (MST 50 days, $n = 8$) (Fig. 1). The alloantibody response matched the development of splenic GCs, suggesting that small helper T cell numbers generate weak extrafollicular responses, but can nevertheless support the development of late GC responses that can effect chronic humoral rejection. Rejection in these recipients was confirmed to be antibody-mediated, as endothelial complement deposition was evident and because heart grafts survived indefinitely, without complement deposition and with minimal vasculopathy, in T cell-reconstituted Rag2−/− recipients. In addition, graft rejection in the Rag2−/− recipients was restored following passive transfer of immune serum from acutely rejecting TCR−/− recipients (Fig. 1).
Discussion: The development of acute or chronic humoral rejection is determined by magnitude of the alloantibody response; this in turn is dependent on availability of T cell help.

O020 INDIRECT CD4 T CELL ALLORECOGNITION OF MHC CLASS II ALLOANTIGEN IS LIMITED BY ADAPTIVE IMMUNE KILLING OF DONOR DCS

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We have previously described a partially-mismatched [bm12.Kd.IE (IAbm12, IEd, Kd, Kb, Db) to BL\6] model of chronic rejection, demonstrating that indirect T cell recognition of donor MHC class II occurs transiently. This work aims to identify factors limiting this response.

Indirect CD4 T cell recognition of donor MHC I and II was assessed by quantifying proliferation of TCR-transgenic TCR75 (H2-Kd specific) and TEa (I-E specific) CD4 T cells, adoptively transferred day 0 or 28 following transplantation of bm12.Kd.IE hearts into either wild-type or RAG2KO BL/6 recipients. The role of donor DCs in priming indirect allorecognition was assessed by incorporating CD11c.DTR donors, enabling ablation of DCs by diphtheria toxin, and by adoptive transfer of cultured bone-marrow derived dendritic cells (BMDCs).

Extensive proliferation of TCR75 CD4 T cells was observed in heart-grafted recipients both early and late. TEa proliferation was detectable only immediately after transplant. We hypothesised that early termination of the class II response reflected rapid loss of donor DCs, as is the case for direct allorecognition; in support, donor DC depletion attenuated the indirect class II response. Donor DCs were not killed by NK cells, because bm12.Kd.IE cells survive long-term in RAG2KO recipients. Equally, late anti-class II indirect responses in RAG2KO recipients were detectable, albeit weaker than the response immediately following transplantation, suggesting that donor DCs are instead lost to natural senescence and adaptive immune killing. Critically, transfer of donor BMDCs into RAG2KO recipients 28 days after heart grafting completely restored late TEa responses, but this was not seen in WT recipients, presumably because rapid killing of donor DCs by primed adaptive alloimmunity prevents antigen presentation.

Class II indirect allorecognition terminates early, because donor DCs, the major source of MHC II alloantigen, are depleted rapidly by adaptive immune responses.

O021 A NOVEL PATHWAY FOR CD8+ T CELL ACTIVATION BY DONOR DERIVED NON-HAEMATOPOIETIC CELLS LEADING TO ACUTE ALLOGRAFT REJECTION

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Background: The late activation of CD8+ T-cells after tranplantation remains poorly understood. Here we examine the hypothesis that CD8+ T cell activation by graft parenchymal cells requires acquisition and re-presentation of intact MHC class I alloantigen by recipient antigen presenting cells (APCs) within SLT.
Methods/Materials: Balb/c cardiac donors were lethally irradiated and treated with depleting antibodies ensuring complete eradication of HPCs. These HPC-depleted Balb/c (Balb/cHPC-) cardiac allografts were transplanted into: (i) 2C transgenic mice (monoclonal population of CD8+ T cells against Ld MHC class I); (ii) Splenectomised aly/aly (aly/alyspl) mice with adoptive transfer of 2C CD8+ T cells; (iii) CD11c-DTR transgenic mice.
Results: 2C transgenic mice rejected Balb/cHPC- grafts as rapidly as non-depleted Balb/c grafts (MST = 5 days vs. 4 days) suggesting an effective mechanism for parenchymal cell driven CD8+ T cell mediated rejection. Balb/cHPC- allografts showed prolonged survival (>50 days) in aly/alyspl mice given 2C CD8+ T cells, whereas in non-splenectomised controls all grafts rejected (MST =17 days; $p = 0.01$) suggesting an essential role for SLT. Furthermore, when aly/alyspl mice were given activated 2C CD8+ T cells (from 2C recipient of Balb/c cardiac graft) they rapidly rejected Balb/cHPC- allografts (MST = 7 days; $p = 0.01$). To examine whether recipient DCs were required to present to CD8+ T cells within SLT, CD11c-DTR mice given 2C CD8+ T cells were transplanted with Balb/cHPC- allografts. When also treated with diphtheria toxin to deplete host DCs they demonstrated delayed rejection kinetics compared with untreated controls (MST = 26 days vs. 16 days; $p = 0.02$).
Conclusions: These results indicate that allorecognition of graft parenchymal cells represents an important mechanism of CD8+ T cell mediated rejection. They support the role of a novel pathway in which recipient DCs acquire intact MHC class I from donor parenchymal cells and present to CD8+ T cells in SLT.

O022 A NOVEL TRANSGENIC MOUSE MODEL TO STUDY IMMUNE RESPONSES TOWARDS NON-MHC HISTOCOMPATIBILITY ANTIGENS

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Background: Recently, the clinical relevance of minor (i.e. non-MHC) antigens in transplantation has been increasingly recognized. Therefore we made use of a novel new transgenic mouse, expressing the well-characterized antigen Phl p 5 ubiquitously on the cell-surface, to analyze antigen recognition, rejection kinetics and humoral responses in this non-MHC mismatched model.
Methods: Tail-skin of Phl p 5-transgenic Balb/c mice was grafted onto naïve Balb/c mice ($n = 18$). To analyze T mechanisms some recipients received either depleting anti-CD4 ($n = 5$), anti-CD8 ($n = 5$) antibodies. Furthermore heart grafts of Phl p 5-transgenic mice were transplanted into naïve Balb/c mice ($n = 4$). Subsequently, kinetics of the rejection were assessed by visual inspection and histological analysis of paraffin sections. Additionally Phl p 5-specific antibody production was analyzed via ELISA.
Results: Surprisingly Phl p 5-transgenic skin and cardiac grafts were rejected as promptly as MHC-mismatched grafts (median graft survival = 10 days). Additionally the rejection was accompanied by strong Phl p 5-specific antibody responses including IgE and IgG isotypes (day 10). Furthermore graft survival in CD8+-cell-depleted recipients (that is dependent predominantly on CD4 cells) was not altered while skin graft survival was significantly prolonged in CD4+-cell-depleted mice, but grafts were eventually rejected (with a median graft survival of 20 days) (depletion was verified in blood via FACS).
Conclusions: Our data show that minor antigen-mismatched skin grafts can be rejected – albeit it with a reduced tempo – in the absence of CD4+ T cells, presumably through CD8 T cells. Additionally antigen-specific IgE develops upon graft rejection. Taken together, this novel model represents a useful tool for studying rejection-mediated mechanisms caused by non-MHC antigens.

O023 COSTIMULATION BLOCKADE-RESISTANT DONOR BONE MARROW REJECTION IS TRIGGERED BY DONOR CD4 T CELLS THROUGH BYSTANDER ACTIVATION REQUIRING INTERLEUKIN 6

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Background: Donor T cells have pleiotropic effects in allogeneic bone marrow transplantation (BMT). Co-transplanting high doses of donor T cells with donor BM causes rejection of donor BM despite costimulation-blockade. In

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the present study we investigate the molecular mechanisms responsible for this seemingly paradoxical phenomenon.
Methods: Recipients (B6) were treated with 3 Gy TBI and received approximately 20 × 106 unseparated Balb/c BMC and costimulation-blockers (CB: anti-CD154mAb, CTLA4Ig). 30 × 106 CD4 T cells (MACS isolation) from Balb/c, CB6F1 (Balb/cxB6), irradiated Balb/c, C3H or B6 were co-transplanted. Groups either received anti-IL-6, anti-IFN-y, anti-IL-17A, anti-LFA1 mAbs or rapamycin. Multilineage chimerism was followed by flow cytometry.
Results: Co-transplantation of 30 × 106 CD4 T cells but not CD8 T cells triggered rapid BM rejection of donor BM under CB within 1 week in an otherwise successful protocol (0/13 vs. 17/20 chimeras, $p < 0.001$). The levels of IL-6, IFN-y, IL-17A ($p < 0.05$) and TGF-ß were found to be higher in mice treated with additional donor T cells. The neutralization of IL-6, but not of IFN-y or IL-17A abrogated the detrimental effect of donor T cells (5/7 vs. 0/5 and 1/6 chimeras; $p < 0.05$). The injection of CB6F1, irradiated Balb/c and recipient (B6) T cells allowed chimerism induction (5/6, 4/5 and 6/6 vs. 0/4 chimeras with Balb/c T cells; $p < 0.05$) whereas C3H T cells led to BM rejection (0/5 vs. 9/9 chimeras BMT, $p < 0.001$). The additional treatment with rapamycin or anti-LFA1 overcame the negative effect of donor T cell injection (5/5 and 6/6 vs. 0/4 chimeras; $p < 0.01$).
Conclusion: The abrogation of BM engraftment through co-transplantation of donor CD4 T cells depends on IL6 and the recognition of the recipient as allogeneic by the transferred T cells. Neutralisation of IL-6, rapamycin and anti-LFA1 overcome the effect of co-transplanted donor CD4 T cells and offer potential targets for therapeutic intervention in CB-resistant rejection.

O024 GERMINAL CENTRE RESPONSES DRIVE EPITOPE DIVERSIFICATION IN A MURINE MODEL OF CHRONIC ALLOGRAFT VASCULOPATHY

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Background: Autoantibody following organ transplantation is increasingly correlated with poor graft outcome. We have reported that in a MHC class II mismatched mouse model, GVH recognition by donor CD4 T cells is critical for initiating autoimmunity, but the response is maintained by recipient CD4 T cells.Here we analyse the role of the recipient population of CD4 T cells in greater detail.
Methods: Heart grafts from either wild type (WT) or T cell deficient (TCRKO) bm12 donors were transplanted into either WT or TCRKO B6 mice. Germinal centres were identified on immunofluorescence staining of splenic sections as peanut agglutinin (PNA) and Ly77 (GL7) positive B cell follicles and quantified by calculating percentage of secondary follicles to total follicles. Autoantibody responses were analysed by Hep-2 indirect immunofluorescence staining. Diversification of this response was examined by anti-vimentin ELISA at early and late time points. Chronic allograft vasculopathy (CAV) was assessed on elastin van Gieson-stained paraffin sections by degree of percentage luminal stenosis.
Results and Conclusion: Donor and recipient CD4 T cells are essential for progression of allograft vasculopathy, most likely because of their cooperation to promote GC autoantibody responses. These diversify to target additional, and potentially damaging, graft-related autoantigens.

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OS05-INFECTIONS I

O025 CYTOMEGALOVIRUS (CMV) PREVENTION STRATEGIES IN SEROPOSITIVE KIDNEY TRANSPLANT (KT) RECIPIENTS RECEIVING ANTILYMPHOCYTE INDUCTION THERAPIES: DATA FROM A MULTICENTER COHORT STUDY (THE OPERA STUDY)

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Background: Induction therapy with antilymphocyte antibodies increases the risk of CMV reactivation in seropositive KT recipients. The optimal duration of universal prophylaxis with valganciclovir (VGCV) in this population remains to be assessed.
Methods: From May 2011 to April 2012 a total of 287 CMV-seropositive KT recipients were included in a multicenter cohort study conducted in 21 Spanish centers. The minimum follow-up period was 6 months. The primary study outcome was the incidence of CMV disease (viral syndrome or tissue-invasive disease) at months 3 and 6. A number of pre-transplant, perioperative, and post-transplant variables were prospectively recorded. Monitoring of CMV infection was performed according to local practice at each institution. The incidence of CMV disease was analyzed in those patients who underwent induction therapy with antilymphocyte antibody preparations according to the type of prevention strategy.
Results: Seventy patients (24.4% of the overall cohort) received antilymphocyte induction therapy (either antithymocyte [68 patients] or antilymphocyte globulin [two patients]). The CMV prevention strategies consisted of universal prophylaxis in 63 patients (90.0%), preemptive therapy in 6 (8.6%), and no specific approach in one (1.4%). VGCV prophylaxis was administered for <100 (14 patients), 100 (41 patients) or 200 days (eight patients). Cumulative incidences of CMV disease at months 3 and 6 were 0.0% and 1.4% (one patient), respectively. According to the duration of VGCV prophylaxis the cumulative incidences of CMV disease at month 6 were 7.1% (<100 days) and 0.0% (≥100 days) (p-value = 0.222).
Conclusions: Universal prophylaxis with VGCV for ≥100 days, compared to shorter regimens, was associated with a lower incidence of CMV disease in seropositive KT recipients receiving antilymphocyte induction therapy.

O026 RANDOMIZED COMPARISON OF VALGANCICLOVIR AND VALACYCLOVIR FOR CYTOMEGALOVIRUS PROPHYLAXIS

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Background: Valganciclovir is the most common drug used for cytomegalovirus (CMV) prophylaxis. Also the efficacy of high-dose valacyclovir was documented in randomized trials.
Methods: A total of 119 renal transplant recipients at risk for CMV were randomized to 3-month prophylaxis either with valganciclovir (900 mg/day, $n = 61$) or valacyclovir (8 g/day, $n = 58$). The primary outcomes were the incidences of CMV viremia and biopsy-proven acute rejection (BPAR) at 12 months.
Results: The 12-month incidence of CMV viremia was comparable (30% vs. 42%, p = 0.182) in the valganciclovir and valacyclovir groups with similar median peak viral load. The incidence of CMV disease was low (5% vs. 2%, p = 0.372). A lower rate of BPAR during 12 months was observed in valganciclovir treated patients (16% vs. 29%, p = 0.072).
Conclusion: Compared with high-dose valacyclovir, valganciclovir prophylaxis shows a trend toward less BPAR in spite of similar rates of CMV viremia and disease.

O027 CAN CYTOMEGALOVIRUS INDUCE TRANSPLANT VASCULAR SCLEROSIS IN RENAL ALLOGRAFT?

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Introduction: Cytomegalovirus (CMV) impact graft outcome through its direct and indirect effects. Experimental models have demonstrated the importance of CMV interaction with the endothelial interface through the induction of an angiogenic response. In clinical setting, an association has been shown between CMV infection and cardiac vasculopathy. The concept of CMV-induced transplant vascular sclerosis (TVS) has thus emerged and may participate to chronic renal allograft injury. However, data from kidney transplant recipients (KTR) are still scarce. We then studied association between CMV infection prior indication biopsies and fibrous intimal thickening (cv > 0) in 87 kidney transplant recipients (KTR).
Methodology: Previouly reported risk factors of cv > 0 lesions (age of the donor (D. age), age of the KTR, ischemia time, presence of DSA, blood pressure at the biopsy, immunosuppressive regimen, e-GFR) and CMV infection, were retrospectively collected for each patient. Risk factors of fibrous intimal thickening were searched using multivariate analysis.
Results: Of 22/32 CMV + KTR (69%) exhibited cv > 0 lesions in comparison with 25/55 (45%) in CMV-KTR, p = 0.04. Cv > 0 lesions were associated with a lower e-GFR at biopsy. Regarding the major impact of D. age on cv > 0 lesions and the absence of implantation biopsy, we then considered only KTR with a D. age < 60 ($N = 56$): cv > 0 lesions were still higher in CMV + KTR than in CMV-KTR (72% vs. 28%, p = 0.01). D. age (OR 2.1[1.1–3.8] for each decade, p = 0.02) and prior CMV infection (OR 5.3[1.1–26.3], p = 0.04) were the only factors associated with cv > 0 lesions in multivariate analysis applied to these patients.
Conclusion: We report for the first time an association between CMV infection prior biopsy and fibrous intimal thickening in a cohort of KTR who underwent a biopsy for cause, suggesting cv > 0 lesions could be one of the picture of CMV induced TVS in renal allograft.

O028 GAMMA DELTA T CELLS INTO CMV INFECTION: AN EARLIER MARKER OF ANTI-VIRAL DRUG RESISTANCE

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CMV infection remains a major issue in kidney transplant recipients because of its relationship with opportunistic infections, rejection, graft survival, lymphoproliferative disorders, and actually with increased mortality risk. Developing anti-CMV drug resistance further increases this risk. Our group have shown that gamma-delta T (γδT) cells were involved in CMV infection control. Immune status, CMV infection and drug resistance emergence interplay remain unclear. In this study, the objective was to assess how the immune status impact on CMV infection and resistance emergence in kidney transplant recipient. The main objective was to study the evolution of CD8 T cells and γδT cells before and after CMV infection. Next, we would identify an immunological status that possibly predict CMV resolution and, anti-CMV drug resistance occurrence. One hundred and seventy four D+R− patients underwent kidney transplantation between January 2003 and November 2009. Among them, 94 made CMV infection. We observed CD8 T cells and γδT cells expansion after CMV infection. Time of γδT cells expansion was correlated with CMV infection recovery, excepted for patients with antiviral drug resistance (p = 0.0003). Moreover, early γδT cells expansion was associated with a shorter CMV infection, all patients with anti-CMV drug resistance had delayed γδT cells expansion (p = 0.0003). Time of gamma-delta T cell expansion seems to be related with CMV infection resolution. Delayed γδT cells expansion is associated with a longer CMV infection and all patients with antiviral drug resistance had delayed γT cells expansion. Mean, resistance was diagnosed after 115 days of virus replication whereas delayed γδT cells expansion was defined as 70 days. So γδT cells may be useful to predict CMV infection resolution and could be used as a monitoring tool but also as an ealier marker of antiviral drug resistance in case of delayed expansion.

O029 EVIDENCE FOR HUMAN BETA-PAPILLOMAVIRUS (-HPV) INFECTION IN SKIN TUMOURS FROM A COHORT OF KIDNEY TRANSPLANT RECIPIENTS

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Background: Non-melanoma skin cancer (NMSC) is a common malignancy in kidney transplant recipients (KTR), with a standardized incidence rate (SIR) >20 in Italy. Strong evidence supports the role of β-HPV infection in skin cancer development in KTRs. However very few studies addressed whether the viruses detected in these circumstances are really localized to malignant cells and transcriptionally active, the confirmation of which would support the carcinogenic role of β-HPV.
Methods: One hundred patients who underwent kidney transplantation at our institution from 1976 to 2011 were included in this study. Out of these, 17 have developed skin lesions, 10 of them have had multiple tumours (range 2–14), for a total of 79 FFPE excisional biopsies including: 32 Basal Cell Carcinoma, 18 Actinic Keratosis, 13 Squamous Cell Carcinoma, 8 Seborrheic Keratosis, 7 Kerathoacantoma and 2 Bowen's disease. HPV DNA detection was performed

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by PM-PCR RHA method. To visualize viral replication/expression, we used FISH to identify sites of viral genome amplification, along with the immunodetection of key viral and cellular proteins, including E4, L1 and MCM.
Results: PCR analysis showed that 68 out of the 79 lesions were β-HPV -positive. The most frequent genotypes were HPV 5, observed in 46 lesions, followed by HPV 8 and HPV 38 in 17 and 12 lesions, respectively. All the tissue samples were probed for the viral markers. Four AK, 3 BCC, 1 SK, 1 SCC and 1 Bowen's disease from six different patients showed expression of cytoplasmic E4 overlapping with FISH-positive nuclei and L1 in the more superficial layers.
Conclusions: Here, we demonstrate that β-HPV transcription is occurring at site of skin transformation in the KTR setting and may therefore be involved in the process of skin carcinogenesis. Virus activation in sun-exposed body sites may cause UV exposures to be more deleterious to host cell, potentially increasing the likelihood that these cells become cancerous.

O030 RAPAMYCIN PROMOTES HEPATITIS C AND E VIRUSES INFECTION INDEPENDENT OF AUTOPHAGY

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Background: Immunosuppressive medication is known to impact the progression of Hepatitis C Virus (HCV) recurrence after liver transplantation and de novo Hepatitis E Virus (HEV) infection in organ transplant recipients. We aim to investigate the direct effect of rapamycin on HCV and HEV infection in cell culture models.
Methods/Materials: Both subgenomic HCV and HEV models containing luciferase reporter genes and the full-length HCV and HEV infectious cell culture models (based on human hepatoma Huh7 cell line) were used. Cells were treated with clinically relevant doses of rapamycin (1–1000 ng/ml). Viral replication or infection was analyzed by luciferase activity or qRT-PCR.
Results: Rapamycin treatment dose dependently increased subgenomic HCV replication (2.3-fold increased luciferase activity at 1000 ng/ml, $p < 0.01$). This increase was also seen in the HCV infectious model. Similar effects of rapamycin were found for HEV replication (2.7-fold increased luciferase at 1000 ng/ml, $p < 0.01$). In accordance, HEV RNA was elevated by 2.6-fold ($p < 0.01$) after treatment of 100 ng/ml rapamycin in the infectious model for 48 h. Treatment of rapamycin for only 4 h during inoculation of naive Huh7 cells with infectious HEV particles increased cellular HEV RNA by 4.5-fold, suggesting enhancement of viral entry by rapamycin. Although rapamycin is a known autophagy inducer and autophagy plays important role in viral infection, treatment of rapamycin did not induce clear autophagy formation in either naive or HEV infected Huh7 cells. Thus, it excluded the involvement of autophagy in the pro-viral action of rapamycin.
Conclusion: Rapamycin enhances both HCV and HEV infection. These findings bear relevance for managing immunosuppression for HCV or HEV infected organ transplant patients.

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OS06-ALLOCATION

O031 WHICH PREDICTION SCORE SYSTEM IS MOST USEFUL IN HIGH RISK LIVER TRANSPLANT CANDIDATES? DOWN CONTROL OF MELD ALLOCATION BY THE BAR SCORE

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Background: Liver transplantation in severe sick candidates has become a major challenge in face of severe organ shortage and MELD allocation. In addition, outcome decrease and allocation scandals in some countries have triggered discussions for new allocation rules. However, cutoff thresholds defining futile outcome in extreme sick patients have been controversially reported. We focused on high MELD candidates and tested four international known and validated prediction scores, e.g. SOFT, DRI, D-MELD and BAR score.
Methods: Of 4196 patients were recorded in the UNOS database between 2002 and 2010 with a lab MELD above 35 (median lab MELD 40, IQR 38–43). Of those, 3507 cases (84%) were not ventilated before transplantation, while 689 patients (16%) needed respirator support. Published thresholds of each prediction score system were used for outcome discrimination (SOFT > 15, D-MELD > 1600, DRI > 1.8, BAR > 18). Survival was stratified by Cox regression analysis.
Results: First, not ventilated high MELD candidates showed significant poor outcome at D-MELD > 1600 ($p = 0.008$) or at BAR > 18 ($p = 0.001$). Importantly, considering D-MELD > 1600 would exclude half of cases from transplant ($n = 1738/3507$) in contrast to BAR > 18, excluding only 13% of cases ($n = 455/3507$). SOFT score > 15 or DRI > 1.8 appeared not helpful for predicting decreased survival ($p = 0.095$, $p = 0.640$). Secondly, ventilated high MELD candidates with significant worse survival were only detectable by BAR score above 18 in two third of cases ($n = 456/689$, $p < 0.001$) with a high specificity of 98%. All other score systems failed to be useful (DRI, $p = 0.509$, D-MELD, $p = 0.242$, SOFT, $p = 0.152$).
Conclusions: Wasteful liver transplants must be avoided but recent score systems have major limitations to reliably detect poor outcome. The BAR score appears currently as the best model to identify those patients with unfavorable prognosis among high risk candidates. Adjustment of the MELD allocation by the BAR score could.

O032 HIGH MELD VERSUS HIGH DONOR AGE: LESSONS LEARNED COMPARING THE AMERICAN AND THE ITALIAN LIVER TRANSPLANT EXPERIENCES

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Background: A comparative analysis of donor-to-recipient match (D2Rm) between US and Italy has not been performed.
Materials and Methods: To investigate geographic peculiarities and differences in D2Rm, UNOS and Italian D-MELD databases (2002–2009) were merged. Pediatric cases, multi-organ Tx, SPLITs, living donor Tx, national share cases and DCDs were excluded. There were 36 795 cases (US = 31 569, from 137 Centers; ITALY = 5226 from 21 Centers). Donor age (X, IQR) was lower in US than in Italy (43, 25–55 vs. 56, 40–68), MELD was higher in US than in Italy (20, 14–28 vs. 15, 11–21). D-MELD was similar. Low D-MELD class (<338) was prevalent in Italy. High D-MELD class (>1628) was prevalent in US.
Results: Un-adjusted patient survival (PS) between US and Italy was similar. Long term predictors of PS at 6-year Cox regression were: Recipient age (Rage) 50–64 (HR 1.1, $p = 0.038$), Rage >64 (HR 1.6, $p < 0.001$), Ethnicity: caucasian versus afro-american (HR 0.9, $p < 0.001$), Acute liver failure (HR 1.8, $p = 0.001$), HCV (HR 1.5, $p < 0.001$), HBV (HR 0.8, $p = 0.003$), Cholestasis (HR 1.5, $p < 0.001$), Low D-MELD versus Intermediate D-MELD (HR 0.7, $p < 0.001$), High D-MELD versus Intermediate D-MELD (HR 1.8, $p < 0.001$), Portal thrombosis (HR 1.3, $p < 0.001$), Italy versus US (HR 0.9, $p = 0.007$); $\chi^2 = 934$. US versus Italy difference in adjusted PS was significant.
Discussion: D2Rm quantified by D-MELD remains a strong predictor of PS in both US and Italy. In Italy the utilization of extended criteria donor grafts is advanced leading to better adjusted survival figures in the way of a utility oriented model. Conversely, in US a larger number of severely decompensated pts receives treatment, following the principles of a urgency oriented model. Our results confirm that combination of two of the major detrimental outcome factors (high-MELD and high donor age), should be avoided, especially in HCV+.

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O033 ADOPTION OF A MELD-BASED ALLOCATION POLICY AT A NATIONAL LEVEL IN ARGENTINA SIGNIFICANTLY IMPROVED WAITLIST OUTCOMES

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Argentina was the first country after the US to introduce MELD for organ allocation in July 2005. Importantly, allocation by MELD in Argentina was instrumented in a single national waiting list (WL) with no center or regional allocation. Goal: to analyze WL outcomes and post-liver transplant (LT) survival in adult candidates before and after adoption of MELD allocation policy.
Methods: Data from all patients (pts) listed for LT over the last decade ($n = 3272$) was analyzed using the national database of INCUCAI. Two consecutive 5-year periods were selected: (i) Pre-MELD Era (Jan, 2000–July 2005) ($n = 1210$) and (ii) MELD Era (Jul, 2005–Dec, 2010), ($n = 2062$). WL registrations, mortality, total dropout (deaths plus removals for being to seek), access to LT and post-LT survival were compared. Data was prospectively collected and analyzed by Kaplan–Meier method.
Results: There was a significant decrease in the WL mortality (28.5% vs. 21.9%, $p < 0.0001$, HR 0.64, 95% CI 0.55–0.73), total dropout rates (38.6% vs. 29.1%, $p < 0.0001$, HR 0.76, 95% CI 0.67–0.86) and a progressive drop in the annual death rate/1000 pts-years at risk (from 273 in 2005 to 173 in 2010) besides the lower LT accessibility observed in the MELD Era (57.4% vs. 50.7%, $p < 0.0001$, HR 0.63, 95% CI 0.59–0.72). In fact, WL size increased by 70% in the MELD Era (1210–2062 listed pts) but LT with cadaveric donors increased only a 50.5% (695–1046) resulting in a lower access to LT. MELD score was an excellent predictor of 3-month-WL mortality with a c-statistic of 0.828 (0.800–0.844, $p < 0.0001$). At the LT time, median MELD score was 26 (6–47) and 31% of pts had a MELD >30. Pts with MELD >30 had a lower survival when compared to those with scores <30 (73.5% vs. 84.4%, $p < 0.0001$). However, MELD score was a poor predictor of post-LT survival with a c-statistic of only 0.523 ($p = 0.507$) and the actuarial 1 year-post LT survival was similar in both eras: 81.1% vs. 81.3%, $p = 0.3$).
Conclusions: The MELD score was an excellent predictor of WL mortality. The adoption of MELD allocation policy in Argentina resulted in a significant improvement in liver organ allocation in spite of the increase in the number of WL registrations unparalleled by a concomitant expansion of the deceased donor pool.

O034 DOES THE MELD/PELD ALLOCATION POLICY CORRECTLY BALANCE WAITING LIST OUTCOMES OF PEDIATRIC AND ADULT PATIENTS?

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In July 2005, Argentina adopted a MELD/PELD-based policy for allocation of livers from deceased donors (DD). All pediatric candidates (<18 years-old) with chronic liver disease (CLD) were listed by PELD until July 2007 when those aged ≥12 years were switched to the MELD system.

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Objectives: (i) To compare waiting list (WL) outcomes of pediatric versus adult patients (pts) and (ii) To evaluate the accuracy of MELD and PELD scores to predict WL mortality in the pediatric population.
Materials and Methods: The study included 377 children and 2093 adults with CLD who were consecutively listed for liver transplantation (LT) by calculated MELD or PELD from July, 2005 to July, 2011. Argentina has a single national WL with no regional o center allocation.
Results: Overall access to LT was higher for pediatric pts (64.4% vs. 43%, $p < 0.0001$, 95% CI 15.2–26.6%). However, this resulted from the combination of a significantly lower access to LT with DD (27% vs. 42%, $p < 0.0001$) and a significantly higher access to LT with live donors (37.4% vs. 1.1%, $p < 0.0001$) in the pediatric population. WL mortality was similar among children and adults (15.7% vs. 20%, $p = 0.0754$, 95% CI 0.28–8.22). Median PELD scores were 16 at listing, 16 at LT and 22 at death. Median MELD scores were 18 at listing, 19 at LT and 26 at death for pts aged ≥12 years and 16, 26 and 25 respectively for adults. The c-statistic (% sensitivity/% specificity) of PELD (<12 years) and MELD (≥12 years) to predict 3-month WL mortality in children was 0.854 (84.2%/80.2%) and 0.864 (79.2%/81.6%) respectively.
Conclusion: Adoption of the MELD/PELD system at a national level in Argentina seems to balance WL among adults and children. Although accessibility to LT with DD was lower in children it is likely that in a significant proportion of listed pediatric patients LDLT is considered the preferred option from the start. PELD and MELD are excellent predictors of 3-month WL mortality for children and adolescents.

O035 PAIRED EXCHANGE KIDNEY DONATION IN INDIA: A FIVE-YEAR SINGLE-CENTER EXPERIENCE

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Introduction: Paired exchange kidney donation (PKD) is an evolving strategy for overcoming the barriers that confront patients with end-stage renal disease, when the only living potential donors who are willing to donate to them are deemed to be unsuitable as donors for them owing to an incompatibility of blood type, of HLA cross-match, or of both. In the PKD, the incompatibility problems with two donor recipient pairs can be solved by exchanging donors. Although PKD is increasing worldwide, we in India have not nearly reached the estimated potential of this modality. Herein, we have reported our results with a living donor exchange program in past 5 years.
Materials and Methods: Between March 2006 and June 2011, we performed 44 living PKD transplantations. All donor and recipient procedures were performed successfully. ABO incompatibility or positive lymphocyte cross-match were found in 20 pairs and 2 pairs, respectively.
Results: The mean recipient age was 42.5 years (range 33–59 years). The mean donor age was 38 years (range 31–56 years). At a median follow-up of 33 months (range 1–59 months), graft survival rate was 100%. All patients have functioning grafts with a median serum Creatinine level of 1.13, 1.5, and 1.35 mg/dl at 3 month, 1 year, and 3 years, respectively. One patient died after 4 month of transplant due to pneumonitis with sepsis. Allograft dysfunction was not seen in any of the recipients.
Conclusion: The PKD transplantation is a viable procedure medically and economically, which can be promoted in centers with a low deceased donor transplantation rate and a high number of incompatible related donors. We achieved excellent graft outcome by using the PKD transplantation program as an option to reduce the donor organ shortage.

O036 COMBINED LIVER AND KIDNEY TRANSPLANTATION: LISTING CRITERIA AND RESULTS

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Background: Creatinine weighs on MELD, increasing the number of combined Liver and Kidney Tx (CLKTx). In contrast with isolated LTx/KTx, listing criteria for CLKTx remain unclear.
Methods: Sixty-two CLKTx from 1 center ('97–'11) were analyzed for recipient/donor characteristics; etiology liver/kidney disease; rejection; 1&10y patient/graft survival and classified according to whether they fulfilled: standard indications for LT × & KT × (Gr1); LTx only (prophylactic KTx;GFR > 20 ml/min) (Gr2); KTx only (prophylactic LTx) (Gr3). Gr2&3 recipients had advanced, not yet terminal -but deemed irreversible- kidney or liver disease.
Results: Table shows characteristics & outcome for each group. Hepatorenal polycystosis was the predominant disease in 21 patients (34%). In 41 (66%) liver disease/indication was: postethyl (13), hepatitis B/C (9), congenital fibrosis (3), reTx (2), α1-antitrypsin deficiency (2), others (12). Kidney disease/indication was: reTx (11), IgA-nephropathy (9), drug-induced (4), hepatorenal syndrome (4), others (13). Early acute rejection occurred in 2 kidneys (3%), 1 liver (2%), 1 simultaneously (2%). All responded to steroids. Kidney DGF developed in 5 (8%), PNF in 1 (2%) and chronic rejection in 3 (5%). 3 (5%) underwent reKTx and 2 (3%) early reLTx. Liver PNF or chronic liver rejection was not seen. No rejection occurred in Gr2/3. 11 patients (18%) died: infection (7), sudden death (2), trauma (1), oropharyngeal carcinoma (1). Overall 1y/10y KTx/LTx graft survival is 92%/74% & 90%/82%. 1y/10y patient survival is 94%/85%.
Conclusion: In addition to patients fulfilling standard criteria for LTx&KTx listing, CLKTx benefits patients with single LTx/KTx listing criteria and advanced kidney/liver disease that would cause morbidity/mortality in case of single organ Tx. In this series (the 3rd largest reported) rejection rates of both organs are extremely low. Ten years patient survival of 85% is achieved.

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CCS01-KIDNEY I

CCS01 AN ONCOCYTOMA ON THE UPPER POLAR RENAL GRAFT COMPLICATING A CADAVERIC KIDNEY TRANSPLANT CASE

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Backgrounds: The continued problem of insufficient supply to meet the demand for kidneys for transplant has recently resulted in an advocacy for using kidneys with small renal and deceased donors have been extended to include older donor.
Clinical Case: We report a case regarding a 60 years old lady who underwent to cadaveric kidney transplant for end stage renal disease. The donor was a 67 years old male with normal kidney function tests and a negative renal Doppler Ultrasound (DUS) for any nodular lesion. On post-operative day 1 the recipient underwent DUS to check the patency of the graft's vessels, as routine first week post-operative follow-up. DUS did not recognize any focal irregularities, but for a suspicious of acute artery thrombosis the patient underwent urgently to CT scan. It was negative for vascular complication but serendipitously showed a lesion on the upper polar kidney graft, not detected during the back table. The histology result biopsy of the lesion showed a benign epithelial proliferation of large cells with a picture that was suitable for oncocytoma. An eosinophilic variant of chromophobe renal cell carcinoma (RCC) was excluded with a negative immunohistochemical reactions for antibody to RCC antigen and Ki67 antibodies. Because of the chance of an oncocytoma behaving in a malignant fashion is quite low, as it is considered a benign tumor we decided to a closed follow the lesion with DUS every 2 months for the 1st year. All of them did not shoved morphologic changes of the lesion and the patient is alive and well after 1 year.
Conclusion: There are case reports of coexistent RCC associated with or even within oncocytomas, again uncommon and we are not aware of any reports that indicate that immunosuppression facilitates malignant transformation of an oncocytoma. After a clearly explanation of the options and potential outcomes to the patient, involving her in the decision-making process, we did not recognize any reason to remove the lesion.

CCS02 KIDNEY TRANSPLANTATION FOLLOWING HSCT FROM THE SAME HAPLOIDENTICAL DONOR WITHOUT IMMUNOSUPPRESSION – A CASE REPORT

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) can lead to donor-specific tolerance. All patients reported in the literature that underwent kidney transplantation (KTX) after a previous HSCT from the same haploidentical donor received short term immunosuppression, mostly for safety reasons and concerns of triggering graft-versus-host-disease (GVHD).
Methods and Results: We describe a 22 year old patient who developed chronic kidney failure after receiving high dose chemotherapy, local irradiation and a haploidentical HSCT from his father for the treatment of metastatic rhabdomyosarcoma. The patient showed 99.983% donor chimerism (rtPCR) in CD3 positively selected cells and donor-specific hypo-responsiveness in mixed lymphocyte reaction (MLR) and INF-γ ELISPOT, and systemic immunosuppression could be withdrawn 1 year after HSCT. Five years after HSCT, the patient remained in complete remission and had no signs of GVHD,. However, following chemotherapy and HSCT, the patient developed progressive renal insufficiency. At that time, he received a pre-emptive kidney transplant from his father. Steroid treatment, which had been prescribed for the underlying kidney disease, was continued until complete withdrawal 2 months post-transplant. No further immunosuppression was given as the patient was regarded to be tolerant and the avoidance of immunosuppression was considered to be of benefit in a patient with previous malignancy. Graft function was excellent throughout the follow-up (5 months post KTX: sCreatinine: 0.98 mg/dl; eGFR: 95.6 ml/min/1.73 m^2). A protocol biopsy performed 1 month after transplantation confirmed the absence of rejection.
Conclusions: To the best of our knowledge, this is the first report of kidney transplantation from the same donor after previous haploidentical HSCT without any immunosuppression. Our results suggest that immunosuppression can be avoided in such cases under specific circumstances.

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CCS02-SURGICAL LIMITS/CHALLENGES

CCS04 HAND-ASSISTED RETROPERITONEALSCOPIC DONOR NEPHRECTOMY; WHAT'S THE LIMIT?

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Background: Successful living kidney donation programmes are allowing the development of safe and novel techniques even when circumstances are less than ideal.
Methods: We discuss a hand assisted retroperitonealscopic donor nephrectomy (HARDN) technique in a donor with prior extensive intra-abdominal surgery.
Results: The 58-year-old female donor had previously undergone an emergency open pancolectomy 30 years ago, with subsequent laparotomy and pouch formation with a covering loop ileostomy and a third laparotomy for adhesions. The donor workup including a urinary stone screen was unremarkable. The CT angiogram demonstrated simple anatomy and the left kidney was deemed suitable for donation. A 6 cm paramedian incision utilizing a previous incision was opened and a muscle splitting technique used to create the retroperitoneal space. This is a modified technique to create the retroperitoneal space which usually utilizes a Pfannensteil incision which was not available due to dense scar tissue. Conventional HARDN technique was then used to mobilize and remove the kidney. The operative time until arterial clamp was 165 mins with a warm ischaemic time of 110 s and blood loss of 50 ml. The donor had an uneventful recovery and was discharged on post-operative day two (See Table 1). The recipient achieved good primary function with a preoperative and day 7 creatinine of 484 and 154 μM respectively.
Conclusion: The HARDN technique is safe in the setting of previous abdominal surgery provided that safe access can be gained into the retroperitoneal space. This technique allows potential donors to proceed with donation in a safe manner who may otherwise be declined if an intra-peritoneal approach were to be used.
Reference: 1.Wadström J, Linström P. Hand-assisted retroperitoneoscopic living-donor nephrectomy superior to laparoscopic nephrectomy. Transplant Proc 2003; 35: 782–783.

CCS05 TRANSFUSION FREE LUNG TRANSPLANTATION IN A PATIENT OF JEHOVAH'S WITNESS FAITH

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Persons of Jehovah's Witness (JW) faith present complex and challenging surgical cases due to their decline to consent for blood and blood products transfusions. Lung transplantation is now recognized treatment for many end stage lung diseases. However, lung transplantation still presents a difficult surgical case as patients can sustain significant blood loss requiring transfusions. Consequently, patients of JW faith with end stage lung disease present a particularly difficult and rare surgical case for lung transplant where blood transfusion is not possible. We would like to present our experience in caring for a lung transplant recipient who is of JW faith. For this study we reviewed the chart of a patient who was the first JW lung transplant recipient at our center. We collected demographic information on the patient, pre-transplant diagnosis, type of transplantation (single or double), progress of surgery including immediate post operative course and immunosuppression at induction and maintenance. Most importantly however, we executed a careful review of patient's pre-transplant medical history, especially researching specific medical preparations for transfusion free lung transplantation and carefully reviewed patient's postoperative course specifically focusing on hemoglobin (Hgb) and hematocrit (Hct) levels few months before transplant as well as in the first year post lung transplant surgery. We have focused on the changing level of Hgb and Hct throughout patient's first year post transplant as well as possible causes of decreased blood levels and solutions to prevent those. We will discuss the surgical and medical outcome as well as the special preparations prior to transplant for this patient, patient's operative and post operative course and the eventual outcome for this individual at post 1 year follow up. Discussion includes a summary of disadvantages and benefits of transfusions specifically related to lung transplantation.

CCS06 A COMPLICATED COURSE OF A PSEUDOANEURYSM FOLLOWING LIVER TRANSPLANTATION

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Background: Leakage of the bile duct anastomosis after liver transplantation is a frequent complication after liver transplantation, but can often be treated with endoscopic stent implantation. Rarely, a bilioma causes an arrosion of the hepatic artery which makes immediate surgery with replacement of the artery necessary. It is known that ischemic damage of liver grafts can generate pseudoaneurysm of intrahepatic arteries. Recurrent hemorrhage of a pseudoaneurysm is typically treated by coiling of the artery. In case of ineffectiveness surgical resection is necessary though only few cases are reported. Case report: We report of a 69 year old patient who received a liver transplant for a Child-Pugh B liver cirrhosis. The patient developed a postoperative bilioma caused by necrosis of the bile duct anastomosis. Two days after laparotomy and diversion to a hepatico-jejunostomy, the patient developed a bleeding caused by an arrosion of the hepatic artery which made an interposition of an iliacal vascular graft necessary. Two weeks later the patient suffered of recurrent GI bleeding caused by an intrahepatic pseudoaneurysm in segment VIII which was repeatedly treated with angiographic coiling. As episodes of spontaneous and life threatening bleedings reoccurred, the right hepatic artery was finally occluded. Bleeding from the aneurysm started again 2 weeks later and finally, a hemihepatectomia was performed. The surgery was uneventful and the patient initially recovered well from the intervention, but suboptimal liver function together with recurrent infections finally caused a sepsis and death from haemodynamic and heart failure 5 months after liver transplantation.
Conclusion: Ischemic lesions of the liver can lead in pseudoaneurysm of intrahepatic arteries, which are usually treated by angiographic coiling. Rarely surgical treatment is necessary and should be evaluated cautious and early to prevent graft damage and infectious complications.

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BAC - BEST ABSTRACT CHALLENGE

BAC01 NATURAL KILLER CELLS IMPROVE ALLOGENEIC LUNG TRANSPLANTS VIA DEPLETION OF DONOR DENDRITIC CELLS

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Background: Natural killer (NK) cells are innate lymphocytes targeting virus infected/tumor cells. Little is known about their ability to limit adaptive immune responses. We here investigated to which extent NKcells can influence lung allograft rejection.
Methods: Using an allogeneic lung transplantation (Tx) mouse model, we stimulated recipient NKcells by IL15-complexes, while using IL15Ra deficient and CD11cDTR mice deficient for dendritic cells (DCs).CD107 degranulation assay, congeneic marker, flow cytometry, magnetic resonance imaging were employed.
Results: NKcells infiltrated allografts prior to Tcells and diminished allograft inflammation while NKcell deficiency enhanced allorejection.IL15-expanded NKcells resulted in decreased Tcell infiltration and improved lung Tx function. These NKcells significantly decreased the number of allogeneic DC in transplanted lungs.
Conclusion: NKcells promote Tx tolerance by depleting graft derived DCs which otherwise prime alloreactive Tcell responses.

BAC02 WHAT ACCOUNTS FOR THE DECLINE IN LIVING KIDNEY DONATION IN THE UNITED STATES AND DOES THIS DECLINE REFLECT A GLOBAL TREND?

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Background: In the USA, there was a remarkable 265% increase in the annual number of living donors from 1988 to 2004. However, since 2004 the annual number of living donors has declined from the previous year in all but 1 year (2009), despite the emergence of novel programs to expand kidney donation.
Method: We extracted data from the Organ Procurement and Transplantation Network (OPTN) website to examine trends in living donation within subgroups. To facilitate our examination of pattern shifts before and after the 2004 peak, we divided living donation into two eras reflecting identical time periods: Era 1 (1998–2004) and Era 2 (2005–2011), The proportions of living donors for each category in the two eras were compared using *t*-tests for proportions. Also, we extracted data from donor registries in several other countries throughout the world.
Results: From Era 1 to Era 2, as a proportion of total living donors, there was a decline in male donors (41.9–39.8%, $p = 0.006$), Black donors (13.4–12.2%, $p = 0.002$), donors 18–34 (33.5–30.6%, $p < 0.001$) and 35–49 years old (46.9–44.0%, $p = 0.002$), and sibling (33.1–24.1%, $p < 0.001$) and parent (13.9–9.4%, $p = 0.001$) donors. In contrast, from Era 1 to Era 2, as a proportion of total living donors, there was an increase in Hispanic (11.9–13.6%, $p < 0.001$) and Asian (2.9–3.4%, $p = 0.010$) donors, and donors 50–64 years old (18.6–23.9%, $p < 0.001$). The overall trends observed in the USA differ from the recent increases in living donation seen in many other regions of the world (e.g. UK, Japan, Netherlands, Mexico, Australia).
Conclusion: The living donation decline appears more pronounced and sustained among men, blacks, younger adults, siblings, and parents, and the observed decline in the USA appears to an outlier globally. We examine these data in the context of financial disincentives in an economic recession, rising obesity rates, and increased emphasis on regulatory oversight of transplant center performance. Programmatic, scientific, policy, and legislative efforts to identify and remove barriers are needed to attenuate the decline in living donation.

BAC03 EARLY GRAFT LOSS POST KIDNEY TRANSPLANTATION IS AN IMPORTANT RISK FACTOR FOR PATIENT MORTALITY

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Background: Kidney transplant outcomes are generally compared by long-term graft survival analysis. However, the catastrophic nature of early graft loss post kidney transplantation warrants a separate analysis of its aetiology, risk factors and its impact on patient survival.
Methods: Recipients of kidney-only transplants between 2002 and 2012 in our centre who suffered graft loss within 30 days were identified from a prospectively maintained database and risk factors analysed using multivariate analysis.
Results: The causes of early grafts loss (52 of 1090 transplants; 4.8%) are shown in table 1. On multivariate analysis only DCD donor type was a significant risk factor for early graft loss (OR 2.43 vs. DBD donors; $p = 0.006$). The increased early graft loss among DCD transplants was due to the higher incidence of PNF and acute vascular occlusions compared to DBD transplants but the difference did not reach statistical significance. However, there were no significant differences in 1-year graft survival between DCD and DBD donor (391 [89.9%] vs. 341 [93.2%]; $p = 0.089$ figure 1). Patients with early graft failure had an 8.5 times increased risk of death ($p < 0.001$). One-year patient survival was inferior in the early graft failure group compared to those whose graft survived more than 30 days (77% vs. 98.4% figure 1). Importantly, donor type itself was not a risk factor for patient death ($p = 0.280$ figure 1).
Conclusion: Early graft failure is more frequent after DCD kidney transplantation, although 1-year graft survival of DCD and DBD kidneys was comparable. Early graft loss, irrespective of the donor type, is a major risk factor for patient mortality.

BAC04 SUSTAINED BETTER RENAL FUNCTION WITH EVEROLIMUS AND REDUCED TACROLIMUS IN LIVER TRANSPLANTATION

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Introduction: Twelve-month (mo) results from the H2304 study showed that everolimus (EVR) and reduced tacrolimus (rTAC) facilitated superior renal function (RF) vs. standard TAC (TAC-C) in *de novo* liver transplant recipients (LTxR). Here we report results at month 24.
Methods: Of 719 LTxR were randomised (1:1:1) to EVR (C0 3–8 ng/ml) + rTAC (C0 3–5 ng/ml; $N = 245$) or EVR (C0 6–10 ng/ml) with TAC withdrawal at mo4 (TAC-WD; $N = 231$) or TAC-C (C0 6–10 ng/ml; $N = 243$) after 30 days (± 5 days; TAC ± MPA) of LTx; all with steroids. Enrolment in TAC-WD arm was stopped early due to high rejection rates. GFR was estimated by MDRD4.
Results: Reduction of eGFR from randomisation to mo24 was significantly smaller for EVR+rTAC versus TAC-C (table). Proteinuria was more frequent with EVR+rTAC versus TAC-C, but declined from month 12 to 24 (244.8 ± 430.1 mg/g) for EVR+rTAC. No proteinuria >3 g/day was observed in both groups.
Conclusion: EVR+rTAC treatment showed superior RF sustained for 24 months versus TAC-C, without worsening of proteinuria.

BAC05 FACE TRANSPLANTATION WITH COMBINED HEMATOPOIETIC STEM CELL INFUSION AND VASCULARIZED BONE MARROW TRANSPLANTATION IS NOT ASSOCIATED WITH MIXED CHIMERISM IN HUMANS

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Background: In rat models of limb allograft transplantation, vascularized bone marrow (VBM) transplantation is associated with mixed chimerism (MC) and donor-specific tolerance. The objective of the study was to analyze the development of MC in face transplant recipients treated by the combination of VBM and hematopoietic stem cell infusion.
Methods: Three face allotransplantations were performed in severely disfigured patients (pts), 1 male and 2 females, aged of 27, 38 and 52 year-old respectively. Facial allograft included nose, lips, cheeks and chin in pt 2, bilateral mandible (VBM), cheeks, lips and chin in pt 1, and bilateral maxilla and mandible (VBM), cheeks, lips, chin and tongue in pt 3. Donor BM was infused after transplantation on day 4 and 11 in pt 2; day 4 in pt 1 and day 7 in pt 3 Immunosuppression included Thymoglobulin, tacrolimus, prednisolone and mycophenolate mofetil. Chimerism was assessed by RQ-PCR on whole blood and on CD3+ cells at days 8, 14, 26, 39, 53, 69, 88, 124, 174, 330, and 545 after transplantation, and on total and purified CD34 + BM cells at days 14, 26, 53, 90, 174, 370, and 545. The lower limit of the assay was 0.1%.
Results: Microchimerism was detected once at M2 (0.1% donor cells among the CD34+ enriched population of BM cells) in pt 2. Transient microchimerism was evidenced in pt 1 in the BM at d7 (0.4% donor CD34+ cells), d14 (0.6% donor CD34+ cells), and d56 (0.4% donor CD34+ cells) and was detected once in peripheral blood (0.6% donor CD3+ lymphocytes at d28). Chimerism

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remained undetectable in pt 3. No graft versus host disease has developed in the 3 pts. Two episodes of acute rejection occurred in pt 2, 6 in pt 1, and 1 pt 3.
Conclusion: VBM transplantation combined with HSC infusion did not induce MC in face transplant recipients treated by Thymoglobulin and tacrolimus. This study suggests that a non-myeloablative regimen is necessary to induce MC and tolerance in the context of donor VBMT and HSC infusion.

BAC06 AMELIORATION OF ISCHAEMIA-REPERFUSION INJURY IN A MOUSE MODEL OF CARDIAC TRANSPLANTATION USING A NOVEL MITOCHONDRIA-TARGETED ANTIOXIDANT

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Introduction: Accumulating evidence supports a key role for mitochondrial oxidative damage in ischemia reperfusion injury (IRI), a major cause of early graft dysfunction in transplantation. We therefore investigated the efficacy of a mitochondria-targeted antioxidant we have developed, MitoQ, in ameliorating IRI.
Methods: To induce a minimal and a severe ischaemic injury in a syngeneic C57Bl/6 mouse model of heterotopic cardiac transplantation, donor hearts were flushed with Soltran($\pm$ 50 μM MitoQ), then stored at 4°C for 30 min or 4 h in UW solution ($\pm$ 50 μM MitoQ) prior to transplant. MitoQ uptake was confirmed using mass spectrometry. IRI severity was assessed by cardiac troponin-I levels (ELISA) and histology. Mitochondrial reactive oxygen species (ROS) generation was measured using a ratiometric probe and mass spectrometry. Oxidative damage was assessed by measuring protein carbonyls (ELISA) and mitochondrial DNA (mtDNA) damage (qPCR). Serum cytokine responses were determined by immunoassay.
Results: Prolonged cold preservation (4 h vs. 30 min) resulted in greater IRI, with higher troponin(4.9 ng/ml $\pm$ 1.2 vs. 0.6 $\pm$ 0.2) and worse histological injury 24 h post-transplantation. This was associated with a 2-fold increase in mitochondrial ROS generation, increased oxidative damage to myocardial proteins and mtDNA and a heightened pro-inflammatory cytokine response. MitoQ was successfully taken up into the donor myocardium and mitochondria at 4°C and reduced the severity of IRI at 24 h post-transplant: there was a reduction in troponin(2.4 ng/ml $\pm$ 0.6 vs. 4.9 $\pm$ 1.2; 4 h group), reduced mitochondrial ROS, a reduction in oxidative damage to proteins and mtDNA, accompanied by a diminished pro-inflammatory cytokine response.
Conclusions: Prolonged cold preservation of donor organs leads to increased mitochondrial oxidative damage at reperfusion and greater IRI severity, which can be successfully ameliorated with MitoQ. MitoQ represents a promising therapeutic candidate for transplant-related IRI.

BAC07 MOLECULAR MARKERS AS DIAGNOSTIC TOOLS OF DONOR ORGAN QUALITY AND PREDICTORS OF TRANSPLANTATION OUTCOME

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Background: As the demand for donor organs exceeds the supply more organs from older and high risk donors are currently accepted for transplantation. The ability to assess viability and quality of these organs prior to transplantation can be vital. Clinical proteomics has the potential to allow clinical and analytical validation of potential proteins as prognostic markers of organ quality and to identify novel therapeutic targets. We have investigated serum samples from three different donor types to evaluate relevant molecular signatures of injury and repair associated with organ function and transplant outcome.
Method: Serum samples from living (LD), brain dead (DBD) and donors after circulatory arrest (DCD) were analysed using 'shotgun' proteomic approach. Samples from 10 donors per group were depleted of the 14 most abundant plasma proteins, precipitated and size-fractionated using SDS-PAGE. Protein bands were cut, digested with trypsin and analysed using tandem mass spectrometry (LC-MS/MS, LTQ Velos). The MS/MS spectra were analysed using using Progenesis and the 'in house' proteomic pipeline (CPF TPP).
Results: Of 305 proteins were significantly and differentially regulated across the three donor groups. Heat-mapping indicates that candidate proteins were differentially expressed among LDs, DBD, DCDs (Figure 1). The three dendrograms demonstrate that proteomic signature of LDs is clustered distinctly when compared with proteomic signature of the deceased donors. There were 40 proteins uniquely expressed in the deceased donors only, 17 in serum of DCDs only and 4 proteins in DBDs suggesting up-regulation of proteins of the coagulation and the inflammatory cascade when compared with living donors.
Conclusion: Our systematic approach demonstrates that proteomic signature of donors is informative to discriminate between donor types suggesting that identification of markers of organ quality is feasible and has to be validated.

BAC08 IMPLICATIONS OF DONOR SPECIFIC ANTIBODIES ON OUTCOMES AFTER PANCREAS TRANSPLANTATION

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Aim: Donor-specific HLA antibodies (DSA) are associated with poorer outcomes in kidney transplantation, however the role of DSA in pancreas transplantation is unknown. This study assesses serial HLA antibody monitoring in identifying grafts at risk of failure after pancreas transplantation.
Method: All pancreas transplants performed 2006–2011 were included (317 SPK, 126 IP). Prospective serial HLA antibody screening was performed pre-transplant, at 0, 6, 12 and 24 months post-operatively, and at the time of clinical events. Samples were screened for antibodies using Luminex LABScreen® Mixed kits and antibody specification performed using LABScreenPRA® and Single Antigen beads. Demographic and graft outcome data was collected. The antibody monitoring results were analyzed for associations to pancreas graft outcomes.
Result: Pre-transplant sensitisation status, HLA mismatches (0–6) and DR mismatch (0–2) were not associated with pancreas graft outcome. 141/354 (39.3%) recipients developed de novo HLA antibodies and 54/354 (15.3%) developed de novo DSA, of which 34 were SPK and 20 IP. There was no association between graft failure and the development of non-DSA, however de novo DSA were significantly associated with poorer graft outcomes. One and 3 year pancreas graft survival rates in SPK recipients who developed de novo DSA were inferior compared to those who did not (1 year graft survival, 78.3% vs. 94.7%; 3 year survival 63.6% vs. 92.5%; log rank $p = 0.001$), with differences more pronounced in the IP group (1 year graft survival, 50.0% vs. 89.4%; 3 year survival 14.3% vs. 85.8%; log rank $p = 0.001$). Kidney rejection episodes were also higher and kidney graft outcomes inferior in the DSA group ($p = 0.001$).
Conclusion: This is the largest study to date to examine the association between de novo HLA antibodies following pancreas transplant and graft outcomes, and clearly demonstrates a strong association between development of DSA and graft failure.

BAC09 POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS: CLINICOPATHOLOGICAL ANALYSIS OF 54 CASES IN A SINGLE CENTER

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Introduction: A post transplant lymphoproliferative disorder (PTLD) is an infrequent but serious complication following solid organ transplantation. The incidence varies and depends on the type of organ, degree of immunosuppression and patient's immune status to Epstein Barr Virus.
Material & Methods: This is a retrospective data analysis in 5133 patients following kidney ($n = 3440$), liver ($n = 1145$), pancreas ($n = 519$) and intestinal/multivisceral ($n = 29$) transplantation. In this patient cohort, 54 cases of PTLD have been observed and correlated with induction therapy, maintenance immunosuppression, EBV status, CMV status, antiviral therapy, acute rejection, graft survival, retransplantation and death.
Results: The overall cumulative incidence of PTLDs was 1.05% (54/5133); 5 year survival was 25.9% (14/54); (highest in PTX 40% (2/5) and lowest in LTX: 20% (3/15). Overall survival was 2.9 years (0–13). PTLD occurred significantly earlier in patients transplanted after 2000 (101 vs. 23 months). Patient with a higher immunological risk received induction therapy and showed decreased patient and graft survival after kidney transplantation as well as a significantly higher risk for PTLD after liver transplantation. Donor age had an impact on graft survival, PTLD onset and patient survival following pancreas transplantation. Interestingly, prognosis was poor in early PTLD and more favorable in late PTLD (all $p < 0.05$).
Discusssion: We have identified a correlation between organ, patient age and induction therapy with PTLD development in a large single center analysis. A shift of PTLD occurrence towards later time points after transplantation with a more favorable outcome was observed in this study.

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BAC10

CONVERSION FROM TACROLIMUS TO CYCLOSPORINE A IMPROVES GLUCOSE METABOLISM IN PATIENTS WITH NEW ONSET DIABETES AFTER RENAL TRANSPLANTATION: INTERIM ANALYSIS OF A PROSPECTIVE AND RANDOMIZED STUDY

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Background: The present multi-centre investigator-driven prospective and randomized study was designed to assess whether conversion from tacrolimus to cyclosporine A can reverse new onset diabetes after renal transplantation in at least 25% of patients.
Methods: Patients with NODAT according to the 2005 ADA criteria, persisting at least 6 month after renal transplantation in spite of minimization or withdrawal of steroids, were randomized to either replacement of tacrolimus with cyclosporine or continuation of their tacrolimus-based regimen. Randomization was stratified for type of glucose-lowering therapy (insulin, oral agents, none), steroid therapy and HCV status.
Results: Sixty-six patients out of the scheduled 110 patients had completed 1 year of follow up and were included in the present interim analysis (CYC $N = 34$; TAC $N = 32$). Half of the patients in both arms were steroid-free at the moment of inclusion. Baseline fasting glycemia was 127 ± 30 mg/dl vs. 129 ± 36 mg/dl and HbA1c 6.5% vs. 6.7% in the CYC and TAC arms respectively. At 1 year, 11 of 26 patients with complete data in the CYC arm (42%) were free of NODAT whereas this was only the case in 1 of 22 patients (5%) in the TAC arm ($p = 0.003$). Twenty-five % of patients were able to stop insulin and the mean insulin dose decreased from 34 to 16 units per day ($p = 0.03$) after conversion to cyclosporine. On the contrary, the number of patients requiring insulin and the mean insulin dose remained stable in the TAC group. HbA1c at 1 year was 6.1 ± 0.8% in the CYC and 7.2 ± 2.0% in the TAC arm ($p = 0.01$). Conversion was safe in terms of acute rejection (1 in the CYC and 2 in the TAC arm, p = NS).
Conclusions: The present interim analysis of the prospective and randomized REVERSE study suggests that conversion from tacrolimus to cyclosporine improves glucose metabolism and reverses NODAT in a significant proportion of patients. Conversion was safe and did not result in an increased incidence of acute rejection episodes.

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OS07-KIDNEY III

O037 LONG TERM OUTCOMES OF HIGHLY SENSITIZED KIDNEY TRANSPLANT RECIPIENTS

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Aim: To follow the clinical outcomes of 45 highly sensitized patients who had undergone a desensitization protocol prior to kidney transplantation, and report the incidence of complications, allograft survival, and patient survival.
Methods: We conducted a retrospective review of 45 kidney transplant recipients transplanted between 9/2002 and10/2011, who had a positive T or B cell complement dependent cytotoxic (CDC) crossmatch assay. B cell CDC crossmatches were confirmed with a solid-phase assay to determine presence of class II anti-HLA antibodies.
Results: All subjects completed a desensitization protocol of plasmapheresis, intravenous immunoglobulin, +/− rituximab to render a negative T cell crossmatch or a negative or weak titer B cell crossmatch 24 h prior to transplantation. Post-transplant all recipients received antibacterial and antiviral prophylaxis; allograft biopsies were performed when clinically indicated. The mean and median follow-up was 5 years. Thirty-three subjects (73%) suffered acute rejection of the allograft, 30 (67%) occurred in the first year post-transplant, and 27 (60%) occurred in the first month post-transplant. There was 1 case of hyperacute rejection necessitating transplant nephrectomy. Twenty-nine of the 33 (88%) were cases of acute antibody mediated rejection. BK viremia occurred in seven patients (15.5%), leading to graft loss in 3. There were five patients that suffered multiple pneumonias, five cases (11%) of bacteremia, 1 case of fungemia, and four patients (8.8%) with cytomegalovirus infection. There were no cases of lymphoproliferative disease, although one patient developed an aggressive cutaneous angiosarcoma and died. There was also one case of renal cell carcinoma, and 4 cases (9%) of skin malignancies. The 1, 3, and 5 year allograft survival was 87%, 76%, and 68% respectively. The 1, 3, and 5 year patient survival was 93%, 91%, and 84% respectively.
Conclusion: Patients with a positive CDC crossmatch that are transplanted after a plasmapheresis-based desensitization protocol have high rates of acute rejection and infectious complications. Despite increased rate of rejection and over-immunosuppression, patient and graft survival in the desensitized group is comparable to the 1, 3, 5 year survival (graft: 89%, 78%, 67% respectively; patient: 95%, 90%, 85% respectively) of recipients of repeat transplants from living donors.

O038 A SINGLE CENTER EXPERIENCE WITH A SELECTIVE USE OF RITUXIMAB FOR DESENSITIZATION

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Identification of donor specific-antibodies (DSA) allows use of desensitization protocols to prevent the occurrence of antibody-mediated rejection (AMR). We report our 6-year experience with a selective use of Rituximab in desensitization protocol.
Methods: We analyzed outcome of 33 live-donor transplants performed after desensitization between 12/06-12/12. All patients were PRA+ (20–100%). DSA was measured by Luminex Single Antigen (Genprobe) technology. All transplants were AHG-CDC cross-match negative. In 16 patients with DSA < 104 MFI desensitization protocol included three sets of plasmapheresis (PP) and IVIG (0.5 g/kg) (Rituximab−). In another 15 patients with DSA > 104 we added Rituximab (Rituximab+). The two groups were compared for the following parameters: ATN, acute rejection, graft and patient survivals as well as renal function along the follow-up.
Results: ATN was noted in two patients in each group (NS) and acute rejection in four patients in each group. AMR was diagnosed in three patients in the Rituximab− group versus none in the Rituximab+ group (p = ns). Actual graft and patient survival were 100% in both groups. On follow-up there was no difference in creatinine levels between the groups (table).
Conclusions: Desensitization with a selective addition of Rituximab in highly sensitized patients may achieve good outcome with a low incidence of AMR.

O039 STRONG ASSOCIATION BETWEEN THE PRESENCE OF DONOR SPECIFIC MICROCHIMERISM AND DONOR SPECIFIC HLA ANTIBODIES IN KIDNEY TRANSPLANT RECIPIENTS

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Background: The presence of donor-specific microchimerism (DSM) in kidney transplant recipients has been proposed as one of the possible mechanism for induction and maintenance of allograft tolerance. On the other hand, donor specific HLA antibodies (DSAs) are significant risk factors for graft dysfunction after kidney transplantation. The association between the presence of DSM and DSA and its clinical outcome has not been understood.
Methods: We enrolled 51 consecutive kidney transplant recipients who with functioning graft at the end of 2012, who all underwent living or cadaveric (n = 39 vs. 12) primary kidney transplantation in a single center in Japan between Jan 1983 and Feb 2011. We cross-sectionally measured DSM and DSA to evaluate the association between them. Multivariate logistic regression analyses were performed for sensitivity analyses.
Results: In 51 patients (half of them were male, and mean eGFR and duration after transplantation was 39.4 ± 12.5 ml/min/1.73 m^2 and 10.8 ± 8.0 years), DSMs were detected in 17 patients (33.3%). The proportion of the patients who didn't have DSAs was 88.2% and 38.3% in DSM positive and negative recipients, respectively (p = 0.0004). The significance of this association was confirmed by sensitivity analyses using several models. However, the rate of patients with acute rejection was not different in both groups (41.2% vs. 50.0%, p = 0.55).
Conclusions: A lower frequency of DSA was observed in DSM positive patients than in DSM negative patients. This might be possible that DSM leads to transplantation tolerance by reducing the occurrence of DSA.

O040 THE INFLUENCE OF NON-HLA ANTIBODIES DIRECTED AGAINST ANGIOTENSIN II TYPE 1-RECEPTOR (AT1R) ON EARLY RENAL TRANSPLANT OUTCOMES

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Non-HLA antibodies (Abs) targeting vascular receptors are thought to have an impact on renal transplant injury. Anti-Angiotensin II type 1-receptor activating antibodies (anti-AT1R) have been mentioned to stimulate a severe vascular rejection but the pre-transplant screening has not been introduced yet. The aim of our study was to assess the incidence and importance of anti-AT1R antibodies and their influence on renal transplant in the first year of observation.
Methods: We evaluated the presence of anti-AT1R antibodies in 117 consecutive renal transplant recipients in pre- and post-transplant screening (before and in 1st, 3rd, 6th, 12th month after transplantation). Anti-AT1R antibodies were assayed by ELISA (Cell-Trend). The level >9 U/l of anti-AT1R was denoted as high (positive). The diagnosis of acute rejection was based on Banff criteria. The immunosuppression consisted of: tacrolimus or cyclosporine, mycophenolate mofetil, steroids and occasionally basiliximab. In case of an acute rejection (AR) the recipients received steroids and/or ATG. Plasmapheresis with IVIG were considered in patients with humoral rejection.
Results: Anti-AT1R antibodies had been observed in 27/117 (23%) of the analyzed recipients already before transplantation. None of the patients developed de novo antibodies post-KTx. The patients were divided into two groups: anti-AT1R positive (+) (n = 27) and anti-AT1R negative (−) (n = 90). The anti-AT1R Abs levels varied at different measurement intervals within the 1-year follow-up but the mean was >9 U/L in (+) group and <5 U/l in (−) group. The function of renal transplant was significantly worse in anti-AT1R (+) group compared to anti-AT1R (−) group during the first post-transplantation year (Table 1). Biopsy proven AR was described in 4/27 (15%) pts in the anti-AT1R (+) group (IIB three times and AHR) and 13/90 (14.4%) in the anti-AT1R (−) group. There was no statistically significant difference regarding recipients' and donors' age or gender, cold ischemia time, the number of HLA mismatches, the number of presensitized patients, immunosuppressive regiment or patients with the presence of anti-HLA antibodies between the groups. Table1. Serum creatinine level (mg/dl).
Conclusions: The occurrence of anti-AT1R antibodies is connected with a worse renal transplant function during the first 12 months after transplantation. Anti-AT1R antibodies should be included in the diagnostics of renal pre- and post-transplant recipient immune status assessment.

O041 THE DONOR HLA MISMATCH GRADE DETERMINES THE RISK OF HLA LOCUS-SPECIFIC SENSITISATION AND ACCESS TO REPEAT KIDNEY TRANSPLANTATION FOLLOWING PRIMARY ALLOGRAFT FAILURE

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University of Cambridge

Background: We have investigated the impact of HLA mismatch grade on intra- and inter-locus specific sensitisation in patients re-listed for transplantation following primary renal transplant failure.
Methods: Primary kidney transplant recipients from 1995 to 2010 whose graft failed and subsequently returned to the waiting list were studied (n = 131). Multiple sera obtained before transplantation and following re-listing were screened using DTT modified lymphocytotoxicity, Luminex HLA class I and II antibody detection beads and single antigen beads. The effect of donor

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mismatches on IgG panel reactive antibodies (PRA) and on calculated reaction frequency (cRF) against 10 000 consecutive HLA typed UK donors was determined for each individual HLA locus.
Results: HLA mismatch grade correlated strongly with overall incidence and magnitude of post-transplant allosensitisation defined by PRA and SAB-defined cRF ($p < 0.001$). The risk and level of sensitisation against individual HLA-A, -B, -DR and -DQ loci increased with increasing number of donor HLA mismatches within each locus; this relationship was stronger for HLA-A and -DR loci [odds ratios of 3.0 (CI: 1.8–4.4) and 2.9 (CI: 2.1–4.2) respectively, $p < 0.001$] which also best predicted overall post-transplant HLA class I and II sensitisation respectively. Following re-listing, the incidence of highly sensitised patients (>85% cRF) was 22%, 48% and 88% for 0–1, 2–7 and 8–10 mismatches respectively ($p < 0.001$). Of patients with 2 HLA-DR mismatched grafts, 70% became highly sensitised and 80% developed donor specific antibody. On multivariate analysis, HLA mismatch grade and immunosuppression weaning were independent predictors of HLA sensitisation whereas transplant nephrectomy was not.
Conclusion: This analysis is the most comprehensive to date, showing that donor mismatching, particularly for HLA-DR may lead to high levels of sensitisation following primary allograft failure, compromising options for future transplantation.

O042 DESENSITIZATION PROTOCOL IN IMMUNIZED LIVING DONOR KIDNEY TRANSPLANTATION – A SINGLE CENTER EXPERIENCE

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Objective: Due to growing waiting times for renal transplants living donor kidney (LDK) transplantation performed in the presence of donor-specific antibodies (DSA) or ABO incompatibility (ABOi) using various desensitization protocols has increased. We herein evaluated graft outcome after desensitization in comparison to immunological low risk LDK recipients at our center.
Methods: Eight patients with Luminex-detected DSA and 20 ABOi patients were successfully desensitized by anti-CD20, plasmapheresis (DSA) or immunoadsorption (ABOi) and induction therapy with thymoglobulin and received a LDK transplant. Graft survival and function, rejections and infectious complications were compared to LDK recipients with non donor-specific antibodies (low risk, $n = 36$) or no antibodies (no risk, $n = 83$), receiving no desensitization but similar maintenance therapy. All patients had a negative CDC crossmatch before desensitization and/or transplantation.
Results: The 1-year graft survival rate was 100% in the DSA, ABOi, low risk and 98% in the no risk group. Renal function at 12 months was slightly reduced after desensitization (serum creatinine: 1.8 mg/dl vs. 1.7 mg/dl vs. 1.6 mg/dl vs. 1.5 mg/dl in DSA, ABOi, low risk and no risk group, respectively). The incidence of acute T-cell mediated rejection did not differ between the groups (25 vs. 25 vs. 22 vs. 20%), while antibody-mediated changes were only found in the DSA (2/8) and ABOi (1/20) group. Three out of 8 patients with DSA showed evidence of persistent DSA. Two of those patients experienced an antibody-mediated rejection and had impaired renal function at last follow-up (serum creatinine 2.6 mg/dl). The incidence of BK nephropathy was more frequent in desensitized patients (2/28 vs. 0/119).
Conclusions: We demonstrate favorable short-term allograft outcome in LKD transplant recipients after desensitization, if DSA can be removed. However, the intensified desensitization was associated with an increased risk of BK nephropathy.

O043 VIRTUAL CROSSMATCH: LOOKING FOR THE MFI THRESHOLD

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Single Antigen Flow Beads (SFAB) assays currently enable to identify anti HLA antibodies (Ab) directed to the donor (DSA) with sensitivity before transplantation. They are routinely used for organ allocation based on virtual crossmatch strategies. Their clinical relevance is yet still a matter of contention. Their non licensed semi quantitative counterpart of Ab level assessment (Mean Fluorescence Intensity MFI) may improve their performance in prediction cell-based crossmatchs (XM) results. We selected 137 sera from exhaustively characterized anti HLA Class I sensitized patients. We then isolated HLA Class I typed T lymphocytes from 90 deceased organ donors'lymph nodes. We finally performed 603 flow cytometry XM (FCXM) and complement dependent cytotoxicity (CDC) assays (positive XM was defined as a Mean Channel Shift deviation >45 MCS and a CDC score >1, respectively). Ab level assessment was based on the sum of DSA MFI including DSA-Cw MFI. Internal crossvalidated ROC analysis of the sum of the MFI-DSA as predictor of a subsequent FCXM (+); $N = 426$, and CDCXM (+); $N = 100$, defined a maximal AUC of 0.78 and 0.8, respectively. From this, we generated two SAFB-DSA MFI thresholds, susceptible to be translated in a clinical practice. A cutoff value of 3000 better predicted a positive FCXM: respective sensitivity-Se, specificity-Sp, positive predicting value-PPV, negative predicting value-NPV of 79%, 64%, 85% and 54% with an odd ratio (OR) for FCXM(+) of 6.6 [CI 95%, 4.5–9.5, $p < 0.001$] when sum of DSA MFI >3000. In contrast, a cutoff value of 8000 better predicted a positive CDCXM: respective Se, Sp, PPV and NPV of 73%, 79%, 40% and 94% for CDCXM(+) with an OR for CDCXM(+) of 9.3 [CI 95%, 5.2–17.6, $p < 0.001$] when sum of DSA MFI >8000. If performance for characterizing SAFB preformed DSA is not enough to omit prospective XM in sensitized patients, we here demonstrated how the Ab level information can be integrated in an algorithm of immunological risk stratification.

O044 OUTCOME OF DESENSITIZATION IN HLA CLASS II AS COMPARED WITH CLASS I DONOR SPECIFIC ANTIBODY (DSA): A PROSPECTIVE STUDY

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Background: We sought to investigate the outcome of desensitization in HLA incompatible living donor (LD) kidney transplantation comparing HLA class I with class II DSA.
Methods: Since 2007, we included in our desensitization program all adult HLA incompatible LD kidney transplant candidates with positive DSA alone, or in combination with either positive flow crossmatch (FCXM) or positive T cell IgG AHG CDC CXM at a titer <1:8. All candidates were risk stratified for acute AMR and were subjected to an individualized desensitization protocol as follows: HLA incompatible candidates with either positive AHG CDC CXM or positive FCXM and repeat HLA MM from previous transplants were deemed as high risk and received single dose anti-CD20 antibody (500 mg IV), therapeutic plasma exchange (TPE) and high dose IVIG (2 g/kg of body weight). HLA incompatible candidates with negative CDC and positive FCXM were deemed as intermediate risk and received anti-CD20 antibody and high dose IVIG. HLA incompatible candidates with negative CDC and FCXM were deemed as low risk and received low dose IVIG (1 g/kg of body weight). At transplant, all patients received r-ATG and were maintained Tacrolimus-based immunosuppressive regimen. In addition to indication biopsies, all patients underwent protocol renal allograft biopsies and post-transplant DSA monitoring at certain time intervals. All renal allograft biopsies were graded and scored as per the updated 2009 Banff criteria.
Results: There were 71 HLA incompatible recipients who met the inclusion criteria, 32 had antibodies against HLA class I specificities and 39 had antibodies against HLA class II specificities. Demographic and baseline characteristics were comparable between the two groups. Clinical outcomes are summarized in the table.

§*Two grafts were lost to non-AMR causes*; δ*All acute AMR episodes were reversed with therapy.*

Over the follow up period, histological grades and scores and the status of DSA in post-transplant monitoring were not different between the two groups.
Conclusion: Within our inclusion criteria, risk stratification scheme and desensitization strategy, and over the short-intermediate follow up, the clinical and histological outcomes of desensitized HLA class II incompatible kidney transplantation do not appear to be different from those of class I. Longer term follow up is needed.

O045 KIDNEY INTRAGRAFT DONOR SPECIFIC ANTIBODIES AS DETERMINANT OF ANTIBODY-MEDIATED LESIONS AND POOR GRAFT OUTCOME

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Allograft pathology, interaction of antibody (Ab) with the tissue as demonstrated by C4d deposition and serologic evidence of Donor Specific Ab (DSA) are the three cardinal features required for the diagnosis of Ab-mediated rejection (ABMR) in kidney transplantation. We here propose to apply the single antigen flow beads assay- the highest resolution technique currently available for anti-HLA Ab characterization- to eluates from kidney biopsies as a response to the two inventoried limits of current diagnosis of AMBR: inability of C4d to detect all phenotyped of AMBR and limited specificity of circulating DSA (sDSA). Intragraft DSA (gDSA) was assessed in 51 graft biopsies, performed for cause (12 acute Ab-mediated rejection [AAMR], four suspicions of AAMR, eight chronic Ab-mediated rejection [CAMR], 8 suspicions of CAMR, 9 acute cellular mediated rejection [ACMR], 6 with lesions of interstitial fibrosis and tubular atrophy [IFTA], and three normals) after acidic elution from the graft tissue, using class I and class II single antigen flow cytometry bead assays on a Luminex platform. Most of the kidney transplant recipients were HLA-sensitized (90%) and 67% displayed circulating sDSA. Histological Banff's items analysis was performed individually and in functional clusters. Fifteen (29%) patients had gDSA. The gDSA were detected in all anti-HLA Ab-positive biopsies and present electively in biopsies with Ab mediated lesions (7/12 AAMR, 5/8 CAMR, 1/11 ACMR). gDSA were indeed significantly associated with micro-circulation lesions (peritubular capillaritis, glomerulitis and transplant glomerulopathy), C4d positivity and a worse short-term transplant outcome. In contrast, these associations were not found for patients presenting only sDSA. Collectively, our results suggest that gDSA positivity could discriminate between pathogenic and non-pathogenic sDSA and thus represent a new tool picturing the "immunopathological evidence" of AMBR.

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OS08- TUMORS IN LIVER TRANSPLANTATION

O046 ISCHEMIA TIME SIGNIFICANTLY IMPACTS RECURRENCE-FREE OUTCOME IN LIVER TRANSPLANT PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: Ischemia-reperfusion (I/R) injury is known to promote tumor recurrence after liver resection in patients with hepatocellular carcinoma (HCC). However, the impact of I/R on HCC in the transplant setting is undefined. The aim of this trial was, therefore, to elucidate the impact of ischemia time on recurrence-free outcome in liver transplant patients with HCC.
Patients and Methods: Ninety-three liver transplant patients with HCC were included in this prospective trial. All of them underwent positron emission tomography (PET + versus PET − tumor) prior liver transplantation (LT). The impact of pretransplant assessed clinical variables and relevant tumor features, including cold and warm ischemia time (CIT, WIT), on recurrence-free survival rates were determined in uni- and multivariate analysis.
Results: Overall 5-year recurrence-free survival rate was 74.1%. Mean cold and warm ischemia times were 360.3 ¡À 172.6 min and 50.3 ¡À 10.8 min, respectively. Five-year tumor-free survival rates were 88% and 45% in patients with CIT ¡Ù / >400 min, and 86% and 20% in patients with WIT ¡Ù / >60 min, respectively (log rank <0.001). In multivariate analysis, none of ischemia times but 18F-FDG-avidity on pretransplant PET, alpha-fetoprotein-levels (AFP) >400 ng/ml and overall tumor diameter >10 cm on radiographic staging were identified as independent predictors of post-LT tumor recurrence ($p < 0.05$). In a multivariate subanalysis of biologically unfavourable tumors (PET + status; increased AFP-level, microvascular tumor invasion), however, WIT >60 min remained as independent predictor of tumor recurrence. In the subset of patients with PET + tumors, 5-year-recurrence-free survival was 61% and 0% in WIT ¡Ù / >60 min.
Conclusion: Both, CIT and WIT impact significantly outcome in liver transplant patients with HCC. Increased WIT is an independent promoter of post-LT tumor recurrence in patients with aggressive tumor features, such as 18F-FDG-uptake on pretransplant PET, and should, therefore, be significantly minimized in this special subpopulation.

O047 TUMOR DOWNSTAGING AND THE RISK OF HCC RECURRENCE AFTER LIVER TRANSPLANTATION

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University of Pisa Medical School Hospital

Background: We aimed to evaluate the risk of recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT) for patients undergoing pre-transplant tumor downstaging with trans-arterial chemo-embolization (TACE).
Methods/Materials: This is a retrospective analysis of a prospectively collected single-center data base. Inclusion criteria called for: adult recipients (>18 years); primary LT from deceased donor; pre-transplant TACE with one post-TACE contrast-enhanced radiology, and availability of explant pathology and clinical data. Radiology was reviewed and response to TACE assessed as per mRECIST criteria. The variables associated with the risk of HCC recurrence were identified and patients were further stratified according to number of risk factors.
Results: From August 1996 to December 2010, 216 patients underwent TACE before LT. Fifty-two patients were excluded due to lack of post-TACE control radiology and 164 entered the present analysis (M/F: 148/16; median age: 57 years). Median follow-up of the entire population was 5.5 years (ranges: 3.0–9.7). Exceeding Milan criteria ($p = 0.006$), post-TACE AFP >200 ng/ml ($p = 0.09$), and lack of a complete post-TACE radiological response ($p = 0.08$) were associated with a higher risk of post-transplant HCC recurrence. The 5-year HCC recurrence rate was 0%, 5.0% and 22.6% for patients with no risk factor (= 36), 1 (= 86) or 2–3 risk factors ($n = 42$), respectively ($p < 0.0001$).
Conclusions: Combination of tumor stage (Milan versus beyond Milan), biology (AFP) and response to TACE allow for better patient stratification and might be used to guide liver graft allocation for patients with HCC.

O048 LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER RESECTION: WHY DENY THIS CHANCE OF CURE?

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Background: Liver Transplantation (LT) after Liver Resection (LR) for Hepatocellular Carcinoma recurrence may be associated with poor patient long term results and higher peri-operative patient morbidity and mortality. This study focused on short- and long-term outcomes of LT recipients due to HCC recurrence after LR in a single-institution cohort, as well as in highly comparable case-matched subgroups.
Methods: Between 2000 and 2009, 570 consecutive patients with documented HCC underwent LR ($n = 355$, 62.2%) or LT ($n = 215$, 37.8%) at our Institute. The case-matched analysis was between two groups: Group A1, LT recipients who had already undergone LR ($n = 26$); Group B1, LT recipients who had not already undergone LR ($n = 26$).
Results: Patient morbidity was higher in the A1 Group in terms of packed red blood cell units transfused, fresh frozen plasma units transfused, median operative time, post-operative bleeding, post-operative re-operations. No differences were detected in terms of patient mortality, patient survival and patient recurrence free survival at the univariate and multivariate analysis.
Conclusions: Although LT among patients who have already undergone LR is associated with higher risk of patient morbidity, patient long term survival and recurrence free survival is not impaired. Therefore, there do not appear to be any valid reasons to deny the chance of LT to patients who have already undergone LR.

O049 BENEFIT OF TREATING HCC RECURRENCE AFTER LIVER TRANSPLANTATION

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Introduction: Studies analyzing the management of post-LT HCC recurrence and risk factors for survival are lacking. AIM Analyze the benefit of treating patients after HCC recurrence and identify risk factors for survival.
Material & Methods: Between 2000 and 2010 209 LT were performed for HCC and 34 (16%) recurred during follow-up. Median time to recurrence was 18.8 (2.2–87) months; 18/34 (52.9%) within the first 2 years. Median follow-up: 24.4 (6–91.1) months.
Results: Twenty-five patients (73.5%) could be treated at time of recurrence (sorafenib 9/25; radiotherapy 6/25; surgery 4/25; chemotherapy 4/25; RFA 2/25). Mean survival after recurrence of those treated was longer compared to those that were not (12.7 ± 12.4 vs. 3.6 ± 2.8, $p = 0.002$). The median post-recurrence survival was 6 (0.1–45) months and the 1-, 3- and 5-year survival after HCC recurrence was 36%, 14% and 0%. One- and 3-year survival of treated and not treated patients independently of tumor location was 50%, 19% vs. 0%, 0%, respectively, $p < 0.001$. On univariate analysis, treatment of recurrence ($p = 0.001$), resection or RFA ($p = 0.031$) and early recurrence (<12 months) ($p = 0.012$) predicted post-recurrence survival.
Conclusions: Most patients may be treated at the time of HCC recurrence and treatments prolong survival. Even though, survival after HCC recurrence is dismal and studies should be focused to prevent recurrence.

O050 FEASIBILITY OF ABLATE AND WAIT STRATEGY WITH A SALVAGE LIVER TRANSPLANT FOR SINGLE HEPATOCELLULAR CARCINOMA LESIONS <3 CM

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Background: With progressive organ shortage, liver resection and radiofrequency ablation (RFA) are alternative treatment modalities to Liver transplantation (LT) for small single HCC lesions (SSL). We analyzed outcomes of "ablate and wait" strategy for patients who underwent RFA treatment for SSL <3 cm.
Methods: Retrospective study of 75 consecutive patients with SSL, treated by primary RFA between 2006 and 2012. After RFA, patients were followed up by CT or MRI scans at 1, 3, 6 months and 3–6 monthly thereafter. The primary outcome was the incidence of HCC recurrence beyond transplant (Milan) criteria.
Results: Of the 75 patients with a median (range) age of 65 (29–84) years, majority (69%) were men. Forty (53%) patients were potential transplant candidates at diagnosis, based on the age and fitness. The median follow up was 16 months (range 1–53 m). There was no procedure related mortality. Overall, 12 patients (16%) developed recurrences which were beyond transplant criteria. Of those, three patients had aggressive tumour biology and recurred within 3 months. Twenty-two patients (29%) developed recurrences, which were within criteria. Seven of these patients were successfully treated by transplantation, while 15 were not transplant candidates for non-oncological reasons. The median time from RFA to recurrence was 13 (1–

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41) months. The overall survival for the entire patients cohort at 1, 2 and 3 years was 90%, 67% and 48% respectively.
Conclusion: Primary RFA for SSL is a viable approach, which offers acceptable medium term survival. Despite the high overall recurrence rates, the incidence of "recurrence beyond criteria" is low. After the exclusion patients with an aggressive HCC biology the effective dropout rate was only 12%. In SSL, an "ablate and wait" strategy may be a preferred alternative to liver resection and salvage LT.

O051 DE NOVO MALIGNANCIES FOLLOWING LIVER TRANSPLANTATION. RESULTS FROM A MULTICENTRIC STUDY IN ITALY: 1990–2010

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Objective: Quantify incidence and risk factors of de novo-tumors (except non melanoma skin ca.) in patients who underwent liver transplant (OLT) in Italy.
Methods: Of 2770 patients (74.7% M) underwent OLT in nine Italian tx centers. Time at risk of cancer (person-years, PY) was computed from OLT to the date of cancer diagnosis, death or last fup. Sex- and age-standardized incidence ratios (SIR) and 95% confidence intervals (CI) were computed dividing the number of observed cancer cases with those expected using Italian cancer registries data. To identify risk factors, incidence rate ratios (IRR) were computed through Poisson regression.
Results: During 15 056 PY (median fup 4.2 years), 170 patients (6%) were diagnosed with a de novo-malignancy (178 total cancers). Thirty-five were post-transplant lymphoproliferative disorders (29 Non Hodgkin Lymphoma, NHL and 2 Hodgkin's Lymphoma, HL), 14 Kaposi's Sarcoma (KS), and 129 solid tumors (32 head & neck (H&N) cancers, 23 lung, 18 colon-rectum, 16 larynx, 9 esophagus, 6 bladder, melanoma, tongue and stomach). Overall incidence was 11.8 cases/103 PY, with a 1.7-fold significantly increased SIR (95% CI: 1.4–1.9). Statistically significant increased SIRs were found for KS (56.0), PTLD (4.2, 7.5 for NHL), larynx (5.0), esophagus (9.0), melanoma (2.8), tongue (8.7) and H&N (4.8) cancers. A significative increased incidence of all and solid tumors in patients with alcohol abuse (IRR = 1.9 and 2.4 respectively) and a decreasing incidence in patients living in Southern Italy (IRR = 0.6 and 0.5).
Conclusions: OLT patients are at higher risk for cancer, mainly malignancies virus-associated or those related to pre-existing risk factors (e.g. alcohol). These observations point to the need of improving cancer surveillance after OLT. The on-going enrollment of patients in the present cohort study will help to further elucidate the burden of cancer after OLT and to better identify risk factors associated with malignancy development.

O052 LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA WITH MARGINAL GRAFTS: INTENTION TO TREAT OUTCOMES

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Background: Liver transplantation (LT) can offer the best long-term survival for patients with early stages of hepatocellular carcinoma (HCC). Improved surveillance of cirrhotic patients has increased the proportion of cases diagnosed with transplantable tumours. To meet the growing demand on background of progressive organ shortage; marginal grafts are frequently allocated to HCC recipients as these are not prioritized on the waiting list (WL) in the UK. This strategy can prevent WL dropouts by shortening the waiting time. We analyzed our "intention to treat outcomes" (ITT) of patients listed for LT for HCC.
Methods: Retrospective study of 215 patients listed for LT between January 2004 and December 2011. Cases were divided into early era (EE; 2004–2007) and late era (LE; 2008–2011) according to the listing year. The primary outcome was ITT survival calculated from LT listing to death or last follow up. The survival was estimated by Kaplan–Meier method and groups compared with log-rank test.
Results: Of the 215 patients with a median (range) age of 58 (30–73) years, the majority (82%) were men. Eighty-three patients were listed in EE and 132 in LE (59% growth). There was no difference in the median waiting time (39 vs. 44 days, $p = 0.333$); nevertheless there was a trend towards an increased dropouts from WL in the LE (7% vs. 14%, $p = 0.082$). There was a higher proportion of LT from donors after circulatory death (DCD) in LE (6% vs. 33%, $p < 0.001$) without a difference in the 90 days post-transplant mortality (7% vs. 8%, $p = 0.214$). The ITT patient's 1- and 3-year survival (95% confidence interval) was 84% (77–92) and 74% (64–83) for EE, and 81% (74–88) and 59% (50–69) for LE respectively ($p = 0.155$).
Conclusions: Allocating marginal grafts to HCC patients might be an alternative strategy to prioritization by additional MELD points. This strategy reaches comparable ITT survival with historical controls despite the trend towards increasing dropouts from the WL.

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OS09-PANCREAS TRANSPLANTATION – INNOVATIONS

O055 QUALITY OF LIFE AND GASTROINTESTINAL SYMPTOMS IN PANCREAS-KIDNEY TRANSPLANTS – BEFORE AND AFTER TRANSPLANTATION

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Pancreas-kidney transplantation (PKT) is commonly considered the best treatment for type1 diabetic patients. Avoidance of hypoglycemic episodes, insulin administration and dialysis after a successful transplant, may significantly improve quality of life (QoL). We assessed the changes felt by PKT patients, through the Gastrointestinal Quality of Life Index (GIQLI). Patients were asked to compare, for each question, how it changed from their status before PKT to the last visit. The GIQLI, a 36-item questionnaire, focuses not only on the impact of GI symptoms that may affect Health-Related Quality of Life (HRQL), but it also assesses other domains: emotional status; physical function; social function; and a question addressing stress of medical treatment. Each question scores from 0 to 4, the higher scores representing the better HRQL. Sixty men and 59 women completed the questionnaire. They were transplanted with a mean age = 35 ± 6 years and had a mean follow-up after PKT of 5.5 ± 3.4 years (ranging from 0.3 to 12.5 years post-PKT). Among the 119 patients, 81.5% have both grafts functioning and 18.5% have only one graft functioning. We compared the scores obtained for each domain, before and after PKT. Concerning the GI complaints, the mean score after PKT was significantly higher than the score before PKT (33 ± 4 vs. 28 ± 6, $p < 0.001$). Also for the physical function, it was felt as significantly better after PKT than before PKT (15 ± 4 vs. 8 ± 5, $p < 0.001$); and the same was observed for the emotional status (18 ± 4 vs. 10 ± 6, $p < 0.001$) and social function (11 ± 3 vs. 7 ± 3, $p < 0.001$). The single question addressing the stress with the medical treatment also scored significantly higher after PKT than before PKT (3.63 vs. 1.31, median, $p < 0.001$). Analyzing by multivariate linear regression possible predictors for higher HRQL scores improvement, acute rejection and longer time of diabetes evolution were negative predictors, instead survival of the two grafts was a positive predictor for higher HRQL scores improvement (ANOVA $p = 0.006$; adjusted R^2 =10.7%). In conclusion, for all the domains assessed, the patients reported a significant improvement in the HRQL after PKT, compared to their situation before PKT. Maintenance of the two grafts functioning, predicted higher improvement of HRQL scores in patients with PKT.

O056 LOW LEVEL PRE-TRANSPLANT DSAS ARE FREQUENT BUT ARE NOT ASSOCIATED WITH A REJECTION DIAGNOSIS IN PANCREAS TRANSPLANT BIOPSIES

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Pancreas Biopsy allows accurate diagnosis of rejection of the pancreas transplant. Our group has shown previously that pancreas biopsy is safe, has a high diagnostic yield.
Aim: To study the incidence of Luminex DSA pre and post-transplant, and their association with rejection in patients biopsied for pancreas rejection.
Patients and Methods: Thirty-seven pancreas biopsies performed were interpreted by a single pathologist. All biopsies were stained for C4d. Recipients had their pretransplant sera investigated for the presence of antibodies to HLA by Luminex for determination of HLA specificity. LABScreen was used to test for DSA during each rejection episode.
Results: Thirty-seven biopsies were performed on 26 patients out of the 108 pancreas transplants performed in the centre. Fourteen biopsies showed ACR whereas three biopsies showed AMR (1 mixed). The biopsies that showed no rejection were performed at a median of 321 days post transplant. Nine of those patients (34.6%) had positive pretransplant DSA whereas 13 (50%) had positive DSA at the time of Biopsy. 15.4% had Luminex DSA with MFI over 2000 pre compared to 30.8% at the time of biopsy. There was no difference in the percentage of patients expressing pretransplant DSA between those who had biopsy proven rejection and those that did not (but still had a biopsy). 57% of those with rejection had positive DSA posttransplant compared to 41% of those without rejection. Interestingly rejection was the same or less common in patients with MFI over 2000 at the time of transplant or the time of biopsy. Only 1 case out of 3 with AMR had preformed DSA, and although they all expressed DSA at the time of rejection in 1 of them was <2000 MFI.
Conclusion: Low-level Luminex DSA pretransplant are common in the pancreas transplant population. They do not seem to be associated with frequency of rejection.A pretransplant DSA MFI level of 2000 does not seem to be associated with more frequent rejection diagnosis.

O057 THE BENEFIT OF EARLY ENTERAL FEEDING AFTER SIMULTANEOUS PANCREAS KIDNEY TRANSPLANTATION

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Introduction: Early post-operative enteral nutrition is an important part of perioperative management and strongly supported by ESPEN Guidelines. However, there is limited evidence into the use of Early Enteral Nutrition (EEN) after Simultaneous Pancreas Kidney Transplantation (SPK). We know malnutrition in type-1 diabetics with ESRF is a common problem and significant risk factor. Therefore, we introduced EEN in our patients.
Method: We monitored and recorded nutritional data on 21 SPK recipients who underwent transplant between 2007 and 2009 without EEN [Monitored Group (MG)] and on 22 SPK recipients between 2010 and 2012 who received EEN (NJ feed or oral intake with supplementation, according to their nutritional status) [Fed Group (FG)]. The end-point was to assess nutritional intake: achievement of ¡Ý60% energy requirements by day-7 (7 day–60%) and at the time of discharge (Total = 60%).
Results: There was no difference between MG and FG; in CIT, recipient-age and donor-age. Both groups had similar Length of Stay (30.8¡À23.7 vs. 24.6¡À12.3, $p = 0.29$), day-0 albumin levels (35.29¡À4.9 vs. 32.43¡À5.7, $p = 0.085$), donor-creatinine (86.3¡À31.4 vs. 64.1¡À20.9, $p = 0.01$), re-operation rates (1 vs. 0.83, $p = 0.56$). FG group more frequently achieved 7d-60% (72.7% vs. 23.8%; $p = 0.02$) and total-60% (95.2% vs. 71.4%; $p = 0.047$). Furthermore, FG patients with early pancreas-graftectomy achieved target intake compared to MG patients with pancreas-graftectomy: 7 day–60% 100% vs. 50%; $p = 0.4$ and total-60% 100% vs. 75%; $p = 0.667$. But MG patients achieved it only with TPN support. There were only 2 FG recipients on TPN (8.7%) compared to 5 MG (23.8%; $p = 0.17$).
Conclusion: EEN is a safe method and helps to deliver adequate nutritional intake early after SPK transplant. It is paramount to recipients experiencing major post-transplant complications. Furthermore, it minimizes need for TPN and avoidance of its complications.

O059 RISK FACTORS FOR EARLY GRAFT FAILURE AFTER PANCREAS TRANSPLANTATION

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Aim: Early graft loss contributes significantly to high attrition rates following pancreas transplantation, and the consequences of graft pancreatitis lead to high patient morbidity. Risk factors of 90-day graft loss may be different to those for longer-term outcomes. Identification of donor pancreases at high risk of early graft failure would lead to more efficient organ utilisation and improved patient experience.
Method: Data were obtained from the UK Transplant Registry on 1265 deceased donor, whole pancreas transplant recipients between 1st April 2004 and 1st July 2011. The dataset was randomly divided in modelling and validation datasets. The modelling dataset was used to investigate donor factors potentially influencing 90-day graft survival using Cox regression, adjusting for significant recipient and transplant factors. A risk index was derived and validated.
Results: Significant variables in the recipient model included recipient BMI ($p = 0.038$), PAK transplant ($p = 0.049$) and transplant centre ($p = 0.023$). Other recipient characteristics including calculated Reaction Frequency and degree of mismatch were not significant. In a multivariate model, significant donor factors predicting poor pancreas graft were donor type (DCD HR 2.395, $p = 0.024$), donor BMI (HR 1.049, $p = 0.117$) and donor ALT (>50 mM HR 2.506, $p = 0.003$). Donor age, cold ischaemia time and other donor factors (donor gender, ethnicity, BMI, biochemistry, serology, past medical history) were not significant predictors of 90-day graft outcome.
Conclusion: Risk factors for early graft failure relate to risk of graft pancreatitis and differ from established risk factors for long-term graft outcome. Risk models for early complications will facilitate individualised decision-making at the time of organ offers.

O060 METABOLIC PROFILES AFTER PANCREAS TRANSPLANTATION

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Aim: Despite good early function, graft attrition rates after pancreas transplantation (PT) remain high. Patients with graft dysfunction usually present requiring a return to insulin treatment. We aimed to determine metabolic profiles after PT to identify graft dysfunction prior to failure.

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Method: Frequently-sampled oral glucose tolerance tests (FSOGTTs) were performed in 91 systemically-drained PT recipients with longstanding pancreas graft function and insulin-independence. Profiles were compared to 16 non-diabetic non-transplant controls, and correlated to clinical data.
Results: A high proportion of patients thought to have good graft function displayed impaired (23/91, 25.3%) or diabetic (6/91, 6.6%) glucose tolerance. PT profiles showed significant heterogeneity in glucose and insulin and differed from controls with higher systemic insulin (mean area under the curve 8464 vs. 3914 mU/l, p = 0001). PT profiles showed delayed insulin secretion (peak by 30 min 10% vs. 44%, p = 0.05). Measures of metabolic function were independent of time post-transplant, change in BMI and donor/recipient factors.
Conclusion: Metabolic measures including glucose tolerance are frequently outside the accepted normal range in PT patients and appear unrelated to graft duration and recognised risk factors for poor graft outcome. Whilst abnormal glucose tolerance may represent a marker of future graft failure, longitudinal studies are required to fully understand the significance of these findings.

O061 THE IMPACT OF GRAFT IMPLANTATION ORDER ON SHORT- AND LONG-TERM GRAFT SURVIVAL IN SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTS

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Introduction: The preferred order of revascularization of pancreas and kidney grafts in simultaneous pancreas-kidney transplants has not yet been established. Increased preservation time might have a negative impact on graft function. In particular increased cold ischemia time is associated with a higher risk of technical failure in pancreas grafts. In this study, we investigate the influence of graft implantation order in simultaneous pancreas-kidney transplants on short- and long-term graft survival.
Methods: Of 12 700 simultaneous pancreas-kidney transplants from the Scientific Registry of Transplant Recipients were analyzed. Graft implantation order was determined based on the ischemia times of pancreas and kidney transplants, respectively. Pancreas and kidney graft survival were analyzed depending on graft implantation order at 3 months, 6 months and 5 years using Kaplan–Meier plots. Significance was tested with logrank test and cox regression model.
Results: In 8454 transplants the pancreas was implanted first (pancreas before kidney, PBK) and in 4246 transplants the kidney was implanted first (kidney before pancreas, KBP). Pancreas graft survival at 3 months was significantly higher in the PBK group (90.6 vs. 89.3%, p = 0.024). Cox regression analysis revealed that graft implantation order as well as time span between pancreas and kidney implantation were significantly associated with pancreas graft survival at 3 months (p = 0.010, respectively). When kidney graft implantation was delayed by >2 h from pancreas implantation, difference in graft survival increased to 2.3% (90.1 vs. 87.8% for PBK and KBP, p = 0.009). Pancreas graft survival at 6 months and 5 years as well as kidney graft survival were similar in both groups.
Conclusions: Pancreas graft implantation first in simultaneous pancreas-kidney transplants increases short-term pancreas graft survival. Graft implantation order does not affect long-term pancreas and kidney graft survival.

O062 ALEMTUZUMAB OR BASILIXIMAB AS ANTIBODY INDUCTION FOR SIMULTANEOUS PANCREAS KIDNEY TRANSPLANTATION

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Objectives: The goal of induction therapy is to reduce acute rejection and early graft loss. Both the interleukin 2 receptor blockers (Basiliximab (BAS), Simulect™) and the CD52 specific antibody (Alemtuzumab (AZB), Campath-1H™) have been used for this purpose. At the inception (1998) of our PT program BAS with triple maintenance (Tac/Pred/Aza or MMF) therapy was the preferred regimen. From 2009 induction therapy was changed to AZB with a dual maintenance regimen. The aim of this study was to compare patient and graft outcomes between these different immunosuppressive protocols.
Methods: We analysed a prospectively maintained database of 58 SPK transplants performed between 1998 and 2011. Since 2009 maintenance immunosuppression was with Tacrolimus (Prograf™) (0.05 mg/kg BD target 8–10 μg/l) and mycophenolate mofetil 500–750 mg BD.
Results: Twenty-one SPK patients received AZB and 37 BAS, demographic data was comparable. More patients had bladder drainage after AZB than with BAS (86% vs. 60%, p = 0.04). At 1 year there was no difference in either pancreas graft (81% AZB vs. 82% BAS, p = NS) or patient survival (94% vs. 93%, p = NS). There was a difference in renal graft function at 1 month (serum creatinine AZB 122 ± 10 vs. BAS 175 ± 25, p < 0.001), which normalised at 1 year (serum creatinine AZB 122 ± 7 vs. BAS 120 ± 5, p = NS). Rates of biopsy proven rejection (AZB 23% vs. BAS 24%, p=NS) were similar. A trend towards lower leak rates in the AZB grafts (AZB 9.5% vs. BAS 13.5%, p = NS) was noted.
Conclusions: In this study there was little to choose between the two induction agents in terms of patient and graft outcome. However, at 1 month renal function was better in the AZB group. This may reflect differences in the pancreatic exocrine drainage and lower leak rates in the AZB group.

O063 UTILITY OF SERUM MARKERS IN EVALUATING GRAFT PANCREATITIS FOLLOWING SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION

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Background: Graft pancreatitis remains difficult to diagnose using clinical assessment alone, leading to indiscriminate use of cross-sectional imaging. We seek to correlate the presence of radiological features of graft pancreatitis to biochemical markers of inflammation and to clinical outcome.
Methods: A retrospective analysis of 109 simultaneous pancreas-kidney transplants performed at our centre between January 2005 and December 2010 was undertaken. All 299 post-operative CT scans performed on this cohort were blindly scored by 2 independent radiologists for features of pancreatitis – graft enlargement (normal = 0; enlarged = 1), graft perfusion (normal = 0; heterogeneous = 1), ascites (absent = 0; present = 1) and peri-pancreatic fat changes (mild = 0; moderate = 1; severe = 2). CT score was correlated to the length of post-operative stay and to levels of candidate serum inflammatory markers measured within 24 h of each scan.
Results: A CT score ≥2 in the post-operative index admission correlated with a significant increase in median length of stay (26 vs. 19 days, p = 0.044). Mean serum CRP levels were significantly higher in patients with positive CT findings (p < 0.001) including enlarged vs. normal graft size (11474 vs. 7680 mg/l) heterogeneous vs. normal perfusion (132 ± 81 vs. 82 ± 76 mg/l), presence versus absence of ascites (125 ± 81 vs. 74 ± 73 mg/l) and mild vs. moderate vs. severe peri-pancreatic fat changes (23 ± 34 vs. 53 ± 59 vs. 107 ± 80 mg/l). Serum CRP correlated closely with the CT score (p < 0.001), and the median length of stay was significantly longer (26 vs. 17 days, p = 0.005) in patients with a CRP >50. Mean serum white cell counts were also significantly higher in patients with enlarged grafts (10 ± 5.1 vs. 8.7 ± 5.5 × 109 cells/l, p = 0.013) and CT-detectable ascites (11 ± 5.2 vs. 8.7 ± 5.6 × 109cells/l, p = 0.006), and correlated linearly with the CT score (p < 0.001). In contrast, serum amylase and lipase levels had no significant correlation with radiological grading of pancreatitis or effect on length of post-operative patient stay.
Conclusion: CRP and white cell count are useful markers of graft pancreatitis and as such may allow avoidance of repeated radiological investigations to assess graft inflammation.
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OS10-CLINICAL IMMUNOSUPPRESSION & BIOMARKERS

O064 3-YEAR OUTCOMES AFTER SWITCHING TO BELATACEPT FROM A CALCINEURIN INHIBITOR IN STABLE KIDNEY TRANSPLANT RECIPIENTS

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Background: We report 3-year open-label data in kidney transplant recipients 6–36 months posttransplant who were randomized to continue calcineurin inhibitor (CNI) ($n = 81$) or switch to belatacept ($n = 81$). After 1 year, patients could enter the long-term extension (LTE) and after 2 years, patients randomized to CNI could switch to belatacept.
Results: Of 162/173 randomized patients entered LTE; 16 CNI patients converting to belatacept at year 2 are excluded from the year 3 CNI group ($n = 65$). At year 3, 79/81 belatacept and 64/65 CNI patients survived with a functioning graft. Three-year outcomes are in the table. Among patients with acute rejection (AR), 1 belatacept patient and 1 CNI patient had graft loss subsequent to AR by year 3. Malignancies occurred in 10% of belatacept and 8% of CNI patients. No post-transplant lymphoproliferative disorder was reported in either study arm.
Conclusions: Renal function improved at 3 years for kidney transplant recipients switching to belatacept from either CNI. Adherence remained high. No new safety signals were identified through 3 years follow-up. This exploratory trial indicates that switching patients from a CNI to belatacept may represent an effective clinical approach that should be validated in a large-scale trial.

O065 LONG-TERM BELATACEPT MAINTAINS EFFICACY & SAFETY: 5-YEAR BENEFIT LONG-TERM EXTENSION (LTE) RESULTS

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Background: BENEFIT compared more (MI) or less intensive (LI) belatacept regimens to cyclosporine (CsA) in patients receiving a living or standard criteria donor kidney transplant. Patients completing 36 months could enter the long-term extension (LTE). We report 5-year results of the LTE.
Results: Four hundred and fifty-six (68% of intent-to-treat) patients entered the LTE at 36 months; 406 (89%) completed 60 months. Infection and malignancy rates from months 36–60 across MI, LI, and CsA were: fungal infections (14%, 15%, 12%), viral infections (21%, 18%, 16%), malignancies (7%, 6%, 9%); no additional post-transplant lymphoproliferative disorder occurred after 36 months. From months 36–60, death occurred in 2% MI, 1% LI, and 5% CsA patients and graft loss in 0 belatacept and 2% CsA patients. Mean cGFR (MDRD; ml/min/1.73 m^2) at month 60: 74 in MI, 76 in LI, and 53 in CsA patients (Figure). Acute rejection in month 36–60 was rare: 0 MI, 1 LI, and 1 CsA.
Conclusions: Early renal function benefits observed with belatacept were sustained through 5 years. There were few deaths or graft loss, and acute rejection was rare during the LTE. The belatacept LI regimen provides sustained renal function benefit and a favorable safety profile through 5 years.

O066 LONG-TERM EXPOSURE TO BELATACEPT IN RECIPIENTS OF EXTENDED CRITERIA DONOR KIDNEYS

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Background: BENEFIT-EXT randomized extended criteria donor kidney recipients to more (MI) or less intensive (LI) belatacept regimens, or cyclosporine (CsA). Patients continuing through year 3 could enter the long-term extension (LTE). We report 5-year outcomes in the LTE cohort.
Results: Of 304 (56% of intent-to-treat) patients entered the LTE and 260 (48% of ITT) continued through 5 years. From year 3 to 5, 20 LTE patients died (5 MI; 9 LI;6 CsA) and 8 had graft loss (2 MI;1 LI; 5 CsA); three patients had an acute rejection episode (2 MI; 1 LI); 70 patients (20 MI; 26 LI; 24 CsA) had serious infections; and 27 (10 MI; 8 LI; 9 CsA) had malignancies. Four post-transplant lymphoproliferative disorder (PTLD) cases occurred between year 3 and 5 (3 LI; 1 CsA); 2/3 PTLD cases in LI were in EBV-negative patients. Mean cGFR (MDRD) at year 5 was 56 (MI), 59 (LI), and 45 (CsA) ml/min/1.73 m^2 (Figure).
Conclusions: For LTE patients, belatacept was associated with a consistent safety profile and sustained renal function improvement versus CsA over time, with no new safety findings through year 5. The greatest risk for developing PTLD in belatacept patients remains EBV-negative serostatus.

O067 IMPROVING OR MAINTAINING RENAL FUNCTION OVER 5 YEARS WITH BELATACEPT IN RECIPIENTS OF EXTENDED-CRITERIA DONOR KIDNEYS

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Background: BENEFIT-EXT randomized extended-criteria donor kidney recipients to more or less intensive (LI) belatacept regimens or cyclosporine (CsA). Patients continuing at 3 years could enter the long-term extension (LTE). We report shifts in cGFR stage (KDOQI CKD classification) from month 12 and 60 in 103/113 LI (approved regimen) and 79/87 CsA pts with data available at both timepoints. cGFR was imputed as 0 for death or graft loss.
Results: No LI patients were in Stage 1 or 5 at month 12; 1 CsA pt worsened from Stage 1 to 5 from months 12–60. In Stage 2 patients at month 12, 80% (20/25) LI and 47% (7/15) CsA maintained or improved GFR stage at month 60. In Stage 3 patients at month 12, 85% (63/74) LI and 76% (38/50) CsA patients maintained or improved GFR stage at month 60; and 3/4 LI and 7/12 CsA Stage 4 patients maintained or improved GFR stage. 1/1 CsA pt improved from Stage 5 to 4 from month 12–60.
Conclusions: In BENEFIT-EXT LTE, a smaller percentage of belatacept versus CsA patients were in Stages 4 and 5 at year 5. Belatacept ECD recipients were more likely to maintain or improve renal function over 5 years.

O068 PREVENTING DSA IN KIDNEY TRANSPLANT RECIPIENTS THROUGH OPTIMAL IMMUNOSUPPRESSION

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Introduction: This study aimed to demonstrate that sub-optimal immunosuppression (IS) post-transplant was associated with the development of *de novo* donor specific antibodies (DSA) in the serum of transplant recipients.
Methods: This retrospective case-control study compared IS regimes in DSA+VE and −VE recipients with similar allograft dysfunction ($n = 89$). No difference was seen in baseline factors.
Results: DSA+VE patient were shown to be exposed to a significantly lower IS burden in the 12 months prior to testing ($p = 0.0022$). Most notably, sub-therapeutic serum CNI levels were associated with DSA detection ($p = 0.0011$). A trend towards lower MPA use was seen in DSA+VE group but this was not significant. 14/49 and 1/48 of grafts failed in the DSA+VE and −VE group respectively. The median allograft survival post-DSA testing was of 36 months.
Conclusion: This study shows sub-optimal IS, is associated with the detection of DSA in a kidney transplant population.

O069 PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES OF TWO DIFFERENT RABBIT ANTITHYMOCYTE ANTIGLOBULIN DOSING REGIMENS

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Rabbit antithymocyte globulin (rATG) is currently used to prevent acute rejection in kidney transplantation. The dose and regimen of rATG have not been optimized and the impact of different treatment regimens on T-cell

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phenotype reconstitution remains unknown. We conducted a prospective randomized study of 17 renal transplant patients to determine the pharmacokinetics of total and active (bound to human cells) and T-cell phenotype reconstitution after rATG administration. Patients received a total dose of 6 mg/kg of rATG, administered either as 1.5 mg/kg/day on days 0–3 (Group 1, $n = 8$) or 3 mg/kg on days 0 and 3 (Group 2, $n = 9$). All patients received tacrolimus, mycophenolate mofetil and steroids. Blood samples were assayed for total rATG by enzyme linked immunosorbent assay and active rATG by flow cytometry. Maximum concentrations and terminal half-lives were similar between the two groups but at month 3 Group 1 had significantly lower values for total rATG (6.2 ± 1.1 μg/ml vs. 10.2 ± 2.9 μg/ml in Group 2, $p = 0.027$) and for total rATG dose-normalized AUC (374 ± 83 day/g/ml vs. 508 ± 149 day/g/ml in Group 2, $p = 0.046$). Time to sub-therapeutic levels (<1 μg/ml) of active rATG was significantly shorter in Group 1 (18.7 ± 56.9 days versus 20 ± 7.5 days in Group2, $p < 0.001$). rATG induced significant depletion followed by slow reconstitution of CD3+, CD4+, CD8+ T cells and CD3-CD56+ NK-cell, with no marked differences between groups. B-cell count was unaffected. rATG induced a significant decrease in the proportion of naïve CD4+ T-cells, which plateaued after month 1 in Group 1 and after month 6 in Group 2. The proportion of central memory CD4+ T-cells increased to a similar extent in both groups (Group 1: 38 ± 18% at baseline, 74 ± 23% at 1 year, $p = 0.009$; Group 2: 32 ± 14% at baseline, 65 ± 14% at 1 year, $p = 0.001$). In conclusion, our results suggest that the dosing regimen for rATG induction influences pharmacokinetic parameters without affecting the quality of immune reconstitution.

O070 TAILORING IMMUNOSUPPRESSION FOR ABO-INCOMPATIBLE KIDNEY TRANSPLANTATION BASED ON THE STRENGTH OF PRETREATMENT ANTI A/B ANTIBODY TITER

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Currently rituximab has been accepted to reduce the prevalence of AMR after ABO-incompatible Kidney Transplantation (ABOi-KTx). We have tested to exclude rituximab in low risk patients.

Patients and Methods: One hundred adult patients, 62 females and 38 males with a mean age of 50 years (21–75), underwent ABOi-KTx between 2007 and 2012. All patients received 2 weeks of mycophenolate mofetile and predonisolone before transplant, followed by calcineurin inhibitor (cyclosporine in 80 or tacrolimus in 20) and basiliximab after transplant. The patients with starting titer of 32× or more (SD group: $n = 77$) received low dose rituximab (100 or 200 mg/body ×2) and 4 times of pre-transplant plasmapheresis (PP). SD group included seven patients with pre-existing donor specific antibody (DSA). For the patients with starting titer below 16× (LR group: $n = 23$), rituximab was exclude from desensitization therapy and pre-transplant PP was reduced to two times.

Results: With a mean observation period of 35 (12–73) months, 3 and 5 years patient and graft survival are 98% in SD group and 100% in LR group. Current serum Cr and eGFR revealed 1.40–0.40 and 42.2–10.7 in SD group, and 1.48–0.39 and 41.5–9.1 in LR group. Nine percent (7/77) of SD group and 13% (3/23) of LD group were treated for clinical and subclinical T cell mediated rejection. Clinical AMR were observed in 3.9% (3/77) of SD group, and successfully treated with additional PP/IVIG and steroid pulse therapy. By stepwise regression analysis, pretransplant IgG titer more than 64× revealed significant predictive factor for clinical AMR. Subclinical AMR was observed 3.9% (3/38) of SD group by protocol biopsies and 2 of them had pre-existing DSA. None of LR group developed AMR.

Conclusions: This study suggests that rituximab can safely be excluded from the desensitization protocol of ABOi-KTx in low risk patient population. Furthermore, successful reduction of pretransplant IgG titer to <32× may reduce the incidence of AMR.

O071 HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN TREATMENT SUPPRESSES DENDRITIC CELL FUNCTION IN HUMANS BY STIMULATION OF THE IL-33-TH2 PATHWAY

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Background: High-dose intravenous immunoglobulin (IVIg) is used for prevention and treatment of antibody-mediated organ transplant rejection, but the mechanism of its anti-inflammatory effect is still enigmatic. Recent studies in mice suggest that IVIg suppresses antibody-driven inflammation by stimulating inhibitory Fcγ-receptor (FcγR)IIb expression on myeloid cells via a cascade of IL-33-Th2 cytokine production. Here, we investigated whether IVIg-therapy in humans stimulates the IL-33-Th2 pathway and modulates FcγR expression on circulating leukocytes.

Methods: Blood was collected from patients with hypo-gammaglobulinemia or autoimmune disease before, immediately after, and 7 days after IVIg-monotherapy.

Results: Plasma levels of IL-33 and the Th2 cytokines IL-4 and IL-13 increased following IVIg infusion and were still elevated 7 days later, while Th1 cytokine levels remained unchanged. Post-treatment IL-33 and Th2 plasma levels were significantly higher upon high-dose IVIg (≥0.6 g/kg) compared to low-dose treatment. Regression analyses suggested an IL-33-dependent induction of IL-4 ($r = 0.69$, $p < 0.001$) and IL-13 ($r = 0.63$, $p < 0.001$) production. *In vitro* IVIg induced IL-33 expression in human lymph node cells, and IL-33 stimulated Th2 cytokine production by human basophils. Expression of the activating FcγRIIa on circulating myeloid dendritic cells (mDC) decreased upon IVIg-treatment, but only in patients treated with high-dose IVIg, while FcγRIIb expression remained unchanged. In addition, a significant decrease of IFN-gamma receptor expression on circulating mDC was observed in patients treated with high-dose IVIg. *In vitro* experiments showed that IL-4-pre-treated mDCs produced less pro-inflammatory cytokines and chemokines upon stimulation with immune complexes or IFN-gamma.

Conclusion: In contrast to mice, high-dose IVIg therapy inhibits in humans mDC function via the IL-33-Th2 cytokine axis by reducing FcγRIIa and IFN-gamma receptor expression, rather than enhancing FcγRIIb expression.

O072 THE ROLE OF THE KIR RECEPTORS EXPRESSED BY NATURAL KILLER CELLS DURING ACUTE CMV INFECTION AFTER KIDNEY TRANSPLANTATION

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Human cytomegalovirus (CMV) infection may cause severe disease after solid organ transplantation. As cytotoxic T-cells are the main weapons to target CMV-infected cells, immunosuppressive drugs suppress T cell proliferation and activation, whereas natural killer (NK) cells are weakly affected. The regulation of NK cells depends on a large range of activating and inhibitory receptors, such as the KIR receptor family. Several human genetic studies have demonstrated the importance of the KIR family in the regulation of NK cells to clear CMV infections. However, the role of the different KIR proteins expressed by NK cells during CMV infection has not been extensively studied. We analyzed the expression of the KIR receptors in a cohort of 16 kidney-transplanted patients. The NK cell population, which expresses KIR3DL1, significantly increases during acute CMV reactivation. Then, we have set up an *in vitro* model, in which NK cells isolated from healthy donors or from transplanted patients, target allogenic fibroblasts infected or not with CMV. A significant correlation between the lysis of allogenic CMV infected fibroblasts and the expression of KIR3DL1 receptor was observed. Our results strongly suggest an important role for NK cells expressing KIR3DL1 during CMV infection.

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OS11-HEART

O073 CARDIOVASCULAR EVENTS WITH *DE NOVO* USE OF EVEROLIMUS IN HEART TRANSPLANT RECIPIENTS

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Background: The antiproliferative properties of everolimus (EVR) may be beneficial in minimising the long-term risk of cardiovascular events (CVE) in heart transplant recipients (HTxR).
Methods: In A2310, an open-label, multicentre study, HTxR were randomised to receive EVR 1.5 mg (C0 3–8 ng/ml; $N = 282$) or EVR 3 mg (C0 6–12 ng/ml; $N = 168$) + reduced cyclosporine (CsA) or MMF 3 g ($N = 271$) + standard CsA; with steroids ± induction. EVR 3.0 mg arm was terminated early due to higher mortality. We report 24-month (mo) results assessing the incidence of CVE (table).
Results: While CVE incidence was higher in EVR 1.5 mg group versus MMF in the 1st month post-Tx, mainly related to post-operative issues, EVR 1.5 mg was associated with a significantly lower CVE risk after 1mo post-Tx than MMF (table). The difference in CVE incidence favouring EVR 1.5 mg was greater during the second year.
Conclusions: The benefit seen in CVE incidence after 24 month of treatment with EVR may be related to its antiproliferative effect on the graft vascular intima.

O074 YOU ARE WHAT YOU EAT: IMPACT OF EARLY METABOLIC SYNDROME ON LONG-TERM OUTCOME AFTER HEART TRANSPLANTATION

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Backround: Metabolic syndrome (MS) is seen in a high rate of heart transplant patients. In recent studies MS has been associated with long-term complications. The aim of this analysis was to evaluate the impact of MS on long-term outcome after heart transplantation.
Patients and Methods: Of 307 adult 1-year survivors after heart transplantation were analysed between 1997 and 2009. All had a BMI <30 at time of transplant. Metabolic syndrome was defined using the NCEP- ATP III criterias and the modification from the AHA 2005. Patients were divided in two groups (I: development of MS within 12 mnoths post transplantation, II: no MS within 12 months post transplantation). Long-term outcome (survival, severe graft-vascuopathy [CAV ≥ 50% stenosis in any coronary vessel]) were compared between groups by Kaplan–Meier- analysis and Cox regression. Pre-TX factors were analyzed on their impact to develop MS post transplantation.
Results: One hundred and twenty-one (39.4%) patients developed MS during the first 12 months after transplantation. Five- and 10-year survival was significantly lower in Group I (5 years: 85.1% vs. 95.1%; p = 0.002; 10 years: 70% vs. 81.1%; p = 0.006) Patients in group I had a higher rate of death from of cancer (7% vs. 1.6%; p = 0.032) and CAV (8.3% vs. 2.7%; p = 0.014) Group 1 had a significantly higher rate of severe CAV (45% vs. 20%;p = 0,008) A Body mass index ≥25 before HTX (30% vs. 51%; p < 0,001) as well as age >35a (20% vs. 41.5% p = 0.022) were associated with a higher risk to develop MS Syndrome during the first year after HTX.
Conclusion: Development of MS during the first year after transplantation is a significant risk factor for Long-term survival and CAV development. Higher age and BMI at the time of transplant are associated with a higher risk to develop MS. Mechanisms of intervention a strongly needed to counteract.

O075 PHENOTYPE OF HEART ALLOGRAFT DYSFUNCTION AND DIAGNOSTIC CRITERIA FOR ANTIBODY-MEDIATED REJECTION: RE-DEFINING THE PROGNOSTIC ROLE OF PATHOLOGY AND DONOR-SPECIFIC ANTIBODIES

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Antibody mediated rejection (AMR) is a serious emerging issue in the management of heart transplant (HT) recipients. Although consensus criteria currently define pathological diagnosis of AMR (pAMR), the clinical drawbacks of the pAMR criteria in term of graft function and prognosis, as well relationships with donor specific antibodies (DSA) are unexplored. Herein we analyze the diagnostic information provided by pAMR and DSA in the context of normal and abnormal graft function (defined by right heart catheterization) and their ability to predict subsequent cardiovascular events (CVE: cardiovascular death or heart failure, coronary or arrhythmic events). One hundred and seventy-nine patients with suspect AMR 2(0.2–5) year after HT entered the study and 102 (57%) presented with graft dysfunction phenotype (GDP). Subsequently, 16% died and 24% experienced CVE. Death and CVE were more common in patients with GDP (p < 0.01). Coronary vasculopathy (CAV) explained 15% of the GDPs, being rare in patients with normal graft (p = 0.02). Cluster analysis found that pAMR was detected more often in the 88 patients with GDP and no CAV than in other subgroups (49 vs. 21–26%; p = 0.03). However, pAMR grading did not identify patients with subsequent CVE. Further dissecting biopsy features in GDP patients, we found that significant cellular infiltrate in the context of pAMR did identify patients at higher prevalence of CVE, as compared with patients with "pure" pAMR (55 vs. 19%; p = 0.04). In the 73 patients with antibody assay availability, we found that in GDP group DSA were significantly associated with CVE (64 vs. 28%; p = 0.01). Patients with DSA and pAMR had 6 times the odds of CVE than those with pAMR only (P < 0.01). This analysis shows that in HT recipients with suspect AMR, outcome is driven by graft dysfunction and DSA. Pathology for AMR may clarify the diagnosis of graft dysfunction (being more common in the GDP patients) but has prognostic relevance only when associated with cellular infiltrate or DSA.

O076 EARLY CALCINEURIN INHIBITORS AVOIDANCE IMPROVES RENAL FUNCTION IN DE NOVO HEART TRANSPLANT RECIPIENTS: THE RESULTS OF A RANDOMIZED CONTROLLED TRIAL (SCHEDULE TRIAL)

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Background: Calcineurin inhibitors remain crucial following heart transplantation, but are associated with significant side effects. We conducted a randomized, open-label, parallel group clinical trial to assess whether early introduction of everolimus followed by withdrawal of cyclosporine (CsA) would lead to superior renal function in de novo heart transplant (HTx) recipients, compared to a standard CsA-based protocol.
Methods: A total of 115 patients were randomly assigned within 5 days postoperatively to low dose everolimus and reduced dose CsA ($n = 56$) or standard CsA dosage ($n = 59$). All received mycophenolate mofetil and corticosteroids. In the former group, CsA was withdrawn and full-dose everolimus initiated after 7–11 weeks. The primary efficacy end point was renal function assessed by measured glomerular filtration rate (mGFR) after 12 months. Secondary objectives were progression of cardiac-allograft vasculopathy (as assessed by intravascular ultrasound (IVUS)), left ventricular function (assessed by echocardiography and NT-proBNP), number of rejections and serious adverse effects.
Results: At 12 months, mGFR was significantly higher in the everolimus group compared to standard CsA-based group (80 ml/kg/1.73 m^2 vs. 62 ml/kg/1.73 m^2; p < 0.0001; Intention To Treat population)). A significantly higher incidence of acute cellular rejection was observed in the everolimus group, while left ventricular dimension and function (assessed by echocardiography and NT-proBNP), were similar between the two groups. With similar rates of bacterial infection, cytomegalovirus infection was significantly less common in everolimus treated patients ($n = 3$ (5.4%) vs. $n = 18$ (30.5%); p < 0.001). IVUS data, not yet ready, will be presented.
Conclusions: Early elimination of CsA and replacement with an everolimus-based immunosuppressive strategy was associated with significant and clinically important improvement in renal function in HTx patients.

O077 VALIDATION OF THE NEW PROTOCOL OF ENDOMYOCARDIAL BIOPSIES AFTER CARDIAC TRANSPLANTATION

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Background: Endomyocardial biopsy (EMB) remains the method of choice for early diagnosis of graft rejection after cardiac transplantation (CTX). According to classical scheme 13 protocolar biopsies are performed during first 12 months after CTX. This invasive procedure is not without risk of complications and also brings some dyscomfort for the patients (pts). Since 10/2010 the

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modified scheme has been used in our Institution with extension of intervals between EMBs.The aim of the study was to evaluace prospectively safety of this modified protocol.
Methods: The group of pts with CTX done between 1/2011 and 1/2012 was analysed. Induction therapy with polyclonal antithymocyte globulin was used in all the pts, long-term prophylaxis consisted of tacrolimus, mycophenolate-mofetil and prednison. EMBs from right ventricle were performed under fluoroscopic control, samples were examined by histological and immunohistochemical methods. Cellular rejection (CR) was graded according to Banff classification. Echocardiographic examination (TTE) was performed the same day as EMB, LVEF < 40% was considered as graft dysfunction (GD). Coronary angiography was performed at 1 year after CTXs in 33 pts.
Results: During abovementioned period 43 CTX were performed, the group of 39 1 year survivors (30 men, aged 22–66 years, IHD/DCMP/other 13/20/6) was evaluated. Eight protocolar biopsies were done in each pt. Cellular rejection Banff gr. ≥2 was found in 5 pts (13%), treated episodes in 4 pts (10%). Graft dysfunction occured in 1 pt only, signs of coronary vasculopathy at 1 year were present in 9 (27%) pts.
Conclusion: In the era of current immunosupresive prophylaxis frequency of CR and GD is low during 1st year after CTX. Extending the intervals between protocolar EMBs is safe and can be reccomended for widespread use. Supported by grant IGA MZ CR NT 11262-6.

O078 LOSS OF DONOR RESPONSIVENESS IN T CELLS EXPOSED TO THE FISH OIL DERIVATIVE EICOSAPENTAENOIC ACID

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Background: CD4+ T cells contribute significantly to allograft rejection and represent a primary target for immunosuppression. The fish oil constituent, eicosapentaenoic acid (EPA) has reported immunomodulatory properties, so we investigated the effect of EPA on T helper cell function and alloresponsiveness.
Methods: Gas chromatography was used to determine EPA plasma membrane incorporation. Flow cytometry enumerated CD3+ CD4+ (CD45RA+/−/RO+/−) T cells. Proteomic analysis of molecules involved in intracellular signalling was performed. The effect of EPA on CD4+ T cell antigen specificity was determined via rapid CD154 capture and CD45RA/RO phenotyping following donor tissue-recipient CD4+ T cell culture.
Results: EPA downregulated CD4+ T cell surface CD45RO expression ($p = 0.012$) and reduced donor antigen specificity, determined via CD154 analysis ($p = 0.008$). Cell viability was unaffected ($p = 0.495$); suggesting EPA acts purely at a functional level. The phosphorylation of intracellular signalling kinases; STAT2, STAT5, STAT4, STAT1, AMPKalpha2, eNOS, HSP-27, p70-S6Kinase and RSK increased, whilst MEK, ERK, JNK, CREB, STAT3, STAT6 and mTOR decreased.
Conclusion: EPA exerts a direct, immunomodulatory effect on CD4+ T cells. Alterations in STAT phosphorylation suggest regulatory T (Treg) cell development, as opposed to TH17. Downregulation of CD45RO, MEK, ERK, JNK and CREB and loss of CD154 following alloantigen exposure indicates EPA impairs T cell alloresponsiveness. Treg development along with HSP27 and eNOS (assisted by AMPKalpha2) may suppress alloantigen specific T cell activation and induce antiinflammatory mediator release. EPA may represent an important therapeutic strategy to reduce graft rejection and other clinical pathologies.

O080 DONOR/RECIPIENT AGE INTERACTION AND RISK FACTORS FOR DEATH AND CARDIAC ALLOGRAFT VASCULOPATHY IN CARDIAC TRANSPLANTATION

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Background: Donor and recipient age in heart transplantation (HTX) are constantly rising. The possible interaction between donor and recipient age and factors that might influence mortality and development of cardiac allograft vasculopathy (CAV) contain great implication for future allocation strategies.
Methods and Results: A retrospective cohort study was conducted with 1190 patients undergoing HTX at the Medical University of Vienna from 1984 to 2011. Adjustment for continuous donor/recipient age, era of transplantation and for sets including confounders and mediators as donor/recipient sex, assist device, admission status, ischemic time, creatinine, diabetes and previous cardiac operation was carried out. Survival after 1, 5 and 10 years was 80, 69 and 56%, respectively. No donor/recipient age interaction was detected and donor age (HR 1.1; CI 1.0-1.2), recipient age (HR 1.1; CI 1.0–1.2), admission from the intensive care unit (ICU) to HTX (HR 1.5; CI 1.2–1.9) and recipient diabetes (HR 1.4; CI 1.1–1.7) were identified as independent risk factors for mortality by Cox regression models. To detect age effects on development of CAV we applied cause-specific (death censored) Cox models and proportional sub-distribution hazard models for competing risk data according to Fine and Grey. No interaction between donor and recipient age was observed. Donor age (HR 1.4; CI 1.3–1.5) and male recipient sex (HR 1.5; CI 1.0–2.2) were identified as independent risk factors whereas recipient age showed a negative association (HR 0.8; CI 0.8–1.0) towards initiation of CAV.
Conclusion: No interaction could be observed between donor and recipient age on mortality and CAV.

O081 IMPACT OF INTERVAL FROM TIME OF DIAGNOSIS OF BRAIN STEM DEATH TO TIME OF PROCUREMENT ON SURVIVAL IN HEART TRANSPLANTATION

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Interval between brain stem death (BSD) and organ procurement has been raised as a possible factor in determining survival and outcome post heart transplantation. Our hypothesis was that a longer time interval from BSD to procurement may allow for recovery of the donor heart from the adverse systemic effects of sympathetic discharge and hypertensive crisis that often accompany BSD. A retrospective analysis was performed of a prospectively maintained database of 1249 heart transplant patients transplanted between 1979 and 2012. Time interval between BSD and organ procurement was correlated with length of ITU stay and survival post cardiac transplantation. Transplants were divided into groups relating to time interval from BSD to procurement. Group 1 = 0–6 h, Group 2 = 6–12 h, Group 3 = 12–18 h, Group 4 = 18–24 h, Group 5 = 24–30 h and Group 6 >30 h. Interval between BSD and procurement was recorded for 969 patients with a mean interval of 12.8 ± 10.3 h. Mean recipient age was 47.0 ± 11.5 years and mean donor age was 33.0 ± 12.5 years. Transplant recipients who received hearts recovered within 6 h of BSD testing had shorter ITU stay (Group 1 2.8 days, Group 2 3.7 days, Group 3 5.1 days, Group 4 4.8 days, Group 5 5.7 days, Group 6 = 3.9 days $p = 0.003$). There was no significant difference between groups in terms of 30 day (mean 90.2% $p = 0.64$) or 1 year (mean 78.2% $p = 0.16$) survival following heart transplantation. These results show no evidence of an impact on survival of time from BSD testing to time of organ procurement. Shorter time to procurement may have a beneficial effect in reducing recovery time on the intensive care unit of heart transplant recipients. This could be due to minimisation of the duration of exposure of the donor heart to the adverse pathophysiological consequences of BSD.

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OS12- BASIC SCIENCE: MISCELLANEOUS

O082 PROLONGED ALLOGRAFT SURVIVAL MEDIATED BY INTERLEUKIN-10 PRODUCING REGULATORY B CELLS REQUIRES B CELL RECEPTOR LIGATION BUT NOT COGNATE T CELL HELP

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Background: Late graft loss is a major problem in clinical transplantation. Interleukin-10 (IL-10) secreting B regulatory cells (Bregs) have been described that ameliorate autoimmune disease. Here we study whether Bregs can prevent chronic rejection using a well-characterised murine model of cardiac allograft vasculopathy (CAV) and propose a mechanism for their action.
Methods: B6.H-2bm12 (bm12) heart allografts provoke strong autoantibody responses in naïve C57BL/6 (B6) recipients, are rejected slowly and develop severe CAV, an effect due to donor bm12 CD4 T cells providing help via the MHCII molecule on recipient autoreactive B cells (Win, T.S. et al. Circ Heart Fail 2009; 2(4):361–9). Recipient Bregs were generated *in vitro* by culturing naive B6 B cells with anti-CD40 monoclonal antibody for 3 days. IL-10 expression by B cells was confirmed by ELISA and flow cytometry. Similarly cultured B cells from IL-10 deficient B6 mice were used as controls. The ability of Bregs to ameliorate graft rejection, effector autoantibody and CAV was tested by adoptive transfer of 2 × 107 cultured B cells into B6 recipients of MHCII-mismatched heart grafts. Similarly cultured B cells from MHCII deficient mice were used to investigate the importance of cognate T cell interaction; and from mice expressing a monoclonal population of B cells specific for the hen egg lysozyme (HEL) antigen only (not expressed in B6 mice) were used to investigate the importance of B cell receptor (BCR) ligation.
Results: Control cultured B cells from IL-10-deficient mice hastened heart graft rejection. Putative IL-10 secreting Bregs resulted in markedly prolonged allograft survival with abrogation of the autoantibody response and development of minimal CAV, an effect maintained with Bregs lacking MHCII, but lost with HEL-specific Bregs unable to bind antigen (see Figure).
Conclusion: IL-10 Bregs may prolong clinical allograft survival; BCR ligation, but not cognate T cell help, is necessary.

O083 DOUBLE-DEFICIENCY FOR RORT AND T-BET INDUCES TH2-MEDIATED ALLOGRAFT REJECTION IN MICE

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While Th1, Th2 and Th17 cells are considered to be major effector cells in adaptive alloimmune responses, their respective contribution to allograft rejection remains unclear. To investigate this, we adoptively transferred T cells from B6.RORγt knockout (KO) mice (non-Th17, prone to Th1), B6.T-bet-KO mice (prone to Th2/Th17), and B6.RORγt-T-bet double-KO mice (RORγt-T-bet-DKO, prone to Th2) to B6.Rag-γ-chain-KO recipients of fully mismatched Balb/c heart allografts (HTx). Importantly, T-bet-KO T cells rejected heart allografts at a more accelerated rate (19.8A ± 6.47day) than cells from RORγt-KO mice (>80 day in 63% of mice), indicating a predominance of Th17- over Th1-driven alloimmunity. Unexpectedly, double-deficiency for T-bet and RORγt resulted in early allograft rejection (22.8A ± 3.65 day) featuring high levels of IL-4 (by flow cytometry), a significantly upregulated intragraft mRNA expression of Th2 related cytokines and eosinophilic allograft infiltration. Importantly, a neutralization of IL-4 in recipients given RORγt-T-bet-KO T cells significantly prolonged allograft survival (>60d in 57% of mice) and reduced eosinophilic infiltration. We conclude that while Th17 cells predictably promote allograft rejection in the absence of T-bet, Th2 cells, which have generally been thought to protect allografts, may be potent effector cells in allograft rejection in the absence of both, T-bet and RORγt.

O084 ENHANCED PRO-INFLAMMATORY PROFILE AND TH17 ALLORESPONSE BY R TARGETING MTORC2 IN MYELOID DC

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Background: Mammalian target of rapamycin (mTOR) is an important integrative kinase that regulates immune cell function. mTOR functions in two independent complexes: mTOR complex (mTORC) 1 and 2. The immunosuppressant Rapamycin inhibits mTORC1 but not mTORC2. Our aim was to study the immune regulatory role and underlying mechanistic properties of mTORC2 in DC.
Methods/Materials: We generated a conditional mTORC2 knockout, targeting Rictor. Bone marrow cells were obtained from KO and WT B6 controls, and DC propagated in GM-CSF and IL-4, with or without LPS. Cell surface phenotype, cytokine production, STAT3 activation and the ability of the DC to induce allogeneic T cell proliferation were evaluated, as well as responder T cell phenotype and cytokine production in MLR. To assess the role of Rictor in host DC following transplantation, we grafted male WT skin on to DC-specific Rictor-KO female mice (generated using the Cre/LoxP system to knockout Rictor on CD11c+ cells).
Results: DC differentiation was not affected, while DC yield was slightly reduced in mTORC2-deficient BM cell cultures compared with WT controls. DC lacking mTORC2 activity displayed similar levels of MHC and co-stimulatory molecules, but diminished B7-H1 expression, increased levels of IL-12p40, diminished STAT3 activation and higher T cell allostimulatory ability following LPS stimulation, compared with WT. Staining of allogeneic T cells stimulated by Rictor-KO DC revealed more IL-17-producing CD4+ cells compared with those stimulated with WT DC. Female DC-specific Rictor-KO mice rejected male WT skin graft faster than controls (median survival of 20 days versus 27 days, respectively; $p < 0.5$, $n = 2$).
Conclusion: These novel data indicate that DC lacking mTORC2 activity exhibit an enhanced pro-inflammatory profile with ability to promote Th17 responses and accelerate skin graft rejection. Thus, targeting mTORC2 provides new insight into molecular regulation of DC function with therapeutic implications in.

O085 INTRAGRAFT DENDRITIC CELLS EVOKE THE MORE POTENT IL-17 MEDIATED IMMUNE RESPONSE AFTER THE TRANSPLANTATION OF ALLOGRAFTS FROM OLDER DONORS

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Organs from older donors are increasingly utilized to meet the discrepancy between supply and demand with organs suitable for transplantation. Clinically, donor age has not only been linked to compromised graft function but also to more frequent acute rejections. Herein we dissected the impact of donor age on the recipient's immune response *in vitro* as well as *in vivo*. Hearts from either young (3 months) or old (18 months) C57BL/6 (B6) mice were transplanted into young (3 months) DBA/2 recipients. Old hearts were rejected significantly faster than young hearts (MST: 9 vs. 11, $p = 0.002$). Significantly higher ISHLT rejection scores ($p < 0.05$) were observed in old cardiac allografts by day 7 after transplantation. Of note, IL-17 cytokine mRNA levels were dramatically increased within old allografts (30 fold increase, $p = 0.0357$). Moreover, recipients of old grafts displayed increased frequencies of alloreactive IFN-γ producing splenocytes (ELISpot), higher percentages of CD8+ effector and CD8+ IFN-γ+ T cells ($p < 0.05$ for all experiments). After confirming that organ age is critically influencing recipient's immune responses we dissected the role of old passenger leukocytes. Chimeric animals were generated by transplanting syngeneic bone marrow from young B6 mice into lethally irradiated old or young B6 mice. Grafting of these chimeric hearts resulted in comparable survival rates (MST: 10 vs. 10), rejection scores and recipient systemic immune responses ($p > 0.05$ for al experiments). Those data highlight that passenger leukocytes but not organ age 'per-se' were responsible for the more potent immune response after the transplantation of organs from older donors. Next, we depleted cardiac DC's using liposomal clodronate as it has been shown that among all passenger leucocytes, DC's are the most potent cells in priming an alloimmune-response. Depletion of CD11c+ cells within the graft resulted in comparable survival rates and rejection scores. Moreover, systemic recipient alloimmune responses were not different after the engraftment of old or young allografts when CD11c+ cells had been depleted. Furthermore, IL-17 mRNA levels were significantly reduced in old allografts when CD11c+ cells had been depleted and reached levels comparable to those in hearts from young donors. Of clinical significance, systemic treatment of the recipient with anti IL-17 resulted in a significantly prolonged survival of old allografts, whereas the treatment did not influence the graft survival of young allografts. Taken together, these data show that donor age enhances CD11c+ cell immunogenicity through a potent Th-17 specific response. Blocking IL-17 in recipients of old allografts abolishes donor age-related compromised survival rates.

O086 MTOR, BUT NOT CALCINEURIN, INHIBITION PRESERVES ANTI-TUMORAL CD8 IMMUNITY IN TRANSPLANT RECIPIENTS

Jordi Rovira[1], Manije Sabet-Baktach[1], Margareta Lantow[1], Margareta Lantow[1], Elke Eggenhofer[1], Gudrun Koehl[1], Hans-Jürgen Schlitt[1], Josep M. Campistol[2], Edward K. Geissler[1], Alexander Kroemer[1]

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Background/Main Objective: The purpose of this study was to investigate the role of mTOR versus calcineurin inhibition in anti-tumoral CD8+ cytotoxic T (cT) cell responses in posttransplant malignancy.
Methods: We explored the differentiation and function of alloreactive cT cells *in vitro* by stimulating cT cells from OTI mice with OVA-transgeneic APCs in the presence of rapamycin (Rapa) or cyclosporine A (CsA). We adoptively transferred purified OTI cT cells into B6 recipients of either OVA-transgeneic skin transplants or subcutaneous OVA-B16F10 tumors. Also, we created CD8-OTI-transgeneic reporter mice by crossbreeding DsRed-expressing B6.Nagy mice with B6.OTI mice to track OTI cT cells in anti-tumoral and alloresponses *in vivo*.
Results: Rapa, but not CsA, induced a dose-dependent phenotypic shift from cT effector-memory (EM) cells to highly tumor-reactive cT central-memory (CM) cells. Importantly, cT memory cells treated with Rapa up-regulated T-bet and Eomes and showed preserved levels of IFNγ and perforin. In contrast, CsA blocked expression of T-bet, IFNγ and perforin. While OVA-skin allograft survival was equally prolonged in both Rapa- and CsA-treated recipients, OVA-melanoma growth was enhanced in CsA-treated mice, but substantially reduced with Rapa-treatment (versus controls). Moreover, DsRed+OTI cT cells of CM phenotype could be readily recovered from secondary lymphoid organs and tumor infiltrates of Rapa-treated B6 recipients.
Conclusion: mTOR, but not calcineurin, inhibition preserves anti-tumoral immune responses in this model, which may be important for understanding and reducing posttransplant malignancy.

O087 THE FUNCTIONAL INFLUENCE OF ACTIVATING NK CELL RECEPTORS DURING SOLID ALLOGRAFT REJECTION

Cornelia Fabritius[1], Paul Ritschl[1], Susanne Ebner[1], Rupert Oberhuber[1], Julia Günther[1], Anh-Vu Nguyen[1], Martina Sauter[2], Karin Klingel[2], Johann Pratschke[1], Katja Kotsch[1]
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Background: Although it has been shown that Natural Killer (NK) cells influence allograft survival, little is known about the involvement of their activating receptors impacting acute rejection.
Material and Methods: To gain more insight into the functional importance of certain NK cell receptors during acute rejection, we used BALB/c mice as allograft donors and NKp46- (Ncr1), NKG2D- and Ly49-deficient mice on a C57BL/6 background as graft recipients in an experimental model of heterotopic heart transplantation. Ncr1 k.o. mice possessed a green fluorescent protein (GFP) cassette knock in at the Ncr1 locus, wildtype C57BL/6 mice served as controls. Animals were either sacrificed at day 5 (d5) or at day of rejection (dRx) for analysis ($n = 6$/group/time point).
Results: Although graft survival revealed no significant differences between wildtype and NK cell receptor deficient mice, a strong infiltration of NKp46¬+ (GFP+) NK cells into the allograft is already observed at d5 for all investigated groups, however, Ncr1- and NKG2D-deficient mice showed significant more frequencies of intragraft NK cells compared with wildtype mice ($p < 0.01$, respectively). At dRx, NKp46+ cells are clearly diminished in the allograft in all groups. Among T cell subsets, all groups displayed a significant intragraft induction of cytotoxic CD3+ CD8+ T cells at dRx, whereas induced frequencies of CD3+ CD4+ T cells were observed in allografts from NK cell receptor deficient mice suggesting an acceleration of CD4+ T cell mediated rejection ($p < 0.01$, respectively). Strikingly, significant enhanced levels of CD8+ CD122+ regulatory T cells in all NK cell receptor deficient mice were observed at dRx in both spleen and lymphnodes ($p < 0.01$ versus wildtype).
Conclusion: Our results reveal novel insights into the kinetic distribution of NK cells in grafts and secondary lymphoid organs and highlight the impact of NK cell receptor deficiency on various lymphocytes subsets during acute cellular rejection.

O088 CROSSTALK BETWEEN INFLAMMATION, ADAM10 PROTEOLYTIC ACTIVITY AND NOTCH SIGNALING IN ANTIBODY-MEDIATED REJECTION AND ENDOTHELIAL DYSFUNCTION

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Background: A Disintegrin And Metalloproteinases (ADAMs) regulate key proteolytic events involved in inflammatory cytokine and chemokine release and in Notch signaling. ADAM10 is constitutively and preferentially expressed in endothelial cells (EC) whereas ADAM17 is usually induced by inflammation. This study investigates the contribution of ADAMs and Notch signaling to vascular injury associated with donor-specific antibody-mediated rejection (AMR) in cardiac allografts.
Methods/Materials: Regulation of ADAM10, −15, −17, Notch receptors (Notch1, 2, 3, 4) and ligands (Jagged1, Dll4), and VCAM1 was analyzed by quantitative PCR and by immunohistochemistry in cardiac biopsies from patients with stable graft ($n = 4$) or with AMR ($n = 9$), non failing heart ($n = 8$) and dilated cardiomyopathy ($n = 9$). Crosstalk between inflammation, ADAM10 proteolytic activity and Notch pathway was further investigated in cultured EC from donor transplants.
Results: We found that AMR induced by donor-specific anti-HLA is characterized by an up-regulation of both ADAM10 and ADAM17 mRNAs (respectively 4.3 and 3.4-fold increase versus controls, $p < 0.01$) without any change in ADAM15 mRNA. ADAM10 is located in graft EC and in infiltrating CD68+ macrophages and some CD3+ T cells. AMR is also associated with a significant increase in Notch ligands Jagged1 and Dll4 and drastic down-regulation of the endothelial Notch4. In cultured EC, TNF recapitulates ADAM10-dependent Dll4/Notch4 imbalance. ADAM10 blockade also efficiently decreases the production of the pro-inflammatory cytokines and chemokines IL6, IL8, MCP1, CXCL16 and CX3CL1.
Conclusion: Our findings suggest that ADAM10 is a major metalloproteinase driving proteolytic events involved in inflammatory responses and immune cell recruitment during AMR through the Notch pathway.

O089 A NOVEL RECOMBINANT FORM OF THE HUMAN MANGANESE SUPEROXIDE DISMUTASE PROTECTS RAT LIVER GRAFTS PROCURED FOR TRANSPLANTATION

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Introduction: Ischemia-reperfusion during liver transplantation causes hepatic injury and early graft dysfunction. The mechanisms involved include vascular dysfunction and oxidative stress. A new recombinant human manganese superoxide dismutase (rMnSOD) has been generated. This protein form freely enters the cells and is constitutively active. The present study aimed at evaluating the protective effects of rMnSOD on the hepatic and endothelial function and viability of liver grafts undergoing cold storage and warm reperfusion injuries.
Methods: (i) Effects of rMnSOD on oxidative stress levels and NO bioavailability were tested in freshly isolated liver sinusoidal endothelial cells (SEC) preserved in cold storage conditions. (ii) Rats were i.v. treated with rMnSOD, or its vehicle, 30 min before liver graft procurement and cold preservation for 16 h. Afterwards, grafts were warm reperfused for 1 h and hepatic injury, endothelial function, antioxidant capacity, oxidative stress, inflammation, and nitric oxide bioavailability were evaluated. (iii) Antioxidant capability of rMnSOD as supplement of a preservation solution was evaluated in hepatic biopsies cold stored for transplantation.
Results: 1- Cold storage induced a marked increase in O2- levels and a decrease in NO bioavailability in SEC, those detrimental effects were abolished in cells preserved with rMnSOD. 2- In rats, administration of rMnSOD ameliorated hepatic injury and endothelial dysfunction derived from cold storage and warm reperfusion injuries. The beneficial effects of rMnSOD were associated with a reduction in hepatic oxidative stress and inflammation together with an improved antioxidant activity and nitric oxide bioavailability. 3- rMnSOD added to a conventional preservation solution maintains its marked antioxidant activity avoiding oxidative stress formation in hepatic tissue preserved for transplantation.
Conclusion: rMnSOD represents a new therapeutic strategy to protect liver grafts undergoing transplantation.

O090 ENDOTHELIAL CELL ALLOGENICITY IS INCREASED BY HLA CLASS II ANTIBODY INDUCED SIGNALING

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Background: Antibody mediated graft rejection (ABMR) targets microvascular endothelial cells (ECs) leading to microcirculation inflammation and transplant glomerulopathy (TG). HLA class II alloantibodies have been associated with TG independently of complement activation. We have reported that HLA-DR expressing allogenic endothelial cells (ECs) expand pro-inflammatory Th17 (via an IL-6/STAT-3 pathway) and regulatory FoxP3+ Tregs (dependent on EC CD54 expression) under inflammatory conditions.
Methods/Materials: ECs were activated by HLA class II Abs before determining signaling, cytokine secretion and CD4 + -T sub-population expansion.
Results: HLA-DR Ab mediated EC activation led to: phosphorylation, increased IL-6 secretion (reproduced by the F(ab')2 fragment), amplified Th17 and decreased Treg expansion.
Conclusion: These data reveal a potential mechanism of HLA-DR alloantibody driven allograft damage due to EC activation resulting in an increased local Th17 response.

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BOS09-KIDNEY - COMPLICATIONS/CARDIOVASCULAR

BO81 THE NATURAL HISTORY OF PREDIABETES AND NEW ONSET DIABETES AFTER TRANSPLANTATION

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Background: Long-term data (beyond 12 months) on the incidence and prevalence of pre-diabetes or new-onset diabetes after transplantation (NODAT) as well as the evolution of prediabetes to NODAT or to normal glucose metabolism in stable renal transplant are scarce.
Methods: Eight Spanish centers contributed 50–100 non-diabetics each. Patients underwent oral glucose tolerance test (OGTT) at 3 months and annually during 3 years, with a subgroup was followed up to 5 years. Patients were categorized in each period as Normal, Prediabetic: impaired fasting glucose (IFG: glucose >100 < 126 mg/dl), impaired glucose tolerance (IGT: 2-h glucose >140 < 200 mg/dl) or NODAT (ADA criteria). Prevalence and changes of category were analyzed. Immunosuppresive therapy was CNI+MMF+low dose steroids in 82.9%.
Results: We evaluated 656 patients at 3-months, 597 (1 year), AT. NODAT ranged from 14% (3-months) to 25.3% (5 year). The majority of NODAT cases (95 of 130, 73%) were observed before 3 months (3 years incidence). Beyond 3 month the incidence of NODAT was lower and almost only patients with prediabetes evolve to NODAT (17/251, 6.7%).Prediabetes prevelence ranged from from 37.4% (3-months) to 17.6% (5 year). The most frequent prediabetic alteration was IGT: 23.8% (3-months) to 13.6% (5 year). Prediabetes evolved into NODAT (16.3%) or normality (37.2%) and 46.5% remained prediabetic (3 year incidence). Most normal and NODAT patients remained stable during follow-up.
Conclusions: NODAT and prediabetes are highly frequent after renal transplantation. The evolution of NODAT has a bimodal pattern: early (before 3 months) and late NODAT (after 3 months). Late NODAT indicates clearly the evolution of prediabetes to diabetes. Early NODAT may indicate patients at high risk dor diabetes in the waiting list. These differenciation may have clinical relevance in preventing NODAT.

BO82 NEW- ONSET DIABETES AND GLUCOSE REGULATION ARE SIGNIFICANT DETERMINANTS OF LEFT VENTRICULAR HYPERTROPHY IN RENAL TRANSPLANTATION PATIENTS

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Baskent University Medical School

Background: New-onset diabetes after solid organ transplantation is an important clinical challenge associated to increased risk of cardiovascular (CV) events. The aim of this study is to evaluate the relationship between post-transplant new-onset diabetes and arterial stiffness and LVMI in kidney transplant recipients.
Methods: One hundred and fifty-nine kidney transplant recipients' (57 with new-onset diabetes) clinical and biochemical parameters pulse wave velocity (PWv) levels and echocardiography measurements were analyzed.
Results: The percentage of patients with high LVMI (>130 g/m^2) was significantly higher in patients with post-transplant diabetes ($p < 0.05$). The body mass indices of patients with new-onset diabetes was significantly higher (p: 0.002). In patients with new-onset diabetes, serum HbA1c levels are significantly correlated with LVMI (p: 0.05). In patients with high LVMI; serum HbA1c levels (p: 0.001), systolic and diastolic blood pressures and age were significantly higher than in patients with low LVMI ($p < 0.05$). Linear regression analysis revealed that HbA1c was the major determinant of LVMI (P:0.026).
Conclusions: Post-transplant increased LVMI is associated with new-onset diabetes after renal transplantation. HbA1c is the major determinant of LVMI, so strict control of serum glucose levels is essential for preventing cardiovascular disease.

BO83 NUTRITIONAL STTAUS AND ADIPOKINES LEVEL IN KIDNEY TRANSPLANT RECIPIENTS

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Background: The disturbances of adipokines concentration are recognized in patients after kidney transplantation (KT). The aim of the study was to evaluate the prevalence of adipokines and body composition abnormalities in a cohort of stable kidney recipients.
Methods: The study was performed in 80 kidney transplant recipients (KTR). Nutritional status was determined by a 7-point Subjective Global Assessment (SGA), anthropometric measurements (BIA) and s-albumin concentration. C-reactive protein (CRP), Il-6 and PAI-1 were used as markers of inflammatory status. Concentration of leptin, adiponectin and visfatin were measured by ELISA.
Results: Mean KTR age was 52.4 ± 14 years Mean time after transplantation was 82.5 ± 56.5 months. Mean eGFR was 42 ± 15 ml/min. Overweight was present in 41% and obesity in 14%. On the basis of SGA evaluation, 52% of KTR were in good nutritional status. The excessive body mass and leptin positively correlated with time after transplantation and negatively with eGFR. KT patients with good allograft function presented significantly lower leptin level and BMI. Nutritional status, visfatin or adiponectin not correlated with eGFR, BMI or transplantation vintage.
Conclusions: Transplantation vintage was directly associated with high BMI, abdominal obesity and higher leptin concentration. These abnormalities possibly associated with elevated risk of cardiovascular diseases observed in KTR.

BO84 ROSUVASTATIN IS A POTENT LIPID-LOWERING STATIN IN RENAL TRANSPLANT RECIPIENTS RECEIVING EVEROLIMUS

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Background: Cardiovascular disease is the leading cause of death in renal transplant recipients (RTR). Everolimus induces dyslipidemia and may increase cardiovascular risk. In non-transplant patients rosuvastatin lowers lipids more effectively than fluvastatin, the current statin of choice in RTR. Since rosuvastatin may interact with everolimus, we evaluated the pharmacokinetics (PK) of both drugs in RTR.
Methods: Twelve stable RTR receiving everolimus and fluvastatin (80 mg/day) had their statin changed to rosuvastatin (20 mg/day). A 12-h PK investigation of everolimus was performed before the switch and a 12/24-h investigation of everolimus/rosuvastatin after 1 month of rosuvastatin therapy. All other drugs were unchanged.
Results: Rosuvastatin decreased LDL-cholesterol by 30 ± 12% ($p < 0.01$), and total cholesterol by 18 ± 10% ($p < 0.01$) compared to fluvastatin therapy. Everolimus AUC was not affected by concomitant rosuvastatin ($p > 0.6$). Mean rosuvastatin AUC0-24 was 157 ± 62 ng*h/ml, 3-fold higher than in non-transplant patients. There were no adverse events.
Conclusion: In stable renal transplant recipients receiving everolimus and fluvastatin, rosuvastatin lowered lipids further after switching from fluvastatin. Rosuvastatin did not affect everolimus AUC, but the rosuvastatin AUC was higher than historical controls. The combination was not associated with any short-term adverse effects.

BO85 TREATMENT EFFICACY OF HYPERTENSION IN DUTCH KIDNEY TRANSPLANT RECIPIENTS

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Background: Hypertension (HT) in kidney transplant recipients (KTR) jeopardizes graft and patient survival. KDIGO target on blood pressure (BP) is <130/80 mmHg and on sodium intake <90 mmol/day. Treatment efficacy of HT among Dutch KTRs is unknown.
Methods: We retrieved data on BP and antihypertensives (AHD) from the Dutch Organ Transplant Registry (NOTR) on 5415 KTRs registered in 2011. We also studied dosages of AHD and 24 h-urinary sodium excretion (NaE) from 534 KTRs treated in our center.
Results: BP in NOTR-patients was 134/80 mmHg (Interquartile range (IQR) 122–145/70–85) In 77.2% of patients, BP was ≥130/80 mmHg of whom 10.4% had no registered use, 30.0% used one, 33.7% used two and 25.9% used ≥3 antihypertensive drugs. In our centre 78.7% of the KTRs had a median BP ≥130/80 mmHg of whom sub-maximal dosages were prescribed in 74.0% of the KTRs with a BP ≥130/80 mmHg and who used at least one antihypertensive agent. Median 24-h urinary NaE was 147 mmol/day (IQR 109–195).
Conclusion: Treatment efficacy of HT in Dutch KTRs is low. Our data suggest that pharmacological treatment and dietary salt restriction can be intensified.

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BO87 INTENSIVE EXERCISE TRAINING AFTER SOLID ORGAN TRANSPLANTATION

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Background: Transplantation (Tx) now offers many patients suffering from end-stage organ failure long-term survival. Cardiorespiratory fitness improves after Tx, but remains reduced by 25% compared to age and gender matched control subjects (Painter et al. Am J Kidney Dis 1987; 10:452–456) The aim of our project was to determine whether stable Tx-recipients could follow an intensive exercise program allowing them to climb a challenging bicycle ride: Mont Ventoux (altitude 2000 m, 7–10% slope).
Methods: Twenty-one stable Tx-recipients (two females/19 males; mean age 40 years; seven kidney, four heart, six lung, three liver and one heart/liver) recipients were selected. They participated in a rigorous individualized training schedule supervised by exercise physiotherapists and Tx-physicians during 6 months. Cardiorespiratory fitness was assessed before (baseline) and after 6 months of training by means of a maximal cardiopulmonary exercise test using a ergospirometer bicycle.
Results: Before the start of the training, cardiorespiratory fitness was impaired in all Tx-recipients: maximal oxygen consumption normalized for body weigth (VO2 max/kg) was 11.5% below the age and gender matched predicted level. After 6 months of training the VO2 max/kg increased with 1.9 ml/min/kg ($p < 0.05$, paired *t*-test). The resting heart rate decreased with a mean of 7.9 beats/min ($p < 0.05$, paired *t*-test). No change in anaerobic threshold, peak power nor resting diastolic and systolic blood pressure was observed. Eventually, 19/21 Tx-recipients successfully climbed to the top of the Mont Ventoux.
Discussion: This project demonstrates that selected Tx-recipients are capable of (i) participating in intensive exercise programs, resulting in a (ii) significantly improvement of their cardiorespiratory fitness and allowing them (iii) to perform strenuous physical activity. Further research to investigate whether such programs increase long-term physical activity and reduce cardiovascular disease post-Tx are needed.

BO88 SERUM NT-PROBNP PREDICTS ADVERSE CARDIAC EVENT AFTER KIDNEY TRANSPLANTATION FROM DONORS AFTER CARDIAC DEATH

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Backgroud: Cardiovascular morbidity and mortality are highly prevalent in kidney transplant (KTx) recipients. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is well known maker of cardiac dysfunction and is a strong predictor of mortality in dialysis patients. However, little is known about the relationship between NT-proBNP and mortality in KTx. We evaluated the serum NT-proBNP as a predictive biomarker for the adverse cardiac events (ACE) after KTx from donors after cardiac death (DCD).
Materials and Methods: Consecutive patients undergoing living-related ([LD] [$n = 28$]), brain dead ([BD] [$n = 4$]) or DCD ($n = 28$) KTx were retrospectively enrolled. Serum samples were collected serially before and after KTx. sNT-proBNP was measured pre-Tx, 1 month (1 month) and 1 year (1 year) post-Tx using Elecsys immunoassay.
Results: In LD and BD KTx, sNT-proBNP decreased rapidly. In contrast, sNT-proBNP decreased slowly in DCD. Six cases suffered adverse cardiac events (ACE) within 1 year after KTx. sNT-proBNP level is significantly higher in ACE cases at 1 month and 1 year after KTx. Analysis of receiver operating characteristic curves demonstrated that ACE was predicted with 80% sensitivity (SE) and 89% specificity (SP) at a cutoff of 1200 ng/ml in 1 month (AUC 0.94) and 83% SE and 83% SP at 450 ng/ml in 1 year (AUC 0.97) after KTx.
Conclusions: These data suggested that serial analysis of sNT-proBNP may predict adverse cardiac events after kidney transplantation from donors after cardiac death.

BO89 PREDICTION OF CARDIOVASCULAR EVENTS AFTER RENAL TRANSPLANTATION

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Background: Pulse wave velocity (PWV) is a marker of arterial stiffness and predicts cardiovascular events in the non-transplant population. Cardiovascular events are the leading cause of death and one of the leading causes of graft failure in renal transplant recipients. The present prospective study investigates, whether there is a correlation between PWV and cardiovascular events in renal transplant recipients as well.
Methods: A prospective study assessing the incidence of a composite cardiovascular endpoint within ≥3 years after pulse wave analysis was performed in 65 stable renal transplant recipients. Measurement of PWV was conducted by the SphygmoCor (AtCorR) device. Composite endpoint of the study was the incidence of either myocardial infarction, stroke, occlusion of peripheral artery, admission to hospital due to decompensation of congestive heart failure, or death.
Results: Fifteen patients (23%) reached the composite endpoint during a follow-up of 4.4 ± 0.5 years. Binary logistic regression using PWV, systolic, diastolic and mean blood pressure as covariates revealed, that PWV (10.1 ± 3.6 m/s in subjects reaching the endpoint vs. 8.5 ± 1.5 m/s in subjects not reaching the endpoint) was significantly associated with cardiovascular incidents ($p = 0.017$). Systolic (130.5 ± 29.9 vs. 131.7 ± 17 mmHg) and diastolic pressure (68.2 ± 18.6 vs. 75.2 ± 14.1 mmHg) as well as mean blood pressure (89 ± 21.5 vs. 94 ± 13.9 mmHg) did not show any significant correlation.
Conclusion: Increased arterial stiffness as assessed by PWV predicts cardiovascular events in renal transplant recipients and may be regarded as a footprint of the accelerated arteriosclerosis in this group of patients.

BO90 LONG TERM OUTCOME AFTER RADIOLOGICAL TREATMENT OF TRANSPLANT RENAL ARTERY STENOSIS: A SINGLE CENTRE EXPERIENCE

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Introduction: This study evaluates long-term graft survival following percutaneous transluminal angioplasty (PTA) ± stent insertion for transplant renal artery stenosis (TRAS). The secondary aims were comparison of immediate and long-term effect of PTA +/− stents on blood pressure and allograft function and to evaluate the value of intra-arterial pressure measurement for monitoring technical success.
Material and Methods: Of the 978 renal transplants performed between 1996 and 2012, analysis was undertaken of patients diagnosed with TRAS following transplantation. Following direct catheter angiography, flow limiting critical stenosis underwent PTA ± stent. Post vasodilatation, invasive intra-arterial pressure measurement was used to confirm the haemodynamic significance of the stenosis in borderline angiographic cases. A pressure gradient of >10% of the systolic blood pressure across the stenosis, after pharmaco-vasodilatation, signified a critical stenosis. Successful dilatation of the TRAS was defined as abolition of the gradient. Primary outcome measurements included subsequent graft function (serum creatinine) and response in blood pressure.
Results: Forty six patients (4.7%, 29 males, mean age 55.1 years ± 21–83.3 years) were diagnosed and treated for conformed flow limiting TRAS, by angioplasty or primary stent insertion. There were no intervention related graft losses. Mean pre interventional BP was 146.7/84.83 mmHg (median 149/86.5 mmHg) and was significantly improved at 1, 3 and 5 year follow up (*t*-test $p < 0.001$). Serum Creatinine pre procedure was 239.9 mm (median 197 mm, range 70–838 mm) and191.2 mm/ (SD ± 109.7 mm) at 1 year, 199.7 mm (SD ± 238.1 mm) at 3 years and 181.3 mm (SD ± 109.4 mm) at 5 years ($p > 0.05$). Assisted graft survival was 100% at 1 year, 97% at 3 years and 95.35% at 5 yrs. There was a trend towards primary stent insertion in the more recent cases
Conclusion: PTA ± stenting has been safely performed with good long term graft outcome and no graft loss. The significant improvement in blood pressure validates this intervention.

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BOS10- HIGH RISK ORGANS FOR LIVER TRANSPLANTATION

BO91 BILE DUCT DAMAGE AFTER COLD STORAGE OF DECEASED DONOR LIVERS PREDICTS BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION

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Background: The aim of this study was to examine the development of biliary epithelial damage between organ retrieval and transplantation and its clinical relevance for patients.
Methods/Materials: Common bile duct samples during donor hepatectomy, after cold storage, and after reperfusion were compared to healthy controls by H&E staining and immunofluorescence for tight junction protein 1 and Claudin-1. A bile duct damage score to quantify biliary epithelial injury was developed and correlated with recipient and donor data and patient outcome.
Results: Control ($N = 16$) and donor hepatectomy bile ducts ($N = 10$) showed regular epithelial morphology and tight junction architecture. After cold storage ($N = 37$; $p = 0.0119$) and even more after reperfusion ($N = 62$; $p = 0.0002$), epithelial damage, as quantified by the bile duct damage score, was markedly increased, and both tight junction proteins were detected with inappropriate morphology. Patients with major bile duct damage after cold storage had a significantly increased risk of biliary complications (relative risk 18.75; $p < 0.0001$) and graft loss ($p = 0.0004$).
Conclusion: In many cases, the common bile duct epithelium shows considerable damage after cold ischemia with further damage occurring after reperfusion. The extent of epithelial damage can be quantified by our newly developed bile duct damage score and is a prognostic parameter for biliary complications and graft loss. Possibly, in an intraoperative histological examination this bile duct damage score may influence decision-making in transplantation surgery.

BO92 IMPORTANCE OF DONOR-RECIPIENT AGE GRADIENT (DRAG) TO THE PREDICTION OF GRAFT OUTCOME AFTER LIVING DONOR LIVER TRANSPLANTATION

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Purpose: Donor age is a well-known risk factor for poor graft function after liver transplantation (LT). In addition, an increased recipient age at the time of transplantation has a significant impact because of the high prevalence of comorbid condition. We investigated the relationship between the donor-recipient age gradient (DRAG) and the posttransplant outcome in living donor LT.
Methods: A total of 821 consecutive adult recipients who were performed live donor LT between June 1997 to May 2011 were included. They were divided into four subgroups according to the value of DRAG; ¡Â −21, −20 to −1, 0–20 and ¡Â 21 years. Their laboratory data, allograft rejection episode as well as graft survival were retrospectively collected.
Results: Median age of donors and recipients were 30 (range, 18–65) and 51 (range, 18–73) years, respectively. Mean follow-up time was 977.8 ¡¾ 1162.9 days. DRAG more than 20 years had negative effect on the level of aspartate transaminase within the first month after transplantation. Allograft rejection rate was significantly different between groups. The lower DRAG ¡Â −21 was associated with the superior 1-, 3-, and 5-year graft survivals (94.2%, 92.5% and 90.7%, respectively). The recipients with higher DRAG ¡Â 21 showed persistently inferior graft survival during the observation period (75.0%, 67.5% and 57.9%, respectively). Besides, two groups with DRAG ranged from −20 to 20 had no difference in graft survival.
Conclusion: This study demonstrated that age gradient between donor and recipient, as well as fixed donor age limit, could be an significant predicting factor to ensure a satisfactory graft outcome after living donor LT. Also, careful consideration was necessary for receiving liver graft from older donor than recipient by 20 years.

BO93 RESCUE OF LIVER GRAFTS AFTER CARDIAC ARREST: FIRST STUDY COMPARING WARM VERSUS COLD MACHINE PERFUSION STRATEGIES IN RODENT MODELS OF LIVER TRANSPLANTATION

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Background: The use of livers from donors after cardiac arrest (DCD) is increasing in many countries to overcome organ shortage. Due to an inherent period of warm ischemia prior to the initiation of preservation, those grafts are at higher risk of failure or bile duct injury. Rescue strategies with machine perfusion have been developed with two competing concepts; i.e. continuous normothermic oxygenated perfusion, or end-ischemic Hypothermic oxygenated perfusion (HOPE), applied only 1 h prior to graft implantation. While several groups have claimed success with each technique, no comparison is currently available.
Methods: Rat livers were subjected to 30 or 60 min in situ warm ischemia, followed by subsequent 4 h cold storage, mimicking DCD organ harvesting followed by conventional organ transport. After warm ischemia, the animals in the normothermic group received a 4 h normothermic oxygenated perfusion through both, the portal vein and hepatic artery, while in the HOPE group livers underwent a passive cold storage for 4 h followed by 1 h HOPE. Outcome after reperfusion was tested in isolated rat liver perfusion and liver transplantation models.
Results: All control animals died after transplantation of a liver graft subjected to 60 min warm ischemia followed by 4 h cold storage. Consistent with this observation, those livers disclosed very poor function in the IPRL. Normothermic oxygenated perfusion after 60 min warm ischemia failed to prevent lethal injury. In contrast, 1 h HOPE after cold storage was associated with 70% animal survival after transplantation with good function in the IPRL. Reduction of warm ischemia to 30 min resulted in survival in all groups, with again clear less injury for HOPE treated grafts. Animal subjected to HOPE were also protected against biliary injury.
Conclusions: This is the first study comparing cold vs. normothermic machine perfusion approaches. The impressive superiority of the HOPE technique must now be tested in human trials.

BO94 DIFFERENTIAL EXPRESSION OF INFLAMMATORY GENES IN LIVERS RETRIEVED FROM CARDIAC DEATH AND BRAIN DEATH DONORS

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Erasmus MC

Background: The liver transplant donor pool has been increased by using not only brain death (DBD) but also living-, (LD) and non-heart-beating (DCD) donors. The process of brain death is well described and strategies to optimize the brain death organ quality are emerging. DCD livers have a higher risk of complications and lower graft and patient survival. The aim of this study was to compare gene expression profiles of DBD and DCD livers with LD livers, directly after procurement and after cold storage.
Methods: Male Brown Norway rats were randomly assigned to a LD, DBD or DCD group ($n = 7$/group). LD rats were mechanically ventilated, after 1 h livers were collected. In the DBD group a frontolateral trepanation was made and a balloon catheter was introduced and inflated which led to brain death. After 6 h the liver was removed. In the DCD group cardiac arrest was induced by isoflurane overdose, livers were collected after 20 min of cardiac arrest. Livers were flushed and stored in 4°C UW solution. At 0, 2, 4, 6, and 12 h mRNA expression levels were measured by qRT-PCR.
Results: At procurement, expression of the inflammatory genes IL-6, IL-1â, TNF-á, P-selectin and E-selectin were upregulated in DBD compared to LD and DCD livers. MCP-1, HMGB-1 and TLR4 were significantly increased in DCD compared to DBD livers. The cytoprotective gene HO-1 was strongly increased in DBD and to a lesser extends in DCD livers. The Bcl-2/Bax ratio was four times higher in DCD grafts. After and during cold ischemia, expression levels of most genes were comparable with those at explantation. Compared to LD, DBD grafts have up-regulated inflammatory and cytoprotective genes at the time of explantation. In contrast, DCD livers show only mild inflammation, but increased levels of MCP-1, TLR4 and HMGB-1.
Conclusion: This study found that the gene expression kinetics of graft injury and inflammation differ between DCD and DBD livers, which may be relevant for outcomes after transplantation.

BO95 OUTCOME EFFECT OF INTRA-ARTERIAL VERAPAMIL INFUSION ON DCD LIVER TRANSPLANTATION

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Arterial and biliary complications remain a significant problem following DCD liver transplantation. We hypothesized that the intraoperative infusion of verapamil 5 mg into the recipient hepatic artery prior to arterial reconstruction and reperfusion would result in lower peak AST, shorter hospitalization, decreased hepatic artery and biliary complication rates.
Patients and Methods: Between Sept 2010 and February 2012, 48 DCD orthotopic liver transplants were performed at our institution. We performed the first 24 without intraop verapamil and the subsequent 24 with intraoperative verapamil. IRB approval was obtained to perform a retrospective chart review.
Results and Conclusion: Our results suggest that intraoperative intra-arterial use of verapamil for DCD liver transplantation results in a lower average and median peak AST. As well, a reduction in hepatic arterial and biliary complications was identified. Our data suggests that verapamil leads to

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improved graft arterial reperfusion and mitigates ischemia-reperfusion injury and complications associated with small vessel thrombosis. We will continue to follow these patients in order to describe the long term outcomes of this technique.

BO96 IMPROVING OUTCOMES IN LIVER TRANSPLANTATION UTILIZING DONATION AFTER CARDIAC DEAHT: A SINGLE CENTER EXPERIENCE

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Donation after circulatory death (DCD) has increased the number of liver transplants (LT) but its utilization have been limited due to lower graft and patient survival rates compared with LT using donation after brain death (DBD).
Materials and Methods: To compare our DCD LT and DBD LT outcomes, we performed a retrospective study that included 600 adult patients who had a primary, solitary liver transplant between January 2006 and June 2012. Kaplan-Meier curves were used for statistical analysis.
Results: Sixty-five (10.8%) were DCD LT. Median follow-up was 22 months (range 3–66). No demographic differences were observed between both groups. At 1 and 3 years after LT, patient survival was 94.3% and 85.7% in DCD patients vs. 93.3% and 89.5% in DBD patients. Graft survival at 1 and 3 years after LT was 83.0% and 71.4% in DCD patients vs. 88.3% and 83.7% in DBD patients. Seven DCD patients (10.7%) patients were retransplanted. Biliary ischemia was observed in three patients and was associated to hepatic artery thrombosis (HAT) although the incidence of HAT was similar between both groups. Several techniques as retrograde hepatic vein flushing, use of tpa and verapamil have been implemented.
Conclusion: In our experience, DCD LT yields patient and graft survival rates comparable to DBD LT survival rates. Low incidence of ischemic cholangiopathy suggests that new technical and appropriate donor-recipient matching decreased the frequency of this complication.

BO98 IS ULTRA-SHORT COLD ISCHEMIA THE KEY TO ISCHEMIC CHOLANGIOPATHY AVOIDANCE IN DCD-LT?

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Introduction: Donation after circulatory death (DCD) donors have been proposed to partially overcome the organ donor shortage. DCD-LT remains controversial, with reported increased risk of ischemic cholangiopathy leading to graft loss. The authors retrospectively reviewed a single centre experience with DCD-LT in a 9-year period.
Patients and Methods: Seventy DCD-LT were performed from 2003 to November 2012. All DCD procedures were performed in operative rooms. Median donor age was 59 years. Most grafts were flushed with HTK solution. Allocation was centre-based. Median total DCD warm ischemia was 19.5 min. Mean follow-up was 36 months. No patient was lost to follow-up.
Results: Median MELD score at LT was 15. Median cold ischemia was 235 min. Median peak AST was 1162 U/l. Median peak bilirubin was 31.2 mg/dl. Patient and graft survivals were 92.8% and 91.3% at 1 year and 79% and 77.7% at 3 years, respectively. One graft was lost due to hepatic artery thrombosis. No PNF or graft loss due to ischemic cholangiopathy was observed in this series. Causes of death were malignancies in eight cases.
Discussion: In this series, DCD LT appears to provide results equal to classical LT. Short cold ischemia and recipient selection with low MELD score may be the keys to good results in DCD LT, in terms of graft survival and avoidance of ischemic cholangiopathy.

BO99 SHOULD WE LIMIT THE DONOR AGE IN LIVER TRANSPLANTATION? HISTORY OF A 100 YEARS LIVER

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Background: Ortothopic liver transplantation (OLT) is the main treatment in patients with end-stage liver disease. At present, the increase of patients on waiting list has forced to look for several alternatives to expand the donor pool. The use of liver grafts from aged donors is an excellent alternative in selected recipients.
Case Report: We report the case of a 59 year old male who underwent OLT because alcoholic and VHB cirrhosis (Child C, and MELD 12). In 1998, when he was 44 years old, OLT was performed using a 85 year old graft from brain death donor. The donor was in the intensive care unit only 48 h without hemodynamic inestability episodes and without vasoactive drugs requirements. A graft biopsy revealed the absence of steatosis. OLT was performed with a cold and warm ischemia mean times of 210 and 45 min, respectively. The postoperative course was uneventful and the patient was discharged home on the 15th post-transplant day. At present time, 15 years later, the patient is asymptomatic with normal graft function and tacrolimus monotherapy.
Conclusions: The use of aged liver grafts is a good alternative to increase the donor pool.

BO100 IS OLD DONOR AGE A CONTRAINDICATION FOR SPLIT? SINGLE CENTRE EXPERIENCE IN 441 CONSECUTIVE SPLIT LIVER TRANSPLANTATION

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Background: Split liver transplantation (SLT) realises two grafts from a single cadaver liver. It is an accepted method to increase pediatric graft availability without compromising the donor pool. Advance donor age is generally considered a contraindication for SLT with limits ranging between 45 and 50 years. We analyzed the outcome of 441 consecutive liver transplants performed in 376 recipients (42 adults and 334 children) using split grafts at a single centre between Nov 1997 and Feb 2013.
Methods: Data were collected prospectively and analysed retrospectively. All donors were brain dead and the livers were splitted in situ except 4. We considered young donors (YD) up to 50 years and old donors (OD) above 50 years.
Results: YD median age was 22.6 years (range 10.2–49.9) and OD median age was 54.81(range 50.1–66.3). YD were used in 388 SLT (48 for Acute Liver Failure -ALF-) and OD in 53 (8 for ALF). The median age at transplantation was 2.6 years for children (range 22 days – 17.4 years) and 47.6 years for adults (range 20.5–63.9). 376 grafts were used for primary transplant, 65 grafts were used for retransplantation, in 48 of these the primary transplant had been with a split graft too. Fifty-six SLT were performed for ALF with a median waiting time of 3 days (range 0–22) and 385 for chronic liver failure with a median waiting time of 37 days (range 0–2.6 years). The median Total Ischemia Time was 395 min (range 50–810 min). With a median post SLT follow up of 5.7 years (range 1 day – 15.3 years), patient and graft survival rates for recipients of YD livers were 89%, 77%, 63% and 81%, 68%, 56% at 1,5,10 years respectively. For recipients of livers from OD they were 89%, 75%, 60% and 82%, 70%, 50% respectively. The differences between the two groups were not significant.
Conclusion: This results didn't show any statistical difference between recipients of livers from OD and YD. Donor age above 50 years shouldn't be considered as an absolute contraindication to SLT.

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BOS11-DONATION/RETRIEVAL

BO101 DONATION AFTER CIRCULATORY DEATH INCREASES THE CADAVERIC DONOR POOL

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University of Liege, CHU Liege

Background: There is a controversy on the possibility to increase the organ donor pool by donation-after-circulatory-death (DCD) and the possible decrease in donation-after-brain-death (DBD) by DCD programs. Our aim is to report the DCD experience at the University Hospital of Liege, Belgium, from 2002 through 2012, in a donor region of about 1 million inhabitants.
Methods: The prospective organ donor and recipient databases were retrospectively reviewed.
Results: Ninety-four and 331 procurements were performed from controlled DCD and DBD donors in the time period, respectively. DCD donors contributed to 22.1% of the deceased donor (DD) organ procurement activity from Jan 2002 to Dec 2012, and up to one-third annually since 2009. DCD liver and kidneys contributed 23.7% and 24.2% of the DD liver and kidney transplantation activity, respectively. There was no decrease of the DBD procurement in the study period. In 2012, overall 54 DD were procured in the Liege region, reaching a high procurement activity.
Conclusions: Controlled DCD donors are a valuable source of transplantable liver and kidney grafts, and in our experience do not adversely affect DBD organ procurement activity.

BO102 ETPOD DISSEMINATION: THE TRANSFERABILITY OF A SUCCESSFUL EUROPEAN TRAINING PROGRAM

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Background: The European Training Program on Organ Donation (ETPOD) is a successful educational initiative addressing three different professional levels in organ donation that achieved a significant improvement in both numbers of utilized donors and organs recovered. One of the three level training programs developed is "Training for Trainers" that aims at providing key donation professionals with the skills required to replicate the "Essentials in Organ Donation Training seminars" (EOD), designed to endow participants with basic knowledge on organ donation.
Objectives: The aim of this study is to ensure the continuity and transferability of the ETPOD training program, disseminate the educational tools created and analyze dissemination impact.
Methods: A dissemination strategy was developed to ensure ETPOD continuity and transferability. Due to its successful outcomes, ETPOD participants were encouraged to continue the implementation of EODs. Moreover, participants from 22 countries, belonging to the European Transplant Network (ETN) and the Mediterranean Transplant Network (MTN), benefitted from Training for Trainers Programs and implemented EODs. The impact of ETPOD results reached non-participating countries and due to its feasibility, new organizations expressed their interest to implement the training program in their countries. A database was created (http://www.etpod-dissemination.eu) to follow up the EODs carried out.
Results: Since 2009 when ETPOD finished, a total of 168 EOD seminars have been carried out and 8320 healthcare professionals trained as following: 71 EODs and 4223 professionals trained by ETPOD participants, 94 EODs and 4097 professionals trained in the ETN and MTN countries, 3 EODs and 59 professionals trained by Life's Donor, Sao Paulo, Brazil.
Conclusions: ETPOD, a successful training that produced significant improvements in organ donation, has been continued reaching out a high number of professionals worldwide.

BO103 THE PARTNERSHIP FOR TRANSPLANTATION: A NEW COMPREHENSIVE PROGRAM IMPROVES ORGAN RECOVERY FROM DECEASED DONORS: IT REALLY WORKS!

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A number of programs aiming to increase deceased donation have been introduced over last years in Europe and US (European Donor Hospital Education Program, Donor Action, European Training Program on Organ Donation, United States Collaborative in Donation). Implementation of these programs increased recovery rates, but after initial enthusiasm, a plateau or even slow recession in organ donation was seen in the long run. In Poland, training of transplant coordinators was started in 2008; to date more than 350 doctors and nurses have graduated from Postgraduate Transplant Coordinators School at Warsaw Medical University and most of them are being employed. To supplement this valuable initiative, a new comprehensive program – the Regional Partnership for Transplantation was initiated in 2010 by the Polish Union for Transplantation Medicine and the National Coordinating Center for Organ Transplantation – Poltransplant in 4 districts of Poland with the lowest donation rates. In addition to employment of transplant coordinators, the program includes continuous monitoring of mortality in the ICU and neurological utilities, training and education of the hospital staff in legal and organizational aspects of donation, brain death recognition, and various aspects of donor care. In addition, the program included communication skills workshops for intensive care unit physicians (with participation of 2 actors, an experienced anesthesiologist, and a psychologist). A novel part of the program includes active participation of the hospital managers, as well as representatives of each hospital founding body, president of local medical school, president of the Physician's Chamber, transplant centers, the Polish Union for Transplantation, and the Polish Transplant Coordinating Center. Program results are shown on the graph. The program helped to identify hospitals with theoretically high potential for organ donation and significantly increased donation rate.

BO104 MISSED BRAIN DEAD DONORS AMONG ICH PATIENTS

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Patients with intracerebral haemorrhage (ICH) have a high mortality but seldom became donors. A retrospective singlecenter chartreview of 955 consecutive ICH patients treated from 2005 to 2010. Of 254 patients (27%) who died within 14 days of onset were assessed by a multi-professional team for suitability for donation at least either kidney or liver. Exclusion criteria for potential donors were: >75 years ($N = 105$), cancer ($N = 14$), severe systemic disease ($N = 32$), no consent ($N = 7$), severe in-hospital infection ($N = 27$), instable haemodynamics ($N = 2$), ALT > 70 ($N = 3$), creatinine >130 ($N = 1$), hypertension (>three drugs) ($N = 5$), leaving 59 potential either liver or kidney donors. Eight/ 59 (14%) became actual donors. Suitable for kidney and liver donation were 31, for liver 11 and kidney nine of ICH patients, which were not indentified as potential donors.
Conclusion: Based on these result our guidelines were revised and in the year 2012 organ donation among ICH patients was increased six fold.

BO105 THE ROLE OF RECRUITMENT MANEUVERS IN IMPROVING THE MARGINAL LUNGS DONORS

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Background: Because of the shortage of lungs for transplantation, finding the suitable lungs in brain-dead donors is an important issue. Recruitment maneuver is a strategy aimed at re-expanding collapsed and edematous lung tissue. The aim of this study was to assess the efficacy of this maneuver on improving marginal lungs for transplantation.

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Methods: From 127 brain-dead organ donors in Masih Daneshvari Organ Procurement Unit of Tehran, 31 (25%) had normal chest X Ray or bilateral infiltration and acceptable bronchoscopy but PaO2/FIO2 200–300 mmHg. The recruitment maneuver was performed for 2 h with Pressure control of 25–30 and PEEP of 10–15. Finally patients with PaO2/FIO2 >300 mmHg were considered suitable for lung transplantation.
Results: PaO2/FIO2 of patients before and after recruitment was 239 ± 62 and 269 ± 91, respectively. Recruitment maneuver could increase PaO2 to more than 300 in 10 (32%) which 8 of them were transplanted.
Conclusions: Recruitment maneuver could increase PaO2 more than 300 in one third of brain-dead donors. So, it is recommended that this maneuver is considered in the assessment protocol of lungs for donation.
Keywords: Marginal donor lungs, Recruitment maneuver.

BO106 FIRST EUROPEAN REPORT OF AN ENTIRELY ROBOTIC RIGHT HEPATECTOMY FOR ADULT LIVING RELATED LIVER TRANSPLANTATION

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Background: Recent advances in robotic surgical technology have enabled application to surgical complex procedures such as robotic living donor right hepatectomy(RLDRH).
Methods/Materials: We report the 1st case in Europe of totally robotic minimally-invasive procedure performed from our group.The donor presented 46 years-old, and was the brother of the adult recipients, 165 cm in heights and 67 kg in weights.Preoperative donor's work-up documented conventional hepatic artery anatomy, a short right portal vein and the presence of two large accessory hepatic veins draining the right lobe along with the right hepatic vein. Donor's biliary tree anatomy was regular, as well as liver histology. He volunteered donated his right liver to his brother, a 50-year-old male affected by hepatitis C related cirrhosis, hyponatremia, refractory ascites and pleural effusion.Recipient's MELD score was 14. Estimated graft-to-recipient weight ratio was 1.5%, while estimated remnant liver-to-donor weight ration was 0.7%.
Results: The entirely minimally invasive procedure was performed utilizing the Da Vinci Robotic Surgical System and the partial liver graft was safely extracted through a Pfannestiel incision.The length of our fully RLDRH was 735′.Graft's warm ischemia time was 7'; the donor's estimated whole liver volume was 1601 cc, while right graft volume of 1134 cc.The donor did not require intensive care unit statement, nor develop complication and he was discharged 7 days after the operation. Two major complications developed in the recipient were hepatic artery thrombosis and biliary anastomotic stricture.These were successfully treated with interventional radiologic procedures of revascularization with thrombolytic agent 2 h after liver transplantation and with ERCP.
Conclusion: Our 1st RLDRH confirmed that this technologic advantage allows performing donor right hepatectomy in a standardized and safe manner for experienced liver transplant groups with strong laparoscopic background.

BO107 HIGH DONOR RESISTIN IS ASSOCIATED WITH DELAYED GRAFT FUNCTION AFTER RENAL TRANSPLANTATION

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The adipokine resistin increases during some inflammatory diseases and after cerebral bleeding or trauma; it may activate endothelia and trigger an inflammatory response. No data are available on resistin in brain dead organ donors (DBD) that usually manifest a marked inflammatory state. We analyzed plasma resistin, endocan and monocyte chemotactic protein (MCP)-1 in 63 DBD and correlated it with donor variables and early clinical results after renal transplantation using organs from these DBDs. Controls were live kidney donors (LD, $n = 26$) and the resulting renal transplants.DBDs had higher resistin than LD (30.75 vs. 7.71 ng/ml, $p < 0.0001$). Resistin in DBDs correlated with recipient DGF (hemodialysis in the first week) ($r = 0.321$, $p < 0.01$). The cut-off value of resistin in predicting DGF was 25 ng/ml. DBDs had higher MCP-1 and endocan levels than LD ($p < 0.0001$); MCP-1 but not endocan was lower in steroid-treated DBDs. High resistin in DBD correlates with DGF.

BO108 EVALUATION OF LATENT TUBERCULOSIS IN CADAVERIC DONORS

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It is known that infectious diseases can be transmitted with transplantation. Tuberculosis is an emergent-severe disease, complex to diagnose, with unknown prevalence in organ deceased donors. Quantiferon-TB gold assay has been approved by FDA for latent TB (LTB) screening. The aim of our study was to investigate the prevalence of LTB in cadaver donors. We analysed all consecutive-potential donors admitted in the Intensive Care Unit in our hospital (1/4/2010–5/8/2012). Epidemiological, demographic and analytical data were recorded. A chest x-ray and Quantiferon-TB gold were also performed. A total of 50 donors were included in the study (62% M, 38% W), mean age of 59.2 (20–18) years. Medium stay in the ICU was 3.6 (1–21) days. Brain death was: 72.3% stroke, 21.3% trauma, 6.4% vascular aneurism. Only two had previous history of TB. 13 patients had received BCG vaccination previously. Quantiferon results were negative in 74%, positive in 18%, indeterminate in the 8%. Prevalence of LTB in deceased donors is frequent, and may increase simultaneously to active TB. LTB screening should be performed, to all potential donors although more studies are needed in order to know the real incidence of this curable infectious disease.

BO109 DONOR LEUCOCYTOSIS PREDICTS BACTERIAL AND FUNGAL CONTAMINATION OF THE PRESERVATION SOLUTION IN VISCERAL ORGAN TRANSPLANTATION

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Background: Contamination of the preservation solution may be in part responsible for the septic complications after transplantation causing increased morbidity and mortality in the recipient. The aim of this study was to examine potential donor related predictors of positive microbiological findings in the preservation solution.
Methods: Microbiological findings in the preservation solution of all solid organ transplants performed in our center from 01-2008 to 12-2011 were retrospectively investigated. The following variables were evaluated: Type of transplantation, donor age, gender, ABO group, Body-Mass-Index, cause of death, Intensive-Care-Unit stay, cardiac arrest, noradrenaline dose, hepatitis and Cytomegalovirus serology, donor leucocytes count, type of perfusion solution, type of organ procurement, sum of procured organs, and cold ischemia time. Data were analysed with uni and multivariate regression analyses.
Results: Nine-hundred seventy six solid organ transplantations (546 liver and 430 kidney transplantations, respectively) were performed during the study period. Hundred-sixty-seven probes were positive (17%). Staphylococcus epidermidis ($n = 43$) was the most frequently detected germ, followed by propionibacterium acnes ($n = 31$). Only donor leucocytes count was predictor of positive microbiological findings in the preservation solution ($p = 0.0162$). In uni- and multivariate analyses donor age ($p = 0.0137$), gender ($p = 0.0001$), type of perfusion solution ($p = 0.0015$), sum of procured organs (0.049) and leucocytes count ($p = 0.0460$) differentiated between different categories of potentially pathogenic germs.
Conclusions: In donors with high leucocytes count one out of five organs the preservation solution is contaminated. Recipients of these organs may benefit from prolonged prophylactic antimicrobial therapy.

BO110 ANTI-INFLAMMATORY EFFECTS OF PREDNISOLONE TREATMENT DID NOT IMPROVE ORGAN QUALITY IN BRAIN DEAD RATS

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Introduction: Corticoid treatment have been used in the aggressive donor management protocols. However the effect over kidney and liver grafts has not been clearly elucidated. In brain dead animal models prednisolone treatment has shown controversial results. Therefore, this study investigated the effect of prednisolone after brain death induction on organ quality in a rat model.
Methods: BD was induced in rats by inflating a subdurally placed balloon catheter. Animals were treated with saline or prednisolone (5, 12.5 or 22.5 mg/kg) 1 h after BD induction. After 4 h of BD serum, kidneys and livers were collected. Tissue gene expression was measured by Real Time qPCR. Tissue protein expression was detected by immunohistochemical analyses.
Results: After BD period the prednisolone treatment causes a significant reduction of IL-6 but not creatinine plasma levels, while increasing AST and LDH plasma levels. Relative expression of inflammatory genes (IL-6, TNF-a, IL-1b and MCP-1) was significantly down-regulated in liver and kidney of treated animal. However relative complement (C3) expression was not decreased in both organs after prednisolone treatment.
Discussion: These preliminary results confirm previously investigated anti-inflammatory effects of prednisolone in BD rats. However, this treatment did not improve kidney function and increased liver injury markers. This effect might be with related with C3 complement activation.

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BOS12- ISCHEMIA REPERFUSION INJURY IN EXPERIMENTAL LIVER TRANSPLANTATION

BO111 N-ACYL-DOPAMINE DERIVATIVES INDUCE THE UNFOLDED PROTEIN RESPONSE IN ENDOTHELIAL CELLS: IS THIS IMPORTANT FOR A PROTECTIVE PHENOTYPE?

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The Unfolded Protein Response (UPR) is an intracellular signaling pathway that is activated by the accumulation of unfolded or misfolded proteins in the endoplasmic reticulum. In hibernating mammals it has been suggested that induction of the UPR is part of the cell protective program entering torpor. Moreover, organs obtained for animals during torpor are more resistant to cold preservation damage compared to those obtained from animals that are not hibernating. We have previously shown that N-acyl-dopamine derivatives (NADD) are able to protect endothelial - and epithelial cells against cold-induced injury. Current evidence indicates that this is likely due to direct structural features of NADDs, i.e. hydrophobicity and redox activity. Since it is not known if NADD may induce the UPR, and if this in turn may also contribute to resistance against cold preservation injury, we tested if synthetic NADDs are able to induce the UPR. To this end, we tested if N-octanoyl-dopamine (NOD), N-pivanoyl-dopamine (NPD) and NOD in which both hydroxy groups are acetylated (A-NOD) are able to induce UPR target genes, activate ESRE or ATF6 driven luciferase reporters, phosphorylate eIF2á and cause XBPI slicing in Human Umbilical Vein Endothelial Cells (HUVEC). All of the tested synthetic NADDs induced the UPR in between 2 and 24 h. NPD was less effective in this regard. Activation was abolished after 48 h. No selective activation of the three branches was observed for either of the compounds. UPR activation was transient and did not result in apoptosis. Cyclohexamide treatment did not abrogate the protective effect of NADDs against cold preservation injury, suggesting that induction of the UPR does not underlie resistance to cold preservation injury when cells are pre-treated with NADD. Nonetheless it remains to be assessed if prolonged NADD treatment brings the the cells in a state of hypometabolism and/or renders cells more resistant to cold preservation.

BO112 ENZYME-TRIGGERED CO-RELEASING MOLECULES (ET-CORMS): EVALUATION OF BIOLOGICAL ACTIVITY IN RELATION TO THEIR STRUCTURE

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Background and Purpose: Acyloxydiene-Fe(CO)3 complexes act as enzyme triggered CO releasing molecules (ET-CORMs) and can deliver CO intracellular via esterase mediated hydrolysis. The protective properties of structurally different ET-CORMs on hypothermic preservation damage and their ability to inhibit VCAM-1 expression were tested on cultured human umbilical vein endothelial cells (HUVEC) and renal proximal tubular epithelial cells (PTEC) using a structure-activity approach.
Experimental Approach: Cytotoxicity of ET-CORMs, protection against hypothermic preservation damage, and inhibition of VCAM-1 expression were assessed.
Key Results: Cytotoxicity of 2-cyclohexenone and 1,3-cyclohexanedione-derived ET-CORMs was more pronounced in HUVEC compared to PTEC and was dependent on the position and type of the ester (acyloxy) substituent(s) (acetate > pivalate > palmitate). Protection against hypothermic preservation injury was only observed for 2-cyclohexenone derived ET-CORMs and was not mediated by the ET-CORM decomposition product 2-cyclohexenone itself. Structural requirements for protection by these ET-CORMs were different for HUVEC and PTEC. Protection was affected by the nature of the ester functionality in both cell lines. VCAM-1 expression was inhibited by both 2-cyclohexenone- and 1,3-cyclohexanedione-derived ET-CORMs. 2-cyclohexenone but not 1,3-cyclohexanedione, also inhibited VCAM-1 expression.
Conclusions and Implications: We demonstrate that structural alterations of ET-CORMs significantly affect their biological activity. Our data also indicate that different ET-CORMs behave differently in various cell types (epithelial versus endothelial). These findings warrant further studies not only to elucidate the structure-activity relation of ET-CORMs in mechanistic terms but also to assess if structural optimization will yield ET-CORMs with restricted cell specificity.

BO114 ASSOCIATION BETWEEN SEVERE ISCHEMIA REPERFUSION INJURY AND PATIENT SURVIVAL AFTER LIVER TRANSPLANTATION

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Background: Peak Aspartate aminotransferase (AST) reflects Ischemia Reperfusion Injury (IRI) severity after Liver Transplantation (LTx). Because of concerns between IRI severity and outcome post-LTx, we aimed to (i) identify risk factors for severe IRI (peak AST>2000 IU/l) and (ii) study its impact on patient survival.
Methods: Between 01/2000 to 12/2010, we performed 552 LTx. Donor/recipient demographics, procurement/preservation/LTx data and patient survival were analyzed retrospectively.
Results: In 83 recipients, peak AST was >2000 IU/l (15%). Univariate and multivariate analyses revealed imported livers (versus locally procured) ($p = 0.01$) and intra-operative warm ischemic time ($p < 0.01$) as independent risk factors to develop a peak AST>2000 IU/l. Recipient ICU/hospital stays and death were significantly associated with peak AST>2000 IU/l ($p < 0.01$). The 1 & 5-years patient survival was lower in recipients with a peak AST>2000 IU/l (80.1, 61.6%) vs. recipients with a peak AST<2000 IU/l (92.7, 80.8%) ($p < 0.01$ respectively).
Conclusion: Imported (contrary to locally procured) livers and intra-operative warm ischemia are risk factors for severe IRI (peak AST>2000 IU/l) post-LTx in our series. Severe IRI is associated with a lower patient survival. This study supports the need to develop appropriate strategies aimed at decreasing IRI.

BO115 IGL-1 PRESERVATION SOLUTION PROTECTS RAT LIVER AGAINST APOPTOSIS IN ORTHOTOPIC LIVER TRANSPLANTATION

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[1]IIBB-CSIC; [2]Molecular Biology and Anthropology applied to development and health (UR12ES11)

Background: Injury due to cold ischemia reperfusion (I/R) is a major cause of graft non-function following liver transplantation and the use of an appropriate preservation solution is crucial for the viability of liver grafts. Glycogen synthase kinase-3b (GSK3b) phosphorylates voltage-dependent anion channel (VDAC), the most abundant protein in the outer membrane of mitochondria, and this in turn increases cell death during the ischemic insult. Thus, the inhibition of GSK3b activity is crucial for mitochondrial protection and the subsequent suppression of apoptosis. In this communication, we investigated the involvement of GSK3b in livers subjected to orthotopic liver transplantation (OLT) when IGL-1 preservation solution was used.
Methods: Male Sprague Dawley (200–250 g.b.w.) rats were classified as follows: Group1 = Sham; Group2 (UW) = Livers were flushed and preserved in UW for 8 h at 4°C and subjected to OLT. Rats were sacrificed at 24 h after transplantation according to Kamada 's cuff technique; Group 3 (IGL-1) = Livers were flushed and preserved in IGL-1 for 8 h at 4°C and subjected to OLT. Rats were sacrificed at 24 h after transplantation and then blood and liver samples were collected.ALT/AST, AMPK, PI3K/AKT and their direct substrate, GSK3-b and pVDAC were determined by Western blot. Mitochondrial injury (GLDH) and oxidative stress (MDA) were measured. Measure of apoptosis parameters was also performed.
Results: (i) IGL-1 significantly reduced liver injury (AST/ ALT) and mitochondrial damage when compared to UW. This graft protection was accompanied by increased AKT phosphorylation and subsequent GSK3-b inhibition, (ii) A significant reduction in pVDAC and release of Cytochrome C and caspases levels were found.
Conclusion: IGL-1 preservation solution increases the tolerance of the liver graft against IRI through inhibition of GSK3b, preventing thus liver apoptosis.

BO116 RELEVANCE OF SIRTUIN 1 IN LIVER PRESERVATION

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Background: Prolonged cold storage remains a risk factor for liver graft outcome, especially when steatosis is present. Steatotic livers exhibit relevant alterations in AMP-activated protein kinase (AMPK) activity and endoplasmic reticulum stress (ERS) in response to cold ischemia reperfusion injury (IRI). Sirtuin 1 (SIRT1) was shown to regulate cellular metabolism and to be associated with ER alterations. In this communication, we report by the first time the relationship between SIRT1, AMPK, ERS and liver autophagy when steatotic and non steatotic rat livers are preserved in IGL-1 solution.
Methods/Materials: Livers were preserved for 24 h (4°C) in IGL-1 solution and then washed with Ringer lactate solution. We assessed hepatic injury (transaminases, histology), SIRT1, AMPK, eNOS protein level and ERS (GRP78, p-elf2, ATF4, IRE1α and Caspase 12), as well as Beclin-1 (a protein associated with autophagy).

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Results: Steatotic livers show enhanced liver transaminases and altered liver architecture when compared to non steartotic ones. This was accompanied by SIRT1 activation and a concomitant upregulation of AMPK and eNOS levels. Interestingly, upregulation of SIRT1 level was not accompanied by an enhanced activity of SIRT1 (assessed by Acp53 protein level) that it was decreased in fatty livers when compared to non steatotic ones. Also, ERS alterations were more important in steatotic livers than non steatotic ones. GRP78, p-elf2, ATF4, IRE1α and caspase 12 were enhanced in fatty liver but no changes in ATF4 and caspase 12 levels in non steatotic livers were observed. This was consistent with increases observed for Beclin-1.
Conclusion: These data suggest a direct relationship between SIRT1, AMPK activation, ERS and autophagy after cold liver graft preservation. The higher susceptibility of steatotic livers against cold IRI could be explained by lower SIRT1 activity, decreased activation of AMPK and eNOS and enhanced ERS.

BO117 NORMOTHERMIC MACHINE PRESERVATION REDUCES BILE DUCT INJURY IN DCD LIVERS: A COMPARATIVE STUDY IN A RAT MODEL

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Background: Ischemia-reperfusion (I/R) injury of bile ducts remains a serious cause of morbidity after transplantation of livers from donation after cardiac death (DCD). We tested the hypothesis that normothermic machine perfusion (NMP) results in better preservation of bile ducts compared to static cold storage (SCS).
Methods: Lewis rats were used. Rats underwent 30 min of cardiac arrest before liver procurement (DCD group) or livers were flushed and removed immediately (standard group). Livers were preserved by either SCS or NMP for 3 h ($n = 6$ in each subgroup). NMP consisted of oxygenated, pressure-controlled continuous portal vein perfusion and pulsatile perfusion via hepatic artery using a red blood cell based perfusion fluid. After 3 h preservation livers were reperfused ex vivo for 2 h using the same dual perfusion system and perfusate as NMP. Samples were taken from perfusate and bile for biochemical analysis and biopsies were taken from livers and bile ducts for histology and electron microscopy (EM).
Results: In DCD group, AST, ALT and LDH in perfusate at 1 h after reperfusion, were significantly higher after SCS, compared with NMP ($p < 0.05$). Bile production and biliary bilirubin concentration were significantly higher in DCD livers preserved by NMP, compared with SCS ($p < 0.05$). Biochemical markers of biliary epithelium injury were significantly higher in bile of DCD livers preserved by SCS, compared with NMP ($p < 0.05$). Scanning EM revealed more injury of bile ducts of DCD livers preserved by SCS, compared with NMP. In the group of standard livers, differences in biochemical and EM parameters were less pronounced between subgroups.
Conclusion: Oxygenated NMP of livers results in significantly better preservation of the bile ducts.The positive effect of NMP is most prominent in livers from DCD donors. NMP is a promising new tool to reduce the incidence of biliary complications after DCD liver transplantation.

BO118 SERUM MICRORNAS AS EARLY AND SENSITIVE MARKERS OF LIVER INJURY AFTER WARM ISCHEMIA

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Background: Donation after cardiac death (DCD) results in extensive warm ischemia and is associated with delayed graft function and increased incidence of biliary complications after liver transplantation. A lack of biomarkers however hampers evaluation of graft injury. Recently, hepatocyte and cholangiocyte-derived microRNAs (HDmiRs and CDmiRs) have been identified as sensitive markers for liver injury in patients' serum after liver transplantation. The aim of this study was to investigate whether HDmiRs and CDmiRs in serum represent sensitive markers for hepatic injury in a pig model for warm ischemia.
Methods: Ten female Yorkshire pigs were subjected to 45 min of hepatic warm ischemia by total vascular exclusion. The hepatic artery, portal vein and hepatic veins were clamped for 45 min and two vascular probes continuously monitored the absence of blood flow during ischemia. Serum and liver biopsies were collected at baseline and up to 90 min after reperfusion and were analysed by RT-qPCR for HDmiR-122, HDmiR-148a, CDmiR-30e, CDmiR-222, and non-hepatic control miRNAs miR-133a (muscle) and miR-191 (blood). Also serum AST, ALT, gamma-GT, total bilirubin & LDH were determined.
Results: Both HDmiRs and CDmiRs were detectable in serum and liver biopsies. Of the conventional markers, only serum AST showed a two-fold increase at earliest 60 min after reperfusion (mean $\pm$ SEM U/l; 63 $\pm$ 9 at baseline vs. 126 $\pm$ 19 at $t = 60$, $p = 0.012$). Serum HDmiR levels however increased directly after reperfusion (mean $\pm$ SEM fold change; 5.5 $\pm$ 1, $p = 0.02$) reaching up to 30-fold within 45 min after reperfusion (31 $\pm$ 9, $p < 0.01$). Interestingly, also serum levels of CDmiR-222 increased after reperfusion (2.5 $\pm$ 0.7, $P = 0.02$) and remained elevated at least 1 h (12 $\pm$ 8, $p < 0.01$). In contrast to serum, miRNA expression in liver biopsies remained unchanged after reperfusion. MiR-133a and miR-191, which served as control miRNAs, both remained unchanged in serum after reperfusion. This suggests that warm ischemia induced miRNA elevations are specific for HDmiRs and CDmiRs.
Conclusion: This study demonstrates the release of specific HDmiRs and CDmiRs in serum after hepatic warm ischemia. The fast increase in serum CDmiR-222 indicates that CDmiRs are potential markers to evaluate the degree of biliary injury in DCD grafts.

BO119 THE PXR AS A DRUG TARGET FOR THE PREVENTION OF EARLY GRAFT LOSS AFTER SEVERE LIVER ISCHAEMIA REPERFUSION INJURY

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Background: Liver transplants from DCD donors are particularly prone to non-anastomotic biliary strictures (NABS). These lesions occur as a result of progressive periportal fibrosis and carry a significant risk of early graft loss. In recent years, there has been increasing interest in the pregnane X receptor (PXR) as a promising drug target for inflammatory liver disease. It has been shown to promote liver regeneration and reduce inflammation and fibrosis. The aim of this study was to investigate the effect of PXR activation on hepatic function and periductal fibrosis in an in-vivo rodent model of severe hepatic ischaemia-reperfusion injury (IRI).
Methods: Sprague-Dawley rats were randomised into either PXR or control group (vehicle alone) ($n = 10$/group). The PXR group received a PXR agonist (pregnenolone-16α-carbonitrile – PCN) subcutaneously for 48 h prior to surgery. Both groups were then exposed to a laparotomy and 60 min of partial hepatic ischaemia followed by reperfusion. PCN (or vehicle control) administration was continued postoperatively up to the termination timepoint (either day 1 or day 10 post-reperfusion) where bile flow was measured and liver tissue harvested. Serum and bile was collected for biochemical analysis. Results are expressed as mean $\pm$ SD.
Results: Bile flow on day 1 was higher by 25% in the PXR group compared to the control group ($p < 0.001$). Ischaemic lobes in the PXR group weighed significantly more on day 10 ($p < 0.001$). Hepatic malondialdehyde (MDA) at day 1 was significantly lower in the PXR group (7.9 $\pm$ 0.6 μM vs. 10.5 $\pm$ 1.8 μM control; $p < 0.05$). The severity of fibrosis on day 10 post-reperfusion was significantly lower in the PXR group (0.8 $\pm$ 0.1% vs. 1.8 $\pm$ 0.6% control; $p < 0.001$). This was associated with reduced expression of α-SMA on day 1 in the PXR group.
Conclusion: We have demonstrated that activation of PXR improves recovery of liver mass, and reduces oxidative stress and periportal fibrosis following severe IRI. These findings have important implications for potentially reducing early graft loss after DCD liver transplantation.

BO120 ROLE OF PULSATILITY IN HYPOTHERMIC RECONDITIONING OF PORCINE KIDNEY GRAFTS BY MACHINE PERFUSION AFTER COLD STORAGE

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Background: Brief in house machine perfusion after cold storage (hypothermic reconditioning) has been proposed as convenient tool to improve kidney graft function. The present study aimed to investigate the mechanistic role of vascular pulsatility in this context.
Methods: Kidney function after cold preservation (4°C, 18 h) and subsequent reconditioning by 90 min of pulsatile (PR) (30/20 mmHg) or non-pulsatile (NPR) (30 mmHg) machine perfusion was studied in an isolated kidney perfusion model in pigs and compared with simply cold stored grafts (CS).
Results: Compared to CS, PR, but nor NPR significantly improved renal perfusate flow and urine production and significantly increased the reduction of perfusate levels of creatinine and urea during reperfusion. Perfusate levels of fatty acid binding protein, a marker of tubular cell injury, were dramatically reduced by PR but not NPR. PR and NPR lowered fractional excretion of sodium but significance was only reached for PR.

Molecular effects of PR comprised a significant (versus CS) mRNA elevation of the endothelial antininflammatory transcription factor KLF2 as well as eNOS, along with significantly higher perfusate levels of the endogenous vasodilator nitric oxide.

Functional efficiency of PR over CS was confirmed in additional porcine transplant experiments by e.g. up to 3-fold improved clearance of creatinine during the first days after transplantation.
Conclusion: Brief pulsatile perfusion seems to be an efficient mechanism to reduce pro-inflammatory endothelial phenotype and improve functional outcome of kidney grafts even after preceding static storage.

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OS13-KIDNEY IV

O101 KIDNEYS FROM DCD TYPE 3 DONORS OLDER THAN 60 YEARS OF AGE PERFORM LESS

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Background: In the Netherlands, organ donation after cardiac death type 3 (DCD3) is common practice. Recently, the percentage of DCD3 donors older than 60 years of age (60 + DCD3) increased. In 2007, for instance, there were 23 (26%) 60 + DCD3 donors, while in 2012 this number is already 47 (40%). We question whether the use of 60 + DCD3 kidneys lead to worse short term graft function and survival.
Methods/Materials: We analyzed short-term graft function and survival in first kidney transplants performed in the Netherlands between 1-1-2007 and 1-1-2012 with kidneys from donors after brain death over 60 years of age (60 + DBD), 60 + DCD3 donors and DCD3 donors of 60 years of age or younger (60-DCD3). Data was obtained from the Dutch Transplant Follow up Registry (NOTR). The results are based on 157 transplanted 60 + DCD kidneys, 446 60-DCD3 kidneys and 258 60 + DBD kidneys. For statistical analysis the Chi-Square, Kaplan–Meier, Log Rank and Cox regression analysis were used.
Results: The 60 + DCD3 kidneys have 62% delayed graft function (DGF) and 13% never function, 60-DCD3 kidneys have 56% DGF, 7% never function, and 60 + DBD kidneys 24% DGF, 5% never function; $p < 0.001$. Death censored half year graft survival was 85% for 60 + DCD3 kidneys, 92% for 60-DCD3 kidneys and 93% for 60 + DBD donors ($p = 0.02$). To include warm ischemia time, the multivariate Cox regression was performed on only the DCD3 kidneys. 60 + DCD3 kidney had a Hazard ratio (HR) of 2.4 (95% Confidence Interval: 1.2–4.5, $p = 0.01$), warm ischemia time above 20 min had a HR of 2.2 (95% CI: 1.2–3.9, $p = 0.01$), cold ischemia time above 20 h a HR of 1.7 (95% CI: 0.92–3.2, $p = 0.09$), donor hypertension a HR of 1.8 (95% CI: 0.99–3.2, $p = 0.055$), donor serum creatinine a HR of 0.99 (95% CI: 0.98–1.01, $p = 0.3$) and recipient age a HR of 0.99 (95% CI: 0.99–1.02, $p = 0.49$).
Conclusion: 60 + DCD3 kidneys perform less than younger DCD3 kidneys after transplantation. Limiting warm ischemia time and choosing donors without hypertension can reduce poor outcome.

O102 GROWTH OF PAIRED LIVING KIDNEY DONATION IN THE UK: THE FIRST 5 YEARS

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Background: The first paired (indirect specified) living kidney donations in the UK were in 2007. This study explores the programme's expansion over 5 years and reports on the benefits of novel prioritisation of possible matches.
Methods: All paired donation matches are identified through a national programme. Prioritisation of possible transplant matches, identified four times a year, is according to specific, novel criteria designed to maximise the number of proceeding transplants.
Results: The list for paired donation has grown to a plateau of 180–200 pairs per matching run in 2011 and 2012. A total of 692 patients have been registered for runs to June 2012, with 168 (24%) receiving a paired donor transplant. 14 (8%) transplants were possible due to novel prioritisation of three-way exchanges with embedded two-way exchanges, such that two transplants may proceed if the 3-way exchange cannot. A further 144 identified transplants were unable to proceed. One-year graft survival is comparable with other compatible LD transplants – 97% (95% CI 92–99%) – despite the longer cold ischaemic period associated with the travel of the kidneys for paired donation transplants. 2012 saw the first successful altruistic donor chain involving a paired donation couple.
Conclusions: The paired donation programme in the UK now contributes 5% of all living donor kidney transplants. Continued refinement of the programme has increased its success, culminating in the first altruistic donor chain transplants.

O103 SHOULD WE TRANSPLANT KIDNEYS FROM VERY OLD DCD DONORS?

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Induction: Kidney transplantation from elderly donors is still a very controversial topic. In recent years, we have seen an increase in the number of elderly DCD donors. From all DCD donors in the UK, 35% were older than 60 in 2011. This reality has had an impact on our practice in Cardiff. Nowadays, we routinely transplant kidneys from elderly DCD donors aged far beyond 70. Therefore we analysed the effect of donor age on the graft function and graft/patient survival.
Method: Between 1/Jan/2010 and 22/Oct/2012 we transplanted 69 kidneys from DCD donor older than 60 years [44 transplants from donors age 60–69 years (60's); and 25 transplants from donors more than 70 years old (70's)]. We compared early outcomes between these two groups.
Results: The average donor age in 60's group was 65.27 ± 2.88 (mean; SD) and 73.77 ± 2.22 (mean; SD) in 70's group. There was no difference in recipient age (62.7 ± 8.3 vs. 63.9 ± 7.8, $p = 0.58$), donor creatinine (69.5 ± 20.9 vs. 65.8 ± 11.1, $p = 0.41$) and CIT (12.4 ± 4.4 vs. 13.5¡Ã5.1, $p = 0.38$); between 60's and 70's. We found no difference in incidence of functional DGF, between 60's and 70's group (84% vs. 72%, $p = 0.23$). Also, the glomerular filtration rate after 1, 3, 6, 12 and 24 months was not statistically different between these two groups (60's vs. 70's); 1-month 29.3 ± 13.5 vs. 33.7 ± 10.3 $p = 0.16$; 3-months 32.6 ± 12.1 vs. 37.4 ± 10.8, $p = 0.12$; 6-months 36.1 ± 11.9 vs. 37.6 ± 11.0, $p = 0.64$; 1-year 36.2 ± 9.9 vs. 35.6 ± 12.3, $p = 0.853$; 2-years 31.2 ± 7.7 vs. 38.4 ± 19.2, $p = 0.25$). Furthermore, there was similar graft survival in 1 and 2 years.
Conclusion: The results of our study showed that early outcomes of kidney transplantation from 70's DCD donors yielded satisfactory results comparable to kidney transplantation from DCD donors in their 60s. This fact encourages us to increase the kidney transplantation from elderly DCD donors.

O104 KIDNEY TRANSPLANTATION FROM NON-HEAT BEATING DONORS: 3-YEAR RESULTS

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Introduction: Transplantation of kidneys from non-heart beating donors (NHBD) in France was first started in 2006. Several questions arose: how to minimize the primary non-function (PNF) rate, what would be the delayed graft function (DGF) rate, how well would these kidneys perform, what would be their long-term survival. Several measures were put in place to tackle these questions, targeting donor selection, procurement and transplantation time-frames, organ perfusion and preservation. These are the results after 3 years of NHBD kidney transplantations in our center.
Material and Methods: Between 2008 and 2011, 205 transplantations from heart-beating deceased donors (HBD) and 53 NHBD transplantations were performed at our institution. Criteria for NHBD selection were established by the Agence de la Biomédecine. We used normothermic recirculation (NRC) over double-lumen catheter (DLC) perfusion prior to procurement whenever possible. Kidneys were preserved using the Lifeport® perfusion machine and transplanted within the shortest possible timeframe.
Results: NRC was used in 33 and DLC in 20 cases. We did not observe any case of PNF; 3 grafts were lost to veinous thrombosis. Graft survival was 91% and patient survival 96%. After a 2-year follow-up, there was no significant difference in renal function estimated by the MDRD equation between NHBD kidneys and HBD-standard criteria (HBD-SC) kidneys (50 ± 13 ml/min vs. 56 ± 25 ml/min, $p = 0.16$); however NHBD kidneys performed significantly better than HBD-extended criteria (HBD-EC) kidneys (50 ± 13 ml/min vs. 38 ± 17 ml/min, $p = 0.007$).
Conclusion: Our results indicate that NHBD grafts can be utilised with comparable results to those of HBD-SC grafts, and better results than HBD-EC grafts.

O105 PRE-TRANSPLANT KIDNEY BIOPSY AND KIDNEY GRAFT ALLOCATION TO SINGLE TRANSPLANTATION: LONG TERM OUTCOME

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The role of pre-transplant kidney biopsy in the allocation of donor kidneys to single (SKT) or double transplant (DKT) is still debated. The aim of this study was to investigate the influence of pre-transplant biopsy score on long-term SKT graft function and survival. We analyzed retrospectively 347 patients who underwent SKT from deceased donors between 1997 and 2007. In all cases we performed a pre-transplant renal biopsy. Graft survival was measured by Kaplan–Meier curves and differences were assessed by the log-rank test. The function of the graft at 1, 5 and 10 years was estimated by the MDRD4 formula. Graft function at 1, 5 and 10 years was significantly better in recipients with histological score 0 compared with 1, 2, 3, 4 and 5. Interestingly there were no differences between patients with score 1, 2, 3 and 4, whereas score 5 grafts showed a significantly worse function. Graft survival at 5 and 10 years confirms a better result for score 0 recipients (95.1 and 90.3%, respectively), while showed no statistical significant difference between score 1 (88.1 and 82.4%), 2 (86.4 and 81.2), 3 (86.1 and 80.0%) and 4 (85.5 and 79.5%). Survival of score

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5 kidneys (70.1 and 68.0%) were significantly worse compared to score1–4 grafts ($p < 0.001$). In a multivariate Cox model (including donor age and renal function, number of mismatches and cold ischemia time) only pre-transplant histology score were significantly associated with graft survival (HR 0.161; IC 95% 0.044–0.593 score 0 vs. 5, $p = 0.006$; HR 0.324; IC 95% 0.110–0.953 score 1–4 vs. 5, $p = 0.04$). Our data suggest that: (i) pre-transplant histological score represents a useful tool to predict long-term graft outcome; (ii) the use of score 4 kidney grafts for SKT is safe and provides in a long term an acceptable graft function and survival.

O106 REPORT OF 6-YEAR EXPERIENCE OF A KIDNEY PAIRED DONATION CENTRALIZED LAB PERFORMING CROSSMATCHES RESULTING IN 160 TRANSPLANTS

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Introduction: Over 85 transplant programs have partnered to establish a kidney paired donation (KPD) program. Flow crossmatch (FXM) results with donor cells were compared to virtual crossmatch (VXM) results in patients stratified by their calculated PRA (cPRA) values to evaluate the accuracy of both methods.
Methods: A total of 1949 VXM te sts were performed in a centralized lab. A single antigen bead (SAB) assay was used for patients with 1–100% cPRA to create a list of unacceptable HLA antigens; VXM results were used to perform daily match runs. Selected donor/recipient pairs were tested by FXM with donor cells. Weekly match runs were performed to identify compatible pairs with negative VXM results.
Results: The comparison of all APD patients between 2007 and 2012 revealed an increasing number of sensitized (1–79% cPRA) and highly sensitized (80–100% cPRA) patients (Figure 1). During the 6-year period 1630 patients with negative VXM had negative FXM with potential donors. The accuracy of negative VXM and actual negative FXM was similar and ranged from 70.5% in 2007 to 74% in 2012 (Figure 2).The number of false negative VXM results, defined by a positive FXM with donor cells, was also similar and ranged from 26% in 2012 to 29.5% in 2007. When all negative VXM results were divided into different cPRA groups, patients with 0% cPRA had no false negative results, those with 1–79% cPRA had 20% positive FXM, and those with 80–100% cPRA had 45% positive FXM. Analysis of the class I and II false negative VXM results reveals that the majority were falsely negative in both class I and II HLA (47%), rather than in class II alone (40%) or in class I alone (13%).
Conclusion: Significant ($\approx$ 25%) false negative VXM (especially for high PRA and Class II sensitized patients) when assessed by actual FXM demonstrates that data reported to centralized repositories by multiple transplant centers results in higher false negative VXM than can be achieved by single centers.

O107 OUTCOMES OF KIDNEY TRANSPLANTATION FROM ECD-DCD ARE COMPARABLE TO ECD-DBD: A SINGLE CENTRE EXPERIENCE

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Introduction: In the current era of organ shortage, ECD (Extended Criteria Donors) and DCD (Donors after Circulatory Death) have become important sources of organs. It is believed that a combination of these two factors has a negative impact on outcomes. In our unit, we now routinely transplant ECD-DCD kidneys. Therefore, we analyzed transplant outcomes of these kidneys and compared them to outcomes from ECD-DBD donors.
Method: Between Nov. 2004 and Mar. 2012, we transplanted 114 kidneys from ECD donors (57 ECD-DCD and 57 ECD-DBD). We compared intermediate-term outcomes (2 years graft function and survival) between these two groups. The UNOS definition of ECD was adopted and applied for both DCDs and DBDs.
Results: There was no difference in donor and recipient demographics between these two groups. The average donor age in ECD-DCD group was 64.1 $\pm$ 4.4 (mean $\pm$ SD) and 63.2 $\pm$ 6.4 in ECD-DBD group ($p = 0.37$). Also, recipient age was similar (62.5 $\pm$ 10.6 in ECD-DCD vs. 62.3 $\pm$ 6.9 in ECD-DBD; $p = 0.91$). In contrast, donors' creatinine was significantly higher in ECD-DBD group (72.8 $\pm$ 21.7 vs. 90.4 $\pm$ 56.4; $p = 0.03$) and ECD-DBD kidneys suffered from longer CIT (16.2 $\pm$ 4.1 h vs. 12.3 $\pm$ 4.3, $p = 0.0001$) compared to ECD-DCD group. Expectedly, ECD-DCD kidneys had higher incidence of functional DGF (82.1%) compared to ECD-DBD group (42.5%; $p = 0.001$), but similar incidence of PNF (ECD-DCD 1.8% vs. ECD-DBD 5.3%; $p = 0.30$). Furthermore, there was no difference in 1-year graft function (eGFR 40.8 $\pm$ 15.2 in ECD-DCD vs. 42.0 $\pm$ 13.5 in ECD-DBD, $p = 0.68$), 1-year death-censored graft survival (DCGS) (98.2% in ECD-DCD vs. 89.5% in ECD-DBD, $p = 0.057$) and 2-year DCGS (92.3% in ECD-DCD vs. 89.5% in ECD-DBD, $p = 0.51$).
Conclusion: In our unit, ECD-DCD kidney transplants achieved excellent intermediate-term outcomes (2 years graft function and graft survival) that are comparable to ECD-DBD kidney transplants. This fact encourages us to increase kidney transplantation from ECD-DCD donors.

O108 OUTCOMES WITH TACROLIMUS-BASED IMMUNOSUPPRESSION AFTER KIDNEY TRANSPLANTATION WITH STANDARD- OR EXTENDED-CRITERIA DONOR ORGANSTHE OSAKA STUDY

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Background: The OSAKA study has shown that tacrolimus once-daily prolonged-release (QD)-based immunosuppression has similar efficacy to tacrolimus twice-daily immediate-release (BID)-based therapy in kidney transplant patients. This analysis investigated the outcome with these regimens in transplants from standard-criteria (SCD) or extended-criteria (ECD) donors.
Methods/Materials: Patients were randomized 1:1:1:1 to starting doses of tacrolimus BID 0.2 mg/kg/day (Arm 1), tacrolimus QD 0.2 mg/kg/day (Arm 2), tacrolimus QD 0.3 mg/kg/day (Arm 3), all with MMF and corticosteroids over 24 weeks (tapered), or tacrolimus QD 0.2 mg/kg/day with MMF, basiliximab and corticosteroids given only perioperatively (Arm 4). ECDs were defined in this analysis as either $\geq$60 years old, or 50–60 years old with $\geq$1 additional factor: death from cerebrovascular accident, last serum creatinine >1.5 mg/dl, hypertension, or donation after death from circulatory causes. The primary composite endpoint of efficacy failure was defined as graft loss, biopsy-confirmed acute rejection (BCAR) or graft dysfunction (eGFR <40 ml/min/1.73 m^2) at Week 24.
Results: The full analysis set included 309, 302, 304 and 283 patients in Arms 1–4, respectively. In total, 578 (48.2%) vs. 620 (51.8%) received SCD versus ECD kidneys, with a similar distribution between arms. The incidence of the primary composite endpoint was 36.5% vs. 52.9% ($p = 0.0001$) with SCD versus ECD kidneys (Arm 1: 37.8% vs. 48.4%, p = ns; Arm 2: 41.1% vs. 46.2%, p = ns; Arm 3: 28.5% vs. 60.1%, $p = 0.0001$; Arm 4: 39.2% vs. 57.0%, $p = 0.004$; Fisher's exact test). Graft loss occurred in 5.0% vs. 9.8% ($p = 0.002$); BCAR: 12.3% vs. 14.0% (p = ns), and renal dysfunction: 27.9% vs. 47.4% ($p = 0.0001$), respectively.
Conclusion: The incidence of the composite endpoint, graft loss or graft dysfunction is significantly higher with ECD versus SCD kidneys.

O109 THREE-YEAR OUTCOMES OF DUAL ADULT RENAL TRANSPLANTS: A SINGLE CENTER EXPERIENCE

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Background: To increase the utilization of marginal deceased donor kidney grafts, we have selectively placed two donor kidneys into a single recipient. We sought to determine long-term outcomes of dual kidney transplants.
Methods: A retrospective review of a single center experience of dual adult kidney transplantation. All kidneys utilized as dual transplants had been turned down by all local centers based on renal function or biopsy criteria. Older transplant candidates were preferentially selected to receive dual grafts. Both kidneys were placed in an ipsilateral position. Immunosuppression consisted of rabbit anti-thymocyte globulin induction followed by tacrolimus, mycophenolate, and prednisone maintenance immunosuppression.
Results: Twenty-six double adult kidney transplants were performed from 2007 to 2012. Mean donor age was 58 $\pm$ 11 years, with 10 donors (38%) older than 60 years. Mean cold ischemia time was 23 $\pm$ 8 h. All kidneys were preserved by pulsatile perfusion, resulting in a 17% rate of delayed graft function. Mean recipient age was 62 $\pm$ 9 years. With a mean follow-up of 30 months, the actuarial patient and graft survivals at 3 years was 100% and 92% respectively. One graft was lost at one month due to recurrent hemolytic uremic syndrome and a second lost to chronic allograft nephropathy at 9 months post-transplant. There were six surgical complications (23%) consisting of four cases of unilateral ureteral obstruction, one incisional hernia, and a unilateral transplant nephrectomy. At most recent follow-up the mean estimated GFR was 63 $\pm$ 16 ml/min.
Conclusions: Utilization of marginal quality donor organs as dual kidney transplants provided excellent graft survival and quality of function. Urological complications remain the Achilles heel of this procedure and will require further study.

O110 ACUTE RENAL FAILURE IN THE DECEASED DONOR WITH A SERUM-CREATININE 250 M is Not a Contraindication for Transplantation

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Introduction: Due to a lack of evidence kidneys from deceased heartbeating donors who had developed acute renal failure are often discarded. The aim of this analysis is to evaluate the outcome of donor kidneys with very high serum serum-creatinine levels at the time of explantation.

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Patients and methods: All consecutive patients who received between 1/00 and 12/12 a kidney transplant from a heartbeating donor with a serum-cretinine level of ≥250 M (2.8 mg/dl) at time of explantation were included in this single center retrospective analysis. Standard donor and recipient data were analyzed with univariate and multivariate regression analysis. Graft and patient survival were calculated using Kaplan–Meier method.
Results: Twenty-seven out of 1186 patients received a graft from a donor with a median donor serum-creatinine level at time of procurement of 327.5 M (250.0–471.1). Eighteen were SCD's and nine were ECD's. After *in-situ* flush, all kidneys were preserved by static cold storage either in UW- ($n = 6$) or HTK-solution ($n = 21$). Median recipient age was 55.5 years (30–69) and median waiting time on dialysis was 4.6 (0–9.3) years. Median follow up time was 6.2 years. 66.6% ($n = 18$) of the patients developed DGF and 3.7% ($n = 1$) PNF. One and 5 year patient and graft survival was 96% and 92% and 88% and 88% respectively. Univariate logistic regression detected donor age, donor serum sodium and donor BMI as significant predictors for DGF.
Conclusion: Kidneys from donors with very high last serum creatinine levels (≥250 M) can be transplanted with fairly good long term results. Future research should investigate the possible role of reconditioning machine perfusion in these donors.

O111 KIDNEY TRANSPLANTATION PERFORMED IN ADULTS WITH PEDIATRIC EN BLOC GRAFTS FROM UNDER 15 KG DONORS: LYON EXPERIENCE

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Background: Due to kidney graft shortage in France, transplantation teams are reviewing their kidney acceptance criteria. Pediatric transplantation teams often refuse kidneys from under 15 kg donors because they lead to a higher rate of thrombosis, especially in low weight pediatric recipients. However, they can be transplanted as a dual unit in adults. The goal of this study was to evaluate the survival and outcome of six dual unit transplantations in Lyon.
Material and methods: Between February 2002 and March 2012 six dual unit transplantations were performed with kidneys harvested under 15 kg pediatric donors. All of the donors were under 3 years old. The cause of death was trauma in all cases. All recipients were non-immunized young adults with a BMI under 25. All patients received the same immunosuppression protocol. During follow-up kidney graft function was estimated by simplified MDRD formula and measured with Inuline and kidney graft size was evaluated by ultrasounds.
Results: After an average follow-up of 34.6 months all grafts were functional. No thrombosis occurred. There was no delay graft function. In one case there was a pelvic hematoma without any repercussion on kidney function. All patients showed signs of hyperfiltration followed by compensating hypertrophy. After 36 months average inuline clearance was 95 ml/min.
Conclusion: Our results are very encouraging. Kidneys harvested from under 15 kg pediatric donors should be proposed for dual unit adult transplantation if they are refused by pediatrics teams as long term function is excellent and the rate of surgical complications is acceptable.

O112 DECEASED DONORS WITH SEVERE ACUTE KIDNEY INJURY – A POTENTIAL SOURCE TO EXPAND THE DONOR POOL

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Background: Our aim was to determine the outcome of transplanting kidneys from selected donors with severe AKI.
Methods: We selected all patients receiving single organ deceased donor kidney transplant at our center transplanted between June 2004 and October 2012. Terminal creatinines (Cr) for all donors were obtained from UNOS. AKI donor was defined as a donor terminal Cr > 2.0. Donor data was obtained from UNET. The acute kidney injury network criteria (AKIN) were used to stage the severity of the AKI in the donor (stage 1–3 with three requiring Cr 3 times baseline elevation or increase Cr ≥ 4 or urine output <0.3 ml/kg for >24 h or anuria > 12 h). Continuous variables are given as mean ± 1SD.
Results: There were 104 in the AKI group and 501 in the non AKI group. Baseline characteristics were similar, except AKI group had longer cold ischemia time (19.8 ± 7.8 vs. 15.6 ± 7.2, $p < 0.0001$), were more likely to be male (76% vs. 57%, $p = 0.02$). HLA mismatch was higher in the AKI group (4.1 ± 1.7 vs. 3.6 ± 2.0, $p = 0.03$). Characteristics of the donors in the AKI group: peak Cr 4.02 ± 1.84, terminal Cr 3.53 ± 1.62, oligoanuric in 39%, renal replacement therapy in 10%. Pulsatile pump was used more often in the AKI group (61% vs. 23%, $p < 0.0001$). Delayed graft function (DGF) was more frequent in the AKI group (69% vs. 27%, $p < 0.0001$). The Cr at 1 week was higher in the AKI group (4.26 ± 2.18 vs. 2.66 ± 1.95, $p < 0.0001$) but Cr and eGFR at 1 year were similar. One year protocol biopsy (Bx) findings were not significantly different. Actuarial graft survival was similar at 1 and 3 year (AKI 92% and 88%, non AKI 92% and 86%). For the AKI group, the kidneys from donors with AKIN stage 3 were more likely to have DGF and a higher Cr at 1 week, but eGFR and Bx findings at 1 year were similar (Table).
*n represents the number of patients at risk for the each analysis.
Conclusion: Kidneys from AKI donors, including carefully selected donors with severe AKI, have similar outcomes to non AKI donor kidneys. More liberal use of these organs will help relieve the organ shortage.

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OS14-KIDNEY V

O113 PRE-TRANSPLANT HISTOLOGICAL SCORE AND 1 YEAR GRAFT OUTCOMES AFTER RENAL TRANSPLANTATION

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Background: The reliability of kidney biopsy as the sole means of assessing kidneys marginal donors to be allocated to single or dual transplantation is still a matter of debate.
Methods: We compared 1-year graft survival and renal function in 44 recipients of a single kidney graft from a marginal donor with good renal function and a Karpinski histological score of ≤3 and 56 recipients of a single transplant with a Karpinski score of 4 or 5. The donors' and recipients' characteristics were compared by means of Wilcoxon's rank-sum test and Fisher's exact test, and survival was analysed using the log-rank test.
Results: The donors with the worse histological scores were slightly younger and had a higher glomerular filtration rate. One year after transplantation, graft loss and renal function was similar between the two groups.
Conclusion: In our experience marginal kidneys with score of 4 or 5 can be transplanted as single kidney, provided that donor renal function is good.

O114 FIBROSIS ASSOCIATED GENES ARE RELATED TO POOR OUTCOME OF KIDNEY ALLOGRAFTS WITH BORDERLINE CHANGES

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The outcome of borderline changes (BL) of kidney allografts has been debated.
Methods: Intragraft microarray gene expression profiling was performed in 28 biopsies with BL either in early or in 3M protocolar biopsies in patients with/out deterioration of kidney graft at 24M and results were validated in 64 patients with BL by RT-qPCR.
Results: In progressors the upregulated genes in early BL involved immune system processes, defense and inflammatory response and response to wounding while in 3M protocol biopsy involved fibrinogen complex and cell surface binding. Validation and binary logistic analysis confirmed higher fibrinogen expression and donor age as predictors of graft dysfunction.
Conclusions: Intragraft up-regulation of fibrosis but not alloimmune response associated genes in BL histology was related to future graft dysfunction.

O115 C1Q-FIXING DONOR-SPECIFIC ANTIBODIES BEFORE KIDNEY TRANSPLANTATION DO NOT PREDICT REJECTION OR LOSS

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Luminex detected anti-HLA donor-specific antibodies (DSA) are questioned for their excess in sensitivity and lack of prediction of clinical events after kidney transplantation (KT). We performed a retrospective study to evaluate if specific types of preformed DSA (class I/II or C1q-fixing) have impact on graft survival.
Methods: Three hundred and fifty-five KT performed 2006–2011 with negative CDC-crossmatch were included. Anti-HLA antibodies were tested using Luminex Screen and Single Antigen Class I/II assays. DSA were further evaluated for the capacity to fix complement with C1q screen kits.
Results: HLA screening was positive in 66 KT: 28 had DSA with MFI > 2000 and were evaluated for C1q fixing. They were 75% female, 64.3% reKT with high rate of biopsy-proven acute rejection (39.3%) and acute antibody-mediated-rejection (AMR = 28.6%). Graft loss was 21.4% at 30 months follow-up. Renal function for surviving grafts was good (median last SCr = 1.27 mg/dl). DSA were C1q+ in 15 patients and C1q- in 13 without significant differences in demographics, acute rejection (33.3% vs. 46.2%), acute AMR (26.7% vs. 30.8%), graft loss (20% vs. 23.1%) or renal function at follow-up. Patients with C1q-fixing DSA had higher MFI of the immunodominant DSA (p = 0.008). PostKT monitoring showed that C1q+ DSA class-II persisted postKT more frequently than C1q- DSA class-II (69% vs. 34%, p = 0.21). Ten patients had anti-HLA DSA class-I with/without class-II and 18 only DSA II. Patients with class-I suffered more AMR (50% vs. 17%, p = 0.06) and significant worse graft survival (p = 0.01). The capacitiy of DSA I to fix C1q did not correlate to AMR (50% in C1q+DSA I and C1q-DSA I), graft loss (50% vs. 33%) or renal function. DSA II post-KT persisted more than of DSA-I (66.7% vs. 16.7%, p = 0.06).
Conclusion: C1q testing in preKT sera with DSA was unable to predict AMR or graft loss, but the presence of DSA class-I compared to class-II did. Despite lack of capacity to fix complement *in vitro* preKT DSA-I C1q- can mediate AMR and graft loss.

O116 MONITORING DSA AFTER KIDNEY TRANSPLANTATION: DQ HLA CLASS II DSA HAVE THE STRONGEST IMPACT

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The impact of donor-specific antibodies (DSA) after kidney transplantation (KT) on graft survival is becoming clearer, but which DSA have the greater impact or how they behave after KT is still imprecise.
Methods: Four hundred and forty KT recipients with grafts functioning more than 3 months performed between 1979 and 2012 with a negative CDC crossmatch were included in a prospective observational study between I/2008 and III/2012. Anti-HLA antibodies were tested using Luminex Screen and LSA Class I and/or Class II assays. Cut-off for a positive reaction was set in MFI raw value > 1000.
Results: During the 4 years of follow-up, 32 patients lost their grafts, 19 died and five were lost to follow-up. We found: – PreKT DSA in 43/289 (14.9%) patients: five HLA-I, 36 HLA-II, seven HLA-I&II. Graft survival was not significantly different to preKT DSA-negative patients. AllpreKT DSA-I and 50% DSA-II disappeared postKT. – First postKT tests showed DSA in 26/247 (6.7%), median 54 months post-KT: three HLA-I and 23 HLA-II (immunodominance: 16 DQ, three DRB1, one DRB3, one DRB4, two DRB5). Graft survival was lower in DSA+ patients (p < 0.0001 uncensored, p = 0.002 censored, median follow-up 32 months). Graft loss occurred in 58% DSA+ KT performed >5 years before, 37.5% transplanted 1–5 years before and 0% DSA+ patients <1 year after KT. Fifty percent DQ DSA > 7000MFI lost their grafts. – Second monitoring showed DSA in 41/288 (10.6%) median 59 months post-KT: three HLA I, 35 HLA-II, three I and II. Immunodominant DSA were again 58% DQ. At least 18 were *de novo* DSA, 19 preformed and five unknown. There were not significant differences between *de novo* and preformed DSA groups except for less retransplants, lower PRA and longer postTR follow-up (103.8 + 78 vs. 38 + 29 months, p = 0.003), but similar DSA specificity and MFI level (11 792 + 7153 vs. 8964 + 6921).
Conclusion: PreKT DSA-I not associated to early graft loss disappeared after KTR under conventional immunosuppression, as well as 50% of DSA-II. Postransplant DSA significantly impact graft survival, especially high MFI DQ DSA or in long-term transplant patients. Around half postransplant DSA are *de novo* but are similar to preformed DSA in MFI or specificity.

O117 PRETRANSPLANT TESTING OF HUMAN CADAVERIC RENAL ALLOGRAFTS

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Background: A major limiting factor in Transplantation is the shortage of cadaveric kidneys. There are no diagnostic tools available to accurately predict graft function which contributes to a discard rate that has been reported as high as 18%. Novel prognostic screening that accurately predicts posttransplant function could help reduce the discard rate. We evaluated whether the restoration of synthetic functions during *ex vivo* warm perfusion could be used prospectively to evaluate function in human cadaveric kidneys. The blinded study involved human kidneys with varying cold ischemic times (CIT), a known mediator of damage, that ranged from 13 to 70 h.
Methods: Human kidneys (n = 16) were procured following discard according to the respective standard institutional criteria. Kidneys were received stored hypothermically, cannulated and transitioned to warm Exsanguineous Metabolic Support (EMS) perfusion (32°C). Perfusate samples were taken at various time points and evaluated using the Luminex xMAP Platform to ascertain the cytokine/chemokine profiles. The results were categorized as Group 1 with <24H and Group 2 with >24H CIT.
Results: From a panel of 35 cytokines/chemokines six parameters: IL-6, G-CSF, MIP-1α, MIP-1β, MCP-1, and IP-10 proved significant. The initial concentrations at 30 min of EMS warm perfusion was compared to the concentrations at 9H. Group 2 kidneys with >24H CIT had significant reduction in the concentration of cytokines/chemokines that is dependent on new synthesis in comparison to Group 1 (figure 1). A surprising finding was that kidneys from diabetic donors with <24H CIT had impaired restored synthetic function compared to kidneys from non-diabetic donors (figure 2).
Conclusion: Evaluating synthetic function by cytokine/chemokine analysis may represent a sensitive and objective means of assessing cadaveric renal allografts prospectively. While prolonged CIT is known to be damaging, the blinded study results suggest that restored synthetic functions during an *ex vivo* warm perfusion could provide a means for evaluating additional parameters as well.

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O118 URINARY CALPROTECTIN DIFFERENTIATES BETWEEN PRERENAL AND INTRINSIC ACUTE RENAL ALLOGRAFT INJURY

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Background: Urinary calprotectin has recently been identified as a promising biomarker for the differentiation between prerenal and intrinsic acute kidney injury (AKI) in the non-transplant population. Calprotectin is highly increased in intrinsic AKI, whereas it is comparable to healthy controls in prerenal disease. The present study investigates, whether calprotectin is able to differentiate between these two entities in transplant recipients as well.
Methods: Urinary calprotectin concentrations were assessed by ELISA in 256 subjects including 82 cases of intrinsic acute allograft failure, 21 cases of prerenal graft failure, 112 patients with stable graft function, and 41 healthy controls without any history of renal disease. Exclusion criteria were obstructive uropathy and metastatic cancer. The clinical differentiation of prerenal and intrinsic graft failure was performed either by biopsy or by a clinical algorithm including response to fluid repletion, history, physical examination, and urine dip stick examination.
Results: Reasons for intrinsic graft failure comprised rejection, acute tubular necrosis, pyelonephritis, and viral/interstitial nephritis. Calprotectin concentrations of patients with stable graft function (100 $\pm$ 120 ng/ml) were comparable to healthy controls (102 $\pm$ 229 ng/ml, p 0.94) and prerenal graft failure (99 $\pm$ 118 ng/ml, p 0.99). Mean urinary calprotectin was 45 times higher in intrinsic AKI (4532 $\pm$ 7428 ng/ml) than in prerenal AKI ($p < 0.01$). ROC-curve analysis revealed a high accuracy of calprotectin (AUC 0.98) in the differentiation of intrinsic versus prerenal AKI. A cut-off level of 250 ng/ml provided a sensitivity of 96.3% and a specificity of 90.5% for the diagnosis of intrinsic AKI.
Conclusion: Urinary calprotectin is a promising biomarker for the differentiation of prerenal and intrinsic acute renal allograft failure. Pyuria, however, leads to increased calprotectin concentrations as well.

O119 NOVEL CANDIDATE MARKERS CHARACTERIZING CELLULAR SENESCENCE IN AGED 0 H KIDNEY BIOPSIES PREDICT POST TRANSPLANT OUTCOME

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Background: Advanced donor age adversely affects allograft outcome following renal transplantation. Candidate genes involved in cell-cycle regulation and telomere shortening have been already described as markers for cellular senescence in aged kidneys. However, there is still a lack of appropriate biomarkers for defining older and marginal organs in order to adopt immunosuppression for improved long-term outcome.
Material and methods: To more comprehensively characterize senescence in the elderly donor organ, we first studied gene expression for selected candidate markers in a small sample cohort consisting of 57 zero hour kidney biopsies derived from deceased donors. Among them 26 biopsies were derived from donors >55 years (mean 66.5 $\pm$ 7.4 years) and 31 specimens were derived from donors <55 years (mean 41.35 $\pm$ 8.4 years).
Results: Compared with younger donors, elderly donors revealed a significant *de novo* mRNA expression of candidate markers including immunoproteasome subunits (PSMB8, 9, 10; $p < 0.001$ respectively), chemokines such as CCL19/21 ($p < 0.05$), MHC class II transcripts including HLA-DRB ($p < 0.01$) or transcripts of the activating receptor NKG2D ($p = 0.0036$). Next, we confirmed gene expression of candidate genes in an independent patient cohort consisting of 139 biopsy samples. Based on sample size, three groups were defined according to donor age: 0–30 years (group I, 21 $\pm$ 4.9 years, $n = 30$), 31–54 years (group II, 46.5 $\pm$ 6.6 years, $n = 50$) and >55 years (group III, 64.07 $\pm$ 7 years, $n = 59$). Whereas no differences were observed between group I and group II, aged kidneys (group III) revealed a significant gene expression of PSMB9 ($p = 0.0405$), PSMB10 ($p = 0.0223$), CCL19 ($p = 0.0318$) compared with middle aged kidneys (group II). In addition, HLA-DRB ($p = 0.0215$), PSMB9 ($p = 0.0129$), and CCL19 ($p = 0.0064$) were significantly induced in group III in comparison with group I. Strikingly, transcripts of the activating NK cell receptor NKG2D revealed the highest gene induction in group III versus group II and group I ($p < 0.001$, respectively) indicating enhanced infiltration of NKG2D+ CD8+ T cells or NK cells in kidneys with advanced age. Moreover, linear restriction analysis revealed a strong correlation especially for pre-transplant NKG2D mRNA expression with serum creatinine levels at hospital discharge ($p = 0.0003$), at 3 months ($p = 0.004$) and at 6 months post transplantation ($p = 0.0031$).
Conclusion: In summary, our results reveal novel candidate markers in aged renal allografts indicating the infiltration of senescent T and NK cells. Our findings may provide help in the assessment of organ quality implicating the potential of pretreatment strategies.

O120 *DE NOVO* PRODUCTION OF C1Q-FIXING DONOR-SPECIFIC ANTIBODIES IS ASSOCIATED WITH KIDNEY ALLOGRAFT LOSS

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The development of donor-specific HLA antibodies (DSA) represents the major risk factor of graft failure in kidney transplantation. However, some patients show persistent presence of circulating DSA without occurrence of graft loss. Solid phase assays, such as Luminex Single Antigen (LSA) beads, are highly sensitive in detecting DSA but not very predictive of transplant outcome because of detection of complement-fixing and less clinically relevant no complement-fixing antibodies. Using the novel LSA-C1q assay, we investigate the clinical relevance of *de novo* DSA in relation to their capability to fix complement. In serum samples from 53 kidney transplanted patients who had developed IgG-LSA DSA after transplantation, we measured complement-fixing ability of detected DSA by Class I and Class II LSA-C1q assay. As for transplant outcome, 32 (60%) patients suffered graft failure and 21 (40%) had good graft function during the follow up period. As for complement-fixing capability of DSA, 35 patients showed production of C1q-positive DSA; the remaining 18 produced C1q-negative DSA. C1q-positive DSA were present in all but three patient who had graft failure; only six of the 21 patients showing C1q-negative DSA suffered graft failure (91% vs. 29% respectively, P*f*–0.0001). As for HLA specificity of DSA, C1q-positive DQA antibodies were only present in three patients showing good graft function. On the contrary, DQB-DSA were present in 21 patients showing C1q-positive HLA antibodies; all but one of these patients suffered graft loss. In conclusion our data suggest that C1q-LSA assay shows the capability to identify the subset of IgG-LSA DSA strongly associated to graft loss in kidney transplantation. Moreover the ability of C1q assay in distinguishing less harmful no complement-fixing DSA from clinically relevant C1q-fixing DSA represent a non-invasive tool for identifying patients who need specific immunosuppressive-therapy strategy to prolong graft survival.

O121 SPOT URINE PROTEIN MEASUREMENTS IN KIDNEY GRAFT REJECTION: A MARKER TO PREDICT REJECTION PHENOTYPE AND GRAFT OUTCOME

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Background: In this study we aimed to improve characterization of proteinuria on kidney graft rejection phenotypes and to identify how changes in proteinuria after rejection affect graft outcome.
Methods: Patients who underwent kidney transplantation between January 2000 and December 2011 and provided biopsy samples for acute rejection were included. Spot urine protein/creatinine ratios (UPCR) were measured at baseline, time of biopsy and 3 months after biopsy. We investigated the associations of change in UPCR before rejection (UPCR at biopsy – baseline UPCR) with distinct rejection patterns and the effect of change in UPCR after rejection (UPCR 3 months after biopsy – baseline UPCR) on graft outcome.
Results: In the observed period 554 patients were transplanted, of whom 98 (18%) had acute rejection. Median increase in UPCR before rejection was 21 mg/mmol in 52 patients with T-cell rejection without vasculitis, 34 mg/mmol in 21 patients with T-cell vascular rejection, and 125 mg/mmol in 25 patients with antibody-mediated rejection. Receiver operator characteristics analysis demonstrated that an increase in UPCR before rejection had good diagnostic accuracy to predict antibody-mediated rejection (area under the curve (AUC) 0.78, 95% CI 0.67–0.88) but had no discriminatory ability to predict T-cell rejections.After a median follow-up of 65 months, 26 patients lost their graft. Increase in UPCR after rejection had good discriminatory ability to predict graft loss (AUC 0.80, 95% CI 0.69–0.90) and cutoff value of 20 mg/mmol was associated with the best performance of the analysis (sensitivity 82%, specificity 68%). In multivariate Cox analysis, an increase in UPCR > 20 mg/mmol was independently associated with graft loss (HR 3.6, 95% CI 1.4–9.1; $p = 0.008$).
Conclusion: An increase in proteinuria before kidney graft rejection is a predictive marker of antibody-mediated rejection. Further increase in proteinuria after rejection could be used as a surrogate marker for poor outcome.

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O122 MULTICENTER VALIDATION OF URINARY CXCL9 AS A RISK-STRATIFYING BIOMARKER FOR ONGOING AND INCIPIENT KIDNEY TRANSPLANT INJURY

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Background: Multicenter validation studies are lacking for most putative noninvasive biomarkers in kidney transplantation.
Methods: In Clinical Trials in Organ Transplantation-01, a multicenter study of 280 primary kidney transplant recipients, we tested the utility of multiple urinary mRNAs (CCR5, CCL5, IL8, Perforin, Granzyme B, CXCR3, CXCL10, CCR1, CXCL9) and proteins (CXCL9 and CXCL10) as biomarkers to diagnose acute rejection (AR) and to predict a 30% decrement in eGFR between 6 and 24 months posttransplant.
Results: The most robust diagnostic markers were urinary CXCL9 mRNA (OR 2.77, CI 1.57–4.8; $p < 0.0003$) and CXCL9 protein (OR 3.4, CI 2.12–5.47; $p < 0.0001$). Urinary CXCL9 protein was elevated up to 30 days before overt AR. CXCL9 protein at 6 months correlated with unsuspected tubulointerstitial inflammation on protocol biopsies. Low levels of urinary CXCL9 protein obtained from stable patients 6 months posttransplant accurately classified individuals least likely to develop future AR or a significant decrement in eGFR (99.3, 92.5% negative predictive values, respectively).
Conclusion: Our findings validate urinary CXCL9 as a biomarker for AR and show that absent urinary CXCL9 is associated with stable allograft function and a low likelihood of incipient immune injury.

O123 MICRORNA: PRE-TRANSPLANT MARKERS FOR ASSESSMENT OF POST-TRANSPLANT ALLOGRAFT FUNCTION

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Background: Pre-transplant prediction of post-transplant renal function and outcome is extremely challenging, particularly when applied to older and marginal donor organs. We have sought to demonstrate that parameters associated with post-transplant allograft function, including delayed graft function (DGF), biopsy proven acute rejection (BPAR) and estimated glomerular filtration rate (eGFR) can be determined by assessment of microRNA (miRNA) expression levels in pre-transplant allograft biopsies.
Material/Methods: Blind screening of the human microtranscriptome was undertaken in "zero hour" allograft biopsies ($n = 39$) and candidate miRNAs showing significant expression changes ($p < 0.01$) with clinical parameters validated using individual PCR assays.
Results: We have determined a miRNA signature in pre-transplant renal allograft biopsies that significantly correlates with post-transplant allograft characteristics. This is centred on cellular bio-ageing and cell stress responses. These miRNA comprise expression of hsa-miR-125b, hsa-miR-505, hsa-miR-96, hsa-miR-217, known to affect these processes. These independently predict DGF, BPAR, high creatinine or poor MDRD4 score at 12 months post transplant, with high sensitivity and specificity. They prove superior to standard measures including the Kidney Donor Risk Index, used as a measure of the post-transplant risk of graft failure.
Conclusions: Our data demonstrate a close relationship between pre-transplant miRNA expression levels and clinical outcomes for renal transplantation and provide the potential for a simple molecular pre-transplant assay to determine post-transplant allograft function. This has exciting potential for clinical application and devising novel pharmacological interventions.

O124 THE COMBINATION OF RENAL DYSFUNCTION PLUS PROTEINURIA AT 1 YEAR IS A STRONG PREDICTOR OF EARLY GRAFT LOSS AFTER RENAL TRANSPLANTATION

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The aim of the study was to analyze the effect of renal dysfunction (serum creatinine SCr) and proteinuria (>300 mg/day) on graft loss after renal transplantation at 4 years. From the Spanish Chronic Allograft Nephropathy database (renal transplants in 1990, 1994, 1998 and 2002) 4842 patients were available, 3950 of them alive and with graft function at one year were included in the study. We divide this population in three groups according to renal function and proteinuria at 1 year: SCr > 1.5 mg/day and negative proteinuria (Group I, 36.1%), SCr > 1.5 mg/day and positive proteinuria (Group II, 20.9%)) and SCr < 1.5 mg/dl and negative proteinuria (Group III, 36.1%). In the global population, patients of Group II showed a significantly lower death-censored-graft (DCGS) and patient survival at 4 years (81.7% and 94% respectively) ($p < 0.001$) compared to group I (95.5% and 96%) and to group III (98% and 98%). As expected, in group II, the main cause of graft loss was chronic rejection (80%) and cardiovascular disease and infection were the main causes of death. In the subpopulation of older recipients who received kidneys from older donors, *n*: 294, at 1 year, 42.5% of patients were included in group I, 34% in group II and only 23.5% in group III, showing a significantly lower DCGS (but not in patient survival) those included in group II.(90% vs. 95.8% and 98.4% respectively) ($p < 0.05$). Although with different percentages in transplantation from young donors for young recipients *n*: 2908: 34.5%, 18.1% and 47.4% respectively, a significant lower DCGS was also observed at 4 years in group II (79.7% vs. 95% and 98.4% ($p < 0.001$) and in patient survival (96% vs. 97% and 98.4% ($p < 0.05$). In summary, the combination of renal dysfunction plus proteinuria at one year posttransplantation has a harmful effect on survival figures. These data strongly suggest that this parameter is an excellent predictor of graft loss in the short-term including transplantation in young and old.

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OS15- LIVER MISCELLANEOUS

O125 PREOPERATIVE CARDIAC RISK EVALUATION (CRE) IN LIVER TRANSPLANT (LTX) CANDIDATES: REVISITING THE PROCESS TO TARGET THE APPROACH

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Background: Accurate preoperative evaluation is essential to minimize adverse outcomes after LTx. In Ltx candidates coronary artery disease (CAD) ranges from 3% to 27%, impacts on short and long term outcome and mandates a systematic approach to identify asymptomatic pts at risk. Agreement on the preTx screening approach is lacking: heart stress tests are performed in up to 80% of the pts with variable results.
Materials and methods: Retrospective study on 172 consecutives pts (males 75%; MELD 15 $\pm$ 7, CHILD Pugh 8 $\pm$ 3) to assess the incidence of CAD and to evaluate the appropriateness of our approach. Basic CRE included clinical history with METs and RCRI (LTx 1 point + 1 point each major risk factor, CAD, diabetes, peripheral vascular disease, pCreatinine > 2 mg/dl), EKG and TT echocardiogram. Criteria for heart stress test (Myocardial Perfusion Scanning, MPS) were age > 50 years or the presence of one major or two minor risk factors. Coronary angiography (SCA) was performed in patients with positive SMPS, known CAD or presence of CA stents.
Results: All the pts underwent LTx: 3 months and 1 year survival rate were 99% and 93% respectively. Diabetes was present in 24%, renal dysfunction in 4%. RCRI score ≥2 was recorded in 49 pts (28%), known CAD in 7 pts (4%). One hundred and one candidates (61%) underwent MPS (criteria: 85% age > 50; 41% RCRI ≥ 2). MPS was positive in 7 pts (7%), all falsely positive according to SCA. No new case was diagnosed. No death or major event related to CAD occurred in this series and no acute coronary event occurred in 1 year FU (MPS NPV 100%, inconsistent PPV).
Conclusions: PreLTx CRE mandates the redefinition of high risk candidates for pt safety (no false negative), screening efficiency (no false positive), cost containment. Basic CRE for the asymptomatic pt should be appropriate in case of pts <60 year, RCRI = 2 or with <2 minor risk factors. MPS was overused: it should be reserved for pts >60 year or in case of RCR > 2, diabetes or renal failure. MPS could have been used in <50% of the cases without increased risk.

O126 PRE-TRANSPLANT TREATMENT OF HEPATOCELLULAR CARCINOMA WITH RADIOEMBOLIZATION USING YTTRIUM-90 MICROSPHERES

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Background: Liver transplantation remains the only curative treatment option for patients with unresectable hepatocellular carcinoma (HCC). Pre-transplant treatment is imperative because of persisting donor organ shortage, prolonged waiting time and increased risk of tumor progression. Radioembolization is mostly employed in the control of large HCCs when other local ablation treatments are not indicated.
Methods: Twenty patients received pre-transplant treatment of HCC with radioembolization using yttrium-90 microspheres at our transplant center since December 2006. The explanted livers were examined histopathologically for treatment response.
Results: Radioembolization was applied to the right liver lobe in 14 patients and to the left liver lobe in one patient. In five patients radioembolization of both lobes was performed. Patients underwent liver transplantation 100 [8–526] days after radioembolization. Histopathological examination of the explanted livers revealed complete necrosis of tumor cells in four patients, partial necrosis in 12 patients and viable tumor cells were detected in four patients. Three patients died of bone metastases and two patients died of recurrent HCC to the liver within 2 years after liver transplantation.
Conclusion: Histopathological assessment of the explanted livers from patients undergoing pre-transplant radioembolization demonstrated at least partial necrosis in 80% of patients treated in our center. We propose that radioembolization is a valuable and safe treatment option for bridging to liver transplantation.

O127 THE IMPACT OF HIGH PRE-TRANSPLANT MELD SCORE ON LIVE DONOR LIVER TRANSPLANT OUTCOME

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Background: Since the New York State Committee on Quality Improvement in Living Liver Donation prohibited live liver donation for potential recipients with Model for End-stage Liver Disease (MELD) scores greater than 25 back in 2002. There has been few studies evaluating the risk and complications of living donor liver transplant with High MELD 25, the western experience have shown that it does not increase mortality post transplant while several Asian studies have shown increase 3 months mortality and complications.
Aim: To compare outcome of living donor liver transplant in patients with high MELD score versus those with low MELD and evaluate the impact on patient and graft survival.
Methods: The charts of 160 adult live donor liver recipients from 2004 to 2012 were reviewed retrospectively and divided into two groups. Group A were patients who had MELD ≤ 25 while Group B included patients with MELD > 25.
Results: Of 160 live donor performed, Group A (MELD ≤ 25) included 143 patients, and group B (MELD > 25) had 17 patients in total. Out of the 17 patients transplanted in Group B, six have died since the transplant (35% mortality) and three of the six died within the 1st 6 months (two of sepsis, one primary graft non-function requiring re-transplantation also died of sepsis). In Group A, 22 out of 143 patients transplanted with MELD < 25 died during the same period (15.4% mortality).
Conclusion: In our cohort, there was more than two fold increase in mortality between the two groups with half the deaths occurring during the first 6 month due to sepsis. Live donor liver transplant for patients with high MELD score seems to carry an increase risk of sepsis and mortality post-transplant.

O128 SUBSTANCE ABUSE TREATMENT AND ITS ASSOCIATION WITH RELAPSE TO ALCOHOL USE FOLLOWING LIVER TRANSPLANTATION

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Background: Many liver transplant (LTx) programs require substance abuse (SA) treatment for patients with a history of alcohol abuse. However, it is unknown if pre-LTx SA treatment prevents post-LTx alcohol relapse. It is also not known whether the intensity of SA treatment attenuates the risk of post-LTx drinking.We hypothesized lower post-LTx alcohol relapse rates in patients who received pre-LTx SA treatment, especially those receiving moderate or high intensity treatment. We also hypothesized that patients who continued SA treatment after transplantation would have a lower rate of alcohol relapse.
Method: Two clinicians blind to LTx outcome independently reviewed medical records to identify patients with a pre-LTx history of alcohol abuse and to identify the nature/intensity of any SA treatment received pre- and post-LTx using operationalized coding scheme. Another clinician coded the primary outcome, which was relapse to any alcohol use post-LTx. This was determined by retrospective review of medical records, laboratory tests, and patient-completed health questionnaire. Intensity of the relapse was also recorded.
Results: Of the 118 recipients with an alcohol abuse history, 61 (52%) received pre-LTx SA treatment. Alcohol relapse occurred in 40 (34%) patients. Alcohol relapse rate of patients with pre-LTx SA treatment (30%) did not differ from that of patients without pre-LTx treatment (39%; p = 0.20). Among relapsers, intensity of the relapse was not significantly associated with pre-LTx SA treatment (÷2 = 1.04, p = 0.59). Relapse was less likely for patients with SA treatment both before and after LTx (16%) compared to patients with no SA treatment (41%) or pre-LTx SA treatment only (45%; p = 0.03).
Conclusion: Pre-LTx SA treatment alone, while beneficial for some, may not prevent post-LTx alcohol relapse. LTx programs should consider placing more emphasis on patients receiving SA treatment both pre- and post-LTx.

O129 COMPARISON OF SCORING SYSTEMS IN PREDICTING SHORT TERM MORTALITY AFTER LIVER TRANSPLANTATION

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Background: Many scoring systems have been suggested to predict the outcomes of liver transplantations. The aim of this study was to compare between four scoring systems: sequential organ failure assessment (SOFA), Model for End-Stage Liver Disease (MELD), Acute physiology and chronic health evaluation II (APACHEII), and Child Turcotte-Pugh (CTP), among patients who underwent living donor liver transplantation (LDLT) seeking to evaluate the best system to correlate with postoperative outcomes.
Methods: This study retrospectively reviewed the medical records of 53 patients who had received LDLT in a tertiary care hospital from January 2005 to December 2010. Demographic, clinical and laboratory data were recorded. Each patient was assessed by four scoring systems before transplantation and on post-operative days 1–7 and at 3 months.
Results: The overall 3 months survival rate was 64%. The pre-transplant SOFA score had the best discriminatory power, moreover, the SOFA score on post- operative day 7 had the best Youden index (0.875). The survival rate at 3 months follow up after liver transplantation differed significantly (p = 0.00023, AUR = 0.952) between patients who had SOFA scores <8 and those who had sofa >8 on post liver transplant day 7. This study also demonstrated that respiratory rate (p = 0.017), serum bilirubin level (p = 0.048) and duration of ICU stay (p = 0.04) are significant risk factors related to early mortality after LDLT.

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Conclusion: The pre-transplant SOFA score was statistically significant predictor of 3 months mortality. SOFA score on post liver transplant day 7 had the best discriminative power for predicting 3 months mortality.

O130 HYPOTHERMIC OXYGENATED PERFUSION (HOPE) PREVENTS BILIARY INJURY AFTER TRANSPLANTATION OF DCD LIVER GRAFTS

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Background: The use of livers from donors after cardiac arrest (DCD) is increasing in many countries to overcome organ shortage. Due to an inherent period of warm ischemia before preservation, those grafts are at higher risk of failure and bile duct injury. Several competing rescue strategies by machine perfusion techniques have been developed with however unclear effect on biliary injury after liver transplantation. Here we analyze the impact of an end-ischemic Hypothermic Oxygenated PErfusion (HOPE) approach, applied only through the portal vein for 1 h before graft implantation.
Methods: Rat livers were subjected to 30 min *in situ* warm ischemia, followed by subsequent 4 h cold storage, mimicking DCD-organ procurement and conventional organ transport. Livers in the HOPE group underwent also passive cold storage for 4 h, but were subsequently machine perfused for 1 h before implantation. Outcome was tested in both groups by liver transplantation (LT) at 12 h after implantation ($n = 8$ each group) and after 4 weeks ($n = 8$ each group), focusing on early reperfusion injury and later intrahepatic biliary injury.
Results: All animals survived after LT. However, reperfusion injury was significantly improved by HOPE treatment after transplantation as tested by hepatocyte injury (AST & HMGB-1 release, TUNEL staining), Kupffer cell activation (CD-68 staining), and endothelial cell activation (sE-selectin staining). In addition, rats receiving non-perfused DCD livers presented 4 weeks after liver transplantation with less body weight gain, increased bilirubin and severe intrahepatic biliary fibrosis. In contrast, HOPE treated DCD livers were protected from biliary injury 4 weeks after LT, as detected by cholestasis parameter and histology (CK-19, sirius red, alpha-sma staining).
Conclusions: We demonstrate for the first time in a DCD liver transplant model that end-ischemic hypothermic oxygenated perfusion is a powerful strategy for protection against biliary injury.

O131 GRAFT TYPE SIGNIFICANTLY ASSOCIATES WITH THE INCIDENCE OF POSTHEPATECTOMY LIVER FAILURE DEFINED BY ISGLS

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Living donor liver transplantation has been performed as a therapeutical option for end stage liver disease to compensate the scarcity of cadaveric donor grafts. Although there have been several publications for donor morbidity, all of these previous reports does not assess posthepatectomy liver failure, which is a major cause for mortality. We analysed morbidity of 66 living donors based on posthepatectomy liver failure defined by the international study group of liver surgery (ISGLS-PHLF), which was recently reported as a novel surrogate endpoint for mortality. ISGLS-PHLF was defined with increased international normalized ratio and hyperbilirubinemia on or after postoperative day 5. ISGLS-PHLF was identified in seven donors (11%). Among the donor background characteristics, all the ISGLS-PHLF donors were performed right hepatectomy ($p < 0.05$), and the incidence increased up to 20% among right lobe donors. Five (8%) and 2 (3%) donors were classified as grades A (with no clinical management) and B (with noninvasive treatment) ISGLS-PHLF respectively, and hospital stay concomitantly extended with ISGLS-PHLF grades ($p < 0.05$). Among the prognostic factors, donor age ≤ 50 ($p < 0.05$) and right hepatectomy ($p < 0.001$) were identified as independent risk factors for developing ISGLS-PHLF. Further analysis revealed that the incidence increased up to 43% among right lobe donors aged ≤ 50 and remnant liver volume $<40\%$. Preventing posthepatectomy liver failure for living donors and achieving zero mortality, we propose a strong caution for selecting right lobe donation.

O132 INCREASING EXPERIENCE IS ASSOCIATED WITH REDUCTION IN HEPATIC VENOUS OUTFLOW (HVOO) OBSTRUCTION WITH PIGGYBACK LIVER (PB) TRANSPLANTATION

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Background: HVOO following PB liver transplantation (LT) is rare but results in significant morbidity and potential graft loss.
Methods: Venographically confirmed HVOO in consecutive LT from a single centre from 1998 to 2013 were identified. Patient demographics, pre, intra, and postoperative variables were obtained.
Results: Five hundred and six LT were performed on 486 patients with a median age of 49 years (range 0.25–71). Nineteen (3.8%) cases of HVOO were identified at a median of 26 days post-LT (1–2312). The incidence fell from 6% in the first 253 LT, to 2% in the second half ($p = 0.03$). Seventeen were due to anastomotic stenosis and two thrombosis. Reconstruction of the supra-hepatic donor Inferior Vena Cava (IVC) onto two or three hepatic veins did not alter the likelihood of HVOO ($p = 0.58$). Recipients with a donor-recipient weight ratio (DRWR) discrepancy of >20% did not have an increased rate of HVOO ($p = 0.39$). 17/19 were managed by stenting (16) or venoplasty (1). Two required thrombectomy, one of which failed and needed re-LT.
Conclusion: The incidence of HVOO appears to fall with increasing experience and does not appear to be related to a discrepancy in DRWR or whether the donor IVC is anastomosed to two or three hepatic veins.

O133 EVOLUTION OF A RELIABLE DUCT-TO-DUCT RECONSTRUCTION TECHNIQUE IN RIGHT LOBE GRAFTS WITH DOUBLE BILIARY ORIFICES

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Duct-to-duct (DD) anastomosis is currently the technique of choice for biliary reconstruction in right lobe (RL) living donor liver transplantation (LDLT). In RL grafts with multiple bile ducts, a higher incidence of biliary complications (BC) are reported. The aim of this study is to compare different DD reconstruction techniques and to evaluate the impact of external biliary catheterization (EBC) in RL grafts with double biliary orifices. Between July 2004 and July 2012, 383 patients underwent RL LDLT at our institution. Of these, 120 patients (31%) who underwent DD reconstruction for double biliary orifices were retrospectively analyzed. DD reconstruction was performed using three different techniques. When bile ducts were far apart, either a back-wall plasty (BWP) ($n = 46$) was performed to create a single opening, or they were anastomosed separately in the double DD (DDD) fashion ($n = 57$). Duct-to-sheath anastomosis (DSA) ($n = 17$) was performed when both bile ducts were encased in a common sheath. In a median follow up of 24 months, 40 (33.3%) patients developed BC, including 18 (15%) strictures and 25 (20.8%) leakages. Until March 2009, BWP was the dominant reconstruction technique consisting of 70% of DD anastomoses in such grafts. Since then, BWP technique has been abandoned and the overall BC rate dropped to 25.9% from 40.3% ($p = 0.1$). The rates of biliary stricture and leakage also decreased from 21% and 24.2% to 8.6% and 17%, respectively. Another technical modification was the routine use of EBC after September 2011. In the routine EBC period, which included 31 patients, BC rate has further improved to 22.6%, with a biliary stricture rate of 9.7% and leakage rate of 12.9%. We conclude that, in RL grafts with double biliary orifices, BWP technique predisposes to higher rate of BC. Abandoning the BWP procedure and routinely inserting double external biliary catheters extending into the intrahepatic ducts offer a more reliable biliary reconstruction technique.

O134 LATE EXTRA-HEPATIC BILIARY STRICTURES AFTER LIVER TRANSPLANTATION ARE ASSOCIATED WITH PRE-EXISTING DONOR-SPECIFIC ANTIBODIES

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This study investigates the association of late biliary strictures and the presence of pre-transplant donor specific antibodies (DSA) and positive cross match. Twenty-nine cases of late extra-hepatic biliary strictures, occurring 6 weeks–3 years after transplantation, were identified in recipients of deceased donor liver transplants ($n = 286$). Twenty recipients with no evidence of biliary pathologies served as control. Cumulative class II MFI >500 and/or B-cell cross-match positivity was found to be strongly associated with the incidence of late extra-hepatic biliary strictures. Class I DSA did not reveal any association. The study group showed cumulative class II DSA >500 MFI in 24/29 patients (83%) and B-cell crossmatch positivity in 20/29 patients (69%). Using both criteria, 26/29 recipients (90%) could have been identified prior to transplantation for being at risk to develop late biliary strictures. Only 3/20 recipients (15%) of the control group showed B-cell cross-match positivity. None of them had a cumulative class II MFI >200. None of 4/20 controls (20%) with cumulative class II MFI >500 showed a positive B-cell cross-match. This is the first evidence indicating that pre-transplant class II DSA and B-cell cross-match positivity are strongly associated with risk of developing late extra-hepatic biliary strictures following liver transplantation.

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O135 DONOR SPECIFIC ANTI-MHC CLASS II ANTIBODIES – RISK FACTOR FOR LIVER GRAFT FAILURE

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Background: The significance of humoral immune response for allograft survival following LT is still a matter of debate.
Aim: To assess the clinical significance of anti-MHC antibodies in 174 LT patients.
Methods: The presence of anti-MHC antibodies was assessed by LABScreen Single Antigen assay.
Results: The following risk factors for graft failure were identified: presence of MHC class II donor specific antibodies (DSA), donor age >50 years, anti-CMV IgG(+) donor, recurrent episodes of cholangitis, ischemic type biliary lesions, diabetes mellitus, HCV cirrhosis. Presence of MHC class II DSA and anti-CMV IgG(+) donor are independent risk factors for graft failure. Patients with HCV and MHC class II DSA had a significantly lower graft survival. C4d deposition was found more frequently in allograft biopsy specimens of patients with HCV recurrence and class II DSA(+).
Conclusion: MHC class II DSA have a negative impact on allograft survival following LT, especially in HCV(+) recipients.

O136 THE ADDITIVE EFFECT OF PRE-TRANSPLANT OBESITY, DIABETES AND CARDIOVASCULAR RISK FACTORS ON OUTCOME AFTER LIVER TRANSPLANTATION: A 10-YEAR NATIONAL EXPERIENCE

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Introduction: The effect of pre-transplant obesity and other metabolic risk factors on outcome after liver transplantation (LT) is controversial. Questions have been raised over the appropriateness of the body mass index (BMI) for assessing obesity in these patients. Both issues have implications for organ allocation. Using gold-standard dual-energy x-ray absorptiometry (DXA) scanning for measuring% body fat (%BF) we examined the relationship between BMI and true%BF in LT patients, and evaluated the independent and additive risks of pre-transplant obesity, diabetes (DM), hypertension (HTN) and coronary artery disease (CAD) on post-LT outcome.
Methods: Retrospective study of consecutive adult patients undergoing LT at our national centre in New Zealand between 2000 and 2010. BMI and%BF were used to assess obesity immediately prior to LT and the level of agreement between the methods determined. The influence of pre-transplant risk variables (including obesity, DM, CAD, HTN) on 30-d post-operative event rate, complication-type and length of hospital stay were analysed using regression models. Thirty-day, 1- and 5-year patient survival was modelled using Kaplan–Meier curves.
Results: Two hundred and two patients were included. There was agreement between BMI and%BF methods for determining obesity in 86% of the study population ($\kappa = 0.73$). Obesity was an independent risk factor for post-operative event rate (counts ratio 1.03, $p < 0.01$), as was DM (CR 1.4, $p < 0.01$). Obesity with concomitant DM however was the strongest predictor of post-operative event rate (CR 1.75, $p < 0.01$), cardiorespiratory and infective complications and longer hospital stay (15.8 vs.10.0 days, $p < 0.01$). Obesity had no effect on 30-day, 1- or 5-year patient survival.
Conclusions: BMI is an adequate tool for assessing obesity-associated risk in LT patients where DXA is not available. Post-LT outcome was poorest in patients with concomitant obesity and DM, highlighting the importance of looking at overall metabolic risks.

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OS16-ISCHEMIA-REPERFUSION INJURY – PRECLINICAL ASPECTS

O137 N-ACETYLCYSTEIN AND HIGH DOSE ATORVASTATIN TO REDUCE OXIDATIVE STRESS IN A ISCHEMIA/ REPERFUSION MODEL IN KIDNEY RAT

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Ischemia/reperfusion injury (I/R) is characterized by an increase in ROS production, pro-inflammatory cytokine release leading to cell damage and death. N-Acetylcystein (NAC) and high dose Atorvastatin (ATOR) have demonstrated their protective effect against oxidative stress via different pathways. Aim of this study was to investigate the protective effects on oxidative stress of NAC and ATOR in a I/R injury model in the rat kidney.
Methods: Forty female Wistar rats were assigned to four groups: NAC = intraperitoneal administration of 140 mg/kg NAC; ATOR = oral administration of 80 mg/kg ATOR; NACATOR = both treatments; Controls: sham operation. Drugs were administered 24 h before surgery; ischemia was induced by 30 min occlusion of the left renal artery. After 24 h renal tissue samples were obtained. Oxidative stress was assessed by measuring the activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and Myeloperoxidases (MPO). Histological slides evaluation was perform to assess histo-pathological damage.
Results: NAC group displayed higher GPx activity versus controls ($p = 0.012$). The ATOR group showed lower MPO levels ($p < 0.001$) and higher GPx activity ($p < 0.05$) versus controls. There was a positive trend in increasing CAT activity in all treated groups compared to controls (p = ns). When compared with NAC, the ATOR group showed a significantly lower MPO activity ($p < 0.05$) and higher GPx ($p < 0.05$) and SOD ($p < 0.05$) activity, while NACATOR group displayed significantly lower levels of MPO ($p < 0.001$) and slightly higher levels of GTPx and SDO (p = ns). No further significant difference were observed between groups. A toward trend was observed in NACATOR group in terms of tubular abnormality rate ($p = 0.085$).
Conclusions: Our findings confirm that treatment with NAC and/or ATOR provides protection against oxidative stress in a model of I/R injury in the rat kidney, and suggest an adjunctive beneficial effects of NAC and ATOR administered together.

O138 SELECTIVE CYTOKINE ADSORPTION IN CORRECTION OF THE ISCHEMIA/REPERFUSION SYNDROME

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Background: Cytokines play an important role in the development of ischemia/reperfusion injury.
Methods/Materials: We applied coupled plasma filtration and adsorption (CPFA) to correct ischemia/reperfusion in 17 renal transplant recipients. We investigated the concentrations of cytokines (TNF, IL-1b, IL-6, IL-8, IL-12) in the blood before surgery, after reperfusion, and in 6, 12 and 24 h after the procedure.
Results: Sorption of cytokines decreased the cytokine concentration immediately after the procedure. In the main group, we noted an increase in diuresis and glomerular filtration rate, improve of microcirculation of the graft (lower resistivity index). The median of duration of anuria time was significantly lower in the treatment group.
Conclusion: Selective removal of cytokines in the early postoperative period after kidney transplantation is an effective and necessary procedure.

O139 GRAFT PRECONDITIONING USING LOCALISING ANTICOAGULANT FUSION PROTEINS IN KIDNEY TRANSPLANTATION

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Allograft thrombosis is a severe complication in renal transplantation. It is implicated worldwide in up to 7% of early adult graft loss, and ~35% in children, with the pathogenesis related to preservation & recipient/donor factors, with "marginal" kidneys at higher risk. The only preventative measure is systemic anti-coagulation, conferring bleeding risks upon patients. An ideal more effective method would be localised anticoagulation directly within allograft. We have developed a series of novel endothelial binding hirudin-anticoagulant fusion-proteins (FP). We hypothesise kidney pretreatment with FP will ameliorate deteriorations in perfusion seen in an established porcine *ex-vivo* renal thrombosis model. We report our pre-clinical findings.
Methods: Fourteen kidneys were retrieved from cadaveric pigs (Warm Ischaemia = 15mins) and transported to the laboratory (Transport cold ischaemia = 5 h). Kidneys were first machine perfused (MP) on a Waters Medical (RM3) perfusion machine, with 4°C UW solution (4 h), then underwent pretreatment via MP with either unmodified (Thrombosis Group, TG = 7) or FP treated (Protein Group, PG = 7) perfusate. All kidneys then underwent autologous whole-blood normothermic perfusion (6 h).
Results: Kidneys demonstrated similar perfusion dynamics during initial UW perfusion. During the normothermic phase there was less deterioration of perfusion in PG versus TG kidneys, with declines in flow rates of 14.1% vs. 33.5% (PG vs. TG, $p < 0.03$); and superior flow (31 versus 23 ml/min/100 g) and perfusion indices (0.42 vs. 0.31 ml/min/100 g/mmHg) [PG vs. TG, $p = 0.02$ and $p = 0.04$ respectively] in PG kidneys. Perfusate DDIMER analysis demonstrated less ($p < 0.05$) fibrin generation in PG versus TG correlating with perfusion results.
Conclusion: We show that kidney preconditioning with anticoagulant proteins allows amelioration of deterioration in perfusion dynamics seen in an *ex-vivo* thrombosis model. There is high potential for the development of an applicable strategy to target delivery of locally-active anti-coagulants directly within the allograft where it is needed and decrease the incidence of early thrombosis, while avoiding the need for systemic anticoagulation and its associated risks.

O140 EFFECTS OF PROLONGED WARM ISCHEMIA IN AN EXPERIMENTAL MODEL OF RENAL TRANSPLANTATION

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Background: Persistent organ shortage remains a major obstacle in transplantation. Donation after circulatory death (DCD) donors provide a large source of kidneys but most centres are reluctant to use uncontrolled DCD kidneys due to prolonged warm ischemic times. There is limited data on the tolerance of kidneys to prolonged warm ischemia.
Methods: Porcine kidneys underwent 15, 60 and 90 min ($n = 6, 6, 5$ respectively) warm ischemia and 2 h cold ischemia followed by normothermic reperfusion with autologous blood for 3 h. Various perfusion characteristics, markers of renal function and of tubular injury were analyzed.
Results: Renal blood flow was significantly lower in the 60 and 90 (vs. 15) min groups at the start of reperfusion (17.3, 13.7 vs. 29.4 ml/min/100 g, $p = 0.038$). However, the blood flow increased in all groups during reperfusion, more so in the 60 and 90 min groups, and there was no difference between the groups from 30 min ($p = 0.092$) through to 3 h ($p = 0.731$).

Urine output (UO) and creatinine clearance (CrCl) were significantly lower in the 90 min compared to the 15 min group (total UO 67 vs. 583 ml, $p = 0.002$; CrCl area under curve 0.7 vs. 11.4 ml/min/100 g, $p = 0.002$). Notably, the urine output in the 90 min group improved during reperfusion and was significantly increased by the third hour compared to the first (31 vs. 12 ml/h, $p = 0.002$). Levels of urinary endothelin-1 were significantly higher in the 60 and 90 (vs. 15) min groups (35.7, 29.1 vs17.3 pg/ml, $p = 0.0014$).
Conclusion: Prolonged warm ischemia caused a significant degree of endothelial injury and loss of renal function. However, kidneys appeared to recover during reperfusion suggesting that even after 90 min of warm ischemia, the injury processes can be reversed. This has important implications for the potential use of uncontrolled DCD kidneys to further push the limits in transplantation.

O141 NEURONAL RATHER THAN INDUCIBLE NITRIC OXIDE SYNTHASE IS CRUCIALLY INVOLVED IN ISCHEMIA REPERFUSION INJURY

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Tetrahydrobiopterin donor therapy has been shown to attenuate ischemia reperfusion injury by targeting the nitric oxide synthase (NOS). We herein investigated, whether the constitutively expressed neuronal (nNOS) or the inducible (iNOS) isoform is responsible for the tetrahydrobiopterin mediated protection using nNOS or iNOS-knockout (–/–) mice. In a heterotopic

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pancreas transplantation model C57Bl6-based nNOS−/− and iNOS−/− mice were used as donors and C57Bl6-mice as recipients. Donors were either untreated or pretreated with 50 mg/kg bw tetrahydrobiopterin. Non-transplanted animals of the different genotypes served as controls. Following 16 h cold ischemia time (CIT) and 4 h reperfusion, microcirculation was determined by intravital fluorescence microscopy. Parenchymal damage and peroxynitrite formation were adjudged histopathologically and immunohistochemically. Pterin tissue-levels were assessed by HPLC. Finally, recipient survival was tested. Compared to non-transplanted controls prolonged CIT resulted in a significant microcirculatory breakdown 4 h following reperfusion ($p < 0.05$), which could be prevented by tetrahydrobiopterin treatment ($p < 0.05$). Similarly, iNOS−/− grafts needed tetrahydrobiopterin pretreatment to prevent microcirculatory damage ($p < 0.05$). In contrast, untreated nNOS−/− grafts preserved their regular capillary pattern even if untreated (p = ns). At this time point no differences in parenchymal damage could be observed between treated and untreated animals, neither in knock-out nor in wild type groups (p = ns). Finally, significantly prolonged recipient survival could only be achieved if donor mice were either lacking nNOS or were pretreated with tetrahydrobiopterin ($p < 0.01$). nNOS−/− rather than iNOS−/− of the donor prevents ischemia reperfusion injury in this pancreas transplantation model. Hence, we strongly suggest a central role of the neuronal NOS isoform in the development of ischemia reperfusion injury following organ transplantation.

O142 TETRAHYDROBIOPTERIN SAVES MURINE PANCREATIC ISOGRAFTS FROM BRAIN DEATH EXACERBATED ISCHEMIA REPERFUSION INJURY

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Brain death (BD) is associated with an immunological priming of grafts and is thought to exacerbate ischemia reperfusion injury (IRI). Recently we were able to demonstrate that the nitric oxide synthase co-factor tetrahydrobiopterin (BH4) abrogates IRI following murine pancreas transplantation. Herein we assessed the impact of BD on IRI and tested the therapeutic potential of BH4. Pancreas transplantation was performed between syngeneic C57BL/6 mice. Animals were followed for 3 h after BD-induction. Experimental groups included: non-treated BD donors, pre-treatment of BD donors with 50 mg/kg BH4, ventilated non-treated donors (sham group), non brain death donors (living donors). Following 2 h of reperfusion, graft-microcirculation (functional capillary density, FCD; capillary diameter, CD) as well as cell viability was assessed by intravital fluorescence microscopy. Parenchymal graft damage was assessed by histology, BH4 levels were determined by HPLC and mRNA expression of inflammatory markers was measured by real-time RT-PCR. BD had dramatic impact on pancreatic microcirculation as highlighted by reduced FCD and CD values when compared to controls ($p < 0.05$). Moreover BD induced intragraft mRNA expression levels of IL-1β, TNFa, IL-6 and ICAM-1. In contrast BH4 treated grafts displayed significantly improved microcirculation as reflected by significantly higher FCD and CD values ($p < 0.001$, respectively). BD impacted cell viability following reperfusion, whereas BH4 treated grafts displayed similar percentages of viable cells as non brain death controls ($p < 0.001$). Parenchymal damage was significantly more pronounced in organs from BD donors when compared to controls ($p < 0.05$). Pre-treatment with BH4 however significantly ameliorated parenchymal damage in organs from BD donors ($p < 0.05$). This study provides *in vivo* evidence that BD aggravates IRI after experimental pancreas transplantation. Donor pre-treatment with BH4 offers a novel therapeutic option in this setting.

O143 DOSE EFFICACY OF THE NATURAL OXYGEN TRANSPORTER HEMO2LIFE IN ORGAN PRESERVATION

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Background: The intensity of ischemia reperfusion injury of donor organ is a well-known factor for long-term graft outcome. The addition of 5 g/l of the natural oxygen carrier M101 (HEMO2life®) demonstrated benefits in cold static preservation of kidney grafts in both UW (Viaspan®) and HTK (Custodiol®) solutions.
Methods: A dose ranging study was performed testing 1, 2 and 5 g/l of HEMO2life® in UW for 24 h cold static preservation in a Large White pig kidney autotransplantation model. Animals were followed during 3 months after transplantation.
Results: Creatininemia during the first 2 weeks was significantly lower in Hemo2life 1.2 and 5 mg/l groups compared to UW ($p < 0.05$), without differences between Hemo2life® groups (AUC = 4000, 4000, 2000 and 8000 μM respectively). A similar pattern was observed for histological analyses of kidney parenchyma on 3-month biopsies, with the following percentages of fibrosis: 9%, 13%, 5% and 23% respectively, $p < 0.05$ for each Hemo2life® group vs. UW). Thus, we confirmed the benefits of HEMO2life® in terms of function recovery, whatever the dose level, in comparison to UW alone.
Conclusion: HEMO2life® used as an additive to static organ preservation showed a significant long-term protection of the kidney graft at a dose ranging from 1 to 5 g/l.

O144 ISCHAEMIA REPERFUSION INJURY EXACERBATES CHRONIC ALLOGRAFT DAMAGE

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Background: Chronic allograft dysfunction is critically dependent on the alloimmune and autoimmune response, although a contribution from ischaemia reperfusion injury (IRI) is also increasingly suggested. It is, however, unclear how IRI interacts with the immune response to exacerbate chronic allograft dysfunction. We therefore aimed to determine the influence of IRI on the immune response in a heterotopic heart transplant model of chronic allograft damage.
Methods: A cold ischaemia time (CIT) of 30mins or 4 h was used to induce mild or severe IRI respectively in a mouse model of heterotopic cardiac transplantation. B6 recipients received syngeneic control or allogeneic heart grafts from Bm12.Kd.IE donors expressing the MHC I alloantigen Kd and the MHC II alloantigens I-Abm12 and I-E. Alloantibody and autoantibody production was quantified using ELISA and Hep2 staining respectively and graft rejection kinetics determined by palpation of the transplanted heart.
Results: Severe (CIT 4 h) IRI exacerbated graft damage and fibrosis in syngeneic B6 recipients, with foci of myocyte loss and inflammatory infiltration. All hearts were beating at day 50. Bm12KdIE hearts were chronically rejected by B6 recipients (mean survival time >50 days), associated with production of alloantibody against Kd and I-E, as well as autoantibody. Severe IRI led to increased alloantibody and autoantibody production (figure 1) and exacerbated allograft damage, with no palpable beat at the time of sacrifice (day 35).
Conclusion: IRI exacerbates chronic allograft dysfunction in both syngeneic and allogeneic models of cardiac transplantation. The late alloimmune and autoimmune responses after transplantation are augmented by IRI and lead to increased graft dysfunction. Amelioration of IRI therefore represents a promising therapeutic approach as a means of reducing chronic allograft dysfunction.

O145 EARLY HEPATIC ISCHEMIA REPERFUSION INJURY IS TRIGGERED BY IL-17A PRODUCING UNCONVENTIONAL T CELLS

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Background: In clinical organ transplantation Ischemia reperfusion injury (IRI) is still an important problem. Although there is growing evidence that CD3+ T cells play a distinct role in mediating early hepatic IRI, the precise phenotype of T cells involved and the underlying mechanisms are poorly understood.
Methods: In this study we investigated early immunological events in a well-established model of hepatic IRI in genetically targeted mice to study the role of IL-17A and it's transcription factor RORγt. We used heterozygous B6.RORγt-gfp/wt-reporter and homozygous B6.RORγt-gfp/gfp-knockout (ko) mice which underwent a 90 min partial warm ischemia, followed 24 h of reperfusion. Hepatocellular injury was evaluated by HE-histology and serum-transaminase measurement. Hepatic leukocyte subsets, cytokine secretion and major effector molecules were characterized by immunohistochemistry, ELISA, RT-PCR and polychromatic FACS.
Results: We found that unconventional CD27-γδTCR+ and CD4-CD8- double negative (DN) T cells are the major RORγt-expressing effector cells in hepatic IRI that play a mechanistic role by being the main source of IRI-mediating IL-17A. Mice deficient for γδTCR+ T cells were protected from hepatic IRI, but liver damage was restored after adoptive transfer of γδTCR+ T cells from wt animals. We further show that unconventional IRI-mediating T cells are dependent on RORγt, as highlighted by the fact that a genetic deficiency for RORγt, or its therapeutic antagonization via digoxin, protected against hepatic IRI.
Conclusion: Identification of CD27-γδTCR+ and CD4-CD8- DN T cells as the major source of IL-17A via RORγt in hepatic IRI opens new therapeutic options to improve LTx outcomes.

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O146 NORMOTHERMIC GRAFT PERFUSION DECREASES HEPATOCELLULAR CARCINOMA RECURRENCE IN A DONATION-AFTER-CARDIAC-DEATH RAT LIVER TRANSPLANTATION MODEL

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Background: Liver transplantation from donation-after-cardiac-death (DCD) is associated to ischemia/reperfusion (I/R) lesions, which may increase the risk of post-transplant hepatocellular carcinoma (HCC) recurrence. Normothermic graft perfusion (including extracorporeal membrane oxygenation –ECMO) can prevent I/R lesions and potentially cancer recurrence. These issues were assessed in rat liver transplantation models.
Methods/Materials: Syngeneic Fisher rat liver transplantations were performed, with the intraportal injection of 2106 HCC cells (JM-1) at the end of the procedure. Donors from the control group ($n = 8$) were heart-beating, those from the DCD group ($n = 8$) underwent 10-min inflow liver clamping prior to retrieval, and those from the ECMO group ($n = 8$) underwent 2-h liver reperfusion after the 10-min liver clamping. I/R lesions were assessed by histology and according to the liver function tests. HCC growth was quantified by MRI (weeks one and two). Serum cytokine and liver gene profiles were assessed 12 h after transplantation.
Results: The presence of I/R lesions was confirmed in the DCD group, with the presence of endothelial and hepatocyte injury, and increased liver function tests. These lesions were reversed by the 2-h reperfusion in the ECMO group. HCC growth was higher in the DCD group ($p = 0.014$ vs. control), and was prevented in the ECMO group ($p = 0.007$ vs. DCD,). These observations were associated to a stronger pro-inflammatory cytokine profile in the DCD group (versus control and ECMO) and the expression of hypoxia and HCC growth-enhancer genes, including Hmox1, Hif1a and Serpine1.
Conclusion: This rat experiment suggests that the ischemia/reperfusion lesions associated to liver transplantation from donation-after-cardiac-death lead to an increased risk of post-transplant HCC recurrence and growth. This observation can be reversed by normothermic graft perfusion prior to retrieval.

O147 PERI-PORTAL FIBROSIS: THE ROLE OF BILIARY EPITHELIAL CELLS FOLLOWING ISCHAEMIA-REPERFUSION INJURY DURING DCD LIVER TRANSPLANTATION

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Background: Hepatic ischemia-reperfusion injury (IRI) causes periportal inflammation and fibrosis which has been implicated in the pathogenesis of non-anastomotic biliary strictures (NABS) following DCD liver transplants. The mechanisms leading to remodelling around the portal tracts are not fully understood. There is increasing evidence that biliary epithelial cells (BECs) may play an important role in liver inflammation and could be implicated in chemotaxis following IRI. The aim of this study was to investigate chemokine expression by BECs in both an *in-vivo* and *in-vitro* model of IRI.
Methods: *In-vivo* model: Sprague Dawley rats were divided into two groups ($n = 10$/group): IRI group subjected to 90 min of hepatic ischaemia followed by reperfusion and sham-operated group. Liver tissue was harvested after 5 h–28 days post-reperfusion to assess fibrosis. Serum/bile samples were collected for chemokine measurement. *In-vitro* model: Human hepatic stellate cells (HSCs) and BECs were isolated from liver resection specimens ($n = 6$). BECs were cultured in hypoxia (1%O2), normoxia (21%O2) or hypoxia for 8 h followed by normoxia to mimic IRI. Conditioned media was collected at 24 or 72 h. A chemotaxis assay was performed by exposing activated HSCs in migration chambers to BEC-conditioned media for 20 h.
Results: The IRI group showed progressive periportal fibrosis *in-vivo*. MCP-1 was significantly raised in this group in bile & serum ($p < 0.05$) on days 1 and 3 post-reperfusion respectively compared to sham. HSCs showed significantly greater migration when exposed to media obtained from BECs exposed to hypoxia followed by normoxia compared to hypoxia/normoxia alone. Migration significantly increased over time. Adding anti MCP-1 to the conditioned media neutralised this effect.
Conclusion: This study suggests that BECs produce MCP-1 in response to IRI. This may explain the periportal inflammation/fibrosis that may be fundamental to the development of NABS following DCD liver transplants.

O148 THE EFFECT OF PRESERVATION SOLUTIONS HTK, HTK-N AND TIPROTEC ON VARIOUS TISSUES AFTER RAT HIND-LIMB ALLOTRANSPLANTATION

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Background: Ischemia/reperfusion (I/R) injury is an early factor damaging grafts in solid organ and composite tissue transplantation. We herein investigate the effect of the novel preservation solutions HTK-N and TiProtec on tissue preservation and damage in a vascularized composite allotransplantation (VCA) model.
Methods: Orthopic hind-limb transplantations were performed in male Lewis-rats following 10 h of CI. Limbs were flushed and stored in HTK-N, TiProtec, HTK or NaCl-solution. Skin, muscle, nerve, vessel and bone-samples were taken at the 10th post-operative day (POD) for histology, confocal and electron-microscopy.
Results: In the NaCl treated group signs of muscle atrophy were observed at POD 10, which were not found in the other groups. The confocal microscopy of the muscle revealed no significant difference of muscle-cell viability on POD 10 between HTK-N (82.2%), HTK (80.6%) and NaCl (85.4%), whereas TiProtec (61.2%) was inferior. Histology showed a superiority ($p = 0.08$) of HTK in muscle preservation displaying a diffuse inflammatory infiltrate and only localized necrosis contrary to mainly major necrosis in the remaining groups. In all other tissues no significant differences concerning tissue damage were observed. The majority of skin alterations included a mild inflammatory infiltrate in the dermis and rarely interface reactions, infiltration of the epidermis and sporadic epithelial necrosis. Nerve samples revealed mostly severe perineural inflammatory infiltrate, vacuolization and mucoid degeneration. Vessels showed intact endothelial cells and only a mild infiltrate. Electron microscopy revealed that vessel-preservation was equaly good in all groups.
Conclusion: Nerve and muscle are most susceptible to I/R injury in a VCA model. Skin and vessels on the other hand are relatively unaffected by I/R. HTK has the best preservation ability for muscle tissue, which is a major component of a VCA and crucial to gain function after limb transplantation.

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OS17- IMMUNOREGULATION

O149 THE EFFECT OF ADIPOSE TISSUE DERIVED MESENCHYMAL STEM CELLS ON B CELL PROLIFERATION AND DIFFERENTIATION

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Background: Mesenchymal stem cells (MSC) have proven immunomodulatory capacity which makes them a promising therapeutic tool in transplantation. While the immunosuppressive effect of MSC on T cell-mediated effector mechanisms has been well studied, less is know about the effects of MSC on B cell-mediated immune responses.
Methods: MSC were isolated from subcutaneous fat tissue from kidney transplant donors. Resting mature B cells from tonsils were obtained by CD43 negative selection with Magnetic Activated Cell Sorting (MACS). MSC were co-cultured with CFSE-labeled B cells stimulated in a T cell-like dependent fashion (anti-IgM+ anti-CD40+ IL2) or by PMA/ionomycin activated CD4 T cells. Proliferation and B cell phenotype were analyzed by Flow Cytometry, and IgG production quantified by ELISA.
Results: An induction of plasmablasts (CD19+ CD27high CD38high) occurred when B cells were stimulated in a T cell dependent manner or in the presence of activated CD4 T cells. MSC abolished the differentiation into plasmablasts completely, which was correlated with decreased IgG production. Furthermore, MSCs induced an increase in the percentage of CD19+ CD27− CD38high CD24high regulatory-like B cells.
Conclusion: MSC might be important in regulating the humoral responses in transplant rejection by inhibiting B cell differentiation and inducing regulatory-like B cells.

O150 IL-17 RECEPTOR- EXPRESSING B CELLS ARE SELECTIVELY ENRICHED AND ACTIVATED IN CHRONICALLY REJECTING MURINE HEART ALLOGRAFTS

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B cells and IL-17A have been reported to play major roles in chronic allograft rejection. This study aims to address potential cross-talk between IL-17A and B cells in a mouse model of chronic rejection. Using the MHC class II − mismatched bm12 to B6 mouse model of chronic heart allograft vasculopathy, we show by histology and RT-PCR, respectively, that B cells accumulate in heart grafts and that IL-17RA and IL-17RC expression increase with time in allografts. In addition, cell suspensions prepared from recipient spleens and heart allografts, and from naïve control mice were analyzed for the presence of B cells by flow cytometry. B cells (CD19+ cells) expressing the IL-17RA were identified among the CD11b+ cells of both spleens and hearts. The majority of IL-17RA+ B cells also expressed IL-17RC: These data suggest that B cells can respond to IL-17A as IL-17A-mediated signal transduction requires co-expression of both the IL-17RA and IL-17RC. IL-17RA+/RC+ B cells specifically accumulated in chronically rejecting hearts but not in normal non-transplanted hearts or in recipient spleens or control spleens. Furthermore, B cells were also analyzed for expression of the surface receptor CD86, which is a marker of cell activation. Importantly, CD86 was selectively upregulated by IL-17RA/RC co-expressing B cells from heart allografts, but not by B cells expressing IL-17RA alone in spleens or hearts, or by IL-17RA/RC co-expressing B cells in recipient spleens, controls spleens or control hearts. These data suggest that B cells capable of responding to IL-17A become selectively recruited and activated in chronically rejecting allografts. To our knowledge, this is the first demonstration of activated IL-17 receptor expressing B cells in murine chronic vasculopathy. Ongoing studies aim to address the function and significance of this B cell subset in chronic rejection, in relation to IL-17 and IL-17-producing cells such as Th17 cells.

O151 LIVER GRAFT-DERIVED MESENCHYMAL STROMAL CELLS ARE IMMUNE LICENSED AND HIGHLY POTENT IN SUPPRESSING ALLO-REACTIVE T CELLS

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Background: Mesenchymal stromal cells (MSCs) have potent immunomodulatory properties. However in the context of transplantation, immune licensing of MSCs in grafts by exposure to inflammatory cytokines may alter their inherent immune regulatory capacity. The aim of this study was to quantify the immunosuppressive capacity of MSCs mobilized from donor liver grafts on allo-reactive T cells.
Methods: MSCs from liver grafts (L-MSCs, $n = 12$) and healthy bone marrow (BM-MSC, $n = 6$) were cultured for 21 days. Fluorescently (CFSE)-labelled PBMCs, with or without MSCs, were stimulated with allogeneic antigen presenting CD40-activated B cells. After 5 days, precursor frequencies of T cell subsets were calculated from CFSE-dilution patterns. In parallel, T cell degranulation capacity and interferon gamma (IFN-γ) production were measured. Also, the immune suppressive capacity of conditioned media (CM) from L-MSCs and BM-MSCs, after priming *ex vivo* with IFN-γ and TNF-α, was tested.
Results: L-MSCs mobilized from donor grafts had an upregulated expression of the immunosuppressive programmed death-ligand 1 (PD-L1), when compared to BM-MSCs. Besides the difference in PD-L1, we found L-MSCs possess stronger suppressive effect on proliferation of allo-reactive T cell subsets. Moreover, L-MSCs potently suppressed the degranulation of activated T cells and their production of IFN-γ. Interestingly, CM from *ex vivo* primed L-MSCs were effective in suppressing the proliferation of T cells, not degranulation. CM from BM-MSCs did not possess any immunosuppressive capacity.
Conclusions: Our study showed that L-MSCs are more potent than BM-MSCs in suppressing T cell activation. These differences may be related to the intragraft priming of L-MSCs. Therefore, liver graft derived-MSCs may promote tolerance after liver transplantation and represent a promising candidate for cell-based therapies.

O152 HUMAN REGULATORY MACROPHAGES INDUCE A FUNCTIONALLY SUPPRESSIVE PHENOTYPE IN ALLOGENEIC T CELLS

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Background: Human regulatory macrophages (M regs) represent a unique and stable state of macrophage activation, characterized by a potent T cell-suppressive capacity. M regs arise from CD14+ blood monocytes after a 6-day culture in the presence of M-CSF, human serum, and a final 24-h pulse of IFNγ. These cells have been investigated as an immunosuppressive cell-based therapy for living-donor renal transplant recipients, and although initial results suggest pre-transplant administration of donor-derived M regs has beneficial effects, the precise mechanisms by which M regs influence T cell responses have not yet been defined.
Methods: Human T cells enriched by MACS positive-selection for CD3 were cocultured for 5 days with M regs generated from healthy leukapheresis donors and subsequently characterized by flow cytometry, microarray, cytokine release, and secondary suppression assays.
Results: When cultured with allogeneic human M regs, but not with control macrophages, polyclonal CD4+ T cells expressed Foxp3, CD25, OX40, GITR, ICOS, and LAG-3, a contact-dependent effect mediated by indoleamine 2,3-dioxygenase (IDO) activity and signaling through B7-dependent pathways. M reg-cocultured CD4+ T cells suppressed αCD3-stimulated polyclonal T cell proliferation and prevented TNFα-induced up-regulation of CD80 and CD83 by immature dendritic cells. Therefore, human M regs are capable of inducing effector T regs that arise by conversion from non-T regs.
Conclusion: These data support the concept that pre-transplant treatment of recipients could engender a pro-tolerogenic immunological milieu and hint at a feed-forward mechanism by which this favorable state could be perpetuated. Clinical applications of M reg immunosuppressive therapy are currently being pursued within The ONE Study framework.

O153 CD154 EXPRESSION SPECIFICALLY IDENTIFIES ALLO-ANTIGEN SPECIFIC TREGS FOR CELLULAR THERAPY

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Background: Identification, isolation and expansion of alloAg-specific regulatory T cells (Tregs) for cellular immunotherapy is preferred over to the use of unspecific Tregs. In this study, we investigated whether CD154 cell surface expression is able to detect Ag-specific Tregs upon allogeneic stimulation.
Methods: AlloAg-specific, CD154+ Tregs were studied extensively using phenotypic as well as functional analyses, testing their suppressive capacity in a mixed lymphocyte reaction (MLR) either immediately upon isolation or following expansion.
Results: Allo-antigen specific CD154+ Tregs could be identified after 24 h stimulation. Sorted CD154+ Tregs (>80% FOXP3+, >95% demethylated TSDR in FOXP3) were superior in suppressing Ag-specific responses when compared to CD154-Tregs and total Tregs. At a 1–5 Treg:Teff ratio the median% of inhibition in a MLR was 57% vs. 25% and 31%, respectively. CD154+ Tregs could be efficiently expanded in an Ag-specific manner. These expanded Tregs were highly suppressive and alloantigen-specific inhibition was seen at Treg:Teff ratio's as low as 1:320.

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Conclusions: AlloAg-specific Tregs can be detected using CD154 expression with subsequent isolation and expansion. CD154+ alloAg-specific Tregs have a stable phenotype of natural Tregs and display superior suppressor function. These cells are therefore suitable candidates for cellular immunotherapy in patients undergoing kidney transplantation.

O154 ALLOANTIGEN SPECIFIC IMMMUNOSUPPRESSION BY INDUCED REGULATORY T CELLS IN HUMANS

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Background: Currently it is unknown whether induced regulatory T cells (iTreg) are generated after transplantation and whether these iTreg specifically suppress alloreactive T cells.
Methods: CD4+ CD25-FOXP3- T cells from healthy donors ($n = 7$) were stimulated with HLA mismatched alloantigen to induce CD4+ CD25+ FOXP3+ T cells (iTreg). These iTregs were subdivided into CD127-iTreg and CD127+ iTreg and tested for their immunosuppressive capacity and specificity.
Results: In the primary MLR, 78 ± 9% (mean ± SD) of the CD4+ cells became CD25+ FOXP3+. In the secondary MLR, the proliferation of CD25- T cells was robustly inhibited by both CD127+ iTreg (93 ± 5%; ratio iTreg: CD25- = 1:5) and CD127-iTreg (95 ± 3%). Antigen specificity was confirmed by the observation that both iTreg subsets inhibited the proliferation of CD25- T cells using a stimulator sharing one HLA-DR with the original stimulator (CD127+ iTreg: 96 ± 1% and CD127-iTreg: 93 ± 2%). Stimulation with a fully mismatched 3P antigen resulted in significant less inhibition (CD127+ iTreg: 68 ± 17%, p = 0.004 and CD127-iTreg: 68 ± 13%, p = 0.0003).
Conclusion: Alloantigen specific iTreg are induced during alloreactivity, suggesting that iTreg could play a role in controlling alloreactive T cells after transplantation.

O155 *EX-VIVO* GENERATION OF HUMAN REGULATORY T CELLS BY CD80/CD86 COSTIMULATION BLOCKADE

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Backgrounds: Infusion of lymphocytes, cultured *ex-vivo* with donor-Ags under CD80/CD86 costimulation blockade induces tolerance to organ allografts. However, which cell-type is contributing to the effect is unclear. We aimed to identify those using human lymphocytes.
Methods: Human PBMCs were co-cultured with irradiated allogeneic PBMCs together with αCD80 and αCD86 mAbs. Two weeks later, cell-phenotypes and inhibitory effect were examined by flowcytometory and MLR.
Results: Generated lymphocytes inhibited MLR in proportional to the cell number (Fig. 1A). The inhibitory effect was relatively stronger to the donor- than 3rd party-Ags. When CD3+ cells were removed from the cultured cells, MLR inhibitory effect was completely lost. Conversely, the effect was restored when added (Fig. B). In contrast, removal or addition of B cells, monocytes, NK cells or DCs did not alter MLR. By culture, CD4+ T cells, especially CD25+Foxp3+ (Fig. 1D) and CD127loFoxp3+ regulatory phenotype significantly increased. In addition, IL-10 producing CD4+CD8+ T cells were generated after co-culture.
Conclusion: CD4+ CD25+ CD127loFoxp3+ and CD4+CD8+ T cells that exert immunoregulatory property are generated *ex-vivo* from human PBMCs after culturing together with allo-antigens under CD80/CD86 costimulation blockade.

O156 MATURE DENDRITIC CELLS ARE SUPERIOR STIMULATOR CELLS FOR EXPANSION OF HUMAN ALLOREACTIVE REGULATORY T CELLS

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Background: Ag-specific regulatory T cells (Tregs) have a great therapeutic clinical potential. However, large numbers are needed before Tregs can be used as cellular immunotherapy in kidney transplantation. In this study, mature monocyte-derived dendritic cells (moDC) were studied for their capacity to generate alloAg-specific Tregs and compared with PBMC-induced and polyclonal Treg expansion.
Methods: Tregs, obtained by FACS-sorting, were expanded polyclonal or through an Ag-specific expansion protocol using HLA-mismatched PBMC or mature moDC as stimulator cells. The different expanded Tregs were stained for FOXP3 and their suppressive capacity was tested in a mixed lymphocyte reaction (MLR).
Results: Mature allogeneic moDC were on average 40-times more potent in inducing Treg expansion when compared to PBMC. Moreover, stable high FOXP3 expression was observed in all expanded Tregs. Both allogeneic DC- and PBMC-expanded Tregs were potent suppressors of allogeneic proliferation compared to polyclonal-expanded Tregs. At a ratio of 1:320, the allogeneic proliferation was inhibited by 60–70% when Ag-specific-expanded Tregs were used whereas no suppressive activity was observed for polyclonal-expanded Tregs.
Conclusions: Mature allogeneic moDC are highly efficient cells for expansion of potent alloAg-specific Tregs. This observation opens a new avenue for generation of Tregs on a large scale for immunotherapy.

O157 RESTRICTION OF HUMAN CD4+CD25+FOXP3+CD127– NTREG AND ITREG PHENOTYPES *IN-VIVO* AND *IN-VITRO* AS DETERMINED BY 8-COLOR FLUORESCENCE FLOW CYTOMETRY

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Background: Differences in phenotype including the cytokine pattern of natural and induced regulatory T cells (nTreg, iTreg) have previously not been studied.
Method: We first investigated the frequency and cytokine pattern of CD4+CD25+FoxP3+CD127– nTreg in freshly separated PBMC of five healthy individuals using 8-color fluorescence flow cytometry. Subsequently, after 9 days of allostimulation in MLC, frequency and cytokine pattern of CD4+CD25+FoxP3+CD127– iTreg were determined anew and analyzed.
Results: Virtually all CD4+CD25+FoxP3+CD127– nTreg (1.5 ± 0.70% of CD4+ PBL) were IFNy–IL2– and co-expressed IL10+TGFß+ (1.1 ± 0.59%) or IL10–TGFß+ (0.39 ± 0.16%). After 9-day stimulation, 2.6 ± 1.6% of the CD4+ T cells expressed CD4+CD25+FoxP3+CD127– (vs. fresh cells: $p < 0.01$). Compared to fresh cells, the proportion of CD4+CD25+FoxP3+CD127–IFNy–IL2– nTreg remained stable (p = n.s.) whereas the proportions of IFNy+IL2+IL10+TGFß+ (0.02 ± 0.05% vs. 0.26 ± 0.21%: $p < 0.01$) and IFNy+IL2–IL10+TGFß+ iTreg (0.02 ± 0.05% vs. 0.55 ± 0.13%: $p < 0.001$) increased during MLC. IFNy–IL2+, IFNy+IL2+IL10–TGFß–, and IFNy+IL2+IL10–TGFß+ Treg were undetectable in fresh cells as well as after 9-day MLC.
Conclusion: nTreg are IFNy–IL2– double-negative, produce IL10 and TGFß or only TGFß without IL10, and do not proliferate *in-vitro*. During allostimulation in MLC, IFNy+ iTreg develop. One-third of induced IFNy-producing CD4+CD25+FoxP3+CD127– Treg are IL2+ and two-thirds IL2–, and both subsets produce TGFß as well as IL10. It appears that Treg phenotypes are restricted: certain phenotypes are not detectable in peripheral blood and not inducible by alloantigenic stimulation. Our results imply that virtually all CD4+CD25+FoxP3+CD127– Treg are potentially immunosuppressive because of their mandatory TGFß and optional IL10 production.
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O158 IL-2 COMPLEXES PRIMARILY EXPAND NATURAL T REGULATORY CELLS BUT ALSO STIMULATE EFFECTOR T CELLS

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Tregs are essential for maintaining self-tolerance and are therefore an attractive therapeutic target for organ transplantation as several models have shown that the adoptive transfer of Tregs can suppress alloresponses. Recently it was shown that mouse IL-2 complexed with a mAb (JES61) against IL-2 is efficient in expanding Tregs *in vivo*. We therefore investigated the specificity of the *in vivo* effects of IL2 complexes. The IL-2 complexes were administered intraperitoneally into C57BL/6 mice, on three consecutive days (d0, d1, d2). Lymphocyte populations and surface marker expression were analyzed in blood, spleen and lymph nodes at distinct time points (d4, d6, d9) by flow cytometry. C57BL/6 mice were treated with 1 Gy TBI and received 20*106 unseperated Balb/C bone marrow cells and costimulation blockade (anti-CD154mAb, CTLA4-Ig) together with IL-2 complexes. To determine whether the expanding Tregs are derived from natural Tregs, we used Helios and Neuropilin-1 as markers for natural Tregs and Ki67 to measure their proliferation. Two days after the last administration, 95% of all CD4 Foxp3 cells in the spleen and lymph nodes were Ki67 positive and 75% expressed Neuropilin-1 and Helios. Seventy percent of all CD8 cells and 80% of all NK cells up-regulated the $f_{¿}$-chain of the IL-2 receptor and thus became susceptible to IL-2. Furthermore, CD8 cells started to proliferate in the periphery and 30% of all CD8 cells exhibited an effector/memory phenotype of CD44hi CD62Llo. Finally we tested the ability of IL-2

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complexes to promote allograft survival in a co-stimulation based bone marrow transplantation model. Unexpectedly, treatment with IL-2 complexes inhibited BM engraftment, leading to a reduced number of successful chimeras (4/6 vs. 0/6 chimeras). IL-2 complexes are a powerful tool to expand natural regulatory T cells *in vivo*. However their effect is not very specific as they also increase the number of activated T and NK cells.

O159 GRAFT ACCEPTANCE (=TOLERANCE) AND INTRAGRAFT GENE PROFILESIMMUNOPRIVILEGED LIVER VERSUS HIGHLY IMMUNOGENIC INTESTINE

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Introduction: Both in human and animal transplantation, the intestine is highly immunogenic while acceptance of the liver is much more frequent that is referred to as immunoprivilege.As graft infiltrating cells are more likely to reflect the immune state of the graft than cells in the peripheral blood, we have investigated intragraft gene profiles after human liver transplantation (Ltx) and intestinal transplantation (Itx).
Method: Fifteen immunosuppression (IS) free Ltx recipients and 4 Itx recipients taking minimal IS were enrolled (Group-tolerance: Gr-Tol). Total RNA was extracted from biopsy specimens to synthesize cDNA and expression of the following genes were semi-quantified by real time PCR: FOXP3, Vδ1γδ T cells to Vδ2γδ T cells ratio (Vδ1/Vδ2 ratio), PD-1, PD-L1, PD-L2, CD4, CD8, CD25, CD19, CD56, Vα24. Donor-zero biopsy and native intestine were used as controls for Ltx and Itx, respectively (Group-control: Gr-Con).
Result: In Ltx, FOXP3 expression was significantly higher in Gr-Tol compared to Gr-Con ($p < 0.01$). Vδ1/Vδ2 ratio tended to be higher in Gr-Tol compared to Gr-Con ($p = 0.01$). CD19 expression was higher in Gr-Tol versus Gr-Con ($p = 0.055$). In Itx, similar to Ltx, FOXP3 and CD19 expressions were up-regulated in Gr-Tol compared to Gr-Con ($p = 0.067$, $p < 0.01$). Of note, PD-1 and PD-L2 were up-regulated in Gr-Tol compared to Gr-Con ($p = 0.09$, $p = 0.077$). Vδ1/Vδ2 ratio did not differ between the two group in Itx, while PD-1 or PD-L2 did not differ in Ltx. Expression of CD4, CD8, CD25, CD56, or Vα24 did not differ between the two groups either in Ltx or Itx.
Conclusion: FOXP3+ Regulatory T cells and CD19+ B cells are likely to be associated with graft acceptance both of the liver and the intestine. γδT cells appear to associated with acceptance of the liver, while PD-1/PD-L2 with the intestine. Those intriguing data may provide a significant clue to explain a definite difference in terms of graft acceptance between immunoprivileged liver and highly immunogenic intestine.

O160 STABLE IMMUNOSUPPRESSION UNDER LOW-DOSE TACROLIMUS MONOTHERAPY DEPENDS UPON IMMUNOLOGICAL REGULATION

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Immunological reaction or non-reaction to an allograft is dictated, it seems, by the net balance of effector and regulatory responses, and not by mechanisms unique to the tolerant state. If this quantitative account of tolerance is believed, then it is a small step to the recognition of "marginal" states in which regulatory responses are just insufficient to prevent rejection, or in which regulatory responses are just sufficient to prevent rejection but are readily disturbed. This work seeks to demonstrate the existence of such marginal states and their dependence on allospecific regulation.

B6 mice on a regular diet laced with tacrolimus (Tac) at 50, 75 or 100 mg/kg had stable serum levels of 0.9 ± 0.2, 3.7 ± 1.4, 8.9 ± 5.4 ng/ml. In a BALB/c to B6 skin transplant model, costimulatory blockade with αCD154, αCD252 and CTLA4-Ig had a significant allograft-protective effect (69.7 ± 10.9 vs. 8.3 ± 0.4 days; $p < 0.001$). αCD154 treatment marginally prolonged allograft survival, whereas combination of αCD154 and donor-specific transfusion (DST) led to a moderate prolongation (40.0 ± 6.0 days vs. untreated; $p < 0.001$). αCD154 and low-dose Tac had no combinatorial benefit. Together, αCD154/DST plus Tac was not more effective than αCD154/DST when Tac commenced on day 0 or −7; however, when 75 mg/kg Tac started on day +7, a remarkable synergism between Tac and αCD154/DST was observed (74.4 ± 4.1 days vs. αCD154/DST; $p = 0.002$). By withdrawing Tac at day 50 (61.4 ± 1.5 days vs. αCD154/DST+Tac; $p = 0.007$), enhancing effector responses (70.7 ± 1.8 days vs. αCD154/DST+Tac; $p = 0.001$) or disturbing regulation in various ways, it was possible to precipitate rejection, proving that stable immunosuppression depends upon the balance of regulatory and effector responses.

Stable immunosuppression with low-dose Tac monotherapy is critically dependent upon immunological regulation. This work has far-reaching implications for patient management, interpretation of immunomonitoring studies and clinical tolerance-induction studies.

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OS18-ETHIC/LAW/PSYCHOSOCIAL/PUBLIC POLICY

O161 CANCER TRANSMISSION FROM ORGAN DONORS

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Background: There is limited evidence for estimating donors' risk of transmitting a cancer to their recipients.
Methods: Data for donors and recipients were obtained from the UKTransplant Registry and Cancer Registries. Council of Europe guidelines were used for classification of cancer transmission risk.
Results: Of the 17 639 donors, 202 (1.2%) had a history of cancer, of whom 61 had unacceptable transmission risk. None of these cancers was transmitted to their 133 recipients. No significant difference was noted in survival of recipients from donors with standard risk or unacceptable risk. At 10 years from transplant, recipients from unacceptable donors survived for 1148 life-years (1027, 1269).
Conclusions: We found that a selected sub-group of donors classed as unacceptable risk of cancer transmission can be a safe and valuable source of additional organs. Careful risk assessment and informed consent can result in significant survival benefit with low cancer transmission risk.

O162 TELEMEDICIN AS AN INNOVATIVE PROJECT-STUDY IN ADHERENCE IMPROVEMENT AFTER LIVING KIDENEY TRANSPLANTATION AT THE TRANSPLANTATION-CENTER FREIBURG

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Background: Living kidney-transplantation is since more than 30 years a main focus at the University Clinic in Freiburg. During this time more than 500 living kidney transplantations were performed. The successful operation is an important factor, but also the post-transplant care and treatment for the possibly longest patient and graft survival. Therefore in Freiburg started a prospective, controlled, randomized and open project-study to screen the adherence and psychosocial factors of living recipients.
Method: A group of 25 patients enter at home daily their data into an interactive web-based telemonitor. The entered data are daily checked by medical staff of the Transplantation-Center. Additionally the patients are monitored by Interviews and Questionnaires. The BAASIS-Interview, including the analog scale VAS, is to gather the adherence concerning the immunosuppression-intake. The ESRD-SCL TM to measure the quality of life and the BSI-18-Instrument to cover the psychological liability for kidney recipients. As a control group 25 living kidney recipients without a telemonitor are matched. The data-evaluation is reviewed with inductive and descriptive statistics.
Results: Medical observation in patient's environment, less activities in health facilities and encouragement of patient's self-responsibility are expected as result of the project-analysis. Also early diagnosis of rejections and infections. All those points result in an early rejection-therapy, increasing patient's safety and quality of life and positive psychosocial aspects. Current observations confirm this thesis.
Conclusion: The project should confirm evidence that a telemedicine supported post-operative care, give the recipient's medical and social benefit. The daily communication between patients and the Transplantation-Center induces a high degree of trust and reduces activities in health facilities and hospital-readmissions and will give the recipients more safety and life quality.

O163 PUBLIC SOLICITATION OF ORGANS FROM LIVING DONORS – AN ELPAT VIEW

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Background: Public solicitation is among the most controversial issues in living organ donation. We aim to critically assess the arguments concerning public solicitation and to offer recommendations. While the legal framework is not that different between the EU and US (both condemn financially-driven solicitation), the practices of both transplant centers and of individuals needing a transplant vary. The main difference can be observed between certain liberal practices in the US (where one can find commercially operated websites soliciting organs altruistically donated from living donors), and more conservative practices in the EU (where such websites are absent).
Methods: We attempt to clarify the terminology concerning public solicitation, the different levels of public solicitation, and the motivations of recipients and donors. Firstly we elaborate an operational definition for public solicitation that is consistent with the ELPAT classification of living donors (Dor et al, Transplantation 2011). Secondly we evaluate the various arguments from the literature, both pro and con.
Results: Although they look contradictory, in most cases the same arguments are used both to defend and condemn the legitimacy of public solicitation. The arguments are classified according to the manner in which they influence the actions of recipients and/or donors, and regarding the influence on the transplantation process at individual and societal level.
Conclusion: Finally, we offer a set of recommendations. While we do not recommend it as a general practice, the acceptability of public solicitation by the patient or medical team could be explored for special cases (e.g. highly sensitized individuals or other patients with little chance of receiving a transplant otherwise).

O164 COMMUNICATION OF THE DECISION IN FAVOUR OF ORGAN DONATION THROUGH DONOR FAMILIES AND THE REACTIONS WITHIN THE CIRCLE OF FAMILIY AND FRIENDS

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Background: In Germany donor relatives are asked for consent to organ donation if the potential donor did not decide himself during life time (informed consent). In approximately 2/3 of the cases the attitude of the potential donor is unknown. We want to investigate how donor relatives communicate the decision of their loved ones or their own decision regarding consent to organ donation to their familes and friends and what reactions occurred as a result.
Methods: In 2005–2010 we organized 16 meetings for donor relatives in the DSO Region Bavaria. A total of 175 people attended. All of the attendees received a questionnaire, 78% answered. Among questions to the care of donor families during and after organ donation through the hospital staff and the DSO coordinators, we also asked about the stability, the communication of the decision and the reactions within the circle of family and friends. We also asked for the basis of their decision regarding consent to organ donation.
Results: Ninety-one percent of the interviewed donor relatives would also agree to it years later. Only 1% would decline organ donation later on and 7% were undecided. Fifty-six percent could rely upon a clear decision of their loved ones in favour of organ donation, 36% never talked about this topic. Ninety-six percent informed the family upon their decision, only 4% did not. Sixty-two percent of this group experienced positive reactions, 37% divided reactions and 1% disapproval. Eighty-seven percent communicated the consent for organ donation to the circle of friends, 13% did not. In this setting, 57% experienced positive reactions, 43% divided reactions, and no disapproval was experienced at all.
Conclusion: In most of our hospitals organ donation is not considered as a normal end of life practice in ICU. If donor families are treated adequately, their decision is stable and they communicate their decision to their families and friends. We think that good donor relative care can help organ donation to become a normal possibility for people dying from brain death.

O165 A QUANTITATIVE SURVEY OF SOUTH ASIAN ATTITUDES TO ORGAN DONATION IN THE UNITED KINGDOM

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Background: South Asians in the United Kingdom are over-represented on the organ transplant waiting list but under-represented as organ donors. In this study we surveyed South Asian opinion with regards to organ donation, aiming to guide national strategic planning.
Methods: Voluntary completion of an anonymous survey was promoted online and in South Asian community/religious centres. For the purpose of sample power calculations, we calculated the South Asian population in the United Kingdom to be 4 303 978 according to the 2011 census report. To minimise the level of uncertainty, we targeted a minimum number of 385 completed surveys (thus achieving 5% error margins and 95% confidence intervals). Logistic regression analysis was performed to assess independent predictors for organ donation approval.
Results: Five hundred and fifty-six survey responses were analysed (survey completion rate 86.5%). Ethnicity was classed as Indian by 42.8% of respondents and Pakistani or Bangladeshi by 57.2%. Religious breakdown of respondents was Muslim (70.8%), Hindu (15.9%) and Sikh (13.3%). 68.4% of

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respondents agreed with organ donation but only 13.3% were registered organ donors. Muslims were less likely than Hindus or Sikhs to agree with organ donation (59.3% vs. 92.2% vs. 88.7% respectively, $p < 0.001$) or be registered donors (5.0% vs. 40.3% vs. 25.8% respectively, $p < 0.001$). Religious guidance was rated very important by 59.4% of the total South Asian cohort, although Muslims gave this more importance than either Hindus or Sikhs (70.2% vs. 27.8% vs. 41.7% respectively, $p < 0.001$). Parental pressure was cited as very important by 50.1% of the total cohort, but reciprocally Hindus gave this more importance compared to either Muslims or Sikhs (65.3% vs. 45.7% vs. 54.8% respectively, $p = 0.008$). Distrust of the health service, poor publicity and apathy was ranked as very important factors by 24.5%, 48.0% and 43.8% of the total cohort, with no discernable difference between different faith groups. On logistic regression analysis variables independently associated with organ donation approval were; young age, independent living from parents, non-Muslims, awareness of organ donation shortages, family member on dialysis or registered donor and strength of religious belief (all $p < 0.05$).
Conclusion: South Asians in the United Kingdom are a heterogeneous group of different faiths, cultures and values. We believe a targeted strategy is required to raise awareness of organ donation based upon a clear understanding of religious, sociocultural and environmental influences.

O166 UK DONATION ETHICS COMMITTEE (UKDEC) DRAFT GUIDANCE ON PRE-MORTEM INTERVENTIONS TO OPTIMISE DONOR ORGAN QUALITY AND IMPROVE TRANSPLANT OUTCOMES IN DCD

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In 2009, the Dept of Health (DH) issued guidance on the legal issues relating to DCD, stating that if a person (P) wished to be a donor, actions which facilitate donation may be in their best interests (BI) if they do not cause or place them at a material risk of experiencing harm or distress. Since then the number of DCD transplants performed in the UK has more than tripled. Reports vary, but the consensus is that pre-mortem interventions that optimise organ quality also improve transplant outcomes. This has prompted further consideration of the BI test in this context. The UKDEC now proposes new guidance to apply when the continuation of life-sustaining treatment is no longer in P's BI & organ donation would be in P's BI. It states that to decide if an intervention would be in P's BI, the potential benefits to P must be balanced against the potential (risk of) harm or distress. The potential benefits encompass both the prospective benefit of knowing their wishes will be facilitated, & the future benefit attaching to their legacy. P will usually have an interest in the well-being of their loved ones & so may also be benefitted indirectly if the donation helps them come to terms with their loss. Examples of potential harm include pain, discomfort, shortening P's life & worsening P's medical condition. Examples of potential distress include feelings of suffocation, panic, weakness & invasion of privacy. The risk of causing distress to P's loved ones should also be considered. Factors affecting the balancing assessment include: the strength of P's desire to become a donor; the potential of an intervention to optimise donor organ quality & improve transplant outcomes; & the possibility of the alleviation of symptoms or avoidance of distress for P & their loved ones. Examples of pharmacological and mechanical pre-mortem interventions, such as the administration of heparin & extubation will be used to test the draft guidance.

O167 FIRST RESULTS OF A RANDOMIZED CONTROLLED TRIAL ON A HOME-BASED EDUCATIONAL INTERVENTION

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Background: In a randomized controlled trial we investigated the efficacy of a home-based educational intervention to support well-informed decision making regarding patients' optimal treatment option.
Methods: One hundred and sixty-one patients on the wait list for a deceased donor kidney transplantation were randomized to improved standard care in the control group or improved standard care plus home-based education in the experimental group. Patients and invitees completed a questionnaire measuring knowledge, risk perception, self-efficacy, and communication.
Results: The home-based education group showed significantly more improvements in their overall knowledge on kidney disease and RRT's ($p < 0.001$), showed less fears and concerns towards LDKT ($p = 0.039$) and communicated more with their social network about RRT ($p = 0.004$) compared to the control group. On average patients invited five invitees for the educational session. These invitees showed pre-post improvements in their overall knowledge ($p < 0.001$), an increase in their self-efficacy regarding discussing RRT's ($p = 0.035$), a reduction in their fears and concerns towards LDKT ($p = 0.001$), and they were more willing to donate a kidney ($p = 0.004$).
Conclusions: Home-based educational interventions support well-informed decision making among renal patients and their social network.

O168 THE IMPACT OF THE ISRAELI TRANSPLANT LAW IN LIVING KIDNEY DONORS

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The Israeli transplantation law (2008) determines strict regulations on living organ donations. It endorses former policies of local evaluation committees for related donors and national evaluation committees for unrelated donors, and sets organ trading as a criminal offense. We examined the impact of the law on the socio-demographic profile of living kidney donors (LKD) at our center.
Methods: We analyzed data on all LKD ($n = 475$) from 1/2004 to 12/2012. Using descriptive and proportional statistics we compared the donors' population before (1/2004–6/2008) and after (7/2008–12/2012) the law. Specifically, we examined the impact of the law on gender, education, marital status, occupation, and age composition.
Results: LKD were increased by 44.8% from 194 prior to the law to 281 in the second era. This trend results from a rise in donations from family members: from 113 prior to the law to 206 after it without a significant change in unrelated donations (81 before and 75 after the law). Whereas related donors were composed mainly of parents prior to the law, the population of related donors has become more diversified, including more family members, mainly wives and siblings. The impact of the law, was most prominent in the change in the social profile of unrelated donors. This population has become more educated (from 31% to 44% with an academic education $p < 0.001$), older (mean age 34.66 and 41.58 years), more familial (from 10% to 46.3% married with children) and more women (from 18.5% to 41.4%). Most notable was the emergence of new group of altruistic religious Jews. They composed 22% of all unrelated donors after the law in comparison to 2% prior to the law.
Conclusions: The increase in living kidney donations results from a higher motivation of family members to become kidney donors. The law has led to a change in the composition of unrelated donors that now come from different social circles.

O169 NON-STANDARD KIDNEYS FOR TRANSPLANTS: CLINICAL MARGINS, MEDICAL MORALITY AND THE LAW

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Advances in kidney transplantation have been impressive, but have not eliminated significant variability of outcome, related to donor organ quality. Organ shortage means that in addition to "standard" deceased donor kidneys (SD), "non-standard donor" (NSD), "expanded criteria donor" (ECD), or "marginal" kidneys, which fail to meet standard criteria and are often associated with less good outcomes, are now being transplanted. This paper outlines the clinical rationale and ethical argument underpinning the use of such donor kidneys and examines their legal status in the UK, which we claim remains largely undefined and untested. While it is probable that the general principles governing medico-legal consent and liability also apply to organ donation, the special circumstances of donation, notably the inadequate supply of donors, make it difficult to know how far existing medico-legal precedents can or should apply. The non-standard status of deceased donor organs creates potential problems for the validity of "appropriate consent" to donation required by statute. It may also be relevant to the use of interventions intended to optimise donor organ quality. Further, the SD/NSD distinction in clinical practice may produce unexpected legal effects. For example, the recent UK Regulations, which bring into force the EU Directive on standards of quality and safety of human organs intended for transplantation, could produce a negative legal restraint on the use of NSD kidneys. There is an urgent need for clarification of the effect of using NSDs in general criminal and civil law liability.

O170 ATTITUDES OF ITALIAN LIVER TRANSPLANTATION (LT) CENTERS TOWARDS ELIGIBILITY OF CONTROVERSIAL CANDIDATES: A NATIONAL SURVEY

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Candidate selection in LT challenges ethical issues requiring consensus. To investigate attitudes in candidacy to LT in controversial candidates in Italy, a National survey was applied. An e-mail questionnaire was sent in February 2012 to the directors of all adult LT centers (20). Items identified both clinical and pshycosocial controversial characteristics for candidacy to LT. Response rate was 95%, from either directors or delegates (21%), and all replied

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questionnaires were fulfilled. Globally, there was consensus in contraindicate LT in patients of age >70 years (95%), and, conversely, LT was widely accepted in impecunious and incarcerated statuses (95% and 79%, respectively), as well as in both cigarettes heavy smokers and in cases of re-LT for HCV recurrence (84%). Favorable attitudes to the expansion of eligibility criteria for HCC were obtained (100%), especially within the up-to-7 rule (79%). HIV infection was accepted by 68% of centers, with some limitation offering re-LT for HCV recurrence in co-infected patients (*con* 47%, uncertain 11%). Lack in 6mo abstinence led to contraindication in alcoholics in 58% of centers. Globally, rates of acceptance in marijuana consumers were 68%, dropping to 37% in cocaine abusers, while patients under methadone treatment were accepted by 58% of the centers. Grouping centers attitudes in their regional procurement agencies minor geographic discrepancies were observed. Sorting results according to center-volume activities (high, mid, low: 6, 6, 7 centers), both *con* (39% vs. 24%) and uncertain opinions (10% vs. 9% and 5%, respectively) were higher among low-volume centers compared with mid- and high-volume centers (see in the figure for *con*opinions rates). Lack of consensus among centers, irrespectively from their volume activity, were observed in their attitudes evaluating patients with lack in social support. In summary, more consensus should be reached in candidate selection in LT in Italy.

O171 DONATION, THE DONOR, AND THE DONOR'S FAMILY: A LONGITUDINAL QUALITATIVE STUDY OF RENAL PATIENTS

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This research aimed at understanding the subjective experience of the patients in deceased donor kidney transplantation (Ktx). Semi-structured interviews were conducted on 30 wait-listed patients (mean age = 53), for first deceased donor's Ktx. Interviews took place at baseline (T1), 6 (T2, $n = 23$), 12 (T3, $n = 24$), and 24 months (T4, $n = 19$) after Ktx. Qualitative analysis was performed: results of 1/12 themes is presented. Deceased donation was preferred by most patients, compared to living donation: because of donor's health risks, possible influences on relationship, fear of control from donor, responsibility in case of rejection, uneven balance between patient's illness load and risk to the donor, medical incompatibility. Ten percent of patients turned to living donation. Regarding deceased donation: (i) Brain death is a difficult topic (T1). Information must be provided for the general public, and in donation promotion to avoid misconceptions, social stigma (T2-3). (ii) Acceptance of anonymity (T4), abandonment of search for information (T2-3) are part of the grieving process. (iii) The donor and his/her family are sensitive topics and elicit intense emotions. The presence of the donor in thoughts (T2-3), responsibility toward the graft and donor (T3), feelings of gratitude, sadness, are described and decrease while learning to live with the donor (T4). (iv) Social pressure surrounding donation is dealt with by taking a pragmatic perspective about the donor, the graft, by informing about dialysis and Ktx, participating in medical research, signing up for donation card with family members. (v) Living donation might be considered in eventual return to dialyses and if life becomes unbearable (T4). In summary, patients waiting for a deceased donor kidney transplant undergo a subjective experience, which evolves with time. Evaluating donation choices while waiting for Ktx is important, as the need to explain different donation contexts to significant ones and to the general public.

O172 THE OPINION OF DUTCH LIVER TRANSPLANT RECIPIENTS ABOUT ANONYMITY OF ORGAN DONATION AND THEIR WISH TO GET IN TOUCH WITH THE DONOR'S RELATIVES

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Background: In the Netherlands the privacy of organ donors is protected by legislation. Nowadays voices are raised to abolish the anonymity of organ donation and to make direct contact between transplant recipients and their donor's relatives possible. However, little is known about the opinion of Dutch organ transplant recipients regarding these topics.
Methods/Materials: To gain insight into the opinion of liver transplant recipients about these topics a cross-sectional study among 244 liver transplant recipients was performed in the fall of 2012. Data were collected by a questionnaire, developed for the purpose of this study. Transplant related variables were derived from the hospitals liver transplant database. The opinion of recipients was examined in relation with demographics, transplant related variables and emotional factors.
Results: Of the 179 respondents 65% indicated that they would like to know more about their donor, but mostly only some general information. Fifty-three percent of the respondents agreed with the principle of anonymity of organ donation, mainly out of respect for the donor. Respondents who lived alone, were younger than 40 or older than 60 years, and those with a lower level of positive affect were significantly more in favour of anonymity. Though 30% thought that it should be possible to get in touch with the donor's relatives, only 19% would like to get in touch with the donor's relatives themselves. Recipients transplanted for alcoholic cirrhosis were less in favour of direct contact. Recipients with more feelings of guilt had a stronger wish to get in touch with the donor's relatives.
Conclusion: These data suggest that there seems no need to change the current legislation and policy regarding anonymity of organ donation. However, most liver transplant recipients would like to receive some general information about their donor. Guidelines about the kind of information that can be given should be established.

O172A WHO HAS EXTREME EXPECTATIONS OF DONATION? EXPLORING THE PSYCHOLOGICAL PROFILE OF LIVING KIDNEY DONORS

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Background: Assessing expectations regarding personal consequences of donation (e.g. personal growth) is a component in the psychosocial screening of living kidney donors. Little is known about who has extreme expectations; therefore we explored the relationship between the psychological profile of potential donors and their expectations.
Methods: In this cross-sectional analysis of data from the first wave of a prospective study, 137 potential living kidney donors completed the Living Donation Expectancies Questionnaire and validated questionnaires that measure mental health, stress, coping, and social support before donation. Linear regression analyses were conducted.
Results: Positive measures of mental health (e.g. life satisfaction) were not related to expectations, only negative measures of mental health were related. Greater negative affect, depression, obsessive-compulsive symptoms, and less use of an active coping style were related to more extreme expectations, in areas such as personal growth and health consequences. In contrast, greater social support and less anxiety were related to stronger positive expectations. The type of relationship with the recipient was also associated with expectations.
Conclusion: Greater negative affect was particularly related to more extreme expectations of donation. Whether expectations relate to subsequent mental health after donation is a question for future research.

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BOS13-KIDNEY - ABO/HLA INCOMPATIBLE

BO121 ABO ANTIBODY REMOVAL OF PLASMAPHERESIS (PP) WITH INTRAVENOUS IMMUNOGLOBULIN (IVIG) BEFORE ABO-INCOMPATIBLE (ABOI) KIDNEY TRANSPLANTATION: SINGLE CENTER EXPERIENCE

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Background: ABOI kidney transplantation is an inevitable option to overcome serious organ shortage. Outcome of ABOI grafts improved and became equivalent to compatible grafts. Variable protocols are adapted in different centers, however, there are few data on success rates of ABO antibody removal or relating to patients in who antibody removal fails. The purpose of this study was to evaluate the likelihood of achieving transplantation depending on ABO antibody titers.
Methods: Fifty-five patients were enrolled between 2007 and 2012. We perform ABOI kidney transplantation using anti-CD20 antibody, tacrolimus and PP with IVIG. The median antibody titer was 1:64 (Range 8-4096). Transplantation was preceded when the ABO titer reached 1:8. To determine the likelihood of achieving transplantation, the number of PP required to proceed transplantation and baseline ABO titer were analyzed.
Results: All 55 patients(100%) successfully completed transplantation after 5.75 4.3 PP with IVIG. Three patients did not reach target ABO titer and their achieved ABO titers at the time of transplantation were 1:16. The median follow-up duration was 18.1 month (Range 0.9–71.8). The mean age was 45.8 9.9 year and 65.6% were female. The median ABO titer was 2 (Range 1–16) at the time of transplantation, 4(Range 1–64) at 1 month posttransplantation and 4 (Range 4–128) at the last follow-up, respectively. The number of PP to reach an ABO titer of 1:8 was significantly correlated with baseline ABO IgG titers ($r^2 = 0.829$, $p < 0.001$; figure1).
Conclusions: All 55 patients successfully preformed ABOI kidney transplantation without failure to achieve transplantation. Three patients even failed to reach target titer at the time of transplantation, however, all of them were successfully transplanted. Though optimal ABO titer at the time of transplantation remains debatable, we carefully need to tailor our protocol with target ABO titer of greater than or equal to 1:16 to expand kidney donor pool.

BO122 THE ABOUT-K STUDY – A MULTI-CENTRE EVALUATION OF ABO INCOMPATIBLE KIDNEY TRANSPLANTATION IN THE UK – SINGLE OPERATOR ASSESSMENT OF ANTIBODY TITRES

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Introduction: The UK antibody incompatible registry finds poorer outcomes in ABOi kidney transplant recipients than expected from international comparator groups. Intracentre and intercentre variability in ABO blood group antibody titres has been reported in many cohorts. The ABOUT-K study of ABOi transplantation includes patients recruited from 10 centres in the UK. We report ABO-Ab titres in 100 participants, comparing local titre variation with a central laboratory and report accepted titres on the day of transplant and the clinical outcomes.
Method: One hundred patients from the ABOUT-K study were tested with pre-transplant samples. Local titre and Central titre results were compared at consent to study before therapy, before antibody removal and at the time of transplant. A single technician undertook all testing using a standardised technique using Diamed cards. Patients were treated according to local protocols.
Results: One year patient survival was 98.9% and 1 year DCGS 95.5%.Acute rejection occurred in 25.5% of recipients of which 22.9% was reported as being antibody mediated (AMR). 58% of patients received Immunoadsorption (IA) versus 31% Plasma Exchage (PEx). Reproducibility for the single operator for ABO titres demonstrated r-squared 0.98 for IgG assays and 0.93 for IgM assays. The median local titre against donor blood group at baseline was 32 (range 0–512) and at transplantation was 4 (0–64), however at transplant the central titres were lower 0 (0–64). The graphs display lower IA than PEx therapies. The central assay demonstrated no difference in maximum titre while the local was significantly different.
Conclusion: In this study 1 year patient and graft survival approach UK antibody compatible live donor outcomes and provides preliminary data on treatment, outcome and complications. It is possible to minimise intra-centre variability in ABO-Ab titres which will inform future multi-centre study and outcome optimisation in ABOi kidney transplantation.

BO123 FIRST EXPERIENCE WITH ABO INCOMPATIBLE KIDNEY TRANSPLANTATION (ABOI) WITHOUT RITUXIMAB IN HAMBURG

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In 2003 ABOi KTx was established with rituximab induction to avoid splenectomy. As B-cell depletion has no direct effect on Ab production the biological relevance of this treatment is uncertain. In 2011 we changed our immunosuppressive (IS) regimen in ABOi and stopped rituximab. Four pat. were transplanted with basiliximab and ATG induction followed by IS with CNI/everolimus. After 1 year graft survival is 3/4. One graft was lost due to recurrence of a retrospectively diagnosed atypical HUS. Two pat. were treated with additional doses of ATG without biopsy proven rejection. 1 year after ABOi three patients have a very good kidney function with s-creatinine of 1.3–1.6 mg/dl.
Conclusion: ABOi is feasible without rituximab. No rejection occurred, but two patients receiving additional ATG developed infectious complications. We assume that the total amount of IS was rather too high in the past than too low in our ABOi recipients.

BO124 ABO-INCOMPATIBLE KIDNEY TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

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In literature results of ABO-incompatible kidney transplantation (ABO-i KT) are similar to ABO-compatible kidney transplantation (ABO-c KT). Reports are limited to a handful of relatively high-volume centers

Between January 2008 and June 2012 16 consecutive ABO-i KT were performed. These cases were compared with living ABO-c KT ($n = 246$) transplanted in the same period. Median follow up was 2.4 ± 1.4 years for ABO-i KT and 2.1 ± 1.3 years for ABO-c KT. Protocol for ABO-i KT combined antigen-specific immunoadsorption and rituximab (Tydén G. et al. Am. J. Transplant. 2005; 5: 145–148).

Patient survival was similar in ABO-i KT and ABO-c KT, resp. 94% in ABO-i KT and 95% in ABO-c KT, $p = 0.99$ with log rank. Graft survival was significantly lower in ABO-i KT than in ABO-c KT, resp. 20% in ABO-i KT and 3% in ABO-c KT, $p = 0.003$ with log rank. Mean creatinine clearance at 12 and 24 months after kidney transplantation was significantly lower in ABO-i KT than in ABO-c KT ($p < 0.05$), see Figure. In indication and 1-year protocol kidney biopsies there was no difference in type and amount of rejection between ABO-i and ABO-c KT. BK nephropathy was not significantly increased in indication biopsies, resp. 10% in ABO-i biopsies vs. 2% in ABO-c biopsies, $p = 0.28$, but was significantly increased in the 1-year protocol kidney biopsies, resp. 22% in ABO-i biopsies vs. 3% in ABO-c biopsies, $p = 0.05$. As described in literature C4D was significantly more often positive in ABO-i than in ABO-c KT in both indication and 1-year protocol kidney biopsies. In indication biopsis 40% of ABO-i biopsies were positive, whereas 8% of ABO-c biopsies were positive, $p = 0.01$. In the 1-year protocol biopsies 38% of ABO-i biopsies were positive, whereas 0% of ABO-c biopsies were positive for C4D, $p < 0.001$.

In conclusion in our single center study results of ABO-i KT were inferior to ABO-c KT. There was significantly more graft failure in ABO-i KT, and significantly more BK nepropathy.

BO125 IMMUNO ADSORPTION INCREASES THE RISK OF BLEEDING IN BLOOD GROUP ABO-INCOMPATIBLE KIDNEY TRANSPLANT RECIPIENTS

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Introduction: Pretransplant removal of anti-blood group ABO antibodies is the cornerstone of all current ABO-incompatible (ABOi) transplantation programs. In our protocol, plasmapheresis is performed with a plasmafilter followed by immunoadsorption (IA) of anti-ABO antibodies using the Glycorex device. The bleeding complications of this technique are not known.
Material and Methods: We analyzed the data of 51 consecutive ABO-i kidney transplantations between March 2006 and May 2012 and compared these with 102 ABO-compatible kidney transplantations, matched for age, sex and donor type. The first 30 patients received also post-operative IA per protocol. Cases differed from controls in the preoperative regimen which included immuno adsorption, rituximab, tacrolimus, mycophenolate mofetil, prednisone and immunoglobulines. All patients received tacrolimus, mycophenolate mofetil and prednisone after transplantation. Data on the number of thrombocytes before and directly after immuno adsorption, and red blood cell transfusions (EC) during two postoperative weeks were collected.
Results: At 48 h post-surgery the ABOi patients had received significantly more units of erythrocyte concentrate (EC) (0.8 versus 0.17 EC, $p < 0.0001$)

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and experienced more major bleedings (24% versus 2%, $p < 0.0001$) compared to the ABO-compatible controls. Baseline thrombocytes decreased by 31% after the pre-operative IA's. In a multivariate model, only the number of preoperative IA was significantly associated with the need for EC's within 48 h post-surgery (OR per IA 2.088, $p < 0.005$). Preoperative coagulation tests (APTT and PT) were normal and did not correlate with numbers of EC's given. The post-operative IA group needed more EC's in the second week than patients without post-operative IA (9/30 versus 1/21, p 0.005).
Conclusion: Plasmapheresis with immunoadsorption in the ABOi kidney transplantation protocol is associated with a significantly higher postoperative bleeding risk.

BO126 ASSESSMENT OF HIGHLY SENSITISED PATIENTS (HSP) FOR HLA-INCOMPATIBLE DECEASED DONOR TRANSPLANTATION

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Antibody reduction therapy (ART) is difficult to achieve for HLA-incompatible (HLAi) deceased donor (DD) transplantation. We have assessed HLA-specific antibody levels in highly sensitised patients (HSP) to determine their suitability for future DD HLAi transplantation. Sera from 20 HSP were tested undiluted and at 1:20 dilution (representative of ART) using single antigen beads. The calculated reaction frequency (%cRF) was determined at MFI >2000, >5000 and >10 000 using the HLA types of 10 000 deceased organ donors. In undiluted sera mean cRF was 99.8%, 99.6% & 98.7% for the cut-off thresholds respectively. At 1:20 dilution mean cRF was 95.9%, 89.8% & 75.3% for cut-off thresholds respectively. At dilution 15 patients still had >85% cRF at MFI>5000 and nine patients at MFI>10 000.Using serum dilution to represent achievable antibody levels following ART, high antibody levels were still present against the majority of potential DD's, indicating DD HLAi is not an option for most HSP.

BO127 ANTI-HLA DONOR SPECIFIC COMPLEMENT FIXING ANTIBODIES IN KIDNEY GRAFT PATIENTS

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Background: Pre-transplant (Tx) complement fixing (CF) donor specific antibodies (DSA) represents a major risk for acute graft rejection. Many reports support that HLA CF antibodies (Ab) are clinically relevant for kidney graft outcomes.
Purpose: To evaluate the presence of anti-HLA CF Ab in pre-Tx sera, detecting C3d bound to Ab/antigen complex by Luminex. The main aims were to study the correlation between: (i) Single antigen bead (SAB)-IgG and SAB-C3d; (ii) SAB-C3d with the PRA-CDC value (panel of reactive Ab detected by cytotoxicity); and (iii) the presence of DSA-C3d with the graft outcome.
Methods: Sixty-three patients from the kidney waiting list who underwent Tx from 2007 to 2011 (mean age: 44 ± 12, 56% male, 44% without previous Tx) with a peak of PRA-CDC >50% but crossmatch-CDC negative, were randomly selected. For the clinical follow-up (1 to 4 years post-Tx), following parameters were considered: (i) Ab Mediated Rejection (AMR) defined by allograft dysfunction evaluated by glomerular filtration rate and DSA detected in recipient serum post-Tx and/or C4d fixed in renal biopsies; (ii) presence of DSA detected by SAB-IgG and SAB-C3d (Gen-Probe Inc, Standford) reactive with HLA antigens donor-specific or not.
Results: Pre-Tx DSA SAB-IgG and DSA SAB-C3d were positive in 48% and 25% of patients, respectively. In some cases, the presence of SAB-C3d was associated with an AMR, but in other cases SAB-C3d does not correlate with the presence of SAB-IgG suggesting possible IgM CF Ab. Statistical correlation between the percentage of PRA-CDC and the SAB-C3d was observed ($p = 0.023$),but it was not observed between clinical follow-up and CF C3d-DSA. However, the detection of DSA-C3d was higher in patients who underwent re-Tx than those receiving the first renal Tx (37% vs. 11%; $p = 0.016$).
Conclusions: Testing DSA with combined SAB-IgG and SAB-C3d tests would be useful to define the clinical relevant DSA in the graft outcome. Further studies are necessary to confirm these results.

BO128 LUMINEX PROZONE EFFECT DEMONSTRATED IN VITRO AND IN VIVO: CLINICAL IMPLICATION

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Background: The prozone effect (PE) leads to false low or negative measurement in Luminex single antigen bead assays and occurs, when there is an excess of antibody in sera. It can be unmasked by sample dilution. Complement C1 is thought to mediate the PE.
Methods: We present two cases, where a high titer Donor Specific Antibody (DSA) was missed due to PE and led to acute antibody-mediated kidney rejection (AMR). We then systematically analyzed our kidney waiting list for the frequency of the PE.
Results: Patients: A 59 years old patient received a 2nd kidney transplant. After 13 days, AMR occurred. Immunoadsorption (IADS) reduced all DSA, except for a novel DSA (DQ7). Because of the paradoxical MFI increase of DSA (DQ7) after IADS. The PE was considered and retrospectively confirmed by dilution of day of transplant serum. A 22 years old patient required a 2nd kidney transplant. After 8 months, AMR occurred. Despite IADS, a novel DSA (DQ5) appeared and its MFI increased after treatment. The PE was confirmed. Waiting list analysis: In July 2012 our waiting list included 261 patients, of which 86 were sensitized. Of those 24% (21/86) showed evidence of a PE found by serum dilution 1:100 (13 HLA class I, 10 class II, 2 class I&II). These sera were also positive by CDC lymphoscreen. In a subgroup of 11/21 patients with PE, an anti-C1q test was performed and confirmed the PE all. In contrast, in 12 sera with negative PE by 1:100 dilution, nine were negative by anti-C1q test. In 3/12 we found an additional PE, which was found by dilution 1:10.
Conclusions: We show for the first time the PE in vivo. The PE is common in immunized patients tested by Luminex technology. Failure to detect DSA due to PE can result in severe AMR and therefore should be considered in immunized patients. The PE can be detected by serum dilution, but also by anti-C1q test. This is a further evidence for the complement-mediated cause of the PE.

BO129 EFFECT OF "VIRTUAL CROSSMATCHING" ON GRAFT OUTCOME IN RENAL TRANSPLANT RECIPIENTS

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Introduction: Selective avoidance of a cytotoxic crossmatch (virtual crossmatch [vXM]) has been adopted in many centres in an attempt to minimise cold ischaemic time (CIT) in renal transplantation. However improvement in graft outcomes has not been demonstrated.
Method: We compare two cohorts: (i) patients transplanted prior to the introduction of vXM (January 2009 – April 2010) who would have been suitable (no previous sensitising events and no pre-formed antibodies) ($n = 58$), (ii) patients transplanted with a vXM (May 2010 – December 2011) ($n = 53$). CIT, DGF and graft outcomes at 1-year were compared. Results are presented as mean (SD). Statistical analysis was performed using student's t-test and chi-squared test. $p < 0.05$ is significant.
Results: Mean age: 50(13.6) years. 55.1% male. There was no difference in the number of DCD donors between the cohorts (20.7% vs. 26.4%; $p = 0.62$). There was a significant reduction in average CIT with the introduction of vXM (15.9(4.0) vs. 9.9(3.6); $p < 0.001$). There was no difference in the rates of DGF or 1-year graft-survival in the "pre-vXM" compared to "post-vXM" cohort (32.1% vs. 24.1%; $p = 0.26$ and 96.5% vs. 94.4%; $p = 0.39$ respectively). However eGFR at 1-year was improved following the introduction of vXM (50.2(19.4) vs. 60.1(24.3) ml/min; $p = 0.02$).
Conclusion: The introduction of vXM has lead to a reduction in CIT with corresponding improvement in eGFR at 1-year in the patient group in whom it is possible to perform a vXM.

BO131 NON-HLA ANTIBODIES: ANTI-AT1R AND ANTI-ETAR ARE ASSOCIATED WITH RENAL ALLOGRAFT INJURY AND GRAFT LOSS

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Non-HLA antibodies specific for angiotensin II type 1 receptor (anti-AT1R) and endothelin-1 type A receptor (anti-ETAR) of vascular cells activate signaling pathways leading to cell proliferation and vascular injury. This pathomechanism can be involved in vascular allograft rejection. The aim of our study was to evaluate the impact of non-HLA antibodies on kidney allograft morphology and function in patients who underwent kidney biopsy due to renal function impairment.
Methods: The study included 65 renal transplant patients, who were evaluated for the presence of non-HLA and anti-HLA antibodies at the time of transplant biopsy. Pre-transplant CDC cross-match was negative. A kidney allograft biopsy was performed between 6 days and 13 years (42 ± 49 months) after transplantation and the diagnosis was based on Banff criteria. Non-HLA antibodies: anti-AT1R and anti-ETAR were assayed by ELISA. The level >9 U/l of anti-AT1R and anti-ETAR antibodies was denoted as high.

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Results: A high level of non-HLA antibodies (anti-AT1R and/or anti-ETAR) was found in 7/65 (10.7%) patients [Abs(+)group] at the time of biopsy. In these seven patients the mean anti-AT1R level was 15.3 ± 9.4 U/l and anti-ETAR level was 13.8 ± 8.6 U/l. In 2 of these patients, anti-HLA antibodies were additionally detected: anti-class I in 1 and anti-class II in both patients. Abs(+) group: renal biopsies were performed 7.7 ± 3.9 years after transplantation in six patients and 40 days in 1 patient. Serum creatinine level was 2.34 ± 0.6 mg/dl at the time of biopsy. An early biopsy revealed acute vascular rejection (Banff grade IIB). In the remaining 6 patients, chronic allograft injury was found (grading cg1–3, cv1–2, ci1–2, ct1–2). C4d was present in 3/7 pts. Five patients (71%) lost their allograft within 7.8 ± 2.6 months after biopsy. The control Abs(−)group consisted of 58 pts. Serum creatinine in Abs(−)group was 2.4 ± 1.1 mg/dl in the 3rd month and 2.3 ± 0.9 mg/dl in the 6th month after biopsy and graft loss was observed in 11% in the 6th month after biopsy.
Conclusions: High levels of anti-AT1R and/or anti-ETAR antibodies are associated with morphological and functional allograft injury and graft loss. Non-HLA antibodies can be helpful in assessing the risk of graft failure.

BO132 OUTCOME OF KIDNEY TRANSPLANTATIONS PERFORMED WITH PREFORMED "NATURAL" DONOR-SPECIFIC ANTIBODIES

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Background: Detection of preformed donor specific alloantibodies (DSA) with Luminex Single Antigen assay led to the common observation that individuals without history of immunizing event could have circulating "natural" anti-HLA antibodies.
Methods: We retrospectively analyzed the risk of antibody-mediated rejection (AMR) and graft outcome in two groups of kidney transplant recipients with "natural" DSA present at time of transplantation. In the first group, 21 patients received a post-transplantation desensitization protocol (thymoglobulin induction and 4 monthly courses of intravenous globulins) and in the second group, 20 patients received a standard protocol (basiliximab induction, no IVIg). We compared them to a third group of 26 kidney transplant recipients with preformed "non-natural" DSA, treated with post-transplant desensitization with a similar intensity of immunization (MFI<3000).
Results: In the two groups of patients with natural DSA, mean MFI was 1424 Ä ± 1689, versus 1443 Ä ± 770 in the "non-natural group", p = 0.9. At 1 year, in patients with natural DSA the incidence of acute AMR was 10%, whatever the immunosuppressive regimen, and was similar to that observed in patients with "non-natural" DSA (15.4%, p = 0.47). At month-12, in the two "natural" and in the "non-natural" groups, protocol biopsies showed a low frequency of microvascular inflamation (g+ptc >1 in 11.1, 6.7 and 13.0% of cases, respectively, p = 0.7), and no transplant glomerulopathy. Graft and patient survival were 100% in the three groups. Estimated GFR was similar in the three groups (57.5, 58.7 and 54.3 ml/min/1.73 m^2).
Conclusion: Patients with natural DSA are able to mount AMR but with a favorable 1-year outcome, similar to that observed in patients with "non-natural" low-level DSA.

BO133 DEVELOPMENT OF HARDY-WEINBERG IN THE POPULATION OF PATIENTS AWAITING A RENAL TRANSPLANT

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Patients suffering from end stage renal disease can be offered a better quality of life by a transplant. Eurotransplant the first international organ exchange organization offers to up to 20% of the patient a fully HLA-A,-B,-DR compatible graft. For highly sensitized patients the acceptable mismatch program has shown to be a successful tool. Patients included in the Acceptable Mismatch (AM) program must have >85% panel reactive antibodies and recently we could demonstrate that this selection leads to distortion of the Hardy-Weinberg equilibrium (HWE). Here we report on the HWE development in patients awaiting a 1st graft (*N* = 356), a 2nd graft (males; *N* = 1311), and in AM patients (*N* = 817). We compared the HLA phenotypes of these patients, to those of healthy blood donors (*N* = 5604). We selected males for the 2nd transplant to avoid any bias introduced by pregnancy induced antibodies. For all these categories we calculated the HWE per locus. Blood donors and patients awaiting 1st transplant with the exception of the diabetogenic HLA-DR3,4 antigens were in HWE. Male patients awaiting 2nd transplant showed a significant disturbance of HWE for both HLA-A, and B in hetero- and homozygous form. Several HLA antigens were under- (eg. HLA-A1, A2, B7, B8) or over- (e.g. B13, B18) represented in the 2nd transplant and AM. This comparative analysis between the patients implies that the use of an algorithm based on mismatching does not reach the goal of equity/efficacy. Patients being HLA homozygous in one or more loci will almost never be offered a fully compatible graft. Organs being HLA homozygous in one or more loci will often be offered to heterozygous recipients for the respective loci. HLA homozygous patients will accumulate on the list or will be offered less compatible organs. This situation is already a fact. In conclusion, we propose to tune organ allocation systems to offer organs on the basis of compatibility (matching) rather than incompatibility (mismatching).

BO134 DONOR HLA MISMATCH DETERMINES THE RISK OF HLA LOCUS-SPECIFIC SENSITISATION AND ACCESS TO REPEAT KIDNEY TRANSPLANTATION FOLLOWING PRIMARY ALLOGRAFT FAILURE

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Background: We have investigated the impact of donor HLA mismatches on intra- and inter-locus specific sensitisation in patients re-listed for a repeat transplant following primary renal transplant failure.
Methods: Primary kidney transplant recipients from 1995 to 2010 whose graft failed and subsequently returned to the waiting list were studied (*n* = 131). Sera obtained before transplantation and following re-listing were screened using DTT modified lymphocytotoxicity, Luminex HLA class I and II antibody detection beads and single antigen beads (SAB). The effect of donor HLA mismatches on IgG panel reactive antibodies (PRA) and on calculated reaction frequency (cRF) against 10 000 consecutive HLA typed UK organ donors was determined for each HLA locus.
Results: Donor HLA mismatch grade correlated strongly with overall incidence and magnitude of post-transplant allosensitisation determined by PRA and SAB-defined cRF ($p < 0.001$). The risk and level of sensitisation against individual HLA-A,-B,-DR and -DQ loci increased with increasing number of donor HLA mismatches within each locus; this relationship was stronger for HLA-A and -DR loci [odds ratios of 3.0 (CI: 1.8–4.4) and 2.9 (CI: 2.1–4.2) respectively, $p < 0.001$] which also best predicted overall post-transplant HLA class I and II sensitisation respectively. Following re-listing, the incidence of highly sensitised patients (>85% cRF) was 22%, 48% and 88% for 0–1, 2–7 and 8–10 mismatches respectively ($p < 0.001$). Of patients with 2 HLA-DR mismatched grafts, 70% became highly sensitised and 80% developed donor specific antibody. On multivariate analysis, HLA mismatch grade and immunosuppression weaning were independent predictors of HLA sensitisation whereas transplant nephrectomy was not.
Conclusion: This analysis is the most comprehensive to date, suggesting that allocation strategies should place more emphasis on HLA matching for recipients awaiting their first transplant and are likely to require future re-transplantation.

BO135 EFFECT OF PROTEASOME INHIBITION BY BORTEZOMIB ON STEROIDS ASSOCIATED WITH ANTI-HLA ANTIBODIES IN PATIENTS A WAITING IMMUNE RENAL TRANSPLANTATION

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Introduction: Treatments for desensitization of immunized patients waiting for a renal transplantation (KT) are often ineffective or transient (plasmapheresis, intravenous immunoglobulin or rituximab) to control the production of anti HLA antibodies by B or plasma memories cells. Bortezomib, a proteasome inhibitor active against multiple myeloma in association with steroids has been proposed for this purpose. Used alone, results are contradictory. The objective of this study is to investigate the effect of corticosteroids and bortezomib on the reduction of anti-HLA antibodies before renal transplantation.
Materials and Methods: A prospective monocentric study from March 2009 to February 2011. Patients included had a stable immunization against HLA, and were waiting for KT. Treatment consisted of Velcade ® (bortezomib) 1.3 mg/m^2 associated with 40 mg of dexamethasone intravenously on days 1, 3, 8 and 10. Anti HLA class 1 and 2 were determined bysingle antigen beads assay at D0, M1, M3 and M6.
Results: Twenty-three patients have been included. There was a mean of 49 (± 21) anti-HLA antibodies on day 0: 31 against class I and 17 against class II HLA. At D0, mean fluorescence was 10,627 ± 5835 for class I immunodominant antibodies (iAb) and 7577 ± 7029 for class II. By M3, 41% of patients had a > 25% decrease in class 1 iAbs, and 60% by M6. By M3, 33% of patients had a > 25% decrease in class II iAbs and 42% by M6. At M6, 54% of anti-HLA antibodies had a sustained decrease by >25%, and 36% were decreased by >50%. No predictive factors for decreased antibodies after bortezomib plus steroid therapy were identified. No serious adverse events were observed. Thereafter, 11/23 patients received successful transplants. Bortezomib plus steroids is an effective alternative therapy for reducing class I and II anti-HLA, regardless of other previous treatments.

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BO136 ADDITION OF RITUXIMAB TO INDUCTION THERAPY DECREASES RISK OF ANTIBODY-MEDIATED REJECTION AND GRAFT LOSS IN RENAL TRANSPLANT RECIPIENTS WITH POSITIVE FLOW CROSSMATCH AND DONOR SPECIFIC ANTIBODIES

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Background: Positive T-cell and B-cell flow crossmatch (FCXM) with a negative complement-dependent cytotoxic crossmatch (CDC-XM) is associated with higher rejection and graft loss in renal transplant recipients (RTR).
Methods: Retrospective analysis of 135 consecutive RTR from 2005-12 with positive FCXM and negative CDC-XM at transplant. Cox proportional hazards model was used to determine risk of rejection and graft failure.
Results: One dose of rituximab (RTX) 200 mg was given at the discretion of the clinician in addition to standard induction therapy if the results of FCXM were available at transplantation, particularly if donor specific antibodies (DSA) were present. Patients were maintained on prednisone, tacrolimus and mycophenolate. RTX group was younger, had more black patients, and more likely to have DSA at transplantation.

Induction with RTX appears to be associated with decreased risk of rejection when correcting for the presence of DSA's (HR 0.169, 95% CI 0.031 – 0.906). There were no antibody-meditated rejections (AMR) in the RTX group.

FCXM mean channel shift (MCS) values were not associated with increased risk of rejection in the presence of RTX. Presence of DSA, positive FXCM at transplantation and peak MCS each convey risk of graft loss in the univariate analysis; however when RTX induction is included in the model, these risks are no longer significant. RTX conveys a decreased risk of graft loss in the multivariate model (HR 0.128, 95% CI 0.019 – 0.877).
Discussion: A single dose of RTX (200 mg) has been shown to effectively deplete peripheral B-cells up to 1-year. This simple addition to standard induction appears to decrease risk of rejection, particularly AMR, in renal transplant recipients with a positive FCXM and DSA.

BO137 EFFECTIVENESS OF PLASMAPHERESIS AS A TREATMENT OF CHOICE IN SENSITIZED RENAL RECIPIENTS

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Background: Plasma exchange is to suppress humoral component of the immune reaction. Herein we searched the effects of plasmapheresis (PP) on renal graft function in patients who had renal transplantation against a low level sensitization barrier.
Methods and Materials: We had retrospectively analyzed 55 patients who admitted to our center between January 2009 to December 2012 for renal transplantation. Patients had PP every other day with 10% human albumin and followed by intravenous immunoglobulin G (IVIG) 0.5–1 g/kg after each session. Panel Reactive Antibody (PRA), flowcytometric crossmatch (FCXM), serum creatinin, renal biopsy findings were recorded. Patients were detected as low level sensitized if their T cell FCXM had reactivity more than 1.3 times and for B cell FCXM more than 1.5 times the negative control and PRA was positive if recorded more than 10%. Also past-transfusion/pregnancy histories were considered for sensitization.
Findings: Patients were 38 $\pm$ 10 years of age, female /male ratio was 35/20 and twenty had cadaveric and thirtyfive had living-related donors. Primer renal disease etiologies were 18% glomerulonephritis/vasculitis, 16% FMF/polycystic renal disease, 8% diabetes, hypertension, 11% urological diseases and 47% unknown etiology. PP was administered as a mean of 18 $\pm$ 16 weeks after transplantation and the mean IVIG administration was 3.3 $\pm$ 2 doses. Mean post-transplant creatinin level was 2.7 $\pm$ 0.9 mg/dl and 1.8 $\pm$ 0.6 mg/dl at the post PP period ($p < 0.05$). Patients with B cell FCXM positivity had less biobsy proven humoral rejection reactions than those with T cell FCXM positive patients.
Conclusion: According to our data, patients had lower serum creatinin and PRA levels after PP and IVIG treatments. Those with low level positivity at Tcell flowcytomeric crossmatch had humoral rejection findings at their graft biobsies. Herein we observed that PP has better clinical impact on patients with Class 2 HLA reactivitiy.

BO138 OUR EXPERIENCE WITH PROTEIN A IMMUNOADSORPTION IN TRANSPLANT MEDICINE

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Background: Immunoadsorption (IA) is a semiselective extracorporal adsorption technique for immunoglobulins applied to patients also before or after solid organ transplantation. It is one of the possible treatment modalities for patients with high value of panel reactivity antibodies (PRA). These patients have high risk of humoral rejection and failure of transplanted organ.
Methods: Plasma separation was carried out on the separators ComTec™ and processed IA was performed on immunoadsorption systems Citem 10™ or ADAsorb™. Both systems use two collumns with staphyloccocal protein A binding (Immunosorba™). We treated a group of nine patients: three patients were preparing for heart transplant surgery with high value of PRA and six patients were indicated with massive humoral rejection after organ transplantation: four heart transplant patients and two patients after transplantation of kidney.
Results: Ninety procedures of IA have been performed, 1.99 patient's plasma volume was average processed. There were no significant complications related to the procedure. The highest reduction was noticed in the value of IgG immunoglobulins (average about 66.5%), mainly of subclass IgG1 (70.5%) and IgG4 (71.3%), the lowest reduction was in subclass IgG3 (24.4%). Average reduction of the IgM value was 42.6% and IgA 21.3% in one IA procedure. The significant PRA drops occured in cases of three patients waiting for heart transplant surgery (from 92% to 36%, from 96% to 23% and from 99% to 10%). The massive humoral rejections were suppressed in cases of the rest six patients after transplantation.
Conclusions: IA was safe and effective procedure. All of our patients had reduction of circulating antibodies and PRA. Combination of repeating IA procedures with application IVIG and other immunosupression drugs helped with overcoming humoral rejection in cases of patients after transplantation. This work was supported by a grant from the Ministry of Health of the Czech Republic - IGA MZCR NT 11262-6.

BO139 CLINICAL IMPACTS OF DESENSITIZATION FOR PRETRANSPLANT FCXM(–) DONOR-SPECIFIC HLA ANTIBODIES(+) KIDNEY TRANSPLANTATION

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Background: Clinical relevance low-level preformed DSA in patients with negative flow cytometry crossmatch(FCXM) and role of desensitization procedure prior to FCXM(–) and DSA(+) kidney transplantation are not well defined.
Methods: HLA antibodies were identified by single antigen flow beads on a luminex platform. Desensitization procedure included rituximab (300 mg) and three sessions of plasmapheresis followed by low dose IVIG (0.2 g/kg). We analyzed 295 consecutive kidney-only transplant recipients between January 2010 and May 2012.
Results: Of these 295 patients, 9 had desensitization procedure prior to FCXM (–) DSA (+) transplantation (desensitization group). Twenty six did not undergo desensitization (DSA only for HLA-DQ [DQ-DSA group, $n = 13$] and DSA for class I and/or II [HLA-DSA group, $n = 13$]). The remaining 260 were performed FCXM (–) DSA (–) kidney transplantation (No-DSA group). The incidence of acute AMR in the No-DSA group was 0.8% within 1 month. The DQ-DSA group did not show any case of acute AMR. The HLA-DSA group and the Desensitization group had higher incidences of acute AMR (30.8% and 33.3%, respectively, $p < 0.001$). Most of acute AMR was subclinical and diagnosed by protocol biopsies at 10 days in the Desensitization group (66.7%) and, in contrast, most of acute AMR in the HLA-DSA group was diagnosed in the setting of delayed graft function (75.0%, $p = 0.037$). No patients lost their graft and all acute AMR were successfully resolved by anti-AMR treatment. The intensity of DSA was decreased after transplantation and ultimately DSA were undetected after 1 month after transplantation in desensitization group. In the patients with clinical or subclinical acute AMR, the DSA also decreased after anti-AMR treatment. Serum creatinine was significantly higher in HLA-DSA group compared with other groups within 1 month after transplantation ($p < 0.01$), and thereafter there was no difference in serum creatinine among study groups.
Conclusion: Although FCXM(–) DSA(+).

BO140 INFLUENCE OF THE FIRST GRAFT NEPHECTOMY IN THE EVOLUTION OF SECOND KIDNEY TRANSPLANT: EARLY VERSUS LATE?

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Nephrectomy is usually indicated after the loss of a first graft (I) when there are clinical reasons. The influence of the nephrectomy in the evolution of the second graft is under discussion. We had conducted a multicenter study of all second kidney transplants performed between January and December in 16 centres in our country. We analyzed: Data from de first graft (donor a recipient age, pretrasplant antibody (AC) titles, rejection rate (RR), acute tubular necrosis (ATN), inmunosupression, causes of graft loss, Indication of nephrectom and second transplant data (pretransplant AC title, RR, ATN, inmunosupression, yearly development of proteinuria and renal function and patient and secon graft survival. The minimun follow-up is 5 years. We evaluated 525 patients, 243 nephrectomized, in 25 had undergone embolization and 258 continued with the first graft. In the first graft we did not found significant differences in donor age, pretransplant Ac title, NTA or RR between nephrectomized and non-nephrectomized patients. The waiting time for the second transplant was higher in nephrectomized patients (33 vs. 23 months $p < 0.01$) In the second graft there are not significant differences in donor age, cause of donor death, recipient age or number of HLA mismatches in patients without or with nephrectomy. The nephrectomized had a significantly higher pretransplant Ac (15.7 vs. 11.8%, $p < 0.001$), higher frequency of NTA (54% vs. 39%, $p < 0.001$) and higher rates of acute rejection (24.7 vs. 17.1%, $p < 0.001$), and more frequently required use of induction therapy (55 vs. 41%, $p < 0.01$). No significant differences in patient survival or graft at 5 years follow-up.

Conclusions: Nephrectomy was performed in 50.9% of the first transplants lost. It is associated with: longer waiting time on dialysis, highest PRA pre-second transplant, more NTA, more acute rejection and more immunosuppression.

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BOS14-KIDNEY - IMMUNOSUPPRESSION

BO142 5-YEAR FOLLOW-UP ON THE ZEUS KTX TRIAL: EVEROLIMUS CONVERSION AFTER CNI WITHDRAWAL

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Aim: To follow-up(FU) on renal function(RF), efficacy and safety after conversion to an Everolimus(EVR)/Enteric-Coated Mycophenolate Sodium (ECMPS) regimen after cyclosporine A(CsA) withdrawal in de novo kidney transplant(KTx) patients(pts) at month 60 post Tx.
Methods: Prospective, open-label, controlled, multi-center study randomizing to an immunosuppressive (IS) regimen of either EVR/ECMPS or CsA/ECMPS at 4.5Mo post KTx with an observational 4 year FU after 12Mo core-study.
Results: Three hundred pts were rdz to either EVR/ECMPS ($n = 155$) or CsA/ECMPS ($n = 145$); 227 (76%) pts completed month 60 FU-visit. RF was similar at month 4.5 and improved in favor of EVR over CsA maintained till Mo60. Events: three deaths, three graft losses in CsA, four deaths, four graft losses in EVR group. Infections: CsA 21 (15%), EVR 32 (21%); hospitalizations month 48–60: CsA 21 (15%), EVR 36 (23%); BPAR month 4.5–60: 11 (8%) CsA, EVR 21 (14%).
Conclusions: The conversion to EVR in de novo KTx pts after CNI withdrawal early after Tx reflects a novel therapeutic approach that maintains better RF over a period of 60 months without compromising efficacy and safety.

BO143 CONVERSION FROM CNI TO MTORI IN RENAL TRANSPLANT RECIPIENTS WITH NEUROTOXICITY

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Background: Calcineurin inhibitors (CNI) are the main drugs involved in neurotoxicity after transplantation. We present our experience with conversion of patients with signs of CNI neurotoxicity to mTOR inhibitors.
Methods: Clinical presentation, efficacy, side effects, and graft function after conversion were examined.
Results: Eleven patients were switched from the CNI to mTORi for treatment of severe neurotoxicity. Clinical symptoms present in our patients included: headaches, altered mental status, seizures, tinnitus, spasticity, paresis, tremor and ataxia. Diagnosis was supported by magnetic resonance imaging in all patients. Patients experienced significant improvement of neurological symptoms after the conversion. Side effects of mTORi treatment included worsening of dyslipidemia in five patients and development of proteinuria in one patient.
Conclusion: Neurotoxicity may occur at any time after renal transplantation with variable clinical presentation. mTOR inhibitors are indicated for patients with neurotoxicity due to CNI treatment.

BO144 RESULTS OF A PROSPECTIVE TWO CENTER TRIAL TO CONVERT FROM CALCINEURIN INHIBITOR TO SIROLIMUS IN RENAL ALLOGRAFT RECIPIENTS WITH MILD TO MODERATE GRAFT INSUFFICIENCY

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Background: Sirolimus (SRL) conversion is one of the calcineurin inhibitor (CNI) withdrawal protocols to avoid CNI toxicity. But whether conversion to SRL can improve the graft function which has been exposed to CNI during a certain period is not known.
Methods: The current study enrolled patients who underwent kidney transplantation from 6 months to 5 years ago at the screening point. CNI was gradually reduced and ceased in 4 weeks. Loading dose of SRL was administered at the first day of conversion. SRL dose was adjusted for target trough level of 7–15 ng/ml or 10–18 ng/ml according to use of antimetabolites. Protocol biopsy was performed at pre-conversion and 1 year after conversion. To evaluate CNI toxicity in histologic feature, scoring system by M. J. Mihatsch was used.
Results: A total of 46 patients were screened. There were one screening failure and four drop-outs. The 45 enrolled patients had received tacrolimus in 28 and cyclosporine in 17. Their mean duration exposed to CNI after kidney transplantation was 28.6 ¾ 16.8 months. Serum creatinine decreased during the observed period of 52 weeks. Creatinine clearance measured by 24 h urine collection increased after conversion to SRL. Microprotein in 24 h urine significantly increased after conversion treatment. There were a total 158 adverse events during the study period. Hyperlipidemia was the second common events following infection. In terms of CNI toxicity, 16 grafts showed no interval change by SRL conversion in Mihatsch score. Seven grafts revealed down grading of CNI toxicity but eleven grafts showed worsening score. Longer duration exposed to CNI showed higher grade of CNI toxicity.
Conclusion: We observed beneficial effect of conversion to SRL in renal function measured by serum creatinine and Cr clearance. Conversion from CNI to SRL is safe and beneficial to improve renal function for patients who were administered CNI for over 6 months and <5 years after kidney transplantation.

BO145 LONGER-TERM EFFICACY AND SAFETY OF EVEROLIMUS IN DE NOVO RENAL TRANSPLANT RECIPIENTS

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Background: A 1202 study showed comparable 12 months efficacy and safety of everolimus (EVR) and reduced cyclosporine (rCsA) versus mycophenolate mofetil (MMF) and standard CsA (sCsA) in Japanese de novo renal transplant recipients (RTxR). A1202E1 evaluated longer-term efficacy and safety of this regimen.
Methods: In this open-label, extension study, 100 RTxR continued receiving EVR (C0 3–8 ng/ml; $N = 50$) +rCsA or MMF (2 g/day; $N = 50$) +sCsA to 24 months all with steroids. Patients in the EVR group were followed up to 48mo. Composite efficacy failure rate, renal function and safety profile were assessed at mo24 and mo48.
Results: Consistent with 12 months results, renal function and efficacy in EVR group was maintained until months 24 and 48. Safety profile was comparable with less viral infections in EVR versus MMF at months 24 (table) and maintained to mo48.
Conclusion: The results at months 24 and 48 further support that a EVR+rCsA regimen is a valid alternative to a standard MMF regimen in Japanese de novo RTxR.

BO146 PLANNED TRANSITION FROM TACROLIMUS TO SIROLIMUS VERSUS CONTINUED TACROLIMUS IN RENAL ALLOGRAFT PATIENTS

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Background: This study aimed to evaluate transition from tacrolimus (TAC) to sirolimus (SRL) versus continued TAC in renal allograft patients (pts).
Methods: This open-label, randomized, phase 4 study screened pts at transplant. Pts received TAC+inosine monophosphate dehydrogenase inhibitor from transplant, were randomized at 90–150 days to continue TAC or switch to SRL, and are followed for 2 years. We present interim safety data.
Results: Preliminary data for 254 pts (SRL 131; TAC 123) are available (mean age 51.5 years; male 65%; white 75%) (see Table); 222 pts completed 1 year and 95 completed 2 years.
Conclusions: Interim results show no significant between-group differences in survival/graft loss. SRL pts had a higher incidence of biopsy-confirmed rejection, adverse events (AEs), and discontinuations due to AEs, consistent with the SRL safety profile.

BO147 EVEROLIMUS VERSUS MICOPHENOLATE SODIUM IN RECIPIENTS OF MARGINAL KIDNEYS

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Background: We compared the outcomes of kidney grafts from marginal donors between 38 recipients receiving everolimus, cyclosporine and steroids (group RAD) versus 46 recipients treated with cyclosporine, enteric coated micophenolate mofetil and steroids (group ECMPS).

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Methods: We compared graft and patient survival, renal function and rate of complications after 2 years of follow up using *t*-test, Wilcoxon's rank-sum, χ^2 test and Fisher's exact test, log rank test when appropriate.
Results: We observed similar rate of graft loss and renal function after2 years of transplantation (graft loss: 79.5% vs. 80.1%, serum creatinine 1.82 ± 0.7 vs. 1.66 ± 0.5 mg/dl, eGFR 51.58 ± 23.32 vs. 59.93 ± 22.47 ml/min. We also observed no differences in the rate of complications except a higher level of cholesterol n the group receiving everolimus (231.63 ± 42.51 vs. 197.1 ± 34.2 mg/dl, p = 0.02).
Conclusions: In our study Everolimus resulted similar to Micophenolate as immunosuppressive regimen for marginal kidneys.

BO148 HERAKLES AT MONTH 24: EFFICACY AND SAFETY OF 3 DIFFERENT REGIMENS IN DE NOVO RENAL TRANSPLANT PATIENTS

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To compare safety and efficacy of three different immunosuppressive (IS) regimens at month (month) 24 post renal transplantation (Tx). Prospective, open-label, randomized (rdz), controlled multi-center 1 year study. 3 months post Tx 499 pts were rdz 1:1:1 to either continue standard (STD) CsA (100–180 ng/ml)+ECMPS (*n* = 166) or convert to CNI-free regimen with everolimus (EVR; 5–10 ng/ml)+ECMPS (*n* = 171) or convert to CNI-low regimen with EVR (3–8 ng/ml)+reduced CsA (50–75 ng/ml) (*n* = 162). Observational Mo24FU-visit performers: 131 (96%) STD, 132 (96%) CNI-free and 125 (93%) CNI-low pts. BPAR from rdz to months 24: 12% STD, 14% CNI-free and 12% CNI-low pts (ITT). Two deaths (1%) in CNI-low, none in other groups. One percent graft loss in the STD and 3% in CNI-free group. Premature discontinuation months 12–24 due to AEs: 1% of STD, 2%CNI-free and 1% of CNI-low treated pts (safety pop). IS regimens of EVR with low-dose or without CNI exposure are a safe and efficacious approach offering opportunity for individualized IS.

BO149 TACROLIMUS DOSING IN RENAL TRANSPLANT RECIPIENTS FOLLOWING INTRODUCTION OF A GENERIC PREPARATION

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Background: Tacrolimus plays a pivotal role in immunosuppression following renal transplantation. Although several formulations are available, Adoport is now the most widely used generic formulation in the UK. We compare week one Prograf versus Adoport blood concentration following renal transplantation in our department.
Methods: Between January 2012 and January 2013, 121 renal transplants were performed in our institution. Tacrolimus was commenced in all patients at a dose of 0.075 mg/kg twice daily with the exception of Black patients where an initial dose of 0.15 mg/kg was used. The initial target range for 12-h post-dose (trough) blood concentration measured by immunoassay was 10–15 ng/ml. Prograf was used up until July 2012 with subsequent use of Adoport. Trough tacrolimus blood concentrations during the first post-operative week were retrospectively reviewed.
Results: Of 121 renal transplants performed during the study period 14 patients were excluded (three renal vein thrombosis within 48 h and 11 patients pre-emptively commenced on tacrolimus). Forty-seven (44%) received Prograf and 60 (56%) received Adoport. Mean maximum trough blood concentration for Prograf versus Adoport during post-operative week 1 was (16.4 ± 6.52 vs. 18.2 ± 7.81 ng/ml, p = 0.20) respectively. For Prograf versus Adoport concentrations on days 2–3 and 6–7 respectively (36.4% vs. 32%, p = 0.67) and (48.5% vs. 34%, p = 0.25) were within the target range. For concentrations outside of the target range on days 2–3, 50% vs. 76.5% (p = 0.04) of readings were above the target range for Prograf and Adoport respectively. There was no significant difference by day 6–7 (p = 0.23).
Conclusion: The proportion of patients dosed within the target range was not statistically different for Adoport versus Prograf within the first post-operative week. For those patients outside of the target range there was a tendency for those treated with Adoport to have higher concentrations within the early post-operative period.

BO150 HIGH DOSAGES OF EVEROLIMUS INDUCE IN VITRO EPITHELIAL MESENCHYMAL TRANSITION OF RENAL PROXIMAL CELLS: A POTENTIAL MECHANISM OF DRUG TOXICITY IN RENAL TRANSPLANTATION

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Background: The mammalian target of rapamycin inhibitors (mTOR-I) sirolimus and everolimus (EVE), seem to have a long term protective effect on graft. However, as other immunosuppressive drugs, they may induce adverse effects such as severe pulmonary fibrosis. In the onset of fibrosis, epithelial to mesenchymal transition (EMT) has a pivotal role. The EMT is the conversion of epithelium to a fibroblastic phenotype. During renal EMT, tubular cells acquire the capacity to migrate into the interstitium through degradation of basement membrane by the release of matrix metalloproteases (MMPs) and heparanase (HPSE).
Material/Methods: The aim of our study has been to analyze whether EVE could induce EMT in vitro in human tubular epithelial cells. Wild-type and stably HPSE-silenced HK-2 cells were cultured with 10, 100 or 500 nM EVE for 6 h. Real-time PCR was performed to evaluate the expression of HPSE, α-SMA, VIM and MMP-9 and zymography was used to assess MMP9 activity in cell conditioned media. Cell migration was measured by scar assay at 24 h.
Results: Treatments with 100 or 500 nM EVE for 6 h increased the expression of HPSE, α-SMA, VIM and MMP9 in wild-type cells. Otherwise, in HPSE-silenced cells EVE produced no changes in the expression of mesenchymal markers. Extracellular MMP9 activity, assessed by gelatin zymography, reflected the gene expression pattern and the treatment with high concentration of EVE (100 and 500 nM) triggered the release of active MMP9 by WT cells whereas it had no effect on HPSE-Silenced cells. At 100 and 500 nM EVE increase migration of WT but not of HPSE-silenced cells. For all markers, no changes were observed at concentration reflecting transplant therapeutic dosage (10 nM).
Conclusions: Our study underlines that EVE treatment at the dosage generally used in renal transplantation does not activate renal pro-fibrotic effects but at higher dosages (as used in oncology) it may induce EMT causing fibrotic nephrotoxic and systemic effects.

BO151 MODULATION OF RAPAMYCIN ON HVEM AND BTLA CONTRIBUTES TO ITS BENEFIT TO CD4+ TREGS IN ALLO-RENAL RECIPIENTS

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Background: Rapamycin (RAP) is believed to be beneficial for CD4+ Tregs and the interaction between HVEM and BTLA is newly reported to contribute to the suppressive function of CD4+ Tregs.
Methods: The expressions of HVEM and BTLA on peripheral T cells of 40 stable RAP-treated allo-renal recipients, 42 FK506-treated allo-renal recipients and 30 healthy volunteers were analyzed by flowcytometry.
Results: The expression of HVEM on conventional T cells was suppressed in both RAP-treated and FK506-treated recipients (pï¿½ï¿½0.05) and the decrease in FK506-treated group was even more significantly (pï¿½ï¿½0.05). The frequency of CD4+ Tregs and the expression of HVEM on CD4+ Tregs were both increased significantly in RAP-treated recipients (pï¿½ï¿½0.05) while both of them were obviously decreased in FK506-treated recipients (pï¿½ï¿½0.05). The expression of BTLA on T cells in RAP-treated recipients increased significantly (pï¿½ï¿½0.05) and was much higher than that in FK506-treated recipients (pï¿½ï¿½0.05) which remained comparable to health-control level (pï¿½ï¿½0.05).
Conclusion: RAP up-regulates the expression of HVEM on CD4+ Tregs and that of BTLA on T cells, benefitting the suppressive function of CD4+ Tregs.

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BO152 IMMUNOSUPPRESSIVE STRATEGIES FOR TRANSPLANTING KIDNEYS AFTER EXCISION OF SMALL RENAL TUMOURS AND ROLE OF ACUTE REJECTION

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Introduction: Kidneys with small renal cell carcinoma have been used for transplantation after ex vivo resection of tumour with excellent results. Concerns regarding the behaviour of tumour under standard immunosuppression prevents this source from being popularised. We studied tumour behaviour with standard immunosuppression and immunosuppressives with anti-proliferative properties and the effect of MHC matching on tumour behaviour.
Methods: Luciferase labelled Wistar rat kidney tumour cells were injected subcutaneously into Wistar/Lewis rats to mimic well and poorly matched groups. Both were divided into groups receiving Cyclosporine Cy, Sirolimus Sr (2 mg/kg) and Sirolimus (0.5 mg/kg) and Leflunomide Lf. Effects of matching on tumour rejection were studied by immunosuppression withdrawal in half of the animals within each group. Tumour progression was monitored with IVIS spectrum imaging system.
Results: With Cy immunosuppression, the tumour continued to grow in both strains. With high dose Sr, the tumour was eradicated within 2 weeks in Wistar and 3 weeks in Lewis rats ($p < 0.001$ between Cy versus Sr). Both strains receiving low dose Sr also eradicated the tumour within 4 weeks of treatment ($p < 0.01$ between Cy and Low dose Sr). In Lf group, 5/7 animals rejected the tumour within the 4 weeks of study period ($p < 0.001$ between Cy and Lf). After treatment withdrawal, the tumour rejection was noted among all groups. Again this rejection was significantly stronger in poorly matched animals than in well-matched ($p < 0.002$).
Conclusions: (i) Transplanted tumour continues to grow under Cy immunosuppression. (ii) For tumour eradication Sr was significantly better than Cy and Lf; while Lf was significantly better than cyclosporine. (iii) Acute rejection can lead to tumour eradication, more effectively in less well-matched animals. (iv) Clinically, recipients of such restored kidneys should perhaps be less well matched and immunosuppressed with agents with anti-proliferative properties.

BO153 EFFECTIVENESS OF INDUCTION THERAPY FOR RENAL TRANSPLANTATION WITH ALEMTUZUMAB COMPARED WITH CONVENTIONAL THERAPY WITH BASILIXIMAB AT ONE YEAR FOLLOW UP

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Background: There are few studies evaluating the efficacy of alemtuzumab as induction agent for renal transplantation in Latin American population, which is important due to low cost of alemtuzumab. The aim of this study is determine if induction therapy with alemtuzumab, steroids, mycophenolate and cyclosporine is more effective in terms of proportion of biopsy proven acute rejection within the first year post-transplant compared with standard induction therapy with basiliximab, in renal transplant patients with low immune risk.
Methods/Materials: We conducted a retrospective observational study of a cohort of renal transplant patients treated at Hospital Universitario San Vicente Foundation (Colombia) between 2005 and 2009. Was performed a random sampling of 200 patients, 100 received alemtuzumab and 100 received basiliximab and all received steroids, mycophenolate and cyclosporine. The main outcome measure was the presence of acute renal rejection with biopsy proven in the first 12 months. Other outcomes was patient survival and graft survival at 1 year. To evaluate effectiveness measure was chosen chi square test. Graft and patient survival was assessed using the Kaplan–Meier method and log-rank test.
Results: At 1 year follow-up the proportion of biopsy proven acute rejection was significantly lower in patients receiving alemtuzumab, compared with basiliximab (8% vs. 34%, $p < 0.001$). The survival of patients at 1 year was similar in both groups (95% vs. 96% $p = 0.73$) in the group of alemtuzumab and basiliximab, respectively, as well as graft survival at 1 year (93% vs. 92% $p = 0.47$). The proportion of patients with cytomegalovirus (CMV) infection were similar in both groups (12%) and no CMV infections than were similar (31% vs. 27% $p = 0.53$).
Conclusion: The proportion of biopsy proven acute rejection was less frequent in the group of deceased donor kidney transplant low immune risk receiving alemtuzumab, basiliximab compared, with a similar safety profile.

BO154 THYMOGLOBULIN PLUS BASILIXIMAB VERSUS BASILIXIMAB INDUCTION IN DECEASED DONOR KIDNEY TRANSPLANT RECIPIENTS TREATED WITH TACROLIMUS AND MMF: 1-YEAR RESULTS OF A PROSPECTIVE CLINICAL TRIAL

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Background: The aim of this prospective, consecutive, single center clinical trial in kidney transplantation was to compare two immunosuppressive induction regimens: thymoglobulin plus basiliximab (THY) versus basiliximab (BAX).
Methods: Sixty deceased donor kidney transplant recipients received as induction THY (30 pts) or BAX (30 pts) and were followed up for 1 year. Patients assigned to THY received a combination of thymoglobulin (50 mg/day IV from day 0 to 3, total dose 200 mg) and basiliximab (20 mg IV on day 0 and 4), while recipients allocated to BAX received basiliximab only (20 mg IV on day 0 and 4). As maintenance, all patients received tacrolimus, MMF and steroids starting on day 4 in THY and on day 1 in BAX. Patients in the THY group received lower tacrolimus exposure. In the THY group steroids were selectively withdrawn 3–6 months after transplantation: in patients with no previous transplant, no acute rejection episode, serum creatinine <2 mg/dl and proteinuria <300 mg/l/24 h.
Results: Demographic characteristics of patients were similar in the two groups. Efficacy and safety parameters after 1 year of follow up are summarized in the table.
Conclusions: Our data show that 1 year after transplantation, the induction with low-dose thymoglobulin and basiliximab when compared to the induction with basiliximab provides same patient and graft survival, same incidence of acute rejection, same renal function with significantly lower tacrolimus exposure and significantly lower steroid daily dose. The THY induction protocol could be useful in elderly recipients of older donors kidneys.

BO155 EFFECT OF STEORID WITHDRAWAL AFTER RENAL TRANSPLANTATION ON PATIENT AND GRAFT SURVIVAL

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Kidney transplantation is the preferred treatment of end stage renal disease. However, acute rejection increases the risk of graft loss twice. A common used therapy includes immunosuppression with steroids to prevent such cases. However, they contribute also to artheriosclerosis, worsening of diabetes and other comorbidities. Therefore, we evaluated the time point of steroid withdrawal after kidney transplantation in respect to outcome. We performed an analysis using the Austrian Dialysis and Transplant Registry. In this registry 2192 patients were first transplanted between 1.1.1990 and 31.12.2008 with initial steroid immunosuppression. For analysis several clinical laboratory variables as well as demographics were included. We used the landmark Cox model in order to reduce bias introduced by patients who have not survived until a possible steroid withdrawal. The outcome used for the model was mortality, actual and functional graft loss. Potential confounding variables were introduced in the model with propensity score. The hazard ratio (HR) for actual graft loss was higher in patients who had a steroid withdrawal in the first year after transplantation though not significant (HR 1.33, 95% CI 0.50–2.15, $p = 0.930$). After the first year the hazard ratio revealed an advantage for graft survival and was significant from the forth year on (HR 0.61, 0.40–0.95, $p = 0.027$). For functional graft loss the first year hazard ratio was 1.36, 95% CI 0.60–3.04, $p = 0.460$. Afterwards the hazard ratio was below one but not significant (4th year: HR 0.88, 95% CI 0.45–1.83, $p = 0.612$). For mortality the hazard ratio was below 1 all the time (1st year HR 0.35, 95% CI 0.07–1.65, $p = 0.183$) and significant from the 2nd year on (HR 0.22, 95% CI 0.06–0.85, $p = 0.029$). Steroid withdrawal in the first year after kidney transplantation shows a trend to a higher hazard ratio for graft loss but after the second year it is beneficial for patient survival.

BO156 15 YEAR FOLLOW-UP OF A MULTICENTRE, RANDOMISED, CALCINEURIN INHIBITOR (CNI) WITHDRAWAL STUDY IN KIDNEY TRANSPLANTATION

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Background: Calcineurin inhibitors (CNI) are essential immunosuppressives after renal transplantation, but they are nephrotoxic.
Methods: Of 212 patients transplanted between 1997 and 1999 participated in a 2 year, randomized multicentre trial. All patients were initially treated with Mycophenolate mofetil (MMF), Cyclosporine A (CsA) and prednisone (pred). At 6 months after transplantation, 63 patients were randomised for MMF/Pred, 76 for MMF/CsA and 73 for MMF/CsA/Pred. Follow-up data until December 2012 were extracted from the NOTR database. Intention to treat and on versus off treatment patient and graft survival censored for death analyses were performed.
Results: At randomisation, groups were not significantly different for recipient, donor and transplantation characteristics. Within 18 months after randomisation 23 patients had a rejection episode (27.0%, 6.8%, and 1.4% in groups MMF/Pred, MMF/CsA, and MMF/CsA/Pred, respectively, $p < 0.001$). At the end of follow-up 73 patients have died with a functioning graft, 43 patients have lost their graft, and 96 are alive with a functioning graft. Intention to treat analysis did not show a significant difference in survival between the groups. Prevalence of or death by malignancy or cardiovascular disease (CVD) was not less in group MMF/Pred. In multivariate analysis, graft survival censored for death was significantly associated with serum creatinine at 6 months after transplantation and maximum PRA, but not with randomisation group. On or off CNI treatment analysis showed that patients reverted to CNI and those with AR after randomisation had a significantly worse graft survival censored for death.
Conclusion: Conversion to CNIfree regimen is not associated with improved long term graft survival, nor with decreased prevalence of or death by malignancy or CVD. On the contrary, graft survival was severely impaired in patients that had to be reverted to CNI or had an AR after conversion.

BO158 CONVERSION FROM PROGRAF TO EXTENDED-RELEASE TACROLIMUS IN STABLE KIDNEY TRANSPLANT RECIPIENTS: BETTER RENAL FUNCTION AFTER 3 YEAR FOLLOW UP

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The complexity of therapy after solid organ transplantation has been related with non-adherence to therapy prescriptions and to reduced graft survival. Aim of this study was to evaluate in renal transplant recipients the middle term effects of the conversion from Prograf,® administered twice daily (TAC), to Extended-Release Tacrolimus (Advagraf®), administered once daily (ADV).
Methods: Conversion from TAC to ADV, dose 1:1 (mg/mg), was planned in 78 renal transplant patients with stable renal function, 71 ± 48 months after renal transplantation. Before conversion, 1 week after conversion and every 6 months up to 3 years, patients were evaluated clinically and by the usual blood chemistry and pharmacologic parameters. Quality of life was also assessed pre and 6 months after conversion.
Results: Twenty patients (26%) refused to change their pre-existing immunosuppressive therapy, 58 patients were enrolled into the study and 45 (77%) completed the 3 year follow up. Patient and allograft survival was 98%. After conversion significant reduction in serum creatinine and increased GFR were observed (preconversion versus 3y creatinine: TAC 1.67 ± 0.47 vs. ADV 1.47 ± 0.62 mg/dl, $p < 0.001$; preconversion versus 3y GFR, MDRD abbreviated: TAC 49 ± 15 vs. ADV 59 ± 24 ml/min, $p < 0.001$). The daily dose and C0 blood levels of tacrolimus were not changed before and after conversion (Dose, preconversion versus 3y postconversion: TAC 3.79 ± 1.81 vs. ADV 3.54 ± 1.86 mg/day, p = ns; C0 tacrolimus blood levels, preconversion versus 3y postconversion: TAC 6.03 ± 1.75 vs. ADV: 5.58 ± 1.38 ng/ml, p = ns). Six months after conversion patients showed an increased positivity and well-being ($p < 0.05$) with better disclosure of having received a transplant ($p < 0.05$). No acute rejection was observed.
Conclusions: Our data support, in the medium-term, the safety and efficacy of converting to Advagraf stable renal transplant patients. We also observed improvement of renal function and better perception of quality of life.

BO159 PREVALENCE OF SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) IN THE GENES CODING FOR TACROLIMUS (TAC) AND MYCOPHENOLATE MOFETIL (MMF) METABOLIC ENZYMES AND TRANSPORTING PROTEINS IN SPANISH KIDNEY TRANSPLANT RECIPIENTS

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Background: The variability of the pharmacokinetics of immunosuppressant drugs is a critical factor in managing immunosuppressive treatment. Tacrolimus (TAC) and mycophenolate mofetil (MMF) are frequently used in combination as immunosuppressive regimen. Altered expression of their metabolic enzymes and/or transporting proteins due to gene single nucleotide polymorphisms (SNPs) may influence TAC and MMF levels and affect transplant outcomes.
Methods: A 1-month follow-up, prospective, observational, multicentre study was conducted in patients, who were to receive a kidney graft and immunosuppressive therapy with steroids, TAC and MMF. Primary objective was to assess the prevalence of gene SNPs for TAC- (CYP3A4, CYP3A5, MDR1) and MMF- (UGT1A9, UGT2B7, MRP2) biotransforming and transporting proteins, and also their impact on drug exposure and possible correlation with drug safety profile.
Results: Out of 216 recruited patients, 189 were eligible for analysis. The most prevalent genotype (>80%) for CYP3A4 SNP −392A > G was the wild type homozygous (A/A), while for CYP3A5 SNP 6986A > G was the variant homozygous (G/G). The most prevalent (>87%) genotype for UGT1A9 SNPs 98T > C, −275T > A and −2152C > T consisted on homozygous wild type alleles for each SNP. Patients carrying CYP3A4 SNP −392A > G A/A and those carrying CYP3A5 SNP 6986A > G G/G genotype showed significantly ($p < 0.05$ and $p < 0.01$, respectively) greater TAC exposure and lower daily dose requirements. No association was observed for any SNP and probability of reaching stable TAC therapeutic range or acute rejection.
Conclusion: The prevalence of the allelic variant for CYP3A4 SNP −392A > G and CYP3A5 SNP 6986A > G in the Spanish kidney transplanted population is 11% and 99%, respectively. The SNPs of CYP3A4 and CYP3A5 have an effect on TAC exposure, with implications for TAC dosing.

BO160 IMPACT OF CYP3A5, CYP3A4 AND MDR1 GENE POLYMORPHISMS ON TROUGH CONCENTRATIONS OF TACROLIMUS, CYCLOSPORINE AND SIROLIMUS IN RENAL TRANSPLANT RECIPIENTS

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Background: The genetic polymorphisms of CYP3A5, CYP3A4 and MDR1 have shown important influence on oral bioavailability of calcinurin inhibitors (CNI) and sirolimus (SRL). This study is aimed to determine whether these polymorphisms would affect trough concentrations and dose requirements of tacrolimus (Tac), cyclosporine (CsA) and sirolimus in renal transplant recipients.
Methods: One hundred and twenty-six renal transplant recipients (42 with Tac-based regimen, 57 with CsA-based regimen and 27 with SRL-based regimen) were enrolled. All the renal transplant recipients were genotyped for CYP3A5 (6986A > G), CYP3A4 intron 6 (CYP3A4*22), MDR-1 exon 26 (3435C > T) and exon 12 (1236 C > T) SNPs, which were determined by high-resolution melting curve analysis (HRM analysis). The trough concentrations of each drug were measured by enzyme-multiplied immunoassay technique (EMIT).
Results: The Tac and SRL concentration/dose ratio (C/D) in recipients with CYP3A5 (*)3/(*)3 were significantly higher than that of those with (*)1 allele ($p < 0.05$). Regarding MDR1 SNP C3435T, the subjects with TT genotype in both Tac group and CsA group had higher C/D than those with CT and CC genotype ($p < 0.05$). As for MDR1 SNP C1236T, the subjects under CsA regimen with TT genotype had higher C/D than those with CT and CC ($p < 0.05$). Unlike the Caucasians, there was only one genotype CC of CYP3A4*22 in Chinese renal transplant recipients.
Conclusions: Renal transplant recipients carrying CYP3A5 (*) 1 allele required significantly larger dosage of Tac or SRL to achieve target concentrations. The MDR1 polymorphisms C3435T and C1236T were associated with CNI based therapy instead of SRL. Analysis of CYP3A4*22 SNP may not help in guiding immunosuppression regimen in Chinese renal transplant recipients. Data were express as media (range), Data were analyzed by the Kruskal–Wallis test. *indicated significant difference with *3/*3, #indicated significant difference with 3435C > T (TT), $indicated significant difference with 1236C > T (TT).

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BOS15- LIVER COMPLICATIONS

BO161 NGAL PREDICTS IRREVERSIBILITY OF PRE-LIVER TRANSPLANTATION KIDNEY DYSFUNCTION

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Background: Kidney outcomes early post-liver transplantation (LT) are crucial for long-term post-LT prognosis, but difficult to predict.
Methods: Among 210 unselected adult patients undergoing first LT, we studied the value of pre-LT plasma neutrophil gelatinase-associated lipocalin (NGAL) for predicting acute kidney injury (AKI) <1 week, dialysis <3 months, and kidney dysfunction (GFR<60 mL/min) at 3 months post-LT. GFR was estimated by creatinine-based (MDRD) and cystatin C-based (CKD-EPI) equations.
Results: NGAL was >200 μg/l among 42% of patients with LT-day GFR <60 ml/min and 47% of patients on dialysis, but only among 2% of patients with GFR >60 ml/min (Figure). NGAL predicted GFR<60 ml/min at 3 months post-LT (OR 1.003, 95%CI 1.000–1.005) independently of age, LT indication, and LT-day kidney function. The best discriminative performance of NGAL for predicting 3-month kidney dysfunction was among patients on pre-LT dialysis; AUC was 0.73 (95% CI 0.56–0.90) with a NGAL >263 μg/l exhibiting 64% sensitivity and 85% specificity. Results were similar when estimating GFR by creatinine- and cystatin C-based equations. NGAL failed to predict post-LT AKI or need for temporary dialysis.
Conclusion: NGAL predicted irreversibility of pre-LT kidney dysfunction and could thus help in the decision to perform combined liver-kidney transplantation.

BO162 RENAL DYSFUNCTION AFTER LIVER TRANSPLANTATION: PRELIMINARY RESULTS OF A CROSS-SECTIONAL, MULTICENTER STUDY (SURF)

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Background: Renal dysfunction (RD) is an unmet medical challenge after liver transplantation (LT).
Methods: To investigate the prevalence of RD, we set up a cross-sectional survey (SURF study) in 15 Italian LT centers. Patients were stratified in 6 risk categories (none, low, intermediate-low, intermediate-high, high, very high) based on combination of estimated glomerular filtration rate (eGFR) according to MDRD (≥90; 89–60; 59–30; <30 ml/min), proteinuria (≥0.5 g/day), and velocity of eGFR deterioration (−4 ml/min/year).
Results: From March, 2012 to January, 2013 a convenience sample of 753 patients was enrolled between 6 months and 5 years after transplantation, and of these 724 were evaluable (males 74.9%; median age 52.8 years; median time since LT 29.1 months). 89% patients were transplanted for cirrhosis with hepatitis C (41.4%), alcohol (27.1%), and hepatitis B (21.4%) as the most frequent indications. Hepatocellular carcinoma was present in 40.3% patients irrespective of native liver disease. At enrolment, median (interquartile range (IQR)) eGFR was 73.8 (32.4) ml/min (range 5.2–271.1 ml/min) and it was <60 ml/min in 184 patients (25.4%), and <30 ml/min and <15 ml/min in 6 (0.83%) each. Mean (standard deviation (SD)) eGFR deterioration was −13.6 (33.6) ml/min/year from LT to enrolment with 38% patients presenting an eGFR decrease >−4 ml/min over the previous year irrespective of their eGFR category. A total of 47% patients presented ≥ intermediate risk of RD.
Conclusion: LT is associated with a remarkable risk of RD and preventative strategies in view of preservation of renal function are highly favored.

BO164 AKIN VERSUS CONVENTIONAL CRITERIA TO DIAGNOSE ACUTE KIDNEY INJURY IN PATIENTS AWAITING LIVER TRANSPLANTATION

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Acute kidney injury (AKI) is associated with increased morbidity and mortality, even in its mildest form (Stage1). Conventional diagnostic criteria for AKI in patients with end-stage liver disease awaiting liver transplantation (ESLD-wOLT) include an increase in serum creatinine (sCr) >1.5 mg/dl. The MELD score, used to prioritize allocation of liver grafts, sets sCr = 1 mg/dl as standard value. AKIN criteria have been validated to define and stratify AKI on the basis of deviation of sCr from baseline. The aim of the study was to compare the prevalence of AKI in patients with ESLD-wOLT based on AKIN vs. conventional and MELD criteria. This is a single-centre retrospective study of 69 patients (56M/13F), mean age 55 ± 9 year, MELD >15, assessed from listing to transplant (2008–2012). Ten and five patients presented undiagnosed AKI with conventional and MELD criteria respectively versus AKIN criteria. Of these, 7 out of 10 and 4 out of 5 had AKI Stage 1. Negative predictive value was 82.8% and 90.6%, respectively. AKIN criteria improve diagnosis of AKI as compared to conventional criteria, allowing early treatment in particular in Stage 1, which has the most favorable response to therapy.

BO165 MELD SCORE AND INCREASED RISK OF ACUTE KIDNEY INJURY POST-LIVER TRANSPLANTATION IN FEMALES

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Renal dysfunction before liver transplantation (OLT) is recognized as risk factor for acute kidney injury (AKI) post-OLT. Women are reported to be disadvantaged in the MELD era because of discrepancies in renal function compared to men, due to reduced serum creatinine (sCr) for equivalent glomerular filtration rate. Aim of the study was to evaluate the prevalence of AKI post-OLT and its association with pre-OLT risk factors, in particular recipient's gender. A single centre study of 91 liver transplanted patients (73/18: M/F; median age 55.6 ± 9.3) 2008–2013. One patient was excluded for missing data. Patient's characteristics and data from listing to the first week post-OLT were collected. AKI was defined according to the AKIN criteria, as peak serum creatinine ≥2 times baseline. Logistic regression was conducted and odd-ratio (OR) and relative 95% confidence intervals (CI) computed to assess the association between AKI risk and relevant characteristics. Those variables found to be significative ($p < 0.20$) were included in the multivariate analysis and the final model selected through backward elimination ($p < 0.20$ to drop variable). The incidence of AKI was 18.9% (17/90 patients). Females were significatively at higher risk of developing AKI when compared to males (38.9% vs. 13.9%, OR 3.95, 95% CI: 1.24–12.58, $p = 0.020$). Lower pre-OLT sCr (<1 vs. >1 64/26, OR = 3.7, $p = 0.101$) and higher MELD (15 + vs. <15, OR = 2.27, $p = 0.186$) showed an increased AKI risk close to significance at univariate analysis. No differences were detected for age, BMI. At multivariate analysis the final model include female gender (MLR-OR = 3.66. $p = 0.036$), lower pre-OLT SCr (OR = 4.49, $p = 0.068$) and higher MELD (OR = 2.91, $p = 0.102$) as the main factors associated with higher AKI risk. MELD was not significantly different between male and female ($p = 0.258$). Under the current liver allocation system, female patients resulted to have an increased risk to develop AKI post-OLT.

BO166 PREDICTIVE VALUE OF TUMOR MARKER ON HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANTATION

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This study investigated whether the combined use of pre-transplant serum alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) levels improve predictive performance of the Milan criteria (MC) for hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT). We analyzed 162 patients that underwent LT for HCC between 2001 and 2012. We design the MC based predictive model for HCC recurrence. This model incorporated pre-transplant serum AFP and DCP levels: model 1 is base model incorporated AFP, model 2 is base model incorporated DCP and model 3 is base model incorporated AFP and DCP. In the time-dependent receiver operating characteristics curve analysis, predictive performance of model 1 and model 2 show no significant difference between the base model. However, model 3 show significantly better predictive performance than base model. Thus, LT candidates with HCC can be assessed more accurately by adding pre-transplant AFP and DCP levels to the MC.

BO167 18F-FDG-PET/CT PREDICTS EARLY TUMOR RECURRENCE IN LIVING DONOR LIVER TRANSPLANTATION FOR HCC

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Purpose: There has been little information about the prognosis including 18F-FDG PET/CT for the early recurrence for HCC after LT.

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Methods: Consecutive patients who underwent 18F-FDG PET/CT and subsequent LDLT for HCC from March 2005 to June 2011 were enrolled.
Results: The 191 patients with a median follow-up of 26.1 months were evaluated. There were 20 patients (10.5%) with early recurrence (íÁ 6 months), 18 patients (9.4%) with late recurrence (>6 months). The median overall survival of patients with early recurrence was very poor (19.0 months), with no survivors beyond 3 years. Three year overall and disease-free survival for PET/CT positive patients were 65.5% and 57.1%, respectively. PET/CT positive status was identified as an independent prognostic factor for disease-free survival influencing early recurrence in multivariable analysis (HR 3.945, 95% CI 1.196–13.016, p = 0.024).
Conclusion: PET/CT is an independent and significant predictor of early tumor recurrence in LT for HCC.

BO168 MOLECULAR-BASED STUDY OF BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION

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Background: The biliary complications (BC) were always considered the "½Achilles heel" of liver transplantation, being one of the leading causes of postoperative morbidity.
Methods/Materials: A total of 30 patients were followed-up prospectively from the pre-transplant for 2 years. The expression of Matrix metalloproteinases (MMP 2, 9) and their tissue inhibitors (TIMP1), the interleukines (IL 2, 8), TNF-alfa, the endotelines and their receptors in the periferhal blood were measured through PCR real-time analysis subsequently certified by "ELISA" tests.
Results: Five patients developed anastomotic stenosis (AS). None of the other patients developed non-anastomotic biliary stenosis, other biliary complications or vascular complications (hepatic artery or portal vein thrombosis). Relative expression of fibrosis-relevant/pro inflammatory genes and their associated serum cytokines/enzymes were analysed between the two groups (with and without AS). A predictive model was created based on the logistic regression equation that allows the calculation of a risk score for AS occurrence after LT. The optimal cut-off value for diagnosis of AS was 0.4816 with a sensitivity, specificity, positive predictive value, and negative predictive value of 80%, 100%, 100% and 95%, respectively.
Conclusion: BC plays an important role in the patients' postoperative morbidity and molecular biomarkers prediction should improve their early recognition and treatment.

BO169 LOW VISCOSITY PERFUSION FLUID DECREASES THE INCIDENCE OF BILIARY STRICTURES IN LIVER TRANSPLANTATION FROM DONORS AFTER CIRCULATORY DEATH

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Background: Biliary strictures (BS) represent a major long-term complication decreasing graft survival following liver transplantation from donors after circulatory death (DCD). We aimed to identify risk factors for the development of BS after DCD liver transplant at our centre.
Methods: The study inclusion criteria were graft survival more than 6 months with a patent hepatic artery, which was met in 117 patients. We analysed donor and recipient characteristics, retrieval and implantation timings. Variables with a p-value ≤ 0.10 were included in the multivariate Cox regression analysis.
Results: The median patients follow up was 33 months (range 6–99). With the majority of donors being male (55%), the median donors age 51 (12–75) years and body mass index was 25 (18–44) kg/m^2. Sixty-seven (57%) grafts were retrieved with University of Wisconsin (UW) solution and fifty (43%) with aortic perfusion with Marshall's hyperosmolar citrate. In situ portal and back-table perfusion were done with UW solution. Donor warm ischaemic time, defined from the systolic blood pressure below 50 mmHg to organ perfusion, was 20 (6–35) and cold ischaemic time 431 (184–709) min. The overall incidence of biliary strictures was 12%. The only variable independently predicting the development of BS was aortic perfusion with UW compared to Marshall's hyperosmolar citrate (odds ratio 4.218; 95% confidence interval 1.141–15.599, p = 0.031).
Conclusion: The incidence of BS correlates with the liver perfusion fluid. Aortic flush with a low viscosity Marshall's hyperosmolar citrate significantly decreases the incidence of biliary strictures following DCD liver transplantation.

BO170 THE MORBIDITY OF INTRA-OPERATIVE BILIARY STENTING FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION

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Background: Biliary complications are among the leading source of surgical morbidity following liver transplantation. We attempted to identify the effect of prophylactic stent placement during orthotopic liver transplantation on subsequent post-transplant morbidity.
Methods: We performed a single-center retrospective study using the records of liver transplant recipients over a 7 year period. Biliary complications were defined as all major and minor anastomotic leaks or strictures, determined clinically or by imaging. Multivariate regression models were performed to estimate the effect of operative biliary stent placement on post-operative morbidity following liver transplantation.
Results: Overall, 513 deceased donor liver transplant recipients were analyzed. 87.3% had a duct-to-duct biliary anastomosis. 43.1% ($n = 221$) had biliary stents placed at operation. The overall biliary complication rate was 45.1% ($n = 232$). Biliary stenting was associated with 74% greater risk of repetitive ERCP procedures (HR 1.74, p = 0.011), and trended toward a lower risk of repetitive PTC interrogations (HR 0.56, p = 0.063). There were no differences in graft or patient survival.
Conclusions: Intra-operative biliary stenting was not protective from overall biliary complications, and was associated with needing multiple ERCPs. Biliary stenting was associated with a trend towards fewer PTC procedures, but this may be affected by other confounders. Intra-operative biliary stenting portends significant morbidity after liver transplant.

BO171 INCISIONAL HERNIA AFTER LIVER TRANSPLANTATION: INCIDENCE AND RISK FACTORS

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Background: Incisional hernia (IH) is a frequent complication after liver transplantation (LT) with a reported incidence of 4-32%. Many of the previous studies on the risk factors for IH after LT have found varying results. The purpose of this study is to look at a wide variety of variables to characterize the risk factors for IH after LT.
Materials and Methods: Our single-study retrospective study, we analyzed 519 consecutive LTs from June 2003 to December 2011. Detection of IH was by computed tomography scan report, by record of objective examinations and of IH repair. Univariate and multivariate analyses were performed on a variety of pre-, intra-, and post-operative factors.
Results: In our population, 74/519 patients (15%) developed IH after LT. Multivariate analysis established the following to be independent risk factors for the development of IH after LT: higher age (Odds Ratio, OR = 1.04), cardiovascular comorbidity (OR = 2.62), pre-transplant end stage liver disease with episodes of severe porto-systemic encephalopathy and presences of esophageal varices (OR = 3.47), abdominal surgery following transplantation (OR = 4.8), steroid use in immunosuppressive therapy (OR = 2.0), and length of hospital stay following transplantation (OR = 0.98). [Table 1].
Conclusion: In our experience, the occurrence of complications which lengthen the hospital stay increases the risk of IH after LT, and when a relaparotomy occurs, it is mandatory to take special care to close the abdominal wall because the IH risk heightens significantly. Usage of immunosuppressive regimen with steroids is an independent risk factor for IH development in patients who have undergone LT.

BO172 PREDICTION OF EARLY ALLOGRAFT DYSFUNCTION IN LIVER TRANSPLANTATION

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Introduction: Poor initial graft function is associated with impaired graft and patient survival and has been recently newly defined as early allograft

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dysfunction (EAD) (Olthoff, KM et al. Liver Transpl 2010; 16:943–949). The aim of this analysis was to evaluate for clinical relevance and predictive donor information of EAD in a large cohort of liver transplant recipients.
Methods: Of 678 consecutive adult patients (mean age 51.6 years; 60.3% males) who received a primary OLT between 09/2003 and 12/2011 were included in this retrospective analysis. Standard donor data including laboratory values, parameters of intensive care treatment, histology and the donor risk index were correlated with development of EAD and outcome by univariable/multivariable logistic regression and cox proportional hazards to identify prognostic donor factors. Relevant factors were utilized for a scoring system providing three groups of risk to develop EAD (low, moderate, high).
Results: 40.1% patients developed EAD. Thirty-day-survival of grafts with and without EAD was 60.3% and 88.9% ($p < 0.0001$). Thirty-day-survival of patients with and without EAD was 69.4% and 92.1% ($p < 0.0001$), respectively. Donor male sex ($p = 0.0293$), gGT ($p = 0.0013$), macrosteatosis ($p = 0.0087$) and cold ischemia time (CIT) ($p = 0.0209$) were predictors for EAD. The new only on donor data based score was highly predictive (OR: 3.054, high risk group vs. low risk group).
Conclusion: EAD correlates with early results of OLT and can be predicted by donor data only. Outcome of high risk organs might be improved by shortening CIT.

BO173 LIVER TRANSPLANTED PATIENTS FAIL TO REGAIN MUSCLE MASS ONE YEAR AFTER SURGERY

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Background: Muscle wasting is a common burden in patients undergoing liver transplantation (LT). Although malnutrition has been identified as a known predictor of poor outcome after surgery, only few information are available regarding the sequential changes of body composition after LT. This study was aimed at investigating changes in body composition during the first year after LT.
Methods: Adult patients eligible for elective LT were included. Nutritional assessment (anthropometry and Dual-energy X-ray absorptiometry (DEXA)) was performed in all patients before and 1, 3, 6 and 12 months after LT. Triceps-skin fold thickness (TSF) was measured and mid-arm muscle circumference (MAMC) was calculated according to standard equation. Fat-Free Mass Index (FFMI, Kg/m2) and Fat Mass Index (FMI, kg/m^2) were calculated by whole body DEXA scan. FFMI depletion was defined in presence of values below 10th percentile, evaluated on an age- and sex-matched population.
Results: Sixty-four adult patients awaiting for LT were initially studied. Results refer to 27 patients who were transplanted and completed 1 year of follow-up (Table 1). At LT, 33% of patients presented a FFMI depletion. During the first year after LT, while fat mass (TSF and FMI) increased progressively (from 15.4 to 19 mm, and from 6.7 to 7.7 kg/m^2, before and 12 months after LT, respectively, $p < 0.05$), fat free mass (MAMC and FFMI) failed to ameliorate (figure 1). The percentage of patients with fat-free mass depletion (FFMI below 10th percentile) was even increased 1 year after LT (from 33% before LT to 63% 12 months after LT $p < 0.05$).
Conclusions: During the first year after LT the fat mass is progressively regained while the recovery of the fat free mass is insignificant and may require a longer period. Steroid therapy, immunosuppressive drugs and relative inactivity may play a role in this slow recover.

BO174 SIGNIFICANT LIVER GRAFT STEATOSIS IS ASSOCIATED WITH WORSE PATIENT AND GRAFT SURVIVAL AFTER THIRD YEAR POSTTRANSPLANT

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Background: Liver graft steatosis is a frequent late complication after liver transplantation (LTx). We aimed to determine the prevalence of steatosis, the impact of liver graft steatosis on patient (pt) and graft survival and the cause of death.
Patients and Methods: A single centre retrospective analysis of 752 LTx in 715 pt was performed. In total, 2876 liver graft biopsies were evaluated. Alcoholic (29.4%) and HCV cirrhosis (18.0%) were the most frequent indications for LTx. Survival of pt/grafts with steatosis grade (g) 2–3 was compared with survival of pt/grafts with steatosis G0-1, age and sex adjustement was performed. Cause of death was recorded.
Results: Liver graft steatosis (g 1–3) was found in 57.2% of pt. Significant steatosis (g 2–3) was found in 16.1% of pt. After age and sex adjustement patients/graft survival after 3rd year posttransplant was worse in patients/grafts with steatosis g 2–3 than with steatosis g 0–1 (stratified Cox regression model). Death for cardiovascular diseases was more frequent in pt with steatosis g2–3 (20.0%) than in pt with steatosis g0–1 (2.5%).
Conclusion: Liver graft steatosis is a frequent complication after LTx. Significant liver graft steatosis is associated with worse patient and graft survival after third year posttransplant and higher cardiovascular mortality.

BO175 SIGNIFICANCE OF NUTRITION ASSESSMENT AND NUTRITION SCREENING TOOLS IN PREDICTING COMPLICATIONS AMONG PATIENTS WITH LIVER CIRRHOSIS

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Background: Protein energy malnutrition (PEM) is a common complication of liver cirrhosis, it has been found to increase morbidity and mortality in these patients. In patients with liver cirrhosis PEM is prevalent among 65–90% of decompensated and 20% of compensated liver cirrhosis. In liver transplantation PEM has been reported in 100% of patients prior to transplantation. Malnourishment was found to be an independent risk factor for morbidity and mortality in patients following liver transplantation.
Objective: Correlate PEM to the incidence of complications in patients with liver cirrhosis. Also correlate PEM assessment tools with the incidence of complications of liver cirrhosis.
Methods: This study was conducted on 45 cirrhotic patients child C with or without complications .The patients were divided into two groups: group I included 3O patients with moderate to severe degree of malnutrition and group II which included 15 patients with mild degree of malnutrition.
Results: Rate of various complications is higher in patients with severe malnutrition,TSFT and MAC has the highest sensitivity 85.71%, 100% & specificity 90%, 60% respectively to rate of complications(p value < 0.0001 &area under the ROC curve = 0.879).
Conclusion: Complications of liver cirrhosis are highly correlated to degree of malnutrition.Anthropometric measures as TSFT &MAC in comparison to other assessment tools showed higher sensitivity & specificity to the rate of complications. Also TSFT showed high sensitivity and specificity with the body fat%.

BO176 INSULIN-LIKE GROWTH FACTOR 1 LEVELS REFLECT GRAFT'S FUNCTION AND PREDICTS SURVIVAL AFTER LIVER TRANSPLANTATION

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Background: Reduction of insulin-like growth factor 1 (IGF-1) plasma levels is associated with the degree of liver dysfunction and mortality in cirrhotic patients. However, few evidences are available about the recovery of IGF-1 level and its prognostic role after liver transplantation (LT).
Methods: From April 2010 to May 2011, 31 patients were prospectively enrolled (25/6 M/F; age: 55.2 ± 7.6 years) and IGF-1 serum levels were assessed preoperatively and at 15, 30, 90, 180, 365 days after transplantation. The influence of donor's and recipient's characteristics (age, use of extended criteria donor grafts, D-MELD and incidence of early allograft dysfunction) on hormonal synthesis was analyzed; the prognostic role of IGF-1 level on patient survival and its correlation with routine liver function tests were also investigated. Immunosuppression was initially based on once daily dose Tacrolimus associated with Everolimus starting on postoperative day 14.
Results: All patients showed low preoperative IGF-1 levels (mean: 29.5 ± 11.6); on day 15, a significant increase of IGF-1 plasma level was observed (102.7 ± 64.1 ng/ml; $p < 0.0001$). During the first year after LT, IGF-1 production remained significantly lower in recipients transplanted with older donors (>65 years) or extended criteria donor grafts. An inverse correlation between IGF-1 and bilirubin serum levels at day 15 and 30 was found ($r = -0.3924$ $p = 0.0320$; $r = -0.3894$ $p = 0.0368$). Early (within 15 days) IGF-1 normalization and donor age >65 years were the only prognostic factors associated with an increased 24-months survival rate (94.4% vs. 53.8% $p = 0.0051$; 100% vs. 65.0% $p = 0.0323$).
Conclusion: IGF-1 postoperative levels correlate with graft's quality and reflect liver function. Early IGF-1 recovery is associated with a higher 2-years survival rate after LT.

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BO177 PREVALENCE OF METABOLIC SYNDROME AFTER LIVER TRANSPLANTATION

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Background: Cardiovascular events occur with a frequency of 9.4% at 5 years post-transplantation and 25% at 10 years, accounting for 21% of deaths in patients surviving more than 3 years after liver transplantation.
Patients and Methods: We retrospectively studied 155 patients with liver transplantation, with a mean age of 47 ± 10 years (males 61.2%). Indications for liver transplantation were: HBV: 39.34%, HCV: 21.3%, hepatocellular carcinoma: 12.26%, alcohol: 7.1%, primary biliary cirrhosis: 5.8%, Wilson's disease: 5.8%, other causes: 8.4%. Immunosuppressive treatment received by patients included Tacrolimus, Cyclosporin, Syrolimus, Tac+SRM or CsA+SRM. In all patients mycophenolate mofetil was associated with corticosteroids 3 months after liver transplantation.
Results: Metabolic syndrome was diagnosed according to current guidelines. Metabolic syndrome was diagnosed overall in 71 pts (45.8%), with prevalence increasing in time after liver transplantation: 28.8% of pts presented metabolic syndrome in the first year after transplantation, 50% of pts after 1–3 years, 46% of pts after 3–5 years and 75% of pts >5 years post-transplant. Long term complications after transplantation were represented by hypertension 30.9%, diabetes 21.2% and hyperlipidemia 49.67%. Major cardio-vascular events after transplantation: acute coronary syndromes in 2 cases, myocardial infarction in 1 case and stroke in 1 patient.
Conclusions: Early recognition, prevention and treatment of post-transplant hypertension, obesity, dyslipidemia and diabetes may impact long-term post-transplant survival. Metabolic derangements are almost universal in patients after liver transplantation. Calcineurin inhibitors, (CsA or Tac) and steroids are associated with hypertension, hyperglycemia and hyperlipidemia. Sirolimus can also contribute independently to dyslipidemia.

BO178 PREVALENCE, INCIDENCE AND RISK FACTORS FOR DONOR SPECIFIC ANTIBODIES AFTER LIVER TRANSPLANTATION

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Chu Toulouse Rangueil

Background: The pathogenic role of pre-existing or de novo human leukocyte-antigen (HLA) donor-specific antibodies (DSAs) is not well known after ABO-compatible liver transplantation (LT). We investigated the prevalence/incidence OF DSAs in our LT population.
Patients and Methods: As of February 2008, all previously LT patients followed in our center ($n = 267$) were screened for anti-HLA antibodies, using a Luminex Single-Antigen™ technique, at least three times. Rejection episodes were diagnosed from liver-allograft histopathology, and classified according to Banff's criteria.
Results: Of 1505 days [11–6723] after LT, 46 patients (17%) had presented with DSAs. After the first anti-HLA detection, the annual incidence of de novo DSAs was 8/221 (3.6%) in year 1, 13/221(5.8%) in year 2, and 5/221 (2.2%) in year 3. During the follow-up, 42 patients died (16%). No difference was observed between patients with or without DSA antibodies with regards to mortality or graft failure. 38/72 patients with positive DSAs, detected during follow-up, had at least one rejection episode versus 69 patients without DSA/195($p = 0.009$). 4/26 patients with de novo DSA have presented an episode of rejection after the first HLA detection versus 3/195 ($p = 0.004$). Of these four episodes of rejection, 3 have been considered and treated as humoral rejection.
Conclusion: After LT, DSAs are frequent and result in clinical implications, including humoral rejection.

BO179 EFFECTS OF COMORBIDITIES ON SURVIVAL IN DIFFERENT EPOCHS AFTER LIVER TRANSPLANTATION

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Background: Post-liver transplant survival models rarely include preoperative recipient comorbidities as risk factors. We assessed the effects of comorbidities in different time periods after liver transplantation.
Methods: A linked UK Liver Transplant - Hospital Episode Statistics database (1997–2010) was analysed. Comorbidities in the Modified Royal College of Surgeons Charlson Score for Liver Transplantation (RCS-LT) were identified during the year immediately prior to transplant. Multivariable cox regression was used to estimate the impact of each comorbidity and RCS-LT score (number of comorbidities) on post-transplant survival in three epochs (within 90 days, 91 days – 1 year and 1 year – 5 years).
Results: We analysed 3,837 adult elective liver transplants from the linked database. Short-term survival (first epoch) was adversely affected by prior history of congestive cardiac failure (HR = 3.2; $p < 0.001$) and atherosclerosis (HR = 1.9; $p = 0.001$). Atherosclerosis was the only comorbidity to affect long-term survival (third epoch: HR = 1.5; $p = 0.03$). Recipients with two or more comorbidities were at higher risk of death during all epochs (HR = 1.9, 1.7 and 1.5; all p-value < 0.01).
Conclusion: Prior history of congestive cardiac failure has a high impact on short-term survival, whereas atherosclerosis has an impact on both short and long-term post-transplant survival. The overall number of comorbidities is important in all epochs.

BO180 WHAT IS APPROPRIATE TREATMENT INDICATION OF LATENT TUBERCULOSIS INFECTION IN LIVER TRANSPLANTATION IN A TUBERCULOSIS ENDEMIC GEOGRAPHIC AREA?

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Background: Treatment of latent tuberculosis infection (LTBI) has been known to have an efficacy in the general population. However, the indication and efficacy of LTBI treatment have not been proved in solid-organ transplant recipients. Indications and outcomes of LTBI treatment was evaluated in liver transplant recipients retrospectively.
Methods: Medical records of all 548 patients who recived primary liver transplantation at Samsung medical center in Seoul, Korea between 2008 and 2012 were reviewed. Isoniazid (INH) prophylaxis of LTBI was recommend to patients with a recent active tuberculosis (TB) exposure or uncomplete treated TB lesion on chest evaluation, which is considered as high risk factor, among positive tuberculin skin test or interferon gammar release assay(IGRA) patients.
Results: IGRA was performed in 338 patients among 548 before liver transplantation. The result was positive in 136 (40.2%), indeterminate in 21 (6.5%) and negative in 181 (53.5%). Thirty eight (27.9%) among 136 patients had with an active tuberculosis (TB) exposure or uncomplete treated TB lesion on chest evaluation, 19 patients received INH prophylaxis, but the other 19 patients did not receive INH prophylaxis. None of the patients with high risk factor who received INH prophylaxis or not developed TB, but 3 among 98 patients without high risk factor patients developed TB.
Conclusion: These results suggest to re-consider the appropriate indication of LTBI treatment in a tuberculosis endemic geographic area.

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BOS16-CLINICAL IMMUNSUPPRESSION & BIOLOGICALS

BO182 LONG-TERM THERAPY WITH EVEROLIMUS IN KIDNEY TRANSPLANT PATIENTS: TWO-YEARS RESULTS OF THE CERTIC REGISTRY

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Based on its mechanism of action, everolimus (EVR) may display some important benefits when associated with low dose calcineurin inhibitors. To gain information on the outcome after long-term use of EVR, we designed the CERTIC 5-year follow-up registry. Seven hundred and eighty-three heart and kidney transplant (KT) recipients on therapy with EVR were enrolled. Of the 382 KT patients, 88% received EVR within 3 months from transplant (de novo group) and were transplanted a mean of 2 years before entering the registry, for a total of 4 years of EVR treatment. In this group, survival rate was 96%, two patients lost the graft (0.6%) and 3 went back to dialysis. Thirteen patients developed neoplasms (1.8% yearly rate), accounting for 6 solid organ and 10 non melanoma skin cancers (NMSC). No PTLDs and Kaposi's sarcoma were recorded. Estimated glomerular filtration rate (eGFR) remained stable (from 55 $\pm$ 23 to 54 $\pm$ 25 ml/min/1.73 m^2). By picturing real-life clinical practice, this large prospective registry shows promising outcome in de novo patients in treatment with EVR for 4 years, with good survival rate, low incidence of malignancies and preservation of renal function.

BO183 CNI FREE IMMUNOSUPPRESSION IN HEART TRANSPLANT PATIENTS TREATED WITH EVEROLIMUS: RESULTS OF A MULTICENTER FRENCH REGISTRY

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Everolimus (EVL) is a mTOR antagonist preventing acute rejection after heart transplantation (HT). It has shown: (i) a non inferior efficacy in combination with low dose of cyclosporine (Cya) compared to Mycophenolate Mofetil (MMF) with standard dose of Cya, (ii) a lower incidence of CMV infection, (iii) a slower progression of chronic allograft vasculopathy (CAV). In selected patients, EVL could spare renal function and prevent some cancers. Studies aiming at anticalcineurins (CNI) weaning after introduction of EVL are however inconsistent. We analysed a retrospective registry of intend to treat HT patients with EVL and planned CNI weaning. Ten french HT centers participated to the registry reporting clinical and biological data before and at the time of EVL introduction, if failing EVL introduction, if failing CNI weaning, and at the end of the study period. 163 patients were included 104 + 73 months after HT. EVL had to be discontinued in nine patients (6%) due to side effects including 2 moderate cellular acute rejection episodes. CNI were weaned in 154 patients 14 $\pm$ 16 month after introducing EVL. CNI weaning however failed in 27 patients (17%) for various reasons including 2 humoral and 1 cellular rejections. One hundred and twenty-seven patients were weaned of CNI during the study period with a mean follow-up of 2 $\pm$ 1.7 year after discontinuation of CNI. Death occurred in 19 patients 19 $\pm$ 15 months after CNI weaning. Causes of death were cancer: 10 patients all diagnosed before EVL introduction, sudden death: six patients all with significant CAV diagnosed before introducing EVL, infection: 1, cerebral hemorrage: 1, unknown: 1. No patient died of rejection. One third of the patient improved significantly renal function after CNI discontinuation.
Conclusion: EVL allows weaning of CNI treatment in maintenance HT patient with a low risk of rejection.

BO184 PREVALENCE OF *DE NOVO* DONOR SPECIFIC ANTIBODIES (DSA) IN ORGAN TRANSPLANTATION AFTER SWITCH TO EVEROLIMUS

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Background: Recent studies reported a mild increase of acute rejection episodes after switch to mTor inhibitors, one showed that everolimus (EVR) could represent a risk factor of DSA.
Aim: To compare the prevalence of de novo DSA in patients switched to EVR and in patients who didn't have modification of immunosuppression.
Methods: DSA were searched at the time of transplantation, before the introduction of EVR and at 3, 6 and 12 months after (group 1). A control group (group 2) was composed of patients who were not switched but analyzed at the same time, and matched for gender, age and graft.
Results: One hundred and thirty-one patients were studied (group 1 $n = 59$, group 2 $n = 72$). The graft was lung (40), kidney (38), heart (35) liver (16), kidney and liver (1) or heart (1) (table1). De novo DSA were found in 9.1%, without significant difference according EVR treatment or not. No difference was observed either between numbers of rejection episodes, numbers of DSA, nor evolution of DSA strength.
Conclusion: In this study, introduction of EVR did not increase the prevalence of de novo DSA.

BO185 BORTEZOMIB ASSOCIATED WITH C5 INHIBITION WITH ECULIZUMAB ENABLES COMBINED CARDIAC-RENAL TRANSPLANTATION IN A HIGHLY IMMUNIZED CHILD

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Backgound: Patients with congenital heart diseases (CHD) often receive multiple blood products and develop high titers anti-HLA antibodies, resulting in a long time spent on waiting lists and possible death whilst waiting for an organ.
Patient and Method: A 7 year old boy with CHD was put on a Berlin heart whilst waiting for a cardiac transplant. Due to recurrent thromboembolic events, he also developed kidney failure. He was highly immunized against anti-HLA class I and Class II antigens, with a strength >10 000 MFI for many HLA antibodies. The patient was desensitized with rituximab (375 mg/kg), high dose IVIG and plasmapheresis (PP) with little benefit. Therefore, he received two cycles of four doses bortezomib (1.3 mg/m^2 each) and PP.
Results: A reduction of the antibody strength occurred only during the second cycle of bortezomib. At that stage, a potential donor with 4 HLA missmatches and a T cell CDC positive cross-match (undiluted) was offered and the patient underwent cardiac and renal transplantation. He received eculizumab [600 mg immediately prior to surgery and 1800 mg afterwards], ATG, tacrolimus, mycophenolate mofetil and steroids. Following transplantation there was immediate function of both grafts. Donor-specific Class I and II antibodies were detected postoperatively but remained low throughout the follow up. Early cardiac biopsies showed a healthy heart with C4d deposition that was no longer observed at 6 months. Similarly, at 6 months renal function (creatinine 0.4 mg/dl) and histology were normal. The patient is 10 months out and runs a normal life.
Conclusions: Bortezomib effectively eliminates anti-HLA antibodies producing cells, especially if associated with PP. In combination with eculizumab, it enables transplantation of high risks pediatric patients who would otherwise never be able to have access to this treatment.

BO186 PROSPECTIVE ANALYSIS OF CD19 DIMCD27 HIGHCD20 NEGATIVE BLOOD PLASMA CELLS IN RENAL TRANSPLANT PATIENTS AFTER COMBINED TREATMENT WITH RITUXIMAB AND BORTEZOMIB IN ANTIBODY MEDIATED REJECTION

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Treatment of antibody-mediated rejection (AMR) in renal transplant (Tx) patients (pts) is challenging and long-term outcomes remain poor. Because plasma cells (PCs) are crucial for donor specific HLA antibody (DSA) formation, targeting this population with proteasome inhibitor bortezomib (BZ) is quiet reasonable. The aim of this study was to investigate the efficacy of a combined AMR therapy with rituximab and BZ on peripheral blood B-cells and PCs in a prospective manner over 6 months. Influence on protective vaccination titers

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was reviewed in this context. AMR therapy was introduced in 9 Tx pts with DSA and biopsy proven AMR according to BANFF classification. Therapy included steroids, Plasmapheresis (6x), 1 cycle of BZ (1.3 mg/m^2; day 1, 4, 8, 11), 500 mg rituximab and IVIG (1.5 g/kg). PBMC were analyzed by FACS for antiCD3, 19, 20, 27, 38, 4, 25 and FOXP3 at baseline (BL), months (M) 1, 3 and 6. Serum IgG titers for mumps, measles and rubella (MMR) were measured by ELISA. 1M after treatment CD19dimCD27highCD20neg PCs count were significantly lower compared to BL (mean: 0.21 $\pm$ 0.1/µl vs. 1.3 $\pm$ 0.3/µl; p = 0.002) respectively. Effects on PCs were evident at 3M (0.09 $\pm$ 0.03/µl) and 6M (0.23 $\pm$ 0.07/µl). Similarly, we observed a significant depletion of CD19B-cells 1M after therapy (BL: 531 $\pm$ 145/µl vs. 2.3 $\pm$ 0.6/µl at M1; p < 0.001). Even after 6M, CD19Bcells did not recover. All pts had protective antibodies against MMR that were not significantly changed due to therapy (Mumps: BL = 2541 vs M6 = 2530 IU/ml). The present study observed a profound and sustained reduction of peripheral PCs and B-cells after 1 cycle of BZ and rituximab in pts with AMR. Interestingly, beside PC reduction in the periphery, protective MMR titers were not affected. Thus, the effect of BZ on tissue-based long lived PCs may be limited. Longer follow-up is necessary to thoroughly investigate the re-population of distinct B-cell and PC cell subsets. This may help to better understand the effects of AMR therapy.

BO187 N-OCTANOYL DOPAMINE IS A POTENTIAL NEW IMMUNOSUPPRESIVE DRUG: TOWARDS LOW CALCINEURIN INHIBITOR IMMUNOSUPPRESION

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Recently we developed a non-hemodynamic dopamine-derivative N-octanoyl dopamine (NOD) which has profound anti-inflammatory effects *in vitro*. Since NOD also protects rats from ischemic acute kidney injury (AKI), the present study tested if NOD is able to modulate cellular immunity for potential use as T-cell suppressive agent in renal transplant recipients. To this end, human T-cells were stimulated with anti-CD3/CD28 antibodies or PMA/ionomycin in the presence or absence of different concentrations of NOD and/or calcineurin inhibitor FK506. T-cell proliferation (by measuring thymidine uptake), activation marker (using flowcytometry) and activation of transcription factors (by electrophoretic mobility shift assay) were assessed. NOD transiently inhibited T-cell proliferation dose-dependently. While T-cell proliferation was significantly inhibited by NOD at day 3, proliferation was restored at day 7 or later depending on the NOD concentration used. Inhibition of proliferation was reflected by a diminished CD25 expression and impaired switch from naive to memory T-cells (decreased percentages of CD45RO+ T-cells). While early T-cell activation events (T-cell receptor capping and activation [Lck and ZAP70 phosphorylation]) were unaffected, NF-κB and AP-1 were strongly inhibited by NOD. Effects of NOD seemed to be dependent on its redox activity, since N-octanoyl tyramine, a redoxinactive NOD derivative, did not influence T-cell proliferation. NOD displayed synergistic effects with FK506 on T-cell proliferation. Our data demonstrate that NOD displays T-cell suppressive activity. In keeping with its profound anti-inflammatory action and its beneficial effect on ischemia-induced AKI, NOD may be an interesting drug candidate as early treatment modality in renal allograft recipients to limit reperfusion-mediated inflammation. This would improve renal function and reduce high CNI dosages that are usually required within the first weeks after transplantation.

BO188 HIGH DOSES OF ONCE-DAILY TACROLIMUS CORRELATE WITH HIGH TACROLIMUS EXPOSURE IN THE EARLY PHASE AFTER KIDNEY TRANSPLANTATION

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Background: Tacrolimus is a commonly used immunosuppressive drug in kidney transplantation. In the clinical practice some patients require higher tacrolimus doses than others despite low C0 concentrations. Therefore, we investigated if high doses of Advagraf might have an impact on AUC0-24 that may not be represented by trough levels solely.
Methods: Reduced AUC0-24 was measured in 40 kidney transplant recipients in the early postoperative course. Patients with Advagraf doses ≥14 mg/day (n = 16) were compared to patients with Advagraf doses <14 mg/day (n = 24).
Results: While C0 and C24 levels showed no difference between the two groups, C1 and C3 levels were significantly higher in patients with ≥14 mg Advagraf per day. As expected, this resulted in a higher AUC0-24 (367.4 (105.4) vs. 469.3 (147.2); [ng*h/ml] p = 0.015).
Conclusions: These results suggest that high doses of ADV are common in the early phase after transplantation. Surprisingly, high doses of Advagraf were significantly connected to an enhanced AUC0-24 in spite of low trough levels. However, an impact on immediate kidney function could not be demonstrated.

BO189 EFFECT OF CONVERSION FROM TWICE-DAILY TO ONCE-DAILY TACROLIMUS ON GLUCOSE INTOLERANCE IN STABLE KIDNEY TRANSPLANT RECIPIENTS – EVALUATION AT 12 MONTHS

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Background: Tacrolimus is an established immunosuppressant for the prevention and treatment of allograft rejection in organ transplantation. However, tacrolimus therapy also has several adverse effects. The main aim of this study was to evaluate the effect of conversion from twice-daily tacrolimus (tacrolimus-BID) to once-daily tacrolimus (tacrolimus-OD) on glucose intolerance in stable kidney transplant patients.
Methods: The study comprised 43 kidney transplant recipients with stable renal function. The same 1 mg: 1 mg dose conversion was used for all patients. Follow-up, which included clinical evaluation and laboratory testing, was performed at 2, 4 and 12 months after conversion. The parameters for which the baseline and end-point values were determined included tacrolimus daily dose, tacrolimus trough concentration, serum insulin levels, fasting glucose levels, hemoglobin A1c (HbA1c) levels, homeostasis model assessment of beta-cell function (HOMA-β) scores, homeostasis model assessment of insulin resistance (HOMA-IR) scores.
Results: The tacrolimus trough levels and daily dose did not differ significantly at 12 months after conversion. There was a significant decrease in HbA1c level at 12 months after conversion (baseline, 5.42–0.42%; end point, 5.22–0.46%; p = 0.004). The HOMA-β) score slightly increased (baseline, 57.69–33.08; end point, 60.79–36.21). The HOMA- IR score slightly decreased (baseline, 1.38–0.69; end point, 1.25–0.57). Serum creatinine concentration, and blood glucose level did not change significantly during follow-up examinations. Episodes of acute rejection or graft loss did not occur.
Conclusion: The results of this study suggests that conversion from tacrolimus-BID to tacrolimus-OD may benefit kidney transplant patients with glucose intolerance because of improved insulin secretion. Further studies involving a larger sample population and longer follow-up time are required to verify the results of this study.

BO190 INFLUENCE OF RECIPIENT CYTOCHROME P450 3A5 POLYMORPHISM ON THE METABOLISM OF PROLONGED RELEASE TACROLIMUS ADMINISTERED *DE NOVO* AFTER RENAL TRANSPLANTATION

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Patients (pts) possessing at least one *CYP3A5*1* allele have an increased tacrolimus (tac) metabolism. This prospective study evaluates the clinical interest of a new simplified starting-dose protocol of the prolonged release formulation of tac, Advagraf ® (adv) after renal transplantation (RT) according to recipient CYP3A5 polymorphism.
Material and Method: CYP3A5 genotype (*CYP3A5*1/*1, CYP3A5*1/*3, CYP3A5*3/*3*) was determined before RT. All pts received one 0.1 mg/kg of Adv prior to RT. On day 1, the Adv dose was adapted according to CYP3A5 genotype: 0.35 and 0.30 mg/kg/day in *CYP3A5*1/*1* and *CYP3A5*1/*3*respectively. CYP3A5 non expressors (*CYP3A5*3/*3*) were stratified to receive either 0.20 (control group) or 0.25 mg/kg/day. The daily dose (dd) remained unchanged during the first 3 days. The first tac trough level (TL) was determined at day 3 and the first dose adaptation performed on day 4. Associated therapy included MMF and CS.
Results: From January 2011 to July 2012, 84 consecutive pts (mean age: 48 years, 53M/31F) were included. Median Follow up (FU) was12 months (3–21). In the12 pts expressing CYP3A5 (two*1/*1, ten*1/*3), the dd needed to achieve a similar tac TLs to *CYP3A5*3/*3* remained significantly higher throughout 'the entire FU (table).***p < 0,001 **p < 0,01 *<0,05 Among pts CYP3A5 non expressors (n:72), 34 and 38 received a starting Adv dose of 0.2 and 0.25 mg/k/day respec-tively. After dose adaptation intended to reach a comparable tac TLs in both groups, we observed a significantly higher infratherapeutic tac TL rate in the control group (p < 0.02).
Conclusion: In conclusion, the use of Adv de novo after RT is effective when *CYP3A5*polymorphism is taken into account. CYP3A5 expressors require a higher dd. In *CYP3A5*3/*3* pts, a higher starting dose than that currently recommended is also advisable to avoid infratherapeutic TL that increases the risk of acute rejection.

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BO191 IMPACT OF DONOR AND RECIPIENT CYP3A5, CYP3A4 AND ABCB1 POLYMORPHISMS ON TACROLIMUS PHARMACOKINETICS AND CLINICAL OUTCOME IN LIVER TRANSPLANT RECIPIENTS

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Background: Single nucleotide polymorphisms (SNPs) of the CYP3A subgroup and ABCB1 (encodes P-gp) are known influence Tacrolimus pharmacokinetics in renal transplant patients. As CYP3A is expressed predominantly in liver tissue, it is possible that donor rather than recipient genotype plays a more significant role in Tac pharmacokinetics of liver transplantation.
Methods: One hundred and twenty-one patients transplanted between 2007 and 2012 were included in the study. Donor and recipient DNA samples were genotyped for SNPs of ABCB1 exon 26 (3435C > T), CYP3A5 (6986A > G) and CYP3A4 intron 6 (CYP3A4*22) using a Taqman® drug metabolism genotyping assay and a real time PCR technique. Tac dose/trough levels were evaluated at 11 time points in the first month and at 3, 6 and 12 months post-transplant and correlated with clinical outcome data (acute rejection episodes, survival, incidence of adverse or side-effects).
Results: Patients receiving a liver from a heterozygote CYP3A5*3/*1 (GA) donor required significantly higher doses of tacrolimus and had a significantly reduced concentration/dose ratio (0.771 vs. 2.10) throughout the first year of follow-up (Mann–Whitney *U*-test, $p < 0.01$). Donor CYP3A5*3/*1 expression also increased the time to reaching therapeutic concentration (8.04 days *3/*1 vs. 5.26 days *3/*3, Mann–Whitney *U*-test, $p = 0.02$). There was a significantly higher incidence of biopsy proven acute rejection in patients receiving a liver from a donor with CYP3A5 *3/*1 genotype (50%, $n = 14$) compared with *3/*3 genotype (19.6%, $n = 102$), Chi-squared, $p = 0.0001$. None of recipient polymorphisms nor the donor ABCB1 or CYP3A4*22 affected tacrolimus pharmacokinetics or the clinical outcome.
Conclusion: Donor rather than recipient expression of the *1 (A) allele of CYP3A5 reduces tacrolimus exposure. The recipients of these livers have a lower concentration/dose ratio of tacrolimus and take a longer time to achieve therapeutic levels. This translates into an increased incidence of acute rejection.

BO192 ADHERENCE EVALUATION, EFFICACY AND SAFETY POST-CONVERSION FROM TWICE- TO ONCE-DAILY TACROLIMUS IN STABLE LIVER RECIPIENTS: THREE YEARS FOLLOW UP

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Background: Non-adherence to post-transplant immunosuppression in liver transplant (LT) recipients has been identified as a important cause of rejection and death.
Methods: Conversion from twice-daily to once-daily tacrolimus was instituted on 84 patients (median age, 54 [19–74] years), receiving Tacrolimus BID from at least 6 months (range 6–232), in mono or double therapy, who had a LT at least 6 months before. The conversion was prescribed 1:1. Follow-up was at least 36 months. A questionnaire was submitted to all the patients to value their adherence before and after conversion. ALT, AST, creatinine, glycemia, lipid pattern and Tacrolimus level were recorded the conversion-day and 1, 3, 6, 12, 24 and 36 months afterward.
Results: Ninety-one percent of them declared an improvement in terms of quality of life after conversion. Mean Tacrolimus levels were decreased at 1 month after conversion, if compared to baseline, in 76% ($p < 0.0003$). Non-inferiority of tacrolimus QD against BID was demonstrated with a relative difference in AST, ALT, creatinine, glycemia and lipids pattern at 1, 3, 6, 12, 24 and 36 months controls. Glycemia levels were statistically lower 36 months after conversion ($p < 0.05$).
Discussion: A drug conversion 1:1 from a twice-daily to a once daily prolonged release drug improves patients' quality of life and reveals its safety for liver and kidney function. The initial decrease in tacrolimus levels do not affect graft and patient survival.

BO193 PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) OF EC-MPS IN KIDNEY TRANSPLANT RECIPIENTS (KTR) CO-TREATED WITH TACROLIMUS IN THE EARLY POSTOPERATIVE PHASE

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We investigated EC-MPS under co-therapy with tacrolimus (tac) in a group of KTR in the first month after transplantation (Tx) and related to clinical events.

Twenty-seven patients (seven females), median age 59 year (range 43–64) were given EC-MPS in a dose of 2 × 720 mg/day. Blood samples were drawn at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h after the morning dose on day 9. Plasma concentrations of mycophenolic acid (MPA), its glucuronide metabolites (MPAG and AcMPAG) and free MPA as well as inosine monophosphate dehydrogenase (IMPDH) activity in mononuclear cells were determined using validated HPLC methods. Glomerular filtration rate was calculated according to MDRD2. All patients received steroids.

The median (95% CI) MPA-AUC (mg*h/l) was 48.4 (40.2–54.4). C0 (mg/l) was 2.63 (2.00–3.21). MPA-Cmax (9.88 mg/l; 7.72–13.2) was at 2 h (1.5–3.0). The median free MPA fraction was 1.35% (95% CI: 1.04–1.48). Multiple regression analysis revealed serum albumin, creatinine and AcMPAG-AUC as independent variables related to fMPA. A significant negative correlation was observed between IMPDH activity at T2 after dosing, but not at T0, and the respective MPA and AcMPAG concentrations. Although the median MPA-AUC (25.6 vs. 48.5 mg*h/l) was lower and the respective 2 h-IMPDH activity higher (7.65 vs. 5.43 nmol/gProt*h) in rejecting patients ($n = 5$), these differences were not significant. MPA-, MPAG- and AcMPAG-AUC were not different between KTR with and without diarrhea ($n = 10$). However, the median AcMPAG-AUC was higher (13.3 vs. 4.9 mg*h/l; $p < 0.05$) in KTR ($n = 3$) with GI affctions.

In contrast to protocols using standard-dose cyclosporine co-therapy, almost all KTR achieved the recommended therapeutic range for MPA-AUC under EC-MPS and tacrolimus.

BO194 CORRELATION BETWEEN CMIN AND AUC FOR NOVEL ONCE-DAILY EXTENDED-RELEASE TACROLIMUS TABLETS LCP-TACRO

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Background: Therapeutic drug monitoring (TDM) of tacrolimus blood levels is required for transplant patients; in clinical practice, trough levels prior to AM dose are generally monitored. A novel extended-release once-daily tacrolimus tablet formulation with controlled agglomeration MeltDose technology has been developed (LCP-Tacro; LCPT). The Cmin and AUC correlation for kidney transplant recipients (KTRs) on LCPT versus twice-daily TAC was examined.
Methods: In a phase 2 study; adult stable KTRs on twice-daily TAC were converted to LCPT once-daily. Patients continued on LCPT for days 8–21; trough levels were to be maintained between 5 and 15 ng/ml; 24-h pharmacokinetic assessments were done on days 7 (baseline pre-switch), 14, and 21.
Results: Forty-seven patients completed LCPT dosing per protocol. Trough levels were stable through the study periods and within the 5–15 ng/ml range. The Cmin and AUC24 correlations were: Day 7 (twice-daily TAC) 0.79 ($p < 0.0001$); Day 14 (LCPT): 0.91 ($p < 0.0001$); Day 21 (LCPT): 0.86 ($p < 0.0001$).
Conclusion: The robust correlation between AUC24 and Cmin with LCPT suggests that current practice of TDM of Cmin as a measure of tacrolimus exposure can also be applied to LCPT.

BO195 TORQUETENOVIRUS VIREMIA KINETICS AS A NOVEL MARKER OF FUNCTIONAL IMMUNE DEFICIENCY IN SOLID ORGAN TRANSPLANTATION

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Torquetenovirus (TTV), longly considered an orphan hepatotropic virus, has been reconsidered in the last decade as a lymphotropic virus. Since viremia is almost universally acquired very early in age, it is an ideal marker for case-control functional studies. It has been reported that patients with immune deficiencies of various etiologies (HIV or other chronic infections, autoimmune diseases, and cancers) have very high viremias, suggesting break of immunosurveillance. In patients undergoing high-dose chemotherapy supported by autologous hematopoietic stem cell transplantation, our group has shown that kinetics of come-back to normal viremia parallel functional immunological reconstitution, assessed as percentage of "senescent" CD57 + T lymphocytes. In this study peripheral blood samples of 46 liver recipients, 90 kidney recipients (40 from deceased donors and 50 from living donors), 19 simultaneous pancreas-kidney recipients and eight pancreas transplant recipients (three primary and five after a previous kidney transplant) were tested for TTV viremia by quantitative real-time PCR before transplant and then at month +1, +3, +6, +12, and +24. Medical history about baseline disease and type of induction and maintenance immunosuppression were collected. We found that, across all solid organ transplant types, TTV viremia levels are related to the type of induction immunosuppression administered (ATG versus basiliximab), and correlate with the number of cell-mediated

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rejection episodes. Furthermore, at the same pharmacological dose of immunesuppressant, TTV viremia varies among recipients, suggesting that its value could be a quick and useful guide for dose intensity.

BO196 IFN-, IL-17 AND IL-2 AS PREDICTIVE BIOMARKERS OF ACUTE REJECTION IN LIVER AND KIDNEY TRANSPLANTATION: RESULTS OF A MULTICENTER STUDY

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Background: Acute rejection (AR) remains a major challenge in solid organ transplantation, and there is a critical need for predictive biomarkers.
Aims: To examine retrospectively intracellular IFNƒ×, IL17 and IL2 and soluble IFNƒ× and IL17 in liver and kidney transplant recipients from 4 institutions and correlated our findings with risk of AR in these patients; and to construct risk prediction models for AR based on a composite panel of biomarkers.
Methods: One hundred and forty-two transplant patients (63 liver & 79 kidney) were included in the study. Intracellular expression (flow cytometry) and soluble production (ELISA) of IFNƒ×, IL17 and IL2 were evaluated both pre- and at 1, 2 weeks and 1 month post-transplantation. All participating centers used identical standard operating procedures.
Results: Twenty-eight of whom (14 liver and 14 kidney) experienced AR. Pre & post-transplantation intracellular expression of %CD4 + CD69 + IFNƒ×+, % CD8 + CD69 + IFNƒ×+ and %CD8 + CD69 + IL2 + identified liver and kidney transplant patients at high risk of AR. Pre-transplantation soluble IL17 identified liver patients at high risk, while post-transplantation soluble IFNƒ× and IL17 identified both liver and kidney patients at high risk. The degree of inhibition of %CD4 + CD69 + IFNƒ×ƒyƒn, %CD8 + CD69 + IFNƒ×ƒy, % CD8 + CD69 + IL2ƒy, as well as of soluble IL17 and IFNƒ×, during the first week after transplantation as compared to their baseline levels could be useful in identifying high susceptibility to immunosuppressive treatment.
Conclusion: This multicenter study demonstrates that the pre- & post-transplantation analysis of intracellular%CD4 + CD69 + IFNƒ×+,% CD8 + CD69 + IFNƒ×+ and%CD8 + CD69 + IL2 + and of soluble IFNƒ× and IL17 can help identify liver and kidney transplant recipients at high risk of AR. Moreover, we have constructed pre- and post-transplantation risk prediction models, which can provide the basis for future prospective studies and will be a useful clinical tool for the selection and adjustment of immunosuppressive treatments.

BO197 IMPACT OF DONOR AGE ON 3-YEAR OUTCOMES OF EXTENDED CRITERIA DONOR KIDNEY RECIPIENTS IN BENEFIT-EXT

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Background: Belatacept was associated with improved renal function and similar patient/graft survival and acute rejection (AR) rates versus cyclosporine (CsA) in BENEFIT-EXT. This posthoc analysis examined these outcomes at 3 years by donor age with the approved less intensive (LI) belatacept regimen versus CsA.
Results: Mean recipient age generally increased with donor age. Patient/graft survival and mean glomerular filtration rate (GFR) decreased with increasing donor age (Table). Patients receiving kidneys from younger donors tended to have better outcomes with LI versus CsA. Recipients of kidneys from elderly donors (>65–<70 and ≥70) tended to have more AR, especially with LI. The proportion of patients with serious adverse events and serious infections were comparable between LI and CsA.
Conclusions: Outcomes were better in recipients from younger donors regardless of treatment group. Belatacept patients with lower aged donors had the best outcomes. Safety for belatacept LI was comparable across donor age groups. Despite limited sample sizes, this posthoc analysis suggests that renal function is improved with belatacept LI regardless of donor age.

BO198 5-YEAR OUTCOMES BY DONOR TYPE FROM THE LONG-TERM EXTENSION OF THE BELATACEPT BENEFIT-EXT STUDY

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Background: We report 5 year long-term extension (LTE) BENEFIT-EXT results by donor type (UNOS extended-criteria deceased donor [ECD]), anticipated cold ischemia time [CIT] ≥24 h, donor with cardiac death [DCD]) in patients randomized to less intensive (LI) belatacept (approved regimen) or cyclosporine (CsA).
Results: 204, 97 and 30 patients receiving ECD, CIT ≥24 h, or DCD kidneys, respectively, entered the LTE. Few deaths or graft losses occurred; cGFR improvements with belatacept versus CsA were maintained across subgroups (Table). 1 LI patient (ECD) had AR during the LTE. Serious adverse events and infection rates in subgroups from randomization through year 5 were consistent with the overall LTE cohort. 4 post-transplant lymphoproliferative disorder cases were reported in the LTE: 3 in LI (2 in CIT ≥24 h [1 EBV−, 1 EBV+], 1 in unknown type [EBV-]) and 1 in CsA (ECD [EBV+]).
Conclusions: Patient/graft survival in belatacept donor subgroups (ECD, CIT≥24 h, DCD) at 5 years post-transplant were consistent with those in the overall LTE cohort. Renal function benefit of belatacept was maintained across the 3 donor types over 5 years.

BO199 IMPROVING OR MAINTAINING RENAL FUNCTION WITH BELATACEPT: 5-YEAR BENEFIT LONG-TERM EXTENSION RESULTS

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Background: BENEFIT randomized living or standard criteria donor kidney recipients to more or less intensive (LI) belatacept regimens or cyclosporine (CsA). Patients completing 3 years could enter the long-term extension (LTE). We report shifts in cGFR stage (KDOQI CKD classification) from month 12 and 60 in 139/165 LI (approved regimen) and 102/136 CsA patients with cGFR data at both time points. cGFR was imputed as 0 for death or graft loss.
Results: From months 12–60, 79% (15/19) LI and 67% (2/3) CsA patients maintained GFR stage 1. In Stage 2 patients at month 12, 91% (77/85) LI and 49% (21/43) CsA maintained or improved their GFR at month 60. In Stage 3 patients, GFR stage was maintained or improved in 94% (33/35) LI and 77% (40/52) CsA at month 60. No LI patients were Stage 4 at month 12; all Stage 4 CsA patients (4/4) at month 12 maintained or improved GFR (0 Stage 5 patients).
Conclusions: In the BENEFIT LTE, a higher percentage of belatacept patients were in Stages 1 and 2, whereas a higher percentage of CsA patients were in Stage 3 at year 5. Belatacept patients were more likely than CsA patients to maintain or improve renal function over 5 years.

BO200 THE UPPSALA EXPERIENCE OF SWITCHING FROM CNI:S TO BELATACEPT AFTER KIDNEY TRANSPLANTATION

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Background: Alternatives to calcineurininhibitors (CNI:s) as immunosuppression after kidney transplantation has been needed for a long time. The new

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immunosuppressant Belatacept, a costimulation blocking agent, has now been approved for immunosuppression together with induction with Basiliximab and prednisolone and Mycophenolatemofetil (MMF). There is this far, scarce experience of switching from CNI.s to Belatacept.

Methods/Material: In total 11 patients have been switched to Belatacept in Uppsala during the last year. The indication was severe neurological side effects on CNI:s (3), aim to circumvent nephrotoxicity in poor graft quality (2), recurrence of vasculitis (1), recurrence of light-chain disease (1). The remaining four patients were primarily started on Belatacept due to hemolytic uremic syndrome (HUS) (2), delayed graft function (DGF) (1).

Results: All patients have tolerated the agent well. The distribution at out patient clinics has been easy and smooth. One of the patients have experienced two rejection episodes and one has acquired a primary cytomegalovirus (CMV)-infection. No patient nor graft losses have been noted and creatinine levels remain stable. The two patients with neurological side effects have recovered completely from palsy and depression, respectively. No relapses in HUS or vasculitis has been noted, however, the patient with light chain disease remain affected.

Conclusion: Our experience, however on a restricted number of patients, is that switching to Belatacept from CNI:s can be done easily and safe. Selected patients can benefit immensely by switching or to be started on Belatacept.

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OS19-KIDNEY VI

O173 IDENTIFICATION OF EXPANDED CRITERIA DONOR KIDNEY GRAFTS AT LOWER RISK OF DELAYED GRAFT FUNCTION

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Organ shortage leads to the increased use ECD kidneys, which contribute to a higher risk of DGF after transplantation. The aim was to determine factors that may better predict the risk of DGF. Histological assessments of donor renal biopsy were used with other clinical variables to predict the risk of DGF after kidney transplantation. In total, 126/344 patients developed DGF after kidney transplantation. The histological score for CI, CT, and CV and the total Banff score were increased in patients with DGF. Only CI and CV were independent predictors of DGF ($p < 0.01$). A CIV score (CI+CV) (OR 2.68, 95% CI 1.55–4.66, $p < 0.001$) was superior to the combination of the total Banff score (OR 1.48, 95% CI 0.85–2.55, p = NS). A CIV score ≥1, a donor age >51, and anoxia donor brain injury were associated with the highest risk of DGF. A CIV <1 identified a subgroup of ECD donors at a lower risk of DGF, comparable to standard criteria donors (29.3% vs. 28.4%). Composite CIV score better identifies ECD kidneys with a lower risk of developing DGF. Morphological evaluation of ECD donor kidneys and donor characteristics may improve kidney allocation.

O174 ASSOCIATION BETWEEN AGE AND MORTALITY POST KIDNEY TRANSPLANTATION IN THE CONTEMPORARY ERA – A POPULATION-BASED COHORT ANALYSIS

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Background: In the current era of immunosuppression data regarding an association between age and mortality is lacking. The aim of this study was to assess the impact of increasing age of kidney transplant recipients with short- and medium-term mortality risk across England over the last decade.
Methods: We examined data from Hospital Episode Statistics (HES) to select all kidney transplant procedures performed in England between April 2001 and March 2012. Patient demographics extracted included age, gender, donor type (living or deceased), ethnicity, transplant year, allograft failure, medical co-morbidities (e.g. diabetes, cardiovascular disease, cerebrovascular disease, cancer) and area socio-economic deprivation (Index of Multiple Deprivation [2010]). Data linkage analysis was performed with the Office for National Statistics (ONS) to identify all deaths occurring amongst this study cohort. Primary and secondary outcome measures were 1- and 5-year mortality respectively, with Cox proportional hazard models performed to identify independent factors associated with mortality ($p < 0.05$ considered significant).
Results: HES data was available for 19 688 kidney transplant procedures, although exclusions for missing data resulted in 19 103 for final analysis. Median follow up for this study cohort was 4.4 years (interquartile range 2.2–7.3 years). Age brackets for the kidney recipients were as follows; <50 (n = 11 421, 59.8%), 50–59 (n = 4195, 22.0%), 60–69 (n = 2887, 15.1%), 70–79 (n = 589, 3.1%) and over 80 (n = 11, 0.1%). Mortality risk per age group was; <50 (5.8%), 50–59 (14.2%), 60–69 (22.0%), 70–79 (31.9%) and over 80 (45.5%). In total 600 recipients were aged 70 or above and 1-year mortality in this cohort was 11.3% (n = 68) – the most common causes of death being infection (35.3%), cardiovascular disease (17.6%) and malignancy (10.3%). Medium-term mortality (over median follow up post transplantation of 4.4 years) was 32.2% (n = 193) with the majority of deaths due to infection (21.2%), cardiovascular disease (21.2%) or malignancy (20.2%). On Cox regression analysis, increasing age was the strongest predictor of both 1- and 5-year mortality post kidney transplantation independent of all other demographic/medical data factored into the proportional hazards model.
Conclusion: Increasing age remains a strong and independent risk factor for mortality post kidney transplantation. Potential elderly kidney allograft recipients should be counselled and risk stratified appropriately. Clinical trials regarding tailored immunosuppression in the elderly should be considered to determine the optimum regimen achieving a balance between risk and benefit.

O175 ASSOCIATION OF HLA-G GENETIC POLYMORPHISMS WITH ACUTE GRAFT REJECTION AND GRAFT SURVIVAL IN RENAL TRANSPLANTATION

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Introduction: Few markers of good outcome of kidney transplants have been demonstrated. We have shown that HLA-G, a protein belonging to the non-classical class I molecules and involved in feta-maternal tolerance is associated with a good outcome of combined liver and kidney transplants. It is associated with a reduced risk of liver and kidney rejection. HLA-G is also associated with a reduced risk of cardiac rejection. In kidney transplantation, the group P. Terazaki showed that soluble HLA-G is associated with a reduction of number and titer of anti-HLA antibodies. Several polymorphisms (SNPs) of HLA-G have been described. The purpose of this study is to determine whether certain HLA-G polymorphisms are associated with a better outcome of renal transplantation.
Materials and methods: Three hundred patients of the TRANSGENE study (declared to the CNIL in 2004) were included. Their genomic DNA was obtained and genotyped for the following SNPs were performed using TaqMan allelic discrimination assay: HLA −725 C> G (rs), HLA 3142 G> C (rs1063320) and deletion/insertion 14 bp. IL10 polymorphism previously described by the group G. Opelz being associated with a good evolution of second transplant was performed: SNP IL10-592C> A (rs1800872) and IL10 −1082 A> G (rs1800896).
Results: In the Caucasian population, the occurrence of acute rejection (RA) was higher in carriers of the −14 bp allele versus those with +14 bp allele (42% vs. 32%, p = 0.02), those with HLA 3142C vs. 3142G (43% vs. 34%, p = 0.04), or HLA-725G vs. HLA-725C (51% vs. 37%, respectively p = 0.07). No association was found for IL10 polymorphism. Only the −725 C allele HLA is associated with better graft survival (HR: 0.30, 95% CI: 0.13–0.69, p = 0.005).
Conclusion: In our Caucasian population, polymorphisms of HLA-G (-725C, 3142C, and Ins/del 14 bp) are associated with a lower incidence of RA and polymorphism-725C has a better outcome of the renal transplantation.

O176 KIDNEY TRANSPLANTATION OF DONORS ≤3 MONTHS: THE ZURICH EXPERIENCE

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Objective: A promising way to enlarge the donor pool is by using infant grafts for adults if matching pediatric recipients are missing. Despite common belief, these grafts are not of inferior quality. Case series suggest an even superior survival and graft function compared to adult grafts. However, when dealing with this special donor- population the particular challenge is to overcome technical hurdles.
Methods: A 22 year old male, a 27 and a 29 year old female underwent pediatric kidney transplantation. Donors were 3, 3 and 2½ month old infants, all weighing 5 kg. Lacking matching pediatric recipients, the kidneys were allocated to adults weighing 48, 56, and 67 kg. All kidneys were transplanted en bloc in an upside down fashion (Figure 1 and 2). Vascular anastomoses were performed with caval and aortic conduits end-to-side to the external iliac vein and artery, respectively. Ureteric reconstruction was carried out with a bladder patch with two separate ureteric stents to avoid kinking due to small ureter diameters. Immunosuppression consisted of a triple therapy including tacrolimus, prednisone, mycophenolat mofetil, and induction therapy with basiliximab.
Results: The first patient had a completely uneventful postoperative course. The graft proved immediate function with constantly decreasing serum creatinine. Hospitalization time was 12 days. After 6 weeks the ureteric stents were removed cystoscopically. The endoscopic view showed an unimpaired perfusion of the bladder patch. Six months post-transplant the patient is in good health with normal serum creatinine and no proteinuria. Within the first 3 months the interpole-distance of the graft doubled from 3 to 7 and 8 cm, respectively. Patient 2 also had an uneventful postoperative course without delayed graft function. Patient 3 needed dialysis in the first week.
Conclusion: To our knowledge, transplantation of kidney grafts below 3 month of age has not been reported yet. Using this new technique, we show excellent 6 month graft survival with normal retention parameters, no surgical complications, no rejection, and no hyperfiltration for the first patient. Six month-data is pending for the two other patients and will be presented at the meeting. In selected cases pediatric kidney grafts, even to a bodyweight of 5 kg, may be a valuable source to extend the donor pool.

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O177 OUTCOMES OF RENAL TRANPLANTATION IN THE ELDERLY

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Background: The mean age of renal transplant recipients is rising, with age in itself no longer considered a contraindication to transplantation. Outcomes in patients at the extremes of age have not, however, been clearly defined.
Methods: All renal transplants performed at a renal transplant unit from January 2001 to December 2010 were analysed ($n = 762$).Outcomes following renal transplantation in older people (over 65 years old) were compared to those in patients under 65 years old. Outcome measures were: delayed graft function (DGF), primary non-function (PNF), biopsy proven acute rejection (BPAR), serum creatinine at 1 year and graft and recipient survival. Length of initial hospital stay and re-admission rates were also assessed. Student's T-Test was used to analyse continuous variables, Pearson's Chi-Squared test for categorical variables and the Kaplan-Meier estimator for survival analysis.
Results: Older recipients received proportionately more kidneys from older donors (27.1% vs. 6.3%; $p < 0.001$). Such kidneys were more likely to have DGF (40.7% vs. 16.9%; $p < 0.001$). Graft loss at 1 year was higher in patients who received kidneys from older donors (15.3% vs. 7.6%; $p = 0.04$). There was no significant difference in overall patient survival at 1 year. Recipient age did not significantly affect DGF (16.9% vs. 18.5%; $p = 0.77$) or graft loss at 1 year (11.9% vs. 7.8%; $p = 0.28$). Older recipients were, however, more likely to die in the first year post transplant (6.8% vs. 2.1%; $p = 0.03$). BPAR was less common in older patients (6.8% vs. 22%; $p < 0.01$). Older recipients were more likely to be readmitted to hospital (31.8% vs. 10.9%; $p < 0.001$).
Conclusions: Whilst kidneys from older donors were associated with DGF and earlier graft loss, older recipients were less likely to have BPAR and there was no association between older recipients and DGF or graft loss at 1 year. Older recipients were associated with higher readmission rates and death in the first year after transplant. These factors have implications for planning renal transplantation and service provision amongst and aging population.

O178 KIDNEY TRANSPLANTATION IN ELDERLY PATIENTS: A PAIRED-KIDNEY ANALYSIS

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Background: The elderly are the fastest growing population among dialysis patients and also on waiting lists for kidney transplantation. Through a donor-paired kidney analysis that cancels out the role of donor factors, we aim to evaluate the results of the renal transplantation in recipients elder than 60 years.
Methods/Materials: We performed a retrospective cohort study using our center database of kidney graft recipients from 1983 to 2010. We identified 473 pairs of adult kidney-only transplants that were procured from the same adult donor, and selected for analysis those that were discordant to recipient age $\geq$ or $<$60 years (i.e., one recipient with age $\geq$ 60 and the other with age $<$ 60 years; $n = 44$ pairs). We performed a comparative analysis (between recipient age groups) of baseline characteristics, kidney graft perioperative data and postengraftment events. Graft and recipient survival was analyzed by the Kaplan–Meier method and compared through the log-rank test. Risk factors for graft failure were explored through a Cox regression model (recipient age group, number of HLA mismatches 3–6, delayed graft function, acute rejection, dialysis vintage $>$36 months, ATG induction use).
Results: Donors ($n = 44$) had a mean age of 46.4 $\pm$ 16.6 (18–71) years, a mean creatinine at death of 0.92 mg/dl and 63.6% were males. Between group comparisions: A trend for an association between elder recipient age group and better death-censured graft survival was detected (85% and 68% when recipient age was $<$60 years, 93% and 93% when recipient age was $\geq$60 years; at 5 and 10-years follow-up; log-rank $p = 0.062$). This trend was annulled when overall graft survival was analyzed (77% and 62% when recipient age was $<$60 years, 88% and 78% when recipient age was $\geq$60 years; at 5 and 10-years follow-up; log-rank $p = 0.289$). Censured graft failure was independently predicted by three or more HLA mismatches (ref. 0–2; HR = 5.32, $p = 0.048$), acute rejection (HR = 30.32, $p < 0.001$), more than 3 years dialysis vintage (reference 0–3 years: HR = 4.47; $p = 0.037$) and recipient age group $<$60y (HR = 4.74; $p = 0.043$). Overall graft failure was independently predicted by acute rejection (HR = 21.08, $p < 0.001$) and more than 3 years dialysis vintage (reference 0–3 years: HR = 4.75; $p = 0.006$).
Conclusion: Our single-center results show that immunological-mediated factors played a role in worse renal outcomes. Notwithstanding, this effect was particularly noticeable in younger recipients censured graft survival. Hence, renal transplantation was a good option of renal replacement therapy in patients over 60 years old, with an overall kidney graft outcome similar to their younger paired recipient, and possibly associated with a reduced immunological risk.

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OS20-KIDNEY VII

O179 ASSOCIATIONS BETWEEN CLINICAL, BIOCHEMICAL INDICATORS AND ANTHROPOMETRIC MEASUREMENTS WITH ARTERIAL STIFFNESS IN RENAL TRANSPLANTATION PATIENTS

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Baskent University Medical School

Background: Although renal transplantation improves survival, cardiovascular morbidity and mortality still remain as a significant problem. The aim of this study is to evaluate the risk factors for arterial stiffness in kidney transplant recipients.
Methods: One hundred and forty-five kidney transplant recipients were evaluated for clinical and biochemical parameters. Pulse wave velocity (PWv) was determined from carotid and femoral arteries.
Results: Carotid-femoral PWv was significantly related with age (p:0.001; r:0.312), systolic (p:0.039; r:0.336) and diastolic blood pressure (p:0.007; r:0.246), uric acid (p:0.0001; r:0.348), hemoglobin (p:0.02; r:0.203), pre-transplant serum total cholesterol (r:0.266, p:0.01) and LDL-C (r: 0.303, p: 0.02) levels. The frequency of patients with PWv > 7 m/s was higher in patients with hypertension (SBP > 140 mmHg), age >50 years, male gender, hyperurisemia, Hb level > 12 g/dl ($p < 0.05$). Pre-transplant hyperlipidemia predicts higher PWv levels in post-transplant period (OR: 2.5, CI:1.1–5.7). PWv was significantly associated with waist circumference and sagittal abdominal diameter (p:0.048; r:0.188, p:0.041; r:0.288).
Conclusions: Pretransplant hyperlipidemia predicts arterial stiffness in post-transplant period. For cardiovascular risk reduction after renal transplantation; blood pressure, serum glucose and uric acid levels should be under strict control.

O180 TRANSPLANT RENAL ARTERIAL INFLOW STENOSIS DEFINED BY CONTRAST ENHANCED MR ANGIOGRAPHY IN EARLY PERIOD AFTER RENAL TRANSPLANTATION

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Background: Our objective was to evaluate the usefulness of three-dimensional contrast enhanced MR angiography (3D CE MRA) for assessment of renal artery anastomosis in the early period after kidney transplantation.
Methods: Between January 2010 and February 2012, a consecutive series of 267 KTs was examined with 3D CE MRA 14 days after transplantation. The study recipients were divided into four groups by the degree of renal artery inflow stenosis qualitatively (group I: "normal"; group II: "mild = <50%"; group III: "moderate = 50–70%"; group IV: "severe >70%"). The following variables were compared: donor and recipient characteristics, multiplicity of renal arteries, the type of the arterial anastomosis [end-to-end anastomosed to IIA or end-to-side anastomosed to EIA], post-operative renal function (mean creatinine levels at 14 days, 1 and 6 months, and 1 year), and graft survival.
Results: Two hundred and sixteen (80.9%) of the 267 patients had normal 3D CE MRA, 29 (10.9%) showed mild, 8 (3.0%) was moderate, and 14 patients (5.2%) had severe stenosis of renal inflow. Eleven patients of severe arterial stenosis on CE MRA underwent selective digital subtraction angiography (DSA). In 10 patients, angioplasty or stenting was performed. The mean creatinine value at 14 days post-transplant (1.27¡¾ 0.48, 1.21¡¾0.48, 1.04¡¾0.32, 1.20¡¾ 0.27, respectively) did not significantly different among the four groups ($p = 0.495$). The prevalence of graft loss ($n = 2$, 14.3%) was high in patients with severe arterial stenosis, but there was no significant differences in these groups ($p = 0.118$). In group IV, multiplicity of renal arteries ($n = 8$, 57.1%) and the type of end-to-end arterial anastomosis ($n = 12$, 85.7%) were much higher frequency ($p = 0.026$, $p = 0.362$, respectively) than other groups.
Conclusion: The incidence of arterial flow stenosis is unexpectedly high in the early period after kidney transplantation even if creatinine level was normal. So, 3D CE MRA allows rapid global assessment of renal transplant arterial system.

O181 THROMBOPHILIA AND PRIORITIZATION DUE TO DIALYSIS ACCESS FAILURE IMPACT EARLY ON PATIENT SURVIVAL AFTER KIDNEY TRANSPLANTATION

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Dialysis vascular access failure, recipient of a non-renal solid organ transplantation and previous kidney donation are current indications of priority allocation (PA) for kidney transplant (KT) at our centre. We analyzed a cohort of patients that received KT from Jan/2007 to Dec/2011. Long-term patient survival was compared between PA and non PA recipients transplanted in this period of time and clinical relevant data were analyzed.
Results: Nine hundred and forty-eight KT were performed at our institution and 93 (9.8%) were included in our PA program. Most PA patients ($n = 86$) had access failure. Mean follow up time was 32 (0 – 69) months. Five-year patient survival was lower in PA patients (76% vs. 86%, $p = 0.001$). Twenty (21.5%) PA patients died, being 70% of them in the first 3 months. Final causes of death: infection (10 patients), bleeding ($n = 6$), uremia ($n = 1$), mesenteric ischemia ($n = 1$) and unspecified shock ($n = 2$). Because of this high mortality rate we compared patients who died in the first 3 months (group A) versus those who survived (group B). Age, gender, previous kidney transplants, sensitization, pre-transplant DSA, pre-transplant diabetes, induction therapy, DGF, rejection, use of heparin and time from inscription in the PA program to transplantation were not statistically different between groups. Among 47 patients who were screened for thrombophilia, 83.3% from group A were positive vs. 31.7% from group B ($p = 0.01$). Infection after transplantation and hemorrhagic complications were more frequent in group A. Groups were not different regarding causes of death. Multivariate Cox proportional hazard models for patient survival showed a HR of 5.2 (95% CI, 1.02–26.74, $p = 0.047$) for thrombophilia.
Conclusion: PA patients have a lower survival and this excessive death rate occurs in the first three months after transplantation. Thrombophilia is very frequent in PA patients with HR 5.2 for death.

O182 SEVERITY OF CORONARY DISEASE, CARDIAC EVENTS AND MORTALITY IN PATIENTS EVALUATED FOR RENAL TRANSPLANTATION

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The best strategy for investigation and treatment of coronary artery disease (CAD) in renal transplant (Tx) candidates is controversial. The aim of this study was to evaluate the relationship between CAD extension and management, Tx status and both the peri-operative and mid-to-long term outcome of CKD stage 5D patients (pts) evaluated for kidney Tx, in a single centre registry. Between June 1996 and January 2009, 167 pts (mean age 53.9 ± 8.6 years-old) considered to be at high risk for CAD performed coronary angiography (CAT) as a part of Tx evaluation. The cohort was divided in three groups according to CAD extent (defined as >50% stenosis of at least one major epicardial vessel): group 1 ($n = 74$) had no significant stenosis, group 2 ($n = 49$) had one vessel disease and group 3 ($n = 44$) had two/three vessel or left main disease. Fifty-eight pts were transplanted during the observation period (mean of 37.7 ± 23 months after CAT): 35 in group 1, 11 in group 2 and 12 in group 3. Increasing CAD severity was independently associated with a 38% decrease in the likelihood of receiving a graft (HR 0.62; 95% CI 0.43–0.91; $p = 0.013$). Despite overall event-free survival was higher in Tx recipients, cardiovascular (CV) events and mortality consistently increased with increasing severity of CAD in both transplanted and non-transplanted pts. Performance of percutaneous coronary intervention (PCI) was not associated with lower event rates. After correction for baseline characteristics and for the probability of receiving a graft, both CAD extension (HR 2.6; 95% CI 1.5–4.6) and Tx-status (HR 0.28; 95% CI 0.13–0.61) were the only independent predictors of death/CV events. CAD extent is a powerful predictor of event free-survival in renal Tx candidates. Despite a high incidence of CV events in severe CAD pts that received a renal graft, total mortality seems to be in an acceptable range. We did not detect any significant difference in the outcome related to the pre-Tx revascularization status.

O183 BLOOD PRESSURE TREATMENT ASSOCIATED WITH LOWER MORTALITY IN KIDNEY TRANSPLANT RECIPIENTS

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Background: There are uncertainties regarding cardiovascular medication in renal transplant recipients and all-cause mortality. We assessed possible associations in a *post hoc* analysis of the ALERT trial.

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Methods: ALERT was a randomized, double-blind, placebo-controlled study to investigate the effect of fluvastatin on cardiovascular and renal outcomes in 2102 renal transplant recipients, followed by a 2-year extension. Patients were recruited at a median time of 4.5 years after transplantation with a stable renal function. We investigated the relationship between cardiovascular medication at baseline and all-cause mortality using Cox regression adjusted for demographic variables, other medication and known cardiovascular risk factors.
Results: In total, 1868 out of 2102 patients were available for analysis. During a median follow-up of 7.4 years, there were 334 deaths. In multivariate analysis, significantly reduced mortality was seen in relation to treatment with Calcium antagonists (HR 0.72, CI 0.56–0.92), beta blockers (HR 0.64 CI 0.51–0.81), or ACE/ARB (HR 0.58 CI 0.46–0.73).
Conclusions: Blood pressure treatment at baseline seems associated with a favourable outcome in kidney transplant recipients.

O184 IS THE SOURCE OF KIDNEY A RISK FACTOR FOR DEVELOPING TRANSPLANT RENAL ARTERY STENOSIS?

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Introduction: Transplant Renal artery stenosis (RAS) is an uncommon cause of deteriorating graft function in transplanted kidneys and often present in association with worsening hypertension. A number of factors have been implicated as risk factors for transplant renal artery stenosis including surgical technique, type of allograft, immunological factors, cold ischemia time and viral infections. There has been an increase in renal transplant from live donors in the UK as well as a significant change in the type of deceased donors. The proportion of DCD donors among deceased transplants has increased from 8% to 40%.
Aim and methods: The aim of study was to determine if the source of kidney is a risk factor for the development of renal artery stenosis.
Results: We analysed 1251 consecutive renal transplants performed in our unit between 2000 and 2012. Any patient with suspected transplant RAS underwent a Doppler ultrasound. When the Doppler also suggested RAS an angiogram was arranged +/−angioplasty/stenting. Overall 72 patients had a Doppler USS suggesting RAS and of these 52 (4% of the total) had the diagnosis confirmed on angiogram. There were 326 recipients from live donors (LD) with 10 case of transplant RAS (3.1%), 694 from Brain Stem Dead (DBD) donors with 32 cases of RAS (4.6%) and 231 from Circulatory Dead (DCD) donors with 10 cases of RAS (4.3%). The median time from transplant to presentation for recipients of LD, DCD and DBD donor kidneys was 3, 7 and 4 months respectively. The distribution of stricture site was similar in all three donor types. All patients had angioplasty with an overall radiological success of over 96%. There were four recurrent stenoses in three patients, all in recipients of DBD kidneys.
Conclusion: Our data show a slightly lower incidence of transplant RAS in recipients of LD kidneys with a shorter median time to presentation. The distribution of stenosis site, success from radiological intervention and post angioplasty complications.

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OS21-IMMUNOLOGICAL ASPECTS IN LIVER TRANSPLANTATION

O185 C-REACTIVE PROTEIN INDEPENDENTLY PREDICTS SHORT-TERM MORTALITY IN LIVER TRANSPLANT PATIENTS WITH (LAB)MELD 30

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Background: As a result of increasing donor organ shortage, the MELD (model for end-stage liver disease) score at liver transplantation (LT) has dramatically increased in recent years in the Eurotransplant region and especially in Germany. Posttransplant outcome is limited in "high-MELD" patients, mainly for postoperative septical complications. The aim of this prospective trial was to evaluate the prognostic value of pretransplant C-reactive protein (CRP)-level for predicting short-term mortality in liver transplant patients with a (lab)MELD score ıY 30.
Patients and methods: A total of 35 consecutive patients with a (lab)MELD score ıY 30 at liver transplantation (LT) were included in this trial. The impact of recipient- and donor-specific variables including final pretransplant CRP-levels on posttransplant 3- and 6-months-survival/mortality were analyzed in uni- and multivariate analysis.
Results: Mean (lab)MELD at LT was 36.5 ıÅ 3.6 (range: 30–40). Three- and 6-months survival rates were 77.1% and 68.6% respectively. In univariate analysis, ıðMELD > 10, pretransplant waiting time >3 months, serum lactate-level >2.4 mM and CRP-level >5 mM were predictive for early post-LT mortality. In multivariate analysis, only CRP-level (OR 23.2) and pretransplant waiting time (OR 7.2) were identified as independent predictors of early post-LT mortality. Three and 6-months survival rates post-LT were 93% and 85.7% in patients with CRP-level ıÜ 5 mM and 14% and 0% in patients with CRP-level >5 mM (log rank < 0.001), respectively. Septical complications were the most important reasons for mortality.
Conclusion: Pretransplant CRP-levels as biological marker of systemic inflammatory response syndrome and waiting time prior LT impact significantly outcome in patients with high (lab)MELD scores and should, therefore, be incorporated in decision-making.

O186 REGULATORY T CELL-BASED CELL THERAPY FOR TOLERANCE INDUCTION IN LIVING DONOR LIVER TRANSPLANTATION

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Background: Tolerance induction is an ultimate goal in organ transplantation. Efficacy and safety of the Treg-based cell therapy were assessed in living donor liver transplantation (LDLT).
Methods: Ten adult LDLTs were enrolled consecutively. Donor-antigen specific Tregs were generated *ex-vivo* by co-culturing recipient- and irradiated-donor- PMBCs with CD80+CD86 mAbs for 2 weeks. IS were initiated with steroid+MMF+tacrolimus (TAC) or cyclosporine (CYA). Cyclophosphamide was given on POD 5, and Tregs were infused on POD 13. Steroid/MMF were stopped within a month. After 6 months, TAC (or CYA) was weaned every 2–3 months, and was finally stopped.
Results: CD25+Foxp3+ (6.7% to 28.1%) and CD127loFoxp3+ (8.2% to 26.2%) CD4+ T cells increased after co-culture. The cells inhibited MLR in a cell-number-dependent manner. All recipients maintained good liver function during IS reduction and after cessation, except for case 5 who was replaced on regular IS due to insufficient Treg generation. No adverse event was noted.
Conclusion: Cell therapy by *ex-vivo* generated Tregs allowed early reduction of IS in nine cases and complete withdrawal in four cases after LDLT.

O187 CIRRHOSIS LIKE APPEARANCE OF THE LIVER WITH P.LEU75PRO APO A-I AMYLOIDOSIS

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Hereditary amyloidosis is often treated by liver transplantation, with the intent to eliminate the main source for the amyloidogenic protein. The lack of hepatic involvement allows to donate the explant liver to another patient in a domino fashion. Most cases are associated with mutations of the transthyretin gene. However several patients with amyloidosis associated with the ApoA1-gene have been reported to have hepatic involvement. With all cases reported so far hepatic involvement was evident by histological analysis or laboratory markers only, with an unremarkable macroscopic picture. Here we present a case of a patient with p.Leu75Pro ApoA-I amyloidosis who underwent combined liver-kidney transplantation for advanced amyloidosis associated chronic kidney dieases and to slow down progression of polyneuropathy. The preoperative clinical picture and laboratory markers did not implicate any hepatic dysfunction. On macroscopic inspection however, with 2130 g the liver was enlarged, with a grossly nodular surface and firm parenchyma. Histologically, the liver architecture was preserved with areas of moderate to severe steatosis. Large confluent deposits of amyloid were found in a rather unique jig saw like distribution pattern, mainly in zones 2 and 3, often enclosing central veins, differing from the typical perisinusoidal deposition pattern of AL amyloidosis. Polarized light revealed the typical apple green birefringence and immunoreaction for ApoA1 was strong. Portal tracts were morphologically unremarkable, with some lymphocytic infiltrates. Electron microscopy detected extracellular fibrils typical for amyloid as well as cytoplasmic accumulation of lysosomes and concentric lamellar inclusion bodies.
Conclusion: This is the first report of an ApoA1-amyloidosis case with macroscopically evident hepatic involvement.

O188 ROLE OF HUMAN LEUKOCYTE ANTIGEN COMPATIBILITY IN GRAFT OUTCOMES FOLLOWING LIVING DONOR LIVER TRANSPLANTATION

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Purpose: The importance of human leukocyte antigen (HLA) matching in liver transplantation has been widely studied, but is still controversial. HLA matching is taken no account of liver graft allocation. The aim of this study is to analyze the influence of HLA compatibility between donor and recipient on the transplant outcomes of living donor liver transplantation (LDLT) in a large single-center.
Methods: A total of 925 consecutive recipients underwent LDLT between March 2000 and April 2011 were retrospectively analyzed. HLA typing was formerly performed by standard complement dependent cytotoxicity technique. The type and degree of HLA-A, B, DR mismatching were assessed. We also investigated the posttransplant level of liver function tests, development of rejection, and graft survival as outcome parameters.
Results: Mean number of HLA mismatching was 3.2 ¡¾ 1.3 and mean follow-up period was 61.3 ¡¾ 38.4 months. Each type and degree of HLA-A, B, DR mismatching had no effect on graft rejection, whereas the effect on graft survival was significant. Except for HLA-A, HLA-B and -DR mismatching was notably associated with graft survival. Recipients with 1 HLA-B or 0–1 HLA-DR mismatched had superior graft survival in contrast to recipients with two HLA-B or two HLA-DR mismatched, respectively. In addition, posttransplant serum bilirubin level and graft survival have been improved by the lower quantity of HLA mismatching, comparing 0–3 vs. 4–6 MM and comparing 0–4 vs. 5–6 MM.
Conclusion: This study confirmed the critical relation between HLA-B, DR mismatching and graft survival, but not rejection incidence. In addition, the degree of HLA mismatching play a great role in graft outcomes. To obtain a prolonged graft survival, the type as well as degree of HLA compatibility should be considered in the setting of LDLT providing enough time to select a favorable combination of donor and recipient.

O189 UNEXPECTED HIGH PREVALENCE OF DONOR SPECIFIC ANTIBODIES IN LIVER TRANSPLANT RECIPIENTS WITH UNEXPLAINED LIVER GRAFT ABNORMALITIES: ROLE OF ANTIBODY-MEDIATED REJECTION IN THE LONG TREM GRAFT DYSFONCTION?

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Introduction: Chronic antibody-mediated rejection (AMR) which is well-defined in kidney transplantation but much less documented after liver transplantation (LT).The aim of this study was to analyze the prevalence of donor specific antibodies (DSA) in LT recipients with unexplained liver graft dysfunction on the long term in order to investigate the role of DSA in this setting.
Patients and methods: Inclusion criteria: consecutive outpatient LT recipients diagnosed between 01and07/2012 with unexplained LFT abnormalities or unexplained liver fibrosis as assessed by Fibroscan, where tested for DSA.The liver biopsy specimens closest to blood samplings were simultaneously reviewed.Exclusion criteria:ischemic cholangiopathy, infection with HCV/HBV or HEV and patients transplanted for autoimmune hepatitis.
Results: Twenty-one patients, 15 males and six females, mean age 53 ± 13 years, were investigated 10 ± 6 years after LT. Indications for LT were:alcoholic cirrhosis (38%), PCS (33%), HCC (5%), FH (9%), HBV (5%) and others (10%). 12/21erpts (57%) had been retransplanted. Mean GGT, ALP,

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ALAT, ASAT and bilirubin values were 352, 247, 59, 69 UI/l and 87 μM, respectively.Anti HLA class I and class II antibodies were found in 85% and 100% respectively, DSA were found in 95%, anti class II in all cases, with a mean MFI of 12 476. DSA were anti DQ2 (40%), DQ7 (20%), DQ5 (15%) and DR1, DR51, DQ6, DQ9 in 5%. Liver biopsies performed in 17 out of 20 pts with DSA, suggested an arterial/ischaemic problem (not proved) in41%, inactive fibrosis in 17%, cholangitis without acute cellular rejection in23%, chronic active hepatitis in12%, biliary obstruction in 17% of the cases.
Conclusion: This study shows that anti class II DSA are very frequently found (95%) at a very high level in LT patients with unexplained liver graft dysfunction 10 years after LT.DSA were frequently associated with histological lesions suggesting biliary ischaemia or advanced fibrosis These findings highly suggest a role of AMR in late graft dysfunctions after LT.

O190 ROLE OF SIRT1 IN LIVER ISCHEMIC PRECONDITIONING

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Background: Ischemia reperfusion (I/R) injury consists an important problem in hepatic surgery and transplantation. Steatotic livers show higher vulnerability against I/R injury than normal ones, due to the altered microcirculation and the enhanced oxidative stress. Ischemic Preconditioning (PC) is the only protective surgical strategy that has been successfully applied in patients. Silent Information Regulator 1 (Sirt1) is an histone deacetylase that regulates a diverse array of cellular functions, including cellular stress response and metabolism. In this communication, we evaluated the possible implication of Sirt1 on the protective mechanisms induced by PC in steatotic livers.
Methods/Materials: Homozygous (Ob) Zucker rats aged 16 weeks were classified as follows:Group 1: Sham; Group 2: I/R:Ob rats were subjected to 60 min of partial (70%) ischemia followed by 24-h reperfusion; Group 3:PC: Hepatic inflow to the median and left lobes was occluded by a clamp for 5 min followed by a reflow for 10 min and then livers were subjected to I/R. Group 4: PC + sirtinol: as in group 3, but treated with sirtinol, a sirtuin 1 inhibitor (0.9 mg/kg intravenously) 5 min before PC. Blood and liver samples were collected after 24 h of reperfusion. Liver injury and oxidative stress prevention were correlated with Sirt1 (and its direct substract Ac-p53), AMPK, eNOS activation and HSP70 expression (determined by Western blot. Apoptosis and related parameters (Ac-p53, Caspase 9, Caspasa 3, Cytochrome C) were also measured.
Results: (i) Increased Sirt1 protein levels were associated with the beneficial effects of PC; (ii) By the contrary, SIRT1 inhibition by sirtinol well correlated with enhanced liver injury and oxidative stress; as well as inhbited e-NOS, activity and AMPK. This was accompanied by increases in liver apoptosis markers.
Conclusions: Sirt1 is involved in the protective mechanisms induced by hepatic PC mediated via eNOS and AMPK.

OS190A CORRELATES OF SUBCLINICAL NON ADHERENCE TO IMMUNOSUPPRESSION AFTER LIVER TRANSPLANTATION

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Background: Using the Integrative Model of Behavior Prediction (IMBP), this cross-sectional single center study investigated the prevalence of self-reported non adherence (NA) to immunosuppression (IS) and its correlates in adult liver transplantation (LTX).
Methods: A convenience sample of 268 adult recipients was enrolled (males 77.2%). NA over the past 4 weeks was measured by self-report and defined as any deviation from schedule. Intention to adhere, attitudes, norms and self-efficacy were assessed using validated tools.
Results: NA was reported by 32.4% of patients (87) and was predicted by barriers (OR 2.79; $p = 0.01$) and lower intention to adhere (OR 0.62; $p = 0.004$). Intention to adhere was predicted by being in favor of IS (OR 0.14; $p < 0.0001$) and higher self-efficacy (OR 1.28; $p = 0.02$).
Conclusions: NA affects one in three recipients and is associated with barriers (forgetfulness) which should be targeted in clinical practice.

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OS22-MTOR AND JAK-3 INHIBITION

O191 RAPAMYCIN INDUCES ILT3HIGHILT4HIGHDENDRITIC CELLS PROMOTING A NEW IMMUNOREGULATORY PATHWAY

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ILT3highILT4highDendritic cells (DC) may cause anergy in CD4+CD45RO+CD25+T cells converting them into regulatory-type T cells (Treg). The aim of the present study was to investigate in renal transplant recipients whether chronic exposure to rapamycin may modulate this immunoregulatory pathway. Forty renal transplant recipients on calcineurin-inhibitor (CNI)-based therapy with biopsy-proven chronic allograft nephropathy were randomly assigned to either CNI dose reduction or CNI withdrawal/rapamycin introduction. At conversion and 2 years thereafter, we evaluated the rapamycin effects on circulating DCs (BDCA1/BDCA2 and ILT3/ILT4 expression), CD4+/CD25hi/Foxp3+Tregs and CD8+/CD28-T cells as well as on ILT3/ILT4 expression and the Th1/Th2 balance in graft biopsies. In rapamycin-treated patients, peripheral BDCA2+cells were significantly increased along with ILT3/ILT4+DC. The number of circulating CD4+/CD25high/Foxp3+/CTLA4+Tregs, CD8+CD28-T cells and HLA-G serum levels were higher in the rapamycin-treated group. ILT3/ILT4+BDCA2+DCs number was directly and significantly correlated with circulating Tregs and CD8+CD28-T cells. Finally, ILT3/ILT4 expression was increased in kidney biopsies at the end of the study period along with a significant bias toward a Th2 response within the graft only in the rapamycin-treated patients. In conclusion, our data demonstrate that rapamycin induces the up-regulation of ILT3 and ILT4 on DC surface and this effect is associated with an increase in the number of Tregs and with the expansion of the CD8+CD28-T cell population. This observation would suggest that mTOR inhibition may promote a novel immunoregulatory pathway.

O192 MTOR INHIBITION AND EVOLUTION URINARY PROTEIN EXCRETION IN NON-RENAL TRANSPLANT PATIENTS

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Background: The interplay of glomerular filtration and tubular absorption of proteins with various molecular weights defines pattern/magnitude of daily urinary protein excretion (UPE). Increased UPE (proteinuria) serves as a clinical surrogate marker for renal injury and progressive damage affecting different parts of the nephron. mTOR-inhibitor treatment has also been associated with increased UPE not only in KTx but also non-renal Tx recipients.
Method: Data were retrieved from study H2304 (NCT00622869), a 24-month (M), randomized, multicenter study in 719 *de novo* LTx recipients comparing everolimus (EVR, C0 3–8 ng/ml) plus reduced tacrolimus (rTAC, C0 3–5 ng/ml) to standard TAC (sTAC-C, C0 6–10 ng/ml). The total daily UPE, measured as urinary protein-to-creatinine ratio, as well as a set of differently sized urinary proteins is described in order to allow a more detailed investigation of the origin and course of UPE in *de novo* LTx patients receiving EVR.
Results: UPE was higher with EVR+rTAC compared to sTAC with highest values at M6 (290 mg/day) followed by decreasing values at M12 and a further decrease to 194 mg/day at M24. Daily UPE maintained stable in TAC Control at 158 mg/day. UPE $\geq$ 500 mg/day occurred in 18.1% of patients in TAC-C vs. 23.6% in EVR+rTAC (18.9% when EVR C0 was in the range of 3–8 ng/ml). Analysis of urinary protein electrophoresis determining the distribution pattern of alpha1 MG (26 kDa), albumin (70 kDa), transferrin (80 kDa), and IgG (150 kDa) are shown in Fig. 1 demonstrating similar patterns for EVR and TAC.

Discussion: Clinical observations suggest that mTOR inhibition might be associated with increased UPE, potentially due to enhanced cell wall permeability and podocyte dysregulation. However, in case of mTORi facilitated CNI reduction the improvement in glomerular blood flow and consequently higher overall protein filtration in combination with mTOR-dependent reduction in tubular protein reabsorption may also contribute to increased UPE.

O193 TWELVE-MONTH OUTCOMES FROM EVIDENCE TRIAL (EVEROLIMUS ONCE-A-DAY REGIMEN WITH CYCLOSPORINE VERSUS CORTICOSTEROID ELIMINATION) IN ADULT KIDNEY TRANSPLANT RECIPIENTS

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Background: Evidence evaluates in *de novo* adult renal transplant recipients the treatment success rate of steroid-withdrawal regimen (SW) based on everolimus and cyclosporine compared to standard twice-a-day regimen (TD) and explores feasibility, efficacy and safety of once-a-day regimen (OD).
Methods: This 12-months, prospective, randomized, multicenter, open-label study assessed, between randomization (M3) and M12, the composite efficacy failure rate (CEFR: BPAR, graft loss, death or lost to follow-up) as primary endpoint and the renal function (eGFR using Nankivell formula) as secondary endpoint.
Results: Among 184 randomized (OD = 45; SW = 68; TD = 71), CEFR was 14.7% in SW compared to 2.8% in TD (HR = 5.1; 95%CI:1.089, 23.658; non-inferiority limit = 10%) and 6.7% in OD. BPAR was the major component of CEFR. Patient and graft survival were 100% at M12. The mean eGFR at 12M was 84.0 $\pm$ 12.7 ml/min in OD, 80.8 $\pm$ 12.8 ml/min in SW compared to 83.6 $\pm$ 16.3 ml/min in TD.
Conclusions: This study shows slightly superior treatment success rate and similar eGFR of standard TD compared to SW regimen. Results confirm that acute rejection tended to occur more frequently in the SW regimen, but always reversed. Of interest are the data suggesting the feasibility, efficacy and safety of OD administration.

O194 A RATIONAL APPROACH TO QUANTIFY THE MTOR TREATMENT EFFECT IN LTX RECIPIENTS

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H2304 Study Group

Background: 12M study results of study CRAD001H2304 (NCT00622869) demonstrated superior renal function and comparable efficacy, including fewer and less severe treated BPAR with everolimus (EVR) plus reduced exposure tacrolimus (rTAC) versus standard exposure TAC (sTAC) in *de novo* liver transplant recipients (LTxR). Here, evidence of TAC exposure-efficacy response relationship and contribution of EVR to efficacy are shown.
Methods: Seven hundred and nineteen *de novo* LTxR received at 1M post LTx either EVR (C0 3–8 ng/ml) + rTAC (C0 3–5 ng/ml), or EVR (C0 6–10 ng/ml) with TAC Elimination or sTAC (C0 6–10 ng/ml). Individual time courses of TAC concentration were estimated using totality of TAC PK and dose administration data using a popPK approach. The relationship between predicted TAC concentrations and event rate was quantified. From this relationship, the effect of rTAC alone is estimated and compared to the effect of EVR+rTAC to demonstrate the compensatory effect of EVR.
Results: In the sTAC arm, 11/22 BPARs occurred while predicted TAC concentration was below the 25th percentile of the distribution in patients without events, versus only three events with concentrations above the 75th percentile indicating a significant effect of predicted TAC concentration on event ($p = 0.0029$). From this relationship, the effect of tacrolimus alone can be estimated (Fig 1), and compared to the efficacy of EVR+rTAC to estimate the contribution of EVR. The corresponding HR at M3 was 5.37, 97.5% CI: [2.14, 13.50], $p < 0.001$. Consistent results were observed at both M3 and 12 for all efficacy endpoints (BPAR, tBPAR, and tBPAR/GL/D).
Conclusion: The presented data indicate that EVR at through concentrations of 3–8 ng/ml contributes a relevant effect to significant better efficacy with EVR+Reduced TAC over TAC Control in LTx recipients.

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Figure 1: Probability of BPAR event with EVR+Reduced TAC versus TAC Control.

O195 LONG-TERM THERAPY WITH EVEROLIMUS IN HEART TRANSPLANT RECIPIENTS: 2-YEARS RESULTS OF THE CERTIC REGISTRY

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Everolimus (EVR) mechanism of action provides a rationale to prevent several heart transplant (HT)-related comorbidities. To collect prospective data on the outcome of long-term use of EVR, we designed the CERTIC 5-year prospective registry. Four hundred and one HT recipients (24% *de novo*) were enrolled. Three hundred and six (76%) patients started EVR 8 $\pm$ 5 years after HT, following renal dysfunction (57%), allograft vasculopathy (21%), or malignancies (13%). Including the period of EVR treatment before study entry, patients had been on EVR for 4 $\pm$ 1 years. Low number of fatal events have been recorded, with a 1.6% yearly death rate in *de novo* and 3.1% in maintenance patients. Nine patients developed malignancies (yearly rate 2%), accounting for eight solid organ and 10 skin cancers. No PTLDs and Kaposi's sarcoma were recorded. Renal function was overall stable during the study (from 66 $\pm$ 45 to 70 $\pm$ 43 ml/min/1.73 m^2 in *de novo* group, and from 56 $\pm$ 42 to 56 37 ml/min/1.73 m^2 in conversion group). By picturing real-life clinical practice, this large prospective registry shows good survival and promising long-term outcome with EVR therapy.

O196 EFFECT OF TOFACITINIB EXPOSURE ON OUTCOMES IN KIDNEY TRANSPLANT PATIENTS (KT PTS)

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Background: We performed ad hoc analyses on a Phase 2 study to evaluate the effect of tofacitinib exposure on clinical outcomes.
Methods: Three hundred and twenty-two KT pts received CsA or fixed-dose tofacitinib regimens. One hundred and eighty-six (87%) tofacitinib-treated pts had evaluable tofacitinib exposure (time-weighted 2-h postdose concentrations over the first 6 months). Outcomes through Month 12 were compared among pts with above-median and below-median tofacitinib exposures (AME and BME groups) and CsA.
Results and conclusions: This ad hoc analysis showed that the tofacitinib BME group had similar infectious and rejection rates as CsA and no PTLD through Month 12 while preserving the advantage of better allograft function and histology seen with fixed-dose regimens. Additional evaluation is needed to assess whether prospective concentration-controlled dosing will optimize clinical outcomes early posttransplant and in longer-term follow-up.

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OS23-TOLERANCE

O198 TARGETING APOPTOSIS TO INDUCE TOLERANCE ACROSS MEMORY T CELL BARRIERS

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Memory T cells represent a major barrier for tolerance induction in sensitized recipients and in large animals. The lack of effective strategies to inhibit memory T cells precludes the clinical translation of tolerance induction protocols based on costimulation blockade. We hypothesized that the pharmacological inhibition of essential anti-apoptotic factors in memory T cell generation and maintenance might represent a new strategy to deplete donor-reactive memory T cells. The small-molecule Bcl-2/Bcl-XL inhibitor ABT-737 efficiently induced apoptosis in alloreactive memory T cells *in vitro* and *in vivo* and prolonged skin graft survival in sensitized mice. A short course of ABT-737 induction therapy was sufficient to overcome memory T cell-mediated resistance in a donor-specific transfusion model and to induce mixed chimerism across memory T cell barriers in combination with costimulation blockade. Since Bcl-2 inhibitors yielded encouraging safety results in clinical cancer trials, this novel approach might represent a substantial advance in the development of clinically applicable tolerance induction protocols.

O199 SOLUBLE HLA-G AS TOLEROGENIC IMMUNOMODULANT IN EXPERIMENTAL SMALL BOWEL TRANSPLANTATION

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Background: HLA-G is a non-classical HLA molecule implicated with a central role in fetomaternal tolerance protecting the semi-allogenic fetus from the mother's immune system via downregulating adaptive (T cell) and innate (NK cell) immunity. Studies have shown promising tolerogenic effects in transplantation and allogenic skin allografts were accepted in mice using HLA-G for immunomodulation1. In this study, soluble HLA-G dimers were evaluated in experimental intestinal transplantation.
Methods: Allogenic intestinal transplantation (ITX) was performed in rats (BN ->Lew). HLA-G was coated on beads and administered intraperitoneally 24 h prior to and upon completion of the transplant. Animals were harvested at 4 and 7 days posttransplant and acute rejection (ACR), as well as effects on T-cell adaptive immune responses were assessed by flow cytometry, histology, graft contractility and qPCR.
Results: HLA-G treatment was observed to significantly protect grafts from histologically proven ACR as assessed by two independent reviewers using the Wu rejection score. In ACR, effector CD8+ cells isolated from graft draining lymphnodes were found to be significantly reduced after HLA-G treatment at 7 days post allogenic ITX. Furthermore, CD4+/CD25+/FoxP3+ Treg cells appeared to be induced by HLA-G treatment. Graft infiltration with myeloperoxidase positive cells was significantly reduced after HLA treatment at 7 days post ITX concomitantly to ameliorated graft contractility. qPCR showed a significant reduction in ACR-related cytokine expression (TNF α, IL 10, IFN γ) after HLA-G treatment at 4 and 7 days post ITX.
Conclusion: Soluble HLA-G dimers exhibit tolerogenic properties in this model of experimental intestinal transplantation. The protective effect may be mediated via inhibition of the effector CD8+ population either directly or by induction of specific Treg populations.
Reference: 1. Favier B. et al. Plos One 2011;6 (7):e21011

O200 THE ROLE OF CD40 COSTIMULATION IN THE INDUCTION OF CHIMERISM AND TOLERANCE

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Introduction: Most tolerance approaches relying on costimulation blockade target the CD40:CD154 pathway which is crucial for B and T-cell immunity. Unfortunately, thromboembolic side-effects were seen with different clones of anti-CD154mAbs in clinical and NHP studies. Defining the roles of donor and recipient CD40 in the establishment of mixed chimerism and tolerance remains of interest for the rational development of human tolerance approaches.
Methods: Groups of B6 mice (WT, CD40−/−, CD154−/−), received mild total body irradiation (2 or 3 Gy), 15–20 × 106 fully mismatched Balb/c (WT, CD40−/−), bone marrow (BM) cells and costimulation-blockade by CTLA4Ig. Multi-linage chimerism was followed by flow-cytometry and tolerance was assessed by skin-grafting.
Results: Omission of anti-CD154 results in abrogation of chimerism and tolerance in WT–WT (0/5), CD40−/−WT (0/8) and WT–CD40−/− (0/5) combinations. Chimerism and donor-specific skin-graft tolerance were induced in WT–CD154−/− (7/8) and CD40−/−CD40−/− (8/8) groups. Depletion of CD4 (but not CD8) T-cells was able to prevent BM rejection in WT–WT (4/5) and CD40−/− WT (3/5) but surprisingly not in WT–CD40−/− (0/4). CD4 depletion promoted induction of donor-specific skin tolerance only in CD40−/− WT (3/3) animals.
Conclusion: These results indicate that neither target cell depletion nor a CD154 signal is a required mechanism of anti-CD154. Ablating recipient CD154 but not either donor or recipient CD40 alone is sufficient for the induction of chimerism and tolerance. Interruption of the CD40:CD154 signalling in both the direct and indirect pathway of allorecognition, but not either pathway alone, allows engraftment of allogeneic BM. Donor APCs lacking CD40 fail to tolerize recipient CD4 cells, whereas CD8 cells alone are unable to reject BM. If WT BM is transplanted in recipients lacking CD40, the presence of either CD4 or CD8 cells is sufficient for BM rejection.

O201 UNIQUE B-CELL DIFFERENTIATION PROFILE IN TOLERANT KIDNEY TRANSPLANT PATIENTS

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Background: Patients tolerant to a kidney graft display a higher number of blood B cells and transcriptional B-cell signature. As these patients rarely develop an allo-immune response they could display an abnormal B-cell differentiation.
Methods/Materials: We used a culture system combining BCR signal, TLR activation, CD40 triggering and cytokines to explore T-dependent differentiation of B cells into terminally differentiated plasma cells. CD20, CD24, CD27, CD38, IgM/IgD expression, B-cell apoptosis and proliferation were measured by flow-cytometry. Cytokine, Ig production and markers of differentiation were followed.
Results: Tolerant recipients show a higher frequency of CD20+CD24hiCD38hi transitional B cells and CD20+CD38loCD24lo naïve B cells compared to patients with stable graft function under immunosuppression, correlating with a decreased frequency of CD20-CD38+CD138+ terminally differentiated plasma cells, suggestive of abnormal B-cell differentiation. Cultured *in vitro*, B cells from tolerant patients proliferate normally but produce more IL10. In addition, B cells from tolerant recipients exhibit a defective expression of IRF4, PRDM1, XBP1, three factors of the end step of differentiation into plasma cells, and show a higher propensity for cell death apoptosis.
Conclusion: These data suggest that a balance between B cells producing regulatory IL10 and a deficiency in plasma cells may encourage an environment favorable to the tolerance maintenance.

O202 ASSESSMENT OF SPECIFIC TOLERANCE-INDUCING EFFECTS OF EXTRACORPORAL PHOTOPHERESIS

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Objective: Extracorporal photopheresis (ECP) has been used as a therapeutic option for acute and chronic rejection after transplantation (Tx). However, for the first time we assessed tolerance-inducing effects of ECP on subsets of Tregs and DCs after heart transplantation (HTx) for a better monitoring of ECP therapy.
Methods: HTx recipients were treated with ECP for the following (n = 21 ECP treatments each group): (i) prophylaxis of acute cellular rejection (ACR) between month 3–6 post-HTx (n = 8), or (ii) histological proven ACR of grade ≥1B (ISHLT 1990, n = 8). Each ECP treatment was performed at two subsequent days. Peripheral blood analysis by FACS of HTx recipients were compared to of healthy human controls (HC; n = 9) as follows: CD4+CD25highCD127low Tregs activating (CD147) and suppressing subsets (CD120b, CD62L, CD39) as well as myeloid (mDCs) and plasmacytoid (pDCs) subsets.

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Results: Incidence of CD4+CD25highCD127low Tregs increased overall after ECP with a pronounced effect in recipients with prophylactic ECP therapy (6.9 ± 0.7%) compared to the ECP-ACR group (6.0 ± 0.3%) and HCs (5.1 ± 0.7%). Treg activation marker CD147 was significantly up-regulated after ECP prophylaxis (99.7 ± 0.1%; $p = 0.02$) compared to HCs (97.7 ± 0.8%). Whereas Treg suppression CD120b and CD62L were significantly decreased in ECP-treated recipients compared to HCs but did not differ between the ECP groups. Numbers of CD39+ Tregs, which are known to suppress pathogenic T helper17 cells, did not change after ECP therapy. In comparison to HCs, percentage of pDCs were reduced (14.5 ± 3.6% vs. 26.0 ± 2.8%, $p = 0.01$) and mDCs were increased (70.1 ± 4.0% vs. 55.6 ± 3.7%, $p = 0.01$) after ECP-prophylaxis but without significant change in ECP-ACR group.

Conclusions: Our results showed that assessment of specific ECP effects on subsets of Tregs and DCs could be valuable to identify responders and non-responders of ECP therapy after Tx.

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OS24-COMPOSITE TISSUE

O203 TREATMENT WITH ANTI-IL-1ß PROLONGS LIMB ALLOGRAFT SURVIVAL IN AN EXPERIMENTAL MODEL OF VASCULARIZED COMPOSITE ALLOTRANSPLANTATION

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Background: Novel targets for a more specific immunosuppressive therapy have been identified in hand transplantation. IL-1ß was found to be highly upregulated in biopsies of rejecting skin in hand transplanted patients.
Methods: Anti-IL-1ß was applied in an experimental rat hindlimb transplantation model (Brown Norway rats to Lewis rats). Four different treatment groups included: No treatment [1]; baseline immunosuppression (FK506 30 mg/kg for 50 days and ALS 0.5 ml POD0 and POD 3) [2], baseline immunosuppression + weekly injections of Anti-IL1ß subcutaneously (s.c.) into the transplanted limb [3], baseline immunosuppression + Anti-IL1ß s.c. into the contralateral, non-transplanted limb [4]. End-point was histological rejection grade III (according to the Banff criteria) or postoperative day 100.
Results: Weekly injections of Anti-IL-1ß into the transplanted limb (group 3) resulted in significant prolongation of allograft survival (mean survival 85.3 ± 11.2 days) as compared to the control group [2] (64 ± 0.7 days); $p \leq 0.05$. Two animals from group 3 were completely free of rejection until day 100. Weekly injections of Anti-IL-1ß into the non-transplanted, contralateral hindlimb [4] also prolonged allograft survival (mean survival 95.3 ± 6.6 days). Animals without any treatment [1] rejected on day 7.5 ± 0.5.
Conclusions: IL-1ß is a promising target for immunosuppression in extremity transplantation. Prolonged survival with intragraft as well as contralateral Anti-IL1ß injections indicates a systemic effect. Further data is warranted to optimize dosing and delivery of Anti-IL-1ß.

O204 MINIMALLY-INVASIVE DIAGNOSIS OF SKIN REJECTION WITH TAPE STRIPPING TECHNOLOGY

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Background: The diagnosis of skin rejection as well as monitoring of ongoing immunologic processes after reconstructive transplantation still requires invasive punch biopsies. Here we present a promising non-invasive approach for early detection of acute rejection in transplanted extremities using skin tape stripping of the stratum corneum to assess cytokine expression profiles.
Methods: Cytokines were extracted from skin tapes at various time points after transplantation in an experimental rat hind limb transplant model. The Milliplex rat cytokine/chemokine panel was used to assess a selection of cytokines with Luminex® analysis. In the allogeneic setting, Brown Norway rats were used as donors, and Lewis rats were used as recipients. Syngeneic transplants and non-transplanted limbs served as controls. Tape sampling (Sebutape®/D-Squame®) was performed according to a standardized protocol in transplanted hind limbs immediately and 4 h posttransplant, as well as on postoperative days (POD) 1, 3, 5 and 7.
Results: Most of the selected markers (IL-5, MCP-1, IL-1b, IL-6, GM-CSF, GRO/KC, IFN-g, IL-1a, IL-10, IL-12p70, IL-18, IL-2, IL-4) were detectable in non-rejecting skin (syngeneic, non-transplanted) and found to be significantly upregulated in the allogeneic group. IL-1a showed the strongest upregulation in allogeneic hind limbs upon rejection, with a twofold increase. Remarkably, this increase was observed on POD 3 and POD 5, prior to any clinical signs of rejection. H&E histology of the skin after tape stripping did not show any signs of inflammation. In order to consider the overall diagnostic potential of the intragraft cytokine profiles we performed multivariate analysis combined with random forrest classifier, which showed a clear distinction (AUROC = 0.874) between syngeneic and allogeneic hind limbs at all time points.
Conclusions: Our results demonstrate for the first time that this non-invasive technique allows for early detection of skin rejection.

O205 IMMUNE TOLERANCE ACROSS A FULL MHC BARRIER IN A SWINE HIND LIMB TRANSPLANTATION MODEL USING A COMBINED CO-STIMULATORY BLOCKADE AND DONOR BONE MARROW CELL APPROACH

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Background: Vascularized Composite Allografts (VCA) contain vascularized bone marrow (BM) and a BM niche representing a constant source of donor-derived stem cells and hence can favor chimerism and tolerance induction. This study investigates the immunological effects of vascularized BM within VCA under co-stimulation blockade-based regimen and its impact on allograft survival and tolerance induction.
Methods: Fully MHC- and gender mismatched MGH miniature swine ($n = 20$) underwent heterotopic hind-limb transplantation containing intact vascularized BM. Recipient animals received a short course (30 days) of tacrolimus with or without donor BM infusion (60 × 106 cells/kg), and CTLA4Ig. Short course tacrolimus only and untreated animals served as controls. Chimerism was assessed by SRY-1 qRT-PCR analysis. Challenge with secondary skin grafts was utilized to demonstrate robust immune tolerance *in vivo*.
Results: The co-stimulation blockade based immunomodulatory protocol resulted in indefinite graft survival (>150 days) in five out of eight animals whereas control and tacrolimus only groups rejected allografts at days 7 ± 1 and 29 ± 2 respectively. Long-term survivors demonstrated only transient peripheral but stable micro-chimerism in various graft and recipient tissues including skin, lymph node, bone marrow, and spleen. CFSE-MLR data showed unresponsiveness to donor but not to third party allogeneic controls. Secondary skin grafting demonstrated advanced rejection of third party grafts on day 7 while donor-matched grafts were accepted indicating donor-specific immune tolerance. There was no evidence of chronic rejection or donor specific antibody formation in long-term survivors.
Conclusion: Combined costimulation blockade and donor BM cell infusion can induce robust immune tolerance in a fully MHC mismatched hind limb transplant model. Such targeted immunomodulatory protocols might eliminate the need for long-term multi-drug immunosuppression after VCA.

O206 CARDIOVASCULAR RISK ASSESSMENT AFTER HAND TRANSPLANTATION IN SHORT AND LONG-TERM OBSERVATION

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Hand transplantation, significantly associated with quality of live improvement, requires lifelong immunosuppresive treatment, which is known to influence major risk factors for atherosclerosis.
Methods: A comprehensive evaluation of risk factors for cardiovascular (CV) disease was performed in five patients (age 32, 33, 36, 40 and 58 year) before and 30–79 months after hand transplantation. Framingham score (allows to estimates the cardiovascular risk for persons without clinical manifestations of coronary heart disease- CHD) was calculated. All patients received tacrolimus, MMF and steroids.
Results: Lipids, blood glucose and blood pressure were normal before transplantation, 3 pts had normal body weight and two were overweighted (BMI 27 and 29 km/m^2), nonsmokers-4, without family history of premature CHD. Posttransplantation diabetes mellitus was diagnosed in all during first quarter and insulin therapy was implemented for 9–31 months. At the end of study one patient remains on insulin and one receives oral agent, slightly elevated HbA1C was observed in 2 pts. All patients were engaged in physical activity though 4 pts had minor increase in BMI: 3 pts were overweighted (BMI 26, 27 and 29 kg/m^2) and one patient was obese (BMI 31 kg/m^2). Moderate hypertension developed in two patients. Lipid disorders were relatively common, with hypercholesterolemia found in 3 pts, elevated LDL cholesterol in 3 pts, elevated triglicerydes in 3 pts, elevated uric acid in 2 pts. Hyperhomocysteinemia was not observed; deterioration of kidney function was found in 1 pts (eGFR 47 ml/min/1.73 m^2). Absolute risk expressed as the percentage likelihood of developing CHD per decade has increased (Table) however CV events did not occur.
Conclusion: Results demonstrate rise in global estimate for CHD risk. Traditional CVD risk factors are highly prevalent among patients after hand transplantation. Increased CV risk would pose a major limitation to the procedure unless the preventive.

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O207 HAND TRANSPLANTATION IN ITS 13TH YEAR – THE INNSBRUCK CLINIC EXPERIENCE

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Background: We describe here the outcome after two bilateral hand, one bilateral forearm and one unilateral hand transplantation at 13, 10, 7 and 4 years after transplantation.
Methods: Four patients received a bilateral hand, a bilateral forearm or a unilateral hand transplantation between March 2000 and July 2009. Induction therapy with ATG or alemtuzumab was followed by tacrolimus, prednisolon MMF or tacrolimus and MMF maintenance IS. Later, sirolimus/everolimus was added under simultaneous withdrawal or dose reduction of tacrolimus or MMF. Steroids were avoided in one and withdrawn in two patients.
Results: Total active range of motion improved continously with a grip strength of 2–10 kg. Hand function correlated well with time after transplant and amputation level. Intrinsic hand muscle function recovery and discriminative sensation were observed in all patients. Complications included CMV infection, fungal infection, hypertension, hyperglycemia, transient creatinine increase and headache and a bullous pemphigoid. Three, six, four, and one rejection episodes were successfully treated with steroids, anti-CD25, anti-CD52 and anti-CD20 antibodies and/or intensified maintenance IS. There have not been any donor specific antibodies (DSA) in our patients until 02/2012. Skin histology at current shows no or mild perivascular lymphocytic infiltrates without signs of progression. Vessels are patent without signs for luminal narrowing or intimal proliferation.
Conclusion: The overall functional outcome and patient satisfaction after bilateral hand, bilateral forearm and unilateral hand transplantation are highly encouraging. All patients are now free of rejection with moderate levels of IS.

O208 NEW CLINICOPATHOLOGICAL FINDINGS IN FACE ALLOTRANSPLANTATION

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So far insufficient clinicopathological data exist to define chronic rejection in composite tissue allotransplantation (CTA). We report here a face-transplant patient who developed clinicopathologic changes not included in the Banff-CTA score, suggestive of chronic rejection. The facial allograft consisted of bilateral mandible, upper and lower lips, cheeks and chin. Induction immunosuppression included steroids, mycophenolate mofetil, tacrolimus, antithymocyte globulins and bone marrow infusion. During follow-up the patient developed primary asymptomatic EBV infection, followed by an EBV+ B-cell lymphoma and hepatic leiomyosarcoma, for which the immunosuppressive treatment was greatly reduced. During the first post-transplant year three episodes of acute rejection (grade III) developed; they manifested with oedema and erythema of the allografted skin and oral mucosa and were completely reversed with steroids. Subsequently several episodes of acute rejection occurred that were difficult to reverse with steroids and Campath-1; they manifested clinically with graft erythema and histologically with lichenoid changes. Since the second post-transplant year the allografted facial skin became progressively sclerotic and dyschromic. Biopsies showed epidermal atrophy, diffuse dermal sclerosis involving blood vessels (whose lumina were reduced), and disappearance of adnexa. These so far undescribed changes are strongly suggestive of chronic rejection.

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CCS03- LIVER

CCS07 COMPLETE RESOLUTION OF ACUTE RENAL FAILURE AND ANURIA 2 MONTHS AFTER LIVER TRANSPLANTATION IN A 2 YEAR OLD CHILD

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Acute renal failure (ARF) is a significant complication of liver transplantation (LT) and it is precipitated by complicated surgery and compromised pre-transplant kidney function. A 24-month, 12 kg child with bilobar, unresectable hepatoblastoma (PRETEXT IV) was referred for LT after nine cycles of chemotherapy which hardly could control the tumor growth. After a donor workup a LDLT of segments II-III from father was performed (GW = 250 g). An extensive portal vein thrombosis up to SMV and SV confluence precluded standard implantation and cavaportal transposition with end-to-end hepatic vein-to-IVC anastomosis were done. Graft failure and ARF with need for RRT due to hepatic artery thrombosis developed in postoperative course. On five POD the child was retransplanted with reduced cadaveric II-III seg graft (GW = 200 g). A cavaportal transposition and end-to-end hepatic vein-to-IVC anastomosis were performed again and CVVH was used intraoperatively. Primary skin closure wasn't possible due to visceral edema. Abdominal wall was closed with a silastic film (Coloplast). Early allograft dysfunction, sepsis along with ARF and need for RRT developed after reTx. Ten reoperations were done for gradual abdominal wall closure and infection control. A mechanical ventilation lasted for 16 days and vasopressor support (norepinephrine)- for 11 days. During hospital stay he received 12 CVVH for 21 days and later 25 iHD for 32 days. ARF and anuria resolved at 2 months after reTx after skin closure was completed, liver function became good, sepsis was controlled and Tacrolimus was switched to Everolimus. His renal function gradually improved. Child was discharged from the hospital on the 82 POD with diuresis 2.3 ml/kg/h and GFR = 93 ml/min. Six months after LT a hepatic vein-to-IVC anastomotic stenosis was diagnosed and four balloon angioplasty procedures were done to resolve the pressure gradient. Thirty-two months after LT child is doing well with no ascites, no failure to thrive and good liver and kidney function.

CCS08 LIVER HEMANGIOMATOSIS. AN UNUSUAL CAUSE FOR LIVING DONOR TRANSPLANTATION

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Background: Hemangiomas are common tumours in the infant age. The cutaneous presentation is the most frequent but liver hemangiomas' (LH) prevalence is only around 10%. Usually LH are smaller than 5 cm, unique and asymptomatic, and the development of complications is very rare.

Methods/Materials: We report the case of a 20-month male, who had a liver and a medular hemangiomatosis. Medular hemangiomatosis was asymptomatic but liver condition coursed with gigant hepatomegaly, respiratory failure and severe coagulopathy. He underwent aggressive pharmacotherapy and two embolizations without any result.

Results: Given the multifocality, liver resection was considered to be impossible, so he entered the program of living donor liver transplantation. Liver transplantation with father's segment II and III was performed, needing arterial graft and double left Roux-en-Y cholangiojejunostomy. The patient was discharged 40 days after surgery. Ten-month follow-up period he had repeated excision of oral angiomata in ambulatory-care setting. He is in excellent condition 10 months after transplantation.

Conclusion: Symptomatic LH must be treated pharmacologically, when it fails, embolization and/or surgery must be considered. If this happens to be the case, the main option for surgical management is enucleation, but in case of multifocal hemangiomatosis, liver transplantation, including living donor liver transplantation should be considered.

CCS09 THROMBOTIC MICROANGIOPATHY ASSOCIATED WITH ANTI-ADAMTS13 ANTIBODY AFTER LIVING DONOR LIVER TRANSPLANTATION: REPORT OF A REFRACTORY CASE

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Background: Thrombotic microangiopathy (TMA) has recently been recognized as a fatal complication after liver transplantation (LTx). It is suggested that ADAMTS13 deficiency and/or appearance of ADAMTS13 inhibitor may be crucial for the pathogenesis of TMA.

Case: A 51-year-old woman underwent ABO-incompatible living-donor LTx for HCV-associated liver cirrhosis. She was preoperatively treated with rituximab and plasma exchange (PE). Immunosuppression was started with tacrolimus, mycophenolate-mofetil, and steroid. However, her platelets counts progressively declined after the operation; 30 000 and 19 000/μL on POD-6 and -9, respectively, with a significant increase of fractionated erythrocytes in blood smear. ADAMTS13 activity was severely decreased down to 8% on POD-6, accompanied by strongly-positive anti-ADAMTS13 antibody/inhibitor. She was thus diagnosed as TMA on POD-11. Tacrolimus was immediately discontinued and PE was started, by which, her platelets and ADAMTS13 activity were recovered up to 109 000/μL and 36%, respectively. Also, ADAMTS13 inhibitor was converted to be negative. Then, Cyclosporine was added because of mild cellular rejection, however, ADAMTS13 inhibitor became strongly-positive again, resulting in TMA relapse on POD-20. She had a few episodes of TMA on every re-administration of calcineurin-inhibitor (CNI) during the first 1 month after LTx. Thereafter, ADAMTS13 activity was gradually recovering, and finally ADAMTS13 inhibitor has not emerged despite CNI re-administration.

Conclusion: In this case, anti-ADAMTS13 antibody/inhibitor, concomitant with CNI administration, might play a crucial role in the pathogenesis of refractory TMA.

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CCS04-OTHER

CCS10 SIX CASES OF SUCCESSFUL DELIVERY AFTER COMBINED KIDNEY-PANCREAS TRANSPLANTATION: A SINGLE CENTER REPORT

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Background: Retrospective analysis of transplant and obstetric outcome in six cases of successful delivery after combined kidney pancreas transplant.
Methods/Materials: Totally six babies were born in mean week 32 from four combined kidney pancreas transplanted women immunosuppressed by Tacrolimus plus Azathioprine.
Results: All six babies were healthy. The maternal pancreas graft function remained stable in five and the kidney function in three cases. In one women a preconceptionally elevated serum creatinine increased over 4 mg/dl after the delivery. The peripartal course in one women with coronary heart disease was severely complicated by myocardial infarction and CMV pneumonia leading to kidney-pancreas graft loss.
Conclusion: Good obstetric outcome and stable transplant function can be achieved in pregnancy after combined kidney pancreas transplant. Careful gynecological and cardiac and transplant visits considering a cautious immunosuppression are recommended.

CCS11 POST-TRANSPLANTATION ENCAPSULATING PERITONEAL SCLEROSIS WITHOUT INFLAMMATION OR RADIOLOGICAL ABNORMALITIES

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Post-transplantation encapsulating peritoneal sclerosis (EPS) causing bowel obstruction has been identified as a serious complication after kidney transplantation (KT) in patients previously treated with peritoneal dialysis (PD). Systemic inflammation and abnormalities on abdominal computed tomography (CT)-scanning are hallmarks of EPS. We report a case of late-onset post-transplantation EPS without systemic inflammation or abnormalities on a CT-scan which could only be diagnosed by laparotomy. A 59-year old female was presented because of symptoms of bowel obstruction 33 months after KT. She had a 26-month history of PD before her first KT and was treated with PD for 4 years before her second KT. Physical examination was unremarkable and laboratory tests showed no signs of systemic inflammation (C-reactive protein <1 mg/l). An abdominal CT-scan did not reveal any abnormalities fitting the diagnosis of EPS, except a "feces sign." Given the severity of the progressive symptoms, a diagnostic laparotomy was performed, visualizing a classical EPS (Fig.A). Total peritonectomy and enterolysis were performed, leading to restoration of peristalsis (Fig.B). In conclusion, EPS may occur several years after KT in the absence of systemic inflammation and typical radiological abnormalities. Obtaining a diagnosis of post-transplantation EPS is challenging, however, a low threshold for surgical exploration in case of high clinical suspicion and negative findings on the CT scan is mandatory.

CCS12 HEART TRANSPLANTATION IN TWO HIV-INFECTED PATIENTS

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HIV-infection used to be considered a relative contraindication to solid-organ transplantation. Since the advent of combined antiretroviral therapy (cART), survival of HIV-infected patients has significantly increased, and these patients have become potential candidates for heart transplantation (Pelletier SJ et al. Review of transplantation in HIV patients during the HAART era.Clin Transpl.2004:63–82). To the best of our knowledge, fewer than 40 cases of heart transplantation in HIV-infected patients have been described in the literature (Grossi PA. Update in HIV infection in organ transplantation. Curr Opin Organ Transplant 2012, 17:586–593). We report two cases of HIV-infected patients affected with dilatative cardiomyopathy who successfully underwent orthotopic heart transplantation at our institute in 2009 and 2011, respectively. The second of the two patients was also affected with chronic Chagas Disease. While on combined antiretroviral and post heart-transplant immunosuppressive therapy (tacrolimus/mycophenolate/prednisone for the first patient, and tacrolimus/prednisone for the second), they had a regular post-transplant course with neither major complications nor episodes of acute rejection. In line with data in the literature, our cases show that short/medium term survival and rate of complications in transplanted HIV patients are similar to those of the general population, making heart transplantation a valid therapeutic option for this group of patients.

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OS25-KIDNEY VIII

O209 CHRONIC PERSISTENT NEUTROPENIA AFTER RENAL TRANSPLANT-CASE REPORT AND REVIEW OF LITERATURE

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Background: Chronic persistent neutropenia (CPN) can be congenital, cyclic or idiopathic. Renal transplant patients receive many bone marrow (BM) suppressives and are exposed to severe infections causing BM suppression.
Case summary: A 51 years old patient had CKD due to ADPKD, received renal transplant with thymoglobulin induction, steroid avoidance, MMF and tacrolimus. He developed CPN ±500 with total leucocytic count (TLC) ±1500 requiring high doses of granulocyte-stimulating factor (G-CSF) up to 1800ugm/week × 9 months without significant side effects. MMF was stopped. BM was hypercellular with myeloid hyperplasia due to G-CSF treatment. Viral screening and serology including ANA were negative. A small dose of steroid was added. TLC improved to ±3000. Repeat BM biopsy after stopping G-CSF was normal. MMF was restarted without further neutropenia.
Conclusion: CPN after renal transplant can be treated safely with high doses of G-CSF and responds to careful drug manipulation & steroids.

O210 RENAL FUNCTION IN TRANSPLANT RECIPIENTS AFTER ROAD CYCLING RACE

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Background: Few studies have evaluated the changes in renal function of transplant recipients (TR) after intense physical activity.
Methods: The purpose of this study was to investigate some aspects of renal function in TR participating in a road cycling race (CR) of 130 km long. Venous blood and urine samples were collected: (i) the day before, (ii) at the finish and (iii) 24 h after CR from 7TR (mean ± SD age 51 ± 10 years), who underwent transplant (two heart, two liver, three kidney) 7.3 ± 5.6 years before. Eighteen healthy subjects (HS) (54 ± 7 years) participating to the same race were recruited as control group.
Results: Results are shown in Table 1.

Table 1. Urea, creatinine, microalbuminuria and urinary proteins values before (Pre), at the finish (Post) and 24 h after the race (24 h) in both groups of subjects

Significant differences were found between Pre-Post *($p < 0.01$), Post-24 h §($p < 0.01$), Pre-24 h †($p < 0.01$) and between TR and HS in Pre #($p < 0.01$), Post ($p < 0.01$) and 24 h ^($p < 0.01$).
Conclusions: HS showed some significant differences between the three stages of analysis, always returning within normal physiological reference values within 24 h after the race. TR showed a similar trend, with higher values after the race, and a slower return to baseline 24 h after the race. TR in good clinical conditions and properly trained, were able to face intense physical effort with transient changes in renal function given by hemodynamic factors and alteration of state of hydratation; moreover, this kind of changes of kidney function are similar in the two groups of people. The lower urine specific gravity in TR is related to a tubular disfunction partially due to immunosoppresive therapy. The increase of proteinuria resolves after rest. Longitudinal studies are necessary to understand the eventual risk of endurance sports activities (CR) for renal function of TR.

O211 EARLY FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS) AS A CAUSE OF RENAL ALLOGRAFT PRIMARY NON-FUNCTION

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Background: Primary focal segmental glomerulosclerosis (FSGS) is one of the commonest causes of glomerular disease and if left untreated will often progress to established renal failure. In many cases the best treatment option is renal transplantation however primary FSGS may rapidly recur in renal allografts and may contribute to delayed graft function. We present a case of primary non-function in a renal allograft due to biopsy-proven FSGS. Case Report: A 32 year old man presented with serum albumin of 22 g/l, proteinuria quantified at 12 g/l and marked peripheral oedema. Native renal biopsy demonstrated tip-variant FSGS. Despite treatment with high-dose prednisolone and ciclosporin the patient developed progressive renal dysfunction and was commenced on haemodialysis. Cadaveric renal transplantation was undertaken in July 2011. This was complicated by primary non-function. Renal biopsies failed to demonstrate any evidence of acute rejection however did demonstrate clear evidence of FSGS. The patient was treated with continued immunosuppression and underwent a course of plasmapheresis to no avail. Discussion: Primary renal allograft non-function following transplantation is often due to acute kidney injury or acute rejection. Recurrent FSGS is recognised as a phenomenon that drives early and late allograft dysfunction. It is not traditionally associated with a significant contribution to primary non-function. In this case recurrent FSGS appears to have driven primary non-function of the allograft with the development of significant renal injury that occurred despite ongoing immunosuppression and a subsequent course of plasmapheresis. This case highlights FSGS as a potentially aggressive process that, once active in the allograft, may prove refractory to targeted treatment. Pre-emptive therapies in patients deemed to be at high risk of recurrent disease may be appropriate and should be considered.

O212 SIGNIFICANT IMPACT OF PROLONGED BRAIN DEATH DURATION ON PATIENT SURVIVAL AFTER KIDNEY TRANSPLANTATION

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Background: In renal transplantation, graft survival using organs from deceased donors is inferior to results after living donation. Little however is known about the effect of brain death duration (BDdur) on long term outcome after kidney transplantation (KTx).
Methods: A single-center retrospective analysis of 1245 consecutive deceased donor KTx, performed between January 2000 and December 2010, was carried out. BDdur was calculated as the period between brain death declaration and start of cold perfusion. All recipient-, donor- and transplant-factors, known at the timepoint of KTx, were investigated for their impact on delayed graft function (DGF), acute rejection (AR), "graft loss" and "death." Uni- as well as multivariate statistical analysis were performed using binary logistic- and Cox-regression analysis.
Results: Mean BDdur was 12.01 ± 6.26 h. DGF was associated with a significantly longer BDdur (12.13 ± 5.815 vs. 11.82 ± 6.177 h, $p = 0.0034$). No significant correlation of AR and BDdur was seen (AR 11.85 ± 6.33 vs.12.04 ± 5.997 h no AR, $p = 0.156$). BDdur did not affect long term graft survival, but had a significant impact on patient survival. Apart from recipient's age, BDdur was the most important independent factor for "death" after KTx (Hazard Ratio (95%CI): 1.041 (1.015–1.067); $p = 0.002$).
Conclusion: Taken together our results highlight the importance of BDdur as an independent factor negatively influencing long term survival after kidney transplantation. Strategies to optimize time management prior as well as during organ retrieval are essential to improve outcome after kidney transplantation.

O213 WATERLOW SCORING SYSTEM: AN INDEPENDENT PREDICTOR FOR DELAYED GRAFT FUNCTION IN RENAL TRANSPLANTATION

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Introduction: The use of pre-operative scoring systems to inform outcome has not proven to be robust in transplantation, largely due to widespread variability in donor and recipient characteristics. We aim to assess the utility of Waterlow score, initially developed as a tool to stratify risk for developing decubitus ulcer development, as a surrogate marker to predict outcome in renal transplantation.
Methods: This is a retrospective study of 109 consecutive renal transplant recipients at a single unit from July2011 to February2012.Patients were stratified based on their pre-operative Waterlow score (a composite analysis including scores for age, gender, body mass index (BMI), nutritional state, and tissue quality.) Scores of <9 were deemed low risk, 10–14 medium risk, and >15 high risk of developing ulcers. Delayed graft function (DGF; requirement for dialysis in the first week after transplant) was utilized as primary endpoint. Confounding factors including recipient age, BMI, ASA score, previous transplants, type of transplant, donor BMI, age and ischemic time were compared.
Results: Among 109 patients, (62 males, 47 females; 21–79 years, 75 deceased and 34 live donor transplants) 73 patients were low risk (47 deceased, 26 live donors); 28 medium risk (19 and 9) and 10 high risk (10 and 0 respectively) by Waterlow scoring. The live donor patients demonstrated no differences in outcomes based on differences in Waterlow score. Among deceased donors, rates of DGF were 17%, 55% and 100% respectively

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($p < 0.005$ and $p < 0.0001$ respectively; Fisher's exact test). No significant differences in any potential confounding factors were found across the group.
Conclusion: DGF is an established surrogate marker of longterm graft outcome. Waterlow score, routinely collected on admission by nursing staff, has been shown to be useful in predicting adverse outcome in emergency surgery. It appears to offer the potential to similarly stratify outcomes in transplant patients thereby ensuring optimal utilitarian use of donor organs.

O214 BODY MASS INDEX AND OUTCOME IN RENAL TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Whether overweight or obese end stage renal disease (ESRD) patients are eligible for renal transplantation (RT) is often debated. No (systematic) reviews have yet been carried out regarding this subject, and more specifically, surgical outcome of these patients. The aim of this review and meta-analysis is to systematically investigate outcome of low- versus high BMI recipients after RT.
Methods: Comprehensive searches were conducted in MEDLINE, Embase and CENTRAL. A meta-analysis was performed by using Review Manager 5.2. Random-effects models were used. The methodology was in accordance with the Cochrane Handbook for interventional systematic reviews, and written based on the PRISMA-statement.
Results: Seventeen studies were selected and reviewed. Twenty-eight outcome measures were reviewed (including 51 810 recipients) and 17 (including 5353 recipients) could be meta-analysed. Of these, the following demonstrated significant differences in favour of low BMI (<30) recipients: death (RR 3.08; $p = 0.002$), delayed graft function (risk ratio (RR) 1.89; $p = 0.006$), graft survival at 1, 2 and 3 years (RR 0.96; $p = 0.02$, RR 0.95; $p = 0.02$ and RR 0.91; $p = 0.001$ respectively), wound infection (RR 4.70; $p = 0.0001$), diabetes (RR 2.24; $p = 0.002$), length of stay (RR 3.06; $p < 0.001$). Differences in other outcome parameters were not significantly different. Remarkably, only five studies describe surgical outcome measures between BMI groups.
Conclusion: This systematic review and meta-analysis combines a large number of articles and outcome measures. Several of these show significant benefit for "low" BMI (<30) recipients. Therefore, we conclude that ESRD patients with a BMI > 30 should lose weight prior to RT. If this cannot be achieved with common measures, in morbidly obese RT candidates, bariatric surgery could be considered. Furthermore, surgical outcome measures in these recipients should be investigated.

O215 COMPARISON OF SPLIT RENAL FUNCTION ASSESSED BY RENOGRAPHY AND CT-ANGIOGRAPHY FOR SIDE DECISION IN LAPAROSCOPIC LIVING DONOR

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Background: As living kidney donors (LKD) should be left with the best kidney function. A single pre-procedural imaging that could assess not only anatomy but also the renal function would be helpful in the decision making process. Our goal was to investigate correlations between CT and scintigraphy to determine split renal function in LKD.
Methods: One hundred and twenty-nine potential LKD with 84 women and 38 men and a mean age of 50 (25–75) were included in the study. CT images were acquired on multidetector CT scanner before and after IV contract media. Regions of interest after semi-automatic segmentation of the left and right kidney were generated. Then split renal volumes and the split kidney glomerular filtration rate were calculated. CT relative renal function (CRF) was expressed as a percent of overall function (100%) in the same way as expressed by scintigraphic renography (SRF). Correlations, using linear regression, included left-right differences of renal volumes, CRFs and SRFs.
Results: Overall left kidney volume and function (SRF) were larger than for the right kidney ($p < 0.04$). There was a linear correlation between difference of left-right volume and SRF ($p < 0.0002$). There was no correlation between differences of left-right function assessed by CRF or SRF (p: 0.6). Asymmetric kidney function was more clearly demonstrated by SRF than by CRF.
Conclusion: Morphologic and functional data from CT angiography alone could not replace functional data provided by scintigraphic renography in order to determine split function. We suggest adding scintigraphic renography to CT for leaving the best kidney to the donor. Further clinical long term prospective analysis with donor's renal function outcomes should determine if this policy significantly decrease donors' morbidity.

O216 THE SOLUBLE RECEPTOR FOR UROKINASE IS NOT ELIMINATED BY IMMUNOABSORPTION ON PROTEIN A COLUMNS IN FSGS AFTER TRANSPLANTATION

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Introduction: Focal and segmental glomerulosclerosis (FSGS) is a serious disease whose pathogenesis is unknown. Its recurrence after transplantation (Tx) and its partial remission after treatment with immunoabsorption (Iabs) on protein A column is in favor of the existence of a circulating factor responsible for the disease and able to bind to the protein A column. Recently, the soluble receptor of urokinase (suPAR) was described as the soluble factor responsible for FSGS. We tested the capacity of suPAR to bind to Iabs and to be eliminated by Iabs.
Materials and methods: suPAR was measured by ELISA Quantikine Human suPAR (R & D) in the elates of six patients with recurrent FSGS after Tx and treated by Iabs (group 3) and in the serum of 11 patients with recurrent FSGS after Tx (group 1) and 11 healthy controls (group 2). In addition, suPAR was immuno-absorbed *in vitro* on protein A Sepharose column C6 MB (sigma) from serum of patients from group 1 and 2. suPAR was quantified in the elutes (glycine pH2, 5) and in post column sera.
Results: The concentration of suPAR in serum is identical before and after Iabs on protein A in group 1 and 2 (respectively for group 1: 1715.7 vs. 1537 pg/ml, p = ns. For group 2 2268.2 vs. 2515.7 pg/ml; p ns). SuPAR concentration was low in elutes from protein A columns incubated with serum of patients from group 1 and 2 (respectively 71 and 83.6 pg/ml). *In vivo*: suPAR concentration from the elute obtained after Iabs of patients with recurrent FSGS was 30 pg/ml (group 3).
Conclusion: suPAR does not bind to protein A *in vitro* or *in vivo*. SuPAR does not seem to be the only circulating factor responsible for recurrent FSGS in our population.

O217 VALUE OF EARLY POSTOPERATIVE ULTRASOUND AFTER KIDNEY TRANSPLANTATION

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Background: Ultrasound is routinely performed in our center on the first post-operative day after kidney transplantation (KTX). Aim of this study was evaluating the impact of ultrasonographic examination regarding surgical complications and outcome.
Methods: Three hundred and twenty-nine patients transplanted between January 2010 and December 2011 at our center were retrospectively analyzed for this study.
Results: Ultrasound was performed in 314 kidney transplant recipients (95.4%) on the first post-operative day. Patients with a biopsy proven rejection (BPAR) within the first three months after KTX had a significantly higher mean RI than patients without (0.71 vs. 0.65; $p = 0.009$). Furthermore, delayed graft function was more common in subjects with a high RI ($\geq$0.7) than in patients with a RI < 0.7 (40.6 vs. 25.3%; $p = 0.011$). A lack of arterial signal was detected in eight patients (2.5%) and five out of these had a vascular complication that required surgical therapy. In 12 patients (3.8%) RI was one without any other signs of vascular impairment. Even though such values can be a sign of venous thrombosis no case was observed in any of these patients.
Conclusion: We conclude that early ultrasound evaluation of the transplanted kidney remains a valuable tool not only to detect vascular complications but also as a predictor for graft outcome regarding DGF and BPAR.

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OS26-KIDNEY IX

O218 RITUX-ERAH: MULTICENTER RANDOMIZED TRIAL OF RITUXIMAB ON ACUTE HUMORAL REJECTION IN TRANSPLANTION

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Background: Treatment of acute humoral rejection (AHR) is currently based on the combination of plasmepheresis (PE), intravenous immune globulin (IVIg) and corticosteroids (CS).
Methods: In this phase 3, multicenter, double-blind, placebo-controlled trial, we randomly assigned patients with biopsy-proven AHR, to receive rituximab (R) (375 mg/m^2) or placebo (P). All patients received PE, IVIg, and CS. Primary endpoint was a composite criterion (graft loss or no improvement of renal function at day 12).
Results: Among the 38 patients included, the primary end point in the R group was 52.6% vs. 57.9% (p = 0.744). At 1 year, no death and one graft loss in each group. Supplementary administrations of rituximab, total number of IVIg and PE were not different in the two groups. There was no difference in serum creatinine and in proteinuria between the two groups. Changes in DSA and histology will be presented subsequently.
Conclusion: R was not superior to P in patients receiving PE, IVIG and CS.

O219 THE HERAKLES STUDY AT 24 MONTH: SUPERIOR RENAL FUNCTION IN AN EVEROLIMUS-BASED CNI-FREE REGIMEN

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To follow-up (FU) on the evolution of renal function (RF) at immunosuppression with different calcineurin inhibitor (CNI) exposures at month (Mo)24 post renal transplantation (Tx).
Methods: Eight hundred and two patients (pts) were included in prospective, open-label, randomized (rdz), controlled multi-center 1 year study, received induction with basiliximab followed by cyclosporine A(CsA), Enteric-Coated MycophenolateSodium (ECMPS) and steroids. 3Mo post Tx 499 pts were rdz 1:1:1 to either continue standard (STD) CsA (100–180 ng/ml)+ECMPS (n = 166) or convert to CNI-free regimen with Everolimus (EVR; 5–10 ng/ml)+ECMPS (n = 171) or convert to CNI-low regimen with EVR (3–8 ng/ml)+reduced CsA (50–75 ng/ml) (n = 162). Observational Mo24FUvisit performers: 131 (96%) STD, 132 (96%) CNI-free and 125 (93%) CNI-low pts.Primary endpoint RF as cGFR (Nankivell) maintained significantly improved in favor of CNI-free pts at Mo24 hence confirming CsA withdrawal with EVR+ECMPS as an overall safe and efficacious therapeutic option.

O220 CONTRAST ENHANCED SONOGRAPHY TARGETING T-CELLS FOR DETECTION OF ACUTE RAT RENAL ALLOGRAFT REJECTION

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We propose antibody-mediated contrast-enhanced sonography (CEUS) using human T-lymphocytes for diagnosis of acute renal allograft rejection (AR) in the rat model. Human T-lymphocytes were injected into adult uni-nephrectomized, allogeneically kidney transplanted rats and after application of anti-CD3 conjugated microbubbles ultrasound intensities were assessed. Allografts undergoing AR (5.41 ± 1.32 AU, $p < 0.05$, n = 5–8 in all groups) showed a significant accumulation of anti-CD3 compared to native control kidneys (1.09 ± 0.18 AU). CD3 signals of kidneys after syngeneical transplantation (sTX), after ischemia/reperfusion injury (IRI), and subjected to acute cyclosporine A toxicity (CSA) serving as controls did not differ from native kidneys (sTX: 0.99 ± 0.30 AU, IRI: 0.46 ± 0.29 AU, CSA 0.12 ± 0.04 AU). *In vivo* CD3 signals correlated well with immunohistochemical alterations. CEUS detecting T-lymphocytes is a novel option to non-invasively detect and differentiate AR from acute tubular necrosis.

O221 LONG-TERM OUTCOME OF HLA-ANTIBODY AND ABO INCOMPATIBLE KIDNEY TRANSPLANTATION

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Background: Highly sensitized patients and blood type O recipients with an ABO incompatible living donor have low rates of transplantation. Therefore, HLA- and ABO-incompatible transplantations (HLAi and ABOi Tx) are becoming increasingly common. However, rates of antibody-mediated rejection (AMR) in both HLAi and ABOi Tx are higher than in compatible transplants, which may impact on graft survival. There are few data directly comparing outcomes between these two groups: the aim of this study was to determine the long term outcomes after HLAi, ABOi and combined ABOi and HLAi transplants. Methods/Materials

One hundred and twenty-five patients undergoing living-donor antibody incompatible transplants were included in this study (69 ABOi, 43 HLAi, 13 combined ABOi/HLAi). Pre-transplant antibody removal (plasma exchange or immunoadsorption) was performed if baseline haemagluttinin titre was above 1/8, or if baseline flow crossmatch MFI ratio was above 2.3. AMR and TCMR were defined according the 2009 Banff classification.
Results: Baseline characteristics are shown in Table 1. 5 year death-censored graft survival was lower in ABOi/HLAi and in HLAi patients than in ABOi patients. AMR and thrombotic microangiopathy occurred more frequently in ABOi/HLAi patients. Incidences of cancer (including PTLD) and bacterial, viral and fungal infection were low and similar between the three groups.
Conclusion: ABOi patients have a better outcome than HLAi or combined patients. Patients undergoing combined ABOi/HLAi Tx have the worst outcome with a high incidence of AMR and severe thrombotic microangiopathy, which appears to be related to HLA antibody. The combination of haemagluttinin and DSA may have a synergistic effect, even if levels are low, and such transplants should be approached cautiously.

O222 THE USE OF IP-10 AND NGAL TO PREDICT EARLY REJECTION IN HLA INCOMPATIBLE RENAL TRANSPLANTATION

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Background: HLA incompatible (HLAi) transplantation provides an option for highly sensitised patients, however, it is hampered by high rates of rejection (15–53%) which impact on longer term outcomes. Peripheral biomarkers present a potentially attractive mechanism to detect rejection in advance of currently used indicators of acute rejection. We sought to determine whether serum biomarkers could predict rejection in HLAi transplants.
Methods: Serum from 94 HLAi transplant recipients from a single centre were analysed for a panel of biomarkers including: NGAL, KIM-1, IP-10, Cystatin C, VEGF and Cathepsin L. Serum samples pre-transplant, day 1 and 30 were analysed and compared between those who developed acute rejection and those who did not.
Results: Significantly higher levels of IP-10 and NGAL were seen day 1 post-transplant in those patients who developed acute rejection ($p < 0.0001$ and 0.005 respectively) and area under the curves (AUC) of 0.74 and 0.67 respectively were generated (Figure 1).
Conclusions: Serum levels of IP-10 and NGAL are significantly higher on day 1 post-transplant in those HLAi recipients who develop acute rejection and could provide a mechanism for stratifying future immunosuppression or surveillance strategies.

O224 SERUM AND URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN AS PREDICTIVE BIOMARKER FOR ACUTE REJECTION AND DELAYED GRAFT FUNCTION AFTER KIDNEY TRANSPLANTATION

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Purpose: Neutrophil gelatinase-associated lipocalin (NGAL) has emerged an early marker protein for kidney dysfunction in various clinical settings. Data on NGAL expression during acute rejection (AR) after kidney transplantation in the early postoperative phase have been missing so far. The main focus of this study was to analyze the possible implication of NGAL during AR and delayed graft function (DGF) following kidney transplantation.
Material and methods: Serum and urine samples of 170 patients undergoing primary kidney transplantation since October 2010 were collected preoperatively and postoperatively from day 1 to 15. NGAL was analyzed by ELISA. Mean values of serum and urinary NGAL before the respective event were compared between AR (event = rejection therapy), DGF (event = last dialysis) and control (C) patients (event = discharge or 15th postoperative day) using non-paramatric Kruskall Wallis Tests without multiple test corrections. A p-value < 0.05 was considered as significant. SPSS 17 was used for statistical calculations.
Results: A total of 170 patients were included in this prospective study. Pre-evaluation of 21 patients (13 C, 4 DGF, 4 AR) showed significant differences of serum ($p = 0.005$) and urinary NGAL ($p = 0.022$) between control and DGF and AR. Mean values of serum NGAL (ng/ml) were as follows: 133.2 (C), 241.3 (DGF), 193.6 (AR). Mean values of urinary NGAL were as follows: 37.1 (C), 99.3 (DGF), 80.5 (AR).
Conclusion: Serum and urinary NGAL are sensitive markers of graft dysfunction and acute rejection in the early postoperative phase after kidney transplantation. They may accelerate initial therapy in allograft recipients with acute rejection.

O225 CORTICOSTEROIDS WITHDRAWAL IN STABLE MAINTENANCE RENAL TRANSPLANT PATIENTS

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Corticosteroids are powerful antiinflamatory with immunosuppressant effects utilized in maintenance therapy following kidney transplantation and are associated with a higher rate of side events in comparison with protocols involving early corticosteroid withdrawl. The present paper reports the results of cessation of steroids in stable maintenance renal transplant patients.
Patients and methods: One hundred fifty seven deceased kidney grafted patients (51% men), aged 56.5 ± 12.4 years, with follow-up of 72 months (1–247) and steroids withdrawl period of 48 months (1–198) follow-up steroid free were studied. Etiology of end stage renal disease was secondary to Glomerulonephritis 31%, Diabetes 22%, Policystic disease 14%, Tubulointerstitial nephropathy 13%, Vascular 5%, Unknown 17%. The patients were on Prednisone 5–10 mg dairy combined with Cyclosporine 50–150 mg/Tacrolimus 0.5–6 mg, associate to Mycophenolate Mophetyl 250–2000 mg, Sodium Micophenolate, 360–900 mg or Azatioprine 50–75 mg, and Everolimus 1–4 mg. Steroids were diminished gradually in three months period and some patients receibe monotherapy only.
Results: Basal serum creatinine was 1.54 ± 0.6 mg/dl and after 5 years followup 1.4 ± 0.5 mg/dl. Basal blood glucose concentration was 130 ± 12 mg/dl and after 5 years 109 ± 0.8 mg/dl. Weight was maintained. At 5 years, graft and patient survival were 100%. There was no acute rejection after steroids withdrawl. After withdrawl blood pressure control was achieved with less antihypertensive drugs. Lipids diminished slightly with less cholesterol-lowering drugs.
Conclusion: Corticosteroids could be withdrawn safely in stable renal transplant patients and avoid morbidity and adverse events related to chronic utilization improving survival and quality of life.

O226 ENTERIC-COATED SODIUM MYCOPHENOLATE IN RENAL TRANSPLANT PATIENTS

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Introduction: Treatment with Sodium Mycofenalate (SMP) in renal transplant improvement tolerance compared to Mophetil Mycophenolate (MMF). We report our experience.
Patients and methods: Eighty patients with deceased donor kidney transplantation (50 men and 30 women), started treatment with MPS in replacing MMF. The age of the patients was 54 ± 12 years, with 8 ± 4 (1–5) years of follow up. Immunosuppression was based on Prednisone, MMF and Cyclosporine/Tacrolimus. The blood concentration of mycophenolate remained between 2 and 4 μg/ml. MMF was discontinued abruptly and MPS began in equimolar doses. Cyclosporine/Tacrolimus and Prednisone was maintained. The MPS indication was for gastrointestinal intolerance, mainly diarrhea.
Results: After MPS the symptoms improved in 85% of patients. Renal function was preserved, with serum creatinine of 1.6 mg/dl. No acute rejection presented. The incidence of gastrointestinal complications (diarrhea) was significantly lower in MPS 65% vs. 89% with MMF. Patients received 720 mg daily MPH.
Conclusion: MMF intolerant patients with gastrointestinal symptoms may increase the dose of MPS and decrease symptoms, with better quality of life.

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OS27- DCD IN LIVER TRANSPLANTATION

O227 DCD LIVER TRANSPLANTATION CONFERS A SIGNIFICANT SURVIVAL BENEFIT COMPARED TO WAITING LONGER FOR A DBD ORGAN

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Background: In the context of shortage of suitable organs for transplantation, it is often not clear whether a patient should receive a "marginal" organ from a DCD donor which might adversely impact survival, or remain on the waiting list for a more "optimal" liver from a DBD donor. We thus aimed to examine the consequence of waiting for an "optimal" organ by comparing the survival of patients after a DCD transplant to those who had a DBD transplant or remained on the waiting list (DBD/WL).
Method: Patients placed on the liver transplant waiting list in Cambridge between 1st January 2008 and 31st December 2011 were identified from a prospectively maintained database. For patients previously transplanted, only the current status was considered (DCD or DBD/WL). A Kaplan-Meier plot and log-rank test were used to compare survival time from listing between DCD and DBD/WL patients. To compare survival from time of transplantation, DCD patients were individually matched to up to 3 DBD/WL patients chosen at random. These DBD/WL patients had to be on the waiting list for the same length of time or longer to the matched DCD patient. Data was analysed using a Cox regression model stratified on matched sets to obtain a hazard ratio, adjusted for age at listing, UKELD score and HCC status. The matching process was repeated 1000 times from which a distribution of hazard ratios was obtained.
Results: Fifty-two DCD patients and 386 DBD/WL patients were included in the analysis. A significant difference was detected between the survival time distributions from listing between the DCD and DBD/WL groups (log rank test $p = 0.040$; figure 1). Using a stratified Cox proportional hazards model, the risk of death was 79% lower in the DCD group than the DBD/WL group (HR=0.207 [95%CI: 0.045, 1.004]).
Conclusion: Receiving a liver transplant from a DCD donor confers a significant survival benefit compared to remaining on the waiting list for an "optimal" DBD organ to become available.

O228 DONATION AFTER CIRCULATORY DEATH LIVER TRANSPLANTATION: IS DONOR AGE AN ISSUE?

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Background: Donation after circulatory death (DCD) donors >55 years are usually not considered suitable for liver transplantation (LT). At our institute, age is not an absolute exclusion criterion to refuse DCD liver grafts. We retrospectively compared the transplant outcome of patients receiving older DCD liver grafts to the younger ones.
Methods: Seventy DCD liver transplants have been performed from 2003 to 2012, which includes 32 liver grafts from younger donors <55 years (group A), 20 between 56 and 69 years (group B), and 18 from older donors ≥70 years (group C). The three groups were compared in terms of donor and recipient demographics, procurement and transplantation conditions, peak laboratory values during the first post-transplant week and results at 1 and 3 years. Results are expressed as median ± IQR.
Results: No difference other than age in donor and recipient characteristics as well as procurement conditions was noted between both groups. Median donor age of the group A was 44 (38–45) years, in group B 62 (60–64) years and 73 (71–75) in group C. Median primary warm ischemia time (WIT) were 20 (17–22), 21 (19–25) and 19 (16–23) min, respectively (NS). Median cold ischemia time (CIT) was 236 (229–294), 245 (227–290) and 210 (195–277) min, respectively (NS). Peak AST (UI/ml) was 1162 (1072–3971), 1416 (1006–2752), and 1067 (902–4037), respectively (NS). There was no primary nonfunction and one patient needed retransplantation for artery thrombosis. Biliary complications occurred similarly in both groups, without graft loss secondary to ischemic cholangiopathy. Graft and patient survivals were not different at one and three years.
Conclusion: This study shows comparable results between DCD liver transplants from younger and older donors. Therefore donor age >55 years should not be a contraindication to DCD liver transplantation if other donor risk factors (such as WIT, CIT) are minimized.

O229 LIVER TRANSPLANT WITH UNCONTROLLED DONORS: INCREASING EXPERIENCE AND IMPROVING RESULTS. THE MADRID EXPERIENCE

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Background: There is a consistent experience in liver transplant with the use of grafts from donors after controlled cardiocirculatory death criteria (DCD), however, reliable information about liver transplantation with uncontrolled DCD (uDCD) is still scarce. In this study, the widest experience in liver transplant in the uncontrolled DCD setting is reported.
Methods/Materials: During the period from January 2006 to September 2012, after 454 extrahospital protocol activations (donor transfer after unsuccessful resuscitation), 58 liver transplant candidates were transplanted on, with grafts obtained from uDCD, under stringent criteria (Group 1). We considered 48 of them eligible for this study. Simultaneously, a control group, consisting of 266 liver transplant recipients, transplanted on with donors after brain death (BDD), during the same period of time, was designed (Group 2). A minimum 6 months follow up time was accomplished.
Results: Both groups 1 and 2 were homogeneous and comparable without relevant differences, but in donor age (donors were younger in group 1, range 18–55 years). HCV cirrhosis was found to be the most prevalent indication for liver transplant in both groups (50% of HCV in Group 1 and 43.6% in Group 2). Eight patients were retransplanted on in goup 1, five of them because of primary nonfunction and other two because of ischemic colangiopathy. No significant differences were observed between the groups when 1 and 3 year recipient survival (85.2% and 69.3% in group 1 vs. 82.4% and 74.5% for group 2 respectively, $p = 0.841$) or graft survival (72.5% and 62% in group 1 vs. 80.5% and 72.1% for group 2, $p = 0.116$) were compared.
Conclusion: uDCD donation, under stringent criteria, has proven to offer a safe and effective source in order to expand the donor pool for liver transplant.

O230 RESULTS USING LIVER GRAFTS FROM DONORS OVER 80 YEARS OLD: A SINGLE-CENTRE RETROSPECTIVE ANALYSIS

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Background: Many liver transplant (LT) centers have adopted the use of extended criteria donors to limit the gap between recipients and available grafts. The use of old donors is the most common strategy to increase the donor pool but it is associated with a higher risk of graft non-function and worse long term results, especially in HCV positive recipients. We analyze our results using grafts from 80 years or older donors in LT.
Patients and methods: Single-center retrospective review of LT performed between January 2001 and December 2010 at the Cisanello Hospital – University of Pisa. LT were divided in four groups based on donor age: below 60 years old; between 60 and 69; between 70 and 79; 80 years old and over. Recipient and donor characteristics, early and late graft loss and graft survival were analyzed.
Results: During the study period we performed 929 orthotopic LT. After excluding retransplantations, ABO incompatible LT and LT for acute liver failure we analyzed 842 LT. There were 348 LT (41.3%) using donors younger than 60 years old, 176 LT (20.9%) between 60 and 69 years old, 233 LT (27.7%) between 70 and 79 years old and 85 LT (10.1%) older than 80. Global early graft loss was 5.1%, mainly from PNF, and there were no differences between groups. There were no differences observed when comparing graft survival by donor age (5-years graft survival under 80 vs. 80 years and over: 78% vs. 77.1%, $p = 0.377$), Young grafts (from donors under 60 years) versus old grafts (from donors of 80 years and over) had similar 5-years graft survival (78.5% vs. 77.1%, $p = 0.308$). In the group of donors over 80 group graft survival in HCV positive recipients we was lower than in HCV negative (3-year survival: 65.4% vs. 85.7%, $p = 0.034$).
Conclusions: Grafts from donors older than 80 years may provide optimal results when using good donor selection and allocation policies.

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O231 DONOR MORBIDITY IN RIGHT AND LEFT LOBE LIVING DONOR LIVER TRANSPLANTATION

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Background: Donor safety must be the top priority in living donor liver transplantation (LDLT). To clarify donor safety, we evaluated the postoperative liver function and morbidity in living donors.
Patients and methods: Between April 2006 and March 2012, donor operations, comprised the right lobe (RL) graft ($n = 168$) and left lobe (LL) graft ($n = 140$), were performed for LDLT. We studied the serial changes of postoperative liver function and the details of donor complications between RL and LL donors, retrospectively.
Results: (i) Postoperative liver function: Postoperative serum T-Bil levels of RL donors were significantly higher than those of LL donors during 2 weeks after donor operation. Serum PT-INR levels of RL donors were significantly higher than those of LL donors during 7 days after operation. Hyperbilirubinemia and coagulopathy were persisted in RL donors, liver function of LL donors were easily normalized within postoperative 7 days. (ii) Donor Morbidity: The overall complication rate of RL and LL donors were 59.5% and 30.7%, respectively ($p < 0.05$). Biliary complication rate was 7.1% in RL donors, and 5.0% in LL donors (p = NS). Regarding complication severity, Clavien's grade II and IIIa complications rate were higher in RL donors than in LL donors (Grade II: 23.2% vs. 9.3%, Grade IIIa: 14.3% vs. 7.9%, $p < 0.05$, respectively). Clavien's grade IIIb complication occurred in only 1 (0.7%) LL donor, and reoperation was required for delayed biliary stricture in 7 months after surgery. No donor mortality was observed in this study period. Compared with our previous outcome (1990–2006), the occurrence rate of RL donor biliary complication (2006–2012) was reduced from 12.2% to 7.2%, and the severity was quite lower.
Conclusion: Biliary complications in donor surgery can be reduced and avoidable by our surgical innovations. Because of good recovery of postoperative liver function and low morbidity, LL graft should be recommended in LDLT for further donor safety.

O232 DONOR QUALITY IN "HIGH URGENCY" LIVER TRANSPLANTATION

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Introduction: There are only a few studies dealing with preoperative outcome determination in high urgency (HU) liver transplantation. We reviewed the database at our centre for outcome determining variables in HU liver transplantation.
Patients and methods: Since 2004, 51 patients in HU-state were transplanted at our institution. We analysed preoperative donor and recipient data and correlated these with the outcome.
Results: The overall, estimated 5-year-survival of our patients was 64.7%. Hereby, the genesis of the liver failure leading to HU-liver transplantation does not play an outcome-determining role. The need of a single organ replacement therapy had no impact on the postoperative outcome but a triple combination of mechanical ventilation, renal replacement therapy and need of vasopressors went along with a significant worsened outcome. A ROC-analysis revealed a cut-off value for Donor-Risk-Index (DRI) < 1.55 for outcome determination. Especially DRI played a major role for the postoperative outcome: patients receiving an organ with DRI < 1.55 showed an estimated five-year-survival rate of 85% compared to patients with DRI-organs > 1.55 (estimated 5-year survival: 51.6%; log-rank test p = 0.027). Analysing the combination of recipient's state (defined as need of triple organ replacement therapy) and donor organ quality revealed that even bad recipients profit from good organs (5-year survival 75%), better than "good" recipients receiving a bad organ (5-year survival 61.9%).
Conclusion: Even HU-patients with need of triple organ replacement can transplanted with an acceptable outcome if they can be transplanted with a good quality organ. The DRI cut-off value in our patients was 1.55 but this should be validated in a larger patient cohort.

O233 USE OF GRAFTS FROM HEPATITIS C VIRUS POSITIVE DONORS IN LIVER TRANSPLANTATION: OUTCOMES UNDER CURRENT SELECTION CRITERIA

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Background: With an increasing demand, selected grafts from HCV-positive donors (D_HCV+) are accepted for liver transplantation (LT) in HCV-positive recipients. We analyzed those grafts for postoperative function, HCV-recurrence and long-term survival.
Methods: In all proposed D_HCV+ livers, biopsy was performed during harvesting: only livers with F0-F1 fibrosis and with low grade of inflammation (≤5/18) were accepted for LT. From 10/2002 to 12/2009, we performed LT in 341 HCV-RNA positive subjects: 23 (7%) received a graft from D_HCV+.
Results: Characteristics of donor (age, cause of death, DRI), recipient (age, BMI, MELD, HCV-RNA level at LT, HCC and HCV-genotype 1 prevalence), donor-recipient match (D-MELD), transplant procedure (graft type, cold ischemia time), re-LT and early allograft dysfunction prevalence were similar in patients who received the liver from D_HCV+ versus HCV-. Donor BMI and macrovesicular steatosis were lower in D_HCV+ group ($p < 0.01$). With a median follow-up of 6.6 years for surviving grafts, prevalence of serologically and histologically proven recurrent HCV hepatitis and 5-year graft survival were exactly equal in the two groups (78% and 60%, respectively).
Conclusions: Current selection criteria for livers from D_HCV+ are effective in extending the donor pool, because use of such grafts in HCV-positive recipients does not worsen their outcomes.

O234 MODEL TO PREDICT THE NEED FOR LIVER TRANSPLANTATION IN POLYCYSTIC LIVER DISEASE BASED ON OBJECTIVE CRITERIA

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Background: Polycystic liver disease (PCLD) with massive hepatomegaly can be an indication for liver transplantation (LTx). The mid-upper arm circumference below a cut-off value (women < 23.1 cm; men < 23.8 cm) is interpreted as a sign of severe malnutrition and is currently used to give patients priority on the LTx waiting list (e.g. Arrazola et al. Liver Transpl 2006; 12: S110–S111). This MELD exception criterion is rather subjective and has never been validated in PCLD. Furthermore, a model to predict the need for LTx in PCLD based on objective criteria does not exist.
Methods/Materials: We retrospectively established a cohort of PCLD patients all treated because of invalidating liver-related complaints from four tertiary centers in Belgium and the Netherlands (exclusion criterion: renal function < 30 ml/min).LV-index was calculated by liver volume (LV) measured by CT scan, and the Estimated Standard LV based on body surface area and Urata's equation (LV-index = LV/ESLV).
Results: The study population consisted of 108 patients: 34 were accepted for LTx based on clinical impression by the multidisciplinary LTx teams (group LTx); 74 (not considered for LTx) were given somatostatin analogues (lanreotide) to decrease liver volume (group LAN) (e.g. van Keimpema et al. Gastroenterology 2009; 137: 1661–1668). All patient characteristics are given in the table. Lower age, lower albumin; and higher LV-index were observed in group LTx. The mid-upper arm circumference was not different between the groups. Logistic regression was used to predict the need for LTx. The Odds ratios of the independent variables (confidence interval) were: age 0.92 (0.85–0.99); albumine 0.15 (0.02–0.9), LV-index 1.52 (1.07–2.16). AUC of the ROC curve analysis was 0.8 (0.7–0.9).
Conclusion: The need for LTx can be predicted based on objective parameters such as LV-index. This model is currently validated in an independent cohort.

O235 UTILITY OF 3-D VOLUME ANALYZER (SYNAPSE VINCENT) FOR EVALUATION OF THE PARTIAL GRAFT IN LIVING DONOR LIVER TRANSPLANTATION

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Background/Purpose: The accurate volumetry of the partial graft is essential in living donor liver transplantation (LDLT). Recently, useful application of 3-D volume analyzer in the field of liver surgery has been reported. The aim of this study was to clarify the utility of 3D volume analyzer for evaluation of the graft volume and estimated congested volume after the implantation in LDLT.
Material/Methods: Twenty cases of right lobe graft LDLT those images are available as digital data were included. Volumetry was performed by 3D volume analyzer SYNAPSE VINCENT (FUJIFILM Medical, JAPAN); the result was compared to the conventional method using by manual tracing of the liver boundary and summation of the liver area on each section. After depicting hepatic veins, estimation of congested area when sacrificing drainage veins of segment 5 (V5), 8 (V8), and accessory hepatic veins.

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Results: Graft weight measured immediately after perfusion at the back table was 81% (range, 70–104) of estimated volume by VINCENT. Estimated drainage area of V5 and V8 were 70 ml (0–171) and 74 ml (0–180) respectively. The summation of V5 and V8 area was equivalent to 11% (4–24) to the standard liver volumes of recipients. Five of six recipients who had right accessory hepatic veins had undergone reconstruction of those veins. The estimated drainage area of right accessory veins was 113 ml (90–117). Reconstructed veins had been patent without congested area of the liver, which was evaluated by postoperative CT.
Conclusions: Compared to conventional method, the similar accuracy was achieved by volumetry using VINCENT. In addition, volumetry by VINCENT is much quicker than conventional method. Furthermore, estimating congested volume by VINCENT was practical in deciding the type of the graft and whether to reconstruct MHV tributary and accessory hepatic veins. In conclusion, VINCENT is considered a quite useful tool to evaluate the partial liver graft in LDLT.

O236 DEFINING INITIAL POOR FUNCTION FOLLOWING LIVER TRANSPLANTATION OF DONORS AFTER CARDIAC DEATH (DCD)

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Background: Many definitions of initial poor function (IPF) following liver transplantation have been described albeit following donation after brainstem death (DBD). However, such definitions can not be extrapolated to the use of DCD grafts as clinical and post operative liver function are frequently inferior. Our primary aim was to define IPF in DCD grafts and its effect on in-hospital and overall patient/graft survival. Our secondary aim was to use peri-operative graft function to predict IPF.
Methods: A retrospective analysis of DCD livers transplanted at a single centre between June 2004 and November 2012 were analysed. IPF was defined as the presence of acute kidney injury in all of the first 3 days following transplantation or a >5 day need for organ support and its effect on outcome analysed. We reviewed liver function following transplantation at predicting IPF with discovery:validation groups (75%:25%).
Results: During the study period, 162 DCD liver transplants were performed. Using the definition, the incidence of IPF was 40%. The presence of IPF predicted in-hospital mortality, patient and graft survival ($p = 0.001$, 0.006, 0.04 respectively). Day 3 AST, Bilirubin and Alk Phos predicted IPF ($p = 0.002$, 0.02, 0.01). A ratio of AST X Bil/Alk Phos >100 on Day 3 significantly predicted IPF in the discovery cohort ($n = 120$; $p = 0.02$). In the validation cohort ($n = 42$), the sensitivity or specificity of this ratio at predicting IPF was 75% and 56% respectively.
Conclusion: We propose a new definition for IPF in DCD liver transplantation with consideration of clinical and post-operative liver function. This definition successfully predicted outcome. A ratio of liver function successfully predicted IPF in a discovery cohort and showed reasonable accuracy in a small validation group. Further large scale studies are required.

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OS28- ISCHEMIA-REPERFUSION INJURY IN CLINICAL ORGAN TRANSPLANTATION

O236 ENDOGENOUS SECRETED RAGE MRNA EXPRESSION IN THE TRANSPLANTED ORGAN IS INVERSELY ASSOCIATED WITH EARLY OUTCOMES OF LIVER TRANSPLANTATION

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Background: In animal testing the blockade of the receptor for advanced glycation end products (RAGE) attenuates the liver injury extent induced by RAGE-ligands. Likewise circulating truncated soluble isoforms of RAGE (sRAGE), acting as decoy of RAGE-ligands, protects by injury.
Aim: We investigate the association of donor (D) RAGE isoforms expression with early outcomes of liver transplantation (LT), the changes of RAGE-ligands and sRAGE after LT and their association with the development of early organ dysfunction.
Methods: We included 28 LT recipients (R) (53 $\pm$ 8.7 years) by deceased D (62.1 $\pm$ 17.3 years). In both D and LT R, we measured the tissue mRNA expression of full-length RAGE and its truncated isoform, the endogenous secreted RAGE (esRAGE). The RAGE-ligands -N (ε)-carboxymethyllysine (CML) and high-mobility group protein 1 (HMGB1)- and the sRAGE plasma levels were measured before LT, after graft reperfusion (GR), 1 and 7 days after LT.
Results: In LT R tissue RAGE levels were higher than in healthy D ($p < 0.01$), and directly correlated with MELD score before LT, likewise to basal HMGB1 plasma levels ($\hat{a} = 0.425$, $p = 0.043$ and $\hat{a} = 0.448$, $p < 0.05$ respectively). Basal CML plasma levels were higher in LT R than D ($p = 0.02$), decreased after GR ($p < 0.0001$) but returned to basal values at 7 days after LT. HMGB1 increased after GR ($p = 0.0001$) and returned to basal values 1 day after LT while sRAGE decreased significantly 7 days after LT ($p = 0.0001$). The MELD score 7 days after LT inversely correlated with esRAGE graft ($\hat{a} = -0.48$, $p = 0.03$) and tended to correlate directly with HMGB1 after GR ($\hat{a} = 0.42$, $p = 0.07$) and with R gender ($\hat{a} = 0.49$, $p = 0.015$). Multivariate analysis showed that only graft esRAGE expression was a significant determinant of MELD score 7 days after LT ($\hat{a} = -0.788$, $p = 0.0005$).
Conclusions: The inverse correlation between graft esRAGE mRNA expression and the MELD score 7 days after LT underline the importance of this protective factor for graft survival and patient outcomes.

O237 TIME-ZERO BIOPSY ISCHAEMIA/REPERFUSION INJURY AFTER LIVER TRANSPLANTATION

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Introduction: The utility of time-zero biopsies after orthotopic liver transplantation (OLT) remains unclear. The aim of this study was to evaluate histological grade of ischaemia/reperfusion injury (IRI) on time-zero biopsy as a prognostic indicator following OLT.
Methods: Between February 2000 and 2010, 647 OLT were performed at our centre. Time-zero biopsies were available for 474 patients. Patients were divided into four groups based on histological grade of IRI: nil (50), mild (280), moderate (124) and severe (22) and clinical data compared for each.
Results: Multivariate analysis confirmed donor age, DCD donation, cold ischaemia time and time-zero biopsy steatosis as independent predictors of IRI severity.

The degree of IRI on biopsy correlated closely with graft outcome. In particular, a severe IRI grade was associated with significantly greater post–transplant morbidity compared to the other three groups, with markedly higher rates of primary non-function (9.1% vs. 0.9%; $p = 0.006$), early graft dysfunction (55% vs. 21% $p < 0.0001$) and the need for re-transplantation within 90 days (14% vs. 2.6%; $p = 0.02$).

One year graft survival in nil, mild and moderate groups were significantly better than in the severe group (88%, 87%, 89% and 55% respectively; $p < 0.0001$).

Notably the degree of steatosis on biopsy did not correlate with graft survival ($p = 0.37$), re-transplantation within 90 days ($p = 0.82$) or PNF rate ($p = 0.07$), suggesting severity of IRI to be an independent predictor of graft outcome.
Conclusion: Time-zero biopsies have value in predicting adverse clinical outcomes following OLT and allow identification of patients at risk of a complicated post-operative course. Our analysis suggests that early re-transplantation should be considered for recipients whose time-zero biopsy reveals severe IRI.

O238 HYPOTHERMIC MACHINE PERFUSION IMPROVES OUTCOMES IN DCD KIDNEYS

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Background: Utilization of kidneys from DCD donors has increased to overcome organ shortage. These kidneys have comparable long term outcomes to DBD kidneys, despite the higher incidence of DGF and worse initial graft function. Aim of this study was to assess the effect of hypothermic machine perfusion (HMP) on the early graft function and to evaluate the correlation between perfusion parameters and early graft function.
Method: We analysed the data of 130 DCD kidney transplants performed in our centre between 1 January 2010 and 22 October 2012. We compared DCD kidneys on HMP ($N = 52$), using the LifePort© (from Organ Recovery Systems) to DCD kidneys preserved in cold storage (CS) ($N = 78$). Kidneys transplanted in combination with pancreas and those performed as double transplants were excluded.
Results: There was no significant difference in recipient age 59.65 $\pm$ 19.84 years in HMP group vs. 57.85 $\pm$ 12.13 years in CS ($p = 0.40$); however Cold Ischaemia Time (CIT) was significantly longer in HMP group (14.73 $\pm$ 4.3 vs. 11.32 $\pm$ 4.5 h), $p < 0.001$. We found no difference in the incidence of functional DGF, 65.4% and 74.4% in HMP and CS groups respectively ($p = 0.27$). Also, the eGFRs were similar at any time point. In a logistic regression analysis, we found that higher donor age (Exp(B) = 1.029, $p = 0.038$), longer CIT (Exp(B) = 1.114, $p = 0.031$) and CS as the type of storage (Exp(B) = 2.5, $p = 0.43$), significantly increased the risk of DGF. In linear regression analysis the donor age, CIT, and type of storage showed significant correlation with the eGFR at 1, 3 and 6 months. At 1 and 2 years only the donor age correlated significantly with the eGFR. Analysing the perfusion parameters only CIT and starting resistance were found to correlate significantly with DGF (Exp(B) = 1.17 and 21.26 respectively, $p = 0.05$) in a logistic regression model.
Conclusion: HPM can neutralise the adverse effect of long CIT. Apart from the start resistance no other perfusion parameter correlated with outcomes.

O239 THE RELATIONSHIP BETWEEN NO_3 AND NO_2 POST PERFUSION IS PIVOTAL IN DCD KIDNEYS IN THE CONTEXT OF REPERFUSION INJURY

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Reperfusion injury (RI) is an important factor in DCD organs due to warm and cold ischemia. The importance of nitric oxide (NO) in the generation of reperfusion injury is pivotal. The role of NO_2 and NO_3 is probably different to each other and varies in phases of the RI. NO produced in both the kidney and systemically might be important.
Aim: Study the changes of NO (NO_2 and NO_3) following RI in DCD kidneys. Associate those changes to known risk factors for DGF.
Methods: NO_3 and NO_2, were measured by the Griess and Ozone-based chemiluminescence methods, preoperatively, post induction, at 30 min, 2 h.
Results: Median (mean) NO_3 base line values measured by Griess reaction (gNO_3) were 27 (30) μmoles/l. The respective median NO_2 and NO_3 values measured with the chemiluminescence method (cNO_2, cNO_3) were 0.50 and 38.6μmoles/l. The baseline cNO_3 was somewhat correlating with the patient age (Spearman cc = 0.55, $p = 0.09$). There is a tight correlation between 2 h cNO_3 and gNO3 (cc = 0.9, $p = 0.0001$). The changes of cNO_2 and cNO_3 at 2 h are independent of recipient age or each other but they are affected by their respective baseline values ($p = 0.02$ for cNO_2 and $p = 0.03$ for cNO_3).Univariate analysis shows that recipient age (0.007), donor age (0.025), first WIT (at donor) [$p = 0.01$], second WIT (at recipient) [$p = 0.02$], but not CIT affect the cNO_3/cNO_2 ratio at 2 h post perfusion. Regression analysis showed that the level of cNO_3/cNO_2 ratio is dependent on the age of the donor ($p = 0.02$), age of the recipient ($p = 0.004$), the 1st WIT ($p = 0.02$), and the 2nd WIT ($p = 0.018$) but not CIT and the baseline values of cNO_3 and cNO_2 ($p = 0.05$). Interestingly the 30 min cNO_3 and ratio is also affected by CIT ($p = 0.04$) but not primary WIT.
Conclusion: The ratio of NO_3 to NO_2 post perfusion might be more strongly associated with the RI in DCD kidneys. These early results show that the change of NO_3 and NO_2 levels post perfusion are associated with donor age, CIT, WIT and recipient age.

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O240 ROLE OF SOLUBLE FGL2 IN RENAL ISCHEMIA REPERFUSION INJURY IN A PORCINE AUTO-TRANSPLANTATION MODEL

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Background: Regulatory T cells (Treg) protect kidney against ischemia reperfusion (IR) injury, while the mechanism is not clear. Soluble fibrinogen-like protein 2 (sFGL2), a novel effector of Treg, is up-regulated in kidney injuries. This study investigated the dynamic change and role of sFGL2 in a porcine auto-transplantation model.
Materials and methods: The left kidney was retrieved from mini pigs ($n = 15$) and infused by University of Wisconsin solution into the renal artery with the renal artery and vein clamped for 24-h cold storage (CS). After the right nephrectomy, the left kidney was auto-transplanted into the right for 2 weeks. Blood samples were taken daily, and three pigs were sacrificed for sample collection at day 2, 5, 7, 10 and 14 posttransplantation respectively. All animal work was performed under the regulation layout by Chinese animal welfare authority.
Results: Serum creatinine and blood urea nitrogen sharply increased at day 1, peaked at day 3, gradually decreased from day 5, and closed to normal level at day 14. Pro-inflammatory cytokines, caspase 3, apoptotic cells and myeloperoxidase+ cells in the kidney showed the same trend, indicating that renal IR injury was maximized during day 3–5 and followed by gradual recovery. Serum sFGL2 presented a fluctuating increase and reached the peak at day 10, while FGL2 mRNA in the peripheral white blood cells kept raising from day 1 to 10 and sharply decreased after day 11. sFGL2 and its receptor FcIÄRIIB were notably higher at day 5 and 7 in the kidney. The high expression of sFGL2 associated with Fc IÀRIIB during renal recovery revealed that sFGL2 may exert protective effects and contribute to kidney recovery.
Conclusion: Both local and peripheral change trend of sFGL2 was closely related to renal recovery, suggesting sFGL2 a potential mediator of renoprotection.

O241 THE ALARMIN CONCEPT APPLIED TO HUMAN RENAL TRANSPLANTATION: EVIDENCE FOR A DIFFERENTIAL IMPLICATION OF HMGB1 AND IL-33

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Background: The endogenous molecules high mobility group box 1 (HMGB1) and interleukin-33 (IL-33) have been identified as alarmins, capable of mediating danger signals from tissue damage. Here, we addressed their possible role as innate-immune mediators in ischemia-reperfusion injury (IRI) following human kidney transplantation.
Methods: Samples were obtained from a single-center prospective pilot study including 27 renal transplant patients. IL33, sST2 and HMGB1 serum or urine levels were measured by ELISA after blood and urine collection at: pre-transplant, 30 min, 3 h, Day 1 and Day 3 after declamping. Leucocyte or iNKT cell activation was evaluated by transcriptomic or flow cytometry analysis. For study on mechanisms, we took advantage of an *in vitro* endothelial cell model of hypoxia/re-oxygenation that is widely recognized for mimicking *in vivo* conditions after IR.
Results: Urinary HMGB1 and IL-33 levels were significantly increased as soon as 30 min after reperfusion, as compared to those before treatment. Moreover, both serum and urinary IL-33 (but not HMGB1) increase was positively correlated with cold ischemia time, from 30 min to 3 days post-transplantation. *In vitro*, human umbilical vein endothelial cells subjected to hypoxia condition released both HMGB-1 and IL-33, while only the latter was further increased upon subsequent re-oxygenation. Finally, we postulate that leukocytes from renal recipient patients are targeted by both HMGB1 and IL-33, as suggested by increased RNA of their respective receptors (TLR2/4 and ST2L) shortly after transplantation. Consistent with this view, we found that iNKT cells, an innate-like T cell subset involved in IRI and targeted by IL-33 but not by HMGB1was activated 1 h post-transplantation.
Conclusion: These results are in keeping with a potential role of IL-33 as an innate-immune mediator during human kidney IRI.

O242 SHOULD LUNGS BE COOLED AGAIN, AFTER NORMOTHERMIC *EX VIVO* LUNG PERFUSION (EVLP)

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Background: After EVLP the graft is usually cooled again, although there is no evidence that this is the best possible option. We compared outcomes between three techniques in a pig single lung transplant model.
Methods: Donor lungs were flushed, explanted and prepared for EVLP (2 h), after which the left lung was implanted in a recipient animal. Three groups ($n = 5$ pigs) were compared: (i) Cold [C]:lungs cooled on device to 15°C in 10–15 min and stored on ice for preparation; (ii) Warm [W]:preparation without cooling; (iii) Continued EVLP [EVLP]:lungs split on device and implanted while perfused with adjusted flow (PAP < 15 mmHg). Animals were monitored for 6 h with hourly functional assessment before/after exclusion of the native lung. Biopsies were performed for wet/dry [W/D].
Results: Implantation was longer in [EVLP] ($p < 0.05$) and survival was lower. Lungs in [W] showed the highest compliance (*$p < 0.05$) and the lowest PlatAwP, but comparable PAP, PVR and PaO2/FiO2 both before and after functional exclusion of native lung.
Conclusion: avoiding cooling of lungs after EVLP is not detrimental but might in fact be protective to the graft.On the other hand continuing EVLP during implantation is cumbersome and not associated to any functional benefit.

O244 A MOLECULAR MODEL OF ACUTE KIDNEY INJURY BY INTEGRATION OF "OMICS" DATA AND LITERATURE MINING

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Early and accurate diagnosis of acute kidney injury (AKI) and novel therapeutic options are still unmet clinical needs. Better understanding of AKI provided by "Omics" technologies may allow for the identification of novel biomarker candidates, drug targets and drugs for improved patient care.

We investigated a molecular model of AKI by combining a broad range of publicly available Omics data. A systematic literature search for AKI Omics studies and an automated literature mining for genes associated with AKI were incorporated into the analysis. A hybrid molecular interaction network covering about 15 000 human proteins and holding about 800 000 interactions were used as reference network to derive an AKI induced protein interaction network. This network was then segmented into distinct molecular subgraphs (processes) apparently relevant in AKI pathology, providing a molecular model of AKI.

The systematic literature search for human AKI Omics profiles revealed 19 studies (four SNPs, three transcriptomics, two metabolomics, eight proteomics, two miRNA), and literature mining identified 139 genes associated with AKI. Ten AKI-specific molecular subgraphs could be identified on the basis of the given AKI-specific feature set.

We further evaluated which of these processes were already being addressed by currently discussed AKI biomarker candidates. Only IL6, IL10 and CXCL10 were members of our molecular model whereas established AKI markers such as NGAL, KIM1, FABP1 and CST3 were found to be distant to the AKI-specific network. We therefore screened for further biomarker candidates able to better represent the molecular model of AKI and tested the principal suitability of such candidates in an independent data set.

We integrated data from human Omics studies and generated a molecular model of AKI providing a basis for rational biomarker panel selection. Next, we will use our derived AKI-specific molecular model to screen for novel treatment options via drug repurposing.

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OS29- CELLULAR TRANSPLANTATION

O247 BONE MARROW AND ADIPOSE TISSUE DERIVED MESENCHYMAL STEM CELLS CAN INDUCE HLA-SPECIFIC LYSIS BY CD8+ T CELLS

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Introduction: Bone marrow and adipose tissue derived mesenchymal stem cells (BM-MSC and A-ASC) are considered for cell therapy in clinical organ transplantation. Allogeneic cell usage has advantages but may harbor the risk of sensitization against foreign HLA. We evaluated whether BM-MSC and A-MSC are capable of inducing HLA specific lysis by CD8+ T cells.
Methods: BM-MSC and A-MSC were stimulated or not with 50 ng/ml IFNâ before co-culture with IL-2 activated HLA class-I mismatched PBMC. CD8+ T cells were isolated from these cultures after 7 days via FACS. BM-MSC and A-MSC (+/− IFNâ) were labeled with Europium and incubated for 4 h with CD8+ T cells. Lysis of MSC was determined by spectrophotometric measurement of free Europium.
Results: Co-culture of PBMC with BM-MSC or A-ASC resulted in the induction of CD8+ T cells capable of HLA-specific lysis of MSC. Lysis was increased when MSC were stimulated with IFNâ, which resulted in increased HLA I expression. Lysis of A-MSC was less prominent than of BM-MSC. CD8+ T cells of individuals that were sensitized against particular HLA subtypes showed increased capability of lysing MSC expressing those HLA subtypes.
Conclusion: BM-MSC and A-MSC can induce HLA class-I specific lysis by CD8+ T cells. These results indicate a potential risk of allogeneic MSC to sensitize against HLA and plea in favor of autologous cell usage for clinical application in organ transplantation.

O248 INFLAMMATORY RESPONSES AFTER INTRAVENOUS INFUSION OF MESENCHYMAL STEM CELLS

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Background: Experimental animal models show beneficial immunomodulatory effects of administration of mesenchymal stem cells (MSC) on ischemia-reperfusion injury and survival of organ transplants. The nature of the immunomodulatory response is, however, unknown.
Methods: C57BL/6-GFP MSC were intravenously infused in C57BL/6 recipient mice and expression of cytokines/chemokines examined in serum and organs.
Results: MSC homed to the lungs immediately after infusion and induced an inflammatory response. This response was characterized by increased mRNA expression of monocyte chemo-attractant protein-1 (MCP1), IL1-ƒó and TNF-ƒÑ in lung tissue 2 h after MSC infusion. Expression levels returned to normal after 20 h. Following the same timeline, serum levels of IL6, CXCL1 and MCP1 protein increased, demonstrating systemic immune activation after MSC infusion. In liver tissue, where no MSC were detected, MCP1 and TNF-ƒÑ mRNA levels peaked 4 h after MSC infusion. The expression of the anti-inflammatory cytokines TGF-ƒó, IL4 and IL10 was only marginally affected by MSC infusion. Nevertheless, 3 days after MSC infusion animals developed a milder inflammatory response to LPS.
Conclusions: The immunomodulatory effects of MSC may originate from an inflammatory response, which results in reduced immune reactivity. Understanding the immunomodulatory mechanisms of MSC treatment will contribute to the development of effective immune therapy with MSC.

O249 DIFFERENTIATION OF HUMAN PLACENTA-DERIVED MESENCHYMAL STEM CELLS INTO INSULIN-PRODUCING CLUSTERS WITH MIR-375

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Background: The most important objective in diabetes therapy is promoting the formation of new beta cells and one of these sources is using mesenchymal stem cells (MSC).Placental tissue holds great promise as a source of mesenchymal stem cells for regenerative medicine due to its plasticity, and easy availability.MicroRNAs (miRNAs) are a class of small non-coding RNAs that regulate gene expression. Accumulated evidence indicates that miRNAs play a central role in controlling a broad range of biological activities. For example miR-375 was one of the first miRNAs identified in the pancreas, and remains one of the best characterized in terms of function. It is expressed in the pancreas. Mir-375 has dual functions: mediating insulin secretion and pancreatic islet development.
Methodology: Human placental decidua basalis (PDB-MSCs) cells were obtained from human placenta. PDB-MSCs cells were then cultured, then in the third passage through chemical transfection entered mir-375 to them. Morphological changes were observed from the second day and the sixth day, cell clusters were formed. RNA extracts were taken at 4, 7 days intervals after transfection. The expression some of the transcription factors were identified through REAL- time qPCR. On the sixth day, the potency of the clusters in response to high glucose were tested through Eliza method.
Result: REAL- time qPCR analyses showed that the low expression some of the specific pancreatic transcription factors in PDB-MSCs cells exist before transfection. The expression of these factors was remarkably higher in the 4 days after transfection and the expression of them increased after seventh days. When glucose density increased, the cells had capable of producing insulin.
Conclusions: Compared with other research work carried out for the production of beta cells from various cell sources by using some of the growth factors, we were able to in a much shorter time produce Insulin-Producing Clusters by adding mir-375 into the mesenchymal stem cells. and they capable of producing insulin in response to glucose with a remarkable ability to express specific pancreatic transcription factors.

O250 THE METABOLIC EFFECT OF HEPATOCYTE TRANSPLANTATION IS INCREASED BY PHARMACOLOGICAL ENHANCEMENT OF DONOR CELL ENGRAFTMENT IN THE GUNN RAT MODEL OF CRIGLER-NAJJAR SYNDROME TYPE 1

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Background: The efficacy of hepatocyte transplantation is limited by the number of donor cells engrafting into the host liver. Barriers limiting engraftment include hepatic sinusoidal endothelial barrier, low sinusoidal blood flow, instant blood mediated immune response and Cyclooxygenase mediated inflammation.
Aim: Pharmacological modulation of these barriers to enhance hepatocyte engraftment was tested in mice. The resulting metabolic benefit of an enhanced cell engraftment was investigated in the UDP-UGT-1 deficient Gunn rat model of Crigler-Najjar syndrome type 1.
Methods: First series: C57/Bl6 mice were pretreated with Dextransulfate, Nitroglycerin, Naproxen, Cyclophosphamide or hepatic X-irradiation (HIR) prior to transplantation of hepatocytes from (Rosa)26 C57BL/6 mice. Engraftment of hepatocyte in the host's liver was quantified 72 h after transplantation. Second set: Gunn rats were pretreated with Cyclophosphamide, Naproxen or Cyclophosphamide+Naproxen and transplanted with donor hepatocytes from congeneic normal Wistar-RHA. Serial serum bilirubin levels were followed for six months.
Results: Mice: Hepatocyte engraftment was increased by Cyclophosphamide, HIR, and Naproxen by 97%, 92% and 52% respectively, over control ($p < 0.001$). No effect was seen with Dextransulfate/Nitroglycerin. Rats: 4 months after transplantation, mean reduction of serum bilirubin levels compared to sham-treated controls were: no drug: 32.0%, Cyclophophosphamide: 54%, Naproxen: 44%, Cyclophosphamide+Naproxen 68%.
Conclusion: A single preparative dose of HIR, Cyclophosphamide or Naproxen significantly increased hepatocyte engraftment in mice. The hypobilirubinemic effect of hepatocyte transplantation was increased by Cyclophosphamide or Naproxen compared to sham treatment. Combining both Cyclophosphamide and Naproxen doubled the metabolic benefit. These findings may be relevant in hepatocyte transplantation-based therapies for inherited metabolic disorders of the liver.

O251 CHARACTERIZATION OF CELLS ISOLATED FROM EXPLANTED DISEASED HUMAN LIVERS AND EVOLUTION AFTER COLD STORAGE

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Background: Mostly, human hepatocytes are isolated from liver-grafts not suitable for transplantation. We are developping cell isolation from the patients own diseased liver for retransplantation after allogeneic organ transplantation. This should confer an immunological advantage and improve outcomes with minimization of immunosuppression.
Methods/Materials: So far, isolation of hepatocytes from 14 explanted human livers from patients with different conditions leading to end-stage liver-disease were performed. Progenitor cell isolation was carried out with density gradient centrifugation and magnetic cell separation (MACS) verified by fluorescence activated cell sorting (FACS). Hepatocytes were cultured directly

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and after cold storage over night in different media (ChillProtec®, ChillProtec®plus, Williams'mediumE) for further analysis.
Results: A mean of 138 × 106 viable hepatocytes with a mean viability of 79.9% were isolated from explanted diseased livers (app.40 g). Density gradient centrifugation led to a mean number of 10.6 × 106 progenitor cells. FACS analysis showed a mean proportion of 8.5% of EpCAM+ cells after density gradient centrifugation, while MACS led to a mean proportion of 40.7% EpCAM+ cells, but extreme loss of cells (mean:0.4 × 106). Preliminary results suggest that diseases like PSC or autoimmune hepatitis lead to a larger number of hepatocytes than alcoholic liver disease, while the proportion of progenitor cell populations seems to be greatest in acute liver failure. Cold storage led to a significant loss of viable cells with WilliamsE culture medium (−24.5% after 24 h, −39.6% after 48 h) compared to the other solutions. Cell culture revealed stable cell function for up to 7 days.
Conclusion: A high number of hepatocytes and progenitor cells can be isolated from human livers with end-stage disease with a very good mean viability of 79.9%. With suitable solutions, cold storage of cells over night is possible with stable cell function in culture.

O252 IMPROVED SHORT TERM COLD STORAGE OF HUMAN HEPATOCYTES FOR TRANSPLANTATION

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Hepatocyte transplantation is a promising treatment for patients with metabolic liver diseases. Repeated cell infusions over 1–2 days improve clinical outcome. Isolated hepatocytes are usually cold-stored in preservation solutions between repeated infusions. However, during cold storage isolated hepatocytes undergo cell death. We investigated if tissue preservation and repeated isolations are better than storage of isolated hepatocytes when cold preserving human hepatocytes.
Methods: Liver tissue obtained from liver surgery or organ donors was divided into two pieces. Hepatocytes were isolated by collagenase digestion. Hepatocytes were analyzed directly after isolation (fresh) or after storage for 48 h at 4° C in University of Wisconsin Solution (UW cells). Liver tissue from the same donor was stored at 4° C in UW and hepatocytes were isolated after 48 h (UW tissue cells). Hepatocyte viability and function was evaluated by trypan blue exclusion, plating efficiency, ammonia metabolism, CYP1A1/2, 2C9, 3A7, 3A4 activities, phase II conjugation, and apoptosis evaluation by TUNEL assay and caspase 3/7 activities.
Results: Hepatocytes stored in UW showed a significantly lower viability compared to fresh cells or hepatocytes isolated from tissue stored for 48 h (54% vs. 71% vs. 79%). Plating efficiency was significantly decreased for cells stored in UW (40%) compared to Fresh and UW tissue cells (63% vs. 55%). No significant differences between UW cells and UW tissue cells could be shown for CYP activities or ammonia metabolism. Hepatocytes stored in UW showed a strong increase of TUNEL positive cells whereas TUNEL staining in hepatocytes isolated after 48 h was unchanged.
Conclusions: Although preservation of isolated hepatocytes in UW maintains function, cold storage of liver tissue and repeated hepatocyte isolations is superior to cold storage of isolated hepatocytes in preserving hepatocyte viability and function.

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OS30-DONATION/BIOLOGY, TECHNIQUE

O254 CREATE AN INTERACTIVE E LEARNING PORTAL TO INCREASE STAFF KNOWLEDGE AND UNDERSTANDING OF THE ORGAN AND TISSUE DONATION PROCESS

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Background: A key activity of the Australian Organ and Tissue Authority (The Authority) 2009 health reform was employing specialist donation staff (SDS) dedicated to improving organ and tissue donation processes in hospitals. Southern Health (SH), which is Victoria's largest health service, has experienced a threefold increase in Organ donation since the implementation. Alternative methods of education delivery have eventuated to meet staff need. The paper reports on the development of an E Learning Portal to deliver interactive and accessible education to all staff involved in the organ and tissue donation process.
Method: SDS utilised a strong knowledge base, and linked with an external IT consultant to place clinical knowledge in a usable interactive format. Four modules were proposed by the SDS. The first was the National Clinical (GIVE) trigger. This module was launched in February 2012 The GIVE Trigger is used in all Emergency Departments and Intensive Care units to identify potential donors. This was subsequently followed by the second module, Eye and Tissue donation, which was launched in October 2012. This module was designed for all medical and nursing staff.
Results: Over 700 SH staff have completed the online modules. Organ and tissue donation recognition, approach and consent rates are at an all-time high for the organisation which can be partly attributed to an increased awareness and understanding formed from the E Learning portal.
Conclusion: Due to the success of the E Learning Portal in SH, Donatelife Victoria has engaged with the SDS to launch the GIVE Trigger module across the jurisdiction. The eye and tissue module is also being adapted and made available to all hospitals across the state. E learning activities are now strategic activities at a National Level.

O255 A MULTIVARIATE ANALYSIS ON QUALITY OF LIFE AFTER LIVE KIDNEY DONATION

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Background: Live kidney donation has been proven to be a safe procedure with a very low mortality rate. However, data on QOL remains scarce. This study aimed to identify factors associated with changes in QOL after live kidney donation.
Methods: Data on QOL was prospectively collected from 501 live donors. The Short Form-36, that includes a physical (PCS) and mental component summary score (MCS), was administered pre-operatively and 1, 3, 6 and 12 months after operation. On both scores 50 resembles the score of the healthy Dutch population. The influence of demographic and peroperative factors on the PCS and MCS with linear, quadratic and logarithmic time interaction effects were analyzed.
Results: The average PCS and MCS scores at baseline were 57.2 (4.8) and 52.9 (6.7) and at month 12 were 54.8 (6.5) and 55.4 (7.5) respectively. Graft loss resulted in a 4.1 point increase on the PCS at month 6 ($p = 0.002$). An increase of 10 kg/m^2 in BMI resulted in a 2.2 point decrease on the PCS at month 12 ($p = 0.015$). The MCS at one year was 2.2 higher compared to baseline ($p < 0.001$). Death of the recipient resulted in a decrease on the MCS at month 1 (-2.9), 3 (-1.8) and 6 (-0.6). A 10 year increase in age resulted in 0.7 point reduction on the PCS and a 0.6 reduction on the MCS. Scores on the PCS and MCS at month 12 were higher than the healthy Dutch population. At month 12 male donors had a lower score on the PCS (decrease 0.6, $p = 0.34$) and overall a higher score on the MCS (increase 1.5, $p = 0.007$) compared to women.
Conclusion: This is the largest, prospective study assessing QOL in a multivariate fashion. Factors associated with a change in health-related QOL were BMI, gender, age and recipient and graft survival. Scores on both the PCS and MCS were excellent, when compared to the healthy Dutch population. Expectations towards a decreased postoperative QOL are unjustified and should pose no barrier to live kidney donation.

O256 END STAGE RENAL DISEASE IN KIDNEY DONORS

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Background: Current evidence suggests no increased risk of end-stage renal disease (ESRD) after kidney donation. Previous reports have lacked adequate controls, and have been underpowered.
Methods: We evaluated the incidence of ESRD in Norwegian kidney donors. A control group was selected from the HUNT1 survey. Through the Norwegian Renal registry end-stage renal disease (ESRD) was identified. Multiple imputation was performed to substantiate the analysis.
Results: We included 1901 Norwegian subjects who donated a kidney during the period 1963 through 2007 with a median follow-up of 15.1 (1.5–43.9) years. Compared with a control group eligible for donation, the risk of ESRD was increased (HR 11.38, 4.37–29.63, $p < 0.001$)). The cause of ESRD was primary renal disease in seven out of nine donors.
Conclusion: Kidney donors have increased incidence of ESRD compared to a healthy control group.

O257 AN ENHANCED RECOVERY PROGRAMME AFTER DONOR NEPHRECTOMY – A COHORT STUDY

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Introduction: Protocols to enhance recovery after surgery aim to reduce perioperative co-morbidity, length of stay and improve patient outcome. Such protocols aim to reduce the physiological stress response of surgery by preventing insulin resistance, restricting fluid and salt administration, using non-opioid analgesia and introducing an early post-operative return to diet and mobilisation. Enhanced recovery protocols have been successfully introduced in colorectal, orthopaedic, gynaecological, urological and hepatobiliary surgery but have not been reported in live donor nephrectomy programmes to date.
Methods: An enhanced recovery protocol was developed using guidelines from the Enhanced Recovery After Surgery (ERAS) group (Lassen et al, Arch Surg. 2009;144 (10):961–9). All patients underwent hand assisted laparoscopic donor nephrectomy (HALDN) via a left upper quadrant transverse incision. Standard perioperative management involved pre-operative overnight fasting with administration of 1000 ml intravenous 0.9% saline followed by intravenous morphine via a Patient Controlled Analgesia (PCA) device, 3000 ml of intravenous 0.9% saline with removal of catheter and return to diet 24 h post-operatively. ERAS patients received an in-dwelling rectus sheath nerve catheter (On-Q pain buster®) containing 0.25% bupivicaine at 5 ml/h, had their urinary catheter removed in the recovery ward, received no post operative intravenous fluid therapy and were encouraged to eat and drink on the evening of surgery. Retrospective analysis of patients ($n = 22$) receiving standard perioperative care (SPC) was compared with patients ($n = 14$) receiving perioperative care according to the ERAS protocol.
Results: Length of post-operative stay in the SPC group was higher than that of the ERAS group (4.4 vs. 3.2 nights $p = 0.11$). Rise in creatinine at day 2 showed no significant difference (SPC 39.0 $\pm$ 16.7 vs. ERAS 35.6 $\pm$ 14.2, $p = 0.57$) however fall in albumin concentration was significantly reduced (SPC 11.78 $\pm$ 4.99 vs. ERAS 5.45 $\pm$ 4.2, $p = 0.001$). 3/22 patients required readmission vs. 0/14 in the ERAS group. 11/22 patients vs. 2/14 had post-operative constipation.
Conclusions: This enhanced recovery protocol can be applied safely to patients undergoing HALDN. Post-operative length of stay, co-morbidity and need for readmission are reduced when compared to a group of patients undergoing standard care. This is a reflection of an improved rate of recovery amongst ERAS patients. Concerns regarding peri-operative fluid restriction on remaining renal function are unlikely to be valid. Fluid restriction and prevention of haemodilution (as demonstrated by preserved albumin concentration) may be beneficial to perioperative recovery.

O258 OPPOSITE EFFECTS OF PREDNISOLONE TREATMENT ON LIVER AND KIDNEY GRAFT FROM BRAIN DEAD RAT DONORS

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Introduction: This study investigated the effect of steroid treatment over liver and kidney obtained from BD animals, since contradictory evidence has been publish about its benefit.
Methods: BD was induced in rats by inflating a subdurally placed balloon catheter after saline or prednisolone treatment. Four hours after BD, serum, kidney and liver tissue were collected. Real Time qPCR and immunohistochemistry were perform for gene and protein expression.

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Results: Prednisolone treatment significantly reduces IL-6 and creatinine plasma levels, polymorphonuclear influx and inflammatory genes expression (IL-6, IL-1b and MCP-1) in both organs. AST, ALT and LDH plasma levels were not modified. Complement (C3) expression was decreased in kidney but increased in liver after prednisolone. Bcl2/BAX ratio was increased in kidney but decreased in liver in BD compared to sham animals, no changes were observed with prednisolone. Cellular protective gene (HSP-70) expression was down-regulated in the liver due to prednisolone treatment.
Discussion: This study shows that prednisolone significantly decreases inflammation and improves renal function, while not reducing liver injury. The persistence of complement activation and a decrease of protective cellular mechanisms in the liver due to steroid treatment may explain prednisolone treatment opposite effect in kidney compared to liver.

O259 DONOR NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL) CONCENTRATION PREDICTS POST TRANSPLANT ALLOGRAFT FUNCTION AFTER KTX

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Background: The donor pool for KTx has plateaued worldwide. Expansion of the pool by including LR-donations and donors who previously were not accepted is the only way to increase the numbers. Data on specific parameters to predict success/failure of KTx are limited. It has been suggested that NGAL may serve as an early marker for renal injury, but have not as yet been investigated in kidney donors (KD). Therefore, it was the objective to evaluate NGAL in KD as a predictor of early allograft function after KTx.
Method: This study prospectively evaluated NGAL (urine, serum) in healthy volunteers ($n = 30$) to compare results with (i) brain dead organ donors (BDOD) before organ procurement ($n = 58$), (ii) living related (LR) KD ($n = 15$), (iii) KTx recipients who received an allograft from a BDOD ($n = 58$) and (iv) KTx recipients who received an allograft from LR donor ($n = 15$). In addition, the study analyzed allograft function in associated kidneys in correspondent recipients that were classified into two groups depending on allograft function after KTx: initial function (IF) versus delayed graft function (DGF). The primary objective was to evaluate the predictive value of NGAL for post Tx allograft function. Secondary objectives were: (i) To compare NGAL levels in BDOD and CKD stage V patients on HD to healthy volunteers, (ii) to evaluate NGAL evolution post (LR)KTx by visit, etc.
Results: Study results demonstrate that urine (and serum) NGAL levels in corresponding KD correlate with post transplant allograft function where higher NGAL levels where predictive for DGF (Figure 1).
Conclusion: In summary, our data indicates that NGAL represents a novel, sensitive and non-invasive urinary (and serum) biomarker predictive for primary graft function after KTx. Even in cases where our classical diagnostic parameters do not allow further differentiation of potential KD (marginal donors), NGAL seems to remain a stable and significant indicator.

O260 FROM A CLASSICAL APPROACH OF "*IN SITU*" PERFUSION TO MODERN PUMPING TECHNIQUES IN DONORS AFTER CARDIAC DEATH

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Background: The contribution of kidney transplants from donors after cardiac death (DCD) is quite considerable. DCD donors in Russia are all uncontrolled (Categories I/II and V) by Maastricht.
Methods/Materials: From 1 January 2011 to 31 December 2012 we had explanted 454 kidneys from 246 donors (142 donors with brain death -DBD and 104 DCD). In 2011 we had explanted 130 DCD kidneys from which 12 were explanted using the normothermic extracorporeal membrane oxygenation (NECMO). In 2012 we had explanted 67 DCD kidneys from which in eight we had used our modified technique of Garcia – Rinaldi. Our modification contains the use of centrifugal pump in non – pulsatile manner.
Results: We compared results of kidney transplantations from DBDs and DCDs by following parameters: primary or delayed graft function, serum creatinin at the hospital discharge, the average number of hemodyalysis sessions. In the group of kidneys from DBDs the rate of DGF consisted 14.73% vs. 45.16% in the whole group of kidneys from DCDs. The rate of serum creatinin at hospital discharge in DBDs group consisted 1.39 mg/dl and in DCDs group – 1.69 mg/dl ($p < 0.01$). The number of hemodyalisis sessions required after kidneys transplantation from DBDs group was 1.31 vs. 2.29 in DCDs group. We also had analyzed results of kidneys transplantation from two small groups of DCDs where different perfusion techniques were used. In 12 cases of kidneys transplantation after NECMO use we have got the rate of DGF as 36.8%, serum creatinine at discharge as 1.31 mg/dl and average number of hemodyalisis is 1.63. In eight cases of kidneys transplantation after use of our modified technique we had observed the DGF in 12.5%, the level of serum creatinin was 1.5 mg/dl and hemodyalisis sessions required consisted 1.37. There are no PNF kidneys grafts have been observed in all groups.
Conclusion: Modern perfusion techniques in DCDs show more favorable results than classical method of "*in situ*" perfusion.

O261 LONGER DONOR BRAIN DEATH CAUSES DECREASED GRAFT SURVIVAL AFTER LIVER TRANSPLANTATION

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Background: Donor brain death has been known to have an independent negative effect on graft survival after transplantation when compared to living organ donation.

However, little is known about the effect of the duration of brain death in the donor on graft survival in the recipient. Earlier research suggests a neutral to slightly beneficial effect of longer brain death on transplant results in kidney transplantation. For liver transplantation (LTx), this has never been investigated.
Methods: We used an OPTN extract with donation and LTx data from 2006 to 2012. Cases with complete information about duration of donor brain death and graft survival after LTx were included. Brain death duration was defined as the interval between date/time of brain death declaration and date/time of cross clamp during organ recovery. The donors were divided into four 25-percentile groups according to brain death duration. Graft survival was calculated per group, and groups were compared using non-parametric tests.
Results: Of 36 405 records, 59.3% of donors were male, and mean donor age was 39.1 years. Cause of death was anoxia in 20.9%, CVA in 38.7% and head trauma in 37.6% of donors. Mean brain death duration was 29.7 h. Median graft survival in the group with shortest brain death duration (up to 20.9 h) was 797 days, compared with 738 days (20.9–27.8 h), 716 days (27.8–35.4 h) and 549 days (over 35.4 h) in the other groups. All differences between groups were significant ($p < 0.001$). Brain death duration did not have an effect on the incidence of acute rejection.
Conclusion: In summary, contrary to kidney transplantation, prolonged brain death has a detrimental effect on graft survival after LTx. Especially, brain death duration >35 h is associated with a clinically relevant shorter graft survival compared with liver grafts from donors with shorter brain death duration. These findings may be important for current donation logistics and allocation procedures.

O262 THE OPTIMAL USE OF AVAILABLE DONOR ORGANS: CLINICIAN VIEWS TOWARD THE CONTROLLED DONATION AFTER CIRCULATORY (DCD) KIDNEY TRANSPLANTATION PROCESS IN THE UNITED KINGDOM

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Background: Since 2007 the number of deceased kidney donors in the UK has increased by 25%, and this increase can be exclusively attributed to the increased use of kidneys from DCD donors. DCD donors now make up 40% of all deceased kidney donors (compared to just 15% in 2007). However, there remains very marked regional variation in DCD donation rates, suggesting that there may be widespread differences in clinical practices and opinions of DCD donation. The present study sought to gain insight into clinicians' views toward DCD kidney transplantation.
Method: Ninety-five key clinicians from 27 transplant and non-transplant centres across the UK, including 28 specialist nurses for organ donation (SNODs), 27 clinical leads for organ donation (CLODs), 20 nephrologists and 20 surgeons involved in transplantation and donation were interviewed using a semi-structured questionnaire. The findings described are from the qualitative arm of the study where the transcripts were analysed using framework analysis.
Results: There were a wide variety of opinions and practices involved in the kidney donation and transplantation process. Factors that were associated with variations in each transplant centre's process included the layout of the hospital, the geographical catchment area for NORS, the use and availability of the electronic organ offering system, the role and the relationship of the SNOD in ICU in discussing organ donation with the family, attitudes of the ICU team and views toward the "right time" for organ donation patient referrals.
Conclusion: For the optimal use of organs, the process plays an important part and was believed to be affected by the way that it had evolved at each centre and the attitudes of clinicians across it. There were a conflict of views between the organ donation and transplantation sides. Clinicians involved in donation would prefer clear guidance on referring potential donation patients however transplant surgeons considered this difficult to achieve.

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RS01 ANTIBODY MEDIATED REJECTION IN VASCULARIZED COMPOSITE ALLOTRANSPLANTATION

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Background: Clinical relevance of antibody-mediated rejection (AMR) in vascularized composite allotransplantation (VCA) remains unknown. While C4d deposition and presence of donor specific antibodies (DSA) have been previously described, the phenotype, clinical symptoms and treatment requirement and options have not been reported.
Patients: Two male patients presented with edematous hands and forearms and described a sensation of tension without any exanthema typical for a rejection episode at nine and three years after bilateral forearm and unilateral hand transplantation, respectively.
Results: Punch-skin biopsies revealed rejection grade Banff II-III in both patients. Immunhistochemical analysis identified large aggregates of lymphocytes with an architecture resembling lymph nodes. CD20 staining identified the center of the aggregates almost entirely consisted of B-lymphocytes. DSA (Luminex) were found at high levels in both patients for the first time since transplantation. Based on the predominance of B-cells and DSA with lack of response to conventional treatment with steroids and Tacrolimus dose increase, Rituximab was given at 375 mg/m^2 BSA. In response, clinical symptoms disappeared and biopsies showed normal skin with absence of B-cells. DSA were negative at 3 months after rituximab.
Conclusion: We herein report the first cases of a B-cell driven rejection with presence of DSA in VCA at nine and three years after forearm and hand transplantation. Rituximab therapy successfully reversed the event in both cases.

RS02 *IN VIVO* ENRICHMENT OF REGULATORY T CELLS BY BCL-2/BCL-XL INHIBITION PROMOTES TOLERANCE IN ALLOTRANSPLANTATION

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Background/Aim: Regulatory T cells (Tregs) are the guardians of immunological tolerance. Since Tregs and effector T cells (Teffs) express a different pattern of pro- and anti-apoptotic factors, the apoptosis pathway might represent a pharmacological target to shift the balance from alloreactive Teffs towards graft-protecting Tregs. In this study, we explored the effect of the pro-apoptotic small molecule Bcl-2/Bcl-xL inhibitor ABT-737 on Tregs and its relevance in transplantation.
Methods/Results: CD4+CD25+FoxP3+ natural and induced Tregs displayed a relative resistance to ABT-737 *in vitro* and *in vivo*, when compared to Teffs in a FoxP3-GFP transgenic mouse model. A short treatment with ABT-737 *in vivo* induced a significant enrichment of Tregs among CD4 T cells. This substantially potentiated the immunomodulatory effect of an induction therapy protocol including donor-specific transfusion and costimulation blockade (anti-CD154), leading to long-term survival of donor-type fully MHC-mismatched skin grafts without immunosuppression. Moreover, Tregs enrichment by ABT-737 was a critical component of a novel protocol to induce mixed chimerism and tolerance without myelosuppression.
Conclusion: Treg enrichment can be achieved *in vivo* by exploiting the relative resistance of Tregs to Bcl-2/Bcl-xL inhibition. This approach might find future clinical application to promote graft survival and tolerance after solid organ transplantation.

RS03 THE POTENTIAL OF PEDIATRIC THYMIC TISSUE AS A SOURCE OF CD25+FOXP3+ REGULATORY T CELLS (TREGS) FOR CELLULAR THERAPY IN ORGAN TRANSPLANTATION

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Introduction: Cellular therapy using Tregs to suppress graft-directed immune responses could reduce the need for life-long immunosuppression. Major challenges include isolating pure Tregs and expanding them to clinically relevant numbers. During infant cardiac surgery, thymectomy is typically performed to gain exposure of the retrosternal operative field. Evidence that therapeutic Tregs do not need to be HLA-identical to the recipient led us to study the potential of discarded thymuses as a source of Tregs for "off-the-shelf" cellular therapy.
Methodology: Thymuses (n = 11) were obtained during pediatric cardiac surgery; thymocytes (TC) were recovered through mechanical dissociation. CD25+ TC were isolated by magnetic cell separation and expanded with anti-CD3, IL-2, rapamycin and artificial antigen-presenting cells; CD25-depleted TC were controls. Phenotype was defined by flow cytometry. Stability of FOXP3 expression was assessed by analyzing the methylation status of the Treg Specific Demethylated Region (TSDR) within the FOXP3 gene. Expanded cells were co-cultured with anti-CD3/CD28-stimulated PBMC to determine suppressive capacity, analyzing proliferation and IL-2 production.
Results: TC isolated from thymic tissue were numerous (mean $\pm$ SEM: 8 $\times$ 109 $\pm$ 4 $\times$ 108); 2.6 $\pm$ 0.1% of TC were CD25+ cells. Isolated CD25+ TC were 73 $\pm$ 1.2% FOXP3+ and were Helios+CTLA-4+PD-1dimTGF-beta-. After 2 weeks culture, CD25+ TC expanded 4–60-fold, were >80% FOXP3+ and produced no IL-2 or IFN-gamma (controls: 0.4–28-fold expansion, <35% FOXP3+ and 58–65% produced IFN-gamma). TGF-beta was upregulated on expanded CD25+FOXP3+ TC. The TSDR was demethylated in >80% of expanded CD25+ TC (controls: <5% demethylated TSDR). Furthermore, in contrast to controls, expanded CD25+FOXP3+ TC efficiently suppressed proliferation and IL-2 production of PBMC >50% even at a 1:10 ratio of Tregs: PBMC.
Conclusion: Large quantities of CD25+FOXP3+ Tregs can be isolated and expanded from pediatric thymic tissue. Expanded Tregs had stable FOXP3 expression, produced no cytokines and strongly suppressed proliferation and IL-2 production of PBMC. Our results indicate that explanted thymuses are potentially an excellent source of Tregs for cellular therapy.

RS04 DEFINING FUNCTIONAL WARM ISCHAEMIC TIME IN DONORS AFTER CARDIOCIRCULATORY DEATH; A POTENTIAL TO EXPAND THE LIVER TRANSPLANT DONOR POOL

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Background: In the UK, the consensus definition of functional warm ischaemia time (fWIT) in DCD donation is the time between aortic perfusion and a systolic blood pressure of <50 mmHg OR oxygen saturations of less than 70%. As these are frequently not synchronous events, there are three different potential fWITs; withdrawal of treatment (WOT) to perfusion (TWOT), fall in sats <70% to perfusion (Tsats) and fall in blood pressure to perfusion (TBP). The aim of this study was to detail the correlation between the three respective timings and the effect of the different definitions on outcomes.
Methods: All DCD donor liver transplants performed between June 2004 and May 2012 were included in the study. TWOT, Tsats and TBP were collated from a prospectively held database locally and nationally. Outcomes analysed include patient/graft survival and biliary complications.
Results: In the study period a total of 139 Maastricht category III DCD liver transplants were performed at the unit. There was no correlation between Tsats and TBP, suggesting that these two times were not suitably used synonymously to mark the start of fWIT (r^2 = 0.43; Figure 1). Data analysis showed on average, a fall in sats preceeded a fall in blood pressure by 4 min. With a median follow-up of 20 months, there was no correlation of TWOT, Tsats and TBP on patient and graft survival and biliary complications.
Conclusion: Our data suggests that a stricter definition of fWIT is required. Using this definition of fWIT, there was no correlation between TWOT, Tsats and TBP on outcome. Defining a drop in BP of <50 mmHg alone as the start of fWIT may provide an expansion of the donor pool without compromising outcomes.

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BOS17-KIDNEY – LONG TERM I

BO201 EARLY DETECTION AND TYPING OF PROTEINURIA AFTER KIDNEY TRANSPLANTATION

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The prevalence of proteinuria after renal transplantation is high (>40%) and proteinuria is associated with reduced patient and graft survival. Usually proteinuria ranges 150–500 mg/24 h. There are two main causes of proteinuria after kidney transplantation: glomerular damage or reduced reabsorption of proteins by tubular cells. There are many data on the progression of proteinuria in long-term follow-up, but few data about quantity and type of proteinuria in short term after transplantation and about its possible clinical correlations and graft survival.
Methods: We analyzed 23 consecutive renal transplants. Before hospital discharge of patients we dosed proteinuria/creatininuria ratio on spot urine and 24 h proteinuria. Then we typed proteinuria on spot urine by nephelometry and we compared the proteinuria type with renal function and bioptic score of the donor kidney.
Results: The mean age of recipients was 63 years (range 37–72), nine were anuric patients on dialysis; mean hospital stay after transplantation 21 days (range 13–48), four patients had DGF, the median of creatinine was 1.87 mg/dl (range 0.87–4). The median proteinuria/creatininuria ratio was 0.414 (range 0.061–1.063), 24 h proteinuria 0.388 g/24 h (range 0.137–1.2). Typing of proteinuria showed eight patients with albuminuria and associated tubular proteinuria, nine patients with glomerular and tubular proteinuria. A total of 20 patients had tubular proteinuria, one patient albuminuria, and 1 had normal proteinuria.
Conclusions: Almost all patients at hospital discharge after kidney transplantation have tubular proteinuria, range 0.3–0.5 g/24 h. Our data confirm a good correlation between 24 h proteinuria and proteinuria/creatininuria ratio. No correlation was found between typing of proteinuria and pre-transplant residual diuresis, bioptic score and DGF.

BO202 RELATIONSHIP BETWEEN SOLUBLE UROKINASE RECEPTOR (SUPAR) AND THE DEVELOPMENT OF PROTEINURIA AFTER CONVERSION TO EVEROLIMUS

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Background: The use of mammalian target of rapamycin inhibitors (mTOR-I) after kidney transplantation has been associated with a higher incidence of proteinuria compared with calcineurin inhibitors (CNIs) and those patients who develop proteinuria have a worse outcome. A detailed understanding of the mechanisms that favour the appearance of proteinuria after mTOR-I conversion will be mandatory for improving the management of these drugs. The important role of the mTOR signaling pathway in podocyte function has been highlighted in recent studies. Soluble urokinase receptor (suPAR) is a new circulating marker of podocyte injury that causes FSGS. The aim of our study was to analyze the relationship between the development of proteinuria after conversion to mTOR-I and the changes in serum suPAR.
Methods: Retrospective study of 61 kidney recipients converted to everolimus with CNI elimination. We studied 24-h proteinuria, serum creatinine, everolimus trough levels and suPAR before and after conversion.
Results: After conversion, serum creatinine (1.73 ± 0.64 mg/dl vs. 1.72 ± 1.02, p = 0.958) and suPAR (7.5 ± 3.5 ng/ml vs. 8.0 ± 3.8 ng/ml, p = 0.307) remained stable, whereas 24-h proteinuria (860 ± 2200 mg vs. 1273 ± 3334 mg, p = 0.049) and the logarithm of 24-h proteinuria (2.66 ± 0.37 vs. 2.77 ± 0.41, p = 0.001) increased significantly. Neither pre-conversion ($r = -0.041$, p = 0.783) nor post-conversion ($r = 0.195$, p = 0.190) suPAR related to 24-h proteinuria. By contrast, post-conversion suPAR related with everolimus trough levels ($r = 0.296$, p = 0.020).
Conclusion: As previously reported, proteinuria increases after conversion from CNI to mTOR-I. We found that the development of proteinuria after switching to everolimus did not relate to the circulating levels of suPAR. In this sense, mTOR-I promote proteinuria through mechanisms independent of urokinase type plasminogen activator receptor, although the circulating suPAR seems related to everolimus levels.

BO203 SOLUBLE UROKINASE RECEPTOR (SUPAR) IN THE URINE AND SERUM OF KIDNEY TRANSPLANT CANDIDATES

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Background: Serum suPAR has been proposed as a permeability factor in focal segmental glomerulosclerosis (FSGS). Previous studies suggest that patients with higher suPAR levels are more likely to experience disease recurrence. We studied suPAR in kidney transplant candidates to determine if suPAR can identify cases of FSGS and those at risk of recurrence.
Methods: Pretransplant serum (S) and urine (U) suPAR was measured in patients with recurrent FSGS, (R-FSGS, $S = 13$, $U = 5$), non-recurrent FSGS (NR-FSGS, $S = 15$, $U = 10$), IgA nephropathy (IgA, $S = 15$, $U = 15$), diabetic nephropathy (DN, $S = 15$, $U = 12$), membranous nephropathy (MN, $S = 13$, $U = 4$) and polycystic kidney disease (ADPKD) ($S = 15$, $U = 15$). Controls were kidney donors (Do, $S = 10$, $U = 10$).
Results: Serum suPAR was elevated in disease cases vs. Do ($p < 0.0001$) but not different between disease groups p = 0.39 (Fig 1). Serum suPAR did not associate with FSGS or R-FSGS ($p > 0.2$). In candidates, serum suPAR did not correlate with eGFR ($r = -0.13$; p = 0.24) but correlated with albuminuria ($r = 0.33$; p = 0.01) and proteinuria ($r = 0.39$; p = 0.002). Urine suPAR was higher in R-FSGS vs. other disease groups (p = 0.032). Urine suPAR correlated with proteinuria ($r = 0.26$; p = 0.04) and albuminuria ($r = 0.26$; p = 0.038). Urine suPAR did associate with R-FSGS OR (1.001 p = 0.013) even when adjusted for albuminuria (OR 1.001 p = 0.023) but not when adjusted for proteinuria (OR 1.001; p = 0.27).
Conclusion: Serum suPAR is elevated in various advanced renal disease states and did not differentiate R-FSGS. Urine suPAR is uniquely elevated in R-FSGS.

BO204 RECURRENCE OF DISEASES FOLLOWING RENAL TRANSPLANTATION-A SINGLE CENTRE STUDY

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Introduction: Recurrent diseases are important causes of graft dysfunction and eventual loss. Purpose of the current study is to determine the prevalence of such diseases and its impact on graft function.
Material and Method: Between 2000 and 2012 about 3000 renal transplant were carried out at our centre. Patients were followed up for an average of 5 years. Recurrent diseases were diagnosed by graft biopsy in 40 patients after an average of 3 months.
Results: Demographic characteristics of patients with and without recurrent diseases were similar. Glomerular diseases were the most common finding, occurring in 32 patients, which included focal segmental glomerulosclerosis in 24, membranoproliferative glomerulonephritis in 3, Membranous glomerulonephritis in 2, IgA in 2. Hemolytic Uremic Syndrome in three patients and Oxalosis in five patients were diagnosed. Graft loss occurred in 25% recipients. The graft survival at 1, 5 and 8 years post transplant with recurrent diseases is comparatively less than in patients without recurrent diseases. The risk of recurrent glomerular diseases increased with length of graft survival.
Conclusion: We conclude that recurrent disease is a significant problem after renal transplant and is associated with a decrease rate of survival.

BO205 HIGH EXPRESSION OF S100 CALCIUM BINDING PROTEINS A8 AND A9 IN MACROPHAGES DURING ACUTE TRANSPLANT REJECTION IS ASSOCIATED WITH A BENEFICIAL IMMUNE RESPONSE

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We initially applied microarray RNA expression profiling on biopsies with acute transplant rejection from patients ($n = 28$), transplanted with a kidney between 1986 and 1995, to detect novel markers of which expression is related to graft outcome. S100 calcium binding proteins A8 and A9 (S100A8 and S100A9) were in the top 10 of most differentially expressed genes between groups: relatively high mRNA expression was associated with favorable graft outcome. This was validated by qPCR and immunohistochemistry. We here confirmed this finding in a 1995–2005 transplant cohort: high S100A8 and A9 mRNA expression during acute rejection (>2 times the median; $n = 36$) led to a 12-year graft survival of 91.5%, whereas low expression ($n = 61$) was related to 69.2% graft survival. S100A9 mRNA expression significantly correlated with

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the extent of S100A9 protein by immunohistochemistry ($p < 0.005$). S100A8 and A9 expression was associated with a significantly elevated expression of anti-inflammatory IL-10 ($p < 0.01$) and regulatory T cell marker FoxP3/CD3 ($p < 0.0001$), and with significantly decreased levels of kidney injury molecule ($p < 0.05$). As S100A8 and S100A9 are mainly expressed by monocytes and macrophages, we investigated protein expression of macrophage activation marker CD163 and pan-marker CD68. Triple immunostaining on paraffin slides showed that the majority of CD68 + macrophages within the tissue were either positive for S100A9 or for the macrophage activation marker CD163, indicating the presence of different macrophage subtypes during acute rejection. In line with the *in vivo* findings, overexpression of the S100A8 and S100A9 genes in the monocytic cell line THP-1 led to de novo production of IL-10. S100A8 and S100A9 are markers of a distinct macrophage subpopulation during acute transplant rejection, which may have regulatory properties leading to a beneficial graft outcome.

BO206 PRE-IMPLANT BIOPSY PREDICTS OUTCOME OF SINGLE-KIDNEY TRANSPLANTATION INDEPENDENT OF CLINICAL DONOR VARIABLES

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Background: Pre-implant biopsy findings account for the discard of many donor kidneys although their clinical value is not fully understood. We investigated the predictive value of pre-implant histology on long-term allograft and recipient outcome after singlekidney transplantation.
Methods: This retrospective single-centre study included 628 consecutive adult recipients of 174 Expanded (ECD) and 454 Standard Criteria Donor (SCD) kidneys. Chronic donor organ injury was assessed applying a chronic lesion score differentiating between mild, moderate and severe histologic organ injury based on the integration of glomerular, vascular and interstitial lesions. Median follow-up time was 7.8 years.
Results: Donor kidneys exhibiting mild or moderate chronic lesions yielded almost identical graft and recipient survival independent of ECD status or other clinical co-variables such as recipient age, number of previous transplantations, recipient sensitization, HLA-mismatch and cold ischemia time. However, if allograft injury was severe, occurring in 3% of transplanted kidneys, graft and recipient survival was significantly reduced (HR 2.75, 95% CI 1.46–5.20, $p < 0.001$ and HR 2.43, 95% CI 1.22–4.84, $p = 0.005$). Allograft function (eGFR) at five years significantly deteriorated with increasing lesion score.
Conclusion: Our results suggest that donor kidneys displaying moderate chronic injury can safely be transplanted as single kidneys, while organs displaying severe injury should be discarded. Thus, pre-implant biopsy might offer an effective approach to increase the utilization of renal donor organs.

BO207 THE IMPACT OF TIME-ZERO BIOPSY ON EARLY GRAFT OUTCOMES AFTER LIVING DONOR KIDNEY TRANSPLANTATION

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Introduction: In contrast to deceased donor transplantation, the clinical significance of pathologic finding in time-zero biopsies are rarely reported prior to living donor kidney transplantation, due to the expectation that histological findings and renal function are normal.
Patients and Methods: Between December 2006 and July 2011, One-hundred forty six living-donor kidney transplant recipients were enrolled in this study. We retrospectively analyzed donor and recipient-related clinical parameters, early graft survival, and eGFRs. Time-zero biopsies were evaluated using the Banff' 07 criteria.
Results: Mean age of donor was 40.71¡¾11.37 years. Most abnormal histological findings were of mild degree as determined by Banff scores. Global glomerulosclerosis (GS, 35.6%), tubular atrophy (CT, 36.3%), interstitial fibrosis (CI, 20.5%), vascular fibrous intimal thickening (CV, 4.1%), arteriolar hyaline thickening (AH, 14.4%), interstitial inflammation (I, 3.4%) were pathologic findings in time-zero biopsies. GS and CT were significantly associated with graft outcome ($p < 0.05$). However, multivariate linear regression analysis showed only donor age was significantly associated with graft outcome ($p = 0.001$ for eGFR at 6 months and 1 year post-transplantation).
Conclusion: Mild degree of subclinical pathological findings on time-zero biopsy did not affect early graft renal function in living-donor kidney transplantation.

BO208 CRITICAL REAPPRAISAL OF BANFF'S CLASSIFICATION IN A CLINICAL PERSPECTIVE

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The application of Banff's classification to renal graft biopsies analysis has led to recognize consensus diagnoses associated with the subsequent outcome of the transplants. Besides, it has been suggested by some to apply a critical review of this classification by returning to the elementary lesion as apprehended by the semi-quantitative score of each item. Moreover, performing functional clusters of these items may be relevant to guide therapeutic decisions. We questioned the relevance of such analysis in a new independent cohort reflecting our current practice. Eighty-seven biopsies for cause were included (mean follow-up: 2 ± 1.1 years): 44 with $t+i > 0$; 23 with $ptc+g+cg>0$; 6 with $ptc+g > 0$; 77 with $ci+ct> 0$ and 32 with $ci+ct>2$; 47 with $cv>0$ and 35 with $ah> 0$. Eighteen patients had DSA at biopsy and 5 display a positive C4d staining. Only $t+i > 0$, $ci+ct>2$ and $cv> 0$ were associated with a poorer DFGi (32 ± 16 vs. 41 ± 20, $p = 0.01$; 29 ± 12 vs. 42 ± 20, $p = 0.001$; 32 ± 17 vs. 41 ± 19 $p = 0.007$, respectively). In contrast, loss of function ([(DFGF-DGFi) / DFGi] 100) was more severe in the presence of $ptc+g+cg>0$ lesions ($-52\% \pm 33$ vs. $-9\% \pm 39$, $p = 0.001$) and $ptc+g > 0$ lesions ($-57 \pm 26\%$ vs. $17\% \pm 42$, $p = 0.02$). Only cg score impacted graft survival in a multivariate analysis including all Banff's items taken as quantitative variable (Odd Ratio = 5.7 [1.4–22.7] of graft loss / cg point, $p = 0.01$). Graft survival (62/87 at the end of follow-up) was worse when $ptc+g+cg>0$ lesions, and $ci+ct>2$ lesions were found. A ROC curve analysis of the $ci+ct+cv+ah$ scarring score, as predictor of the subsequent death censored graft loss, determined a maximal AUC of 0.78 for a threshold of 5. Banff's cluster analysis is relevant in a clinical perspective. Microcirculation lesions were associated with the more severe prognosis. They thus may justify the implementation of immunosuppression, weighting its intensity to the associated scarring lesions.

BO209 PRESERVATION OF HYPOXIA-INDUCIBLE FACTOR-1 INDUCED BY ERK PHOSPHORYLATION IS INVOLVED IN HYPOTHERMIC PROTECTION OF RENAL ISCHEMIA-REPERFUSION INJURY

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Background: Although hypothermia attenuates renal injury induced by ischemia-reperfusion (IR), precise molecular pathways have not been known well yet. Our previous study showed ERK phosphrylation plays an important role in hypothermic protection in renal IR injury. Hypoxia-inducible factor-1(HIF-1) has been known as one of the potent protective proteins in IR injury. We evaluated the role of HIF-1 and interaction with ERK phosphorylation in hypothermic protection of renal IR injury.
Methods: C57Bl/6 mice were divided into four groups; sham operated mice, cold IR mice (30°C), warm IR mice (37° C) and PD98059(MAP kinase kinase inhibitor) treated cold IR mice (IR injury; reperfusion 27 minutes after clamping of both renal artery and vein). Kidneys were harvested at 10 min and 27 min after both renal artery ischemia and 24 h after IR injury. Renal HIF-1, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC 1-alpha), AMP-activated protein kinase (AMPK), and 8-hydroxydeoxyguanosine (8-OHdG) was evaluated by western blot and immuohistochemical stain. We examined BUN, serum creatinine (s-Cr), TUNEL and light microscopic findings of kidneys.
Results: Serum creatinine (s-Cr), tissue injury score, and 8-OHdG and TUNEL positive cells in cold IR mice were significantly lower than those of warm IR mice (all, $p < 0.01$). s-Cr, and tissue injury score, 8-OHdG and TUNEL positive cells in kidneys of PD98059 treated cold IR mice were significantly higher than those of untreated cold IR mice (all, $p < 0.05$). Renal HIF-1, PGC 1-alpha, and AMPK expression were significantly increased in the kidneys of cold ischemic mice at 10 min and 27 min after both renal artery clamping compared to sham operated mice. PD98059 treatment in cold IR mice decreased renal HIF-1 significantly ($p < 0.01$). However, PGC-1 alpha and AMPK were not changed.
Conclusions: HIF-1 preservation induced by ERK phosphorylation may be involved in hypothermic protection of renal ischemia-reperfusion injury.

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BO210

THE DISCREPANCY BETWEEN BIOLOGICAL AGE AND CALENDAR AGE: A HISTOLOGY STUDY IN IMPLANTATION BIOPSIES

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Replicative senescence caused by telomere shortening plays an important roll in biological aging. Telomere length (T) was measured by rt PCR. T in peripheral blood correlated significantly with donor calendar age ($p = 0.0002$). Older donor age was significantly associated with ci, ct and gs ($p < 0.01$). There was no association between the histological appearance of the baseline biopsy and T. None of the other donor demographic variables correlated with T. Donor cardiovascular risk associated significantly with ah and cv, but did neither associate with donor calendar age nor with T. This dichotomy between calendar-age associated renal histological lesions and cardiovascular risk-associated lesions was confirmed by PCA. The study suggests that biological aging does not lead to alterations in renal histology. Additional studies that evaluate the senescent phenotype (gene expression and IHC) of) of baseline biopsies before kidney tx are underway, to investigate this unexpected finding.

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BOS18- PEDIATRIC TRANSPLANTATION

BO211 A 7-YEARS EXPERIENCE IN USING SIROLIMUS IN PAEDIATRIC RENAL TRANSPLANTATION WITH CNI TOXICITY

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Background: To study the efficacy and safety of Sirolimus in Paediatric renal transplantation with CNI toxicity.
Method: Paediatric renal transplantation patients (< 19-year-old) converted to Sirolimus from CNI because of suspected or biopsy-proven CNI toxicity from January 2006 till December 2012 were included for analysis (seven years period). Their serum creatinine, eGFR, cholesterol, LDL, proteinuria, full blood counts and liver function were profiled to compare the pre-/post-conversion changes. Common adverse effects, acute rejection, opportunistic infection and need of treatment for hypercholesterolaemia and proteinuria were investigated.
Results: Fifteen patients with M: F = 7: 8. The mean age at transplantation was 12.4 ± 4.8 year-old. Sirolimus was used for a mean duration of 3.8 ± 1.7 years. They tolerated the drugs very well with no report of adverse reaction. The mean baseline Cr was 180 μM and eGFR was 51 ml/min/1.73 m^2 with significant improvement to lowest mean Cr of 118 μM at 2 year ($p = 0.0005$) and best eGFR of 78.4 ml/min/1.73 m2 at 4 year ($p = 0.004$) after conversion. The benefit was observed and maintained up to 4.5 years ($p < 0.05$). Hyperlipidaemia was observed in nine patients (60%) and significant proteinuria in four patients (27%). There was no adverse effect on blood counts and liver function. There was no opportunistic infection observed. There was one acute cellular rejection (Ia) one month after conversion to Sirolimus and responded to pulse methylprednisolone.
Conclusion: Using Sirolimus in Paediatric renal transplantation patients with CNI was effective and the benefit was shown up to 54 months. It was in general safe with little adverse effect.

BO212 THE USE OF MTOR INHIBITORS IN PEDIATRIC LIVER TRANSPLANTATION

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Background: Introduction of calcineurin inhibitors (CNI) constituted one of the most important advances in solid-organ transplantation. However, CNI cause many adverse events. In pediatric liver transplantation (pLtx) mTOR inhibitors (mTORi) may represent a valid alternative in order to reduce CNI side effects. Here we report our experience with mTORi in pLtx.
Methods/Materials: Between October 1999 and February 2013, 114 pLtx in 106 patients were performed at our Center. We retrospectively reviewed all patients placed on mTORi immunosuppression. Here we consider the indications for initiating these drugs, their benefits and side effects.
Results: A total of 10 patients received mTORi (6 everolimus and 4 sirolimus): three as monotheraphy after CNI discontinuation, six in combination with CNI, and one with mycophenolate mofetil. The median age at pLtx was 3.4 years (range 0.9–16.7). Indications for starting mTORi were: acute rejection persistence (ARP) $n = 2$, PTLD $n = 2$, PTLD and HCC as primary indication for pLtx $n = 2$, PTLD and ARP $n = 1$, chronic rejection $n = 1$, CNI intolerance $n = 1$, and change in immunosuppression protocol $n = 1$. Median timing of mTORi introduction was 7.7 months after pLtx (range 1.1–21.3). The median follow-up was 24.6 months (range 2.7–60). Graft biopsy after mTORi introduction was performed in six children; it showed normal histology in five and centrolobular necrosis in one. Eight out of ten patients showed a complete resolution of their post-pLtx complications, in one patient with chronic rejection liver enzymes still remain elevated, and one patient had to receive radiotherapy for HCC recurrence. Side effects were observed in three patients: oral aphtous lesions in two and raised serum triglycerides in one. They all resolved without mTORi reduction or discontinuation.
Conclusion: In our experience, mTORi immunosuppression in children who had pLtx is safe and may represent a valid option in the treatment of ARP and PTLD.

BO213 CONVERSION OF TWICE-DAILY TACROLIMUS TO ONCE-DAILY TACROLIMUS FORMULATION IN STABLE PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS: PHARMACOKINETICS AND EFFICACY

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Background: In pediatric transplant recipients, there are scarce data of once-daily tacrolimus (Tac-OD) pharmacokinetics. Method: The pharmacokinetics, efficacy and safety of Tac-OD were assessed in 34 stable pediatric kidney transplant recipients (ClinicalTrials.gov NCT01476488). Enrolled patients received their dose of twice-daily tacrolimus (Tac-BID) on study days 0 through 7. On the morning of study day 8, patients were converted to Tac-OD on a mg:mg basis for their total daily dose and maintained on a once-daily morning dosing regimen. Tacrolimus pharmacokinetic profiles were obtained on study days 7, 14 and 28 (after dose adjustment). This study has 6 month extension period for evaluation of safety and effectiveness.
Results: The mean age of enrolled patients was 12.3 ï¿½ï¿½ 2.8 years (range: 7.9–15.9 years). Total daily dose of Tac-BID was 3.7ï¿½ï¿½1.4 mg before drug conversion. Although mean C 0 concentrations (4.10 ï¿½ï¿½1.16 to 3.53 ï¿½ï¿½ 1.10 ng/ml, $p = 0.004$), and AUC 0–24 (151.8 ï¿½ï¿½ 41.6 to 129.8 ï¿½ï¿½ 39.3 ng.h/ml, $p = 0.001$) were decreased significantly after a 1:1 based conversion, there was high inter-individual variability. Tacrolimus trough concentration and even Cmax was increased in nine patients. Therefore, more than seventy percent of patients required to adjust Tac-OD dose. Patients with C YP3A5 3/*3 genotype tended to experience significantly decreased dose-normalized C 0 and AUC 0–24. Drug conversion to Tac-OD had a positive effect on hypertension. The number of anti-hypertensive medication was significantly decreased from 0.7 to 0.5 ($p = 0.007$).
Conclusion: In conclusion, Tac-BID can be safely converted to Tac-OD in stable pediatric kidney transplant patients with additional benefits on cardiovascular risk factors and adherence to immunosuppressants.

BO214 PLEADING FOR INTEGRATING HLA-CW ANTIGENS AS UNACCEPTABLE

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Significant prevalence of antibodies (Ab) against HLA-Cw antigens (HLA-Cw) in sensitized patients on the waiting list is now well established thanks to the generalization of the high resolution solid-phase immunoassays (SPI). The appropriateness of inclusion of HLA-Cw as unacceptable in the allocation systems is yet still debated. The first step to ascertain their pathogenicity is to analyze how they impact crossmatch (XM) results in a control system. To that end, we performed 51 T-lymphocytes XMs combining flow cytometry (FCXM) and complement dependent cytotoxicity (CDC) assays by using 30 sera from sensitized patients, exhaustively characterized with SPI on a Luminex platform and 41 organ donors' lymph nodes. Inclusion was conditioned by the absence of other anti HLA Class I non HLA-Cw Ab directed against HLA antigens expressed on TL (DSA): 11 HLA-Cw were tested as immunodominant DSA (2 Cw1, 3 Cw2, 2 Cw3, 3 Cw5, 6 Cw6, 21 Cw7, 1 Cw8, 7 Cw10, 3 Cw12, 2 Cw16). In 16 XM, sera contained several different HLA-Cw DSA. Isolated HLA-Cw DSA could lead to positive XMs (i) 25(49%) low FCXM(+); Mean Channel Shift deviation (MCS) >45, (ii) 8(16%) high FCXM(+); MCS>200 (iii) but only one CDCXM(+). Ab levels given by the MFI of the SPI were correlated with the MCS of FCXM (Spearman coefficient Rho = 0.45; $p = 0.001$). Consequently, the sum of the MFI-DSA was higher in low FCXM(+) and in high FCXM(+) than in FCXM(−): 6260 ± 4636 vs. 2867 ± 2936; $p = 0.01$ and 8921 ± 4040 vs. 3714 ± 3719; $p = 0.01$, respectively. A ROC curve analysis of the sum of the MFI-DSA as predictor of a subsequent low and high FCXM(+) determined a maximal AUC of 0.71 and 0.78, respectively. Collectively, these results suggested that HLA-Cw DSA should be considered in organ allocation policies given their ability to trigger unexpected positive XM if omitted. Beyond, they should be included to qualify immunologic risk stratification starting from the well-known poor outcome of XM(+) transplantations.

BO215 SHORT TERM RENAL TRANSPLANT OUTCOME AND SERUM AND URINARY NGAL CONCENTRATION ASSOCIATION IN CHILDREN

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NGAL is a member of the lipocalin protein family that has diverse function but similar structure. The functions of NGAL are not clear, but it appears to be expressed in stress conditions and in tissues undergoing involution. Varied studies have shown increased levels of plasma or urinary NGAL in diverse renal damages. The aim of this study was the serial measurement of serum and urinary NGAL within the first week after renal transplantation in children to predict immediate and short-term graft function. A total of 27 patients were assessed. These patients were classified into those with rapid reduction in

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serum creatinine (more than 50% reduction in serum creatinine in the first day after transplantation) and patients with slow reduction in serum creatinine (<50% reduction in serum creatinine). We also assessed the absolute reduction in serum creatinine before and after transplantation. Serum and urinary NGAL on the first day post-transplantation were higher in recipients with slow reduction in serum creatinine (urinary NGAL at the first day: 197 ± 153 [SEM] vs. 22.54 ± 8.5 [SEM], p = 0.04; serum NGAL at the first day: 199 vs. 69.8, p = 0.003). The cutoff point of serum NGAL at the first day after transplantation for prediction of slow creatinine reduction was 174 ng/ml with a sensitivity of 100% and specificity of 95.5%. However, we did not find association between the absolute reduction in serum creatinine before and after transplantation with the amount of serum and urinary NGAL posttransplant. Additionally, we did not find any effect of high serum and urine NGAL concentration on the graft function at the first year posttransplant. Although it is supposed that high serum and urine NGAL may predict ischemia of graft in early phases; however, it appears that this mild ischemic injury to graft without DGF or SGF cannot affect the graft function in short-term period. Further studies are needed using larger transplant recipients in pediatric age group. It is also needed to determine the effects of mild ischemic injuries on the graft function in long-term period in future studies.

BO216 STENTED PULL-THROUGH ATRAUMATIC URETERO-NEOCYSTOSTOMY TECHNIQUE FOR THE VERY SMALL PEDIATRIC EN BLOC KIDNEYS TRANSPLANTS (VSPKS)

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Urinary complications are dreadful when VSPKs were used. Eighty VSPKs were reviewed.
Methods: 65% of kidneys were imported (23 from DCD donors). Donors were 0.32 ± 0.02 yo and weighed 6.2 ± 1.62 kg. Kidneys were removed en bloc with aorta and cava bifurcation, pumped for 7 ± 3 h and transplanted after 21 ± 7.82 h of CIT. After revascularization, an extra mucosal incision was performed in the superior-medial aspect of the bladder allowing the mucosa to bulge out. Careful hemostasis was achieved. The spatulated ureter tip was cauterized at low intensity, and a full thichness double arm U- stich with 5-0 polydioxanone was placed and brought inside the bladder through a small opening of the caudal mucosal pouch. Both needle excited 1 cm distal to the myotomy. The ureter was stented. The ureter was pulled into the bladder and the anchoring sutures tied. The lateral ureter was brought through the same tunnel and mucosa opening in 34 instances. In other 36 cases, the ureters were implanted through two separate incisions. The anastomoses were tested by distending the bladder with antibiotic solution stained with indigocarmine. Leakages required additional sutures. Preop antibiotics were continued for 24 h and switched to sulfamethoxazole. The Foley was left in for 4–10 days depending on bladder capacity. The stents were removed at 3 weeks.
Results: Light hematuria was transient and did not require therapy. Two single kidneys clotted in the single tunnel group. At nephrectomy, the thrombosed ureter was pulled out after the anchoring suture was cut. The detrusor was closed with an additional stitch. During flexible cystoscopy, the distal ureters were well covered with normal mucosa. Leaks and pyelonephritis were not observed. Three-year GS was 95%.
Conclusions: The atraumatic pull-through technique is safe for VSPKs transplants and is easy to perform.

BO217 SURGICAL AND RADIOLOGICAL TREATMENT OF BILIARY COMPLICATIONS IN PEDIATRIC LIVER TRANSPLANTATION

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Background: Biliary complications still occur in 20–35% of pediatric liver transplantations (PLTx). The aim of this study is to investigate risk factors and therapeutic approaches.
Materials/Methods: We reviewed 104 PLTx on 97 children performed at our Center between October 1999 and February 2012. Mean age at PLTx was 5.1 years. Transplants were performed using 47 whole livers, 42 split, 12 reduced livers; three grafts were from living donors. In 98 cases biliary reconstruction was performed by hepato-jejunal anastomosis, in six by duct to duct anastomosis. Biliary complications were classified according to timing as early (<30 days) or late (>30 days), to location as anastomotic or intrahepatic, to type as fistulae or stenosis. As risk factors we considered for the recipients, age, sex, weight, diagnosis and PELD score; for the grafts, graft/body weight ratio, ABO system, cross-match, type of graft, biliary anatomy, cold, warm, arterial and total ischemic times, arterial reconstruction, hepatic artery thrombosis, acute rejection and CMV infection.
Results: A total of 26 biliary complications were observed (25%): eight fistulae and 18 stenoses. All fistulae required surgical treatment. Among the 18 stenoses, 14 affected the biliodigestive anastomosis, 4 involved the intrahepatic bile ducts. Stenoses were treated as follows: nine radiologically only, three surgically only, six by combined surgical and radiological approach. In three cases radiological intervention followed surgery, in three it preceded surgery. In one case biliary stenosis led to graft loss while another patient developed secondary biliary cirrhosis. The only statistically significant risk factor identified for stenosis was a prolonged warm ischemic time.
Conclusions: In our experience, early or late onset biliary complications have similar prognosis. Stenotic complications might be reduced by strict control of warm ischemic time. Cooperation between surgeon and radiologists leads to optimal treatment with a 96% 10-year graft survival.

BO218 IS DONOR GENDER A RISK FACTOR FOR ACUTE REJECTION IN PEDIATRIC PARENTAL LIVING DONOR LIVER TRANSPLANTATION?

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Background: Acute rejection (AR) is still a significant complication in pediatric living donor liver transplantation (LDLT). Finding rejection predictors is thus essential to prevent or anticipate this immunological outcome. Sex mismatch (male to female) kidney transplants have been associated with poorer outcomes due to H-Y antigens. More recently, lower graft failure was observed with maternal donors in pediatric LDLT for biliary atresia that could be explained by the presence of maternal cells in the recipient's organism maternal (microchimerism). Then, we decided to study the impact of sex mismatch and donor sex on AR in our pediatric LDLT program.
Methods: We retrospectively collected demographic, as well as days 0–90 clinical, biological and histological data of 76 pediatric parental LDLT (0.5–14.3 years) immunosuppressed with a Basiliximab induction and tacrolimus monotherapy. Rejection-free survival (RFS) was studied according to donor and recipient gender.
Results: At day 90 post transplantation, the incidence of AR was lower in the mother to daughter group (1, $n = 20$), followed by mother to son (2, $n = 21$), father to daughter (3, $n = 19$) and father to son (4, $n = 16$) with RFS = 79%, 56%, 47%, and 38% respectively (p = 0.007 when comparing group 1–4). As there was no difference in terms of RFS between group 3 and 4, the H-Y antigen hypothesis could not be confirmed as an AR risk factor in this settings. Recipients with maternal donors when compared to paternal donors had higher RFS (67% vs. 43% respectively, p = 0.046), irrespective of their diagnosis and age.
Conclusion: (1) According to our preliminary data, the H-Y antigen (sex mismatch) was not found to impact on AR incidence in our pediatric LDLT. (2) However, donor gender constitutes a risk predictor for AR in pediatric parental LDLT since lower rejection rate is observed when the donor is the mother, probably due to maternal microchimerism.

BO219 THE TRANSITION OF YOUNG ADULT TRANSPLANT RECIPIENTS INTO ADULT CARE: A WEST OF SCOTLAND PERSPECTIVE

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Background: The transition between paediatric and adult care is a crucial time in the management of young adults with ESRD. As many as 35% of adolescent transplant recipients suffer graft loss within 3 years of transfer to adult care, which increases the strain on an already resource limited transplantation service as well as causing significant morbidity. In this retrospective study we investigated the outcomes of transition patients in the west of Scotland, and explored the reasons behind the high rates of graft failure.
Methods: Data was retrospectively analysed from patients aged under 25 who underwent renal transplantation at either a dedicated paediatric unit or at an adult unit in the west of Scotland between 2001 and 2010. Graft failure rates at one year and five years were compared with the corresponding adult population, between patients who transitioned to adult care before and after transplantation, and between previously reported rates.
Results: An overall graft failure rate of 8% after one year and of 21% after 5 years ($n = 90$) was seen in patients transplanted aged under 25, which is lower than that reported in the current literature for this age range. No significant difference in failure rates was seen between those who transitioned to adult care before or after transplantation, however, the failure rate in young adults (16–25) was double that of children aged 15 and under, at 22% compared with 11%.
Conclusion: Transition to adult care generally takes place during the 16–25 year age group and the higher rate of failure seen in this group is likely a result of patient non-adherence during this challenging period. It has been shown elsewhere that a fully integrated transition service can significantly improve compliance rates and reduce these high rates of graft loss in young adults. Improving this transition period nationwide is key to increasing the rates of long-term graft survival and lowering morbidity in young adult transplant recipients.

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BOS19-LUNG

BO221 PATIENTS WITH EXTRA CORPOREAL LUNG ASSIST AS BRIDGE TO LUNG TRANSPLANTATION VERSUS PATIENTS WITHOUT

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Objectives: This study was designed to evaluate the impact of preoperative mechanical lung assist (MLA) on operative outcome including longer term survival in patients undergoing in comparison to patients undergoing LTX without preoperative MLA.
Methods: Forty-three of patients presented with idiopathic pulmonary fibrosis of whom 71% presented severely elevated pulmonary artery pressure.
Results: Overall 15 patients (22%) required pre LTX MLA support (age 44 ± 13 years, double-LTX 73.3%, female 53%) whereas 130 patients did not (age 52 ± 11 years, double-LTX 41.5%, female 36.9%). The short-term and long-term postoperative survival of the MLA patient group was not significantly different from the non-MLA group (LogRank;p = 0.28). The 30-day, 90-day and 1-year survival was 95%, 90% and 71% in the patients without MLA compared to 85%, 77% and 68% in the MLA group.
Conclusions: MLA has no impact on postoperative outcome in LTX patients. It is however a valuable tool as bridge to LTX in instable patients.

BO223 THE CHARACTERISATION OF MACROPHAGES IN AN ACUTE LUNG INJURY MODEL

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Background: Lung allograft rejection (AR) remains a major caveat to successful transplantation. Monocytes constantly survey the lung, before differentiating to a dendritic cell (DC) or macrophage (MAC) phenotype depending on the inflammatory status of the local environment. Both DC and MAC are involved in graft rejection, but the origins of MACs are unknown. The aim of this study was to characterise monocyte to MAC differentiation using *in vitro* lung models.
Methods: Peripheral blood monocytes were cultured with M-CSF in the presence or absence of lung epithelial cells (A549). An *in vitro* air-liquid lung model was constructed using A549 and pulmonary vascular endothelial cells, and the differentiation pattern of monocytes within the lung to either MAC1 or MAC2 phenotypes was assessed via flow cytometry.
Results: Monocyte differentiation to macrophages (CD68 +, p = 0.001) was significantly increased following exposure to alveolar epithelia. Following diapedesis from the vascular bed to the alveolus of the lung, monocytes also differentiated to CD68 + macrophages regardless of stimuli. Of the MAC1 (CD68 + HLA-DR+ cells) 87% were CD163 +, denoting a triple-positive phenotype (i.e. MAC1 + MAC2 +). In the absence of A549 cells, the number of triple positive cells increased.
Conclusion: This *in vitro* study demonstrates physiological interactions between monocytes and alveolar epithelia. Triple-positive MACs represent a phenotypic intermediate, expressing MAC1 and MAC2 markers. In the absence of A549 cells, triple-positive cells increased, suggesting lung epithelium regulates macrophage phenotype. The identification and characterisation of a novel reservoir of triple positive alveolar macrophages clearly warrants further investigation.

BO224 OUTCOME AFTER EARLY TRACHEAL EXTUBATION (ETE) IN LUNG TRANSPLANTATION (LT)

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Hopital Foch

Background: ETE has ever been described after LT. However, only few studies reported evaluation of outcome mostly after single procedures.
Patients and Methods: Between February 2008 and July 2012, 191 patients (pts) underwent LT in a single center. The study cohort was divided into an ETE group and a delayed tracheal extubation group (DTE). The anesthetic protocol used to extubate pts in operating room was based on PaO2/FiO2 > 300 mmHg at the end of surgical time. Non invasive ventilation was routinely used in ETE pts just after extubation with progressive weaning in intensive care unit.
Main Results: Among 191 LT pts, 71 (36%) were extubated in the operating room (ETE group). Main lung disease was cystic fibrosis and LT was mostly bilateral in both groups. ETE group had higher rate of epidural analgesia (87.7% vs. 65%, p = 0.001), required significantly less cardiopulmonary bypass or ECMO (13.7% vs. 64.2%, p < 0.001), and needed less red cell transfusion (p = 0.001). ETE group had a significantly shorter length of ICU stay (p < 0.001) and less frequently severe Primary Graft Dysfunction grade 2 or 3 (p < 0.001). There was no significant decrease of early nosocomial pneumonia (31.6% in ETE group vs. 44.7% in DTE group p = 0.10) and inhospital mortality (9.7% vs. 19.7%; p = 0.11). In ETE group, 11 pts (15.5%) needed reintubation due to pneumonia (5 pts), early surgical complication (2), hypercapnia (2), humoral rejection (1) and convulsion (1). Lower Pa02/Fi02 at day 0 was the only parameter significantly associated with ETE failure (p = 0.001). Median delay for reintubation was 4 days.
Conclusion: ETE after bilateral lung transplantation is safe and associated with a low rate of reintubation and a reduced length of stay in ICU. Factors associated with failure of ETE should be evaluated in further study.

BO225 PREVENTION OF ISCHEMIA-REPERFUSION LUNG INJURY BY SUPPLEMENTATION OF THE PRESERVATION SOLUTION WITH HEMO2LIFE IN PORCINE LUNG TRANSPLANT MODEL

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Background: Hemo2life® is a new natural oxygen carrier extracted from Arenicola marina with high oxygen affinity acting at low temperature. We assessed the effect of Hemo2life® associated with a static preservation solution on primary graft dysfunction after lung transplantation.
Methods/Materials: A left lung transplant was performed in pigs after 24 h of preservation at 4°C with Perfadex® (Perfadex® group, *n* = 5) or with Perfadex® associated with Hemo2life® (2 g/l) (Hemo2life® group, *n* = 5) and compared to a sham animals (*n* = 5). Expression of HIF1α was quantified on iterative samples from the right lung during preservation. During 5 h of lung reperfusion, hemodynamics, oxygenation and dynamic compliance were monitored. HMG-B1, TNFα, and NO were measured in serum. After 5 h of reperfusion, TNFα and IL-8 were assayed in bronchoalveolar lavage (BAL).
Results: During cold ischemia, expression of HIF1 α and histology remained unchanged and similar to control. After 5 h of reperfusion, Hemo2life® group led to a significant reduction of graft vascular resistance (p < 0.05), graft oxygenation ratio was significantly higher (p < 0.05). Expression of HMG B1 in serum tended to be lower (2.1 ± 0.8 vs. 4.6 ± 1.5) compared with Perfadex® group. TNF-alpha and IL-8 in BAL were significantly higher in the 2 experimental groups compared to control (p < 0.05).
Conclusion: In this preliminary study, adjunction of a new oxygen carrier Hemo2life® in lung preservation solution improves early graft function after prolonged cold ischemia.

BO226 A PERIOPERATIVE STRATEGY IN LUNG TRANSPLANTATION (LT) WITH PREFORMED HLA DONOR-SPECIFIC ANTIBODIES (P DSA)

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Background: Different peri-operative regimen were developed in kidney and cardiac transplanted patients (pts) with pDSA to reduce the occurence of acute humoral rejection (AMR). But, few is known in LT.
Methods: In a single center, 118 pts underwent LT between 01/10 and 07/12, mosly for cystic fibrosis. A single preoperative plasmapheresis was performed in case of MFI max <1000 (luminex single antigen assay), 5 other plasmapheresis post operatively associated with IvIg and rituximab face to 1000 < MFI max < 5000. The occurence of definite or possible (DSA and clinical symptoms or immuno-histological criteria) AMR was analyzed in pts with or without p DSA.
Results: Forty three pts (36.5%) had pDSA with MFI max < 1000 in 63% of them. Perioperative data and early outcome were similar in both groups except for a longer ischemic time in DSA pts (p < 0.01). Retrospective crossmatch was negative in all pts. At D 30, definite AMR occured in 1 pt in each group and possible AMR in three DSA pts (p = 0.06). At 1 year, definite or possible AMR had occured in 6 pts in each group (p = 0.035).
Conclusion: This regimen allows LT in our center without increasing humoral rejection episodes in presensitized pts. Maintenance therapy and long term outcome should be assessed in further study.

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BO227 CALCINEURIN INHIBITOR (CNI) RE-EXPOSURE AFTER A 'CNI HOLIDAY' IS ASSOCIATED WITH STABILISATION OF RENAL FUNCTION IN LUNG TRANSPLANT RECIPIENTS WITH CNI-NEPHROTOXICITY

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Introduction: Calcineurin inhibitors (CNI's) are used routinely as maintenance immunosuppression in lung transplant recipients, though a 7–21% risk of end-stage renal failure (ESRF) at 5 years complicates their use. The alternative use of sirolimus, an m-TOR inhibitor (mTORi), has been shown to reduce drug-related nephrotoxicity, but with an increased risk of fungal infection and poor wound healing. We aimed to demonstrate that re-introduction of a CNI, after a 'CNI holiday' bridged with mTORi immunosuppression, leads to a slower decline in renal function.
Methods: Fourteen patients who received a 'CNI holiday' with mTORi bridging, were identified from pharmacy records and clinical and laboratory data was collected from our electronic database.
Results: The indication for switching to mTORi was renal dysfunction in 13/14 patients and the indications for returning to a CNI were fungal infection (10/14 patients), pre-empting renal transplant surgery (2) acute rejection (1) and sirolimus-induced lung injury (1). Serum CNI levels in both treatment phases were comparable. The median rate of decline of serum creatinine on first CNI exposure 88ìM/year (IQR: 49–137ìM/year) during first CNI exposure. Creatinine improved at a median rate of 22ìM/year (IQR: 13–411ìM/year) during mTORi use, and stabilised on CNI re-exposure (net median improvement of 3ìM/year; IQR: −22 to 18 μM/year). Three patients (20%) progressed to ESRF; two during their 1st CNI course (both haemodialysed) and one during CNI holiday (hadrenal transplant). Median FEV1 was 94.1% (IQR: 67.5% – 98.3%) of post-transplant best after first CNI course, 81.2% (IQR: 76.8% – 91.2%) after mTORi course, and 87% (IQR: 83.9% – 93.8%) after second CNI course.
Conclusion: A CNI holiday appears to promote stabilisation of renal function, even in patients re-exposed to CNI's. However, lung function decline and infection (especially fungal), but not rejection, were more common during the mTORi phase.

BO228 LUNG TRANSPLANTATION (LTX) IN HIV POSITIVE PATIENTS

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LTX in immune compromised patients with retroviral infection is a challenge in maintaining their post operative immune suppressants and increased risk of infection. Having such infection is a contraindication for LTX. We present two cases of successful LTX in HIV patients with IPF. 65 year male with FVC 47%, and DLCo 23%. 6 MW was 849 feet, NYHA 3. He required 6 l/min of O2, resting PaO2 was 53 mmHg. He was diagnosed with HIV 9 years ago and had a CD4 count of 450/μl, the HIV load was undetectable. Regimen included emtricitabine, tenofovir and atazanavir. He underwent double LTX. Immunosuppression included tacrolimus (TAC), mycophenolate (MMF) and prednisone (PSE), and prophylaxis included gancyclovir, then valganciclovir, voriconazole and bactrim. Patient was started on HAART 5 days after LTX, and placed on broad spectrum antimicrobials throughout the hospital course. He continues to do well after 35 month follow up. His last CD4 count remains around 200/μL, HIV load is undetectable. Sixty years male with a history of Hodgkin's lymphoma, treated with radiation and bleomycin. He presented with FVC 56% two months prior to LTX with a worsening SOB and NYHA 3. He was on 6 l/min continuous flow of O2. 6 MW was 611 feet. He had a long standing HIV treated with abacavir, ritonavir, and atazanavir. At LTX he had an undetectable HIV. His HAART was suspended at LTX and restarted a day after. The biopsy revealed an A2 rejection treated with methylprednisolone. He was on maintenance immunosuppression consisting of TAC, MMF, PSE, and placed on broad spectrum antimicrobials. Six months after LTX he had an undetectable HIV load and a CD4 + count of 211/μL. In both these patients there were no opportunistic infections detected in the follow up period. With the advent of HAART the outcomes of these patients improved and a life saving intervention like LTX can be considered. HAART made a shift in HIV+ population from AIDS-related diseases ones affecting the general population. Based on our results LTX should be considered as a treatment option in select HIV+ patients with end stage lung diseases.

BO229 HIGH EMERGENCY LUNG TRANSPLANTATION: THE EXPERIENCE OF A FRENCH CENTRE

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Hopital Foch

Background: Numerous candidates to lung transplantation (LT) still died on waiting list, asking the question of graft availability and organ allocation. In France, a national priority called High Emergency LT (HELT) has been defined in 2007 to favour allocation of organs to patients with a high and short term risk of death. To report the experience of HELT since its implementation in our centre.
Materials and Methods: From 1st July 2007 to 31th May 2012, 201 patients (38 HELT, 163 classic LT) have received LT.
Results: Pre LT primary diagnosis was in HELT and classic LT patients respectively: Cystic Fibrosis (81.1 vs. 48, 7%), Interstitial Lung disease (16.2 vs. 15, 2%) and Emphysema (0 vs. 27, 4%). HELT candidates had a significantly higher impairment grade on respiratory and hemodynamic status and higher LAS. HELT patients had a higher incidence of peroperative complications such as extracorporeal circulatory assistance (75% vs. 36.6%, $p = 0.0005$), peroperative bleeding. No significant difference was observed in term of mechanical ventilation duration (15.5d vs. 11d, $p = 0.27$), ICU length of stay (15d. vs. 10d, $p = 0.22$), total length of stay (37d vs. 28d, $p = 0.15$) and survival rate at 6, 12, 24 months post LT.
Conclusion: In our experience, HELT provided similar survival rates than classic LT despite a more severe clinical status of the candidates on waiting list. Such results are associated with a dramatic reduction of our mortality rate of patient on the waiting list.

BO230 HIGH PREVALENCE OF ANTI-SACCHAROMYCES CEREVISIAE ANTIBODIES IN CYSTIC FIBROSIS PATIENTS AFTER LUNG TRANSPLANTATION

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Background: Autoimmune antibodies (Ab) can be found in up to 80% of CF patients prior to lung transplantation and anti-neutrophil cytoplasmic antibodies (ANCA) may be associated with severity of lung disease and disease prognosis1. In this pilot study, we investigated the prevalence of autoimmune antibodies in CF patients after lung transplantation (LuTx).
Methods: Consecutive patients attending our outpatient clinic were screened for a wide range of autoantibodies in serum (ANA, AMA, SMA, EMA, TTG Ab, p-ANCA, c-ANCA, ASCA, SLA, LC-1 Ab), as well as immunoglobulins (IgG, IgA and IgM). Autoimmune diseases were excluded.
Results: Thiry-six patients (median age 30 years, IQR 25–38 years; 42% male) were included in the study. Median time since LuTx was 4.5 years (IQR: 2.3–8.3 years). IgG levels were elevated in 8% (3/36) of patients. Overall prevalence of autoantibodies was 83%. However, only 12% (4/34) of patients had elevated ANAs, only one patient tested positive for SMAs. Of note, 83% (24/29) of patients had elevated anti-saccharomyces cerevisiae antibodies (ASCA), so far implicated in Crohn's disease of the small bowel. Of these, 4 of 24 ASCA IgG only, in 8 of 24 ASCA IgA only, and in 12 of 24 both were positive. Yet, in none of the patients neither AMA, EMA, TTG Ab, SLA, LC-1 Ab, nor ANCA were detected.
Conclusion: In contrast to published data in pre LuTx CF patients, in this study ASCAs were found in about twice as many patients, whereas ANCA were not found post LuTx. ASCAs were the dominant fraction in our panel of autoantibodies. These data draw attention to the clinical course of CF-associated small bowel disease after LuTx.

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BOS20-IMMUNOBIOLOGY/BASIC SCIENCE

BO231 EPIGENETIC ANALYSIS DEMONSTRATES THAT NATURAL REGULATORY T CELLS INFILTRATE THE CARDIAC ALLOGRAFT BEFORE AN ACUTE REJECTION EPISODE

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Background: The regulation of intragraft allogeneic responses in heart transplant patients by either thymically derived natural regulatory T cells (nTreg) or peripherically induced Treg (iTreg) is unknown.
Methods: Endomyocardial biopsies (EMB) of 42 patients were examined; 28 patients experienced at least one rejection (ISHLT rejection grade 2R; rejectors) and 14 patients remained free from rejection (non-rejectors). The percentage of demethylated TSDR (Treg Specific Demethylated Region) in the FOXP3 gene represents the percentage of nTreg. FOXP3 mRNA levels represent the total regulatory T cell population.
Results: In grade 1R EMB of non-rejectors no significant accumulation of nTreg was observed. In contrast, in rejectors, in all grade 1R EMB (before AR) and 2R EMB, nTreg were detected with a significant higher percentage ($p \leq 0.001$). Remarkably, no significant difference was observed in the FOXP3 mRNA levels in 1R EMB of non-rejectors compared to 1R EMB of rejectors ($p = 0.32$), suggesting more iTreg in the non-rejectors.
Conclusion: The characteristics of the FOXP3 gene support a role for antigen-specific iTreg in the prevention of rejection, while nTreg are unable to prevent the rejection process.

BO232 IMMUNOLOGICAL RESPONSE OF HUMAN CORNEAL ENDOTHELIAL CELLS – STEPS TOWARDS A BETTER UNDERSTANDING OF KERATOPLASTY GRAFT SUCCESS

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Purpose: Human corneal endothelial cells (HCEC) are a potential target of immune attack after corneal transplantation. The aim of this *in vitro* study was to investigate the role of HCEC during the allo-immune response of T-cells by examining cytokine profiles, function of the immunosuppressive enzyme indoleamine 2,3-dioxigenase (IDO), major histocompatibility complex (MHC -I/ -II), T-cell proliferation, and the induction of cell death.
Methods: Real time-PCR and RP-HPLC were used to determine IDO expression and activity. Multiplex assay was performed for quantification of cytokine levels. T-cell proliferation was assessed by thymidine incorporation and HCEC cell death was measured by flow cytometry.
Results: HCEC induce strong proliferation of allogeneic T-cells and an increase of pro-inflammatory cytokines such as interleukin-1 α (IL-1α), IL-1β, IL-6, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). IFN-γ (and to a lesser extent TNF-α) induces apoptosis. Moreover, IFN-γ strongly upregulates MHC-II molecules and IDO activity in HCEC as reflected by high kynurenine (Kyn) concentrations. Interestingly, the T-cell response was not affected by increased IDO activity, since blocking of IDO did not affect the proliferation rate. IDO-induced Kyn levels did not exceed concentrations of 175 ± 20 μM. Concentrations of ≥ 400 μM Kyn were required to suppress T-cell proliferation.
Conclusions: Our data show that T-cell attack on HCEC leads to increased concentrations of pro-inflammatory cytokines. Inflammatory cytokines induce apoptosis and upregulate MHC-II molecules and IDO in HCEC. Although increased IDO activity does not influence the T-cell response, it constitutes an inflammatory marker of the allo-immune response towards HCEC.

BO233 CXCR5 + CD4 + FOLLICULAR HELPER T CELLS ACCUMULATE IN RESTING HUMAN LYMPH NODES AND HAVE SUPERIOR B CELL HELPER ACTIVITY

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Although many relevant immune reactions are initiated in the lymph nodes (LN), this compartment has not been systematically studied in humans. Analyses have been performed on immune cells derived from tonsils, but as this tissue is (chronically) inflamed, generalization of these data is difficult. Here, we analyzed the phenotype and function of human CD4 + T cell subsets and lineages in 21 paired resting lymph node and peripheral blood (PB) samples. Naive, central memory and effector memory cells as well as Th1, Th2, Th17 and Tregs were equally represented in both compartments. On the other hand, cytotoxic CD4 + T cells were strikingly absent in LN (LN 0.42%; PB 4.4%; $p < 0.01$). The percentage of CXCR5 expressing CD4 + T cells, representing putative follicular T helper (Tfh) cells, was significantly higher in LN than in PB (LN 27%; PB 12%; $p < 0.005$). LN CXCR5 + CD4 + T cells also expressed higher levels of Tfh markers than their PB counterparts. Last but not least LN derived CXCR5 + CD4 + T cells were superior in providing help to B cells, as assessed by the induction of IgG and IgM production, when co-cultured with LN B cells (IgG: LN 87% of max; PB 14% of max; IgM: LN 76% of max; PB 16% of max) or PB B cells (IgG: LN 15% of max; PB 2% of max; IgM: LN 38% of max; PB 10% of max). Thus, functionally competent Tfh accumulate in resting human lymph nodes providing a swift induction of naive and memory antibody responses upon antigenic challenge.

BO234 KIDNEY TRANSPLANTATION DOES NOT REVERSE PREMATURE AGEING OF T CELLS IN END-STAGE RENAL DISEASE PATIENTS

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Background: The uremia-induced inflammatory environment in end-stage renal disease (ESRD) patients is associated with premature T-cell ageing, which results in defective immunity. As kidney transplantation (kTx) sharply reduces the pro-inflammatory environment, we hypothesized that T-cell ageing is thereby reversed.
Methods: T-cell-ageing parameters were determined in 140 kTx recipients before kTx, and 3, 6 and 12 months afterwards. All patients received the same immunosuppressive medication. Thymic output was assessed by determining the T-cell receptor excision circle (TREC) content and percentage of CD31 + naïve T cells. As a measure for proliferative history, the relative telomere length (RTL) was determined and the differentiation status was determined by immunophenotyping.
Results: TREC content, percentage of CD31 + naïve T cells and the RTL of T cells remained unaltered within the first year of kTx. Three months after kTx, the number of memory T cells had decreased. Twelve months afterwards, the number of CD8 + EMRA T cells had reached pre-kTx values, whereas the number of CD4 + EM T cells remained significantly reduced ($p < 0.05$).
Conclusion: As the prematurely aged T-cell compartment of ESRD patients is not reversed by kTx, it remains a determinant of the dysfunctional immune system. (This study was financially supported by the Dutch Kidney Foundation (KSPB.10.12)).

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BO235 RAT LIVER ALLO-GRAFT REJECTION PROMOTES CANCER CLEARANCE: A MODEL OF TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

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Background: Liver transplantation for hepatocellular carcinoma (HCC) results in a specific condition where the immune response is directed both against allogeneic and cancer antigens. This study assessed the level of anti-cancer immunity during allogeneic rejection after rat liver transplantation.
Methods: Dark Agouti-to-Lewis (allogeneic) and Lewis-to-Lewis (syngeneic) rat liver transplantations were performed. The occurrence of a rejection was assessed. The phenotype, the level of activation and the anti-cancer cytotoxic activity of mononuclear, monocytes and NK cells were tested in the peripheral blood, the liver and the spleen. Similar analyses were performed on PBMCs isolated from liver-transplanted patients.
Results: Allogeneic rats experienced rejection as testified by shorter survivals (13 vs. >60 days in syngeneic rats, $p < 0.01$), the presence of rejection on histology (Banff 8) and increased liver function tests ($p < 0.01$). At time of rejection, blood cells demonstrated increased anti-cancer cell cytotoxicity (25.2 vs. 14.7% in syngeneic recipients, $p < 0.005$). This activity was related to increased blood NK cell frequencies (10.79% vs. 4.9%, $p < 0.05$) and higher blood monocyte activation levels ($p < 0.01$). Similarly, the number of liver mononuclear cells was increased (16.106 vs. 5.35.106 cells/liver, $p < 0.01$), as were liver NK cell-specific cytotoxicity (58.8% vs. 32% respectively, $p < 0.005$) and liver monocyte activation levels ($p < 0.01$). The phenotype and the anti-cancer function of spleen cells were not altered. Blood cells from patients who had experienced a rejection also demonstrated increased anti-cancer cell cytotoxicity.
Conclusion: Liver graft rejection is associated to increased peripheral and liver cytotoxicity against cancer cells. This observation supports the use of specific immunosuppression after transplantation for HCC with the idea to improve post-transplant immune clearance of HCC cells.

BO236 SOLUBLE INTERLEUKIN-2 RECEPTOR INHIBITS PERIPHERAL BLOOD MONONUCLEAR CELL FUNCTION VIA INERT SEQUESTRATION OF INTERLEUKIN-2 FOLLOWING CARDIAC TRANSPLANTATION

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Introduction: Allograft rejection is a major caveat to long term success following cardiac transplantation. Previous work demonstrates that soluble IL-2 receptor (sIL-2R) inhibits the clonal expansion of allospecific immune cells. We aim to identify the downstream effects of sIL-2R on immune cell signalling and function.
Methods: IL-2 depletion by sIL-2R was assessed via IL-2 specific ELISA following *in vitro* co-culture. Peripheral blood mononuclear cells (PBMCs) were extracted from cardiac transplant recipients and stimulated with IL-2 alone or IL-2 and sIL-2R. A proteomic analysis of major apoptosis/cell survival pathways, phosphokinase activity and cytokine secretion was performed on cells from $n = 5$ recipients. The effect of sIL-2R on the T cell chemotactic response to RANTES was quantified *in vitro* in samples from $n = 20$ patients.
Results: sIL-2R significantly reduced IL-2 availability in *in vitro* cultures within 10 min ($p = 0.005$), an effect which was sustained up to 24 h ($p = 0.001$). The withdrawal of IL-2 by sIL-2R increased cell survival protein expression and reduced intrinsic/extrinsic apoptosis pathway activity. sIL-2R downregulated a number of signalling pathways, including JAK/STAT, Akt and p53. The inflammatory cytokine/chemokine profile was also altered by sIL-2R treatment, observed as diminished MIF, IL-8 and RANTES secretion. Additionally, T cell chemotaxis in response to RANTES was significantly ameliorated in the presence of sIL-2R ($p < 0.001$).
Discussion: sIL-2R decreases IL-2 availability thereby disrupting a number of signalling cascades that control viability, proliferation, activation and immune cell cross-talk. Furthermore, the significant reduction in T cell migration upon sIL-2R treatment may translate into clinical benefit via diminished graft infiltration *in vivo*. Consequently, our results suggest that sIL-2R may hold potential as a novel method of immunomodulation following cardiac transplantation.

BO237 RABBIT ANTI-THYMOCYTE GLOBULIN THERAPY INDUCES DONOR-SPECIFIC HELIOSNEGFOXP3POS REGULATORY T-CELLS

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Introduction: After rabbit antithymocyte globulin (rATG) the T-cell pool repopulates with a phenotypic shift towards memory and regulatory T cells (Tregs). We hypothesized that this shift into Tregs is the result of compensatory mechanisms; i.e. homeostatic proliferation and thymopoiesis and of the conversion of T-cells into donor-specific-induced Treg (iTreg).
Methods: Patients received induction therapy; rATG ($n = 16$) or anti-CD25 antibody ($n = 16$). Flow cytometric analysis was performed to analyze CD4 + CD25 + +CD127-FOXP3 + Tregs for Ki67, CD31, and Helios expression. Function of FACSsorted CD4 + CD25 + +CD127-Treg was determined in co-culture experiments with donor and third-party activated effector T-cells.
Results: The first six months after rATG therapy the percentage of Tregs steadily increased ($p < 0.01$). This increase was associated with higher percentages of proliferating, Ki67 + CD45RO+Tregs ($p < 0.01$) but not with CD31 + CD45RO-thymically derived Tregs one month after rATG. In addition the expression of Ki67 in Tregs was inversely correlated with Helios expression ($r^2 = 0.4904$, $p < 0.001$), resulting in a higher percentage of Helios- iTreg after rATG therapy ($p = 0.01$). At the functional level FACSsorted Treg from rATG treated patients inhibited the proliferation of donor antigen-activated but not of third-party activated effector T-cells ($p < 0.05$).
Conclusion: Regulatory T-cells repopulate by homeostatic proliferation after rATG induction therapy resulting in functional donor-specific iTreg.

BO238 EFFECTS OF RAPAMYCIN AND CTLA4-IG ON ALLOGRAFT SURVIVAL AND IMMUNE RESPONSES ARE AGE-SPECIFIC

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Aging has a broad impact on immune responses, yet, immunosuppression is not adapted to age-specific changes. Skin allografts from young (3 months) DBA donor mice were transplanted into young (3 months) or old (18 mo) C57BL/6 recipients; animals were treated with either CTLA4-Ig (0.2 mg/day, d 0, 2, 4, 6), rapamycin (1 mg/KG/days, d 0, 1, 2, 4, 6, 8, 10, 12, 14) or PBS and alloimmune response was assessed. Without immunosuppressant administration we observed a median survival time (MST) of 7 days and 9 days in young and old recipients, respectively ($p = 0.0123$). Interestingly, co-stimulatory blockade with CTLA4-Ig resulted in an age-independent prolongation of graft survival (MST = 10.5 days and 10.5 days, respectively) for young and old recipients. In contrast, rapamycin treatment demonstrated impressive age-dependent effects: while MST was only marginally extended to 12 d in young recipients, skin graft survival was significantly prolonged on older recipients (MST = 17 days, $p = 0.0314$). Both, CTLA4-Ig and rapamycin reduced IL-2 and IFN-γ mRNA in young recipients. IL-2 mRNA levels were reduced in older recipients prior to transplantation and immunosuppression did not impact IL-2 mRNA in the elderly. Splenocytes from young recipient mice treated with either CTLA4-Ig or rapamycin showed a significant increase of naive CD4 + T cells ($p = 0.0018$ and 0.0172, respectively) and decreased CD4 + central memory cells ($p < 0.0001$). Next, we assessed the cytokine producing-capacity of T cells by ELISA in a mixed lymphocyte reaction. Splenocytes isolated from old recipients treated with rapamycin and CTLA4-Ig produced significantly lower levels of IL-2 ($p = 0.0218$ and 0.0133, respectively) and IL-4 ($p = 0.0024$ and 0.0469, respectively) and moreover, rapamycin but not CTLA4-Ig treatment resulted in a significant IFN-γ decrease ($p = 0.0137$) when compared to placebo-treated animals animals. Immunosenscence impacts the efficacy of rapamycin and CTLA4-Ig dramatically. These results are of critical clinical significance.

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BO239 DOSE-DEPENDENT IMMUNUSUPPRESSIVE EFFICACY OF CHRONIC CTLA4IG THERAPY IN MICE

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Background: The CTLA4Ig derivative belatacept has recently been approved for immunosuppression in kidney transplant recipients. As the mechanism(s) of action of this costimulation blocker have not been fully delineated, we aimed to develop a murine protocol of chronic immunosuppression with CTLA4Ig that closely models the approved clinical treatment regimen.
Methods: Fully mismatched cardiac transplantation (Balb/C → B6) was performed with the following dosing regimens of CTLA4Ig monotherapy: induction therapy: 0.5 mg CTLA4Ig d0, 0.25 mg d2, 4, 6; low dose (LD): 0.25 mg (i.e. 10 mg/kg BW) d0, 4, 14, 28, 56, 84; high dose (HD): 1.25 mg d0, 4, 14, 28, 56, 84). Grafts were followed for 100 days.
Results: Both induction ($n = 5$) and LD ($n = 6$) therapy with CTLA4Ig resulted in a significantly prolonged allograft survival compared to untreated controls (Figure 1). However, a considerable percentage of grafts was rejected and all mice with long-term surviving grafts developed DSA. The HD regimen ($n = 11$), in contrast, led to permanent (i.e. ≥100d) allograft survival in ≈90% of recipients ($p = 0.003$ vs. LD) and 80% of mice remained free of DSA. Besides, histology revealed markedly decreased rejection scores with the HD regimen (ISHLT [mean ± SD]: HD: 1.2 ± 1.6; LD: 3.5 ± 1.2; induction: 2.2 ± 1.6).
Discussion: Our data show that chronic immunosuppressive therapy with CTLA4Ig prolongs murine heart graft survival in a dose-dependent manner.

BO240 DELETION OF CD39 IS ASSOCIATED WITH DECREASED SECRETION OF IL-22 AND IMPAIRED LIVER REGENERATION

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Background: The cytokine IL-22 exhibits specific hepatoprotective properties in various models of liver injury and repair. Nucleotides, such as ATP, are released by such cellular injury, bind to purinergic receptors expressed on hepatic parenchymal and non-parenchymal cells and modulate cellular cross-talk. We have now explored the cellular fractions in the liver that secrete IL-22 and if extracellular nucleotides impact upon IL-22 secretion of innate lymphoid cells in the liver.
Methods: Using surface and intracellular cytokine staining, cytokine secretion was assessed in response to IL-23 and PMA/Ionomycin. Further, cytokine secretion was assessed in a mouse model with genetic deletion of CD39 the major vascular ectonucleotidase that hydrolyses extracellular ATP to ADP and AMP under basal conditions and after partial hepatectomy.
Results: The fractions of IL-22 producing cells are lower in the liver compared to colon and Intestine but elevated compared to mesenteric lymph nodes and spleens. In the liver, fractions that secrete IL-22 are mainly innate lymphoid cells such as conventional NK cells that are NK1.1 + but NKp46- and minute levels of Rorγt+ NKp46 + , LTi+ cells. Further fractions that secrete IL-22 are NKT cells, T cells that are CD4-, CD4 + , and CD4low. Interestingly, most fractions that secrete IL-22 express CD39. In mice null for CD39 the secretion of IL-22 was significantly decresed in various cell types. Further, deletion of CD39 is associated with decreased serum levels of circulating IL-22 and decreased liver proliferation in a model of partial hepatectomy in mice.
Conclusion: These results reveal that secretion of IL-22 is modulated by CD39 under basal condition and post partial hepatectomy.

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BOS21-KIDNEY – TECHNICAL/SURGICAL

BO241 ENCAPSULATING PERITONEAL SCLEROSIS (EPS) AFTER KIDNEY TRANSPLANTATION (KT): A SINGLE CENTER EXPERIENCE

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Background: EPS is rare but serious complication of unknown origin in patients on peritoneal dialysis (PD). Incidence post KT: 4.2/1000 patient/year; mortality post Tx: 30–68%. EPS is an inflammatory and fibrotic process resulting in partial or complete intestinal obstruction.
Methods/Materials: Seven hundred and thirty six patients KT performed in our Center 2001–2008. 157 / 736 patients were on PD before KT. Median follow-up post KT 68.4 months (29–107).
Results: 7 EPS cases /157 KT (prevalence 4.4%) were found. Mean patients age 49.9 years (26–59), mean PD duration 55 months (33–121); immunosuppressive therapy: tacrolimus, mycophenolate mofetil and steroids. EPS developed 12.2 months after KT (4.7–18.9). Presentation: weight loss, abdominal pain, nausea, vomiting and subocclusion episodes. Diagnosis: 7/7 abdomen computerized-tomography and 4/7 confirmed with peritoneal biopsy. Treatment: 6/7 surgery, 3/7 conversion to mTOR inhibitor with low-dose tacrolimus, 7/7 steroid; 3/7 tamoxifen. 1/7 patient died for other causes; 1/7 patient died for sepsis after intestinal occlusion; 5/7 patients have good renal function, complete symptoms resolution and no disease recurrence.
Conclusion: EPS is serious complication but susceptible of improvement if diagnosed early. No established measure for EPS prophylaxis and therapy is available. Early diagnosis confirmed by peritoneal biopsy and conversion to mTOR inhibitor associated with steroid and tamoxifen could be a successful medical strategy.

BO242 URETERO-VESICAL ANASTOMOSIS TECHNIQUES FOR KIDNEY TRANSPLANTATION: A SYSTEMATIC REVIEW

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Background: Urological complications are the most frequent cause of surgical morbidity after kidney transplantation. No consensus exists about which ureterovesical anastomosis technique to apply.
Methods: Two independent researchers performed a systematic review using the PubMed and MEDLINE databases.
Results: Twelve observational studies and two randomized clinical trials were included. We performed a meta-analysis on the Lich-Gregoir (LG) versus Politano-Leadbetter (PL) techniques and LG versus U-stitch techniques. The LG technique had a significantly lower incidence of urinary leakage compared with the PL technique (odds ratio (OR) 0.57, 95% confidence interval (CI) 0.32–0.99) and a significantly lower incidence of hematuria when compared with both PL and U-stitch techniques (OR 0.21, 95% CI 0.08–0.53 and OR 0.21, 95% CI 0.06–0.75).
Conclusion: The LG technique results in fewer urological complications than the PL and U-stitch technique after kidney transplantation.

BO243 IMPACT OF URETERAL STENTING ON UROLOGICAL COMPLICATIONS AFTER KIDNEY TRANSPLANTATION SURGERY: A SINGLE CENTER EXPERIENCE

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Background: Urological complications such as ureteral strictures, ureteral leakage can affect the outcome of kidney transplantation by increasing the morbidity and mortality, including the graft loss. Controversy still exists regarding the role of stents in renal transplantation. The aim of this study was to evaluate the role of ureteral stenting in kidney transplantation.
Methods: A series of 798 consecutive renal transplantations were performed between 1st of January 2004 and 31st of December 2011. Recipient mean age: 35.17 ± 12.73 years old. Renal grafts were obtained in 199 cases (24.93%) from cadaveric and in 599 cases (75.07%) from living-related donors. Ureteral stents were used in 152 cases (19.1%) of total (stent group) and were removed between 2–4 weeks postoperatively.
Results: The overall incidence of urological complications was 7.89% (63 cases). Ureteral stenosis (3.13%) and ureteral leakage (2.38%) were the most common complications. 39.7% (25 cases) complications were recorded in the first month after transplantation (early complications) and after this interval were considered late complications (60.3%). Ureteral complications rate was 2.6% in stent group compared to 8.9% in no-stent group ($p = 0.04$). Stents did not influence the incidence of urological complications in relationship with donor type or gender of the recipients ($p > 0.05$). However, stent use was associated with increase of UTI rate in stent group (51.3%) compared to no-stent group (17.9%) ($p = 0.03$).
Conclusions: In our study the use of ureteral stents significantly decreases urological complications in kidney transplant recipients but increases risk of developing UTI. Routine ureteral stenting in renal transplantation should balance the benefits of urological complications with certain risks of developing UTI.

BO244 MULTIPLE ARTHERY ANASTOMOSIS IN KIDNEY TRANSPLANTATION: INTERNAL ILIAC ARTERY INTERPOSITION GRAFT

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Background: Anastomosis of multiple renal arteries in kidney transplantation is technically demanding. Previously this condition was considered a relative contraindication to use of the donor, due to an increased risk of vascular and urologic complications.
Methods/Materials: Between August 1990 and February 2013, we have performed 625 renal transplants, among which 86 patients (13.8%) of the multiple donor arteries were encountered and total 94 cases of procedure was done. We reviewed these cases for the type of vascular reconstruction and outcome of 15 interposition graft cases using branched internal iliac artery.
Results: The type of reconstruction were illustrated as follows; ligation of an upper polar artery in 29 cases, double barrel anastomosis in 33 cases, end to side anastomosis between a polar artery and main renal artery in eight cases, separate anastomosis of two renal arteries to the branch of the internal iliac artery in one case, use of the inferior epigastric artery of the recipient for end to end anastomosis to lower polar artery in eight cases, interposition graft using branched internal iliac artery in 15 cases. We reviewed the 15 cases of the internal iliac artery interposition. Anastomosis between donor renal artery and recipient's interposed internal iliac artery was done at bench extracorporeal technique. By use of this technique, warm ischemic time was not prolonged and postoperative course was good without vascular and urologic complications.
Conclusion: Our method enables to select an appropriate recipient's interposed arterial branch to be anastomosed that is compatible with donor's multiple renal artery and is easy to perform. Anastomotic arterial pseudoaneurysm formation or rupture is thought to be possibly low compared with that of the double barrel anastomosis. And multiple arterial anastomosis are conducted in cold extracorporeal environment and a simple end to end arterial anastomosis is done in recipient's body. This technique would reduced warm ischemic time, therefore renal damage could be diminished.

BO245 ENDOVASCULAR MANAGEMENT OF TRANSPLANT ALLOGRAFT RELATED PSEUDOANEURYSMS

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Background: Anastomosis site pseudoaneurysm are a rare complication that can occur following allograft transplantation. The aetiology and natural history of these are not fully understood. Expansion and rupture can lead to life threatening haemorrhage. Minimally invasive endovascular repair allows for definitive management of the pseudoaneurysm in some instances and in emergency cases control haemorrhage to allow definitive open repair to be planned.
Methods/Materials: Retrospective review of the Transplant and Interventional Radiology Databases.
Results: Nine cases (1 bilateral) (5 male: 3 female) underwent endovascular repair. 3/9 cases presented acutely with major haemorrhage. All three cases exhibited some evidence of sepsis at presentation. 2/3 cases underwent placement of a stent graft as a bridge to stabilise the patient prior to open repair. In 1/3 cases the pseudoaneurysm was coil embolised as definitive therapy. All patients made good post operative recovering with no adverse sequelae on

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follow up (range 3–18 months). 6/9 cases presented with localised pain or non-specific systemic symptoms and on imaging were diagnosed with anastomosis site pseudoaneurysms. In 5/6 cases the anastomosis site was the External Iliac Artery and the pseudoaneurysm was treated by placement of a stent graft to exclude it. In 1/6 cases the anastomosis site was the Aorta (transplantation having taken place aged 3). This case was managed by stent assisted coil embolisation.
Conclusion: Endovascular repair is safe and effective in the management of anastomosis site pseudoaneurysms with good mid-term follow up.

BO246 ADULT PREEMPTIVE KIDNEY TRANSPLANTATION: A PAIRED KIDNEY ANALYSIS

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Background: From November 2003 to December 2012, in Gdań sk Center, 64 patients (30 m, 34 f) received preemptive transplantation (PET) – 7 living and 57 deceased donors. PET consisted 8% of all 794 kidney transplantations performed during this time. Aim. The benefits for individual patients and for the health care system are discussed.
Methods: The present study mainly compares the outcomes of these PET patients who had their kidney donor pairs transplanted after variable duration of dialysis (PTD). 51/64 PET (22 m, 29 f) patients aged from 18 to 68 (mean 42 ± 14) had their PTD kidney pair (35 m, 16 f) aged from 19 to 72 (mean 47.5 ± 13.6).
Results: Both groups did not differ significantly with respect to: one-year patient (100% vs. 98%) and graft survival (96% vs. 94%), incidences of acute rejection, Charlson co-morbidity index (3.04 vs. 2.57) and number of mismatches. Also the one-year patient (98.4% vs. 98.7%), and graft (96.8% vs. 95.3%) survival rates for all 64 preemptive recipients was similar to 730 dialyzed recipients who received transplants in our unit within the same period of time. Five (9.8%) PET patients and 20 (39%) PTD patients experienced delayed graft function, PTD patients required over twelve times more hemodialysis sessions than PET patients ($p < 0.05$). The graft function (creatinin serum concentration and eGFR-4 points MDRD) one year after transplantation was similar in both groups. The comparison of the creatinine concentration, measured during last ambulatory control (0.5 month to 107 months since transplantation) – revealed no differences between groups. PTD patients were hospitalized more frequently during the first year after transplantation and received longer (mean about 6 days) hospitalization during the post-transplant period than PET. More PET patients led normal professional activities or continued education before and after transplantation ($p < 0.05$).
Conclusions: Our single-center results confirmed that PET is an optimal mo.

BO247 TOTAL LAPAROSCOPIC RETROPERITONEAL APPROACH FOR LIVING DONOR NEPHRECTOMY: FIRST REPORTED COMPARATIVE STUDY FROM A EUROPEAN CENTE

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Background: Total Laparoscopic Retroperitoneal Donor nephrectomy (TLRDN) implies direct access to kidney without interfering with the intraperitoneal organs. Liverpool transplant Unit in the UK is the first European centre to commence this procedure in June 2011. We report our initial experience of TLRDN and compare the results with standard Hand assisted donor nephrectomies (HADN) done during the same period.
Methods: Forty-four Laparoscopic live donor nephrectomies performed in last 18 months at our centre were retrospectively reviewed and results of (TLRDN) group were compared to HADN group. Patient demographics, donor kidney laterality, intra and perioperative outcomes and recipient graft function were compared.
Results: Left donor nephrectomies were included in the study. 15/41 patients underwent TLRDN. In both TLRDN and HADN groups, the median age was 36 years vs. 39 years, BMI was 26 vs. 27, operative time was 146 vs. 141 min and warm ischemia was 2.6 vs. 2.5 min ($p = 0.7$) respectively. There were no major intra and post-operative complications and conversions in TLRDN, however there was one conversion to open due to bleeding from lumbar vein. Minor complications (wound infection and ileus) occurred in 2/14 TLRDN and 3/26 patients of HADN group. Median hospital stay was 2.5 days v/s 3.3 days, $p = 0.08$). None of the donors needed readmission. Median creatinine clearance of recipients at month 1 and month 3 was 76 ± 2.4, 82 ± 1.6 v/s 72 ± 2.1, 79 ± 1.8 ($p = 0.7$) in TLRDN and HADN groups respectively.
Conclusions: In our initial experience TLDRN has no adverse impact on donor outcomes and early graft function in recipient. For its potential benefits, it's an attractive alternative to transperitoneal techniques. We feel that the learning curve is comparatively shorter and should be able to demonstrate in the subsequent report.

BO248 SYSTEMIC HERPARINISATION IN LAPAROSCOPIC LIVE DONOR NEPHRECTOMY

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Background: Systemic heparinisation is advocated during laparoscopic live donor nephrectomy (LDN) as a preventative measure against renal vascular thrombosis during the warm ischaemic interval. This study compares the outcome with and without the administration of systemic heparinisation.
Methods: A retrospective analysis was performed on 186 consecutive LDN patients from April 2008 to November 2012. All laparoscopic donor nephrectomies and the subsequent transplants were carried out by a single consultant transplant surgeon. Systemic heparin (2000–3000 IU) was administered intravenously to donors (Hep $n = 109$), prior to arterial clamping and following dissection of the renal vessels. The second half of the series from January 2010, heparin was not used systemically in this group of LDN (No hep $n = 77$). Outcome measures included donor and recipient complications, initial graft function, and 12 month graft survival.
Results: The demographics of both heparinised and non-heparinised donors were comparable. First warm ischaemic times were (5 ± 3 vs. 5 ± 3 min; $p = 1.000$) for both groups. Total operating times were comparable in both groups; Hep 306 ± 80 min vs. 295 ± 60 min; $p = 1.000$. Donor complications did not increase when intravenous heparin was not used. There were no episodes of graft thrombosis in either group. No incidences of primary non function occurred in either group. Delayed graft function occurred in 4/109 and 1/77 (3.6% vs. 1.2%; $p = 0.405$). In the heparin group six recipients received blood transfusions, compared to three in non-heparin group (5.5% vs. 3.8%; $p = 0.740$). One recipient in the heparin group returned to theatre due to haemorrhage. Overall graft survival at 12 months was similar at 96.4% in the heparin group and 96.2% in the non-heparinised group; ($p = 0.650$).
Conclusion: Omitting systemic heparinisation in laparoscopic donor nephrectomy is a safe and viable approach that does not compromise donor or recipient outcome. Furthermo.

BO249 PERI-OPERATIVE CARE IN DECEASED DONOR RENAL TRANSPLANTATION – ARE WE MISSING A TRICK?

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Introduction: Goal-Directed Therapy (GDT) and Enhanced Recovery After Surgery (ERAS) protocols improve a variety of outcomes after major surgery. It is unknown whether the organ transplantation community has adopted these approaches by default. We aimed to establish current national practice in terms of the peri-operative care of deceased donor renal allograft recipients.
Methods: In a national survey of practice, senior members of clinical staff from all adult UK renal transplant units were invited to complete a validated questionnaire exploring the peri-operative care of deceased donor renal allograft recipients.
Results: There was an 80% (19/24) response rate. Despite most (84%) units employing written protocols, peri-operative care varied widely. Thromboprophylaxis type, diuretic use, intravenous fluid choice and the preferred cardiovascular monitoring platform differed particularly. Two (8%) units described protocol-driven fluid and inotrope therapy guided by arterial and central venous pressure. One unit employed non-invasive cardiac output monitoring to guide therapy albeit without a formal protocol.
Discussion: Certain aspects of peri-operative care of renal transplant recipients vary widely across the UK. GDT/ERAS protocols *per se* do not appear to have been adopted. The reason for this is unclear but is probably explained by the absence of a clear evidence base for these approaches within transplantation. A randomized trial is indicated and will clarify the role of GDT/ERAS protocols in renal transplantation.

BO250 FIRST HUMAN TRIAL OF ISCHEMIC POSTCONDITIONING IN KIDNEY TRANSPLANTATION FROM DONATIONS AFTER CARDIAC DEATH

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Erasmus MC

Ischemic postconditioning (IPoC) may reduce renal ischemia-reperfusion injury (IRI) after kidney transplantation (KT). We performed a first human pilot trial to study the feasibility and safety of IPoC in human deceased-after-cardiac death (DCD) KT. All patients undergoing DCD KT were eligible. The IPoC algorithm consisted of 1 min reperfusion followed by 1 min of ischemia, repeated three

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times. All complications of this procedure were listed. The primary outcome was the incidence of delayed graft function (DGF). Secondary outcome was renal function at 12 weeks. Data were compared to a historical control group ($n = 40$), consisting of our most recent cohort of DCD KT patients before trial initiation. Follow-up was 12 weeks. A total of $n = 20$ patients was included. Mean donor age and serum creatinine were higher in the experimental group: 61 years (20–71) vs. 51.5 years (24–74) ($p < 0.05$) and 79 μM ± 34.2 vs. 63.8 μM ± 23.4 $p < 0.05$), respectively. In the experimental group, more kidneys had massive atherosclerosis: 25% vs. 2.5% ($p < 0.05$). IPoC was successfully applied in all patients. In one patient a renal vein laceration occurred during IPoC due to clamp manipulation, which could be repaired immediately. The incidence of DGF was 85% vs. 62.5% (not significant). Renal function was comparable between groups at 12 weeks after transplantation: 161 μM (109–536) vs.149 μM (81–315) (not significant). Postoperatively, no additional risks or complications were seen as a consequence of IPoC. We demonstrate for the first time that IPoC is feasible and appears to be safe in human KT. No benefit in terms of reduced DGF or better renal function was observed as a result of IPoC. However, donor organ quality was clearly worse in the experimental group. The fact that similar results were obtained, despite this significant difference in graft quality, is an observation that merits further research of the potential of IPoC in KT.

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BOS22-KIDNEY – REJECTION

BO251 RELEVANCE OF "VIRTUAL CROSSMATCH" FOR KIDNEY GRAFT OUTCOME IN HYPERSENSITIZED PATIENTS

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An increasing number of clinical studies have demonstrated adverse allograft survival in patients with a positive Virtual Cross-match (V-XM). The impact of the donor-specific HLA antibodies (DSA) can be more important in hyper sensitized patients. Objective: To evaluate the risk of graft loss function and antibody-mediated rejection (AMR) in a high risk population in relation to the presence of anti-HLA donor-specific antibodies (DSA) pre-transplant in hyper sensitized patients (PRAmax ≥ 50%).
Materials and Methods: The study includes 150 hyper sensitized patients who received a graft from deceased or living donors with a negative CDC-cross-match between January 2007 and December 2011. A single-antigen bead test by Luminex® technology (LSA-I and LSA-II Gen-probe Inc. San Diego CA) were retrospectively performed in pre-transplant sera. A virtual cross-match positive was assigned according to the MFI values > 1500 and ratio [MFI / MFI lowest bead] >5 against the donor specific antigens and the results were correlated with the occurrence of antibody-mediated rejections and graft loss.
Results: The graft survival in patients with positive V-XM to both HLA-DSA class I and HLA-DSA class II is lower (66.6%) than either HLA-DSA only class I positive V-XM (83% p = 0.24) or HLA-DSA only class II (91%; p = 0.09) and patients with negative V-XM (90%; p = 0.035). Patients with positive V-XM showed more AMR episodes (65%) when comparing with patients with negative V-XM (6.3%) or without DSA (28.2%).
Conclusions: Patients with preformed anti-HLA-DSA showed more likelihood to suffer rejection episodes. The combination of both DSA anti class I and class II seems to be more deleterious for the kidney graft outcome than the presence of only antibodies to class I or class II, therefore transplant should be avoided in these patients. The virtual cross-match should be recommended in hyper sensitized patients to select the most suitable donor to assure a better graft function.

BO252 SINGLE CENTER EXPERIENCE OF ABO INCOMPATIBLE KIDNEY TRANSPLANTATION

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Asan Medical Center

Background: In order to overcome the shortage of donors, we have performed ABO-incompatible kidney transplantation (ABOI KT) to expand the indication in living donor kidney transplantation.
Methods: From January 2009 to February 2013 we had performed 153 cases of ABOI KT. Rituximab (200 mg), plasmapheresis (PP), and early use immunosuppressant based preconditioning was used. Pre-operative target isoagglutinine titer was (tube method) less than 1:8.
Results: ABOI KT accounts for approximately 20% of all living donor kidney transplantations performed in our center. Mean recipient age was 44.7 year old („b11.7). Median pre-conditioning titer was 1:64, and median pre-operative titer was decreased to 1:2 after mean 4.7 session of PP. Regarding postoperative titer, titer over 1:16 was observed in 24 patients. Among whom 23 patients had stable graft function and one patient ABO antibody associated AMR. There was no immunological graft loss during 539 days („b396) follow up. We experienced 16 acute rejections in 12 patients; Steroid was initially used in 14 ACR and plasmasphere in two AMR with complete responses. We experienced six mortalities in early period (6/89), one from cardiac, and the others from infection, especially in old recipient (>55 years). After introduction of reduced immunosuppressants such as MMF dose reduction (1.5 g to 1 g per day) within 2 weeks, and cyclosporine in aged patients, with the coverage of antibacterial and antiviral agent there was no mortality in latter period (0/64).
Conclusions: ABOI KT following preconditioning is a feasible treatment modally. In regard to high morbidity and mortality from generously accepted preconditioning regimen, modification of perioperative care is mandatory especially in aged patient (>55 years old).

BO253 CXCL9 AND CXCL 10 LEVELS IN URINE ARE SUITABLE PARAMETERS FOR DIAGNOSIS AND PREDICTION OF ACUTE REJECTION

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The interferon gamma dependent chemokines CXCL9 and CXCL10 are chemoattractive molecules that appear early in the process of acute kidney rejection. The expression of these molecules typically precedes immune mediated damage to the transplanted organ. Monitoring of these molecules in biological fluids such as serum or urine may present a non-invasive early detection method for acute rejection. We selected 34 kidney transplant recipients that experienced an acute rejection episode within 6 months after transplantation and 55 patients with stable renal function, receiving the same immunosuppressive regime. Serum was collected before transplantation, at discharge and at time of rejection, or at a follow-up time point similar to the rejection time-points for the non-rejecting patients. Urine was collected concomitantly, except for the pre-transplant time-point. CXCL9 and CXCL10 levels were determined for all samples by multiplex Luminex assays. Receiver operator characteristic (ROC) analysis was performed to determine their sensitivity and specificity, defined here as area under the curve (AUC). CXCL9 and CXC10 levels in the serum were not predictive, neither diagnostic for acute rejection. In contrast, urinary CXCL9 and CXCL10 levels at time of discharge were increased in patients with a consecutive acute rejection ($p < 0.005$ and $p < 0.0001$) and resulted in an AUC of 0.67 and 0.77, respectively. Urinary CXCL9 and CXCL10 levels measured at time of rejection were also increased compared to controls ($p < 0.0001$ and $p < 0.005$) and resulted in an AUC of 0.82 and 0.73, respectively. Combination of CXCL9 and CXCL10 levels did not improve the predictive or diagnostic value. In conclusion, our data show that urinary CXCL10 levels at discharge have the highest predictive value for acute kidney rejection, whereas urinary CXCL9 at time of rejection levels have the highest diagnostic value for acute kidney rejection.

BO254 PERDICTIVE VALUE AND DYNAMIC CHANGES OF IL10, 17, IL23, TGF-B AND IFN-G PRODUCING CELLS IN RENAL TX

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Background: A growing body of evidence demonstrated an immune eatilogy mechanisms for episodes of clinical AR and long-term allograft dysfunction. aim: investigate the correlation of IL10, IL17&IFN-â producing cells &TGF-â /IL23 in supernatant of coculture of recipient and donor inactivated cells with incidence of clinical AR episodes.
Method: This study was performed on 57 kidney allograft recipents from living unrelated donors (2011–12). PBMCs were collected from all patients pre-Tx, days 14, 30 and 90 after Tx.& followed 1 year. reciepient PBMCs were used as responding and ictivated donor cells as stimulator in ELISPOT.
Results: During follow up period, 78.9% were SGF (a) and 21.1% experienced clinical AR episodes(b). IL17 & IFN-â-producing cells & IL23 were higher in rejecting group ($p < 0.001$). whereas IL10 and TGF-â showed higher contents in group a versus group b ($p < 0.001$).
Conclusion: Serial post Tx monitoring of IL17,IL23 & IFN-â helping diagnosis high risk allograf forAR.

BO256 EPITOPE SPREADING AND EPITOPE SHARING ARE INVOLVED IN ACUTE IGG1 ANTIBODY-MEDIATED REJECTION OF A KIDNEY TRANSPLANT WITH DISPARITY ONLY AT HLA-DP

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Background: Donor-specific alloantibodies (DSA) directed to HLA-DP alone may cause acute antibody-mediated rejection (AMR), especially in re-transplanted patients. Since the origin of such DSA is not clear, we have examined the sensitization history of a patient who received 3 consecutive kidney transplants.
Methods/Results: Single antigen bead (SAB) analysis showed immunization by the 1st transplant (TX) with multiple class I/II HLA mismatches; this transplant lasted 9 years and was lost to chronic nephropathy. The HLA-matched (except for DRB3 02:02 and DPB1 04:02) 2nd TX failed within 1 year due to chronic rejection. The 3rd TX was mismatched only for DPA1 02:01 and DPB1 01:01/*04:02. Although prior to the 3rd TX the patient had 100% PRA and DPA1 02:01-reactive DSA in SAB (3518 MFI), the flow crossmatch (FXM) was negative. Within 10 days, the patient had elevated creatinine (3 mg/dl) and C4d+ AMR (Banff 2a). This correlated with DSA of IgG1 (no other subclasses) directed to DPA1 02:01 in SAB (18483 MFI) and SAB-C1q (25940 MFI) as well as to DPB1 01:01 in SAB (5359 MFI). HLAMatchmaker analysis revealed that the 1st TX and 3rd TX shared 4 epitopes (111R, 51RA, 83A, 127P) on DPA1 02:01 as well as 2 epitopes (35YA, 84DEAV) on DPB1 11:01 of the 1st TX and DPB1 01:01 of the 3rd TX (Fig. 1). The DSA after the 1st TX towards one immunizing epitope (111R) on DPA1 02:01 was joined by reactivity to three additional epitopes (51RA, 83A and 127P) during AMR after the 3rd TX (panels A, B, and C). Furthermore, two immunizing epitopes (35YA and 84DEAV) on DPB1 11:01 of the 1st TX (panel D) conferred reactivity to DPB1 01:01 of the 3rd TX (panel E).

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Conclusions: (1) DP alleles alone induce acute AMR in previously immunized patients; (2) FXM fails to detect DSA to DP alleles detectable by SAB assay; and (3) both epitope spreading and epitope sharing enhance IgG1-mediated DSA leading to the robust acute AMR.

BO257 PLASMAPHERESIS IN ANTIBODY-MEDIATED RENAL ALLOGRAFT REJECTION. SINGLE CENTER STUDY

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Background: Antibody-mediated renal allograft rejection (AMR) after kidney transplantation KT has poor prognosis for graft survival. The plasmapheresis has achieved controversial results, few randomised controlled trials indicate a trend towards superior graft survival in patients receiving this treatment. However, the evidence remains weak. We decribe the outcome of plasmapheresis as a therapy for patients with AMR.
Material Methods: The objective of this study was to report our experience in treating AMR with only plasmapheresis in kidney transplant recipients. This is a retrospective and descriptive study of the patients that underwent plasmapheresis as a treatment of severe AMR.
Results: Between January 2008 and December 2012, 480 patients underwent kidney transplantation at our institution, 16 patients developed AMR (3.3%). Nine male and seven female. All patients received induction therapy. Manteinance therapy used was tacrolimus, mycophenolic acid and steroids in 73.3% of the patients and cyclosporine, micophenolic acid and steroids in 13.3%. AMR had an early onset in 81% of the cases. Creatinine value at diagnosis was 5.45 mg/dl (p25 3.3 – p75 8.07). Patients had an average of 4.93 plasmapheresis. At the end of the first year, 31.25% of the patients had a creatinine below 1.5 mg/dl and, 66% of the patients were back on dialysis. Complications were reported in 13.3% of the patients (hypotension and anaphylaxia).
Discussion: Plasmapheresis alone, has not prove to be an outstanding therapy in AMR. It is necesary to explore new alternatives in the management of this entity: IgIVs, rituximab, eculizumab, bortezomib.

BO258 BORTEZOMIB IN THE TREATMENT OF RESISTANT ACUTE ANTIBODY – MEDIATED REJECTION: A SINGLE CENTRE EXPERIENCE

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Background: Acute antibody-mediated rejection (AMR) represents a rare complication after kidney transplantation that often leads to renal allograft loss. Previously reported therapeutic superiority of combination of plasmapheresis (PP) and intravenous immunoglobulin (IVIG) may however fail in some resistant cases. Thus, the aim of this study was to analyze the efficacy and safety of bortezomib based treatment of resistant AMR in kidney transplant recipients.
Methods: Resistant AMR was defined as a persisting deterioration or nonfunction of renal allograft in patients with histological verification of AMR, positive C4d+ staining and detection of donor specific antibodies (DSA) receiving standard antirejection treatment with PP + IVIG. Novel therapeutic approach to resistant acute AMR Protocol was based on administration of bortezomib [1 cycle of 4 doses of bortezomib (1.3 mg/m^2)], plasmapheresis and a dose of Rituximab (375 mg/m^2). Patients were followed for 3–12 months.
Results: Seven patients received bortezomib based protocol to cure resistant AMR. Their peak PRA was 47.57 ± 36.69%, mean HLA mismatch in HLA- A 1.57 ± 0.53, HLA-B 1.57 ± 0.53, HLA- DR 1 ± 0, and median dialysis vintage was 53. Two patients underwent 1st kidney transplantation, while four patients retransplantation (2nd Tx $n = 2$, 4th Tx $n = 3$). Immunosuppressive protocol consisted of induction with antithymocyte globulin ($n = 6$) or basiliximab ($n = 1$). Diagnosis of resistant acute AMR was made on 15th POD (9–450 days). Based on therapeutic effect, three patients received 1 cycle, while four patients received 2 cycles of therapy. The side- effects observed were urinary tract infection ($n = 2.$), colitis ($n = 2$), polyneuropathia ($n = 2$), hepatotopathia ($n = 3$) and fluid retention ($n = 5$) After bortezomib based regimen, the DSA decreased in both HLA class I (MFI before treatment 9614 ± 9531 vs. MFI after treatment 1393 ± 1760, $p < 0.05$) and class II (12822 ± 6264, 6200 ± 6099, respectively, $p = 0.03$). A.

BO259 REPORT ON THE INEFFICACY OF ECULIZUMAB IN TWO CASES OF SEVERE ANTIBODY MEDIATED REJECTION OF RENAL GRAFTS

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Acute antibody-mediated rejection (AMR) is responsible for up to 20–30% of acute rejection following kidney transplantation and requires an immediate response. Thus new therapeutic agents have recently emerged such as eculizmab, a humanized anti-C5 monoclonal antibody, acting as an inhibitor of terminal complement activation. Stegall et al. have shown that eculizumab administered preventively at time of transplantation decreased the incidence of early AMR in 26 sensitized renal transplant recipients. Locke et al. reported a case of successful treatment of severe AMR using eculizumab and plasmapheresis (PP)/intravenous immunoglogulin (IVIg). As far as we are aware there has not been any case reported of inefficacy of eculizumab in the setting of AMR. Herein, we report the case of one kidney recipient with a previous history of HUS and consequently treated with eculizumab for 9 months, who still experienced severe AMR (failure of prevention); plus one other case of a sensitized kidney recipient who had an episode of AMR which was refractory to conventional therapy (steroids, immunoadsorption, IVIg, rituximab) and in whom eculizumab did not bring any further benefit (failure of treatment). At time of diagnosis, deterioration of renal function led to renal transplant biopsy and disclosed in both cases AMR with intense glomerulitis and peritubular capillaritis(g3, cpt3). Both patients had DSA. Importantly, these cases share two common features: (1) C4d staining was negative, and (2) DSA were unable to bind C1q. Therefore, we speculate that AMR lesions were essentially independent from the complement pathway and we question the efficacy of using eculizumab off-label to prevent or treat AMR in the absence of evidence for complement activation *in situ* (as positivity for C4d staining, and/or C1q binding).

BO260 TREATING TRANSPLANT GLOMERULOPATHY: TOO LATE TO SUCCEED?

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Transplant glomerulopathy-TG is a major cause of chronic kidney allograft injury and graft loss. Using B-cell targeting molecules represent a rational strategy to treat TG during chronic antibody-mediated rejection-CAMR: associated with donor-specific antibodies-DSA and/or C4d deposition. This potential interest is counterbalanced by the advanced stage of chronic lesions, which may not regess anymore once the diagnosis has been made. We design a pilot study to define the relevance of a therapeutic intervention on TG during CAMR, in a clinical setting. Twenty one patients with TG during CAMR were included. All these patients received four doses of intravenous immunoglobulins (IVIG, 1 g/kg) and 2 doses of rituximab (RTX, 375 mg/m). TG was diagnosed 104 ± 80 months after transplantation on a biopsy for cause. Baseline e-GFR and proteinuria were 30.6 ± 13.8 mL/min/1.73 m and 2.1 ± 2 g/l, respectively. Six patients (29%) had a history of acute rejection. The phenotype of TG distributed as follows: 8 TG+C4d+DSA, 7 TG+C4d, 6 TG+DSA. Out of the 14 DSA+ patients, 9 (64%) had de novo DSA and the mean number of DSA was 1.9 ± 1.2. Despite IVIG/RTX therapy, graft survival at 24 months was poor ($N = 10$, 47%, dividing equally between the different phenotypes and including one death with a functioning graft) even worse than the previously reported during natural history of TG. Among the DSA+ patients, 9 (64%) displayed a decrease of the DSA Single Antigen Flow Bead Mean Fluorescence Intensity. This decrease was associated with a better death censored graft survival (87.5% vs. 33%, $p = 0.03$) but could not be predicted at the initiation of the treatment. Adverse events (AE) were also registered: 6 (29%) infections, 5 (24%) thombopenia/neutropenias, 2 (10%) hemolytic anemias, 5 (24%) liver cytolysis and one (5%) neoplasia. Treated patients exhibited a mean number of 2 [0.8–2.2] AE. In routine practice, the risk-benefit balance is clearly not in favor of an intervention based on IVIG/RTX therapy.

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BOS23-LIVER MISCELLANEOUS I

BO261 EVEROLIMUS AND ONCE-DAILY TACROLIMUS AFTER LIVER TRANSPLANTATION

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Background: This was a study on everolimus (EVR) administered once daily (OD-EVR) or twice daily (TD-EVR) in combination with once-daily tacrolimus (OD-TAC), using TD-EVR + twice-daily TAC (TD-TAC) as the referent case.
Methods: Adult recipients on TAC were enrolled. Patients on OD-TAC were randomized to OD-EVR (Group A) vs. TD-EVR (Group B). Patients on TD-TAC received TD-EVR (Group C). EVR was initiated at of 1.0 mg bid (target 3–8 ng/ml) and TAC was adapted to 3–5 ng/ml.
Results: Eighteen patients were enrolled. Group A showed slightly lower trough EVR levels on day 7 and a slightly longer time to reach EVR target range (p = ns). At month 3, patients on OD-EVR+OD-TAC were on slightly higher (2.75 (0.75) mg) median (IQR) EVR daily dose vs. Group B (2.25 (0.5) mg) and C (1.75 (0.5) mg) (p = ns).
Conclusion: OD-EVR + OD-TAC proved as effective as TD-EVR with OD-TAC/TD-TAC, although slightly lower EVR trough levels were observed after switching.

BO262 SAFETY OF EVEROLIMUS IN KIDNEY AND LIVER TRANSPLANTATIONS: DOES THE ORGAN MATTER?

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Background: Everolimus (EVR) has a known adverse event (AE) profile in kidney transplant recipients (KTxR). Data from a recent phase III liver (L) Tx study allows to compare the AEs from both populations.
Methods: A2309 and H2304 were 24-month (mo) multicenter, randomized, open label studies in *de novo*KTxR (N = 825) and LTxR (N = 719), respectively. In A2309, immediate start of EVR + reduced cyclosporine (CsA) was compared with mycophenolic acid + standard CsA. In H2304, EVR + reduced tacrolimus (TAC) at 1 mo post-Tx was compared with standard TAC.
Results: Generally, the incidence of selected, mammalian target of rapamycin (mTOR) inhibitor related-AEs in LTxR was lower vs. KTxR (table). The rate of AEs between EVR and control was comparable in both studies.
Conclusion: The safety profile of EVR in LTxR is comparable to the one known in KTxR. The numerical differences may be attributed to variation in studied populations, study design and choice of calcineurin inhibitor.

BO263 A SINGLE-CENTER EXPERIENCE WITH ONCE-DAILY PROLONGED-RELEASE TACROLIMUS IN LIVER TRANSPLANTATION

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Background: The prolonged release formulation of tacrolimus is administered in the morning once daily. The aim of this study was to show our experience in the utilization of this drug as de novo immunosuppressive agent after liver transplantation (LT). Herein we analyzed the safety, efficacy and drug doses.
Methods: We analyzed 95 recipients of a first liver transplantation form November 2000 with 6 months follow-up. Fourty-two patients were administered the once-daily prolonged release formulation of tacrolimus as de novo drug (group A) while 53 as conversion after the twice-daily formulation administration (group B). We collected the efficacy and safety variables as the incidence of acute rejection, the impact of the drug on liver function, patient and graft survivals, and the incidences of diabetes mellitus and arterial hypertension after LT.
Results: The incidence of biopsy proven acute rejection episodes was 4% (n = 2), in group A and 15% (n = 8) in group B. Renal failure (meant as mean serum creatinine level higher than 1.5 mg/dl or eGFR less than 50 ml/min) occurred in 33.3% of patients (n = 14) and in 28.3% of patients (n = 15) in group B. Both groups showed a high incidence of diabetes mellitus after LT that is 28.65 (n = 12) in group A and 24.5% (n = 13) in group B. Only two patients in group A and 4 patients in group B developed arterial hypertension necessitating more than one pharmacological agent.
Conclusion: Oral administration of prolonged release formulation of tacrolimus for de novo liver transplantation recipients was well tolerated in our experience showing no difference in terms of efficacy and safety compared to the twice-daily tacrolimus. A close control in the adjustment of drug doses is necessary in the early administration period. A variable learning curve is also necessary for the physicians involved in the management of these patients to get confident with this immunosuppressive agent.

BO264 ANTIHBC POSITIVE LIVER GRAFTS ARE SUITABLE ORGANS FOR LIVER TRANSPLANTATION USING COMBINED ANTIVIRAL PROPHYLAXIS

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Background: Due to organ shortage the use of so called "marginal livers" is increasing in deceased donor liver transplantation. Herein we investigate the long term outcome of recipients and grafts from Hepatitis B core positive donors and the impact of antiviral prophylaxis.
Methods and Materials: This is a retrospective study including all liver transplants performed at our centre between 4/1977 and 3/2012. HBV infection was defined as positive HBV PCR. Statistics were carried out by Kaplan Meier analysis and ANOVA.
Results: Among 1167 liver transplants, 59 (5.1%) were carried out using grafts of antiHBc+ donors. Five-year graft- and patient-survival in patients receiving antiHBc+ grafts was 63.9% and 75.8% respectively. 28.2% of all patients receiving antiHBc+ grafts were HBV PCR+ post transplant, occurring after a mean of 2.7 years and was lowest for patients who received antiviral prophylaxis with lamivudin and HBs-immunoglobulin (19.0%) compared to no prophylaxis (35.0%), lamivudin alone (33.3%) and other mono- or combination therapies (adefovir, tenofovir, HBIg; 37.5%). HBV PCR in the postoperative course was positive in 0% of vaccinated patients (antiHBs >100 iU/ml at the time of transplantation) vs. 25.0% for non vaccinated (antiHBs <100 iU/ml) and 62.5% for HBsAg+ patients with no significant difference in mortality.
Conclusion: AntiHBc+ livers can be transplanted with reasonable results in long term patient and graft survival. The combined use of lamivudin + HBIg as prophylaxis is superior to other prophylaxis regimes regarding infection rate. antiHBc+ liver grafts should primarily be allocated to vaccinated patients.

BO265 SAFETY AND EFFICACY OF SUBCUTANEOUS HEPATITIS B IMMUNOPROPHYLAXIS USING "ON DEMAND" APPROACH: A SINGLE CENTER EXPERIENCE

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Background: HB immunoglobulin(HBIG)administration is the backbone for prophylaxis of HBV re-infection after liver transplantation (LT). Long term effects and efficacy of HBIG are well known only for intravenous(IV)and intramuscular(IM)formulations.
Aim: To investigate efficacy,safety and feasibility of "on demand" subcutaneous (SC) administration of the new formulation of HBIG BT088 (Zutectra®)LT patients.
Materials and Methods: A total of 37 LT patients(9 F, 28 M, mean age 60 ± 7 years)were switched from IV or IM to SC HBIG administration during a period of 2 years from January 2011. The conversion to SC administration occurred at a mean time of 44 months from the LT. They were prospectively enrolled and followed up for at least 48 weeks. The dose of HBIG was initially standardized to 1000 IU/week. After a period of stabilization, patients were offered a"on demand"approach,with a targeted level of serum antiHBs of minimum100UI/L.
Results: All patients were HBV-DNA negative at the time of transplantation(5 spontaneously-14%,32 under NUCs -86%). All patients were on a combination prophylaxis with HBIG and NUCs. All patients became rapidly independent for the weekly SC self-injection. The treatment was effective in maintaining trough anti-HBs levels greater than 100 UI/l in all patients. Ninty of patients showed a mean HBsAb titer greater than 155 UI/l. Overall, mean values of HBsAb were 262 UI/l(±118). The mean HBsAb titre prior to switching to SC formulation was 318 ± 124, with a mean monthly injection of 5000 U/L. No drug related side effects or injection site problems were observed.
Conclusions: SC HBIG for long term prophylaxis of post LT HBV re-infection has proven to be safe, well-accepted and effective in maintaining the targeted protective anti-HBs levels. Moreover individualization of immuneprophylaxis according to the lowest protective anti-HBs titers is easily applicable with the SC formulation, allowing the exploration of new schedules in order to improve costs while maintaining efficacy.

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BO266 DETERMINATION OF ALCOHOL MARKER FOR DETECTION OF ALCOHOL CONSUMPTION AFTER LIVER TRANSPLANTATION

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For detection of alcohol consumption hair ethyl glucuronide (hEtG), urine EtG, CDT and methanol were determined in 104 OLT recipients and compared with pts' self reports and physician's assessment. 22%, 3% and 17% of pts were suspected to consume alcohol by physician's assessment, self report and alcohol marker, respectively. In ALD pts consumption was significantly more often suspected (36% vs. 16%, $p < 0.05$) and alcohol marker were significantly more commonly positive (58% vs. 10%; $p < 0.0002$) as in non-ALD pts. 25 alcohol marker were positive in 18 pts. In all but 2 pts (89%) alcohol consumption was detected by a positive hEtG. hEtG was more commonly positive (10/31; 32% vs. 6/73; 8%, $p < 0.005$) in ALD pts and the mean proximal hEtG concentration was higher (136.4 + 142.2 vs. 25.1 + 14.3; $p = 0.04$). Correlation between alcohol marker and questionnaire ($k = 0.326$) and physicians' assessment ($k = 0.490$) was poor. So hEtG testing was the best marker for detection of alcohol consumption.

BO267 SOLUBLE LIGANDS FOR NKG2D – INDICATORS FOR SEVERE FIBROSIS IN LIVER TRANSPLANT RECIPIENTS

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Introduction: The role of HLA mismatches and soluble ligands for activating natural killer group 2 (NKG2D) in fibrosis progression has not yet been investigated in LT setting. Aim: To investigate risk factors for progression of hepatic fibrosis following LT.
Methods: A total of 174 LT recipients were enrolled in the study.
Results: Donor age >50 years ($p = 0.001$), presence of anastomosis stenosis ($p = 0.009$), high AST ($p < 0.0001$), ALT ($p = 0.001$), total bilirubin ($p = 0.0004$) and ALP ($p = 0.01$) were associated with progression to cirrhosis. Immunological risk factors included high serum levels of inflammatory cytokines (TNFá [$p = 0.01$], IL-10 [$p = 0.004$], IL-6 [$p < 0.0001$]), presence of anti-HLA II antibodies ($p = 0.01$), high sMICA ($p = 0.04$), sMICB ($p = 0.004$) and ULPB2 ($p < 0.0001$). High serum levels of total bilirubin, sMICB and ULPB2 were independent predictors for cirrhosis after LT.
Conclusion: Early screening of sMICA and ULPB2 may identify LT patients at high risk of hepatic fibrosis progression.

BO268 DIRECT BIOELECTRICAL IMPEDANCE FOR EVALUATION OF LIVER STEATOSIS IN AN ANIMAL MODEL

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Background: Steatosis of the liver graft is a key determinant of the outcome of hepatic transplantation. Frozen section biopsy of the graft is the gold standard for its determination, but its availability is limited. The aim of our study was to validate bioelectrical impedance (BI), for the evaluation of liver steatosis (LS) in an animal model.
Methods: Thirty-one C57BL6 mice were divided in two groups: a fatty liver group induced by a methionine-coline deficient (MCD) diet ($n = 17$) and control group receiving a normal diet ($n = 14$); laparotomy was performed after 10 weeks in both groups. Direct liver BI was performed using two planar electrodes at four different times: during laparotomy, after local freezing with ice, after 3º C Ringer portal vein perfusion and *ex vivo*. Real time impedance, phase angle, resistance and admittance were recorded. Liver samples were taken to determine hepatic triglyceride (HT) content and histology. Biopsies were graded according to the degree of steatosis.
Results: Both groups differed in body weight, liver weight and liver volume ($p < 0.01$). MCD group had a 7.6-fold increase in HT than controls. There were no differences in the univariate analysis of the BI variables. In an adjusted linear model, animal weight and temperature at the time of laparotomy were inversely correlated with HT. Conversely, liver weight and phase angle *ex vivo* were directly correlated (R2: 0.72). The analysis of phase angle at the time of the laparotomy did not reach statistical signification ($p = 0.08$). An ordinal regression was constructed to develop a predictive model for the grade of steatosis considering all BI variables. The final model included liver volume and density ($p = 0.06$), temperature at any time point (p = NS), resistance after the 3º C Ringer perfusion ($p = 0.09$) and at laparotomy ($p = 0.05$). This model correctly categorized all mice when a LS cut-off was set at 33%.
Conclusion: In a multivariate model, BI accurately discriminated moderate and severe LS in mice.

BO269 ORAL MUCOSAL LESIONS IN LIVER TRANSPLANT RECIPIENTS AND CONTROLS

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Background: Immunosuppressive medication may cause several side effects. Data on oral side effects in liver transplant (LT) recipients are limited.
Methods/Materials: A cross-sectional study included 84 LT recipients (64 chronic liver disease (CLD), 20 acute liver disease) who were recruited for oral examination in connection with a protocol follow-up visit (median follow-up 5.5 years) at transplant center. Salivary flow was measured and oral mucosal samples were taken for *Candida* cultivation. Prevalence for oral mucosal lesions (OML) was calculated in different etiology and immunosuppressant groups. Prevalences were also compared to population-based matched controls that came from the National Finnish Health 2000 Survey ($n = 252$). Risk factors for OML were further investigated by logistic regression.
Results: OML were more frequent in LT recipients than in controls (43% vs. 15%, $p < 0.001$); use of steroids increased the risk to 53%. Drug-induced gingival overgrowth was most common type of OML and with cyclosporine, prevalence was higher compared to tacrolimus (30% vs. 5%, $p = 0.007$) and even higher with simultaneous calcium channel blocker use (47% vs. 8%, $p = 0.002$). Pre-cancerotic OML occurred in 13% of CLD patients and 6% in controls. CLD patients had more often reduced salivary flow compared with acute patients (31% vs. 10%, ns.). More than half of all patients were positive for *Candida* and this risk was higher with steroids. Risks for OML was highest in LT recipients (OR = 9.2, 95%CI: 4.5–19.0, $p < 0.001$). Other risk factors included the number of teeth, current alcohol use and smoking (OR = 0.9, 95% CI: 0.9–1.0, $p < 0.001$; OR = 2.4, 95%CI: 1.2–5.0, $p = 0.018$; OR = 2.0, 95%CI: 1.0–3.8, $p = 0.042$; respectively).
Conclusion: Not only immunosuppressant but a high number of other medications may explain why OML lesions were frequent in LT recipients. Lifestyle habits predisposed to OML and since they may carry a risk of becoming malignant, regular oral examinations are indicated.

BO270 TUMOR LYMPHOCYTE INFILTRATION AND PROGNOSIS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED BY LIVER TRANSPLANTATION

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Background: Liver transplantation (LT) is an established treatment method in patients with hepatocellular carcinoma (HCC). However, a number of patients experience early recurrence and poor results as a consequence of aggressive tumor biology. Due to the ever increasing organ shortage, new biologic prognostic factors are necessary in order to stratify the patients regarding prognosis.
Methods: Forty-four patients with HCC treated by LT were included in this retrospective study. Analyzed clinical and pathologic data include age, sex, number and size of tumors, tumor differentiation, presence of vascular invasion, adherence to Milan criteria, alpha-fetoprotein level. Immunostaining was used to assess the infiltration of CD3 + , CD4 + , CD8 + and Foxp3 + cells. Kaplan Meier curves and receiver operator characteristic (ROC) analysis were used to analyze recurrence free and overall survival.
Results: Presence of microvascular invasion was found to be associated with HCC recurrence ($p = 0.035$). Analysis of immune parameters showed that the patients with increased total lymphocyte infiltration measured by the number of tumor infiltrating CD3 + cells are less likely to experience recurrence ($p = 0.05$). ROC curve analysis showed that patients with a CD4/CD8 ratio greater than one had better chances of recurrence free survival. Also, patients with lower numbers of infiltrating T reg cells were found less likely to experience HCC recurrence ($p = 0.025$).
Conclusion: Our results indicate that total lymphocyte infiltration, CD4/CD8 ratio and T reg infiltration have prognostic significance in HCC. These parameters could add valuable information to the presently used morphologic criteria in order to stratify HCC patients who benefit from liver transplantation.

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BOS24-ETHIC/LAW/PSYCHOSOCIAL/PUBLIC POLICY

BO271 UNDERSTANDING MEDICAL STUDENTS' VIEWS ON ORGAN DONATION AND TRANSPLANTATION IN THE UNITED KINGDOM: A CROSS-SECTIONAL SURVEY IN GLASGOW

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Background: Changes to increase donation rates and streamline the donation process may pose ethical dilemmas to clinicians and society in general. Undergraduate medical students, "tomorrow's doctors", may be required to implement such changes.
Methods: We performed a cross-sectional questionnaire study of undergraduate medical students at the School of Medicine, University of Glasgow, UK. One hundred and eighty five responses were received with a completion rate of 88.6%. We present an interim analysis of these responses.
Results: 98.2% of students agree with solid organ donation, yet only 82.8% have signed up to the donor register. 98.2% of students understand that there is a relative deficit of organ donors. A number of proposed changes were supported by a majority of students: opt-out system (78.4%); compensation for loss of earnings or other expenses incurred by live donor nephrectomy (70.8%); uncontrolled donation from non-heart-beating donors (64.3%); elective ventilation (59.1%); aggressive ITU donor management (55.0%). IA majority of students also expressed disagreement with: financial remuneration (in excess of expenses) for live donor-nephrectomy (79.5%); prioritisation of individuals already on the organ donor register (69.0%); and financial incentivisation of staff involved in the donation-transplantation process (62.0%).
Conclusions: Early data suggest that medical students support a range of measures to increase donation rates but this is tempered by a clear demarcation of boundaries to maintain an ethical regulatory framework.

BO272 THE NATIONAL TRANSPLANTATION SYSTEM IN THE REPUBLIC OF MOLDOVA – PAST, PRESENT AND FUTURE

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Transplant Agency

Objective: Due to the support of the Council of Europe and the European Commission experts within the Joint Programme the law on transplantation of organs, tissues and cells of human origin was adopted by the Parliament of the Republic of Moldova (RM) in March 2008. To ensure safety and quality in the field of transplantation, RM aims to adopt and implement the law in compliance with the principles of the European Union health acquis.
Methods: According to the new legislation the Transplant Agency was created as a public body in May 2010. In the context of setting up the transplant system a number of legislative acts were adopted, including the Regulation on organization of the Independent Commission for approval of organ/tissues/cells procurement from live donors, the clinical protocols "Brain Death" and "Maintenance of the potential brain death donor". The integrated computer system for transplant management and organ allocation was implemented.
Results: Ten hospitals were authorized for the procurement and transplantation of numan organs, tissues and cells. The transplant coordinators – eight doctors, personnel responsible for organ and tissue transplantation – 13 doctors were appointed and trained. Technical devices for the HLA Laboratory were installed and validated. Equipment for brain death detection and management of potential organ donors was installed. In December 2011 renal transplant activity was initiated with an intervention from a living donor. The kidney retrievals from living donors and transplantation – five cases. First living donor liver transplantation has been performed on February 22nd this year. The National Transplant Programme 2012–2016 was approved by the Government in October 2012. The first multi-tissue bank was authorized in January 2013.
Conclusions: There is an ongoing development in law enforcement. The next step forward is implementation of the "Brain Death" protocol and initiation of organ and tissue procurement from deceased donors.

BO273 VOICES FROM THE FIELD: AN ANALYSIS OF STRENGHTS AND WEAKNESSES OF THE ITALIAN ORGAN TRANSPLANT NETWORK FROM THE POINT OF VIEW OF THE LOCAL COORDINATORS

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The present study reports the results of a research project on the Governance of the Rete Nazionale Trapianti – National Transplant Network (RNT) commissioned by the Centro Nazionale Trapianti – National Transplant Centre (CNT) and performed by LUISS Business School. The aim of the research is to analyse the strengths and weaknesses of the RNT in order to produce recommendations for governance and organisational improvements. The aim of this to study is to explore the point of view of local coordinators in order to understand a major part of this system. What do coordinators think of the Network? How does it affect their day-by-day job? What are the main problems they face in order to complete their tasks? What the other governance levels need to change in order to better coordinators work?
Methods: We developed a questionnaire targeted to local coordinators that was submitted to the entire population (280 coordinators across Italy) on July 2011. One hundred and ninty eight usable responses (response rate = 70%) were collected by September 2011. The questionnaire included questions about the local transplant centre (mission, activities, personnel, relations with the hospital managers) and the main points of strength and of weakness of the RNT at all levels. On the same period we interviewed nine regional coordinators and three inter-regional coordinators, in order to understand the main differences across regions and inter-regional transplant networks. All these data has been used to analyse the organisational models of transplant networks at the four levels from the point of view of local coordinators.
Results: We summarise here the main preliminary results. Main strengths of the RNT – Main weaknesses of the RNT.
Conclusions: The results show that the governance of the network, from the point of view of local coordinators, is mainly in the hands of the regional level, while the national level provides guidelines and training for the standardisation of procedures and monitors performances.

BO274 EULOD: THE EU-FUNDED PROJECT ON LIVING ORGAN DONATION IN EUROPE

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Introduction: The EULOD project, funded by the European Commission, aimed to establish an inventory of living donation practices, explore and promote living donation as a way to increase organ availability, and develop tools that improve the quality and safety of living organ donations in Europe. The project ran from April 2010 to September 2012.
Methods: EULOD consisted of two research teams. The first team focused on living donation practices in Europe. The second team worked on legal restrictions and safeguards for living donations in Europe. EULOD was supported by the European Platform on Ethical, Legal and Psychosocial Aspects of Organ Transplantation (ELPAT) and the European Society for Organ Transplantation (ESOT).
Results: The project generated the following results: (1) an inventory on Living Donation Practices in Europe; (2) a study on Attitudes, Barriers and Opportunities: Results from Focus Groups Conducted in Four European Countries; (3) Ethical Analysis of the Arguments for and against Living Organ

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Donation, (4) a Comparative Analysis of European Transplant Laws Regarding Living Organ Donation; (5) a delivery that analyses the Normative Arguments that Dominate the Policy Arena about Necessity and Legitimacy of Legal Restrictions in Living Donor Transplantation; 6) a Best Practice Proposal: Legal Safeguards for Living Organ Donation in Europe which intends to establish a Common Frame of Reference for European Laws on Living Organ Donation; 7) a report on Improving the Effectiveness of the Organ Trade Prohibition. The reports are now available at WWW.EULOD.EU and are published into the book titled, 'EULOD project: Living Organ Donation in Europe.
Conclusion: This Consortium has contributed to European policy needs, by generating knowledge on how to increase organ availability, making transplantation systems more efficient and accessible and improving the quality and safety of organ donation and transplantation in Europe.

BO275 ORGAN DONATION EUROPEAN QUALITY SYSTEM: ODEQUS PROJECT

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Background: Differences in the number of organ donors among hospitals cannot be explained only by the number of ICU beds or neurologic patients treated. The real figures obtained are influenced by the organizational structure of donation process and how efficient it is. ODEQUS is a three years project (October 2010 to September 2013) co-financed by the European Agency for Health and Consumers (EAHC20091108) which aims to define a methodology to evaluate the organ procurement performance at hospital level.
Methods: ODEQUS specific objectives are to identify Quality Criteria (QC) and to develop Quality Indicators (QI) in three types of organ donation: after Brain Death, after Cardiac Death and Living Donation. Those tools will be useful for hospitals self-assessment as well as for developing an international auditing model. In order to do so, a consortium has been established involving 14 associated partners from Austria, Croatia, France, Germany, Italy, Poland, Portugal, Romania, Spain, Sweden and United Kingdom, and five collaborating partners from Greece, Hungary, Malta, Slovenia and Turkey. Afterwards, the project has been established in three steps: 1. Design of a survey about the use of quality tools in a wide sample of European hospitals. 2. Development of QC and QI by the project experts. The main fields considered have been organizational structures, clinical procedures and outcomes. 3. Elaboration of an evaluation system to test the QI in European hospitals. Moreover, two types of training have been designed and performed: one concerns the development of QC and QI, while another is focused on how to use evaluation tools.
Results: The project has achieved so far to identify 131 Quality Criteria and develop 31 Quality Indicators. Those indicators have been tested in 12 European hospitals by means of internal and external evaluations. Currently, the results of those evaluations are being processed.

BO276 IMPROVING OUTCOMES IN US RENAL TRANSPLANT RECIPIENTS – A 3 YEAR POSTSECONDARY EDUCATION INTERVENTION

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Background: There are significant differences in the 5 and10 year graft survival rates between Europe and the United States (US) that have not been well studied (Gondos, A. et al. Transplantation 2013: 95:267–74). Medicare coverage for immunosuppression has been proposed as a contributing factor differentially affecting US outcomes (Gill, J.S. et al. New England Journal of Medicine 2012: 366:586–89). Optimizing graft outcomes as patients approach the 3 year limit of Medicare coverage is challenging. A regional group of US renal transplant recipients was offered a postsecondary education opportunity with the goal of increasing compliance, psychosocial and socioeconomic status and return-to-work rates with maintenance of health care coverage.
Methods/Materials: From 2010 to 2013, a total of 21 transplant recipients from seven centers attended 13 educational institutions. Students received financial and supplemental assistance including mentoring, tutoring and support. Outcomes followed were patient/graft survival, rejection episodes, retention rate and return-to-work rate.
Results: Subjects have realized 100% patient and graft survival to date. Eighteen of 21 students remain enrolled for an 86% retention rate. One participant reported episode of antibody-mediated graft rejection. Of the 21 participants, six were working at the time of enrollment and continue to work. Of the 14 that were not working, eight have returned to work since beginning this program. Two students have graduated with degrees; two graduations are pending.
Conclusion: An educational intervention designed to increase postsecondary education access for renal transplant recipients can result in improved health outcomes and return-to-work rates. In addition, patients are further equipped for the transition period when Medicare immunosuppression coverage ceases three years post-transplant.

BO277 IMPROVEMENT OF FAMILY APPROACH BY INTENSIVE CARE PHYSICIANS

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Background: In Germany families are often asked for consent to organ donation by ICU staff without experience in family approach. In contrast coordinators of the DSO (German OPO) are specialized in communication skills regarding this special situations. In order to improve the situation for the families of potential donors we started to train the ICU staff in communication skills in 2010. The donor families have the possibility to join our family care program. In the scope of this we ask them about their experiences in the acute bedside bereavement situation and the stability of their given consent.
Methods: We created an anonymous questionnaire for donor families, which was filled out by 133 families. We focused on their feelings regarding the conversation about organ donation. Secondly we evaluated our training program for ICU staff.
Results: 62% of the donor families ($n = 86$) had the possibility to talk to a DSO coordinator in hospital. They judged the approach done by the DSO coordinator as very helpful or helpful in 96%. In contrast the support of the ICU doctors were experienced as helpful in 72% ($n = 96$). Eighteen percent ($n = 24$) of the respondents sensed the support of the ICU staff as less or not helpful. On the other hand ICU doctors reported that our training was very helpful for their task in 98% ($n = 202$). Ninty-two percent were sure that they got helpful suggestions for conversations with the relatives of potential organ donors in future.
Conclusion: A trustful and emphatic family approach is important for a stable decision of donor relatives. Therefore the family approach should be done by a skilled and experienced person. One important tool to ensure this, is to train the ICU staff in communication skills as shown in our study.

BO278 CERTIFICATION OF OTPCS: A SUPPORT TO IMPROVE QUALITY AND SAFETY OF ORGANS AND TISSUES PROCUREMENT

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Background: In France, organs procurement and transplantation is a national health priority. Organs procurement is a complex process. It requires 24 h a day competent and trained hospital staff, technical skills and an excellent and reactive organisation. From 2005, the Agence de la biomedicine (ABM), competent authority for organs, tissues and cells procurement and transplantation, set up a certification system dedicated to the hospital organs and tissues procurement coordination (OTPC). The certification has three main objectives: to improve organisation and resources allocation of the OTPC, to decrease risks associated to organs and tissues procurement, to improve patients' access to transplantation by increasing organs and tissues procurement activities.
Methods/Materials: The OTPC certificatison includes several phases: an official application by the hospital direction, a self-evaluation using a standardised evaluation questionnaire, a peer-reviewed audit, a certification review by a national steering committee and a follow-up. An adhoc scoring system has been set up allowing to measure how national organs and tissues procurement activities are controlled. Observed scores are used to manage and guide ABM national actions.
Results: By the end of 2012, 32% of the 197 OTPC got into the certification process. Overall, procurement activities are well mastered by all OPTCs: organisation of procurement, donor identification, diagnosis of brain death. However, improvements are still needed on the following fields, namely: use of qualitative indicators to monitor procurement activity, identify risks and follow-up (a priori risk mapping, residual risks etc.).
Conclusion: OTPCs certification showed that quality system and risk management related to organs and tissues procurement should be improved. Moreover, it helps OTPCs to be better integrated within hospitals and allow the ABM to target education and training of the OTPCs staff.

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BO279 PSYCHOSOCIAL RISK AND PROTECTIVE FACTORS FOR KIDNEY LIVING DONATION – RESULTS FROM A EUROPEAN MULTICENTRE PROSPECTIVE STUDY (ELIPSY)

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Background: ELIPSY has been co-funded by EAHC and conducted in six centres. Objective: To prospectively assess the psychosocial outcome of Kidney Living Donors (KLDs) one year after donation.
Methods: KLDs were assessed pre donation and at one year follow-up. To identify those donors showing a worse than expected outcome, the percentage of change in their Quality Of Life (QOL) was assessed by Cluster Analysis. Differences between clusters allowed for selecting potential predictive variables that were further assessed by logistic regression.
Results: 72KLDs were assessed by multivariate analyses. Two clusters were identified. After donation both clusters showed QOL scores within the normal range. However, Cluster-2 showed worse physical QOL. The profile risk of Cluster-2 outcome was characterized by a lower socioeconomic status, a reduction in the Sense of coherence, a higher relevance of disapproval of donation by significant others, and fearing the potential complications of the donation.
Conclusion: KLDs psychosocial outcome at one year follow-up was favourable. A small number of donors showed slight deterioration of physical QOL. Considering predictive factors of this worse outcome might help to further improve the psychosocial outcome.

BO280 HAVE PUBLIC ATTITUDES TO ORGAN DONATION IN AN EMERGING ECONOMY CHANGED IN THE LAST 20 YEARS?

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Background: South Africa is a unique emerging economy in which to study organ transplantation. With characteristics of both a developing and developed country, and wide population diversity, South Africa is comparable to other developed and developing populations. A 1993 study demonstrated that the South African population generally have positive sentiments about organ donation (Pike, R. E. et al. SAMJ 1993; Feb(83): 91–94). However, the number of actual transplants taking place annually in South Africa has declined significantly. This research is a longitudinal replication of the 1993 study. We aimed to determine whether public attitudes towards organ donation have changed over the past nineteen years and whether the decline in transplants can be attributed to changing public attitudes.
Methodology: The 1993 survey was repeated amongst a representative population of 1028 South African adults. Raw data from the 1993 study (2125 participants) was compared to raw data from the 2012 replication study. Initial analysis used the Pearson's χ^2 test, Fisher's exact test, Cramer's V. Secondary analysis was by means of percentage comparisons. Ethics approval was obtained from all three affiliated institutional IRB's.
Results: Overall, public attitudes towards organ donation in South Africa have not changed over the past nineteen years, they remain positive. However results suggest that relatives are now less willing to consent to organ donation than previously, citing discomfort making decisions on behalf of the deceased when their donation preferences are unknown. The study population is also less willing to donate solid organs (other than kidneys) than they were in 1993.
Conclusion: The decline in transplant numbers cannot be attributed to changes in public attitudes. Communication about donation intentions within families and institutions needs improvement to assist with obtaining consent. Wider, more sensitive public education about donation is required.

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OS31-KIDNEY X

O263 ADENOVIRAL INFECTION AS A CAUSE OF FEVER OF UNKNOWN ORIGIN AND GRAFT DYSFUNCTION IN A KIDNEY TRANSPLANT RECIPIENT

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We report a case of 41 years-old male with end stage renal disease secondary to recurrent nephrolithiasis who underwent deceased kidney transplantation from a 12 years-old female donor. He received anti-thymocyte globulin, tacrolimus, mycophenolic mofetil and steroid. At post-operative D10, he developed urinary tract infection with persistent high-grade fever despite wide spectrum antibiotic therapy. At D15, he exhibited leukopenia and lymphopenia (absolute lymphocyte count: ALC < 500). Repeated blood and urine cultures as well as viral serology were all negative. Abdominal pelvic computed tomography revealed multiple hypodense lesions within the graft. Serum creatinine (Scr) reached 1.87 mg/dl. Graft biopsy at D33 showed 60% necrosis with tubulo-interstitial hemorrhage, thrombotic microangiopathy and negative viral stains. Blood Adenovirus (ADV) PCR revealed >1 750 000 copies/ml. Immunosuppression was tapered and all antimicrobial drugs were discontinued. Within 2 weeks period, fever disappearance coincided with drastic reduction in the ADV PCR, increase in ALC and improvement in graft function. Second graft biopsy revealed considerable resolution in the previously described histologic lesions. Reduction in immunosuppression was sufficient for the resolution of the infection and the reversal of graft dysfunction.

O264 POST-TRANSPLANT DISSEMINATED TUBERCULOSIS: AN UPHILL JOURNEY TO DIAGNOSIS AND MANAGEMENT

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A 47-year old Caucasian male with IgA nephropathy received renal transplant from a DCD donor in April 2012. Alemtuzemab at induction, Prograf and Cellcept were used for maintenance immunosuppression. Three weeks following his hospital discharge with a well functioning graft, he re-presented with swinging pyrexia, rigors, abdominal discomfort, and neutrophillia and rising CRP. Ultrasound showed 9 × 4 × 6 cm collection around the graft, however aspiration was unsuccessful. He was treated empirically with ertapenem. The antibiotics were changed to Piperacillin/Tazobactum and teicoplanin in the following week with no improvement. PET-CT done at that time showed multiple hotspots in perinephric collection, spleen and bones. Bone marrow examination showed non-caseating granulomas. Microbial stains were negative There was no clinical improvement in the subsequent 2 weeks. The perinephric collection was surgically drained which consisted of old clotted blood with very small amount of pus. The pus culture was negative and gave a mixed sequence on 16-s PCR. He deteriorated further despite treatment with antibiotics and antifungals. He developed hepatic insufficiency and thrombocytopenia. CT scan revealed multiple abscesses in Liver and spleen and osteolytic lesions in the bones. A liver biopsy showed smear positive for acid-fast bacilli. Blood cultures and bone marrow cultures yielded mycobacterium tuberculosis after 28 and 23 days respectively. After commencing on ATT, his liver function improved slowly and thrombocytopenia resolved. The immunosuppression management was complicated by drug interactions. The general condition improved though the graft function never improved to baseline. Ten weeks post ATT he presented with further deterioration of graft function and allograft biopsy revealed granulomatous nephritis. Currently he is well clinically, with deteriorated renal function. Learning points: Tuberculosis should always be considered in transplant patients with difficult situations of PUO despite of the ethnic origin and past contact history. Delayed diagnosis can jeopardise the graft function. Is pretransplant screening for tuberculosis necessary?

O265 URINARY POLYOMAVIRUS-HAUFEN SHEDDING MARKS POLYOMAVIRUS NEPHROPATHY: A PROOF-OF-CONCEPT STUDY FOR A NOVEL DIAGNOSTIC NON-INVASIVE URINE BIOMARKER

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Background: Polyomavirus Nephropathy (PVN) is the most significant viral renal allograft infection with 4% incidence. Currently a definitive diagnosis is only established by renal biopsy. Recently we described a novel, non-invasive urinary assay to diagnose PVN, i.e. the "polyomavirus (PV)-Haufen-test," with positive and negative predictive values of >95%. This test has great diagnostic potential. Hypothesis: PV-aggregation and Haufen formation depend on a high concentration of Tamm-Horsfall protein (THP) that is only present in injured renal tubules and not in voided urine. Thus the presence of PV-Haufen in voided urines is specific for intrarenal disease.
Methods: Part-A- association of PV-Haufen and THP: A1) Immunohistochemistry of PVN cases ($n = 3$) with double labeling to detect PV and THP in renal tubules. A2) Immunogold electron microscopy of urinary PV-Haufen to detect Haufen-bound THP ($n = 3$). A3) Immunoprecipitation studies on urinary PV-Haufen ($n = 6$). A4) Dilution curves altering THP concentrations in fluids mimicking primary and secondary urines and evaluating for PV-aggregation and Haufen formation ($n = 5$). Part-B – THP concentrations in voided urine samples (with concurrent kidney biopsies; $n = 20$).
Results: Part-A. A1) In PVN intratubular PV aggregates show abundant THP. A2) Urinary PV-Haufen are intimately admixed with THP. A3) Immunoprecipitation of urinary PV-Haufen shows abundant coprecipitation of PV and THP. A4) PV aggregation and PV-Haufen formation is THP dose dependent and only occurs with high THP concentrations of >1 mg THP/ml fluid mimicking primary urine in injured tubules. Part-B. THP concentrations in voided urine samples are low, median THP 4.5 μg/ml urine, range: 0.7–19.5.
Conclusions: PV-Haufen are closely associated with THP. PV-Haufen formation occurs in the setting of very high THP concentrations found in injured renal tubules exceeding voided urine THP concentrations 50 fold. The genesis of PV-Haufen is similar to the formation.

O266 POLYOMA VIRAL LOAD SURVEILLANCE AS A MONITOR OF IMMUNOSUPPRESSIVE TREATMENT FOLLOWING KIDNEY TRANSPLANTATION

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Polyoma quantitative PCR (PQPCR) surveillance has been adopted recently as an early diagnosis strategy. We report our center's experience in using this test as an immune-monitoring tool.
Patients and methods: The study included 183 adults who underwent kidney transplantation between 1/1/2010 and 31/12/2011. Blood and urine samples for PQPCR were taken monthly at 1–6 months and at 9 and 12 months post-transplantation. Upon appearance of positive PQPCR in the blood, MMF/A dose was reduced or discontinued; otherwise, Prograf dose was gradually reduced, until viremia disappeared. We analyzed the incidence of polyoma viruria and viremia, the intervals from transplantation to viremia and persistent PQPCR. We compared kidney function between patients with and without viremia at 3, 6 and 12 months.
Results: Viremia was found in 38/183 patients (20.8%); viruria only– in 23 (12.6%). The median interval from transplantation to viremia was 99 days (31–365 days). Viremia persisted for 15–381 days. No case of polyoma nephropathy was diagnosed during this period. Creatinine levels at 3, 6 and 12 months were similar between patients with and without polyoma infection.
Conclusion: Polyoma quantitative PCR surveillance is an effective strategy for preventing polyoma nephropathy and may be a useful tool for immune-monitoring of kidney transplant recipients.

O267 POLYOMAVIRUS-AGGREGATES - TERMED "HAUFEN" – IN VOIDED URINE SAMPLES ARE ACCURATE BIOMARKERS FOR INTRA RENAL POLYOMAVIRUS NEPHROPATHY

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Background: Polyomavirus nephropathy (PVN) is the most significant viral renal allograft infection with 4% incidence. A diagnosis is only made by renal biopsy; laboratory tests including PCR are non-diagnostic. Recently we described a novel, non-invasive urinary assay that might predict PVN, the "polyomavirus (PV)-Haufen-test."
Hypothesis: PV- Haufen formation originates in renal tubules and depends on high concentrations of Tamm-Horsfall protein (THP). PV-Haufen in voided urines are accurate biomarkers for intrarenal disease/PVN.
Methods: PV Haufen, i.e.dense, cast-like PV aggregates, in voided urine samples were identified by negative staining electron microscopy according to standard techniques. Part-A – association of PV-Haufen and THP: A1) Immunogold electron microscopy of urinary PV-Haufen to detect Haufen-bound THP ($n = 3$). A2) Immunoprecipitation studies on urinary PV-Haufen ($n = 6$). A3) Dilution curves altering THP concentrations in fluids mimicking urine and evaluating for PV- Haufen formation ($n = 5$). Part B –patients: PVN and Haufen shedding in 330 selected high-risk renal transplant recipients with evidence of PV viruria and/or viremia.
Results: *Part-A* A1) Urinary PV-Haufen are intimately admixed with THP. A2) Immunoprecipitation of urinary PV-Haufen shows abundant coprecipitation of PV and THP. A3) PV Haufen formation only occurs with high THP concentrations of >1 mg THP/ml mimicking conditions in injured tubules. *Part-B - patient analysis* 56/330 high risk patients had urinary PV-Haufen shedding; 53/

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56 had biopsy proven PVN. Two hundred and seventy-seven patients never developed PVN and 274/277 were urinary PV-Haufen negative. In PVN urinary Haufen shedding followed the disease course; it changed from Haufen-negative to positive to negative during longitudinal follow-up ($n = 21$).
Conclusion: The presence of PV-Haufen in urine marks (intrarenal) PVN with positive and negative predictive values of 95%. Urinary PV-Haufen are accurate biomarkers for PVN.

O268 THE CAUSES OF KIDNEY TRANSPLANT FAILURE: SPECIFIC DISEASES VERSUS NON-SPECIFIC INJURY

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Background: The relative impact on renal allograft outcome of specific histological diseases versus non-specific histological injury remains unclear.
Methods: We followed all 1197 renal allograft recipients transplanted at a single center between 1991 and 2001. During follow-up (mean 14.5 ± 2.80 years post-transplant for patients with a functioning graft), 1365 post-transplant renal allograft indication biopsies from 738 recipients were performed. Risk models for graft loss were calculated using multivariate Cox proportional hazards analysis.
Results: The presence of a specific disease significantly associated with loss of graft function (adjusted HR for aABMR 3.00 [1.70–5.30], $p = 0.0001$; for borderline changes 1.74 [1.02–2.97], $p = 0.04$; for TCMR 3.41 [2.14–5.43], $p < 0.0001$; for cABMR 2.01 [1.27–3.20], $p = 0.003$; for PVAN 3.17 [1.34–7.51], $p = 0.009$; and for GN 1.92 [1.12–3.29], $p = 0.02$). These specific diseases were present in the large majority of kidneys that ultimately lost function (69% of graft losses). However, in 31% of patients, grafts were lost without specific disease process prior to graft loss. Non-specific chronic histological injury (IF/TA and glomerulosclerosis) accounted for these losses. Importantly, these non-specific lesions associated were highly significant and independent risk factors for graft loss (adjusted HR 2.33, $p < 0.0001$) in biopsies without specific disease. Moreover, the extent of IF/TA determined the final outcome of all specific disease processes. In the absence of scarring, the outcome of specific diseases was generally good on the long term, while extensive scarring portended a bad prognosis on short term.
Conclusion: We demonstrate that renal allograft loss is multifactorial, and most often secondary to a combination of specific disease processes and non-specific injury. Non-specific chronic histological damage should be taken into account in in treatment algorithms, irrespective of whether a specific disease is present or not.

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OS32-KIDNEY XI

O269 LONG TERM RESULTS OF THE FIRST 50 ABO BLOOD TYPE INCOMPATIBLE (ABOI) KIDNEY TRANSPLANTATIONS IN THE NETHERLANDS

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Background: The development of specific desensitization protocols has boosted kidney transplantations despite ABO blood group incompatability (ABOi). However, a relative paucity of data is present for long-term results of the ABOi transplantation program compared to the standard ABO compatible (ABOc) program. This study describes the long term results of the ABOi kidney transplantation program of the Erasmus Medical Center in the Netherlands.
Methods: Desensitization pretransplantation consisted of a single dose rituximab, triple immune suppression (tacrolimus, MMF, prednisolon), immunoadsorption (IA) and IVIG after the last IA. At 3 months the prednisone was withdrawn. Fifty patients received a ABOi kidney transplant from 2006 to 2012 and all patients had a follow-up for at least 1 year.
Results: All patients were transplanted when the ABO antibody titer was decreased to <1:8. Within the first week, 11 antibody mediated humoral rejections were noted of which three were mixed rejections (humoral and cellular mediated). Also 9 cellulair mediated rejections occurred, mostly within the first week after transplantation. During the first year only two grafts were lost due to rejection. One year graft survival and renal allograft function of the ABOi grafts were similar to 100 matched ABO compatible renal grafts, 96% vs. 99%. After a 5 year follow up period graft survival was 90% in the ABOi vs. 97% in the control group. Adverse infectious events, specifically related to the ABOi protocol, were not observed.
Conclusion: Our currently used ABOi protocol shows good long-term results despite a relatively high frequency of humoral rejection in comparison to previous studies. It facilitates an optimal use of the available living kidney donors and is specifically beneficial for the bloodtype O patient.

O270 EARLY BACTERIAL INFECTIONS IN SIMULTANEOUS KIDNEY AND PANCREAS TRANSPLANTATION: IMPACT OF PRESERVATION FLUID CONTAMINATION

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Background: Contamination of preservation fluid (PF) has been associated with donor-transmitted infection in renal transplantation. Despite the infectious morbidity in simultaneous pancreas-kidney transplantation (SPKT), the role of PF contamination has never been evaluated. The aim of the study was to analyze the impact of PF contamination on bacterial infections in SPKT recipients.
Methods: We retrospectively reviewed 75 SPKT performed in our centre between 2007 and 2010, whose PF were systematically analysed. A systemic venous drainage and enteric drainage for exocrine secretions were performed for all pancreas transplants. We examined the incidence of first bacterial infections within the first three months after transplantation. A multivariate Cox survival model was used to assess the impact of contaminated PF on infection risk.
Results: A total of 30 out of 75 (40%) patients presented with at least one infection. The incidence of infection at 3 months was 6.6 per 1000 patient-days. Infection sites were predominantly intra-abdominal and urinary (30% and 26.7%, respectively). The most common bacteria were gastrointestinal (44.4%). PF cultures were positive in 27 (36%) kidney grafts and 38 (50.7%) pancreas grafts. Overall 19 (25.3%) recipients had positive cultures in both kidney and pancreas PF samples, with similar bacteria in13 (18.3%) patients. There was no difference between the incidence of post-transplant infections at 1 and 3 months in the group with a contaminated PF compared to the group with a sterile PF ($p > 0.8$).In multivariate analysis pancreatic fistula was significantly associated with early bacterial infection (HR = 3.95, 95% CI [1.66–9.04], $p = 0.002$). No association was found between positive PF and early bacterial infection (HR = 0.99 95% CI [0.47–2.08], $p = 0.97$).
Conclusion: In SPKT, a positive PF was not associated with early bacterial infections. Pancreatic fistula appears to be a significant risk factor for early bacterial infections.

O271 ECULIZUMAB DECREASES EARLY ANTIBODY-MEDIATED REJECTION IN SENSITIZED DECEASED DONOR KIDNEY TRANSPLANT RECIPIENTS

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Background: Highly sensitized kidney transplant recipients (peak historical or current DSA by single antigen flow bead [SAFB] > 3000 MFI) experience >30% incidence of early acute antibody-mediated rejection (aAMR). Terminal complement inhibition with the anti-C5 antibody eculizumab (Ec) was previously reported to be effective prophylaxis against aAMR in highly sensitized living donor kidney recipients. This abstract reports interim results of a multicenter single-arm trial of Ec prophylaxis in deceased donor (DD) kidney recipients with DSA by SAFB > 3000 MFI.
Methods: Recipients received Ec 1200 mg Day 0 prior to reperfusion, then 900 mg POD 1, 7, 14, and 28, and 1200 mg weeks 5, 7, and 9. Immunosuppression included rabbit anti-thymocyte globulin induction and maintenance prednisone, tacrolimus, mycophenolate. Protocol biopsies were obtained at 0.5, 1, and 3 months. Post-transplant plasmapheresis was not allowed. The primary endpoint (clinically significant biopsy proven aAMR) was evaluated in recipients who reached 9 weeks posttransplantation.
Results: Sixteen recipients (10F, 6M) median age 46.5 years (range 30–69) were evaluated (enrollment continuing). Median DSA = 3.5 (±1.7), qualifying DSA by SAFB = 3000 MFI, median total MFI = 10 994 (±5204). Sixteen of 16 patients were successfully transplanted. The incidence of aAMR was 6.2% (1/16). Nineteen percent (3/16) of patients had indwelling catheter infections, and 6.2% (1/16) had delayed graft function.
Conclusion: Eculizumab appeared to be effective prophylaxis against early aAMR in sensitized DD kidney recipients.

O272 EXCELLENT LONG-TERM OUTCOME OF ABO-INCOMPATIBLE LIVING DONOR KIDNEY TRANSPLANTATION; A SINGLE CENTER EXPERIENCE FOR OVER 20 YEARS

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ABO-incompatible living kidney transplantation (ABO-ILKT) has been a popular alternative to deceased kidney transplantation. In this retrospective single center study, we analyzed the long-term graft survival of ABO-incompatible living donor kidney transplant for over 20 years by comparing with ABO-compatible living kidney transplantation (ABO-CLKT) as control. In all, 1096 patients with ESRD underwent living donor kidney transplantation at our institute between 1989 and 2012. Two hundred and sixty-three cases were ABO-ILKT and 833 cases were ABO-CLKT. The mean age of ABO-ILKT group was 43.0 years (range 17–75), with 164 males and 99 females. Log-rank testing was performed to determine differences in survival data. Patient survival of ABO-ILKT at 1, 5, 10, 15, and 20 years post-transplant were 98, 97.5, 92.7, 87.1, and 87.1%, respectively. Graft survival of ABO-ILKT at 1, 5, 10, 15, and 20 years post-transplant were 90.8, 87.1, 71.7, 58.4, and 51.5%, respectively. Whereas, Graft survival of ABO-CLKT at 1, 5, 10, 15, and 20 years post-transplant were 97.5, 88.8, 76.4, 66.4, and 59.7%, respectively. Patient survival had no significant difference from that of ABO-CLKT ($p = 0.664$). Although graft survival of ABO-ILKT at 20 years post-transplant had approximately 10% reduction from that of ABO-CLKT, there was no statistical difference between ABO-ILKT and ABO-CLKT ($p = 0.08$). Despite receiving intensified desensitization protocol compared to ABO-CLKT, ABO-ILKT is an acceptable treatment for patients with ESRD in terms of patient survival and graft survival.

O273 TRANSCONTINENTAL INTERNATIONAL KIDNEY PAIRED DONATION

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Introduction: Many countries now offer kidney paired donation (KPD) to their citizens and in some countries multiple kidney exchange programs operate. Experimental data suggests that the larger the pool size, the greater the opportunity for matching, so that collaboration between these disparate programs may be valuable. Therefore, we initiated a transcontinental, interna-

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tional kidney exchange between the United States and Greece as a proof of concept.
Methods: After failing to acheive successful desensitization, a Greek End Stage Renal Disease (ESRD) patient and his blood type incompatible wife were enrolled in a large, multiregional paired exchange program in the US. An initial match was found, but Greek law prevented paired exchange as recipients were not allowed to receive a kidney from an unrelated donor. Over the following year, the Greek law was changed to specifically allow KPD and to allow for the Greek government to pay for a KPD transplant in the US if not available in Greece. A Nonsimultaneous, Extended Altruisic Donor (NEAD) chain was initiated.
Results: In December 2011, an American non-directed donor gave her kidney to a Greek ESRD patient who travelled to the US for his transplant. The next recipient, to whom the Greek donor was to donate became ill, so the Greek couple returned to Greece, trusting that the Greek woman would return to the US in the future to donate her kidney to a stranger. Four months later a match was found and the Greek woman returned to America, at her own expense, to donate her kidney to an American. Subsequently this international chain incorporated a second international patient from Trinidad and Tobago, and has now resulted in 12 kidney transplants over 15 months at nine American transplant centers. The last transplant in the chain was performed in March 2013.
Conclusion: Transcontinental, international collaboration to achieve kidney paired donation is feasible.
Reference: 1. Rees, MA et al N Engl J Med 2009; 360:1096–1101.

O274 COLLABORATIONS IN KIDNEY PAIRED EXCHANGE, LOCAL AND INTERNATIONAL

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Introduction: To date, several KPD programs operate separately within the US and around the world, searching for exchanges in their own pools. We have studied the impact of collaborations between US programs and between US programs and a Korean program utilizing two approaches: (i) Simple – searching for exchanges among pairs that are not matched by the programs; and (ii) Complete – searching for matches in a pool consisting of all pairs.
Methods: We use clinical data from a large US multi-regional program (APD), a large US single center program (SA) and a Korean program (KO). The APD, SA and KO data include snapshots of 196, 141 and 81 incompatible pairs respectively. Missing DQ antigens in the Korean data have been imputed using Korean HLA distributions.
Results: APD, SA and KO can match separately 44, 51, 14 patients with average PRAs 58.5, 53 and 6.4 respectively and 9, 3 and 0 of these pairs have PRA 97 or more. Characteristics of extra matches from simple and complete collaborations are given in Table 1 and are presented in columns for each program being studied, with the added program's pool in (parentheses). For each type of collaboration (simple:complete) reported are number of extra matches (as in the 1st row), or their average PRAs (as in the 2nd row). Blood-type compatible (BC) pairs are used as a surrogate for sensitized pairs.
Conclusion: Pooling pairs finds additional matches even if only unmatched pairs are used, but complete pooling identifies the most matches. Additional matches particularly benefit highly sensitized patients, but Korean patients benefit from additional O donors. On average the, simple approach garnered 7.4% more matches and the complete approach identified 18.3% more matches than each program could find on their own. We are now exploring how this collaboration increases matches such as increased pool size and/or improved HLA matching for highly sensitized patients as a result of ethnic heterogeneity.

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OS33-IMMUNOSUPPRESSION IN LIVER TRANSPLANTATION

O275 THE PROTECT STUDY: SUSTAINED SUPERIOR RENAL FUNCTION IN LIVER TRANSPLANT RECIPIENTS AFTER 35 MONTHS

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Liver transplant patients were randomized to either continue calcineurin inhibitor (CNI) ($n = 96$) or to switch to Everolimus (EVR, $n = 98$; C0 5–12 ng/ml) with stepwise CNI withdrawal. After completion of the 11 month (M) core study 81 patients (EVR, $n = 41$; CNI, $n = 40$) were followed up to 35 months in the extension phase. From M11 to M35 renal function further deteriorated in the CNI-arm but remained stable in patients receiving EVR. Difference in eGFR between EVR and CNI: Nankivell formula (M11: −6.6 ml/min [p = 0.084]; M23: −8.8 ml/min [p = 0.039]; M35: −10.5 ml/min [p = 0.015]). At M35 there were no significant differences in mortality, BPAR, and composite efficacy failure. 35M follow up data from PROTECT shows that conversion of liver transplant patients from CNI- to EVR-based immunosuppression is safe and maintains renal function.

O276 THE IMPACT OF EVEROLIMUS ON RENAL FUNCTION AFTER LIVER TRANSPLANTATION

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Background: Limited information is still available on use of everolimus (EVR) in everyday clinical practice.
Materials and methods: This was a retrospective analysis of EVR-based immunosuppression after liver transplantation (LT) at a single center. The primary endpoint was the change from baseline in estimated glomerular filtration rate (eGFR).
Results: Two hundred and eleven adult LT recipients were included for analysis. Thirteen (6.1%) patients discontinued EVR within 1 month, and 198 were included in the evaluation of renal function (RF). One hundred and forty-one patients (73.5%) are alive at a mean follow-up of 40.8 ± 13.7 months after EVR initiation (range 1–84 months). In the ITT and on-treatment populations the mean eGFR change from baseline was 8.3 ± 3.1 and 11.3 ± 4.2 ml/min, respectively, with patients successfully converted to EVR monotherapy showing a 13.9 ± 5.6 ml/min increase at last evaluation.
Conclusions: EVR-based immunosuppression after LT is associated with preservation of renal function.

O277 EFFICACY AND SAFETY OF EVEROLIMUS-FACILITATED TACROLIMUS REDUCTION VERSUS STANDARD TACROLIMUS

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Background: Immunosuppressive therapy with reduced nephrotoxicity to treat *de novo* liver transplant recipients (LTxR) is an unmet medical need. We report 24-month (mo) results from the H2304 study.
Methods: Seven hundred and nineteen LTxR were randomized on day 30 post-LTx to receive everolimus (EVR) with reduced tacrolimus (rTAC) or EVR with TAC withdrawal at mo 4 (TAC-WD) or standard TAC (TAC-C), all with steroids. Key endpoints: rate of composite efficacy failure (CEF) and renal function, as measured by estimated GFR.
Results: CEF rates were comparable in LTxR treated with EVR+rTAC or TAC-C (Table). Patients on EVR+rTAC had significantly fewer and less severe biopsy proven acute rejections and maintained superior renal function versus those on TAC-C. No new safety signals were detected. Drug discontinuations due to adverse events were 29.8% vs. 21.5% (EVR+TAC vs. TAC-C).
Conclusions: Early EVR-facilitated TAC reduction in LTxR maintains anti-rejection efficacy and leads to superior renal function versus TAC-C.

O278 EFFICACY AND SAFETY OF THE PKC-INHIBITOR SOTRASTAURIN IN *DE NOVO* LIVER TRANSPLANT RECIPIENTS

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Background: This 24-month phase II study evaluated the efficacy and safety of sotrastaurin + tacrolimus (STN+TAC)-based regimens in 200 *de novo* liver transplant recipients.
Methods: Recipients were randomised (1:1:1:1) to STN 200 or 300 mg b.i.d. + reduced-exposure TAC (rTAC), STN 200 mg b.i.d. + standard-exposure TAC (sTAC), and MMF 1 g b.i.d. + sTAC, all with steroids. Primary endpoint was composite efficacy failure (treated biopsy-proven acute rejection, graft loss and death) at month 6. Main safety objective was GFR (estimated using MDRD formula).
Results: Key efficacy and safety results are summarised in table. Efficacy failure was higher in all STN groups versus the MMF+sTAC group. Gastrointestinal events (constipation, diarrhoea and nausea), infections and tachycardia were more frequent in STN groups.
Conclusions: STN-based regimens showed higher efficacy failure rates and a trend towards better renal function than MMF+sTAC.

O279 PROGRESSION OF FIBROSIS IN HCV+ LIVER TRANSPLANT RECIPIENTS TREATED WITH CYCLOSPORINE OR TACROLIMUS

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Background: REFINE is the largest prospective study to examine whether the choice of calcineurin inhibitor (CNI) affects fibrosis progression in HCV+ liver transplant recipients (LTRs).
Methods: Adult HCV+ LTRs ($n = 361$) were randomised to cyclosporine microemulsion (CsA-ME) or tacrolimus (TAC)-based regimen for 12 months. Centres used either a steroid-free regimen (induction with IL-2 receptor antagonists + mycophenolic acid) or a regimen with slow steroid dose reduction.
Results: Overall incidence of fibrosis score (FS) ≥2 (Ishak-Knodell FS ≥ 2) at 1 year post-transplant was similar with CsA-ME or TAC, but in the steroid-free cohort, a significantly lower incidence of fibrosis was reported in CsA-ME patients (Table). There were no differences in patient survival, graft loss, and incidence of biopsy-proven acute rejection.
Conclusion: No differences between CNIs were found in the overall population, but less HCV-induced fibrosis was observed with CsA-ME in steroid-free patients.

O280 CLINICAL CONSEQUENCES OF SUBCLINICAL NON ADHERENCE TO IMMUNOSUPPRESSION AFTER LIVER TRANSPLANTATION

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Background: From 2008 onwards, we prospectively followed a cohort of 268 adult liver transplant (LTX) recipients (convenience sample; males 77.2%) over a 5-year period to assessed if nonadherence (NA) to immunosuppressants (IS) predicted onset of treated and/or biopsy proven acute rejection (t/BPAR) and any unexpected drop in IS in adult LTX.
Methods: NA over the past 4 weeks was measured by self-report and defined as any deviation from schedule. t/BPAR and IS were determined based on chart review.
Results: NA was reported by 32.4% of patients. Nonadherers had a 4.95 higher odds for t/BPAR than adherers (p = 0.0034), and a higher incidence of unexpected drop in IS (22.9% vs. 9.6%; p = 0.0047).
Conclusion: To our knowledge, this is the first prospective study in LTX showing that subclinical NA increases the risk of t/BPAR.

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OS34-INTESTINE

O281 ESTIMATED PREVALENCE AND OF SHORT BOWEL SYNDROME AND ANALYSIS OF INTESTINAL REHABILITATION AND TRANSPLANTATION CENTER INFRASTRUCTURE IN GERMANY

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Background: This study conducted in 2011/12 aimed to estimate the prevalence of patients with short bowel syndrome (SBS) in Germany for the first time in a standardized manner and analyze their access to spezialized care like intestinal rehabilitation and transplantation.
Methods: A randomized sample of all hospitals in Germany ($n = 478$), stratified by number of beds, was drawn and a three step survey was conducted to calculate a robust prevalence estimation (based on hospital size strata) for short bowel syndrome treated in German hospitals in 2011/12. Assessed were the number of patients with SBS and specialized outpatient clinics as well as a 6-item Likert scale to reflect the standard of care of SBS patients from a caregiver-point of view. Questionnaires were sent to surgeons, physicians and pediatricians of the sample hospitals over a 3 month period.
Results: Eighty-five percent of sampled hospitals replied to the survey. One thousand three hundred and forty-one patients with SBS were identified in the sample. Based on these numbers, the strata-derived estimation yielded a total estimate of 2808 SBS patients in Germany in 2011 (95%CI: 1750, 3865). This translates to a prevalence-estimation of 34 SBS patients per million (95% CI: 21, 47). The standard of care for SBS patients concerning diagnostics and conservative treatment of SBS was rated as "satisfactory" by most caregivers and 86 specialized outpatient clinics were identified. The knowledge concerning specialized intestinal rehabilitation procedures and especially the option of intestinal transplantation was rated "not satisfactory" by a large majority of caregivers regardless of specialty.
Conclusion: Short bowel syndrome, with a newly estimated prevalence of 34 per million inhabitants, can no longer be considered a rare medical condition in Germany. The interdisciplinary approach necessary to provide optimal care to these patients would be greatly facilitated by the introduction of a centrally organized registry.

O282 GARDNER SYNDROME AS A CAUSE OF INTESTINAL TRANSPLANT

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Background: Gardner syndrome (GS) is a rare autosomal dominant inherited disorder characterized by bowel polyposis and desmoids tumours (DT). DT can be very difficult to manage and may needs massive bowel resection leading to intestinal failure (IF) and requiring long term parenteral nutrition (PN) or intestinal transplant (Itx). The aim of our study is to analyze the outcomes of Itx recipients with GS.
Methods: From 2004 to 2012, 19 recipients underwent Itx. Seven of them (36.8%) had GS. All patients included in this study have at least 6 months of follow-up.
Results: Seventy one percent of the patients were male. The average age of recipients and donors was 37.14 (+ 8.2) and 25 (+ 15.3) years, respectively. The most common cause of donor's death was traumatic brain injury. All patients required a surgical procedure before Itx and the mean number of procedures required was 3.3. Two patients (28.6%) had a stoma before transplant. The average time on PN before Itx was 4.8 (+ 9.1) months. Forty three percent of patients were diagnosed with chronic liver disease before Itx. The average time in the waiting list was 237.8 (±162.8) days. All patients require an ileostomy after Itx and one has already closed it. The average number of mild and severe rejection events was 1.3 (+1.4) and 0.7 (+ 1.1) respectively. In only two cases a primary closure of the abdominal wall could be done, the rest require a dual mesh. The average time between transplantation and first rejection event was 21 (+ 16.8) days. The overall recipient and graft survival rate at 1.3 and 5 years was 100%, 71.5% and 71.5% and 85.7%, 71.5% and 71.5%, respectively.
Conclusions: GS is a rare disease considered as a variant of the FAP, with an incidence <1 per 10 000 inhabitants. DT might have an aggressive behavior leading patients to IF. Itx is a good alternative in these situations thus providing complete food and digestive autonomy with good long-term outcomes and survivals.

O283 INTESTINAL TRANSPLANT. A GOOD TREATMENT FOR PATIENTS WITH INTESTINAL FAILURE SECONDARY TO ISCHEMIA

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Background: Massive bowel resection due to acute mesentery ischemia (AMI) causes short bowel syndrome (SBS). Elective treatment needed in such situations is long term Parenteral Nutrition (PN). However, severe and potentially lethal complications may occur. In these patients Intestinal transplantation (Itx) is the only alternative to restore digestive autonomy and warrant long term survival.
Methods: From July 2004 to December 2012, 19 recipients underwent intestinal transplant. Four of these recipients (21%) had a SBS due to AMI requiring extensive resections. All patients included in this study have at least six months of follow-up.
Results: Fifty percent of the patients were male. The average age of recipients and donors was 45.7 (+ 12.5) and 20.5 (+ 10.2) years, respectively. The average time on PN before Itx was 59 (+ 73.1) months. Two patients (50%) had liver disease due to long term PN administration before Itx. The average number of thrombosis and sepsis per year in these patients were 1 (+ 1.1) and 1.3 (+ 1.1) episodes, respectively. The average time in the waiting list was 59.5 (+ 63.7) days. The average number of interventions required per patient before Itx was 4 (+ 2.3). All recipients obtained a total graft function with full intestinal autonomy. The overall recipient and graft survival at 1 and 3 years was 75% and 75% and 75% and 75%, respectively. Mortality in our series was due to aspiration pneumonia with sepsis and multiorgan failure 6 months after transplantation.
Conclusions: PN have severe consequences, such as thrombosis of the main venous access, local and systemic infections and liver disease. In such situations, alternative treatments such Itx, has to be taking into account, allowing complete PN independence with long term survival, making Itx a good treatment alternative.

O284 LOSS OF MUCOSAL ANTIMICROBIAL PEPTIDE EXPRESSION DURING ACUTE REJECTION AFTER EXPERIMENTAL INTESTINAL TRANSPLANTATION CAN BE REVERSED BY ANTI-REJECTION TREATMENT

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Background: In intestinal transplantation (ITX), episodes of acute rejection (ACR) are frequent and often associated with severe SIRS and sepsis. Bacterial overgrowth and translocation of microorganisms through the mucosal barrier could be facilitated due to reduced expression of mucosal antimicrobial peptides (AMPs) in ACR. Effective immunosuppression was hypothesized to reverse the loss of mucosal AMPs in intestinal allografts.
Methods: To analyze the impact of ACR and immunosuppressive treatment on mucosal AMP expression in intestinal grafts, allogenic ITX (BN->Lewis) was performed with different treatment regimens (no immunosuppression/continuous Tacrolimus/Tacrolimus rescue treatment). Isogenic ITX (Lewis->Lewis) and native mucosa samples served as controls. Graft mucosa was sampled at 4 and 7 day post ITX for qPCR analysis of mucosal AMPs. Histologic ACR-grading was performed by two independent reviewers, using the Wu-rejection score on HE-stained graft sections.
Results: Histology at 7d post ITX displayed ACR in allogenic grafts without immunosuppression, ACR prevention by continuous Tacrolimus, ACR reversal by Tacrolimus-rescue treatment and residual inflammatory changes in isogenic grafts. In qPCR expression analysis of graft mucosa normalized to ß-Actin, Cryptdin 5, Cryptdin 7 and NP 3 were significantly reduced in allogenic graft mucosa versus isogenic graft mucosa. Compared to native mucosa, the Cryptdins 5 + 7, NP3 and lysozym were likewise significantly reduced in allogenic -but not in isogenic- graft mucosa. Tacrolimus treatment (both continuous and rescue treatment) was able to prevent and/or reverse loss of AMP expression as ACR resolved.
Conclusion: Mucosal AMP expression was significantly reduced in rejecting intestinal grafts. Isogenic ITX failed to negatively affect AMP expression. Thus, the impairment of mucosal barrier function is mainly related to immune processes associated with ACR and may be countered by effective immunosuppression.

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O285 CLINICAL RELEVANCE OF NON-HLA-ANTIBODIES AFTER INTESTINAL TRANSPLANTATION

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Non-HLA-allo- and autoantibodies are involved in allograft rejection in kidney and heart transplantation. Their role in intestinal transplantation (ITX) has not yet been described. We examined the development of anti-Angiotensin II-Type I receptor antibodies (anti-AT1R) and anti-Endothelin-Type A receptor antibodies (anti-ETAR) in association with the clinical course and histopathological findings of 20 ITX-recipients. Between 06/2000 and 08/2011, 30 patients with a median age of 37.6 $\pm$ 9.8 years received an isolated intestinal graft (n = 18) or a multivisceral transplantation (MVTX, n = 12). Since 2005 anti-AT1R and anti-ETAR were screened regularly. Levels of >12 U/l were considered as highly-positive. All non-HLA antibody levels were evaluated retrospectively in regards of simultaneous rejection episodes or other clinical events. Anti-AT1R and anti-ETAR levels were determined in 20 out of 30 ITX- and MVTX-recipients. Fifteen of the 20 patients (75%) developed high levels of either anti-AT1R, or anti-ETAR, or both. Twelve of the 15 patients (80%) had rejection episodes around the time of positive non-HLA antibody sampling. Rejection episodes were either exclusively cellular rejections (n = 4) or mixed cellular and antibody-mediated rejections (AMR) with positive detection of donorspecific anti-HLA antibodies (DSA, n = 8). The other three patients showed non-donorspecific anti-HLA antibodies and viral infections (n = 2) during the time of anti-AT1R- or anti-ETAR antibody detection, but did not have any signs of rejection. Our data suggest that antibody-mediated mechanisms targeting antigens beyond HLA-may additionally trigger and accelerate immune responses. Given the possibility of pharmacologic targeting of both receptors, future studies will focus on the explanation of mechanisms how non-HLA antibodies may enhance allograft rejection and deteriorate long-term allograft survival after ITX and MVTX.

O286 POSTOPERATIVE INFECTIONS FOLLOWING INTESTINAL TRANSPLANTATION

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Due to high immunosuppression, recurring allograft rejections, and altered mucosal permeability, bacterial translocation and invasive fungal infections are significant challenges after intestinal transplantation. Additionally, the small bowel is the primary target organ of Rota-, Noro- and Adenovirus, so that the timely recognition of viral infections and differentiation from cellular rejection remain difficult. Between 06/2000 and 12/2012, 31 patients (median age 39.5 $\pm$ 13.4 years) received an intestinal graft (n = 18) or a multivisceral transplantation (n = 13). We observed the 1-year postoperative course concerning bacterial, viral, and fungal infections, considering time of onset, treatment, immunosuppression, and survival. Most infections developed within 3 months posttransplant. Bacterial infections (39% of patients) appeared with a peak at 4 weeks. Forty-six percent were infections of the urinary tract, 32% blood stream, 11% wounds, 7% respiratory tract, 5% cholangitis. Sixty percent of patients developed viral infections (peak 3 months posttransplant). They were often related to antirejection therapy and included CMV-infections (64%), Rota- (17%), Adeno- (12%) and Norovirus infections (7%). Four patients developed invasive Aspergillosis within the first year, requiring triple antifungal therapy and surgical debridement. The 6-months and 1-year survival rate was 80.6% and 71%, respectively. Most patients cleared their infections under efficient treatment, two died of infection-related multiorgan failure following bacterial pneumonia. The reduction of initial immunosuppression and the introduction of antibacterial, antifungal, and antiviral prophylaxis helped to reduce infection rates after ITX and MVTX.

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OS35-IMMUNOMONITORING

O287 CD137, A MARKER TO DETECT THE TOTAL ALLOREACTIVE T CELL COMPARTMENT?

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Background: Alloreactive T cells are important mediators of rejection or tolerance of the transplanted organ. In this study CD137 (4-1BB) was investigated for its potential to identify circulating alloreactive T cells.
Methods: Optimal conditions for sensitive and specific detection of allogeneic-induced CD137 expression on circulating T cells were established. Thereafter, CD137+ alloreactive T cells were phenotypically and functionally characterized by multiparameter flowcytometry.
Results: Alloantigen-induced CD137 expression identified alloreactive T cells. CD137+ alloreactive T cells were detected in different T cell subsets, including naïve T cells, but were preferentially found in CD28+ T cells and not in the terminally differentiated T cell subsets. Upon allogeneic stimulation, cytokine producing, but not proliferating, T cells mainly resided within the CD137-expressing fraction. A minority of the CD137+ alloreactive cytokine producing T cells (<10%) produced any combination of IFN-g, IL-2 and TNF-a. Polyfunctional alloreactive T cells, defined by multiple cytokine expression, were infrequently observed.
Conclusions: Activation-induced CD137 expression allows for detection of the total cytokine producing, but not the total proliferating, alloreactive T cell compartment at the single cell level by multiparameter flowcytometry. CD137 expression might be a useful marker to gain more insight into the development of alloreactive T cells following kidney transplantation.

O288 TEMRA CD8 CELLS AND ALTERED TCR VB REPERTOIRE IDENTIFIES PATIENTS AT-RISK OF KIDNEY GRAFT DYSFUNCTION

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Background: One hundred and thirty-three kidney recipients with a stable graft function at the time of enrollment (median time post-transplantation 7.78 years) were prospectively monitored for more than 6 years. Twenty-one patients exhibit kidney dysfunction during the follow-up.
Methods: Upon enrollment, the TCR Vb repertoire usage was characterized using TcLandscape, and a detailed multicolor flow cytometry was performed to characterize the phenotype (CD45RA, CCR7, CD27, CD28, CD127) and the function (GZM-B, PERF, T-Bet, CD57) of CD8 T cells.
Results: At the time of enrollment, 47 of the 133 kidney recipients with a stable graft function exhibited an altered TCR Vβ repertoire. This altered TCR Vb repertoire was associated with a mark increase in TEMRA CD45RA+CCR7-CD8 T cells. They also exhibited an activated phenotype (CD27-CD28-CD127-) and potent effector functions characterized by an upregulation of cytotoxic molecules (PERFhiGZM-b+) and effector-associated molecules (TBX21hi and CD57+). Finally, we report that an altered TCR Vβ repertoire is a risk factor of graft dysfunction (HR 2.96; $p = 0.0522$; multivariate Cox model).
Conclusions: Monitoring the TCR Vβ repertoire of circulating CD8 T cells as well as their phenotype and their function may help improve the identification of at-risk patients. Our data shed new light on the status of T cell immunity in long-term graft outcome.

O289 DISAPPEARANCE OF IMMUNOGLOBULIN PRODUCING PLASMABLASTS IN KIDNEY TRANSPLANT PATIENTS

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Introduction: Follicular T-helper cells play a pivotal role in differentiation of B-lymphocytes into plasmablasts (CD19+CD20-CD27+CD38++), via IL-21 production. CD4+CXCR5+ T-cells are their peripheral counterparts (Thf-cells), sharing functional properties with them. We examined frequency and functions of peripheral Thf-cells and plasmablasts in kidney transplantion (KTx) patients.
Methods: Numbers of Thf-cells plus their IL-21 production and numbers of plasmablasts were measured before and after KTx ($N = 30$), and in healthy controls ($N = 16$). Functional interaction was studied by co-culture experiments of either Thf-cells or CD4+CXCR5- T-cells with endotoxin activated B-cells.
Results: Before KTx numbers of Thf-cells were lower than in healthy controls ($p = 0.02$), and these numbers remained stable after KTx. However, the IL-21 production capacity by Thf-cells was reduced after KTx ($p < 0.01$). Moreover, patients had lower plasmablast counts than healthy controls ($p < 0.02$). Interestingly, after KTx a complete vanishing of plasmablasts was observed ($p < 0.0001$). Co-culture studies revealed that only Thf-cells provided help to B-cell differentiation into Ig-producing plasmablasts in both KTx patients as healthy controls ($p < 0.05$).
Conclusion: After KTx, lower IL-21 production capacity by Thf-cells, i.e. lack of B-cell guided differentiation, indicates the possible involvement of Tfh cells in the disappearance of Ig-producing plasmablasts after transplantation.

O290 NON-INVASIVE SCREENING FOR ACUTE REJECTION IN MURINE RENAL TRANSPLANTATION USING DIFFUSION WEIGHTED MRI

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Introduction: Biopsies are often required to detect the underlying condition for deterioration of the transplant function. Here, we tested a novel substance which inhibits the MCP1/CCR2 pathway via oligonucleotides in a murine renal Tx model. The aim was 1.) to detect potential effects of this drug on acute rejection processes and 2.) show that diffusion weighted MRI (DWI) may be a valuable tool to non-invasively monitor these rejection processes.
Methods: Kidneys of Balb/c mice were transplanted onto B6. Mice were either treated with the anti-MCP1-Spiegelmer in monotherapy or in combination with subtherapeutic CsA (10 mg/kgBW). For further analysis immunohistochemistry, FACS, doppler ultrasound and diffusion-weighted MRI were used.
Results: The number of F4/80+ cells was efficiently suppressed and kidney cortex perfusion measurements improved under combination therapy. The apparent diffusion coefficient (ADC) of native kidneys and syngenic allografts did not show significant differences. Allogenic allografts without treatment showed significantly lower ADC ($p < 0.001$). Under combination therapy the ADC significantly improved ($p = 0.002$). Discussion: The novel drug based on oligonucleotide technology inhibiting the MCP1 alleviates acute rejection. Diffusion-weighted MRI may serve as a valuable tool to detect rejection processes.

O291 CIRCULATING POLYOMAVIRUS-SPECIFIC CD8+ T-CELLS IN HEALTHY ADULTS ARE POLYFUNCTIONAL MEMORY CELLS

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Background: In severely immunocompromised individuals polyomavirus (PyV) BK may cause interstitial nephritis and PyV JC may cause progressive multifocal leukoencephalopathy. No specific and effective antiviral therapy is available. For the development of PyV-specific T-cell therapies or vaccination strategies, it is crucial to understand the normal PyV-specific immunological response.
Methods/Materials: Using PyV-tetramers and stimulation assays we were able to determine phenotype and function of circulating HLA-A02-resticted VP1-specific CD8+ T-cells in five of 20 HLA-A02-positive healthy adults.
Results: VP1-specific CD8+ T-cells were found to be memory cells highly expressing CXCR3 and CD49d. They were polyfunctional since they were able to rapidly secrete interleukin-2, interferon-γ, tumour necrosis factor-α, MIP-1-β and CD107 upon antigenic recall.
Conclusion: Circulating VP1-specific CD8+ T-cells are polyfunctional memory cells.

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OS36-DONATION/RETRIEVAL, GENERAL

O293 POTENTIAL FOR DECEASED ORGAN DONATION IN THE EMERGENCY DEPARTMENT: RESULTS OF A SPANISH MULTICENTER STUDY

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Background: Emergency services daily evaluate patients with devastating brain injury whose admission in intensive care unit (ICU) is not considered due to poor prognosis removing the possibility of donation. Although being a recognized area for increasing organ availability, there is limited knowledge on the potential of donation in emergency departments (ED).
Objectives: This study intended to assess the potential of donation in ED, identifying hospital units where possible donors evaluated in ED finally die.
Methods/Materials: Observational study, with 28 participating Spanish hospitals. Medical records of possible donors attended at the ED during 05/01/2011–10/31/2011 were reviewed. Possible donors were defined as "adult patients who died within 72 h following admission in ED with at least one ICD-code related with severe brain injury."
Results: Five hundred and forty-three possible donors were identified, representing 5.2% of hospital deaths, 16% of hospital deaths within 72 h following admission and 8.2% of deaths in ED. One out of 2000 attended emergencies was estimated to be a possible donor. Table 1 shows characteristics of possible donors and hospital units where death occurred. Donation was considered as an option at the ED in 43 (7.9%) of cases, with consent obtained for organ donation in 28 (68.3%). Emergency-care professionals participated in family approach in 14 (34.1%) of cases. Out of the 500 possible donors attended at the ED in whom donation was not posed as an option, 326 (65%) died outside of ICU with no apparent contraindication to organ donation.
Conclusions: Donation is considered as an option by emergency professionals in 7.9% of possible donors attended at the ED, while 70.8% of them died out of the ICU. These data show the high number of unrealized opportunities for deceased donation and the key role of emergency-care professionals in the activation of the deceased donation process.

O294 DONATION AFTER CIRCULATORY DEATH IS THE MOST COMMON DECEASED DONATION PATHWAY IN THE UK

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Background: We sought to investigate when donors after circulatory death (DCD) overtook donors after brain death (DBD) in the UK as the most common organ donation pathway.
Method: Data were obtained from the UK Potential Donor Audit (PDA) to look at the number of potential donors in the UK where consent for donation was obtained from the family.
Results: Between Oct 2009 and Nov 2012 there were 2172 DBD consents and 2359 DCD consents. The first month that DCD consented donors exceeded DBD was Feb 2010. The pattern can be clearly seen when consents are explored in six-monthly periods (see Figure 1).
Conclusion: This milestone in UK organ donation practice passed generally unnoticed in the early part of 2010, as the number of actual DCDs (despite a 615% increase over the last 10 years) is still lower than actual DBD. Paradoxically, DCD in the UK is both new to most current hospital staff and yet more common than traditional DBD.

O295 HIGH AND LOW DONATION RATE: WHERE IS THE DIFFERENCE?

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After introduction of local coordinators network across the country hospitals, Spain is an example of success in organ donation. Similar effect was observed in Northern Italy, where some districts actually doubled their donation rates. However, similar efforts made in some districts of Poland with very low donation rates (5.8 pmp in 2012) did not bring any improvement and employment of local coordinator in every major hospital in the district did not result in additional donations. We have sent questionnaires to 28 ICU units across the Northern Italy and 13 ICUs in Poland in a region with the lowest donation rate. Number of ICU beds, their turnover, percentage of patients treated for head trauma or cerebrovascular incident, legal regulations, presence of protocols for neurological death diagnosis, obstacles in diagnosis were similar in both groups of ICUs. However, in Northern Italy, of 2481 patients who had expired in ICUs the brain death was declared in 453 (18.3%) while of 566 ICU deaths in low-donation rate region in Poland only 11 patients were diagnosed brain-dead (1.9%). The most significant difference was, that tests necessary for brain death diagnosis in Poland were approached (apart from 1 ICU) only, when there was a chance for organ donation. Only one ICU in Italy claimed brain death diagnosis is connected to organ donation in their practice. Besides, brain death diagnosis in Northern Italy almost universally means termination of mechanical ventilation, while practice of many ICUs in Poland would be continuation of ethically dubious treatment when there is no chance for organ donation. In conclusion, a critical step to increase deceased donor organ donation is not employment of local coordinator *per se*, but effective identification of every brain death which occurs within an ICU, and confidence of all ICU crew with the criteria and procedure to a degree, that they are read to terminate mechanical ventilation whenever organ donation is not an option.

O296 NEONATAL DONATION; IS THERE A FUTURE IN THE UK?

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Background: Historically in the UK neonatal donation is a rare event. Introducing embedded specialist nurses into hospitals has afforded debate around donation from this group of patients. To be dismissive of this purely on historical practice prevents advances and opportunities to offer donation to these families if a possibility. There is a lack of consensus amongst transplant surgeons regarding the suitability of these organs and therefore there is a need to seek clarification.
Method: An audit of potential donors age 37 weeks gestation to 2 months of age was completed in a 16 month period. This audit was carried out on the Neonatal and Paediatric ITU at one London tertiary centre.
Results: Patients identified; total 23 deaths, nine deaths considered imminent and treatment was actively withdrawn. One patient had MOF, eight were considered potential donors. In three cases families were not approached due to the patient's general condition with organs declined by centres prior to a formal approach. In five cases at least one organ was provisionally accepted, the family were offered the option of donation. Four families declined donation, one family consented to donation. En-bloc kidneys were transplanted successfully to a young adult recipient.
Conclusions: There is no doubt that there are patients in this age group where donation is a possibility. A further audit of deaths at the hospital, within this patient group between 2006 and 2012 noted 34 potential DCD and 11 DBD if BSDT were supported in this group in the UK. There has been a positive response from some UK transplanting surgeons; data in Europe and the US shows excellent graft survival1. This is a limited audit, work to include all level three neonatal units in London is ongoing. In continuing to approach and work towards actual donation in this group we will be able to ascertain UK data on graft survival and establish clarity on practice.
Reference: 1. Dharnidharka V.R et al. American Journal of Transplantation 2005; 1513–15.

O297 POTENTIALITY OF DONATION AFTER CONTROLLED CARDIAC DEATH (DCCD) PROGRAM IN A SPANISH HOSPITAL

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Methods: Prospective, observational, 6-month study on all patients who died or underwent live support therapy limitation (LSTL) in a 30-bed adult polivalent ICU. Potentiality for DCCD was assessed through analysis of clinical, analytical and warm ischemia times (WIt) in patients in whom mechanical ventilation (MV) and/or vasoactive support (VAS) was withdrawn as a form of LSTL.
Results: Eighty-five of 434 patients (62.8% male; 61.1 $\pm$ 17.1 years old) died (seven brain-death donors), 78 of whom (91.8%) did so after LSTL initiation. Definitive LSTL actions were taken at 8.35 $\pm$ 10.15 days after admission. Patients died 18 h and 36 min $\pm$ 35 h, 43 min after definitive LTSL initiation being significantly shorter in those (n = 19; 41.3%) whom MV and/or VAS was abruptly stopped (4 h, 47 $\pm$ 4 h, 31 min; $p < 0.05$). Of those, 13 were <70 years old, seven were medically eligible, two had Wit < 60 min and one had no organ-specific contraindications for organ donation.
Conclusions: A DCCD program would increase by 14.2% our hospital donor number.

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O298 POTENTIAL PEDIATRIC DONOR POOL IN SPAIN

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Background: There is limited knowledge on the potential pediatric donor pool and the causes of potential donor losses, information needed to optimize the availability of these organs.
Objectives: To assess the pool of pediatric potential donors after brain death (DBD) in Spain evaluating the process of pediatric deceased donation.
Methods: Data were obtained from the national Quality Assurance Program in Deceased Donation, identifying those with a clinical condition consistent with brain death and reasons why they were not converted into actual donors. We established comparisons between pediatrics and adults.
Results: In 1999–2011, 1115 pediatric potential DBDs were identified, accounting for 11.3% of pediatric deaths in CCUs. The majority were identified in PICUs (901; 80.8%). The estimated national pool of pediatric potential DBD was over 23 cases pmp <14 years in 1999 and 2000, but remained below 10 in 2011. The conversion rate of potential into actual donors was lower for pediatric (41.7% vs. 56.1%; $p < 0.05$) and, while conversion rate improved over time for the adults, this was not the case for pediatrics, with values below 50%. Reasons for a decreased conversion rate among pediatric versus adult potential DBDs were a higher percentage of losses due to medical unsuitability (28.1% vs. 22.5%), hemodynamic instability or cardiac arrest (5.7% vs. 2.6%) and lack of suitable recipients (2.3% vs. 0.6%x). No significant differences were observed in losses due to declined consent or judicial authorization.
Conclusions: There is a decline in the pool of pediatric potential DBDs and their conversion into actual donors is complex, with some identified areas for improvement. International agreements to avoid losses due to lack of adequate recipients and a smooth cooperation between transplant coordinators and PICUs seem essential strategies.

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BOS25-KIDNEY – LONG TERM II

BO281 VITAMIN D STATUS AND REPLETION IN KIDNEY TRANSPLANTATION – THE TIME FOR ACTION IS NOW

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Background: Vitamin D insufficiency (>25 < 50 nM) and deficiency (<25 nM) are common in stable ambulant renal transplant patients (RTx). This has been associated with adverse skeletal, renal, cardiovascular and cancer outcomes in this population, but a formal repletion RCT with hard end-points has never been completed. We undertook a comprehensive survey of vitamin D levels, with active repletion using oral Dekristol™ cholecalciferol, in a group of long-term RTx survivors, all of whom had sustained vitamin D deficiency, to assess both efficacy and safety of this intervention.
Methods: Results from all blood samples drawn from outpatient-attending RTx patients and sent for vitamin D measurements (2010–2012) were retrieved and analysed. We found 57 subjects with sustained very low (<25 nM) serum vitamin D concentrations. We prescribed all of these patients 40 000 IU Dekristol™ cholecalciferol for 6 months (total dose 240 000 IU) and then interrogated the biochemical changes in plasma vitamin D, PTH, alkaline phosphatase, calcium, phosphate and creatinine (eGFR) concentrations over the course of the repletion period.
Results: Eight hundred and fifty-six vitamin D values from 449 patients (age mean 53, median 55, IQR 44–65, range 18–89 years). Vitamin D concentrations were significantly correlated with PTH, eGFR, ALP and urinary protein. There was an inverse correlation with plasma PTH concentration (-0.344, $p \leq 0.001$), with eGFR (0.095, $p = 0.007$), with ALP (-0.159, $p \leq 0.001$) and with urinary protein (-0.102, $p = 0.043$). Repletion was efficiently achieved in 54 out of 57 patients, with highly significant rises in vitamin D concentrations, with corresponding falls in PTH, ALP, without significant hypercalcaemia or change in renal function.
Conclusions: Vitamin D deficiency is common, with skeletal consequences, and associated proteinuria, while repletion is cheap, safe, tolerated and easy. Continued neglect of this factor is suboptimal care.

BO282 VITAMIN D DEFICIENCY IN KIDNEY TRANSPLANT RECIPIENTS; A COLORADO EXPERIENCE

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Background: Kidney transplant recipients (KTR) are susceptible to low vitamin D level. The purpose of this study was to determine incidence and risk factors for 25-OHD deficiency in KTR. Patients and Methods

Five hundred and ninety-four patients were classified as vitamin D normal (25-OHD > 30 ng/ml) and deficient (Â15 ng/ml). To determine factors affect 25-OHD deficiency, multivariate logistic regression analysis was performed.
Results: 48.3% were vitamin D deficient. A higher percentage of African Americans (AA) were vitamin D deficient compared to Non-Hispanic White ($p < 0.01$), Hispanic ($p = 0.004$) and others ($p = 0.046$). Vitamin D levels had a weak positive correlation with transplant duration ($r = 0.14$, $p < 0.01$). Multivariate analysis demonstrated female, AA, Hispanics, transplantation duration and deceased donors were significant predictors of vitamin D deficiency.
Conclusions: Vitamin D deficiency was common and was significantly shown in female, AA, Hispanics, deceased donors and short duration of transplantation.

BO283 RELATIONSNIP BETWEEN VITAMIN D STATUS AND TYPE OF IMMUNOSUPPRESSION IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction and Aims: The role of Vitamin D (VD) in bone health, preventing cancers, diabetes, cardiovascular, autoimmune diseases, infections, and total mortality, has been well demonstrated. Immunomodulatory and renoprotective effects of VD reveal potential for improving transplantation outcomes, including optimization of immunosuppressive therapy. The aim of this study was to assess the relationship between VD status and type of immunosuppression in Bulgarian kidney transplant recipients (KTRs).
Patients and Methods: Three hundred and twenty-eight KTRs were included in this study with their VD status analyzed at least 6 months after operation, if they had intact parathyroid and stable graft function. Statistical analysis included descriptive, univariate, multivariate, and log-linear regression. Determination of 25-hydroxyvitamin D (25D, 25D3 + 25D2) was performed by a validated LC-MS/MS method.
Results: VD status of our KTRs was as follows: 61 subjects (18.6%), 47 males (M) and 14 females (F) were in sufficiency (25D > 80.0 nM); 138 (42.1%, M93, F45) had mild insufficiency (25D 50.0–79.9 nM); 105 (32.0%, M65, F40) had profound insufficiency (25D 25.0–49.9 nM), and 24 (7.3%, M8, F16) had deficiency (25D < 25 nM). Apart from well known inverse relationships between VD status and diabetes, gender (F), body mass index, season and PTH, plasma 25D was inversely associated with use of calcineurine inhibitors (CNIs), $p < 0.05$, and positively correlated with use of m-TOR inhibitors (m-TORI), $p < 0.05$; 189 patients were on cyclosporine A (CsA, 57.6%, M116, F73), 105 were on tacrolimus (TACRO, 32.0%, M65, F40), and 34 were on m-TORI (10.4%, M23, F11); regression coefficients -0.15 (CsA), -0.18 (TACRO), and $+0.15$ (m-TORI).
Conclusions: Our study demonstrated that factors influencing 25D levels in KTRs included inverse CNIs and positive m-TORI effects. Optimization of VD status with respect to immunosuppressive therapy reveals a potential to improve patient care and outcomes.

BO284 COMPARISON OF CALCIDIOL REPOSITION REGIMES AFTER KIDNEY TRANSPLANTATION

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Deficiency of vitamin D is not only prevalent in general population and CKD patients, but also in kidney-transplanted recipients (KTR). This deficiency has been associated not only with poor bone health outcome, but also with cardiovascular, infectious and rejection risk. The aim of the present study is to compare two regimes of vitamin D supplementation with calcifediol (266 μg, liquid form) in stable KTR, prescribed monthly or biweekly. We designed retrospective observational study including 232 KTR followed in outpatient clinics of Hospital Clinic of Barcelona. Exclusion criteria: KT performed within the last 6 months, absence of calcidiol level determination within the last year, treatment with other vitamin D form or calcimimetics. A total of 168 KTR transplanted between January 1987 and December 2011 were included. Calcidiol was measured at baseline and after 4.5 months (3–12 months). In the group of patients with monthly regime ($n = 72$) we observed a significant increase in 25OHD levels and significant decrease in PTH. Serum levels of calcium (sCa), phosphate (sPO4) and parameters of renal function remained stable. When we divided patients by GFR (<30, 30–60, >60 ml/min/1.73 m^2) we only observed decrease in PTH in patients with GFR > 60 ml/min/1.73 m^2: from 123 pg/ml (71–163 pg/ml) to 93 pg/ml (IQR 78–123 pg/ml); $p = 0.043$ (see Table 1). In the group of patients with biweekly regime ($n = 96$) we observed a significant increase in 25OHD levels and decrease in PTH, that was significant in all GFR groups. There was a significant but not clinically relevant increase of sPO4. Parameters of renal function and sCa remained stable (see Table 1). In conclusion, biweekly and monthly calcifediol supplementation regimes are safe and ensure adequate 25OHD levels. Biweekly regime also decreases PTH levels, whereas monthly regime decrease PTH in patients with GFR > 60 ml/min/1.73 m^2. Comparison between baseline and after calcifediol supplementation in monthly and biweekly regimes.

BO285 EFFECT OF APOPTOSIS AND INFLAMMATION GENE POLYMORPHISMS ON TRANSPLANTED KIDNEY FUNCTION

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Background: This study investigated the impact of polymorphisms of inflammation- and apoptosis-related genes on chronic allograft dysfunction (CAD) in kidney transplant recipients.
Methods: Three hundred and seventy-six patients transplanted between 2005 and 2011 were enrolled (follow-up: 2.6 ± 1.4 years). The potential associations of CAD with interleukin 6 (IL-6), transforming growth factor beta 1 (TGFB1) and Fas gene polymorphisms were investigated in a case-control study. The control group included 256 stable renal transplant recipients (SGF group), whereas the case group consisted of 120 patients with worsening graft function (CAD group). The patients were genotyped for IL-6/G–174C, TGFB1/L10P, TGFB1/R25P, Fas/G-670A polymorphisms.
Results: Similar genotype frequencies between the groups were found for IL-6, TGFB1 and Fas polymorphisms. In search of mutual effects between polymorphisms, all the possible dual genotypic associations were tested and the combination of IL-6 high producer and Fas low producer genotype resulted in a 0.79-fold reduced risk of CAD (OR = 0.79; 95% C.I. = 0.72–0.86).
Conclusions: These results suggest a protective effect against CAD conferred by the carriage of IL-6 high producer/Fas low producer genotype, indicating a prognostic value of gene polymorphisms involved in inflammatory response and programmed cell death on kidney transplant outcome.

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BO286 RECIPIENT DEATH AND GRAFT LOSS IN RENAL TRANSPLANTATION: THE CHALLENGE OF INFECTIOUS COMPLICATIONS

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Background: Causes of recipient death/renal allograft loss are still modestly evaluated, and there may be several differences according to epidemiological characteristics of each population.
Methods: From 1 January 2011 to 31 October 2012, there were 6319 recipients at risk of death or graft loss. Causes of death and graft loss were evaluated according to the time after kidney transplant (within 30 days, 31–180 days, 180 days–1 year, 1–5 years and after 5 years).
Results: There were 596 renal graft losses. Population was male (63%) and Caucasian (58%) subjects, aged 42 ± 15 years, first kidney transplant (94%) with deceased donor (62%). There were 297 (50%) graft losses due to death with renal function, 6 (1%) due to primary nonfunction and 329 (49%) due to graft failure censored for death. Latter group was divided into atrophy/fibrosis (161, 55%), surgical complications (38, 13%), acute rejection (36, 12%), glomerular diseases (30, 10%) and other causes (28, 10%). Atrophy/fibrosis was associated with immunological phenomena (recurrent rejection) in 103/161 (64%), bacterial pyelonephritis in 13/161 (8%) and poliomavirus nephropathy in 6/161 (4%) of the cases. Contribution of acute rejection to graft loss was constant during the period (3.9% in the first 6 months vs. 6.4% thereafter, $p = 0.26$). Surgical complications occurred in the first month posttransplant (27/38). When analyzed the causes of death ($n = 297$), infectious events responded by most cases (162, 55%) during all evaluated periods, followed by cardiovascular events (47, 14%) and cancer (21, 7%).
Conclusion: The high mortality from infectious causes points to the need for better screening and prophylaxis strategies. Regular contribution of acute rejection to graft loss, and the predominance of immunological phenomena related to atrophy/fibrosis suggest poor adherence to treatment, and identifies possibilities of intervention that may result in improved kidney transplantation outcomes.

BO287 CIRCULATING ANGIOPOETIN-2 LEVELS ARE CORRELATED WITH RENAL RESISTANCE INDEX AND PREDICT MORTALITY IN KIDNEY ALLOGRAFT RECIPIENTS

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Background: Angiopoetin-2 (Ang-2) is released from Weibel-Palade-bodies upon inflammatory stimulus and an antagonistic ligand of the endothelial-specific Tie2, a vascular specific tyrosine kinase that mediates endothelial cell function. We tested the hypothesis whether Ang-2 serum concentrations are associated with renal transplant function, measures of renal and systemic hemodynamics and mortality.
Methods: We performed a prospective single centre cohort study of 200 renal allograft recipient (mean time after tx at inclusion 7.0 ± 6.2 years). Ang-2 serum concentrations were measured by an in-house immuno-luminometric assay. RI was determined in segmental arteries of the allograft by color-coded duplex ultrasound. All technical measurements were performed at study inclusion.
Results: Mean (SD) patient age at inclusion was 53 ± 13 years, eGFR 61 ± 20 ml/min, serum albumin 3.9 ± 0.3 g/dl, cholesterol 206 ± 42 mg/dl, pulse pressure 52 ± 17 mmHg, RI 0.71 ± 0.07, Framingham risk score 4.0 ± 4.4 and Ang-2 serum concentrations 2.8 ± 1.7 ng/ml. Ang-2 correlated with renal resistance index ($r = 0.32$; $p < 0.001$), eGFRNankivell ($r = -0.29$, $p < 0.001$), recipient age ($r = 0.27$; $p < 0.005$), serum albumin ($r = -0.26$; $p < 0.005$; C-reactive protein ($r = 0.26$; $p < 0.01$), Framingham risk score ($r = 0.22$; $p < 0.05$) and mean arterial pressure ($r = 0.23$; $p < 0.05$), but not with donor age, arterial stiffness measured by pulse pressure, total cholesterol, HbA1c or PTH. After 5 years follow up, a total of 30 patients died, 19 out of the highest tertile of Ang2 levels (Ang2 high) measured at inclusion.
Conclusion: In renal transplant recipients, endothelial cell dysfunction, reflected by Ang-2 concentrations, is related to renal and systemic hemodynamics. Ang-2 is a possible predictor for patient survival after renal transplantation and requires further evalutation.

BO288 PERITONEAL DIALYSIS RELATIVE TO HEMODIALYSIS IMPROVES LONG-TERM SURVIVAL OF KIDNEY TRANSPLANT PATIENTS. A SINGLE-CENTER OBSERVATIONAL STUDY

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The transplant outcome may be influenced by pretransplant dialysis modality. We evaluate whether the pretransplantation dialysis modality influences patient and allograft survival past 10 years.
Methods: We included 236 patients (118 from peritoneal dialysis and 118 from hemodialysis) who proceeded to transplantation during the period from December 1990 to December 2002. The follow-up period was defined as extending to the patient's death, the loss of the allograft, or loss of follow-up. March 2012 was set as the end date of the study.
Results: In the multivariate analysis the long-term patient survival rate was higher for the PD group than for the HD group ($p = 0.04$, HR 2.62) however the allograft survival rate was not statistically different between the two groups ($p = 0.12$, HR 0.68).
Conclusion: Pretransplant dialysis modality is associated with long-term patient survival, with the results favoring PD over HD. However the pretransplant dialysis modality does not influence graft loss risk.

BO289 SURVIVAL BENEFIT OF KIDNEY TRANSPLANTATION IN PATIENTS OVER THE AGE OF 65

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Introduction: Older patients (age > 65) currently represent the largest population starting renal replacement therapy in the UK. However, their access to, and benefit from, transplantation remains unclear.
Methods: A retrospective case review was undertaken of all adult patients listed for renal transplantation between 1st July 2002 and 31st July 2012. Older patients (age > 65) were compared to a younger cohort (age < 45).
Results: One thousand four hundred and ninety-one patients were listed in total; 167 (11%) were older than 65 years old and 551 (37%) were younger than 45 years old. The number of older patients listed per year increased from 8 (6% of annual total) in 2002 to 25 (17%) in 2012. Removal from the waiting list (due to death or development of comorbidity) occurred more frequently in older patients (26%) than the young (5%, $p < 0.01$). Only 5% of older patients were listed in the first 6 years currently remain active, compared with 31% of the young, with Kaplan–Meier analysis confirming that median time to de-listing is much shorter in older patients (897 vs. 2027 days, $p < 0.01$). 49% of the older patients and 71% of the young was transplanted. Times from listing to transplant were similar in both groups (age > 65 median 424 days vs. age < 45; 388), but notably, older patients received a higher proportion of DCD kidneys ($p < 0.01$; Figure 1). Older patients generally received kidneys from older donors (median donor age 61 vs. 43 years, $p < 0.001$); this held true for DCD kidneys (68 vs. 41, $p < 0.001$). Graft survival was similar in the two groups (1 year 91% vs. 98%, $p = 0.66$), and in both, transplantation offered a significant survival benefit (92% vs. 85% 3 years from listing for those transplanted in the elderly group versus those who were not transplanted, $p < 0.05$; Figure 2).
Conclusions: The time frame for transplantation of older patients (age > 65) is limited. As numbers listed increase, greater use of older DCD donors may alleviate demand, yet still provide survival benefit.

BO290 ASSESSING THE RELATIONSHIP BETWEEN RENAL ALLOGRAFT SURVIVAL TIME, COST AND HEALTH OUTCOMES OVER A TEN-YEAR PERIOD

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Introduction: Renal replacement therapy (RRT) accounts for over 2% of the total NHS budget, which is disproportionately greater than the 0.05% prevalence of this patient population among the general population. Transplantation increases survival, improves quality of life and maintenance costs are substantially lower than dialysis. The objective of this study was to predict the future burden of RRT and quantify the relationship between graft survival, cost and health outcomes.
Methods: We utilized a population based simulation model with published disease progression, incidence and prevalence parameters specific to the UK. We estimated a future RRT incidence profile and a future increase in the number of transplants per year, based on extrapolating observed data between 2000 and 2010. We used the model to estimate future prevalence levels stratified by age and treatment modality, evaluating the potential cost and health outcome benefits of increasing graft survival. Future costs and benefits were discounted at 3.5%.
Results: Over the period 2013–2023 we estimate that the prevalence of RRT will increase to 69 139, with 33 325 people receiving dialysis treatment and 35 824 living with a functioning graft. Of those, 29 634 are estimated to be aged 65 and over. Improving graft survival has the potential to decrease the number of patients on dialysis by 1978, decrease the amount spent on dialysis by approximately £250 million, increase the amount spent on transplants by £100 million and create a total cost saving of approximately £150 million over a 10 year period. Improving graft survival could provide an additional gain of approximately 8000 QALYs.
Conclusion: With the prevalence of RRT estimated to increase cost saving has become a priority to the NHS. Improving graft survival has the potential to save £150 million over a ten-year period, decrease the number of patients treated with dialysis and improve patients' quality of life.

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BOS26-KIDNEY – COMPLICATIONS/OTHERS

BO291 POST – TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS IN RENAL TRANSPLANT: ANY CHANGE IN TWO DECADES? A STUDY OF 24232 RECIPIENTS

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Posttransplant lymphoproliferative disorders (PTLD) are heterogeneous lymphoid proliferations in recipients of solid organs which seem to be related to Epstein Barr Virus (EBV). EBV seronegativity in the receptor, use of antilymphocyte antibodies, acute rejection and CMV infection have been identified as classical risk factors. We have studied in a cohort study the incidence of PTLD and its relationship with EBV in 24 232 simple adult renal transplant recipients from cadaveric and living donors, transplanted in 20 hospitals from 1990 to 2009. We compared PTLD incidence, classical risk factors, presence of EBV in lymphoproliferative cells, time between transplant and PTLD and outcome of recipients in two decades: 1990–1999 and 2000–2009 with 10 973 and 13 259 patients respectively. The follow-up varied between 1 and 252 months. A total of 216 recipients developed PTLD (0.88%). Seventy nine out of 216 patients (36.6%) had no classical risk factor. EBV in the tissue was reported in 81 out of the 126 studied recipients (64.2%); 87.8% of the proliferations were B lymphocytes. PTLD median appearance after transplant were 84.0 months in recipients with EBV positive (24; 129) and negative (41; 109) in tissue ($p = 0.572$). Table shows the comparision of characteristics, classical risk factors, time between transplant and PTLD, immunosuppressive therapy at diagnosis, incidence of PTLD, presence ot EBV in lymphoproliferative cells, patient and graft survival between the 2 decades in study. In conclusion, most of the proliferations are due to B lymphocytes and seem to have a close relationship with EBV. PTLD can develop in the absence of classical risk factors. There is no relationship between presence of EBV and appeareance of PTLD after transplant. The decrease in PTLD incidence may be related to a change in immunosuppression and a reduced presence of EBV, but without any variation in risk factors, appeareance after transplant and outcome.

BO292 MAINTAINING A CNI AFTER THE DIAGNOSIS OF PTLD IS SAFE AND IMPROVES RENAL GRAFT SURVIVAL

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Treatment of PTLD includes a reduction of immunosuppression (RIS). PTLD patients have an increased risk for graft loss suggesting that RIS strategies need to be optimised with regard to graft outcome. The files of 101 renal graft recipients diagnosed with PTLD were reviewed. During the follow-up (median: 70 months) 39 died and 21 lose their graft. Multivariate analysis established that eGFR < 30 ml/min/1.73 m^2 at diagnosis, acute rejection episode following RIS, and absence of a CNI in maintenance immunosuppression (Figure) are independent risk factors for allograft loss. Histological analysis revealed that maintaining a CNI after the diagnosis of PTLD reduces the risk of humoral rejection. Remarkably, CNI maintenance was neither associated with a higher mortality, nor with a worse progression free survival. We conclude that maintaining a CNI at reduced dose after the diagnosis of PTLD is safe and improves renal graft outcome, possibly through a better control of humoral immune response.

BO293 RECURRENCE OF PRE-EXISTING CANCER FOLLOWING KIDNEY TRANSPLANTATION

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A past history of cancer is a relative contraindication to undergoing kidney transplant because of the risk of cancer recurrence but the evidence is limited. Using the UKTransplant Registry, we selected all kidney recipients (1985–2010) in the West Midlands region and identified all cases of pre-transplant cancer and post-transplant recurrence from the Cancer Registry. Of 3321 recipients, 35 (1.1%) had a history of cancer: ca bladder (4), breast (5), colon (4), kidney (6), prostate (3), melanoma (2), others (11). Two recipients developed cancer recurrence (both melanoma) with rate of recurrence within 12 years of transplant of 19.4% (0, 49). Both recipients with recurrence had been cancer-free for <5 years pre-transplant and both died due to recurrent cancer. There was no recurrence of cancer in 33 recipients of whom 22 underwent transplant ≥5 years after diagnosis. We conclude that a cancer-free period of ≥5 years is associated with a very low risk of cancer recurrence.

BO294 OCCURENCE OF SECOND PRIMARY MALIGNANCIES IN KIDNEY TRANSPLANTED PATIENTS

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Introduction: The risk of developing second primary cancer (SPC) after transplantation is increasing with time. Advances in cancer treatment have led to more survivors, subsequently to more patients with second primary tumour. The risk of developing a second primary cancer is increased at least by 20% among transplant patients. Immunosuppressive therapy increases the risk of tumours. Aim of our study was to analyse the data of patients who had cancer prior to transplantation or developed two entirely different tumours after kidney transplantation.
Patients and Method: Two hundred and thirty-one solid organ tumours were diagnosed between 1973 and 2012 at our Department. Eighty-nine of them were diagnosed during the last 5 years. Eleven patients developed second primary cancer after transplantation; four of them had tumours prior to transplantation.
Results: Average age of patients at transplantation was 46, 72 ± 14, 98 years. Average time between transplantation and tumour diagnosis was 80, 72 ± 63, 53 months. Between the detection of the first and the second tumour 26, 18 months elapsed. During this time nine patients were converted to PSI treatment. Second tumour developed in three patients in the first year; (sigma- prostate, Burkitt lymphoma- testis, native kidney- lung). In one patient tumour occurred after 11 years; (native kidney- oral cavity) and in seven patients between 1 and 3 years. Three patients died. Average survival time form the first tumour diagnosis until death was 81, 66 months. Six patients are still alive with a good kidney function. Survival time since tumour diagnosis was 41, 66 ± 40, 67 months. Two patients had to return to dialysis, their survival time since tumour diagnosis was 41 months.
Conclusion: With increasing age of transplanted patients the possibility of non detected tumours is increasing. More attention should be paid to the possibility of synchronous tumours. With the use of the new immunosuppressive drugs a good survival rate can be achieved among transplanted tumour p.

BO295 DOES TRANSPLANT TRANSLATE TO REDUCED BACTERAEMIA IN END STAGE RENAL DISEASE?

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Background: The aim was to compare bacteraemia rates between renal replacement therapy (RRT) and investigate the effect of switching from haemodialysis (HD) via a central venous catheter (CVC) to either a fistula (AVF) or renal transplant on bacteraemia rates. Methodology: A multicentre retrospective audit of all 1997 patients requiring new vascular access for RRT or switch in RRT modality over an 18-month period was undertaken. Bacteraemia rates are expressed per 1000 patient days.
Results: HD via a CVC carried the greatest risk of bacteraemia, 1.93 ($n = 403$); followed by HD via an AVF, 0.23 ($n = 670$); peritoneal dialysis, 0.09 ($n = 157$). Renal transplantation conferred the lowest risk, 0.03 ($n = 1091$). Assuming that an average access-related bacteraemia costs approximately £10 000, total costs after 1 year are as follows: CVC £33295.50; AVF £25802.50; peritoneal dialysis £19414.50; renal transplantation £22109.50 in the first year and £5109.50 for each subsequent year. In patients who switched RRT from HD via a CVC to AVF ($n = 90$) the bacteraemia rate fell from 1.96 to 0.55 respectively ($p = 0.01$) and from CVC to transplant ($n = 38$) the bacteraemia rate fell from 2.72 to 0.73 respectively ($p = 0.06$).
Conclusion: HD via a CVC carries the greatest risk of bacteraemia. Conversion to either AVF or renal transplant reduced bacteraemia rates. These figures support an integrated RRT strategy, including ongoing investment towards maximising opportunities for renal transplantation as a cost-effective means to minimise bacteraemia rates in patients with ESRD.

BO296 A PROSPECTIVE RANDOMIZED TRIAL AIMED TO REDUCE THE INCIDENCE OF CYTOMEGALOVIRUS (CMV) INFECTION IN KIDNEY TRANSPLANT (KT) RECIPIENTS

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Background: CMV infection has been associated with inferior long-term patient and graft survival. This single center prospective study compares the

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effect of three immunosuppressive regimens on the incidence of CMV infection.
Methods/Materials: Low immunological risk KT recipients were randomized to: (G1) single 3 mg/kg dose of thymoglobuline, tacrolimus (TAC, 4 ng/ml), everolimus (EVR, 4–8 ng/ml) and prednisone; (G2) basiliximab (BSL), TAC (6 ng/ml), EVR (4–8 ng/ml) and prednisone, or (G3) BSL, TAC (8 ng/ml), mycophenolate and prednisone. Patients did not receive CMV prophylaxis. CMV infection was monitored weekly by antigenemia and PCR tests. We show preliminary results of the first 170 (G1 = 45; G2 = 68; G3 = 57) out of 300 anticipated patients with mean follow up of 239 days.
Results: There were no differences in main demographic characteristics including pre-transplant CMV donor/recipient serostatus. The incidence of CMV infection was lower in EVR groups (2 vs. 12 vs. 37%, $p < 0.001$). Furthermore, 18% patients in G3 ($n = 10$) developed at least one recurrent event of CMV infection. Nine patients were converted from MPA to EVR and 1 patient still had a further recurrence. Among the high risk donor +/recipient − pretransplant CMV serostatus the incidence of CMV infection was 0%, 63% and 100%, respectively. There were no differences in the incidence acute rejection (9 vs. 19 vs. 16%, $p = 0.383$), wound-healing adverse events (18 vs. 28 vs. 23%, $p = 0.454$), respectively. There were no differences in mean serum creatinine (1.4 ± 0.5 vs. 1.5 ± 0.4 vs. 1.3 ± 0.4 mg/dl, $p = 0.204$) and proteinuria (0.3 ± 0.4 vs. 0.4 ± 0.6 vs. 0.2 ± 0.3 mg/dl, $p = 0.324$) at 6 months. There were 6 deaths (G1 = 1; G2 = 3; G3 = 2) and 5 graft losses (G2 = 3; G3 = 2).
Conclusions: Patients receiving EVR are at lower risk of developing CMV infection compared to patients receiving MPA with no significant differences in efficacy and other safety parameters.

BO297 SILDENAFIL CITRATE IN A DONATION AFTER CIRCULATORY DEATH EXPERIMENTAL MODEL OF RENAL ISCHAEMIA REPERFUSION INJURY

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Background: Ischaemia reperfusion injury (IRI) after transplantation is associated with severe cellular dysfunction. Cyclic guanosine 3′,5′monophosphate (cGMP) maintains cellular function and promotes vascular smooth muscle relaxation. Phosphodiesterase-5 (PDE-5) inhibitors prevent breakdown of cGMP and may reduce IRI. We assessed the effects of the PDE-5 inhibitor sildenafil on IRI in a porcine model of donation after circulatory death (DCD) kidneys.
Methods: Kidneys were subjected to 20 min warm ischaemia and 2 or 18 h cold ischaemia (CI) and reperfused *ex-vivo* for 3 h with an oxygenated blood based solution, and treated with 1.4 mg/kg sildenafil infused 10 min before and 20 min after reperfusion ($n = 6$) or not treated ($n = 6$). Renal function and injury markers were measured during reperfusion.
Results: Prolonged CI significantly reduced cGMP (2 h 3.6 ± 1.4 vs. 18 h 1.32 ± 1.00 pmol/ml; $p = 0.01$). Sildenafil increased cGMP in the 2 h (7.3 ± 3.8pmol/ml; $p = 0.047$) and 18 h groups (5.4 ± 5.6 pmol/ml; $p = 0.064$). Sildenafil improved renal blood flow for 30 min in the 2 h group (sildenafil 79.4 ± 22.7 vs. control 37.9 ± 24.3 ml/min/100 g; $p = 0.026$) and up to 60 min in the 18 h group (sildenafil 67.1 ± 18.8 vs. control 38.7 ± 8.2 ml/min/100 g; $p = 0.009$). Renal blood flow (AUC) was improved with sildenafil in kidneys with 18 h CI (sildenafil 482 ± 99.7 vs. control 360 ± 46.8 ml/min/100 g.h; $p = 0.021$) but not those with 2 h CI ($p = 0.082$). Renal function was impaired after 18 h CI (creatinine clearance; 2 h 14.7 ± 10.4 vs. 18 h 4.5 ± 2.0 ml/min/100 g.h; $p = 0.0.26$). Sildenafil did not improve creatinine clearance in the 2 h ($p = 0.384$) or 18 h CI ($p = 0.099$) groups. There was no difference in levels of neutrophil gelatinase-associated lipocalin (NGAL); $p = 0.48$, 0.31) between the groups.
Conclusion: Sildenafil increased levels of cGMP and had a vasodilatory effect but did not improve renal function. This suggests sildenafil is not protective during early reperfusion in an *ex-vivo* DCD mo.

BO298 DEATH WITHIN THE FIRST YEAR AFTER KIDNEY TRANSPLANTATION IN ENGLAND – AN OBSERVATIONAL COHORT STUDY

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Background: Death occurring within the first year post-transplant is an important audit measure for kidney transplant centres. The aim of this study was to explore deaths occurring within the first year post kidney transplantation in England since 2000 to determine causes, classifications and predictors of 1-year mortality.
Methods: We examined data from Hospital Episode Statistics (HES) to select all kidney transplant procedures performed in England between April 2001 and March 2012 (HES is an administrative data warehouse containing admissions to all National Health Service hospitals). Patient demographics were collected including age, gender, donor type (living or deceased), ethnicity, transplant year, allograft failure, medical co-morbidities (e.g. diabetes, cardiovascular disease, cerebrovascular disease, cancer) and area socio-economic deprivation (Index of Multiple Deprivation [2010]). Data linkage analysis was performed with the Office for National Statistics (ONS) to identify all deaths occurring amongst this study cohort. Primary outcome measure was 1-year mortality, with Cox proportional hazard models performed to identify independent factors associated with mortality ($p < 0.05$ considered significant).
Results: Five hundred and sixty-six deaths (3.0%) occurred within the first year post-transplant (from a total of 19 688 kidney transplant procedures performed). Infection, cardiovascular events and malignancy were classified in 30.9%, 15.9% and 7.2% of all death certificates respectively. Recipients with a previous history of myocardial infarct or heart failure had a greater risk of death from a cardiovascular-related event within the first year post transplantation versus those recipients with no relevant prior history (20.4% vs. 4.3% respectively, $p < 0.001$). Kidney allograft recipients with a history of cancer had a 34.8% risk of death from malignancy within the first year post transplantation, versus a 1.8% risk for recipient with no previous cancer history ($p < 0.001$). 22.1% of deaths included kidney failure as a contributory factor on the death certificate (3.3% specifically stated allograft failure). Variables independently associated with 1-year mortality on Cox regression analysis included deceased-donor (versus live-donor) kidney transplantation, increasing age, residence in areas of socioeconomic deprivation and history of select medical comorbidities pre-operatively (myocardial infarct, diabetes mellitus, heart failure, peripheral vascular disease, liver disease and cancer).
Conclusion: One-year mortality post kidney transplantation is low at 3.0% but risk of death increases considerably in select cohorts. This risk should be identified pre-transplantation to guide subsequent counselling and risk stratification.

BO299 POOR SLEEP IN RENAL TRANSPLANT RECIPIENTS: A DISTURBING PROBLEM?

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The aims of this study were to determine the prevalence of sleep disruption in renal transplant recipients and assess contributing factors using a questionnaire between 3 and 6 weeks post transplant. Ninety out of 100 patients responded of which these 32 (36%) reported no sleep disturbance. The remaining 58 reported their sleep quality as fairly good ($n = 9$), fairly bad ($n = 27$) or very bad ($n = 22$). Of those waking >3 times per week 94% reported nocturia and 70% a frequency of three or more times per night. In these patients the median fluid intake was 3 l/d with most (96%) patients drinking after 9 pm and 60% drinking fluids after 10 pm. Twenty-seven patients experienced pain more than once per week (46%) with 14 (24%) patients experiencing frequent pain (>3×/wk). 71% of patients had trouble getting to sleep and 47% had frequent problems (>3 times per week) getting to sleep. Eleven patients cited bad dreams and 11 reported breathing difficulties. Sleep disturbance appears to be a common yet rarely reported issue post renal transplant and is likely to contribute to reduced quality of life. Nocturia due to excessive mis-timed fluid intake appears a cause which education may easily improve.

BO300 REGRET IN UNSPECIFIED KIDNEY DONATION IN THE UK

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Background: Unspecified (altruistic) living kidney donation is increasing in popularity in the UK with over 150 donations since the scheme began in 2007. This is the first large study of psychosocial outcomes and regret in unspecified donors.
Methods: All 148 UK unspecified living kidney donors (UD) were sent a postal questionnaire alongside a comparison sample of directed donors (DD) from a single UK centre. Pre-validated questionnaires were used where available.
Results: One hundred and eighty-two responses were received (109 UD vs. 73 DD; $p > 0.05$). There was no difference in post-operative mood, stress, anxiety, self-esteem or wellbeing ($p > 0.05$). UD reported lower perceived social support and social comparison ($p < 0.05$). UD engaged in more altruistic behaviours such as blood donation and charity work ($p < 0.001$). Twelve donors regretted donating (4 UD (3.7%) vs. 8 DD (11.0%); $p < 0.05$). Seventy-one UD (65.1%) knew their recipient's outcome; 3 (4.2%) regretted knowing so.
Conclusion: Unspecified donors have comparable psychosocial outcomes to directed donors but report lower social support and social comparison. Few unspecified donors regret, implying that continuation of the scheme is appropriate. A minority of donors regret knowing the fate of their organ; this should be considered when counselling potential donors.

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BOS27-LIVER MISCELLANEOUS II

BO302 3-D CT-GUIDED "CARVING" LIVER PARTITIONING TECHNIQUE FOR GRAFT HEPATECTOMY IN ADULT-TO-ADULT LIVE DONOR LIVER TRANSPLANTATION. A SINGLE CENTRE EXPERIENCE

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Background: Postoperative venous congestion of graft and remnant livers can lead to life-threatening complications in adult live donor liver transplantation (ALDLT). Evaluation of the safety and benefits of 3-D CT-guided donor hepatectomy "carving" partitioning technique.
Methods: Eighty-three consecutive ALDLT were performed based on data obtained from individualized pre-operative 3-D CT reconstructions and virtual graft hepatectomies.
Results: There were 71 right and 12 left grafts. Small grafts [graft volume body weight ratio (GVBWR) < 1.0] were used in 20 instances. We observed no significant differences in postoperative function between right and left grafts. Four recipients developed lethal small for size syndrome. Reversible small for size syndrome was observed in one right graft recipient and in two right graft donors.
Conclusions: Pre-operative 3-D CT virtual liver partitioning allowed for: (i) individualized carving technique based on specific donor anatomical characteristics, (ii) donor safety based on individualized venous outflow patterns, (iii) optimized drainage of the medial area of the graft based on the preferentially inclusion of the middle hepatic vein.

BO303 SAFETY AND FEASIBILITY OF AUTOLOGOUS BONE MARROW MONONUCLEAR CELL TRANSPLANTATION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS. PHASE I CLINICAL TRIAL

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Background: Cirrhosis represents the end stage of progressive hepatic fibrosis for the majority of chronic liver diseases. Most patients with cirrhosis die from one or more clinical complications including ascites, hepatic encephalopathy, and variceal hemorrhage. Liver transplantation is considered as the standard treatment for advanced decompensated liver cirrhosis. However, it has several limitations such as long waiting list, high cost, and several complications. Therefore, alternative methods such as cell therapy are necessary to increase patient survival on the liver transplant waiting list. Bone marrow is the most accessible and interesting since it contains different stem cells that can generate a variety of cell types found in other tissues.
Methods: This study was performed to determine the safety and tolerability of intrahepatic transplantation of autologous bone marrow mononuclear cells into 40 patients with liver advanced liver cirrhosis due to hepatitis C virus infection. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Central University Hospital, Tbilisi, Georgia. The bone marrow mononuclear cells were isolated and infused into liver via hepatic artery. At different time points after the transplantation, the liver function and prothrombin time (PT) were evaluated, and the survival rate and symptoms of the patients were recorded.
Results: No complications or specific side effects related to the procedure were observed; all patients showed improvements in serum albumin, bilirubin and ALT after 1 month from the cell infusion.
Conclusion: Our study has shown both the safety and feasibility of this type of liver cell therapy and may be a bridge to liver transplantation.

BO304 THROMBOPHILIA SCREENING IN LIVING LIVER DONORS

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In living donor liver transplantation (LDLT), venous thromboembolism (VTE) has appeared as a significant source of fatal events in donors. Among the inherited risk factors for VTE, factor V Leiden (FVL) and prothrombin G20210A (FII) mutations have the highest frequency. The aim of this study is to assess the results of thrombophilia screening in potential living liver donors and to evaluate the occurrence of VTE after donor hepatectomy. From June 2004 to July 2012, 405 LDLTs were performed at our institution, without donor mortality. Until we started routine thrombophilia screening in April 2010, 2/215 (0.9%) donors developed VTE (one pulmonary embolism (PE) and one portal vein thrombosis), both of whom were found with homozygous (HO) FII mutation. Between April 2010 and July 2012, all potential donors underwent thrombophilia screening. The rate of heterozygous (HE) and HO mutations for Factor V Leiden (FVL) and FII were 1.2% and 0.6%, and 4.5% and 0.5%, respectively. All potential donors with HO-FVL and HO-FII mutations were eliminated. A total of 19 donors with HE-FVL mutation and 6 donors with HE-FII mutation underwent donor hepatectomy. These donors were given low molecular weight heparin for VTE prophylaxis until they were discharged from the hospital. In a median follow-up of 17.0 (11.0–25.0) months, none of the donors with either FVL or FII mutations had VTE. In the routine thrombophilia screening period, 4/190 (2.1%) donors developed VTE (three PE and one deep vein thrombosis). Further hematologic work-up of these donors did not reveal any prothrombotic disorder. VTE is often a multifactorial disease, and acquired risk factors, such as hypercoagulability after partial hepatectomy may play a more important than inherited risk factors. However, carriers of FVL and FII mutations are at an increased risk for VTE. Since donor safety is an absolute prerequisite in LDLT, we recommend thrombophilia screening during evaluation of potential living liver donors.

BO305 IS "INTRA-OPERATORY ROOM" THROMBOELASTOMETRY USEFUL IN LIVER TRANSPLANTATION? A CASE–CONTROL STUDY IN 303 PATIENTS

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Background: Rotation thromboelastometry (TEM) and thromboelastography (TEG) are point-of-care devices that provide a comprehensive, real-time assessment of hemostasis from the start of clot formation to fibrinolysis. Does the use of an "intra operating-room" TEM (orTEM) and consequently minimization of blood products during OLT modifies the pattern of complications?
Methods/Materials: We evaluated 303 consecutive OLTs. Patient characteristics, details of surgery, intraoperioperative bleeding, transfusion requirements, complications and patient survival were prospectively analyzed.
Results: There is a statistically significant decrease in the number of blood products used in orTEM group; a lower rate of complications when used orTEM during OLT ($p < 0.05$); decrease in the incidence of postoperative renal failure, surgical complications and postoperative bleeding, hematopenias, graft primary dysfunction and re-OLT. Early mortality rate is lower when used orTEM. Greater number of viral infections (CMV) and ascites. We observed lower survival in transplanted patients group where not used orTEM for the group using orTEM.
Conclusion: orTEM is associated to: (i) a reduction in the use of blood products during OLT, (ii) reducing complications and postoperative renal failure and (iii) a better preservation of liver graft, with lower rates of dysfunction and reOLT It also identified two groups with greater benefit of orTEM: (i) Patients with MELD > 21. (ii) Polytransfused patients by significant intraoperative bleeding Figure 2: blood requirements in orTEM group and no-orTEM group (m = average; M = median).

BO306 CENTRAL VENOUS PRESSURE IS A POTENTIAL PREDICTOR OF PEAK PORTAL VEIN FLOW VELOCITY IN THE PATIENTS UNDERGOING LIVING DONOR LIVER TRANSPLANTATION

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Background: Despite the possibility of inadequate intraoperative tissue perfusion to various organs, particularly to the kidneys, lowering central venous pressure (CVP) was recommended in living donor liver transplantation (LDLT) because maintenance of high CVP during the neohepatic phase may

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impair hepatic venous outflow, potentially jeopardizing graft function. However, the value of this filling pressure has been questioned. Recently, stroke volume variation (SVV), one of the dynamic preload indices, has been advocated for fluid management in mechanically ventilated patients undergoing LDLT. The aim of this study was to investigate the correlation of preload indices (CVP, femoral vein pressure (FVP), and SVV) with flow velocities of the portal vein and hepatic artery in the recipients undergoing LDLT.
Methods/Materials: Twenty nine LDLT recipients were enrolled in this study. CVP, FVP, and SVV were recorded and flow velocities of the portal vein and hepatic artery were measured using intraoperative spectral Doppler ultrasonography immediately after hepatic artery anastomosis and bile duct reconstruction were completed. Correlations were studied by Pearson's correlation coefficient (r).
Results: A significant correlation was found between CVP and peak portal vein flow velocity ($r = -0.392$, $p = 0.036$, Figure), while there were no correlation of SVV with the flow velocities. Although FVP was well correlated with CVP ($r = 0.677$, $p < 0.001$), its significant correlation with peak portal vein flow velocity was not found.
Conclusion: CVP may be a potential predictor of the portal vein flow velocity of the hepatic allograft in the patients undergoing LDLT when compared to SVV and FVP. However, its correlation with the portal vein flow velocity is weak ($r = -0.392$). Therefore, further evaluation is warranted to determine its predictive value for portal vein flow velocity.
Reference: 1. Saner, F.H. et al. Transplantation 2008; 27: 1863–1866.

BO307 A PREOPERATIVE AMINO ACID FREE DIET PROTECTS AGAINST HEPATIC ISCHEMIA REPERFUSION INJURY

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Ischemia and reperfusion injury (IRI) is a serious complication after liver transplantation. We previously showed that 3 days of preoperative fasting protects against hepatic IRI. The protective effect was induced by the absence of protein, since a protein-free diet induced similar protection. To investigate whether total protein or single essential amino acids are responsible, we investigated the effects of a 3 day preoperative amino acid free diet on hepatic IRI. Male C57BL/6 mice were randomized into 4 groups ($n = 6$/group). Three days before the induction of hepatic IRI they received either a control, a leucin-free, methionine-free or tryptophan-free diet. Bodyweight was recorded during the dietary intervention and after surgery. Hepatic IRI was induced by clamping 70% of the liver for 75 min. Serum ALAT and LDH levels and the percentage of necrosis in liver tissue were used to assess damage. Control diet fed mice gained 3% in weight. A leucin-free diet led to a reduction of 6.2%, tryptophan-free of8.4% and methionine-free 9.5%. Postoperatively the control mice lost 10% of their weight, while the mice on the deficient diets lost 0.5%. Six hours after reperfusion ALAT and LDH levels were significant lower in the leucin- and tryptophan-free groups compared to the controls ($p < 0.05$), and 24 h after reperfusion liver enzymes were lower in the leucin-, methionine- and tryptophan-free groups ($p < 0.01$). Liver tissue 24 h after reperfusion showed significantly less necrosis in the methionine-free (33.3% ± SEM 6.2%) compared with the control group (77.5% ± SEM 10.8%; $p < 0.05$). The leucine-free (34.4% ± SEM 14.8%) and tryptophan-free (45.8% ± SEM 11.5%) diets showed a reduction that did not reach statistical significance. A preoperative amino acid free diet limits the damage caused by hepatic IRI similar to fasting and a protein-free diet. Compared to fasting an amino acid free diet reduce weight loss. Therefore an amino acid free diet is a promising strategy to apply in the clinical setting.

BO308 IMPACT OF ABDOMINAL DRAINAGES ON POSTOPERATIVE COMPLICATION RATES POST LIVER TRANSPLANTATION

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Background: Due to the extent of surgery, the impaired coagulation status and the number of anastomoses, drainages are routinely used during liver transplantation. Aim of this study was to compare different types of drainages with regard to abdominal complication rates.
Methods: Over a 7-year period, all consecutive full-size orthotopic liver transplantations (LTX) with primary closure of the abdomen were included in this retrospective analysis. Abdominal drainages groups were divided in closed-circuit silicone drainages (Robinson drain, group I), open-circuit silicone drainages (Easy flow drain, group II), or no drainage (group III). Data are reported as total number (%) or median (range). For all comparisons, a p-value < 0.05 was considered statistically significant.
Results: A total of 318 LTX (age 56.89 (0.30–75.21) years; BMI 24.68 (12.35–35.10) kg/m^2; MELD 14.5 (5–50)) were included. Of 280 patients (88.05%) with drain, 219 (68.87%) received a Robinson-drain (group I), 61 (19.18%) an Easyflow-drain (group II), and 37 patients (11.64%) were not drained (group III). For groups I, II, and III, overall infection rates were 57.99%, 77.05%, 72.97% ($p = 0.009$), abdominal infection rates 21.92%, 50.82%, 10.81% ($p = 0.0001$), yeast infection rates 22.37%, 36.07%, 16.22% ($p = 0.015$), abdominal bleeding rates 18.26%, 27.87%, 5.41% ($p = 0.033$), biliary complication rates 14.16%, 14.75%, 0% ($p = 0.355$) and arterial complication rates 5.93%, 8.20%, 2.70% ($p = 0.295$), respectively.
Conclusion: In this retrospective series, use of open-circuit drainages was associated with more abdominal complications, mainly due to intraabdominal infections, as compared to closed-circuit drainages. While patients with no drainage post LTX faired best, this might be attributable to a selection bias in this patient subgroup.

BO310 POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN A LIVER TRANSPLANT PATIENT

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Posterior reversible encephalopathy syndrome (PRES), mostly associated with tacrolimus (Tac) based neurotoxicity, occurs in 1% of solid organ transplantations. We report a 43-year-old man who underwent liver transplantation (LT) for liver cirrhosis. He was initially maintained on Tac, mycophenalate mofetil (MMF) and medrol. Six days after LT generalized seizures occurred. Tac was changed to cyclosporine (Cy) and antiepileptic treatment was started. Twelve days later, due to homonymous hemianopsy and repeated generalized seizures, the patient was intubated. Magnetic resonance imaging (MRI) revealed PRES-inducted brain lesions. Considering possible calcineurin inhibitors toxicity, Cy was switched to sirolimus. On the following day the patient was extubated, neurological deficit disappeared. Two months later, a follow-up MRI revealed resolved PRES-inducted brain lesions. Currently, 6 months after LT, the patient is maintained on sirolimus and MMF without neurological disturbances.

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BOS28-ISCHEMIA REPERFUSION INJURY IN EXPERIMENTAL KIDNEY TRANSPLANTATION

BO311 SHORT EXPOSURE TO THYROID HORMONE PROTECTS AGAINST RENAL ISCHEMIA-REPERFUSION INJURY

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Background: Preconditioning is a strategy to prevent ischemia-reperfusion (I/R) injury by causing a brief eposide of I/R injury or an increase in oxygen demand, thus resulting in protective actions in tissues and cells. 3,5,3-triiodothyronine (T3) was found to reduce cardiac or hepatic I/R injury in animal models when preconditioned 48 hours in advance. The purpose of this study was to evaluate the protective effects of T3 preconditioning on renal I/R injury with different intervals of time.
Methods: In male C57BL/6 mice, renal I/R injury was induced by temporary ligation of the bilateral renal pedicle for 45 min followed by a reperfusion period of 24 h. Preconditioning with T3 was performed 24 or 6 h before or at the time of I/R injury.
Results: From the histologic exam, tubular injury was significantly reduced in mice preconditioned with T3 6 h before I/R injury. The levels of proinflammatory cytokines in renal tissues were decreased with T3-preconditioning 6 hours before or at the time of I/R injury. The levels of glutathione (GSH) were definitely increased in all treatment groups. Expressions of neuronal NOS (nNOS) was significantly increased in all treatment groups, especially in mice preconditioned with T3 6 h before or at the time of I/R injury. However, inducible NOS (iNOS) and endothelial (eNOS) were significantly decreased when mice were preconditioned with T3 6 h before or at the time of I/R injury. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assay revealed a significant decrease in the number of apoptotic tubular epithelial cell in mice preconditioned at the time of I/R injury.
Conclusions: Preconditioning with T3 in a short interval of time before I/R injury had a significant protective effect on renal I/R injury. It may be an applicable therapeutic protocol for deceased donor kindey transplantation in clinical practice.

BO312 OXIDATIVE STRESS CANDIDATE BIOMARKERS OF WARM ISCHAEMIA IN A LARGE ANIMAL DCD MODEL

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Introduction: The use of donation after circulatory death (DCD) kidneys for transplantation is increasing. Subsequent delayed graft function is related to warm ischemia (WI) exposure. Potential molecular markers of renal WI are limited to small animal and *in vitro* reports. The identification of a biomarker of WI may enable graft viability assessment or therapeutic development. Gene microarray and two-dimensional gel electrophoresis (2-DE) were used to identify potential candidate biomarkers of WI in a large animal DCD model.
Methods: Six large white pigs were terminated, with open renal biopsies taken at 30 min intervals up to 180 min of WI. Total RNA was copied and hybridised to one colour 44 k microarray slides. Gene expression analysis was performed using Genespring v9.0. Protein extracts were subjected to 2-DE using differential in-gel electrophoresis technology (DIGE). Resulting protein maps were analysed with Progenesis SameSpots and differentially expressed proteins ($p < 0.05$, ANOVA) were excised for identification via tandem mass spectrometry.
Results: Seven hundred and eighty-four genes were differentially expressed ($p < 0.01$, ANOVA), pathways analysis revealed regulation of cell death, cytoskeletal protein binding and cellular stress response to be common. In particular CCL5, HSP-70, PCD-1 and TUB2A was increased (>2-fold change) at all time points versus controls. Forty uniquely identifiable protein spots were differentially expressed across all time points versus controls. Differential increased expression of PRX-4, -6 and HSP-70 in particular was found (>2-fold change) throughout the time points ($p < 0.05$, ANOVA).
Conclusions: Several apoptotic upstream markers of WI were identified using microarray with oxidative stress biomarkers revealed in down stream proteomics. The CCL5 gene is an inducer of integrins and metalloproteinase regulator. The exhibited expression during ischaemia is novel. HSP-70 has been associated with vascular endothelial growth factor (VEGF) in aortic cell lines. Our study demonstrated significant expression at both the mRNA and protein level. Previously HSP-70 has shown gene upregulation in murine WI liver studies and *in vitro* cell lines only. This is the first large animal model to confirm this.

BO313 EFFECTS OF HYDROGEN SULPHIDE ON CYCLOSPORIN (CSA) INDUCED NEPHROTOXICITY AT REPERFUSION

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Introduction: The shortage of kidneys for transplantation has led to the use of donation after circulatory death donors. These grafts are more susceptible to reperfusion injury and have higher rates of delayed graft function. Hydrogen sulphide (H2S) is an anti-inflamatory gasotransmitter which may reverse the nephrotoxic side effects of the commonly used immunosuppressant cyclosporine (CsA) whilst preserving its potential benefits during reperfusion. The aim of this study was to assess the effects of CsA and H2S on early reperfusion injury.
Materials and Methods: Porcine kidneys underwent 15 min warm ischaemia and 16 h cold storage. They were reperfused with an oxygenated autologous blood preparation on an *ex-vivo* normothermic perfusion apparatus.

Renal haemodynamics, function and injury were assessed in groups of kidneys exposed to CsA (levels 186 ± 27 ng/ml) ($n = 6$), CsA + H2S (delivered from 20 mg Na2S (aq) infused over 40 min) ($n = 4$). This was compared to a control group (C) ($n = 6$).
Results: CsA caused a decrease in renal blood flow, H2S partially reversed this.

Area under the curve (AUC) renal blood flow (RBF); C 680 ± 182, CsA 298 ± 62, CsA & H2S 407 ± 106 ml/min/100 g.h; p = 0.001).

CsA decreased urinary IL-1β. CsA & H2S decreased it further.

Control 100 ± 56, CsA 45 ± 34, CsA & H2S 27 ± 15.1 pg/ml; p = 0.04.

Creatinine clearance (CrCL) was reduced in the CsA group compared to C, but not significantly (p = 0.1). H2S did not improve renal function (AUC CrCl; C 6.1 ± 3.8, CsA 3.1 ± 1.5, CsA+ H2S 3.9 ± 0.7 ml/min/100 g.h; p = 0.151).

Levels of endothelin-1 (ET-1) were similar in all groups (ET-1; C 37 ± 8, CsA 32 ± 13, CsA + H2S 34 ± 14 pg/ml; p = 0.76).

Conclusions: The co-administration of H2S with CsA during reperfusion may gain the benefits of early immunosuppression without vasoconstrictive side effects usually associated with this drug. There is also evidence for a synergistic suppression of IL-1β.

BO314 MNTMPYP, A SELECTIVE SUPEROXIDE DISMUTASE MIMETIC, REDUCES OXIDATIVE STRESS IN BRAIN DEAD DONORS

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Renal allografts retrieved from brain dead donors show inferior transplant outcomes compared to living donor grafts. Brain death (BD) leads to immunological activation and hemodynamic instability. Reactive oxygen species (ROS) are implicated in BD-induced organ damage. This study investigated whether pre-treatment with the free radical scavenger MnTMPyP reduces inflammation and renal injury in brain-dead organ donors. BD was induced in male F344 rats (275–300 g, $n = 7$) by inflating a subdurally placed balloon catheter. Rats were treated with saline or MnTMPyP (5 mg/kg) 1 h before brain death. After 4 h of BD, serum and kidneys were collected. Sham-operated rats treated with saline or MnTMPyP served as controls. Malondialdehyde (MDA) levels, indicative for oxidative stress, were measured with the thiobarbituric acid (TBA) assay. Tissue gene expression was measured by Real Time qPCR. Tissue protein expression was detected by immunohistochemical analyses. Pre-treatment of brain-dead donor organs with MnTMPyP significantly reduced serum MDA levels and renal expression of the stress protein HO-1. Interestingly, renal mRNA levels of HO-1 were increased. Furthermore, renal mRNA levels of TNF-α and E-selectin were decreased but not significantly. This study shows that treatment of brain-dead donors with MnTMPyP is effective in reducing systemic oxidative stress.

BO315 HYPERBARIC OXYGENATION OF UW SOLUTION POSITIVELY IMPACTS ON THE ENERGY STATE OF PORCINE PANCREATIC TISSUE

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Introduction: Pancreatic islet transplantation is a promising option for the treatment of diabetic patients; xenotransplantation of porcine islet cells would be a possibility to overcome the shortage of donor organs. Usually the donor pancreas is preserved with University of Wisconsin (UW) solution. A large

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number of reports have shown that the two-layer method (TLM), which employs oxygenated perfluorochemical and UW solution, is superior to simple cold storage. However, the extensive use of TLM is cost intensive and there is evidence that TLM only oxygenates small parts of the organ preserved. Another possibility to increase the oxygen supply during organ preservation would be the use of hyperbaric oxygenation (HBO) which enables to increase the oxygen tension in fluids. Therefore the aim of this study was to evaluate the effect of pre-oxygenation of different preservation solutions on organ quality in terms of high energy phosphate levels as well as the occurrence of apoptosis and the induction of heat shock proteins and nitrosative stress induced cell death in porcine pancreatic tissue.
Methods: Porcine pancreatic tissue was preserved in different preservation solutions with or without pre-oxygenation for 6 h of cold ischemic time (CIT). Then, tissue specimen were harvested and high energy phosphate levels were determined. Moreover, immunohistochemistry was performed in order to detect occurrence of apoptosis, heat shock protein 70 (HSP70) as well as nitrosative stress induced cell death.
Results: Organs stored in pre-oxygenated UW solution showed best results in terms of high energy phosphate levels; apoptotic cells per islet as well as HSP70 positivity were significantly less when compared to simple UW storage and all other organ preservation solution with or without pre-oxygenation.
Conclusion: Pre-oxygenation of UW solution is a simple and promising method to improve islet cell quality after cold organ storage.

BO316 NORMOTHERMIC PERFUSION OF DISCARDED HUMAN PANCREASES

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Background: Pancreas transplantation (solid organ or islets) is the most effective treatment for patients with progressive complications of diabetes, or patients with labile blood sugar control and hypoglycaemia unawareness. Increasing demand for transplants requires the use of more marginal donor organs, including those from DCD donors. However, the deleterious effects of cold ischaemia affect the viability of the organ and are exacerbated by prior injury. Currently there is no validated means to test the viability of the organ before transplantation. There is accumulating evidence of the benefits of a more physiological approach using continuous perfusion of an oxygenated, blood-based perfusate at normal body temperature. We describe here the feasibility of normothermic *ex-vivo* perfusion of human pancreases.
Methods: Human pancreases that were turned down by all transplant units have been utilised. A cardiopulmonary circuit consisting of oxygenator, heat exchanger, centrifugal pump, reservoir, flow probes and gate clamp is primed with time-expired packed red cells and the temperature maintained at 380C. The arterial inflow of the pancreas is cannulated and venous outflow collected and recirculated. Effluent from the duodenal segment is collected and measured.
Results: Using this circuit, it is possible to achieve stable normal arterial pressures and flows. During preservation, physiological flows and pressures are maintained in the splenic artery and the superior mesenteric artery by controlling the pump head speed and adjusting the proportional pinch valve on the bypass circuit. Discussion: This is the first demonstration of successful normothermic perfusion of the human pancreas. This has the potential to increase the viability, assessment and safety of donor organs in this expanding field.

BO317 DIETARY RESTRICTION AND FASTING PROTECTS AGAINST RENAL ISCHEMIA-REPERFUSION INJURY VIA MBL-PATHWAY

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Introduction: Ischemia-reperfusion injury (IRI) remains an important problem in transplantation. We recently showed that Mannan-binding lectin (MBL), the initiator of the lectin pathway of complement activation, plays a pivotal role. Preoperative dietary restriction (DR) offers robust protection against renal IRI in mice. However, the mechanism remains to be elucidated. Therefore, we investigated the impact of DR on MBL and the role of MBL in the protective mechanism of DR.
Materials and Methods: Male C57Bl/6 mice were fed ad libitum (AL) or underwent 72 h fasting (FA) or 2 weeks 30% DR (n = 8/group). *In vitro* mRNA, protein and functional activity of MBL-A and -C were measured. *In vivo*, IRI was induced by 37 min. of bilateral clamping of the renal pedicles in all three groups. After clamping, some groups of mice were reconstituted via intra-peritoneal injection of 100 μg/ml of human MBL and were observed for a period of 7 days.
Results: The mRNA studies showed a significant downregulation in the liver MBL expression in both DR and FA ($p \leq 0.004$) groups. In line with this, both MBL-A and MBL-C concentrations were significantly lower ($p \leq 0.001$) after DR (MBL-A = 15.4 μg/ml; MBL-C = 89.4 μg/ml) and FA (MBL-A = 12.4 μg/ml; MBL-C = 49.5 μg/ml) compared to respectively 19.9 μg/ml (MBL-A) and 109.6 μg/ml (MBL-C) in the AL group. We found that reconstitution of hMBL breaks the protection against IRI in the DR group. However, the protection in FA group was not affected suggesting that in this group the MBL level did not come back to normal, since the most prominent downregulation of MBL was observed in this group.
Conclusion: Dietary interventions downregulate the expression and presence of MBL. Reconstitution of the purified hMBL back to the IRI induced mice breaks this protection and strongly suggests that downregulation via the lectin pathway may be one of the mechanisms by which dietary interventions protect against renal IRI.

BO318 PROTECTIVE EFFECTS OF TETRAHYDROBIOPTERIN IN ISCHEMIA REPERFUSION INJURY DO NOT DEPEND ON DIMERISATION STATUS OF ENOS

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Introduction: The essential co-factor of endothelial nitric oxide synthase (eNOS) tetrahydrobiopterin (BH4) has been repeatedly shown to protect transplanted organs from ischemia reperfusion injury (IRI). So far, the underlying mechanism has not been described. One hypothesis is that BH4 treatment prevents disruption of the functional nitric oxide producing form of eNOS, the so-called "uncoupling" and its related superoxide production, by sustaining the dimeric status of the enzyme. Herein we tested this hypothesis in a murine transplantation model.
Material/Methods: Hearts were transplanted from C57BL/6 donors into C57BL/6 recipients. Transplanted hearts were subjected to 10 h cold ischemia before reperfusion. Donor mice were either treated with 50 mg/kg b.w. BH4, administered i.m. before organ retrieval, or were untreated. Graft performance was measured according to a well-established functioning score. Ten minutes following reperfusion, grafts were removed for further analysis. Intragraft BH4 was measured by means of HPLC. eNOS dimerisation was analysed by western blot and NOS-related superoxide production was quantified by DHE (dihydroethidium) assay.
Results: Untreated donor hearts recovered worse. Already 10 min following reperfusion the heart performance of these donor mice was significantly lower compared to treated donor hearts ($p = 0.02$), and this finding correlated directly with intragraft tetrahydrobiopterin levels, which were clearly lower than in hearts from pretreated donor mice. Interestingly, at that time point of reperfusion the eNOS dimerisation rate did not show any difference between the two groups. Similarly, DHE analyses as well did not reveal increased eNOS-derived superoxide production.
Conclusion: Protective effects of BH4 in IRI do not depend on the prevention of eNOS dimer dissociation. DHE analyses at different reperfusion time points will be necessary to clearly define the role of eNOS as superoxide producer early after organ reperfusion.

BO319 PROTECTIVE EFFECTS OF BILIVERDIN ON RENAL ISCHEMIA REPERFUSION INJURY

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Background: Ischemia-reperfusion injury (IRI) represents an unresolved issue in renal transplantation. Recent findings indicate that the application of bile pigments can exert beneficial effects. However, little is known about a potentially protective role of the bile pigment biliverdin (Bv).
Methods: In a rat model of IRI, male Lewis rats weighing 250–270 g underwent unilateral renal artery clamping for 90 min followed by reperfusion. Animals in the treatment group received three injections of 10 mg/kg biliverdin 15 min before ischemia, 15 min before reperfusion, and 10 min after reperfusion. The control group was treated analogously, receiving three injections of saline. Renal function parameters were analyzed at baseline, and 20 min, 24 and 48 h after reperfusion.
Results: Whereas no differences could be observed immediately after reperfusion (20 min), administration of Bv significantly reduced IRI-related renal function impairment after 24 and 48 h. After 24 h serum creatinine (mg/dl) in the Bv group measured: 2.17 ± 0.3 vs. control: 2.87 ± 0.2 ($p = 0.001$); and after 48 h: 2.86 ± 0.5 vs. 4.18 ± 0.8 ($p = 0.008$). Likewise, after 24 h urea levels (mg/dl) in the Bv-group measured 230.7 ± 20.9 vs. 293 ± 21.6 ($p = 0.001$), and after 48 h: 293.2 ± 72.1 vs. 485.4 ± 76.4 ($p = 0.004$). Serum levels of the Bv degradation product bilirubin peaked at 20 min after

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clamping (2.5 ± 1.7 mg/dl vs. control 0.1 mg/dl) and normalized to baseline levels after 24 and 48 h (0.1 mg/dl; n.s.).
Conclusion: Exogenous biliverdin can drastically alleviate renal IRI and accomplishes significantly improved kidney function after reperfusion. Furthermore, the combination of good bioavailability and cost effectiveness could qualify this endogenous substance as a possible candidate for human application in future clinical trials.

BO320 TRANSGENIC MICE WITH HIGH ENDOGENOUS OMEGA-3 FATTY ACID ARE PROTECTED FROM ISCHEMIA-REPERFUSION-INDUCED ACUTE KIDNEY INJURY

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Background: Acute kidney injury (AKI) is common clinical event and has high mortality rate despite advanced curative strategies. Several studies found that omega-3 polyunsaturated fatty acid (PUFA) diet reduces kidney dysfunction followed by ischemic injury. However oral appliance of omega-3 PUFA, in fact, can cause much variability arisen from diet procedure. *fat-1* transgenic mouse produce abundant omega-3 PUFA, result in balanced omega-6: omega-3 ratio than wild type mouse. The purpose of this study, therefore, is to see whether omega-3 PUFA has advantages in AKI caused by ischemic injury using *fat-1* transgenic mice.
Methods/Materials: Bilateral kidneys were subjected to 30 min of ischemia, renal ischemia-reperfusion injury (IRI) was performed. Animals (fat-1 mice and C57BL/6 mice) are sacrificed 24 and 72 h of reperfusion. The effects of omega-3 PUFA on renal IRI were evaluated in terms of renal function, tubular necrosis, inflammatory cell infiltration. After that, renal function and severity of renal injury were estimated.
Result: fat-1 mice could reduce to increased BUN, serum creatinine and tissue Kim-1 levels (Figure), and reduce neutrophil infiltration in body after IRI, compared with Wild Type mice.
Conclusions: Long-term and high dose of omega-3 supplement can protect renal function and facilitate renal recovery following IRI.

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BOS29-HEART

BO321 EUROTRANSPLANT DONOR SCORE APPLIED IN AN ITALIAN REGIONAL SETTING: VALIDATION, TIME COURSE AND INTERACTION WITH RECIPIENTS FEATURES

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Background: Increasingly fewer hearts have been retrieved from European organ donors in the latest years, likely driven by increasing population age and changes in the epidemiology of brain deaths. In the effort to improve donor quality assessment, allocation policies, and heart acceptance rate we calculated Eurotransplant donor score (EDS) to the heart offers reported to Emilia-Romagna (Italy) organ procurement agency (ER-AIRT) during a 14 years period, and analyzed the interplay between EDS and recipient features on post-transplant outcome.
Methods: EDS takes into account up to 12 donor variables, including medical history and clinical course during organ procurement procedures. We calculated EDS in all the adult heart offers reported from 1999 and 2012 to ER-AIRT, and related it to discard probability and post-transplant survival.
Results: Among the 1544 heart offers, 639 (41%) were accepted. High EDS was associated with discarded donors (19.4 ± 5.6 vs. 16.5 ± 2.4; $p < 0.01$), with 17 as most accurate cutoff to identify discarded organs. In the recent era (2006–12) EDS was significantly higher than the previous 7 years ($p = 0.01$), with difference mainly driven by older age and higher inotrope doses. Similarly, EDS in recently accepted organs was slightly higher than the 1999–2005 period ($p = 0.05$). Four hundred and seven of the accepted organs were transplanted in our center. EDS $\geq$ 17 identified a 60% independent increase in risk of death, even after conditioning the analysis to recipients surviving the post-operative period. Subgroup analysis revealed that high EDS worsened the outcome in recipients with high, but with normal, pulmonary resistances (Figure).
Conclusions: While validating EDS in ER-AIRT context, this study highlights the worsening features of available heart donors in recent era. EDS predicts post-transplant survival, and appears to interact with specific recipient features. EDS may provide guidance for organ acceptance and may guide allocation strategies improving donor-recipient matching.
Reference: 1. Smits JM et al. J Heart Lung Transplant 2012; 31: 387–97.

BO322 SURGERY OF THE ATRIOVENTRICULAR VALVES AFTER ORTHOTOPIC HEART TRANSPLANTATION

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Background: Improved long-term outcome after orthotopic heart transplantation (HTx) leads to a growing number of valvular diseases late after HTx. Tricuspid regurgitation is the most frequent valvular heart disease after HTx. Nevertheless, there is a small group of patients who develop post-transplant mitral valve disease. We report on nonretransplant surgical results of both groups.
Methods: Nine patients (eight male/one female) presented with massive tricuspid regurgitation (mean interval between HTx and valve surgery 4.8 years), five patients (four male/one female) developed severe mitral valve insufficiency after HTx (mean interval between HTx and valve surgery 5.5 years). Among these 14 patients seven patients underwent valve replacement (TKR $n = 4$; MKR $n = 3$). Five patients had tricuspid valve repair, two patients underwent mitral valve repair, one of these via minimally invasive approach.
Results: The mean ICU stay was 2.5 days. Two patients who initially had mitral valve repair were readmitted because of recurrent mitral insufficiency for mitral valve replacement. All patients undergoing mitral valve surgery are long-term survivors. Out of the tricuspid valve surgery patients one died in the long-term follow-up because of malignancy.
Conclusions: According to our results surgery of atrioventricular valves after HTx is a safe and effective therapeutic approach with good long-term results. Long-term immunosuppression may possibly influence the results after mitral valve repair. Minimally invasive approach may reduce the surgical trauma in this special patient group.

BO324 IMPACT OF DONOR AND RECIPIENT PARAMETERS ON THE OUTCOME OF HEART TRANSPLANTATION IN GERMANY

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Background: Due to organ shortage in heart-transplantation (HT) grafts were used from donors with substantial risk factors increasingly. However, it is discussed controversially which donor characteristics may be detrimental for the outcome of HT. Therefore, we evaluated the combined impact of recipient and donor related factors in HT on patient survival by multivariate analyses in a nationwide multicenter study.
Methods: A database was created from data on hearts donated and transplanted in Germany between 2006 and 2008 as provided by Deutsche Stiftung Organtransplantation and the BQS-Institute. Multivariate Cox regression was conducted ($n = 774$, recipient age $\geq$18 years, significance level 5%, risk ratio [95% CI]).
Results: Patient survival was significantly decreased by donor-age (1.026 [1.014–1.039] per year), Troponin >0.1 ng/ml (2.006 [1.426–2.823]), ischemia time (1.188 [1.033–1.366] per hour), recipient-age (1.017 [1.003–1.032] per year) and in recipients with pulmonary resistance $\geq$320 dyn s/cm^5 (1.723 [1.090–2.723]) or with complex previous heart surgery (1.750 [1.260–2.430]). Also, Calicneurin and leucocyte proliferation inhibitors at hospital discharge were of significant impact (0.377 [0.250–0.569] and 0.444 [0.325–0.607]). Hypotensive periods or catecholamine administration in donors were without significant influence.
Conclusion: After proper donor selection survival after HT was limited by increasing donor- and recipient age, increasing ischemia times and other recipient related problems (e.g. pulmonary hypertension, previous complex heart surgery).

BO325 EARLY VERSUS DELAYED EVEROLIMUS INTRODUCTION IN HEART TRANSPLANTATION: ANALYSIS OF SAFETY ON THE FIRST 100 PATIENTS OF THE EVERHEART STUDY

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Background: EVERHEART study is a clinical trial designed to compare early versus delayed everolimus (EVE) introduction after heart transplantation (HT). A descriptive interim analysis has been performed to assess safety of early EVE administration.
Methods: One hundred pts have been randomized to receive EVE immediately after HT (i-EVE: 49 pts) or after 4–6 weeks (d-EVE: 51 pts). Trial primary composite end-point is 6-months cumulative incidence of wound healing complications, pleural/pericardial effusions and acute renal insufficiency (ARI: eGFR $\leq$ 30 ml/min). Secondary end-points are: incidence of acute rejection (BPAR), rejection with hemodynamic compromise, graft loss and death.
Results: Rate of occurrence of the composite end-point was i-EVE: 61.2%, d-EVE: 58.8%. Comparison of wound healing complications, pericardial effusion, ARI was similar in the two groups despite occurrence of pleural effusions was higher in the d-EVE (31.4% vs. 16.3%). One patient in each arm died. BPAR episodes were slightly more frequent in the d-EVE (28.6% vs. 33.3%) but rejection with hemodynamic compromise was higher in the i-EVE (8.2% vs. 3.9%).
Conclusion: Although final data of the study are required, both strategies appear safe and effective in heart transplantation.

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BO326 PRIMARY GRAFT DYSFUNCTION VERSUS PRIMARY GRAFT FAILURE: ARE ALL GRAFT PROBLEMS CREATED EQUAL?

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Background: Primary graft dysfunction (PGD) and failure (PGF) are severe complications after heart transplantation. Until now there are no common guidelines to differentiate between these complications. In this single center analysis, the impact of both PGD and PGF on outcome after transplantation was analyzed.
Methods: We investigated 1238 patients after heart transplantation between 1984 and 2011. PGD was defined as high inotropic support to wean a patient from bypass after transplantation. PGF was defined as need for mechanical support. Incidence, outcome and causes of death in both groups were compared during different time periods (A: 1984–1999, B: 2000–2011). Survival was compared by Kaplan–Meier analysis. A p-value of <0.05 was defined as significant.
Results: Overall incidence of primary Graft problems was 15.4%. 116 patients developed PGD (9.3%) and 76 patients showed PGF (6.1%). Incidence of PGD and PGF changed significantly over time (PGD: A: 10%, B: 8.4%, $p < 0.001$; PGF: A: 3.6%, B: 9.1%; $p < 0.001$). Thirty day as well a 1-year survival was higher in the PGD group (30 days: PGD: 65% vs. PGF: 51.4%: $p = 0.091$; 1-year: PGD: 58.3% vs. PGF: 34.7%: $p = 0.004$). Thirty-day survival with PGD did not change over time (A: 61.5%, B: 75.9%, p = n.s.), whereas it increased significantly in the PGF group (A: 23.8%, B: 62.7%, $p < 0.001$). 1-year survival increased in both groups (PGD: A: 53.8%, B: 72.4%; p = 0075; PGF: A: 23.8%, B: 39.2%, $p = 0.015$).
Conclusions: Survival of patients with PGD and PGF is significantly reduced. In recent time eras survival has increased. International guidelines for prevention and treatment of these complications are needed.

BO327 IMPACT OF EXTRACORPORAL PHOTOPHERESIS IN HEART TRANSPLANTAT PATIENTS WITH DIFFERENT IMMUNE STATUS

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Objective: Immunmodulatory effects of extracorporal photopheresis (ECP) after organ transplantation are known. However, the response of ECP on heart transplant patients (HTx pts) with different immune status is still missing. Thus, in this study we measured regulatory CD4+ T cells (Tregs) and dendritic cells (DCs) in HTx pts treated with ECP for prophylaxis of rejection (PRX), to treat acute rejection (AR) or to treat chronic rejection (CR).
Methods: HTx pts were treated monthly three times with ECP: PRX-group ($n = 5$) at month 4 after HTx; AR-group ($n = 7$) at time of biopsy proven rejection (ISHLT 2004) and two times thereafter; CR-group ($n = 4$) monthly at time of angiographic proven diagnosis of allograft vasculopathy at two times afterwards. Peripheral blood was analyzed each time before ECP therapy to assess Tregs and myeloid (m) and plasmocytoid (p) DCs by FACS. Blood samples before ECP treatment and 1 month after the last ECP therapy were compared (%±SD).
Results: In the PRX-group pDC levels decreased from 28 ± 25.4% to 15.2 ± 9.2% (p = 0.10), while mDC levels increased from 58.7 ± 26.0% to 68.7 ± 12.2%, respectively (p = 0.23). Whereas Tregs slightly increased from 6.3 ± 3.5% to 7.2 ± 2.6% (p = 0.46). HTx pts of the AR-group showed an increase of both mDCs and pDCs 56.6 ± 21.1% to 68.5 ± 10.4% and 4.2 ± 3.9% to 14.2 ± 5.7%, respectively (p = 0.05). Tregs did not changed before and after ECP (6.8 ± 4.25% to 6.2 ± 2.0%). In contrast was the Tregs expression in the CR-group with 4.8 ± 0.8% prior to ECP and 7.3 ± 3.7% after ECP ($p < 0.05$). mDC levels in the CR-group rose from 63.2 ± 12.7% to 73.7 ± 7.7% (p = 0.48), whereas pDC levels declined from 24.0 ± 8.8% to 13.3 ± 9.7% (p = 0.33).
Conclusion: In our study we showed that ECP therapy had different effects on Tregs and DCs in HTx pts with different immune status. Further studies in larger cohorts are needed to identify the optimal time point and duration of ECP therapy depending on the indication after HTx.

BO328 EVEROLIMUS IN LATE IMMUNOSUPPRESSION AFTER HEART TRANSPLANTATION: IN SEARCH OF THE RIGHT PROTOCOL FOR THE RIGHT PATIENT

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Background: Everolimus is a potent novel immunosuppressor with a powerful antiproliferative effect and an intriguing mechanism of action. Its antiproliferative effect has been advocated as an unique therapeutic tool in the treatment and prevention of Cardiac Allograft Vasculopathy, in prevent neoplasms and PTLD and as a strategy to minimize CNI exposure and the related renal toxicity. Aim of the study is to describe the effect of the introduction of the Eve on the results of the management of the most common complications of heart transplantation.
Methods/Matherials: Since 2005, Eve has been introduced in the immunosuppressive therapy as maintenance therapy in 71 patients. Both the timing and clinical indications have been registered. The switch to eve was in 30.9% for CAV, in 18.6% for CRF, and in 22.5% for neoplastic disorders (PTLD or solid). CNI Minimization was the most frequent regimen; a CNI-free regimen was maintained in eight patients (11.6%). Incidence of dyalisis was 8.45% with an actuarial freedom of 80.6% at 3 years. GFR after the switch did not ameliorate as expected but in the early experience proteinuria was never assessed and the switch was probably performed too late (mean GFR at the switch of patients undergoing dialysis 22.77 ± 11.9). No patients experienced Acute Cellular Rejection nor Humoral rejection despite the low level of Cyclosporine (CSA-TL). A significantly more aggressive reduction of CSA TL was disclosed in the patients with a stable or ameliorating renal function when compared with the patients experiencing a reduction of GFR after 1 year of treatment (50% of Pts). In the long-term Eve warrant an excellent protection from both late and acute rejection, alone or in combination with CNI or MMF. In consideration of the low incidence of allograft dysfunction or rejection and of the better renal protection achieved when CSA TL is aggressively reduced more efforts have to be done in the long term therapy to reduce the TL of cyclosporin.

BO329 PREDICTING CARDIOVASCULAR OUTCOMES LONG-TERM AFTER HEART TRANSPLANT BY LATE CHANGES IN MAXIMAL INTIMAL THICKNESS: BEYOND THE HYSTORICAL 1-YEAR LIMIT

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Background: Intravascular ultrasound (IVUS) provides prognostic information on allograft vasculopathy progression by detecting increase in maximal intimal thickness (MIT) during the first post-heart transplant (HT) year. Later changes in coronary morphology, their prognostic relevance, and risk factors are unexplored.
Methods: We investigated whether changes in coronary morphology assessed in patients receiving serial IVUS at 1 and 5 years after HT predicted fatal and non-fatal cardiovascular (CV) events. We additionally analyzed the impact of metabolic risk factors on changes in IVUS measurements.
Results: One hundred and nineteen consecutive patients receiving HT between 1999 and 2007 entered the study. During the 11 years of follow-up, incidence of CV death was 13 + 5% and of a combined endpoint of CV events and CV death 27 + 6%. Between year 1 and 5, MIT and intimal volume increased, lumen volume decreased ($p < 0.001$ for all), while vessel volume was unchanged. By Cox's model, MIT increase predicted both CV death (RR = 4.2 [1.2–12.1] per mm, p = 0.02) and combined endpoint (RR = 2.4 [1.0–5.0] per mm; p = 0.05). By ROC curves, we found that a MIT change cut-off of 0.35 mm best identified patients at risk for CV death and events (Figure). Among metabolic risk factors, HDL-cholesterol predicted CV death (p = 0.01), diabetes CV events (p = 0.04). Increasing triglycerides predicted MIT increase >0.35 mm (p = 0.01), and plaque volume increase ($p < 0.05$).
Conclusions: This study provides the first suggestive evidence that MIT increase represents a relevant prognostic marker also after the first year after HT. In addition, the finding that clinically relevant MIT is predicted by lipid pattern typical of insulin resistance, provide a strong rationale supporting aggressive therapeutic interventions against metabolic abnormalities mid and long-term after HT.

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BOS30-IMMUNOBIOLOGY/BASIC SCIENCE

BO331 VIRAL INFECTION TITRES ARE PROPORTIONAL TO ACTIVATED NKT CELLS IN BALS FOLLOWING LUNG TRANSPLANTATION

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Introduction: Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) are common infections associated with significant morbidity and financial burden following lung transplantation. NKT cells represent a major component of the anti-viral response. However, the association between viral titres and NKT cells remains unknown. In this study, we aimed to determine the relationship between viral titres and NKT cell numbers in bronchoalveolar lavage from a cohort of lung transplant recipients.
Methods: Thirty-nine BALs and clinical data were collected from lung transplant patients during routine clinic visits. Samples were washed and mucus plug dissolved. Resuspended cell pellets were analysed by flow cytometry. NKT cells were quantified using fluorescent-labelled antibodies: CD3, CD16 and CD56. Phenotypes were characterised using markers of activation (CD107a, CD161 and NKG2D) and tolerance (CD200 and CD200R). The relationship between NKT cells and viral infection titres was determined via partial correlation co-efficient analysis to control for time. p-values < 0.05 were considered to be statistically significant.
Results: A significant, positive correlation was found between titres of CMV and activated (CD161+) NKT cell numbers ($p = 0.019$, $R = 0.385$), as well as tolerising (CD200R+) NKT cell numbers ($p = 0.035$, $R = 0.401$). Also, a significant, positive correlation between activated NKT cells (CD107a+, $p = 0.049$, $R = 0.326$), (CD161+, $p = 0.032$, $R = 0.354$) and EBV titres was observed.
Conclusions: NKT cells migrate to the alveolus of the lung during CMV and EBV infection following lung transplantation. Interestingly, CMV infection elicits the migration of both inflammatory and tolerogenic NKT cells, whereas EBV infection was only associated with inflammatory NKT cell migration.

BO332 THE CHANGE IN THE GLYCOSYLATION OF HUMAN MONOCYTES IN IMMUNOSUPPRESSIVE ENVIRONMENT

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Cell and organ transplantation has become a mainstay of therapy for end-stage organ failure. Recipients of the organs require lifelong immunosuppression therapy. The global effect of immunosuppressive drugs on the immune system predisposes a patient to the development of infection and cancer and may have a deleterious long-term effect on graft function. An effect of immunosuppressive drugs, crucial for the successful transplantation of organs, on glycosylation of immune cells is not known.

Glycans decorate the surfaces of all of the key molecules involved in the innate and adaptive immune response. The proper functioning of immune cells in response to alloantygeny, depends on the process of glycosylation of receptor proteins. The aim of this study was to determine the effect of mTOR inhibitor (rapamycin, RAPA) and calcineurin inhibitors (cyclosporin A, CsA and tacrolimus, Tac), used singly and in two-drug combinations, on the glycosylation of mononuclear human cells (MNCs). MNCs were induced in two-way mixed leucocytes reaction (MLR) in the environment of different regimens of immunosuppression. The surface glycosylation of CD14+ cells was identified by flow cytometry using lectins which selectively recognite specific carbohydrate structures. We observed changes in glycosylation of the analysed cells in the presence of mTOR and/or calcineurin inhibitors. Moreover, the environment of two-drug combinations influenced the glycosylation of MLR immune cells. The immunosuppressive drugs decreased the amount of PHAL- and VVL-positive cells, but the lowest percentage of staining cell it was observed in case of CsA and Tac treated cells. The calcineurin inhibitors reduced of PNA-, UEA- and GNA-positive glycans, while mTOR inhibitor enhanced glycans recognized by UEA lectin. Changes in the glycosylation profile of T cell receptor may influence the induction of response against the transplant.

BO333 HISTONE DEACETYLASE 6 INHIBITION REVEALS A POTENT IMMUNOSUPPRESSANT EFFECT IN AN *IN VITRO* MODEL OF TRANSPLANTATION

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Background: Current renal transplant immunosuppression regimens have numerous limitations. Recent evidence suggests Histone Deacetylase Inhibitors (HDACis) may represent a class of immunosuppressant drug with potential application toward transplantation. This study compares Cyclosporine (CyA) and the non-selective HDACi suberoylanilide hydroxamic acid (SAHA) with a novel HDAC6-specific inhibitor – KAR3000 in *in vitro* models of alloreactivity.
Methods: Proliferation and MLR-based assays using PBMC's from healthy volunteers were used to assess the immunosuppressive effect of compounds. Proliferation was assessed by labelling responders cells with CFSE and alloreactivity was measured using IFN-γ release.
Results: KAR3000 displayed a potent inhibitory effect on the proliferation of PBMC's superior to CyA and SAHA. In one-way MLR-assays, HDAC inhibition compounds displayed the most potent inhibitory effect. KAR3000 inhibited division of 32.5% of parent population, compared to 14.77% in an untreated control. In a two-way assay IFN-γ release was reduced by 82% and 91% (SAHA and KAR3000 respectively at 1 μM concentration) – see figure. Dose response curves reveal IC50 of 567, 13 and 82 nM for CyA, SAHA and KAR3000 respectively.
Conclusions: HDACi represent a novel class of potent immunosuppressant therapeutics. These data support the hypothesis that HDAC-6 inhibition mediates potent suppression of human alloreactive T-cell responses *in vitro* supporting potential utility in transplantation.

BO334 MOBILIZATION OF HEMATOPOIETIC STEM CELLS FROM HUMAN LIVER GRAFTS OF HEART BEATING AND NON-HEART BEATING DONORS

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Erasmusm MC

Background: Organs procured for transplantation from heart beating donors after brain death (DBD) or non-heart beating donors after cardiac death (DCD) sustain different types of tissue injury, affecting graft function after transplantation. Tissue injury following organ donation may induce mobilization of hematopoietic stem/progenitor cells (HSPCs). Adult human livers are known to harbor HSPCs and which are thought to contribute to hematopoietic chimerism after liver transplantation. The aim of this study was to determine mobilization of HSPCs from liver grafts procured from DBD and DCD donors.
Methods: Recipient peripheral blood and liver graft preservation solutions (perfusates) of DBD and DCD donor livers were collected and mononuclear cells isolated. Colony-forming assays were performed to assess the lineage-restriction of the liver-derived HSPCs. HSPCs were qualified by polychromatic flow cytometry using labeled monoclonal antibodies specific for CD34 (PE), CD90 (APC), CD38 (APC-Cy7), CD45RA (PB) and lineage (Lin) markers (FITC).
Results: The colony forming assays revealed that mean 325 erythroid and 36 granulocyte progenitors colonies were present per million perfusate mononuclear cells. This progenitor frequency is almost 10-fold higher than found generally in peripheral blood. After liver transplantation, donor HSPCs continued to migrate from the graft. In the first month, 2.0–8.3% of blood CD34+ cells were of donor origin (HLA-A2+ donor transplanted in HLA-A2- recipients; $n = 6$). Flow cytometric analysis of perfusates revealed a significant difference in the mobilization of undifferentiated Lin-CD34+CD38−CD90+CD45RA− HSPCs from DBD (mean 0.36% "b 0.48 SD, $n = 9$) vs. DCD livers (0.04% "b 0.04, $n = 7$; $p = 0.003$).
Conclusion: HSPCs mobilize from adult human liver grafts during and after transplantation and may contribute to chimerism and allohyporesponsiveness. Mobilization of HSPCs was higher in livers procured from DBD compared to DCD donors.

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BO335 KINETIC AND PHENOTYPIC PROFILE OF MONOCYTE SUBSETS IN STABLE KIDNEY TRANSPLANT RECIPIENTS

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Introduction: To date, monocyte cell lineage appears to play an important role in post transplant immunity. Here, we aimed to define the functional and phenotypic profile of monocyte subset composition in stable transplant recipients longitudinally in time.
Materials and Methods: Using flow cytometry, phenotype, activation status and cytokine production of classical (CD14++CD16−), intermediate (CD14++CD16+) and non-classical (CD14+CD16++) monocytes were determined in a cohort of renal transplant recipients ($n = 28$) at pre-transplantation, 3 and 6 months post-transplantation.
Results: In kidney transplant recipients, despite recovered kidney function and immunosuppression, the balance in monocyte subsets is skewed towards pro-inflammatory CD16+ monocyte subsets during the first 6 months post-transplant. The activation status of monocytes was similar at all time points tested. Moreover, the production of pro-inflammatory cytokines during the post-transplant phase remained as high as at time of transplantation. Production capacity of the anti-inflammatory cytokine IL-10 was even significantly increased 3 months after transplantation ($p = 0.005$).
Conclusion: In stable kidney transplant recipients the monocyte subset composition was consistently skewed towards pro-inflammatory CD16+ subsets. This skewed balance is present at time of transplantation and retained during post-transplant period.

BO336 TLR2 IS SIGNIFICANTLY UP-REGULATED IN ACUTE REJECTION OF KIDNEY TRANSPLANTS

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TLRs recognize PAMPs as well as endogenous inflammation associated molecules. TLR2 heterodimerize to PAMPs, necrotic cells and heat shock proteins.

TLR4 is the LPS receptor but recognizes several endogenous ligands too. There is controversy in human TX about TLRs. We evaluated TLR2 and 4 expressions in aspiration biopsies (AB) from kidney transplants (KTX). 38 KTX were divided into I (31) rejection free for the 1st year post KTX and II (7) acutely rejecting (AR) that occurred during the 60 days post KTX. AB was done on day 7 in I and on rejection day in II. Cytoslides were stained by a mouse IgG2a anti-human TLR2 and 4 by ABC. TLR2 was significantly up-regulated in II +cells ($p = 0.0009$), +/renal cells ($p = 0.0009$) and +/mononuclear cells ratio ($p = 0.0009$). No difference was found for TLR4. Our results surmise that TLR2 plays a significantly role during AR. TLR2 ligand on necrotic/apoptotic cells post surgery may be an important link of ischaemia to adaptive immune reaction in human KTX.

BO337 ALEMTUZUMAB ANTI-REJECTION THERAPY INDUCES HOMEOSTATIC PROLIFERATION IN THE PRESENCE OF DIMINISHED IL7 REACTIVITY

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Background: Induction therapy with alemtuzumab results in T-cell depletion followed by immune-reconstitution and donor hypo-responsiveness. Whether these effects also occur when alemtuzumab is given during immune activation, i.e. as anti-rejection therapy, is unknown.
Methods: Patients ($n = 12$) were treated with alemtuzumab for steroid-resistant rejection. Whole blood flow cytometric analysis was performed to measure the marker for cell division Ki67 and IL2 and IL7 mediated phosphorylation of STAT5 in T-cells, before and 3 months after rejection therapy.
Results: Three months after alemtuzumab anti-rejection therapy the T-cell population recovered to 6% of baseline level, which was associated with an increased percentage of Ki67+ T-cells ($p < 0.02$). CD4 and CD8 T-cells showed no differences in T-cell recovery and in the expression of Ki67, however only CD4 T-cells showed a phenotypic shift towards effector memory T cells ($p < 0.001$). At the functional level we observed a diminished IL7 reactivity of CD4 T-cells, reflected by a decreased capacity to phosphorylate STAT5 ($p < 0.03$), while the reactivity to IL2 was preserved.
Conclusion: Alemtuzumab anti-rejection therapy induces homeostatic proliferation of memory T-cells in the presence of diminished responsiveness to the homeostatic cytokine IL7, while the responsiveness to IL2 is preserved.

BO338 A STRATEGY FOR REDUCING THE IMMUNOGENICITY OF HUMAN RENAL ALLOGRAFTS

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Background: Transplantation is unique immunologically due to both donor and recipient antigen presenting cells being present at reperfusion. As part of their normal immune surveillance, Dendritic Cells (DC) and other passenger leukocytes (PL) are trapped in the renal parenchyma at the time of organ procurement. On reperfusion, DC migrate into secondary lymphatics where recipient immune cells encounter donor antigens via direct antigen presentation. We tested the feasibility of minimizing initial allorecognition by the removal of DC during *ex vivo* warm perfusion.
Methods: We used an acellular Exsanguinous Metabolic Support (EMS) perfusion technology at 32°C. Human allografts were procured for this study. The human kidneys were received on ice, flushed with EMS solution (32°C) and placed on perfusion. Biopsies were taken pre- and post-EMS perfusion (24H). Frozen sections were made from representative sections of the kidneys. The number and location of the DC within the kidneys were determined using an indirect immunofluorescence assay with CD209 (DC-sign) antibody and a secondary antibody of Alexafluor488, along with fluoroshield plus DAPI. The results were obtained using ImageJ software that measured positive fluorescence per field.
Results: There was a significant reduction in the number of resident DC following 24H of EMS perfusion (Table1). Histologic evaluations supported the removal of DC from the various compartments within the nephron (Figure 1). This finding is mirrored by the increasing concentration of DC found in the circulating EMS solution after perfusion.
Conclusion: Results demonstrate the feasibility of depleting renal allografts of PL pretransplant during warm acellular perfusion. If these migrating cells can be trapped to prevent reentry into the kidney it may be feasible to eliminate direct antigen presentation by PL. Such reduction in immunogenicity could positively impact outcomes. We are currently evaluating further enhancement of depletion.

BO340 DIFFERENTIAL EFFECTS OF THE INNATE VERSUS ADAPTIVE IMMUNITY IN LYSING HUMAN RENAL TUBULAR EPITHELIAL CELLS

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Introduction: While T-cells are involved in cellular rejection, NK-cells are considered to play a key role in antibody-mediated rejection. We studied the differences in net lysis-efficacy of TECs by NK-cells and CD8+ T-cells during alloreactivity *in vitro* and the differential effects of immunosuppression on this phenomenon.
Methods/Material: PBMCs were cocultured with IFN-γ and TNF-α preactivated TECs in the presence of IL-2 and IL-15. We performed europium cytotoxicity- and CD107a degranulation assays using sorted alloactivated NK and CD8 T-cells. In addition, the proliferative response of PKH-labelled NK and CD8 T-cells was measured.
Results: An allogeneic response induced 6.6 $\pm$ 3.1% CD8+ T-cell proliferation and 32.6 $\pm$ 7.5% NK cell proliferation. TEC specific CD8+ T-cells lysed 20–30% of TECs at an effector:target ratio (40:1). NK-cell lysed 51–78% of the TECs (20:1). TEC specific CD8+ T-cells expressed CD107a up to 24% and 27% of the NK-cells expressed CD107a. While everolimus and prednisolone reduced CD107a expression up to 30%, tacrolimus was capable of 50% reduction in CD107a expression.
Conclusion: Our data show a stronger cytolytic activity of NK-cells against preactivated TECs compared to CD8+ T-cells. Tacrolimus was a more potent inhibitor of TEC lysis compared to prednisolon and everolimus. NK-rich graft infiltration may cause relatively more renal tubular damage than CD8+ T cells.

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BOS31-INFECTIONS

BO341 ROLE OF CYTOMEGALOVIRUS INFECTION IN *DE NOVO* CANCER AFTER ORGAN TRANSPLANTATION

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The role of Cytomegalovirus (CMV) in development of post-transplant *de novo* cancer is not established. The data from UKTransplant Registry were linked with Office for National Statistics to identify all cases of post-transplant cancer in recipients of first solid organ transplant (1980–2007). A total of 22464 recipients were included. Of these, 55% were CMV-exposed prior to transplant (group1), 20% received a CMV positive graft (group 2), 25% were not exposed to CMV (group 3). The unadjusted incidence rates of cancer in groups 1, 2 and 3 were 8.9% (8.3, 9.5), 7% (6, 7.9) and 6.4% (5.5, 7.2) respectively ($p < 0.001$), however the age-adjusted hazard of cancer was not significantly different (HR compared to group1): group2, 1.0 (0.8, 1.1) and group3, 0.96 (0.8, 1.1), $p = 0.84$. Cox regression analysis showed no significant difference between three groups for the risk-adjusted hazard of developing any of 21 types of cancers. We conclude that exposure to CMV does not affect the incidence of post-transplant cancer.

BO342 A PROSPECTIVE STUDY OF HHV-6 AND CMV INFECTIONS IN KIDNEY ALLOGRAFT PROTOCOL BIOPSIES

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Background: Human herpesvirus-6 (HHV-6) and cytomegalovirus (CMV) commonly reactivate after kidney transplantation. CMV is able to persistently infect the kidney allograft, and in selected retrospective patient materials this has been associated with inferior outcome. HHV-6 proteins have also been detected in the allograft, but the clinical significance of this is unknown. The aim of this prospective study was to evaluate the incidence and clinical significance of intragraft HHV-6 and CMV infections in kidney transplant protocol biopsies taken 6 months after transplantation.
Methods/Materials: From 76 consecutive recipients of kidney transplants between 4/2010 and 8/2011 attending follow-up at our institution, a protocol biopsy at 6 months was taken from 37 patients, who all participated in this prospective study. The presence of HHV-6B and CMVpp65 antigens in the biopsies was demonstrated by immunohistochemistry. HHV-6 and CMV DNAemia were screened with quantitative PCR. Histopathologal changes in the biopsies were graded according to chronic allograft damage index (CADI).
Results: Low-level HHV-6 DNAemia was seen in 1/37 (3%) asymptomatic patient at 6 months after transplantation. HHV-6B antigens were detected in biopsies of 5/37 (14%) patients at 6 months mostly in inflammatory cells, but also in tubular cells. CMV DNAemia occurred after transplantation in 17/37 (46%) patients, but in none of the patients at the time of the protocol biopsy. CMVpp65 antigens were seen in biopsies of 5/37 patients (14%) at 6 months, mostly in inflammatory cells. Two biopsies (5%) showed both HHV-6 and CMV. No specific histopathological changes were associated with intragraft HHV-6 or CMV infections, and no differences in CADI score or graft function were seen between patients with or without intragraft HHV-6 or CMV.
Conclusion: HHV-6 and CMV are able to infect the kidney allograft without concurrent viremia, but the clinical significance of this phenomenon is probably low.

BO343 VALGANCICLOVIR PROPHYLAXIS – WHAT IS THE IMPACT?

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Background Cytomegalovirus (CMV) infection negatively affects outcomes in renal transplantation. Many transplant units have extended the duration of valganciclovir prophylaxis for at risk (D+/R−) patients from 3 to 6 months following the IMPACT study. We aimed to corroborate the findings of this study in an out-of-trial setting.
Methods: This was a single-centre, historical cohort study. Consecutive renal transplant recipients between March 2007 and October 2011 were included. Demographic data and data concerning valganciclovir prescription, pre-transplant CMV status, CMV viraemia and tissue-invasive CMV disease were extracted from a computerised patient record system and the regional virology database. Six-month post prophylaxis CMV viraemia and tissue invasive disease rates were established in two groups (3 vs. 6 months of VGC prophylaxis) and compared using Fisher's test and X2 on an intention-to-treat basis.
Results: Three hundred and seventy-five patients underwent successful transplantation. 20.1% (76/379) were at risk (D+/R−). Of the at risk patients, 43/76 were in the 3 month cohort and 33/76 were in the 6 month cohort. 53.5% (23/43) of the 3 month cohort developed CMV viraemia vs. 36.4% (12/33) of the 6-month cohort ($p = 0.138$). 27.9% (12/43) of the 3 month cohort developed tissue-invasive CMV disease vs. 9.1% (3/33) of the 6 month cohort ($p = 0.048$).
Conclusion: The benefits of prolonged valganciclovir prophylaxis shown in the selected in-trial population of the IMPACT study appear to apply in a real-life setting.

BO344 THE USEFULNESS OF PROCALCITONIN (PCT), INTERLUKINE-6 (IL-6), C REACTIVE PROTEIN (CRP) AND SERUM AMYLOID PROTEIN A (SAA) IN DIAGNOSIS OF NONVIRAL INFECTION OF LIVER/KIDNEY TRANSPLANTED PATIENTS

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Background: The aim of our study was to evaluate PCT/IL-6/CRP/SAA as postoperative infection markers in liver/kidney transplanted patients compared with patients with localized infection/inflammatory processes.
Methods: We retrospected 152 post-transplanted infectious patients from 465 patients admitted to West China hospital, recorded clinical characteristics, PCT, IL-6, CRP, SAA levels and blood culture results.
Results: Thirty-nine recipients experienced a sepsis. They had significantly higher PCT (median 6.41 [IQR 2.93–11.8] vs. 0.28 [0.13–0.73]) and higher CRP (73.4 [29.8–142] vs. 29.8 [11.4–85.5]) and higher IL-6 (87.6 [19.2–288.7] vs. 26.9 [6.6–79.6]) in comparison with recipients without sepsis. PCT performed with an AUC value of 0.968 which was higher than CRP (AUC 0.659) and IL-6 (AUC 0.675) ($p < 0.05$). As an early indicator of sepsis, the cut-off value of PCT was 1.01 ng/ml, with a sensitivity of 97.4%, a specificity of 87.6%, positive and negative predictive values of 72.0% and 97.1%, positive and negative likelihood ratio of 7.87 and 0.03. Meanwhile, PCT level was less elevated in patients with candidemia (1.83 [1.50–2.53]) than in those with bacteremia (6.92 [3.48–11.9]) ($p < 0.05$). Acute rejection or cytomegalovirus infections did not significantly increase the serum PCT levels.
Conclusion: PCT can be used as a sensitive marker to distinguish systemic infections from other complications in organ transplantation.

BO345 IS MYCOPHENOLATE ACID (MPA) EXPOSURE A RISK FACTOR FOR BK VIRUS INFECTION (BKVI)?

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Background: In this prospective study, we analysed the association between the MPA exposure and the occurrence of BKVI during the first year post-renal transplantation.
Methods: 179 consecutive patients transplanted between 2006 and 2009 were included. They all received an induction (thymoglobulin for 98%), steroids associated with mycophenolate mofetil (100%) and calcineurine inhibitor (CNI) (cyclosporine (56%) or tacrolimus (44%)). MPA area under the concentration-time curves (MPA AUC) were performed at day 7 and months 1, 3, 6 and 12. The detection of BKVI relied on count of urine decoy cells once a week until month 2 and at months 3, 6 and 12. A blood qPCR was done above six decoy cells by microscope slide.
Results: Thirty-four (19%) patients have a BKVI (Gr1) after a mean delay of 57 days while 145 (81%) were free of BKVI at any time (Gr2). In Gr1, 18/34 patients have a positive blood qPCR and five of them (2.7%) developed a BKV nephropathy with only one graft loss. In Gr1, the MPA AUCs at the time of BKVI (63.74 mg.h.l) were not significantly different than time paired AUCs of Gr2 (55.93 mg.h.l) ($p = 0.095$). 48% of patients in Gr1 while only 30% of patients in Gr2 have a MPA AUC superior or equal to 60 mg.h.l. ($p = 0.055$). No significant association between the type of CNI and BKVI was observed.
Conclusion: These results suggest the lack of significant association between the magnitude of MPA exposure and the occurrence of BKVI.

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BO346 INCIDENCE AND OUTCOME OF BK INFECTION IN A RANDOMIZED CONTROLLED MULTICENTER STUDY WITH RENAL TRANSPLANT PATIENTS RECEIVING DUO-THERAPY

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Background: It remains unclear whether the overall degree of immunosuppression or a combination of immunosuppressiva are mainly responsible for the increased risk of BK infection in renal transplant patients.
Methods: A randomized controlled, prospective multicentre trial in 362 *de novo* renal transplant recipients was performed. Ninety-one patients were excluded during the course of the study. At 6 months patients were randomised into three treatment groups with dual therapy consisting of prednisolon with either cyclosporine, mycophenolate sodium or everolimus. Urine and serum samples were collected and at time point 6 and 24 months a renal biopsy was performed. BKV DNA was measured in all samples and pre-transplant BK-specific serology was performed. Primary outcome was incidence of BK viruria, BK viremia and BK nephopathy during 2 years of follow up.
Results: Pre-transplant seroprevalence was 48.2%. In total, 84 of the 271 renal transplant recipients (31.0%) had at least one positive test for BK DNA. Viruria could be detected in 29.5% (10.3% transient vs. 19.2% sustained), viremia was found in 15.5% of the patients (12.9% transient vs. 2.6% sustained). BK nephropathy was diagnosed in three patients (1.1%). Incidence of BK viremia/viruria in de the mycophenolate sodium group was significantly higher than in the other groups ($p = 0.04$) but there were no significant differences in severity of BK induced disease between the groups ($p = 0.67$). A positive trend between primo BK infections and increased incidence of viremia was observed ($p = 0.07$).
Conclusions: In this cohort with relative low BK seroprevalence, dual mild immunosuppressive regimes were associated with a lower incidence of BK nephropathy compared to the literature. Furthermore, the use of prednisolone and MPS was correlated with a higher incidence of BK viremia/viruria, but did not have an effect on the severity of the disease. Finally, primo infections seem to be correlated with an increased incidence of BK viremia.

BO347 URINARY TRACT INFECTION AFTER KIDNEY TRANSPLANTATION: A RETROSPECTIVE OBSERVATIONAL STUDY

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Background: The growing cases of multidrug resistance infections worldwide, poses kidney transplant recipients (KTR) in particular risk. The aim of this study was to understand the etiology, pattern of antibiotic (ATB) resistance and clinical presentation of UTI in our KTR.
Methods: This was a retrospective cohort study, that analysed all adult KTR that were transplanted in our unit from January 2010 to December 2011 and followed until the end of 2012. UTI was considered when bacteriuria was treated with ATB and multiresistant microorganisms (MrM) were considered if resistant to ≥ 2 distinct classes of ATB.
Results: One hundred and forty recipients (89 female; mean age 47.8 ± 11.9 years) were included in the study with mean follow up of 17.4 ± 4.9 months (96948 days at risk). Seventy seven patients (55%) had at least one episode of bacteriuria and 29 (21%) at least one UTI. The number of asymptomatic bacteriuria and UTI episodes were respectively 154 (1.59/1000 days) and 75 (0.77/1000 days). *E. coli* (58%) and *Klebsiella* spp. (20%) were the most frequent agents identified in UTI, except in the first month, where both *E. coli* and *Enterococcus* spp. (30% each) were predominant. MrM were identified in 19 of UTI (25%) episodes. The global rate of quinolone resistance was 40%. In univariate analysis, the occurrence of UTI was associated with female gender ($p < 0.001$), presence of cardiovascular disease ($p = 0.046$), higher body mass index (BMI) ($r = 0.21$; $p < 0.05$), longer cold ischemia time ($r = 0.21$; $p = 0.023$) and delayed graft function ($r = 0.165$; $p < 0.05$). In multivariate analysis female gender ($p < 0.001$), days of bladder catheterization (8.7 ± 4.3 vs. 7.7 ± 5, $p = 0.004$) and longer cold ischemia time ($p < 0.05$) were all predictors of UTI. Need for dialysis after KT (Exp(B) 3.75, $p < 0.02$) and a BMI > 30 (Exp(B) = 7, $p < 0.05$) were both predictors of later ITU (after 3 months of KT). In this cohort, the occurrence of UTI had no impact on graft survival.
Conclusion: There was a high rate of MrM and also resistance to first choice empirical ATB drugs. ITU were related with female gender and with modifiable variables as long cold ischemia time and a larger period of bladder catheterization. Obesity and delayed graft function were also predictors of ITU after the first 3 months. We should have these considerations in mind when leading with UTI in KT recipients.

BO348 *KLEBSIELLA* SPP URINARY TRACT INFECTIONS DURING FIRST YEAR AFTER RENAL TRANSPLANTATION

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Background: Urinary tract infections (UTIs) are the most common infections in renal transplant recipients. *Klebsiella* spp is well recognized source of nosocomial infections in immunocompromised patients and is also the most common pathogen capable of producing extended-spectrum β-lactamases (ESBL).
Methods: We performed a retrospective cohort study reviewing medical records of patients followed-up at Gdańsk Transplantation Centre. We analyzed urine cultures performed within first 12 months after RTx with reference to clinical data. We recorded all *Klebsiella* spp urinary tract infections (UTIs).
Results: We studied urine cultures and clinical data from 279 RTx recipients. We observed 45 *Klebsiella* spp episodes in 20 RTx patients, including seven cases of acute graft pyelonephritis and six of urosepsis. More than half were caused by ESBL+, while there were no carbapenemase producing strains. Almost 80% of episodes were diagnosed beginning from the second post-transplant month. Over 60% of upper *Klebsiella* spp UTI were due to ESBL+ strains, while we did not identify any host risk factors including vesico-ureteral reflux, strictures at the uretero-vesical junction, history of recurrent UTIs before RTx, gender, use of induction, comorbidity measured by Charlson Comorbidity Index, history of acute rejection and CMV infection and type of immunosuppression used.
Conclusions: *Klebsiella* spp virulence factors, not the host factors seem to be responsible for developing upper UTIs.

BO349 THE TNFA −238A ALLELE PREVENTS SEVERE BACTERIAL INFECTION IN PATIENTS WITH END-STAGE LIVER DISEASE AWAITING LIVER TRANSPLANTATION

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Background: Augmented susceptibility to infections increases mortality in patients with end-stage liver disease (ESLD). We aimed to determine the contribution of genetic variants in *TLR4* and pro-inflammatory cytokines to severe bacterial infections (SBIs) in patients with ESLD.
Methods: We retrospectively assessed incidence of SBIs requiring hospitalization and i.v. antibiotics administration in a cohort of 243 adult cirrhotic ESLD patients enlisted for orthotopic liver transplantation (OLT) from 1995 to 2010. Patients with Child-Pugh's classification A, Caroli disease, primary or secondary sclerosing cholangitis and those with acute liver failure were excluded. All enrolled subjects were genotyped for *TLR4* c. +1196C/T, *CD14* c.-159C/T, *TNFA*c.-238G/A, *TNFA* c.-863C/A, *IL-1B* c.-31C/T and *IL-1RA* variable number of tandem repeats allelic variants. Associations were validated in a cohort of 237 ESLD patients awaiting OLT from another centre.
Results: Sixty nine (69/243, 28%) patients with ESLD presented with SBIs while enlisted for OLT in the identification cohort. The patients with the *TNFA* c.-238GA genotype showed a significantly decreased risk of SBIs (OR 0.11, 95% CI 0.01–0.81, $p = 0.009$) compared to the patients homozygous for *TNFA* c.-238G. In the validation cohort, 72 of 237 (30%) ESLD patients awaiting OLT suffered from SBIs and the association between *TNFA* c.-238GA and decreased risk for SBI was confirmed (OR 0.27, 95% CI 0–0.94, $p = 0.032$). Its contribution to the decreased risk for SBIs was independent of clinical variables included in multivariate analysis.
Conclusion: Our results indicate that the *TNFA* promoter variant c.-238A independently decreases the risk of SBIs in patients with ESLD.

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BO350 TUBERCULOSIS IN KIDNEY TRANSPLANT – 10 YEARS EXPERIENCE

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Background: Tuberculosis infection (TB) increases morbidity after kidney transplantation (TX) and poses diagnostic and therapeutic challenges. Brazil has a higher general incidence of TB (37.7 cases per 105 inhabitants) compared to developed countries, but nothing is known about this infection among kidney transplant recipients.
Methods: Retrospective cohort study analyzed data concerning to all kidney TX performed between 2002 and the 10/31/2012. TB was diagnosed by the presence of acid-fast bacilli on sputum smear, histological findings and/or positive culture. Disseminated TB was defined when two or more organs were compromised.
Results: From 2002 to 2012, 7335 kidney transplants were performed. There were 73 cases of TB (995 cases/105 recipients). Mean age was 40 $\pm$ 13 years (median 39 years), being 67% male, 76% recipients of first transplant and 51% from live donor. Median time to develop TB was 33 months post transplantation. Extra pulmonary TB represented 48% of cases, pulmonary 37%, disseminated 11% and only 4% for empiric treatment due to prolonged fever from unknown origin. There were histological positive findings in 84% of cases and positive culture in 64%. Sputum smears were positive in 32% of pulmonary cases. All patients were treated for at least 6 months with a triple regimen (izoniazid, rifampin and pyrazinamide), plus ethambutol in cases diagnosed after 2010. Attributed mortality was 18%. Graft loss occurred in 21% of survivors (nine cases of acute rejection and six cases of chronic allograft dysfunction).
Conclusions: TB incidence in kidney transplanted recipients was 28 times higher than in the general Brazilian population. Most cases have extra pulmonary presentation, which poses considerable diagnosis difficulties. TB have an important social and economical impact, since it affected young recipients from mostly live donors, was associated with high mortality rates and a high proportion of graft loss.

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BOS32-COMPOSITE TISSUES

BO351 THE FEATURE OF SKIN REJECTION AT VARIOUS ANATOMICAL SITES OF A RAT HIND LIMB ALLOGRAFT

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Background: Atypical manifestation of skin rejection made in a series of hand transplant recipients suggests that appearance and mechanisms of the alloimmune response may vary within the allograft. We herein characterize skin rejection at three different sites of a rat hind limb allograft.
Methods: After rat hind limb allotransplantation allograft skin (thigh, planta pedis and dorsum) and muscle (thigh and planta pedis) were harvested on postoperative day 5 and analyzed for histopathologic changes, the composition of the cellular infiltrate (T cells) and expression of a panel of cytokines associated with skin inflammation.
Results: Histology of the skin revealed that the infiltrate was distributed diffuse in the dermis and at the dermal-epidermal interface in the thigh and dorsum, whereas in the planta pedis it was mainly located perivascularly in the dermis. At all sites epidermal involvement such as apoptotic keratinocytes were observed. The proportion of CD3+CD45+ T cells was significantly higher in the thigh compared to planta pedis and dorsum (76.49% vs. 46.14% vs. 40.53%). About 62% were CD3+CD45+CD4+ and 31% CD3+CD45+CD8+ T cells with no difference between the various sites. MCP-1, IL-1ß, IL-6, IL-10 and GRO-CK were upregulated during rejection on day 5 at all sites, however, highest levels of IL-1ß, IL-6 and IL-10 were found in the planta pedis. Histology of muscle showed a tendency towards a less prominent infiltrate in the thigh compared to the planta pedis. The proportion of CD3+CD45+CD4+ T cells was increased in planta pedis muscle, whereas CD3+CD45+CD8+ T cells were increased in thigh muscle.
Conclusion: Differences in histopathologic appearance, T cell composition and cytokine expression in skin/muscle suggest site-specific mechanisms of rejection in a vascularized composite allograft, which should be considered for sample collection and rejection therapy.

BO352 MECHANICAL TRAUMA CAN REACTIVATE AN ALLOIMMUNE RESPONSE AGAINST THE SKIN-COMPONENT IN A LARGE ANIMAL VASCULARIZED COMPOSITE ALLOTRANSPLANTATION (VCA) MODEL OF OPERATIONAL TOLERANCE

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Background: The skin component of Vascularized Composite Allografts (VCA) is unique since it is directly exposed to the environment. It thereby not only offers opportunities for non-invasive immune monitoring but also poses challenges related to its immunogenicity and interaction with the environment. Although the clinical scope of VCA has widened and the immunologic mechanisms involved in skin rejection are better defined, there is very limited data related to the impact of mechanical trauma on rejection of the skin component of VCA.
Methods: Fully SLA and gender mismatched MGH miniature swine underwent heterotopic hind-limb transplantation and received a short course (30 days) of tacrolimus monotherapy ($n = 3$–5 per group). Group 1 (control): no treatment. Group 2: short-term tacrolimus only; and Group 3: BM, tacrolimus and CTLA4Ig. Sequential skin and muscle biopsies were performed for histologic analysis. Mixed lymphocyte reaction was used to determine donor specific hypo responsiveness while secondary skin grafts were used to demonstrate *in vivo* robust immune tolerance.
Results: Co-stimulation blockade based immunomodulatory protocol resulted in indefinite graft survival (operational tolerance) in five out of eight animals whereas control and tacrolimus only groups rejected allografts at days 6 ± 1 and 28 ± 2 respectively. One of the long-term survivors in costimulation blockade group experienced repetitive mechanical trauma from cage wires at POD 96 (off IS > 2 months). This was followed by histologic evidence of skin rejection (Banff Grade 2) at POD 100 and accelerated allograft rejection and loss of epidermis by POD 110 as evidenced by clinical and histologic examination.
Conclusion: Combined costimulation blockade and donor bone marrow cell infusion can induce operational tolerance in a fully MHC-mismatched hind limb transplant model. Mechanical trauma can potentially reactivate an alloimmune response and accelerate graft rejection.

BO353 *IN VITRO* ASSESSMENT OF IMMUNE TOLERANCE ACROSS A FULL MHC BARRIER IN A SWINE HIND LIMB TRANSPLANTATION MODEL USING A COMBINED CO-STIMULATORY BLOCKADE AND DONOR BONE MARROW APPROACH

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Background: We have investigated Vascular Composite Allografts (VCA) across a full-MHC barrier using a combined co-stimulatory blockade and donor bone marrow cell (BMC) approach, which lead to long-term immunosuppression free graft survival. Here we discuss the immunological assessment of donor unresponsiveness, as a proof of tolerance induction, using a Carboxy-fluorescein succinimidyl ester-based mixed lymphocyte reaction (CFSE-MLR) assay.
Methods: MHC-mismatched MGH miniature swine underwent heterotopic hind-limb transplantation. Recipient animals received a short course (30 days) of tacrolimus monotherapy, +/−donor BM infusion (6×107cells/kg), and CTLA4Ig. Short course tacrolimus only and untreated animals served as controls. Sequential skin and muscle biopsies were performed for histology. Alloreactivity against donor antigens was assessed *in vitro* by CFSE-MLR assays.
Results: The co-stimulation blockade (CTLA4Ig)-based immunomodulatory protocol resulted in indefinite graft survival (>150 days) in three out of five animals whereas control and tacrolimus only groups rejected allografts at days 7 (SD = ± 1) and 29 (SD = ± 1) respectively. Combined CTLA4Ig with augmented donor BM infusion resulted in indefinite graft survival in two out of three animals (>150 days). CFSE-MLR data reliably showed unresponsiveness to donor and swine carriers of mixed donor-like/recipient SLA haplotypes. Responsiveness to third party outbred allogeneic controls was unaltered. In addition, secondary donor-matched skin grafts were accepted confirming *in vivo* donor-specific immune tolerance.
Conclusion: Combined costimulation blockade and donor BM cell infusion can induce robust immune tolerance, as evidenced by CFSE-MLR, in a fully MHC mismatched hind limb transplant model. Such targeted immunomodulatory protocols might eliminate the need for long-term multi-drug immunosuppression after reconstructive transplantation.

BO354 *IN VITRO* CHARACTERIZATION OF VERTEBRAL BONE MARROW USED FOR IMMUNOMODULATION IN HAND TRANSPLANTATION

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Purpose: Peri-operative cadaveric donor vertebral body bone marrow (VBBM) infusion has shown promising immunomodulatory effects (graft maintenance on low-dose tacrolimus monotherapy) in clinical trials of hand transplantation. Mechanisms behind such effects are not yet well-characterized.
Methods: VBBM was prepared, cryopreserved, and thawed as in clinical trials. Samples were stained with monoclonal antibodies to detect various cell populations including subsets of T lymphocyte and mesenchymal stem cell (MSC) populations. Antibodies included anti-human CD3, CD4, CD8, CD45RA, CD34, CD25, Foxp3, CD127, TCRaβ and markers for Th1, Th2, and Th17 cells. MSCs were detected as CD34−/11b−/19−/45−/HLADR−/CD73+CD105+CD90+ or CD271+cells. Conventional iliac-crest bone marrow aspirates from consenting donors were similarly analyzed. Mixed lymphocyte reaction assays: allogeneically stimulated CFSE-stained PBMCs were co-cultured with whole bone marrow or flow cytometrically sorted bone marrow subpopulations as regulators.
Results: VBBM contains cell populations with known immunomodulatory properties. Composition is grossly comparable to conventionally obtained bone marrow, with differences in some important populations. Both whole bone marrow and sorted sub-populations demonstrated immunomodulatory properties. Whole bone marrow co-cultured in a 5:1 responder-regulator ratio suppressed allogeneic stimulation by 90.8%. The T regulatory cell (CD4+CD25highCD127lo) sub-population was particularly potent when fractionated.
Conclusion: VBBM contains cell populations with potent immunomodulatory effects. Upcoming studies include cytokine analysis and donor-specific versus third-party experiments. Our ongoing immunophenotypical and functional characterization helps identify the mechanism behind VBBM's immunomodulatory properties, paving the way towards opportunitiesto refine the cell product and maximize its clinical effectiveness.

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BO355 IMPACT OF IMMUNOSUPPRESSION ON CARDIOVASCULAR SYSTEM AFTER HAND TRANSPLANTATION

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Cardiovascular disease is a major cause of mortality in solid organ allograft recipients. Hand transplantation is not a life-saving procedure, thus the effect of long-term immunosuppression on cardiovascular system in these patients (pts) should be monitored. The aim of the study was to evaluate the morphology and function of heart and blood vessels in pts after hand transplantation.
Methods: The study entailed 5 pts (at age 32–58, mean 39 years) who underwent hand transplantation in 2006–2010. Immunosuppression included basiliximab in induction and tacrolimus, MMF and prednisone. Nobody had prior cardiovascular risk factors, but after transplantation three had insulin-dependent diabetes for >1 year, and three developed dyslipidemia. Cardiac status was assessed by echocardiography (according to the American Society of Echocardiography) and cardiac biomarkers; blood vessels by carotid intima-media thickness (IMT), pulse wave velocity (PWV), and brachial artery flow-mediated dilatation (FMD). The examinations were performed 28–79 (mean 43) months after transplantation.
Results: Concentric left ventricular hypertrophy was found in 1 patient, and ventricular concentric remodeling in 4 pts. Impaired diastolic function ($E/e' > 8$) was observed in 2 pts. The indexed volume of left atrium was higher in all pts (mean 31 ml/m^2). Cardiac biomarkers: N-terminal pro-brain natriuretic peptide, CRP and troponins were in normal range. IMT was higher in one patient (0.745 mm), and normal in 4 pts (0.559 $\pm$ 0.11 mm). Arterial stiffness measured by PWV was not increased (6.82 $\pm$ 1.14 m/s) in all pts. Native brachial artery FMD response, an index of endothelium-dependent function, was abnormal in 2 pts, but in the transplanted extremity FMD was abnormal in 4 pts.
Conclusions: Pathologic changes in cardiac structures were found in all pts, but the arterial wall changes and endothelial dysfunction were observed in some pts. The patients after hand transplantation are at higher risk for cardiovascular disease.

BO356 ALLOTRANSPLANTATION OF THE LOWER TWO-THIRDS OF THE FACE INCLUDING DOUBLE JAW AND TONGUE

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Aim of the present study was to report on the outcomes of a partial face allotransplantation performed on June 13, 2012. The recipient was a 52-year old woman severely disfigured by an arteriovenous malformation that recurred after conventional surgery. Surgical amputation of the mid- and lower part of the face was performed in February 2012 to remove it. The patient was fed by gastrostomy and the speeching was unintelligible. The graft included cheeks and lips, chin, neck, double jam, tongue and salivary glands. Immunosuppression included induction by Thymoglobulin, tacrolimus, prednisolone, mycophenolate mofetil. Moreover donor bone marrow was infused at day 7 post-transplantation to improve graft acceptance. The follow-up was marked by an episode of acute rejection on day 12 (grade III) easily reversed by steroid bolus. Despite donor bone marrow infusion and the vascularized bone marrow transplantation (inside the double jaw) the patient never showed microchimerism which was searched using RQ-PCR (Taqman). Six months after transplantation the patient was able to swallow, drink but not chew or smile, and she found really difficult to speak. She is satisfied of the aesthetic aspect of the grafted face. In conclusion face transplantation is an alternative therapy to patients severely disfigured by arteriovenous malformation.

BO357 MESENCHYMAL STEM CELL THERAPY FOR NERVE REGENERATION AND IMMUNOMODULATION AFTER RECONSTRUCTIVE TRANSPLANTATION

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Background: This study proposes a novel cell-based therapy utilizing mesenchymal stem cells (MSCs) that augments neuroregeneration while minimizing the need for immunosuppression after Reconstructive Transplantation (RT).
Methods: Bone marrow-derived MSCs were harvested and purified from Brown Norway rats. Sciatic nerve transections and repairs (SNTR) were performed on Lewis rats in control, local (intraneural) and systemic (intravenous) MSC injection groups ($n = 8$ each). Syngeneic and allogeneic hind-limb transplants (S-HLT and A-HLT) were performed to analyze neuroregeneration with and without an allo-immune response ($n = 4$–6 per group). Advanced gait analysis, nerve conduction studies (compound muscle action potential; CMAP), and nerve histomorphometry were performed.
Results: SNTR rats treated with local MSC had statistically significant increases in postural positioning, 12-week CMAP amplitudes, and 16-week axon counts. Similarly, A-HLT rats treated with local MSC exhibited significantly increased axon counts, correlating with decreased intraneural collagen deposition. Systemic MSC treatment resulted in increased 12-week CMAP amplitudes in SNTR rats and increased axon counts in A-HLT rats. However, the single dose MSC treatment did not prolong graft survival.
Conclusions: Local and systemic MSC injections improve the pace and degree of nerve regeneration after nerve injury and hind-limb transplantation.

BO358 CUTANEOUS COLLATERAL AXONAL SPROUTING RE-INNERVATES THE SKIN COMPONENT AND RESTORES SENSATION OF DENERVATED SWINE OSTEOMYOCUTANEOUS ALLOFLAPS

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Johns Hopkins University

Background: Sensorimotor recovery is a critical determinant of overall success of reconstructive transplants. Although the recovery of motor function has been studied extensively, the mechanisms of sensory re-innervation are not well established. Recent clinical reports of face transplants confirm progressive sensory improvement even in cases where optimal repair of sensory nerves was not possible. This can be attributed to slow and steady collateral axonal sprouting from the periphery.
Methods: Denervated osteomyocutaneous flaps ($n = 3$) in the form of a heterotopic hind limb transplant from MHC-defined MGH miniature swine were used to explore the contribution of collateral sprouting in sensory re-innervation. Immunotherapy consisted of donor bone marrow infusion, costimulatory blockade and short term Tacrolimus monotherapy. Serial sections were immunostained against a pan-axonal marker (PGP9.5) to visualize regenerating axonal structures in the epidermis. Collateral axonal sprouting rates were quantified using established stereology techniques.
Results: In all denervated alloflaps collateral axonal sprouts from adjacent recipient skin grew into the denervated skin component along the dermal-epidermal junction towards the center of the flap. On day 100 post-transplant, regenerating sprouts reached 0.5 cm into the flap centripetally. Eight months following transplant, scattered axonal fibers were visualized 1.5 cm from the margin (rate of regeneration 60 μm/day). All animals had pinprick sensation in the peripheral part of transplanted skin within 3 months post-transplant.
Conclusion: Collateral axonal sprouting from the periphery can extend along the dermal-epidermal junction to provide cutaneous re-innervation to the skin component of reconstructive transplants. Return of normal sensation through collateral axonal sprouting can revive interaction with the environment, initiate defense mechanisms and aid in cortical re-integration of such transplants.

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BO359

INVESTIGATION OF PERSUFFLATION (PSF) AS A NOVEL METHOD OF COMPOSITE TISSUE (CT) PRESERVATION FOR REPLANT AND TRANSPLANT IN A PIG MODEL

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Background: Tissue preservation is a major issue in CT replantation and transplantation. Presently, CT must be revascularized in 4–6 h. PSF is an emerging preservation method, which has shown promise in liver and islet transplantation. We hypothesize that by providing continuous vascular oxygenation, PSF will improve upon traditional preservation and enable preservation ≥24 h. If this is achieved, outcomes may be significantly improved by enabling longer transfer times and better HLA matching.
Methods: 10 forelimbs were procured from 56 to 68 kg heparinized donor pigs following cardiac arrest. Forelimbs were flushed via the brachial arteries with 1L HTK solution and packed with ice. PSF was performed via the brachial arteries using a portable electrochemical oxygen concentrator (Giner Inc, USA) with 25 cc/min of 40% oxygen gas. Efficacy was assessed visually when submerged in water. MRI and 31P-NMR spectroscopy were performed at 4.7T to assess gas distribution and monitor ATP.
Results: Brachial arteries were cannulated and gas delivered to all tissues. Gas was observed exiting from the cut bone and cephalic vein for all forelimbs. MRI of the distal forelimb confirmed the presence of gas in the muscle plane, vessels within the toes and subcutaneous veins.31P-NMR spectra exhibited no detectable ATP in static cold preserved tissue whereas ATP was observed in persufflated tissue. PSF was continuously performed on CT for 24 h with stable pressures and no deterioration of muscle tissue or edema observed.
Conclusion: This study establishes the feasibility of PSF to extend CT preservation to ≥24 h. Oxygen gas can be delivered throughout CT as demonstrated by MRI. Unlike cold storage, PSF maintained ATP during preservation. CT-PSF may enable the establishment of a nationwide distribution network providing improved color, size, and HLA matching for transplant. In addition, PSF may extend preservation times prior to replantation. Further investigation of CT-PSF is warranted.

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LATE BREAKING ORALS

WEDNESDAY, SEPTEMBER 11, 2013
LATE BREAKING LB01–LB06

LB01 CHEMOTHERAPY OR LIVER TRANSPLANTATION FOR NON-RESECTABLE LIVER METASTASES FROM COLORECTAL CANCER?

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Background: Oncological treatment of non-resectable colorectal liver metastases (nrCLM) is palliative only; 5 year overall survival (OS) is <10%. We have demonstrated 5 year OS of 60% after Liver Transplantation (Lt) for nrCLM. (Hagness M et al. Ann Surg 2013; 257:800–806). Here, we compare these results with nrCLM confined to liver from the chemotherapy study Nordic VII. (Tveit KM et al. J Clin Oncol 2012; 30:1755–1762).
Materials/Methods: Forty-seven patients with non-resectable, liver only metastases, age of <66 years and no BRAF mutations were identified from the NORDIC VII study database, a randomized multicenter phase III trial on Flox vs. two different regimens on Flox and Cetuximab; no difference between study arms. These were compared with 21 patients receiving Lt for nrCLM.
Results: Five year OS was 4.1% in the chemotherapy group, 60% in the Lt group, ($p < 0.001$) For the 21 patients with longest survival with chemotherapy the 5 years OS were 8.6% ($p = 0.077$). For patients that had progressed on all standard lines of chemotherapy, the median OS was 7 months in chemotherapy group ($n = 26$), 40.5 months in Lt group ($n = 6$; $p = 0.004$; Figure 1).
Conclusion: For non-resectable liver only CLM; Lt seems superior to chemotherapy.

LB02 PRESERVING RENAL FUNCTION WITH PROLONGED-RELEASE TACROLIMUS-BASED IMMUNOSUPPRESSION IN *DE NOVO* LIVER TRANSPLANTATION: INITIAL RESULTS FROM THE DIAMOND STUDY

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Background: DIAMOND: multicentre, randomised study to investigate renal function with once-daily, prolonged-release tacrolimus (QD; oral)-based immunosuppression.
Methods: Patients received: Arm 1: tacrolimus QD (initial dose: 0.2 mg/kg/day), Arm 2: tacrolimus QD (0.15–0.175 mg/kg/day) plus basiliximab; Arm 3: tacrolimus QD (0.2 mg/kg/day delayed to Day 5) plus basiliximab. All patients received MMF (IV 3–5 days then oral) and a single bolus of corticosteroid. Primary analyses (full-analyses set; FAS): eGFR (MDRD4) at Week 24. Secondary endpoints (per-protocol set) included graft and patient survival, and acute rejection (AR). Mortality rates were calculated using the safety-analyses set.
Results: Nine hundred and one patients randomised; FAS: 295, 286 and 276 in Arms 1–3, respectively. Baseline characteristics were comparable. Mean tacrolimus QD trough levels were initially lower in Arm 2 vs. 1 and 3; by Day 14, levels were comparable between arms and remained stable. Week 24: eGFR was higher in Arms 2 and 3 vs. 1 (76.4 and 73.3 vs. 67.4 ml/min/1.73 m^2; $p < 0.001$ and $p < 0.047$, respectively; ANOVA), and eGFR was numerically higher in Arm 2 vs. 3 (p = ns); renal function was preserved in all arms (Figure). Kaplan–Meier estimates of graft survival in Arms 1–3: 86.5%, 87.7% and 88.6% (p = ns; Wilcoxon–Gehan); patient survival: 89.3%, 89.1% and 90.4% (p = ns); and without AR: 79.9%, 85.7% and 79.6% (Arm 2 vs. 1: $p = 0.0249$, Arm 3 vs. 1: p = ns; Arm 2 vs. 3: $p = 0.0192$). Overall mortality rate: 5.1% and mortality rate for males versus females: 5.8% and 3.6%, respectively. AEs were comparable between arms, with a low incidence of diabetes mellitus and no major neurologic disorders.
Conclusion: An initial low dose of prolonged-release tacrolimus (0.15–0.175 mg/kg/day) plus MMF and induction therapy (without maintenance steroids) had better renal function and a significantly lower incidence of AR over 24 weeks versus the other regimens. There were no advantages observed with delaying the initiation of tacrolimus QD.

LB03 COMPARISON BETWEEN ORGAN PRESERVATION SOLUTIONS IGL-1, HTK, CELSIOR AND UW IN DECEASED DONOR LIVER TRANSPLANTATION (DDLT)

Mario Henrique Meine, Maria Lucia Zanotelli, Ian Leipnitz, Eduardo Schlindwein, Guillermo Kiss, Juliano Martini, Flavia Feier, Ajácio Brandão, Cláudio Augusto Marroni, Alfeu Fleck Jr, Marcus Mucenic, Guido Cantisani
Complexo Hospitalar Santa Casa

Introduction: Actually transplantations centers can use different types of preservation solutions and it have been shown useful to replace the gold standard UW solution in liver transplant. The growing use of extended donor, and cost effectiveness are issues to be considered to find the better solution to preserve livers.
Method: Prospective cohort since January 2010 to May 2013. Patients submitted a DDLT were allocated in four groups according availability of each solution in our center during this time. The statistical analyses were performed by SPSS software using logistical regression, chi square and Fischer exact tests when appropriate.
Results: One hundred and eighty one liver transplant receptors with cirrhosis caused by B or C virus, alcohol, hemochromatosis, primary biliary cirrhosis or sclerosing cholangitis, which 66.3% with hepatocellular carcinoma, were studied in IGL-1 (71, 39.2%), HTK (58, 32.1%), Celsior (36, 19.9%) and UW (16, 8.8%) groups. The receptor age, race, gender and MELD score were similar between groups. The donor age, race, gender, hemodynamics variables, cold ischemia time and Donor Risk Index means were similar between groups. The incidence of delay graft function (DGF) was 5.6% with IGL-1, 5.2% with HTK, 5.6% with Celsior and 12.5% with UW ($p > 0.05$). The incidence of primary non function (PNF) was 2.8% with IGL-1, 1.7% with HTK, 16.7% with Celsior and 6.3% with UW ($p = 0.016$). The incidence perioperative death for any cause was 13.8%, within 11.3% in IGL-1, 12.1% in HTK, 22.2% in Celsior and 12.5% in UW group ($p > 0.05$). The Odds Ratio to PNF with Celsior was 14.0 (CI 95% = 1.5–131.4; $p = 0.021$).
Conclusion: All four preservation solutions seem to be efficient to protect liver grafts to DDLT. The major incidence of PNF and consequent perioperative death in Celsior group needs to be further reviewed.

LB04 ONCE-DAILY LCP-TACRO DEMONSTRATES COMPARABLE EFFICACY AND SAFETY TO TWICE-DAILY PROGRAF: A PHASE 3 STUDY FOR PREVENTION OF ACUTE ALLOGRAFT REJECTION IN *DE NOVO* ADULT KIDNEY TRANSPLANT RECIPIENTS

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Background: In prior studies in stable renal transplant recipients converted from Prograf to LCP-Tacro, LCP-Tacro showed greater bioavailability, a more consistent concentration profile, non-inferior efficacy and similar safety and with lower total daily dose.
Methods: The design was a double-blind, double-dummy, multicenter study to establish the efficacy and safety of LCP Tacro Tablets for prevention of allograft rejection in *de novo* adult kidney transplant recipients. Primary efficacy was evaluated at Month 12 by a composite endpoint comprised of acute rejection, graft loss and patient loss with a pre-specified non-inferiority margin of 10%.
Results: Five hundred and forty three patients were randomized across Europe, USA, Latin America and Asia-Pacific. LCP-Tacro demonstrated non-inferiority to Prograf® based on the composite endpoint of treatment failure (LCP-Tacro 18.3%, Prograf 19.6%). Treatment failure rates through the first three months were 10.4% and 14.2% respectively. The safety analyses of adverse events showed no statistically significant differences. LCP-Tacro patients rapidly attained targeted trough levels within 2 days of first dose while Prograf levels were achieved within ~7 days.
Conclusions: The results of this large well-controlled trial suggest that new kidney transplant patients can begin with a regimen of once-daily LCP-Tacro without compromising efficacy and tolerability. Results demonstrated that from Month 3 onwards, LCP-Tacro patients required a daily dose that was lower than patients receiving Prograf, reflecting the improved absorption provided by MeltDose® formulation.
Figure 1: Primary endpoint.
Figure 2: Rapid attainment of therapeutic. Blood Levels (Targeted Levels: Days 1–30, 6–11 ng/ml and Days 31–365, 4–11 ng/ml).

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LB05 CNI- AND STEROID-FREE IMMUNOSUPPRESSION AFTER SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION: ONE-YEAR RESULTS OF A PROSPECTIVE AND RANDOMIZED STUDY

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We report here the actual one-year efficacy and safety results of a single-center, prospective and randomized study comparing tacrolimus-based (Tac) against sirolimus-based (SRL) immunosuppresssion after SPK-Tx. A total of 100 type-1 diabetic patients (mean age 40 years; range 21–56) were included. All patients received a cadaver SPK-Tx (whole pancreas with portal and enteric drainages), Thymoglobulin induction for 5 days, mycophenolate mofetil,Tac and low-dose steroids. Between day 60 and 90, SRL replaced Tac in 50 patients. After achieving normal SRL trough level, steroids were stoped in all Tac and SRL patients (Tac/MMF and SRL/MMF). The study design included a 1-year protocol kidney biopsy and a follow-up of 5 years. The actual 1-year patient, pancreas and kidney survival was 100%, 84% and 100% in the Tac group, and 100%, 88% and 100% in the SRL one (intention to treat analyses). The 1-year freedom from clinical diagnosed and treated kidney and pancreas rejection episode was 90% and 96% in the Tac group, and 86% and 86% in the SRL one. Serum creatinine (μmol/l) and proteinuria (g/day) at one year was 122 (range 61–289) and 0.32 (0–1.03) in the Tac group, and 115 (57–412) and 0.38 (0–1.5) in the SRL one. Nine months after randomization (1 year after Tx), 96% of patients in the Tac group were still under Tac compared to 54% in the SRL one ($p < 0.001$). One-year kidney protocol biopsies showed more active immune lesions in the SRL group as well as significantly more patients with *de novo* DSA (14 vs. 5, $p < 0.05$). In conclusion, at one year following SPK-Tx, Tac-based immunosuppression compared to SRL-based immunosuppression was better tolerated with significant less number of patients switched, was associated with less acute rejection episodes, less active immune renal histology features and less *de novo* DSA.

LB06 *IN-SITU* NORMOTHERMIC REGIONAL PERFUSION (NRP) – A REVOLUTION IN CATEGORY 3 DCD ORGAN RETRIEVAL? THE UK EXPERIENCE

Gabriel Oniscu[1], Lucy Randle[2], Paolo Muiesan[3], Andrew Butler[2], Ian Currie[1], Thamara Perera[3], John Forsythe[1], Christopher J.E. Watson[2]

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Background: Organ recovery is undergoing a revolution with the introduction of *in situ* warm perfusion. This study presents the initial UK experience with organ retrieval from Maastricht category 3 DCD donors using in-situ normothermic regional (abdominal) perfusion (NRP).
Methods: Sixteen NRP DCD retrievals were performed at three UK centres. NRP was established post-asystole via laparotomy, aortic and IVC cannulation and maintained for two hours prior to organ retrieval. Lung retrieval was carried out with isolated cold thoracic perfusion. Blood gases and biochemistry were monitored every 30' to assess organ function.
Results: Forty-seven organs (29 kidneys, 8 livers, 4 pancreata and 3 lung pairs) were recovered (2.93/donor vs. 2.6 national average) and transplanted in 37 recipients. The median donor functional warm ischaemic time was 23′ (15′–31′) whilst the time from asystole to NRP was 16′ (10′–23′). The median donor age was 46 years old (19–74). Two donors were on CVVHD. Twenty-four patients received a kidney transplant (3 double) with a median cold ischaemic time (CIT) of 12 h22′ (5 h25′–18 h22′). The median creatinine at 1 and 3 months was 110 μmol/l (73–367) and 109 μmol/l (72–217) respectively. 5/24 kidney recipients had delayed graft function (20.8% vs. 50% national average). Four kidney recipients lost the grafts (2-venous thrombosis, 1-thrombotic microangiopathy, 1-infarction). Eight patients received a liver transplant with a median CIT of 4 h10′ (2 h49′–6 h21′). The median peak ALT during 1st week was 257 (58–3043). One patient had PNF requiring re-transplantation. Two SPK transplants and three double lung transplants were performed with primary function. The rate of organs transplanted from all potential organs was higher than the current national rates for kidney (93% vs. 82%), liver (50% vs. 30%) and lungs (18% vs. 4%).
Conclusions: This initial experience indicates that NRP increases organ recovery with beneficial short term outcomes compared to standard cold perfusion DCD retrievals.

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OS37-KIDNEY XII

O299 EVOLUTION OF ROBOTIC NEPHRECTOMY FOR LIVING DONATION: FROM HAND-ASSISTED TO TOTALLY ROBOTIC

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Background: The application of Robotic-Assisted Surgery provides endo-wrist instruments and 3-D visualization of the operative field which are better than the ones offered by traditional laparoscopy. The results of the few research studies published so far have demonstrated that living donor nephrectomy using the Robot-assisted technique is safe, feasible, and provides advantages for the patients.
Materials and methods: Since November 2009, 16 patients underwent Robotic-assisted living donor nephrectomy at our Institute. Patients were divided into two groups because of the different surgical technique adopted for the procedure: Group A, hand-assisted robotic nephrectomy (eight patients); Group B, totally robotic nephrectomy (eight patients).
Results: Intra-operative bleeding was not significantly different between the two groups (respectively, 90 vs. 100 ml for Group A and B). The median warm ischemia time was significantly lower in the Group A (respectively, 2.3 vs. 5.1 min for Group A and B, p-value = 0.05). No case of conversion to open procedure occurred neither in the Group A neither in the Group B. Median operation time resulted not significantly longer in the Group A than Group B (respectively, 275 vs. 250 min).
Conclusion: Robotic assisted living kidney recover is a safe and effective procedure. Considering the overall technical, clinical, and feasibility aspects of the kidney living donation, we consider the robotic assisted technique to be the method of choice for surgeon's comfort and donors' safety.

O300 UNSPECIFIED LIVE DONATION IN CASE OF NEPHRECTOMY FOR MEDICAL REASONS

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Unspecified donations (altruistic donations) have been successfully implemented in our live donor kidney transplantation (KT) program. Amongst these donors were patients diagnosed with a kidney disorder not impairing renal function, but nonetheless requiring nephrectomy. These kidneys are often suitable for KT. As auto transplantation increases risk of complications, and has no benefit for these patients with normal renal function, unspecified kidney donation would be a good alternative. We searched all clinical data of our live kidney donation program from 1994 to 2013 for unspecified kidney donors and their recipients ($n = 77$). Of these, seven donors had pre-existing kidney disorders necessitating nephrectomy. We examined clinical course of these donors and recipients. Of seven patients, five had an indication for nephrectomy because of therapy-resistant loin pain, one had a renal artery aneurysm, and one insisted on a nephrectomy, refusing a urostomy. Of the five patients treated for loin pain, one previously had a small infarction of the kidney, one had persistent pain after stone extraction. All donor nephrectomies were performed without major complications and all patients treated for pain were free of complaints after surgery. Seven donors enabled 9 KT. In the recipients, there was one death due to cardiac arrest, in a patient with pre-existent cardiac failure. All others but one had excellent graft function.
Discussion: The possibility of KT from live donors with pre-existing kidney complaints necessitating a nephrectomy has not been reported previously. Obviously, these unspecified donors should meet all criteria for live kidney donation. Our data show that donation as part of the treatment in selected kidney disorders is possible with excellent results in both donors and recipients.

O301 VASCULAR MANAGEMENT DURING LIVE DONOR NEPHRECTOMY– AN ONLINE SURVEY AMONG ESOT SURGEONS

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Background: The number of live donor nephrectomies (LDN) is increasing. Since live donors are healthy individuals, it is essential to minimize complications. A survey, conducted among American Society of Transplant Surgeons members, showed significant hemorrhagic complications of vascular management (VM) during LDN. In the current study we assessed which vascular control methods are used, which are considered most safe, and the incidence of hemorrhagic complications.
Methods: After amending the aforementioned survey, an online survey was sent to 598 European Society for Organ Transplantation members, who profiled their profession as "surgeon" and selected "kidney" as organ type. Questions included: used LDN techniques, used vascular control methods, experience of technical failures, and control methods considered most safe.
Results: Of the 243 returned surveys (41%), only those of who perform LDN (64%) were included in the results. Preferably 67% would perform endoscopic and 33% would perform open LDN. In venous and arterial VM, the GIA stapler and TA stapler are used most frequently. Oversowing is also used frequently for the vein, and suture ligature with simple ties for the artery. Although GIA stapler (66%) is considered most safe for veins and TA stapler (63%) for arteries, other closing methods are being used. Sixty-six venous and arterial complications were reported, mainly by slipping (locking) clips (45%) and stapler malfunction (38%), resulting in blood transfusions, conversion and even death. Geographically, there is a widespread variety in LDN techniques as well as VM within Europe.
Conclusion: Hemorrhagic complications of LDN with fatal and non-fatal outcome still occur in Europe. They vary by preferred technique of LDN and the used control methods for VM. Strikingly, many surgeons do not use the vascular control method that they consider most safe. More research is needed to assess the used methods and their failures, to strive for maximal donor safety.

O302 CORRELATION BETWEEN PRE AND POST-TRANSPLANT RENAL GRAFT VASCULAR RESISTANCE MEASURES AS PREDICTORS OF ACUTE TUBULAR NECROSIS

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Objective: To evaluate the relationship between pre-transplantation Renal Resistance (RR) – as measured with Hypothermic Machine Perfusion (HMP) – and Resistance Index (RI) measured with Doppler-ultrasonography in the immediate post-transplantation period.
Methods: Retrospective analysis of 22 kidneys from Donors after Cardiac Death (DCD) Type II and 36 kidneys from Expanded Criteria Donors after Brain Death (DBD), transplanted from 2009 through 2011, all preserved with HMP. The degree of correlation between RR and RI was assessed through a simple linear regression. Grafts with clinical criteria for Acute Tubular Necrosis (ATN) were analyzed.
Results: DBD kidneys had a lower RR than DCD kidneys (0.22 v 0.29 mmHg/ml/min; $p = 0.02$). However, no differences were found among these groups regarding RI (0.78 vs. 0.73; $p = 0.12$). Simple linear regression failed to prove a significant degree of correlation between pre-transplant RR and post-transplant RI ($p = 0.76$). A higher number of clinical ATN cases was found in the DCD group in comparison to the DBD group (75% v. 25%: $p < 0.001$). In five cases, an elevated RI was associated with histological confirmed ATN (sensitivity 18%, specificity 57%). Just one case of ATN and venous thrombosis required transplantectomy.
Conclusions: RR and RI are used to evaluate the hemodynamic situation of the graft. Even though both are surrogate measures of renal vascular resistance, they are neither correlated nor able to predict ATN in this study. The different environments in which these measures are taken may be accountable for these results *in vivo* assessment with RI can be affected with a higher amount of clinical variables than *ex vivo* evaluation of RR, obtained as a calculation from direct measurement of renal flow and pressure. This study may be further affected by selection bias, considering that only kidneys with low RR (<0.4) are deemed viable for transplantation and probably those with higher RR that are rejected would have more risk of ATN.

O303 HAND-ASSISTED LIVING DONOR NEPHRECTOMY: A COMPARISON OF TWO TECHNIQUES

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Background: Living donor nephrectomy (LRDN) is challenging as surgery is performed in healthy individuals. Meanwhile minimal invasive techniques for LRDN have become standard such as pure laparoscopic, hand-assisted laparoscopic (HALS), hand-assisted retroperitoneoscopic (HARS) and pure

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retroperitoneoscopic. According to literature hand-assisted approaches results in lower morbidity and are recommended for this very reason. In Zurich University Hospital both HARS and HALS are performed. This analysis aims to explore the impact of these two surgical techniques on donor outcome.
Methods: Between 10/2010 and 12/2011 a total of 42 consecutive LRDNs (HALS $n = 21$; HARS $n = 21$) were preformed. In HARS the hand port is introduced at the very beginning whereas in HALS at the end of operation. The incision for the handport is made at lower abdomen in both. For HARS 2–3 and for HALS 3–4 additional trocars were used. Retrospective analysis was performed to compare the two operative techniques.
Results: There was no mortality and no conversion to open surgery was necessary. Right kidneys were recovered in 62% by HARS and in 43% by HALS procedure. Overall complication rate was smaller for HARS compared to HALS (10% vs. 19%) and severity was little (max. Clavien Score Grade 3b). There was a tendency for shorter median hospital stay for HARS (5 days, range 2–10 vs. HALS 6 days, range 3–18). HALS donors required significantly more stimulation with laxatives and presented a higher incidence of postoperative nausea and vomiting. Pre- and postoperative delta creatinine was similar for both groups. There was no primary graft non-function.
Conclusions: Both presented techniques appear safe for donors and donated organs. HARS seems to be associated with donor benefits, being reflected by shorter hospital stay, fewer scars and lesser incidence of associated morbidities. Contrary to the present literature HARS and HALS can easily be applied for right sided donation.

O304 THE DISCREPANCY BETWEEN BIOLOGICAL AGE AND CALENDAR AGE: A LARGE HISTOLOGY STUDY IN IMPLANTATION BIOPSIES

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Background: The histology and function of the kidney deteriorates with age. Replicative senescence caused by telomere shortening plays an important roll in this aging process (biological aging). The relationship between donor demographics, calendar age, telomere length and renal histology is currently unknown.
Results: Mean telomere length was 1.1 ± 0.53. Mean donor calendar age was 47.6 ± 14.0. 35.6% of donors died from stroke, and 32.1% were extended criteria donors. Telomere length in peripheral blood correlated highly significantly with donor calendar age ($r = -0.3$; $p = 0.0002$), which is concordant with previous literature data. Older donor calendar age was highly significantly associated with baseline histology of interstitial fibrosis, tubular atrophy and glomerulosclerosis (all $p < 0.01$). Although there was a significant correlation between donor calendar age and telomere length, there was no association between the histological appearance of the baseline biopsy and telomere length. None of the other donor demographic variables correlated with telomere length in donor peripheral blood. Donor cardiovascular risk factors associated significantly with arteriolar hyalinosis and vascular intimal thickening, but did neither associate with donor calendar age nor with telomere length. This dichotomy between calendar-age associated renal histological lesions and cardiovascular risk-associated lesions was confirmed by principal component analysis.
Conclusions: Calendar age and cardiovascular risk determine renal histological damage, but biological aging and telomere shortening do not associate with histological damage of renal tissue. The current study suggests that biological aging in itself does not lead to alterations in renal histology. Additional studies that evaluate the senescent phenotype (micro-array gene expression and immunohistochemistry) of baseline biopsies before kidney transplantation are underway, to investigate this unexpected finding.

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OS38-KIDNEY XIII

O305 GENETIC PREDISPOSITIONS FOR THE DEVELOPMENT OF NEW-ONSET OF DIABETES AFTER KIDNEY TRANSPLANTATION

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Background: New-onset diabetes after transplantation (NODAT) is a serious consequence after transplantation. Peroxisome proliferator activated receptor α (PPARα) and P450 oxidoreductase (POR) play a central role in controlling energy metabolism. *PPARα* rs4253728G>A and *POR* rs1057868 (*POR*28*; A503V) affect the activity of their encoded proteins, which may thus influence NODAT occurrence.
Methods: Medical records from 101 renal transplant patients receiving Tacrolimus-based immunosuppressive therapy were screened for development of NODAT and compared with *PPARα* and *POR* genotypes, using Kaplan–Meier and Cox's proportional hazard analysis.
Results: *PPARα* and *POR*28* SNPs were independently associated with an increased risk of developing NODAT with OR 8.6 (CI95% = [1.4; 54.2], p = 0.02) and 8.1 (CI95% = [1.1; 58.3], p = 0.04), respectively. Other risk predictors included gender and body weight.
Conclusions: Polymorphisms in *PPARα* and *POR* might predispose to the development of NODAT.

O306 SIMULTANEOUS LIVER-KIDNEY TRANSPLANTATION FOR ATYPICAL HEMOLYTIC UREMIC SYNDROME DUE TO A FACTOR H DOUBLE MUTATION

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Atypical hemolytic uremic syndrome (aHUS) is caused by genetic abnormalities in the complement system leading to thrombocytopenia, hemolytic anemia, and acute kidney injury. Factor H mutations are found in the majority of patients with aHUS resulting in end-stage renal failure. The clinical course consists of high rates of disease recurrence after isolated kidney transplantation with a significant risk for graft loss. Perioperative plasma exchange to supplement factor H has been reported to prevent early graft dysfunction. We report a 29-year old woman who was diagnosed with aHUS. Sequencing of the *CHF* gene revealed two heterozygous mutations in the short consensus repeat 4 (c.720T>C, p.Ile216Thr) and 8 (c.1586T>G, p.Cys505Gly). She developed end-stage renal failure in 2007. Six years after diagnosis, a simultaneous liver-kidney transplantation was performed. The immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil, and prednisone. Additionally, she received pre- and postoperatively plasma exchange and intraoperatively plasma infusion during the anhepatic phase to provide functional factor H and prevent complement activation. The postoperative course was uneventful with immediate function of both grafts. Plasma exchange was performed daily in the first and bi-daily in the second week post-transplant. Her GFR, LDH and blood cell count remained normal. Currently, 6 weeks post-transplant, there is no evidence for complement activation.

O307 ECULIZUMAB IN KIDNEY TRANSPLANTATION: SHOULD WE CHANGE OUR TREATMENT ALGORITHM?

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Eculizumab is generally used post-kidney transplant as a rescue therapy in patients with *de novo* HUS and severe AMR which are resistant to conventional treatments. However, severe AMR and *de novo* HUS might present with an acute onset of renal dysfunction and histologic changes in the graft rapidly progressing to renal cortical necrosis resulting in allograft loss. We present two cases of severe AMR and a single case of severe *de novo* HUS which were resistant to conventional therapies and eculizumab was given as a salvage treatment. Case 1: A 26-year-old patient with a DSA (HLA-B13 > 7000 MFI and C1q assay was negative) had a LRDK transplant after desensitization with reduced DSA (MFI < 3000). The patient had an AMR which was resistant to conventional therapies with PP/IVIg and rituximab and received eculizumab on POD 22. The patient responded to therapy and was discharged with a serum cr of 1.8 mg/dl. Case 2: A 46-year-old patient with a DSA (HLA-DR4 > 20 000 MFI and C1q assay was positive) had a LRDK transplant from her husband after desensitization with reduced DSA (MFI < 8000). The patient had a severe AMR presenting with acute oligouria and graft biopsy on POD 5 revealed severe AMR with cortical necrosis. The patient was resistant to conventional therapy with PP/IVIg and rituximab and a repeat biopsy revealed worsening cortical necrosis. The patient received eculizumab and no remarkable clinical response was observed and a third kidney biopsy on POD 47 showed diffuse cortical necrosis. Treatment was stopped and she was discharged from the hospital on hemodialysis. Case 3: A 30-year-old patient had severe *de novo* HUS on POD 2 with oligouria and rising creatinine following LRDK transplant and graft biopsy on POD 4 showed diffuse TMA rapidly progressing to cortical necrosis. Eculizumab was started on POD 7 without waiting the clinical response for conventional therapies. The patient was discharged with a serum cr level of 1.95 mg/dl. Given the bad prognosis for renal transplantations displaying acute injury progressing rapidly to cortical necrosis on the biopsy, the prompt use of eculizumab could have the advantage of immediate effects by stopping cellular injury.This can provide a therapeutic window to allow conventional treatment modalities.

O308 EFFICACY AND SAFETY OF VILDAGLIPTIN IN NEWLY DIAGNOSED DIABETES AFTER KIDNEY TRANSPLANTATION

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Introduction: New-onset diabetes after transplantation (NODAT) is a severe complication after kidney transplantation. Dipeptidyl peptidase-4 (DPP-4) inhibitors seem to be an interesting novel approach for the treatment of NODAT. The aim of this study was to assess the safety and efficacy of the DDP-4 inhibitor vildagliptin in kidney transplant patients.
Methods: This randomized, placebo-controlled, double-blind, phase II trial was performed to assess the glycemic control in patients with newly diagnosed NODAT as defined by a 2-h plasma glucose (2HPG) level ≥200 mg/dl. A total of 32 patients were randomized to receive vildagliptin or placebo for 3 months. Thereafter, oral glucose tolerance tests (OGTTs) were performed and HbA1c levels along with body mass index (BMI), metabolic and safety parameters were evaluated.
Results: There were no differences in baseline data with regard to fasting plasma glucose, HbA1c, 2HPG, time after transplantation, immunosuppression, and BMI. In the vildagliptin group 2HPG (vildagliptin: 182.7 mg/dl; placebo: 231.2 mg/dl; $p \leq 0.05$) and HbA1c (vildagliptin:6.1%; placebo: 6.5%; $p \leq 0.05$) values were significantly reduced. Furthermore, HbA1c was still significantly reduced one month after study drug discontinuation. Adverse events were mild in nature and occurred at a similar rate in both groups. Discussion: Vildagliptin was safe and efficacious in patients with newly diagnosed NODAT after renal transplantation.

O309 THE EFFECT OF SITAGLIPTIN TREATMENT ON HYPERGLYCEMIA AND INSULIN SECRETION AFTER RENAL TRANSPLANTATION

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Background: New-onset diabetes after transplantation (NODAT) is a common complication after renal transplantation. Treating diabetes in this population is a challenge due to potential interactions with the immunosuppressant drugs or adverse effects related to increased cardiovascular risk. DPP-4 inhibitors may represent a novel alternative.
Methods: Twenty-five renal transplant recipients with impaired glucose tolerance (IGT) or NODAT were included in a controlled, cross-over study and randomized to first receive either sitagliptin 50–100 mg/day or a drug free period of 4 weeks. Home measurements of plasma glucose and repeated oral glucose tolerance tests (OGTT) with insulin and C-peptide responses were performed. Endothelial function was determined with laser Doppler flowmetry.
Results: The average age was 63.6 ± 10.9 years (16 males/nine females), studied 3.5 ± 5.3 years after transplantation. The patients received cyclosporine (n = 18), tacrolimus (n = 5) or everolimus (n = 3) combined with mycophenolate (n = 23) and prednisolone (n = 24). The first- (87.7 ± 136.9%, p = 0.002) and second phase insulin secretion (43.8 ± 57.8%, p = 0.003) were significantly increased by sitagliptin while both fasting (−0.9 ± 1.2 mM) and 2 h plasma glucose (−2.4 ± 3.3 mM) were significantly reduced

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($p = 0.001$). Home measurements of plasma glucose four times daily also showed a consistent reduction in plasma glucose (-0.8 ± 0.7 mM, $p = 0.001$). Endothelial function and plasma markers for cardiovascular risk remained unaffected. No serious adverse events were observed.
Conclusion: Sitagliptin significantly reduces fasting and postprandial plasma glucose by increased insulin secretion and is well tolerated in renal transplant recipients with NODAT.

O310 ECULIZUMAB IN ATYPICAL HAEMOLYTIC URAEMIC SYNDROME (AHUS) PATIENTS WITH OR WITHOUT PRIOR TRANSPLANT

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Background: Case reports suggest that eculizumab (Ecu) inhibits complement-mediated thrombotic microangiopathy (TMA) and prevents graft loss in patients with TMA post-transplant (Zuber J, Am J Transplant 2012;12:3337).
Methods: Ecu efficacy and safety were evaluated in two single-arm, 26-week phase two trials with long-term extensions in 37 aHUS patients aged ≥ 12 years. Outcomes in non-transplant (NT, $n = 10 + 12$) and prior transplant (T, $n = 7 + 8$) aHUS patients with 2 years of ongoing Ecu treatment were analysed.
Results: Ecu improved renal function in all groups. In patients with progressing TMA improvement was greater in NT versus T patients ($p = 0.0165$; Table). Baseline eGFR was not predictive of eGFR change in any group. Earlier treatment was associated with greater eGFR gain ($p < 0.05$).
Conclusions: Ecu is effective in improving renal function in NT and T patients. The data support early initiation of Ecu treatment to preserve renal function and suggest that prophylactic Ecu treatment in aHUS patients undergoing transplant may be of benefit.

Table 1. Baseline characteristics and 2-year efficacy outcomes in Ecu-treated patients with or without prior transplant. eGFR, estimated glomerular filtration rate; MDRD formula used in adults >18 years and Schwartz formula in children.

*Platelet count $< 150 \times 109$/L after $\geq$4 plasma exchange/infusion sessions in the prior wk with average platelet count decrease >25% prior to most recent TMA presentation. Median Ecu duration 100 week. † Receiving chronic plasma exchange/infusion on a stable regimen with no platelet count decrease >25% during 8-wk observation period before Ecu treatment. Median Ecu duration 114 week. § 1 pt had two prior transplants. #3 pts had two prior transplants. **Months.

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OS39-TECHNICAL ASPECTS AND COMPLICATIONS IN LIVER TRANSPLANTATION

O311 TWO ARTERIAL ANASTOMOSIS IN LIVER TRANSPLANTATION

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Background: Arterial revascularization during liver transplantation (LT) is normally achieved by anastomosing the graft hepatic artery to the largest artery available at the recipient pedicle – either the common hepatic artery (CHA) or an accessory right hepatic artery (RHA) originating from the superior mesenteric artery (SMA). When a small caliber RHA is present, the artery is ligated and a single anastomosis with the CHA is performed. In the absence of a vascular reconstruction of the graft, the gastroduodenal artery (GDA) is usually ligated as well.
Methods: We describe a new type of arterial anastomosis in the case of a small accessory RHA and/or severe graft hepatic artery atherosclerosis that is commonly seen in elderly donors.
Results: his technique can be easily performed without increasing the arterial revascularization time or increasing the risk of complications associated with arteriosclerotic arteries. A 12 months follow-up revealed excellent function of the liver graft.

O312 THROMBOSIS OF PORTAL VEIN AND HEPATIC ARTERY AFTER OLT WITH MODIFIED CAVOPORTAL HEMITRANSPOSITION

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We report a case of orthotopic liver transplantation (OLT) with modified cavoportal hemitransposition. The patient underwent OLT for hepatitis B virus-related cirrhosis with diffused portomesenteric vein thrombosis (PVT), and underwent splenectomy 9 years ago before OLT. At day 7 and 10 after OLT, caused of severe liver dysfunction, we found thrombosis formed in donor portal vein system and hepatic artery under doppler and digital subtraction angiography (DSA). After thrombolytic therapy, the blood into allografted liver recoveried and the liver function returned to normal. During 7 months follow-up, the patient is alive and with continuously normal hepatic function. For the recipients with diffuse portomesenteric vein thrombosis (PVT), orthotopic liver transplantation (OLT) with modified cavoportal hemitransposition is an effective choice. The blood from vena cava can increase the flow into portal vein of allografted liver so as to keep the donor work normally.

O313 COMBINED AORTIC VALVE REPLACEMENT AND LIVING DONOR LIVER TRANSPLANTATION: CASE REPORT

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A 58 year-old woman was presented with decompensated cryptogenic cirrhosis (MELD = 15, Child-Pugh Class C). During liver transplantion (LT) work-up, she was found with NYHA class II dyspnea and echocardiography showed severe aortic stenosis (AS) (valve area = 0.8 cm^2, transvalvular peak stress gradient = 70 mmHg, and ejection fraction = 57%). Potential living donor candidate was found suitable for right liver donation. In a multidisciplinary conference where the case was discussed extensively, the decision was made that a combined aortic valve replacement (AVR) and living donor LT (LDLT) would be the best treatment option. First, the patient underwent successful AVR with the use of a bioprostethic valve (No:21 St. Jude Medical-Biocor Aortic Valve). After weaning from extracorporeal circulation (time = 90 min), heparin was reversed and median sternotomy was left open. Recipient hepatectomy was completed concomitantly with donor hepatectomy. Right lobe LDLT was performed with the side clamping of the inferior vena cava. The total time of surgery was 11 h and 45 min. The patient had an uneventful postoperative course with an ICU stay of 5 days and a complete hospital stay of 15 days. The echocardiography performed at 1st and 6th postoperative months showed normal aortic valve function. Severe AS considerably increases the risk of non-cardiac surgery, meanwhile, mortality of cardiac surgery has been shown to significantly increase in Child-Pugh class C patients. To optimize the outcome, the decision to perform combined AVR-LDLT was made in this case. The elective nature of LDLT provides optimal timing for cardiac surgery. The theoretical advantage of the use of bioprosthetic valve is freedom from anticoagulation. To the best of our knowledge, this is the first reported case of combined AVR and LDLT.

O314 LIVE DONOR LIVER TRANSPLANTATION USING DUAL GRAFTS

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Most important factor for the success of live donor liver transplantation (LDLT) is good size matching between donor and recipient. But some donor and recipient pair cannot progress to transplantation with usual single lobe graft due to various reasons. If donor remnant liver volume is less than 35% of total liver volume or moderate fatty change of liver more than 30%, right lobe donation in not recommended. And if graft-recipient weight ratio (GRWR) of right lobe graft is less than 0.8%, small-for-size syndrome may developed and resulted in poor outcome. Dual donor LDLT which using two grafts for one rescipient is a good alternative modality for these group. In Asan Medical Center, we performed 331 cases of dual graft LDLT from 2000 to 2011. Mean GRWR of dual graft LDLT was 1.03, which is similar with that of single right lobe graft (GRWR was 1.04). Though this method requires three operation simultaneously, if two left lobe grafts were used its overall donor complication rate is smaller than standard right lobe graft. Various combinations are possible between various grafts including left lateral segment, left lobe, right lobe and right posterior segment. This combination is decided by recipient's requirement and donor liver condition and right-left proportion. Most common course of dual graft is cooperative regeneration but competitive regeneration can be occurred between two grafts. But atrophy of inferior graft occurred slowly and due to its gradual functional shifting to dominant graft, recipient's condition was good without any complication. Acute cellular rejection rate after dual graft LDLT is similar to that of single lobe graft. It can be occurred in unilateral graft or bilateral grafts. Overall survival results for dual graft LDLT after learning curve is similar to that of single graft LDLT. In conclusion, dual grafts LDLT is a good alternative option to the selective donor-recipient patients who cannot perform conventional single graft.

O315 INEFFECTIVE BRIDGING TREATMENTS FOR HEPATOCELLULAR CARCINOMA IN LIVER TRANSPLANT RECIPIENTS: HIGHEST RISK FACTOR FOR TUMOR PROGRESSION

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Background: Locoregional treatments (LRT) for HCC in liver cirrhosis in patients suitable for liver transplantation (LT) allows a significant decrease of patients drop-out from the LT waiting list, improving of post-LT recurrence free-survival, and improving of the overall intention-to-treat survival. Tumor progression before LT seems to be a significant independent risk factor associated with poor post-LT prognosis.
Methods: Between January 2000 and December 2007, 118 patients underwent LT after LRT for HCC on liver cirrhosis. We analyzed the association between the efficacy of the last LRT before LT and the risk of tumor progression. We have analyzed the 5 year survival rate and recurrence free survival rate basing on efficacy of LRT before LT and tumor response to the pre-LT LRT. Patients were stratified in two groups: Group A (tumor progression before LT); group BCD (complete, partial or stable disease before LT). Results

Distribution of effective LRT resulted significantly higher in the group BCD than in the group A (respectively, 76.3% e 38.0%, p-value = 0.000). Five-year recurrence free survival resulted significantly higher among patients who received effective LRT than patients who have received ineffective LRT (respectively, 93.6% vs. 75.5%, p-value = 0.016). Effective LRT resulted an independent risk factor for lower recurrence free survival and higher risk of tumor progression prior to LT.
Conclusions: Evaluation of LRT efficacy prior to LT appears a valid tool for predicting risk of tumor progression and, subsequently, risk of poor recurrence free survival rate. The inefficacy of LRT resulted a highly significant risk factor at the univariate and multivariate analysis for poor post-LT prognosis. Future prospective studies may clarify what would be the best clinical management of patients who receive ineffective LRT before LT and figure out if the most benefit for these patients would be to prioritize, to drop-out or to re-treat these patients before LT.

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O316

IMPROVED PATIENT SURVIVAL IN LIVER RETRANSPLATANTED PATIENTS

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Background: Retransplantation (ReTx) is the only treatment available for patients with irreversible graft failure. The aim of this study was to analyze liver ReTx characteristics, and evaluate the potential impact on the overall survival rate.

Methods: ReTx population was analyzed according to the following parameters: patient demographics; primary diagnosis; indications for ReTx; incidence of early or late retransplants, and overall patient survival.

Results: Between June 2005 and September 2012, a total of 860 liver transplants with deceased donor were performed and among them, 102 were retransplants (12%) performed in 96 patients. The most common etiology for which retransplantation was required was Hepatitis C (33%). Early ReTx (within the first 15 days) was indicated for 47 patients (46%) and among them 60% by Primary non-function, followed by hepatic artery thrombosis (23%). On the other hand, 55 retransplants were indicated at late posttransplant time (54%), 45% due to hepatic artery thrombosis, followed by recurrence of primary disease (22%).The 1-year patient survival rate for ReTx cases was 86.5%, whereas for patients which performed one transplant was 85.7% (log rank pvalue = 0.609).

Conclusion: This study suggests that Retx provides benefits based on results of one year survival.

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OS40-LUNG

O317 *DE NOVO* POST TRANSPLANT LUNG CANCER: UK EXPERIENCE

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Lung cancer is one of the commonest *de novo* cancers after organ transplantation. Solid organ recipients (1990–2007) were selected from UKTransplant Registry. Recipients with lung ca after transplant were identified from the cancer registry. Of 33 658 recipients, 300 (0.89%) developed lung ca. The standardised incidence ratio for lung ca was significantly higher ($p < 0.0001$) in lung recipients (9.3) compared to other organ recipients (2.2). Lung recipients developed lung cancer significantly sooner following transplantation ($p = 0.001$) than other organ recipients (median time to diagnosis, 3.4 [1.6, 5.2] and 5.5 years [4.9, 6.1] respectively). Median survival from diagnosis of lung cancer among lung recipients was not significantly different from other organ recipients (131 [65, 220] and 137 days [99, 190] respectively). Small cell type was less frequent in lung recipients. Lung cancer is a significantly greater challenge among lung recipients, affecting more patients sooner after transplantation.

O318 KILLER IMMUNOGLOBULIN-LIKE RECEPTOR (KIR)-LIGAND MISMATCHES DO NOT AFFECT THE DURATION OF PERIPHERAL BLOOD DONOR CD4 T CELL CHIMERISM FOLLOWING LUNG TRANSPLANTATION

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Background: Graft passenger lymphocytes are known to influence the auto- and allo-immune responses following transplantation. The fate of the donor passenger CD4 T cells is unclear and maybe influenced by recipient natural killer (NK) cells. NK cells have a unique ability to respond and kill target cells in the presence of HLA (human leukocyte antigen) class I disparities. We investigated the relationship between the duration of donor CD4 T cell chimerism and the recipient-versus-donor (RvD) NK cell alloreactivity in HLA incompatible lung transplant recipients.
Method: Donor CD4 T cells were detected in recipients' peripheral blood by targeting donor HLA mismatched antigens with human monoclonal HLA antibodies ($n = 20$). NK cell alloreactivity was expected if there was at least one KIR-ligand mismatch between the recipient inhibitory KIRs and their corresponding HLA ligands expressed on donor cells Table 1.
Results: Donor CD4 T cell chimerism was observed in all patients. The level of chimerism detected varied from 0.06% to 6% of the recipient CD4 T cell population. Donor CD4 T cells disappeared from the recipients' peripheral blood with three distinct patterns: early, intermediate and late loss of chimerism that occurred within one, 3, and more than 4 months post-transplant, respectively. Ten of 20 recipient/donor pairs were KIR-ligand mismatched in RvD direction. Three donors were HLA-C2, 3 were HLA-C1, and six were HLA-Bw4 mismatched. There was no difference in duration of donor CD4 T cell chimerism in the KIR-ligand mismatched and matched groups.
Conclusion: Donor CD4 T cell chimersim is common but transient after lung transplantation and its clinical significance is yet to be determined. Our data do not support a role for NK cell alloreactivity in elimination of the graft passenger CD4 T cells from the recipients' peripheral blood following lung transplantation. The effect of KIR-ligand mismatching may be obscured in the presence of strong alloimmune response.

O319 CLINICAL RELEVANCE OF EARLY DETECTION OF DONOR-SPECIFIC ANTIBODIES (DSA) AFTER LUNG TRANSPLANTATION (LT)

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Background: Antibody-mediated rejection (AMR) is not yet a full-blown described entity after LT mainly due to the lack of specific immuno-histological criteria. In this context, DSA detection is of paramount importance for the diagnosis.
Methods: In a prospective observational study conducted in a single-center from 02/08 to 12/09, the occurrence of DSA, using Luminex single-antigen assay, was assessed in the early post-operative period in 62 consecutive LT patients.
Results: DSA were detected in 23 patients within the first 10 post operative days (37%). Five of them developed acute AMR and they all experienced a significant increase in the mean sum of class I or II MFImax DSA between the first post-transplantation sample and the clinical onset of acute AMR unlike the other patients with DSA. They improved clinically and biologically after specific treatment based on plasmapheresis, IvIg and rituximab. A higher number of HLA mismatches ($p = 0.02$) and a longer ICU length of stay ($p < 0.01$) were observed in DSA patients.
Conclusions: The occurrence of DSA is common in the early postoperative period after LT. Early detection and increasing kinetics of DSA may allow prompt diagnosis and treatment of acute AMR. Further study is needed to set up perioperative strategy and prevent AMR in those patients.

O320 DO LUNG RECIPIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY HAVE AN INCREASED RISK OF EARLY GASTROINTESTINAL COMPLICATIONS REQUIRING SURGERY?

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Background: Gastrointestinal complications (GIC) after lung transplantation (LT) have been reported to be common. We aimed to describe a seemingly increased incidence of explorative laparotomies (EL) after LT in patients with alpha-1 antitrypsin deficiency (A1AD).
Methods: We examined prospectively collected data of all patients receiving LT at Rigshospitalet, Denmark from 2004 to 2012. Patient demographics and characteristics were analyzed. The study period consisted of the first 90 days after LT.
Results: LT was performed in 258 patients. Indications were chronic obstructive pulmonary disease ($n = 75$), A1AD ($n = 51$), cystic fibrosis ($n = 46$), pulmonary fibrosis ($n = 43$), sarcoidosis ($n = 20$), primary pulmonary hypertension ($n = 6$) and other lung diseases ($n = 17$). Eighty two patients (32%) underwent a conventional X-ray of the abdomen because of various GI symptoms and 23 patients (9%) required EL. Patients with A1AD comprised 20% of recipients in total, 23% (19/82) of patients in need of an abdominal X-ray ($p = 0.40$) but 48% (11/23) of patients requiring EL after LT ($p < 0.001$). In 7/11 (64%) of patients with A1AD undergoing EL the surgical treatment included right hemicolectomy because of dilated, perforated or ischemic coecum or ascending colon. EL was performed 5–17 days after LT (median 10 days). There were no deaths related to GIC requiring EL in patients with A1AD. The ICU stay was slightly prolonged but time of mechanical ventilation was not and the long-time survival was not affected. No other pulmonary diseases were overrepresented among patients requiring EL after LT, although also patients with cystic fibrosis had a slightly higher than expected occurrence of abdominal X-ray. No other risk factors for GIC requiring EL after LT were identified among patient demographics or characteristics including use of immunosuppressives.
Conclusion: EL after LT was frequent and patients with A1AD were significantly overrepresented and comprised 48% of patients requiring EL.

O321 THE MUNICH LUNG TRANSPLANT GROUP: THE WAITING LIST DURING THE FIRST 9 MONTH OF THE LUNG ALLOCATION SCORE (LAS)-ERA

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Objective and methods: The Eurotransplant Foundation introduced the Lung Allocation Score (LAS) in Germany on December 10th, 2011. We analyzed characteristics of the Munich Lung Transplant Group (MLTG) waiting list during the first 9 month after introduction of the LAS.
Results: A mean number of 39b1 patients was constantly listed for lung transplantation and 60 transplant were performed by the MLTG during the observation period. While the majority (42,,b0%) of patients waiting for transplant comprised of chronic obstructive pulmonary disease (COPD)/emphysema patients, only 26% of transplanted patients suffered from COPD/emphysema. Instead, the majority (42%) of transplanted patients suffered from interstitial lung disease. Waiting times did not markedly change in the LAS era. Notably, patients with interstitial lung disease had shorter waiting times when compared to COPD/emphysema and cystic fibrosis patients, both on the waiting list and at the time of transplant.
Conclusion: The MLTG lung transplant waiting list has not markedly changed during the first 9 month after introduction of the LAS. Our data indicate that the LAS accomodates disease-specific patient statuses well. Although patients with interstitial lung disease are preferably transplanted, the LAS system provides a very reasonable basis to also list and transplant COPD/empysema patients.

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O322

LIVING-RELATED LOBAR LUNG TRANSPLANTATION (LRLLT) – A POSSIBILITY FOR END-STAGE LUNG DISEASE PATIENTS

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Background: Living-related lobar lung transplantation (LRLLT) is an alternative to cadaveric lung transplantation. At the Department of Thoracic Surgery, General Hospital Vienna, five patients underwent LRLLT from 1999 to 2012.
Methods: Four patients suffered from end-stage CF and one patient from GvHD and were therefore urgently waiting for a donor lung. We performed four double LRLLT where each mother donated her left lower lobe, and each father donated his right lower lobe. The GvHD patient just got the lower lobe of his mother. We retrospectively analysed the patients' and parents' pre- and post-surgery lung function data and performance status.
Results: In all five LRLLT cases there were no surgical complications. Two CF patients who where transplanted in 1999 and 2000 died 3 months after LRLLT due to severe infections. After reinitiation of the LRLLT program in 2009, all recipients as well as all donors are still alive. The three surviving recipients showed good postoperative functional tests. The donors recovered from surgery very fast and returned back into normal life. Discussion: LRLLT is a possibility to safe severely ill patients' life in an urgent time frame. The advantages of a LRLLT are the elimination of the waiting period, the better immunological matching and the short time of cold ischemia.

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OS41-PEDIATRIC TRANSPLANTATION

O323 WHAT IS THE RIGHT VALGANCICLOVIR DOSE IN CHILDREN?

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Background: CMV infections are common after solid organ transplantation (SOT). Use of valganciclovir (v-GCV) to prevent and treat CMV is increasing in children. Several pediatric dosing algorithms have been proposed. The aims of the present study were to develop an algorithm based on a novel non-parametric population model and to compare it with the Pescovitz algorithm (Dose = 7*BSA*CrCl).
Methods: Data from 104 pediatric SOT recipients (kidney, liver and heart) aged 0.3–16.9 years and receiving v-GCV once a day were used for model development and validation with the Pmetrics package for R. Monte Carlo simulations were performed to compare the probability of a GCV AUC $\geq$ 40 or $\geq$60 mg*h/l with the Pescovitz algorithm and our own algorithm across a range of ages, weights, and glomerular filtration rates (GFRs).
Results: Ganciclovir PK was well described in these patients by an allometrically scaled 2-compartment model with clearance dependent on GFR. Cockcroft-Gault GFR estimates improved the model fit over Schwartz GFR, despite the pediatric population. Simulations showed that the Pescovitz algorithm resulted in GCV overexposure in young and underexposure in older pediatric patients. In contrast our new algorithm showed more evenly distributed percent target achievement (AUC 40–60 mg*h/l) across different body weights and GFRs, where v-GCV dose is: body weight [kg]*(0.07*GFR [mL/min] + k), where k = 5 for GFR $\leq$ 30 ml/min, k = 10 for GFR > 30 ml/min and weight >30 kg and k = 15 for GFR > 30 ml/min and weight $\leq$30 kg. With this new algorithm, 33% of all patients achieve an exposure above and 21% within the therapeutic window.
Conclusion: We propose a simple algorithm for initial v-GCV dosing in children and adolescents with normal or abnormal renal function that standardizes plasma drug exposure better than current algorithms. Regardless of initial dose, subsequent therapeutic drug monitoring is strongly suggested to achieve individual drug levels within the therapeutic window.

O324 DONOR-SPECIFIC ANTIBODIES AFTER PEDIATRIC LIVER TRANSPLANTATION: A CROSS-SECTIONAL STUDY OF 50 PATIENTS

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Background: Donor-specific HLA antibodies (DSA) play an important role in solid-organ transplantation although their role in pediatric liver transplantation (LT) is less firm. In this cross-sectional study, we investigated prevalence of HLA antibodies and DSAs, and their association on liver biopsy.
Patients and methods: Ninety-nine patients (age < 18 years) underwent deceased donor LT between 1987 and 2007. Post-LT serum samples were drawn from 50 (79% out of 66 alive) patients for antibody analyses. Liver biopsy was available from 47 patients.

HLA antibodies were studied using One Lambda LabScreen mixed and single antigen beads and analyzed with HLA Fusion 2.0-program. Mean fluorescence index (MFI) 1000 was used as cut-off point for positive in single antigen analyses. Liver biopsies were fixed and stained with conventional methods and cytokeratin 7 (CK7) and C4d immunostaining was performed.
Results: Median (interquartile range) follow-up for whole group was 10.0 (4.0–16.4) years. Thirty-three patients (66%) had either class I or II HLA antibodies and 17 (34%) patients had neither. Twenty-seven patients (54% of total) had DSAs (class I in 5 and class II in 22 patients). In 19 of 22 patients (86%) with class II DSAs, MFI was >5000.

Portal inflammation was more frequent in patients with HLA antibodies versus without (10/31 vs. 0/16, p = 0.010) and also more frequent in patients with DSAs versus without (9/25 vs. 1/22, p = 0.012). No differences were found in liver fibrosis, CK7 staining for periportal hepatocytes or bile duct proliferation in patients with and without HLA antibodies or DSAs. C4d was present in four patients (9% of 44) and only one of these patient had DSAs.
Conclusions: Our preliminary results show that unexpected high proportion of patients had especially class II DSAs in their post-LT serum samples. Portal inflammation was more frequent in patients with HLA antibodies or DSAs.

O325 PLASMA LEVELS OF GROWTH FACTORS AND IMMUNE BIOMARKERS IN PEDIATRIC PATIENTS AFTER ABO-INCOMPATIBLE LIVING DONOR LIVER TRANSPLANTATION

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Background: ABO-incompatible (ABOi) transplantation in children with end-stage liver disease (ESLD) is a real possibility to safe life without ABO-compatible (ABOc) living related donors. It was shown that plasma levels of immune biomarkers (soluble forms of ligand CD40 (sCD40L), CD30 (sCD30), neopterine (NP)) are associated with risk of post-transplantational complications in pediatric living donor liver transplantation (LDLT). The levels of transforming growth factor-β (TGF-β) and insulin-like growth factor-I (IFR-I) point out to liver damage. The aim was to compare levels of TGF-β, IFR-I, sCD30, sCD40L, NP after ABOi and ABOc LDLT in children.
Methods: Seventy children with ESLD aged 3–50 (1210) months were followed-up before and after LDLT (14 patients of them had ABOi transplantation). The operation procedure included hepatectomy, orthotopic implantation of left lateral sector, biliary reconstruction by hepaticojejunostomy. All recipients received 2- or 3-drug immunosuppressive therapy including tacrolimus. In five ABOi patients with high anti-ABO titres plasmapheresis and rituximab infusion were carried out preoperatively. Plasma concentrations of immune biomarkers, IFR-I, TGF-β were measured before and in one month after LDLT by ELISA.
Results: The concentration of IFR-I increased after transplantation (median [interquartile range] ABOc 0.09 [0.01–5.8] μg/l to 70.7 [45.8–112.5] μg/l, p = 0.0002, ABOi 0.01 [0.001–0.11] to 61.8 [33.1–104.1] μg/l, p = 0.0016) and indicated the recovery of liver function. No significant difference in levels of the biomarkers and growth factors in patients in one month after ABOi and ABOc LDLT was observed: sCD40L – 5.7 ± 3.3 vs. 3.8 ± 3.7 ng/ml, p = 0.12, sCD30 –141.9 ± 48.2 vs. 66.6 ± 47.6 ng/ml, p = 0.7, NP – 16.7 ± 12.7 vs. 31.0 ± 35.7 nм, p = 0.18, TGF-β – 4.7 ± 3.0 vs. 5.5 ± 4.5 μg/ml, p = 0.54, IFR-I – 66.7 ± 48.6 vs. 89.1 ± 62.0 μg/l, p = 0.3, but these levels were associated with the post-transplan.

O326 PRE- AND POSTOPERATIVE MANAGEMENT IN ABO-INCOMPATIBLE PEDIATRIC LIVING DONOR LIVER TRANSPLANTATION

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Background: ABO-incompatible (ABOi) living donor liver transplantation (LDLT) is a valuable option for children with end-stage liver disease without ABO-compatible (ABOc) living related donors. The aim of the study was to describe the treatment strategy in ABOi LDLT for recipients <15 kg.
Methods: Fifteen patients (seven boys and eight girls) have passed ABOi LDLT. Median age was 13.1 (4–29) months and median weight was 8.1 (5–14) kg.
Results: In 10 patients with baseline IgG and IgM anti-ABO titres were 1:8 or less, no special preparation was necessary. In eight of these 10 children the anti-ABO titres postoperatively remained low. Two other patients received plasmapheresis after transplantation. In five patients with high anti-ABO titres plasmapheresis and rituximab infusion were carried out preoperatively; one of them needed plasmapheresis postoperatively too. All patients received basiliximab induction. Postransplant immunosuppressive protocol included tacrolimus and steroids; in three patients mycofenolates was added. One patient died after a month postoperatively due to severe gastro-intestinal bleedings. Other 12 patients are now alive. The mean follow-up period is 17 (1–36 months). They demonstrate good graft function. Acute rejection developed in two patients, in one case it was successfully treated by plasmapheresis, in other case – by intravenous steroid pulse. There were no vascular complications. The patient and graft survival and the incidence of biliary and infectious complications were comparable to ABOc transplantation in similar recipients.
Conclusion: ABOi transplantation in recipients <15 kg can be safely performed with no significant augmenting of immunosuppressive therapy and using plasmapheresis for antibody removal if necessary. Short and long-term results of ABOi LDLT in children are similar to those of ABOc LDLT.

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O327 DONOR HYPERNATREMIA DOES NOT INFLUENCE OUTCOMES FOLLOWING PEDIATRIC LIVER TRANSPLANTATION

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Background: Currently, there is conflicting evidence regarding the effects of donor hypernatremia (DHNa) on outcomes following liver transplantation (LT), even more so in children. We evaluated the effects of DHNa on pediatric LT patients using the SRTR database.
Materials/Methods: We performed a retrospective analysis of 3444 pediatric patients divided into two groups: patients receiving grafts from normonatremic (n = 3204) donors and patients receiving grafts from hypernatremic (n = 240) donors. DHNa was defined as donor sodium level ≥160 μM. Analyzed factors were: patient age, weight, MELD scores, cold ischemia times, postoperative INR, mortality, infectious, biliary, and vascular complications. We determined statistical significance using the Fisher's exact test. The Bonferroni correction was used when the number of events was low with significance set at 0.0083 (*).
Results: Mean recipient ages/weights, MELD scores, and mean cold ischemia times were similar in both groups. There were no significant differences in post-transplant discharge INR levels (1.41 vs. 1.35, p = 0.54), mortality (odds ratio (OR) = 1.16, p = 0.43), graft failure (OR = 1.06, p = 0.9), vascular thrombosis (OR = 1.02, p = 0.96), biliary complications (OR = 2.23, p = 0.45), and acute rejection (OR = 4.5, p > 0.0083*).
Conclusion: LT-children receiving grafts with DHNa showed no statistically significant difference in outcomes compared to patients receiving grafts from normonatremic donors.

O328 HEPATIC HEMODYNAMICS IN CIRRHOTIC CHILDREN: CORRELATION TO PELD AND VASCULAR COMPLICATIONS AFTER LIVER TRANSPLANTATION (LT)

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Background: Pre-LT liver hemodynamic disturbances and post-LT portal vein (PV) complications are frequently observed in pediatric LT. We hypothesized that cirrhosis in children is associated with particular liver hemodynamic features which could lead to vascular complications after LT.
Methods: We retrospectively analyzed 198 LT recipients (median age: 1.6 year; range: 0.2–17.5), including 130 biliary atresia (BA). Pre-LT hemodynamics was studied using Doppler ultrasound, and correlated with the incidence of post-LT vascular complications. Moreover, invasive flowmetry of native liver hemodynamics, gradient between PV and central venous pressures (PVP-CVP) were studied prospectively at LT in 10 cirrhotic children (median age: 1.0 year; range: 0.5–14), including eight BA.
Results: At retrospective analysis, hepatic arterial resistance index ≥1 at pre-LT ultrasound was associated with a higher rate of PV complications (p = 0.041). In children with BA-related PV hypoplasia (79 cases), the portoplasty technique alleviated the extra risk of PV complications (6.2% with portoplasty vs. 19.3% without portoplasty). The prospective hemodynamic studies showed that: (i) pediatric cirrhosis was associated with a reduction of pre-LT total liver flow of 50% (median 50.4 ml/min/100gr of liver; (19–110.5)), compared to expected values (100 ml/min/100gr); this reduction of total liver flow was correlated with PELD (r = 0.32). (ii) pediatric cirrhosis was also associated with a severe portal hypertension (median PVP-CVP gradient = 14.5 mmHg [−7 to 26]); the degree of portal hypertension was correlated with PELD (r = 0.54), and was more severe in BA (median gradient = 17 mmHg) compared to non-BA (median gradient = 2.5 mmHg).
Conclusions: Pediatric cirrhosis is associated to severe liver hemodynamic disturbances, which are correlated with PELD. Pre-LT hemodynamic assessment may help to predict, and efficiently manage liver vascular anomalies in pediatric LT, including BA-related PV hypoplasia.

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CCS05-KIDNEY II

CCS13 SEVERE RECURRENCE OF FSGS IN IMMEDIATE POST-TRANSPLANT PERIOD WITHOUT THERAPEUTIC RESPONSE TO NEW IMMUNOSUPPRESSIVE DRUGS

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Introduction: Approximately 20–40% of patients develop recurrence of FSGS in the first allograft and 90–100% has recurrence in the second allograft in a previous renal transplant failed. Several papers in the literature have shown new strategies in the treatment of FSGS recurrence modifying factors in its pathogenesis. Regardless rituximab effect on B cells, it would also works on podocytes sphingolipids expression which has an important role in the pathogenesis of FSGS recurrence. Moreover, it was observed that costimulatory molecules B7-1 in podocyte modify the glomerular permselectivity in the pathogenesis of glomerular disease and according to this concept we used a fusion protein CTLA4-Ig (abatacept) which binds to B7-1/CD80.
Clinical Case with Biopsy: A 28 year-old female patient with chronic renal failure due to FSGS (Tip Lesion) which was diagnosed in 2006 with no response to immunosuppressive therapy and rapid and progressive deterioration of renal function. She underwent peritoneal dialysis in 2008 She received a renal transplantation from an optimal deceased donor on October, 2012. A 24 hours-cold ischemia time and cross match for B and T negative. She received plasmapheresis (PP) before transplantation and induction with quadruple immunosupressive therapy with thymoglobulin (6 mg/kg) methylprednisolone and mycophenolate, adding tacrolimus 0.1 mg/kg doses on 2nd day. This patient continued with PP sessions three times a week and she required hemodialysis treatment. Due to her medical history and the persistence of oligoanuria, a first renal biopsy (OM, IF, C4d and EM) on day 5 after transplantation. This biopsy revealed acute tubular necrosis (ATN); interstitial fibrosis/tubular atrophy grade I, and diffuse epithelial foot process effacement, confirming recurrent FSGS, without signs of rejection. It was decided to maintain PP sessions three times a week adding an anti CD20 (rituximab) in post PP 5th (375 mg/m^2). The patient persists with DGF and oligoanuria with index prot/creat > 10 and lack of response to rituximab. A new renal biopsy was performed (15th day) with persistent diffuse epithelial foot process effacement and moderate ATN. Therefore, abatacept was administered in two doses of 750 mg/each in a 2 weeks- term. After first doses the patient achieved urinary volumes up to 1200 ml/day with nephrotic proteinuria range. She continued with dialysis treatment and there was no evidence of renal function progress. She completed a total of 20 PP sessions and after a third renal biopsy (44th day) which showed severe glomerular and interstitial commitment, it was determined to discontinue the immunosuppressive therapy.

CCS14 THE USE OF MTOR INHIBITORS IN IMMUNOSUPPRESSIVE TREATMENT OF TUBEROUS SCLEROSIS PATIENTS AFTER KIDNEY TRANSPLANTATION

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Background: Tuberous sclerosis complex (TSC) is a genetically determined disorder caused by mutations of TSC1 or TSC2 genes. The loss of function of these genes leads to constitutive activation of mammalian target of rapamycin (mTOR) resulting in abnormal cells proliferation, migration and differentiation. Multiorgan dysfunctions appear, but primarily skin, brain, kidneys and lungs are affected. The underlying defect in TSC, constitutive mTOR activation, is potentially corrected by mTOR inhibitors. Experimental and clinical data prove the beneficial effect of rapamycin and everolimus on wide spectrum of disease manifestations.
Case Reports: We report the first cases of two TSC patients with end stage renal disease, that initiated immunosuppressive treatment with mTOR inhibitor at the moment of kidney transplantation. The first patient received renal transplant in 2005, and immunosuppressive protocol with rapamycin was applied. In 2012, the second patient was transplanted, and everolimus was started. The grafts functions remain stable. Moreover prolonged use of mTOR inhibitor brought some beneficial effects on other TSC manifestations.
Conclusion: The mTOR inhibitors appear as the treatment of choice in immunosuppressive treatment of TSC patients after kidney transplantation.

CCS15 SPLANCHNIC VEIN THROMBOSIS IN A KIDNEY TRANSPLANT PATIENT WITH JAK-2 GENE MUTATION: A CASE REPORT

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Renal transplant patients have increased incidence of thrombotic events. Portosplenic vein thrombosis is an extremely rare and Janus Kinase 2 (JAK2) gene mutation may be responsible for the pathogenesis of Portosplenic vein thrombosis in general population. However, JAK2 gene mutation as a prothrombic risk factor in renal transplant patients is yet to be defined. Herein; we present a case of portosplenic vein thrombosis in a primary renal transplant patient with JAK2 V617F mutation.
Case: A 59 year old female patient with end stage renal disease underwent a preemptive living donor kidney transplant from her son on the 6th April 2011. Post-transplant recovery was complicated by acute graft dysfunction at day 7. Kidney biopsy revealed *de novo* thrombotic microangiopathy and she had completely recovered in 2 weeks with good graft function (SCr: 1.0 mg/dl) and discharged from the hospital with a maintenance immunosuppression including prednisolone 10 mg/day, mycophenolic acid 900 mg/day. and everolimus 0.5 mg/day. Her routine follow-up was normal until the outpatient visit in November 2012. She admitted with vague abdominal pain principally located at left upper quadrant. Abdominal imaging demonstrated splenomegaly with hyperechoic trombi almost completely occluding splenic vein and portal vein upto portal hilum. The patient was diagnosed as portosplenic vein thrombosis due to myeloproliferative disease and JAK2 V617F gene mutation. She was initially treated with enoxaparin and switched to warfarin (≥5 mg/day) afterwards to achieve target INR values of 1.9–2.5. After 3 months of treatment, control MRI angiography and Doppler USG demonstrated partial (>50%) resolution of thrombosis.
Conclusion: Renal transplant patients with thrombosis in uncommon sites may be responsible for JAK 2 V617F mutation and myeloproliferative diseases.

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CCS06-LIVER II

CCS16 A CASE OF ACUTE HUMORAL REJECTION IN LIVER TRANSPLANTATION AS CAUSE OF ACUTE LIVER FAILURE 1 YEAR AFTER LIVER TRANSPLANTATION

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A case of 50-years-old male who underwent ABO-compatible liver transplantation (LTx) for hepatitis C and hepatocellular carcinoma under Milan criteria. Donor-recipient crossmatch was negative and panel-reactive antibody rate was 0%. Initial immunosuppression was tacrolimus + mofetil mycophenolate. Two months later he presented liver dysfunction and liver biopsy showed acute hepatitis plus mild acute rejection that was treated with Everolimus in triple therapy. Eleven months post-LTx, he was admitted in the hospital due to malaise and jaundice (TBilirrubine 14 mg/dl, AST 2508, ALT 2651, PT28%). Doppler-ultrasound was normal and a liver biopsy revealed severe acute rejection. Specific IgG antibodies directed against specific graft antigens (anti-DRB1 04) were positive. Due to the rapid nature of the deterioration, two boluses of steroids (500 mg i.v.) and two doses of anti-thymocyte globulins (1 mg/kg) were administered. In the absence of any improvement, the patient was included in waiting list for retransplantation 5 days later. Meanwhile, he was treated with plasmapheresis and 100 mg/kg of human immunoglobulin (one course). However, he died 8 days after symptoms were initiated. Retrospective immunostaining for C4d was carried out with negative result.

CCS17 POSTTRANSPLANT CLINICAL COURCE OF HCV-INFECTION IN PATIENT WITH HIGH SERUM LEVEL ALPHAFETOPROTEIN

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In June 2012 we performed OLT to 37 years old man with HCV (genotype 1b) associated liver cirrhosis.

Pretransplant Data: Viral load – not investigated, but positive alphafetoprotein level elevated in 65! times, no evidence of HCC and/or an other oncology two unsuccessful attempts to antiviral therapy in history In postOLT period patient had mixed renal impairment (HCV + CNI + postoperative) required eight hemodialysis, recidivating pleural effusion and ascitis required multiple punctures. In Lab data: daily proteinuria 11.4 g/l, creatinin 70–211 mm, urea 14–34 mm, alphafetoprotein in normal range, AST 12 N, ALT 10 N, T.Bil 2 N, GGN 32 N, ALP 6 N, HCV RNA 1.2 $\times$ 10^6 IU/ml.

Immunosupression: TAC+MMF Results of antiviral therapy from 2nd to 8th month after OLT with PEG IFN + ribavirin: partially EVR on 12 week and nonresponse on 24 week. Fibroscan F4 (3rd and 8th months after OLT) with signs of steatosis.

Conclusion: High alphafetoprotein serum level with no evidence of HCC and/or an other oncology in HCV-cirrhosis recipients probably should be recognized as an indirect sign of poor prognosis in HCV-infection reccurence after OLT. We must keep this in mind putting such recipients in waiting list, because probably soon they will ask us about retransplantation.

CCS18 RECOVERY AFTER EARLY HEPATIC ARTERY THROMBOSIS AFTER WHOLE LIVER TRANSPLANTATION IN CHILDHOOD: A CASE REPORT

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Background: Hepatic artery thrombosis (HAT) is a major cause of graft loss after pediatric liver transplantation. We report HAT in an 11-month patient with biliary cirrhosis secondary to biliary atresia, which underwent a whole liver transplant (WLT) with bilioenteric anastomosis.

Clinical Cases: The baby was listed at the age of 10 months after a previously "failing" Kasai portoenterostomy performed at the age of 2 months. Patient underwent relaparotomy on POD1 for hemoperitoneum. On POD5, in the setting of improving labs, Doppler-ultrasound (DUS) suspected HAT. Arteriogram confirmed HAT and thrombolysis was not performed for the unsuccessful catheterization. The patient was listed for urgent retransplantation, but no suitable liver grafts became available. On POD13 a sepsis caused by *S. maltophilia* was solved with Levofloxacin. On POD15 a liver biopsy showed microfoci of hepatocyte necrosis with hepatocyte regeneration. On POD20, for the first time, DUS was able to demonstrate hepatic artery flow in the left lobe of the graft and thereafter clinical improvement along with the presence of bilobar intraparenchymal arterial flow was observed, inducing to remove the patient from the waiting list. On POD48 a new liver biopsy for liver enzymes elevation showed biliary duct proliferation suspicious for biliary stricure. A percutaneous transhepatic biliary drainage was placed and after that the patient was successfully treated with three balloon bilioplasty. A new arteriogram confirmed arterial collaterals from the previous Roux en-Y limb. The baby was discharged on POD74 with a progressive labs improvement. He is now well with normal liver function, 28 months after WLT.

Conclusion: In our case report early HAT did not cause acute necrosis. Bilioenteric anastomosis could favor collateral arterial connections between the enteric loop and the liver, following its arterial revascularization. Biliary complications are typical sequelae of HAT and early diagnosis could preserve the liver allograft.

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