LECTURES

KIDNEY I (WAITLIST MANAGEMENT)

V007 PRESENSITIZATION WITH ALLOREACTIVE T-CELLS PREDICTS OUTCOME IN KIDNEY TRANSPLANT RECIPIENTS

T. Schachtner, P. Reinke*
Charité CVK, Nephrologie, Berlin, Germany

Introduction and Background: Alloreactive T-cells have been suggested to impact allograft outcome due to a higher incidence of acute cellular rejection. Knowledge on risk factors for the development of preformed and de-novo alloreactive T-cells, however, remains scarce.
Methods: We analyzed 327 primary kidney transplant recipients (KTRs) transplanted from 2008 to 2014. KTRs were grouped regarding the pretransplant alloreactive T-cells. KTRs without pretransplant alloreactive T-cells were grouped regarding the development of de-novo alloreactive T-cells. Samples were collected pretransplantation, at +1, +2, +3 months post-transplantation, and alloreactive T-cells were measured by interferon-γ Elispot assay.
Results and Conclusions: Among 327 KTRs, 107 KTRs (33%) showed pretransplant alloreactive T-cells. Risk factors for the presence of preformed alloreactive T-cells included older age, diabetes, and prior malignancies ($P < 0.05$). Preformed alloreactive T-cells were associated with a higher incidence of delayed graft function ($P = 0.017$). Among 220 KTRs without alloreactive T-cells pretransplantation, 31 KTRs (14%) showed de-novo alloreactive T-cells. Risk factors included female sex and prior malignancies ($P < 0.05$). KTRs with preformed/de-novo alloreactive T-cells showed inferior patient survival, allograft survival, and allograft function, a higher incidence of acute cellular rejections, sepsis, and post-transplant malignancies ($P < 0.05$).

The presence of alloreactive T-cells strongly impacts patient and allograft outcomes. Insulin therapy, and treated or undetected malignancies may lead to presensitization with preformed alloreactive T-cells. Caution should be taken in KTRs with alloreactive T-cells with regards to minimizing immunosuppression.

LIVER I (SURGICAL CHALLENGES)

V010 DISPARITIES IN LIVER TRANSPLANTATION WAIT-LIST OUTCOME BETWEEN PATIENTS WITH AND WITHOUT EXCEPTIONAL MELD IN THE EUROTRANSPLANT AREA

A. Umgelter[1], A. Hapfelmeier[2], W. Kopp[3], M. von Rosmalen[3], M. Guba[4]*
[1]Technische Univeristät München, 2nd Medical Department, München, Germany; [2]Technische Univeristät München, Institute of Medical Statistics and Epidemiology, München, Germany; [3]Eurotransplant International Foundation, Leiden, Netherlands; [4]University of Munich, Department of General, Visceral and Transplant Surgery, München, Germany

Introduction and Background: The Eurotransplant (ET) liver transplant allocation system is based on the Model for End-Stage Liver Disease (MELD) score and prioritizes patients with higher scores within a defined ET member country. Mortality in certain other disease entities is not reflected by the MELD-score. Therefore certain patient populations, such as patients with hepatocellular carcinoma, receive standard MELD exception points (SE) or individual nonstandard exception points (NSE) under predefined circumstances to confer equitable access to donor organs. We assessed rates of transplantation of cirrhotic patients and patients with standard (SE) and nonstandard exceptions (NSE)
Methods: Based on ET-waitlist-data, we analyzed wait-list outflow of adult (non-HU) patients waiting with and without N(SE)s in ET MELD countries (Germany, Belgium, Netherlands) between 2007 and 2015.
Results and Conclusions: Of 17506 patients, 10201 were transplanted (TRANS), 1379 were delisted recovered (DL-R) 4051 died on the waitlist (DOWL) and 1295 were delisted unfit for transplantation (DL-U). The most common SEs were HCC (2511), PSC (292) biliary sepsis/SSC (225) and polycystic liver disease PcLD (225). Of patients with HCC, PSC BS/SSC and PcLD 75.0%, 81.5%, 59.1% and 85.5% were transplanted, among patients with NSE, with SE and without (N)SE 80.6%, 75.3% and 53.9%, respectively.

Regarding positive (TRANS/DL-R) vs (DOWL/DL_U) negative outcome, statistical analysis by model based recursive partitioning identified five subgroups. The most important predictor of TRANS/DL-R vs DOWL/DL_U was belonging to a group comprising SEs for porto-pulmonary hypertension, biliary sepsis or no SE versus a group comprising SEs for HCC, PSC, hepatopulmonary syndrome (HPS) or PcLD.

From this data it appears that (N)SE based liver allocation may overshoot the original aim of conferring equitable access to donor organs across different disease entities and that patients without (N)SE have a higher wait-list mortality. Accordingly, (N)SE criteria should be recalibrated.

V011 INDIVIDUALIZED THERAPY ALGORITHMS MAY GIVE HCC PATIENTS A GENUINE CHANCE OF CURE BY SURGICAL TREATMENT WHO WOULD OTHERWISE BE SUBJECTED TO PALLIATIVE TREATMENT

H. Anger, M. Schoenberg, J. Hao, A. Vater, J. Bucher, A. Bazhin, M. Angele, J. Werner, M. Guba*
Klinikum der Universität München, Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, München, Germany

Introduction and Background: The BCLC system excludes many patients from potentially curative treatment. Integration of individual markers of tumor biology may help to identify patients that benefit from surgical treatment.
Methods: In our institution we use a modified BCLC treatment algorithm that also includes markers of individual, tumor biology such as response to therapy, grading, and AFP. We have analyzed the outcome of our HCC resection and transplantation cohort (2007–2015) with BCLC stage 0-B.
Results and Conclusions: A total of 259 patients were analyzed, 109 of them received a liver transplantation. 5 year-survival after resection was 51.1% after transplantation 72.8%. The MILAN stage had no influence on outcome (n.s.).

Even patients who would be subjected to palliative treatment by using the BCLC treatment algorithm can be cured after surgical treatment. The inclusion of markers of individual tumor biology may be more adequate in treatment allocation as compared to plain BCLC score.

V012 RESULTS OF MELD BASED ALLOCATION 10 YEARS AFTER ITS IMPLEMENTATION

P. Ritschl, L. Wiering, M. Hippler-Benscheidt, F. Aigner, M. Biebl, M. Schmelzle, K. Kotsch, J. Pratschke, R. Öllinger*
Charité-Universitätsmedizin Berlin, Department of Surgery, Campus Virchow and Mitte, Berlin, Germany

Introduction and Background: The MELD-based allocation system has been implemented in Germany in 2006 in order to decrease waiting list mortality in patients with end stage liver disease. However, the MELD score not only reflects the probability to die within 3 months, but simultaneously represents a major risk factor for post-transplantation graft and patient survival. Purpose of this study is to evaluate post-transplant results and their development since the introduction of MELD-based allocation.
Methods: MELD scores at time of transplantation, 1- and 3-year graft- as well as patient survival were assessed from 2005 to 2015 using our own and Eurotransplant data. Statistical analysis was carried out using GraphPad Prism 5.01.
Results and Conclusions: In our department 1172 liver transplantations were performed from 2005 to 2015. The average Lab-MELD at time of transplantation increased from 16.19 to 21.22 (Pearson $r = 0.55$, $P = 0.078$). The Match-MELD growth in this era was even higher from 16.19 to 24.47 (Pearson $r = 0.68$, $P = 0.021$). Concomitantly, while no significant changes were seen in 1-year survival over time, 3-year patient survival decreased from 85% in 2005 to 70% in 2012 (Pearson $r = -0.78$, $P = 0.022$). Similarly, in the Eurotransplant area the average 3-year patient survival was 77% in the years 2000–2006 and decreased to 72% in the period 2007–2012. In these years approximately 60 percent of all liver transplantations were performed in Germany. At our center, donor and/or recipient age have not significantly changed over the analyzed period, however the number of transplantations per year has dramatically decreased from 158 in 2005 to 79 in 2015.

Lab- and Match-MELD values have significantly increased since the implementation of the MELD based allocation system, accompanied by a diminished 3-year survival. This data has to be reevaluated, analyzed and discussed in the context of organ scarcity and waitlist mortality. Hence, under current circumstances MELD-based allocation may need reconsideration or at least modifications.

PSYCHOSOMATICS

V015 A DIFFICULT DECISION AND A BAD TEST: THE 6 MONTHS RULE IN LIVER TRANSPLANTATION FOR ALCOHOLIC LIVER DISEASE

M. Tobiasch[*,1,2], *A. Hapfelmeier*[1], *A. Umgelter*[1]
[1]*Klinikum rechts der Isar, II. Medizinische Klinik und Poliklinik, München, Germany;* [2]*Universitätskliniken LKH Innsbruck, II. Medizinische Klinik, Innsbruck, Austria*

Introduction and Background: Liver transplantation is an established therapy for end stage alcoholic liver disease (ALD). In many centres, patients are required to abstain from alcohol for 6 months to qualify for LT. However, this policy excludes some patients from a possibly life saving procedure. Additionally, earlier studies reported a bad test performance and little supporting evidence. Therefore, this rule is often criticised.
Methods: We conducted a systematic review and a meta-analysis on relapse frequencies and outcomes in ALD. A web based search was combined with forward and backward citation tracking. Studies were grouped for centres, to account for multiple publications. We excluded studies before the introduction of cyclosporine, earlier systematic reviews, meta-analyses, and registry studies. Hazard ratios were computed where possible, survival estimates were combined by meta-regression using a mixed-effects model.
Results and Conclusions: We identified 124 studies of 52 centres, reporting on 48 different cohorts. For 42 cohorts, the 6-MR policy was stated. In 16 cohorts, data were reported for either relapse, mortality, or both, in relation to the 6-MR.

Aggregate cohort data showed an inverse correlation between the median pretransplant abstinence time and relapse rates. The mean relapse rate to all use was 18% (IQR, 9–29%), to harmful abuse 10% (IQR, 6–12%). Hazard ratios for relapse were compared between cohorts, the 6-MR showed no significant correlation to relapse or mortality, neither for all use or harmful recidivism.

Sensitivity, specificity, and PPV/NPV were calculated, given appropriate data were reported. The 6-MR showed astonishingly bad performance values, with a mean sensitivity of 30% for harmful relapse, and an unacceptable low PPV for harmful relapse of 27%.

In conclusion, the currently available data do not support a cutoff of six months of pretransplant abstinence as exclusive parameter for precluding LT in individual patients.

V016 COGNITIVE FUNCTIONING IN RENAL TRANSPLANT RECIPIENTS: RESULTS ARE COMPARABLE TO NORMATIVE DATA, BUT SUBGROUP ANALYSIS REVEALED POSSIBLE RISK FACTORS

K. Schieber[*,1], *L. Stößel*[1], *S. Jank*[2], *S. Reber*[1], *F. Grundmann*[3], *C. Lüker*[4], *F. Vitinius*[4], *G. Paslakis*[1], *K.-U. Eckardt*[2], *Y. Erim*[1]
[1]*Universitätsklinikum Erlangen, Psychosomatische und Psychotherapeutische Abteilung, Erlangen, Germany;* [2]*Universitätsklinikum Erlangen, Nephrologie, Erlangen, Germany;* [3]*Universitätsklinikum Köln, Nephrologie, Köln, Germany;* [4]*Universitätsklinikum Köln, Psychosomatik, Köln, Germany*

Introduction and Background: After kidney transplantation, recipients have shown improvements in cognitive function. Only a few studies have examined the cognitive functioning of renal transplant recipients in comparison with normative data, however the results are heterogeneous. In the present study, cognitive functioning of renal transplant recipients was compared to normative data. Furthermore, sociodemographic and clinical parameters that were associated with low cognitive performance were identified.
Methods: A total of 109 renal transplant recipients participated in the study with a mean age of 51.8 (SD = 14.2) years and a higher percentage of men (63%). The cognitive test battery consisted of measurements assessing memory, attention, executive function, reproductive and deductive ability: TMT A+B, VLMT, DS, SPM. Furthermore, we assessed sociodemographic and biochemical data.
Results and Conclusions: In all tests, participants showed mean scores ranging within one SD of the population means. However, except for tests measuring memory, the percentage of participants scoring more than one SD below normed means was higher than expected in a normal distribution of performance. Furthermore, participants with continuous low-performance showed higher age, poorer education, were more likely to have a cadaveric allograft, a longer time since transplantation, and higher blood levels of urea and creatinine.
Conclusion: Generally, cognitive functioning of renal transplant recipients was comparable to normative data. However, about one third of renal transplant recipients suffered from deficiencies in executive function, attention, processing speed, planning ability and deductive as well as reproductive abilities. The identified sociodemographic and biochemical factors in the group of participants with low performance might be helpful to identify renal transplant recipients at risk.

V017 PHOSPHATIDYLETHANOL FOR MONITORING ALCOHOL CONSUMPTION IN LIVER TRANSPLANT CANDIDATES

F. Braun[*,1,2], *F. Mötter*[1], *N. Ehmke*[2], *A. Bernsmeier*[2], *R. Günther*[3], *W. Weimann*[4], *M. Yegles*[5], *T. Becker*[2], *F. Wurst*[6,7]
[1]*UKSH, Campus Kiel, Sektion Klinische Transplantation, Kiel, Germany;* [2]*UKSH, Campus Kiel, Klinik für Allgemeine, Viszeral-, Thorax-, Transplantations- und Kinderchirurgie, Kiel, Germany;* [3]*UKSH, Campus Kiel, Klinik für Innere Medizin I, Kiel, Germany;* [4]*University of Bern, Forensic Toxicology and Chemistry, Bern, Switzerland;* [5]*University, Forensic Toxicology, Dudelange, Luxembourg;* [6]*Paracelsus Medizinische Privatuniversität, Salzburg, Austria;* [7]*Zentrum für Interdisziplinäre Suchtforschung (ZIS), Hamburg, Germany*

Introduction and Background: Alcohol cirrhosis is a common diagnosis in liver transplant (LTx) candidates. Monitoring sobriety with biomarkers is oligate in Germany using ethyl-glucuronide (ETG) in urine or hair. However, false positive results or renal impairment might limit its use. Therefore, we aimed at evaluating phosphatidylethanol (PEth) by comparing the results with routine parameters, uETG, hETG and self-reports.
Methods: The study design was open, mono-centre and prospective (ethic committee D437/15). Each patient received the Alcohol Use Disorders Identification Test and timeline follow-back questionnaire. Blood, urine and hair samples were drawn for monitoring of alcohol intake: uETG clinical routine, hETG current gold standard and PEth dry-blood spot experimental parameter.
Results and Conclusions: In total, 66 patients have been enrolled for the study: 53 listed for LTx (45 T, 8 NT) and 13 potential candidates. 25 patients had an alcohol use disorder listed as a diagnosis (8 not listed, 11 T, 6 NT).

Positive results were detected in 5/65 for uETG, 9/65 for hETG and 30/62 for PEth. 22 patients reported alcohol consumption in the questionnaires: 13 positive PEth, 3 positive uETG, 7 positive hETG. All status T listed patients with alcoholic cirrhosis had negative uETG, but 1 was hETG and 4 PEth positive. The 6 status NT patients with alcoholic cirrhosis were also negative for uETG, but 3/6 hETG and 4/5 PEth positive. Of 34 status T listed patients with other diagnosis 16/32 were tested positive for PEth, 1/33 for hETG and 3/33 for uETG.

There was a strong correlation between positive uETG and hETG with a positive PEth. Positive uETG and hETG tests correlated significantly with higher PEth values. Alcohol consumption over the last 2 weeks, last month and last 6 months correlated with PEth values, especially last 2 weeks and last months. The waiting list status T correlated significantly with negative PEth values. Therefore, our data suggest, that PEth is a promising specific and sensitive parameter in this setting.

PATHOLOGY

V021 NUCLEAR MAGNETIC RESONANCE ANALYSIS OF FAT IN PRETRANSPLANT LIVER BIOPSIES – A NOVEL APPROACH TO ASSESS LIVER STEATOSIS

S. Bertram[*,1], *C. Myland*[1], *S. Swoboda*[2], *A. Gallinat*[2], *T. Minor*[2], *M. Thie*[2], *N. Lehmann*[3], *J. Kälsch*[4], *L. Pott*[1], *A. Canbay*[4], *T. Bajanowski*[5], *H. Reis*[1], *A. Paul*[2], *H.A. Baba*[1]
[1]*Universitätsklinikum Essen, Institut für Pathologie, Essen, Germany;* [2]*Universitätsklinikum Essen, Klinik für Allgemein-, Viszeral- und Transplantionschirurgie, Essen, Germany;* [3]*Universität Duisburg-Essen, Institut für Medizinische Informatik, Biometrie und Epidemiologie, Essen, Germany;* [4]*Universitätsklinikum Essen, Klinik für Gastroenterologie und Hepatologie, Essen, Germany;* [5]*Universitätsklinikum Essen, Institut für Rechtsmedizin, Essen, Germany*

Introduction and Background: Marginal grafts or extended criteria for donor livers are more frequently accepted due to the growing discrepancy of demand and availability of donor organs. Steatotic donor livers belong to these marginal grafts, which are more sensitive to ischemia-reperfusion injury. Thus assessment of steatosis is crucial prior to liver transplantation.
Methods: Steatosis of 49 prereperfusion liver biopsies from patients who received orthotopic liver transplantation was assessed by three techniques. These included semiquantitative histological evaluation, a computerized histomorphometrical approach and the NMR-based technique. The findings were correlated to clinical data and to histological examinations of corresponding postreperfusion biopsies for quantification of ischemia-reperfusion injury.
Results and Conclusions: Values obtained from all three steatosis assessment methods were positively correlated. Steatosis from either method was not significantly associated with clinical outcome and extent of ischemia-reperfusion injury.

Steatosis evaluation with NMR technique yields comparable results as histological and morphometrical assessment. This technique represents a

rapid (<5 min) and accurate method for quantification of fat in donor livers and may reliably be used in cases where pathological evaluation is not available.

KIDNEY II (MARGINAL ORGANS)

V028 BKV AND CMV COINFECTION IN RENAL TRANSPLANT PATIENTS: RESULTS FROM A LARGE MULTICENTER STUDY

A. Blázquez-Navarro[*1], *C. Dang-Heine*[1], *M. Or-Guil*[2], *C. Bauer*[3], *T. Westhoff*[4], *C. Hugo*[5], *P. Reinke*[1], *B. Sawitzki*[1], *N. Babel*[1]
[1]*Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany;* [2]*Humboldt-Universität zu Berlin, Systems Immunology Laboratory, Berlin, Germany;* [3]*MicroDiscovery GmbH, Berlin, Germany;* [4]*Universitätsklinikum der Ruhr-Universität Bochum, Medizinische Klinik I, Herne, Germany;* [5]*Universitätsklinikum Carl Gustav Carus, Medizinische Klinik III – Bereich Nephrologie, Dresden, Germany*

Introduction and Background: BK virus (BKV) and Cytomegalovirus (CMV) reactivations are common after kidney transplantation (Tx), being associated with graft failure and increased morbidity and mortality. CMV is a risk factor for BKV reactivation, but the effects of a BKV-CMV coinfection remain unknown.
Methods: In a large prospective multicenter study, 3797 blood samples from 541 kidney transplant recipients were analyzed for BKV, and CMV load by qPCR. The measurements were performed throughout eight visits during the first post-Tx year. Clinical characteristics, including graft function (GFR) were collected in parallel.
Results and Conclusions: 260 and 193 patients had detectable BKV and CMV, respectively. 71.9% of BKV^+ and 79.2% of CMV^+ patients cleared viral infection 1 year post-Tx. Infected patients showed an impairment of renal function: in comparison to noninfected patients, patients with viral monoinfection (BKV > 2000 copies/ml or CMV > 6000 copies/ml) showed a significant ($P < 0.05$) GFR decline 1-year post-Tx. Of interest were the data on BKV and CMV coinfection. 115 patients were BKV^+CMV^+; both infections were significantly associated ($P < 0.0001$). The temporal sequence of the two infections was not uniform: 52 patients showed BKV reactivation before CMV, 42 had CMV before BKV and in 21, both were detected simultaneously. Co-infected patients did not have higher viremias than monoinfected and did not show more rejection episodes. Nevertheless, coinfected patients showed a significant loss of renal function in comparison to monoinfected patients. Even at much lower thresholds (BKV > 1000 and CMV > 1500) than for monoinfected patients, coinfected patients showed a significant loss of GFR of 8.5 ml/min 1-year post-Tx ($P < 0.05$) when compared to noninfected patients.

Our results demonstrate the significance of BKV and CMV coinfection for the long-term allograft function and highlight the importance of a good therapeutic monitoring and control of the viral reactivations, even at low viremia levels.

V029 ACUTE REJECTION BY BELATACEPT DOSING FREQUENCY: RESULTS FROM A PHASE II STUDY OF KIDNEY TRANSPLANT RECIPIENTS

F. Vincenti[1], *G. Blancho*[2], *A. Durrbach*[3], *G. Grannas*[*4], *J. Grinyó*[5], *U. Meier-Kriesche*[6], *M. Polinsky*[6], *H. Zhao*[6], *C. Larsen*[7]
[1]*University of California, San Francisco, United States of America;* [2]*University Hospital of Nantes, Nantes, France;* [3]*University Hôpital of Bicêtre, Le Kremlin-Bicêtre, France;* [4]*Medizinische Hochschule Hannover, Hannover, Germany;* [5]*University Hospital of Bellvitge, Barcelona, Spain;* [6]*Bristol-Myers Squibb, Lawrenceville, United States of America;* [7]*Emory University, Atlanta, United States of America*

Introduction and Background: This analysis examined biopsy-proven acute rejection (BPAR) at 10 years post-transplant in cyclosporine (CsA)-treated and belatacept (bela)-treated patients participating in the phase II IM103-100 (NCT00035555) study.
Methods: Patients were first randomized to bela more intense (MI; $n = 74$), bela less intense (LI; $n = 71$), or CsA ($n = 73$). At 3–6 months post-transplant, bela-treated patients underwent a second randomization to bela 5 mg/kg every 4 weeks ($n = 62$) or every 8 weeks ($n = 60$). All randomized, transplanted patients were analyzed through 10 years post-transplant. BPAR was confirmed centrally and compared between regimens using Cox regression.
Results and Conclusions: Cumulative rates for BPAR from first randomization to 10 years post-transplant were 23%, 37%, and 26% for bela MI, bela LI, and CsA, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) comparing BPAR did not differ statistically: bela MI vs CsA, 0.95 (0.47–1.92, $P = 0.89$); bela LI vs CsA, 1.61 (0.85–3.05, $P = 0.15$). BPAR from second randomization to 10 years post-transplant was most common for bela 8-weekly; cumulative rates for BPAR at 10 years post-transplant for bela 4-weekly, bela 8-weekly, and CsA were 11%, 22%, and 14%, respectively. One patient (randomized to bela 4-weekly) had grade IIB BPAR. No patient had grade III BPAR. Irrespective of dosing frequency, HRs (95% CIs) comparing BPAR in bela-treated and CsA-treated patients did not differ significantly: bela 4-weekly vs CsA, 1.06 (0.35–3.17, $P = 0.92$); bela 8-weekly vs CsA, 2.00 (0.75–5.35, $P = 0.17$). In a further subset analysis, the cumulative rate of BPAR was lowest for patients receiving bela MI every 4 weeks (7%) and highest for patients receiving bela LI every 8 weeks (30%). To conclude, at 10 years post-transplant, rates of BPAR were similar between bela-treated and CsA-treated patients, with numerically higher rates of BPAR in the bela LI group subsequently randomized to every 8-week dosing.

V030 DETECTION OF BK VIRUS IN PATIENTS AFTER KIDNEY TRANSPLANTATION

J. Korth[*1], *M. Widera*[2], *U. Dittmer*[2], *J. Verheyen*[2], *O. Witzke*[3]
[1]*Universitätsklinikum Essen, Nephrologie, Essen, Germany;* [2]*Universitätsklinikum Essen, Virologie, Essen, Germany;* [3]*Universitätsklinikum Essen, Infektiologie, Essen, Germany*

Introduction and Background: The Polyomavirus associated nephropathy (PVAN) affects up to 10% of the kidney transplant recipients and comes with a high risk of transplant failure. The main risk factor for BKPyV reactivation and PVAN is the immunosuppressive therapy. Viral factors like the viral load or mutational patterns might also contribute the transplant function and the occurrence of PVAN.
Methods: We performed a retrospective analysis of 271 patients after kidney transplantation from 2012 to 2014 from our University Hospital Essen. All patients were screened for BKV viremia and the transplant function at month 3, 6, 12 and 24 after transplantation. In a subset of 21 patients the NCCR-region of BKPyV variants was amplified and sequenced.
Results and Conclusions: In 162 of 271 (60%) BKPyV-DNA could never be detected after transplantation. In 41 of 271 (15%) patients BKPyV-DNA could be detected but viral load was below limit of quantification of 400 copies/ml. 35 of 271 (13%) patients were found positive for BKPyV-DNA between 400 and 10 000 copies/ml. 33 of 271 (12%) patients showed a viral load above 10 000 copies/ml. In patients with viral load above 10 000 copies/ml the transplant function tended to decline over time. PVAN was diagnosed by biopsy in 15 (5%) patients. In 3 of 15 (20%) patients PVAN did result in the loss of the transplant and 7 of 256 (2.7%) patients without PVAN lost transplant function due to other reasons. The analysis of the NCCR showed that 3 (14%) of the 21 analyzed BKPyV variants detected in patients with PVAN harbored insertions or deletions in the NCCR, which were not present in BKPyV variants obtained from patients without PVAN.

High levels of BKPyV-DNA were correlated with the diagnosis of PVAN in patients after kidney transplantation and decline of transplant function. Insertions or deletions in the NCCR region of BKPyV were exclusively detected in isolates obtained from patients diagnosed with PVAN.

LIVER II (INTERDISCIPLINARY CHALLENGES)

V034 EVALUATION OF THE LONG-TERM OUTCOMES WITH EVEROLIMUS, AFTER CALCINEURIN INHIBITOR WITHDRAWAL: 36 M RESULTS OF THE H2304 AND PROTECT EXTENSION STUDIES

L. Fischer[*1], *J. Fung*[2], *H.J. Metselaar*[3], *G. Kaiser*[1], *P. Schemmer*[4], *P. Neuhaus*[4], *I. Kroeger*[5], *P. Lopez*[6], *P. Bernhardt*[6], *H.-J. Schlitt*[7]
[1]*H2304 Study Group, PROTECT Study Group, Germany;* [2]*H2304 Study Group, United States of America;* [3]*H2304 Study Group, Netherlands;* [4]*H2304 Study Group, Germany;* [5]*Novartis Pharma GmbH, Nuermberg, Germany;* [6]*Novartis Pharma AG, Basel, Switzerland;* [7]*Protect Study Group, Germany*

Introduction and Background: The H2304 and PROTECT studies demonstrated reduced nephrotoxicity with everolimus (EVR)-based calcineurin inhibitor (CNI; cyclosporine: CsA, tacrolimus: TAC)-free regimens at Month (M) 12. Here, we evaluate the approaches based on 36 M results from CNI withdrawal (WD) vs standard (C) CNI regimens from these studies.
Methods: H2304 study recruited patients in CNI-WD ($N = 231$) arm to receive EVR (C0 3–8 ng/ml; increased to C0 6–10 ng/ml by end of M4) + rTAC (C0 3–5 ng/ml; withdrawn at M4), 1 M postliver transplantation (LTx). Enrollment into CNI-WD arm was prematurely terminated due to higher acute rejection rate during CNI withdrawal; however, patients on study treatment for >4 M could continue in the regimen. In PROTECT, patients in CNI-WD ($N = 101$) arm received EVR + CNI (TAC or CsA) 4–8 weeks post-LTx with EVR C0 target of 5–12 when combined with TAC or 8–12 ng/ml in combination with CsA. After CNI withdrawal EVR C0 was maintained at 5–12 ng/ml. CNI was completely withdrawn when patients were stable with 70% CNI reduction (for at least 2 M) latest by M6 post-LTx and all patients received basiliximab induction therapy.
Results and Conclusions: At M36, incidence of tBPAR was higher in CNI-WD arm vs CNI-C in both studies. However, there was no increase in graft loss

in CNI-WD vs CNI-C arm (H2304: 2.8% vs 4.0%; PROTECT: 2.2% vs 2.1%). In both the studies, renal function (eGFR; MDRD4) improved significantly in CNI-WD vs CNI-C arms and incidence of AEs and SAEs was similar in CNI-WD vs CNI-C arm. Although an increased risk of rejection was seen at the time of CNI withdrawal in H2304 study, complete CNI withdrawal without risk of subsequent efficacy failure, can be achieved with the introduction of induction therapy and stepwise CNI reduction as seen in PROTECT. Despite the differences in rejection rates, CNI-WD arm in both studies showed better renal function preservation vs CNI-C arm.

V035 ANALYSIS OF THE PNPLA3 GENOTYPE AND FIBROSIS PROGRESSION OF THE LIVER ALLOGRAFT IN 426 LIVER TRANSPLANT RECIPIENTS

J. Mittler[*,1], C. Mittler[2], F. Abel[2], M. Hoppe-Lotichius[1], A. Lautem[1], A. Schad[3], P.R. Galle[2], H. Lang[1], T. Zimmermann[2]

[1]*Universitätsmedizin Mainz, Klinik für Allgemein-, Viszeral- und Transplantchirurgie, Mainz, Germany;* [2]*Universitätsmedizin Mainz, 1. Medizinische Klinik, Mainz, Germany;* [3]*Universitätsmedizin Mainz, Institut für Pathologie, Mainz, Germany*

Introduction and Background: Predictors of fibrosis progression in chronic liver disease in the setting of liver transplantation (LT) are urgently needed. Adiponutrin (PNPLA3) rs738409 genotype has been associated with graft steatosis and fibrosis progression. Aim of this study was to investigate whether the PNPLA3 genotypes of the donor and/or recipient influence fibrosis progression after LT.
Methods: This study included 426 patients who underwent LT between 1997 and 2015. Recipient genotypes were determined from blood leucocytes, donor genotypes from wedge biopsies. The end-point was histological findings of fibrosis stage F2 or F3 according to Desmet score. Statistical analysis was based on Kaplan–Meier survival curves and cox regression analysis.
Results and Conclusions: Transplanted patients ($n = 426$) were classified according to the pretransplant underlying chronic liver disease: alcohol ($n = 130$), HCV ($n = 79$), HBV ($n = 54$), viral hepatitis and alcohol ($n = 50$), HCC ($n = 17$), auto-immune ($n = 38$) and other indications ($n = 58$). Donor and recipient allele-frequencies were in Hardy–Weinberg equilibrium. 426 recipients were genotyped with a G allele frequency of 39%. In 196 of 426 donors the G allele frequency was significantly lower (28%; $P < 0.05$). In Kaplan–Meier survival functions considering all patients together on a follow-up period of 20 years, recipients with genotype CC would reach a F2 fibrosis sooner than carrier of G variant of PNPLA3 ($P = 0.03$). In the group of patients transplanted for HCV-cirrhosis, again the CC carriers would reach sooner a F2 or F3 fibrosis that their G counterparts ($P = 0.07$ over 5 years, $P = 0.01$ over 17 years for F2 fibrosis and $P = 0.02$ over 5 years and $P = 0.001$ over 17 years for F3 fibrosis). When considering donor genotypes instead of recipient genotypes in the survival functions, no difference came to light when comparing the evolution of fibrosis.

In our large cohort of patients the presence of G variant of PNPLA3 was not associated with a faster development of fibrosis in the liver after transplantation.

V036 LIMITED IMPACT OF PRE-EXISTING DONOR SPECIFIC HLA ANTIBODIES ON LONG TERM SURVIVAL AFTER FIRST LIVER TRANSPLANTATION

M. Koch[*,1], M. Marget[2], V. Spetzler[1], H. Thude[1], M. Sterneck[3], B. Nashan[1]

[1]*UKE, Hepatobiliäre Chirurgie und Transplantationschirurgie, Hamburg, Germany;* [2]*UKE, Transfusionsmedizin, HLA-Labor, Hamburg, Germany;* [3]*UKE, MVZ-Lebertransplantation, Hamburg, Germany*

Introduction and Background: Donor specific antibodies (Ab) are known to play a pivotal role in long term kidney allograft survival. Their importance in liver transplanted patients (LTX) is still controversial.
Methods: We retrospectively analyzed sera of 136 first adult LTX patients transplanted between 2008 and 2014 for HLA Ab by Luminex single antigen bead assays. Patients dying within the first 12 month post-LTX were excluded. The mean follow up (FU) of the patients was 38 month.
Results and Conclusions: In 100/136 patients (73.5%) HLA Ab were detectable before LTX. In 44/136 (32.4%) the Ab were identified to be donor specific (DSA) in retrospect. Patients with and without Ab did not significantly differ in age, BMI, labMELD pre-LTX or primary liver disease.

During FU 6 graft losses occurred. 1 graft was lost in a patient without Ab (primary nonfunction, PNF) and five in patients with HLA Ab (3 PNF, 1 chronic rejection, 1 bile duct necrosis). All patients were successfully retransplanted.

Eight patients died during the FU: 3 patients without Ab (2 HCC recurrence, 1 sepsis) and 5 with HLA Ab (3 HCC recurrence, 2 sepsis).

Early bile duct complications were higher in the HLA Ab group (19/100 (19%)) and in the DSA group (8/44 (18%)) compared to the patients without Ab (3/36 (8%)) but this difference did not reach statistical significance. Acute rejections were not significantly higher in patients with Ab (29%), or with DSA (36%) compared to patients without Ab (25%). Bilirubin and gGT in sera were not different between the groups 1, 2 and 3 years post-transplantation.

We conclude that HLA Ab and DSA are frequent in liver transplant patients. During the FU of three years only one graft loss due to chronic rejection occurred (<1%). There was no difference in patient or graft survival between patients with preformed HLA Ab, DSA or no Ab. Liver function was not different between the groups 1, 2 and 3 years post-transplantation.

Pretransplant HLA Ab analysis or HLA matching seems not to be useful in adult first liver transplant patients.

V037 DAA-TREATMENT OF HEPATITIS C-VIRUS GENOTYPE 1 INFECTION AFTER LIVER TRANSPLANTATION IN A HARD-TO-TREAT REAL-LIFE-COHORT

S. Bernuth[*,1], D. Grimm[1], J. Vollmar[1], M. Hoppe-Lotichius[2], J. Mittler[2], H. Lang[2], P.R. Galle[1], T. Zimmermann[1]

[1]*Universitätsmedizin Mainz, 1. Medizinische Klinik und Poliklinik, Mainz, Germany;* [2]*Universitätsmedizin Mainz, Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Mainz, Germany*

Introduction and Background: Hepatitis C virus (HCV) re-infection after liver transplantation (LT) is a frequent problem, which resulted in a high mortality until new direct acting antivirals (DAA)-based therapies recently became available. We evaluated efficacy and safety of new IFN-free therapies in a large single-center real life cohort of HCV genotype (GT) 1 patients after LT who have been unsuccessfully treated over two decades.
Methods: We analyzed a cohort of 157 LT patients infected with HCV (72.6% GT1) who underwent deceased donor LT between 1997 and 2012. DAA therapy, baseline predictors, previous antiviral treatment, fibrosis stage as well as outcome and side effects were assessed.
Results and Conclusions: Organ-survival with recurrent HCV GT 1 infection was inferior to other HCV genotypes ($P = 0.01$). 27.8% of HCV GT1 patients died from recurrent cirrhosis or HCC (one patient after DAA-treatment). Only 28% (44/157) were therapy-naïve, 43.2% were treated at least twice. 72.0% of all HCV-positive patients and 75.7% of DAA-treated patients were previous nonresponders.

Patients with advanced disease and/or high urgency received preferential treatment: 44 patients were selected, 37 of whom (5 with F3/F4-Fibrosis) were treated with DAA regimens (Sofosbuvir/Ledipasvir (SOF/LDV): 10; SOF/LDV/Ribavirin (RBV): 7; SOF/Daclatasvir (DCV): 4; SOF/DCV/RBV 4; SOF/Simeprevir: 2; SOF/RBV: 6; SOF/RBV/Interferon: 3; Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir: 1). 7 patients received no antiviral therapy due to severe co-morbidities.

The SVR rate with DAA in this hard to treat real world cohort was 94.6%. Two patients relapsed. The DAA therapy was safe and well-tolerated. Anemia was the most frequent side-effect ($n = 20$; 54.1%). One patient discontinued therapy in week 12 due to kidney- and liver failure and reached SVR.

In conclusion, DAA therapy was highly effective and safe in this hard-to-treat real-life cohort.

THORACIC ORGANS I (HEART)

V042 A FRIEND IN NEED IS A FRIEND INDEED – THE ORGAN CARE SYSTEM IN THE SETTING OF HEART TRANSPLANTATION IN LVAD PATIENTS

B. Schmack[*,1,2], A. Sabashnikov[1], A. Weymann[1,2], D. Garcia-Saez[1], B. Zych[1], M. Zeriouh[1], A. Koch[1,3], F. de Robertis[1], N.R. Banner[4], M. Karck[2], A.R. Simon[1], A.-F. Popov[1]

[1]*Royal Brompton & Harefield NHS Trust Foundation, Cardiothoracic Surgery and Transplantation, Mechanical Support, Harefield, United Kingdom;* [2]*University Hospital Heidelberg, Department of Cardiac Surgery, Heidelberg, Germany;* [3]*Westdeutsches Herzzentrum Essen, Abteilung für Herzchirurgie, Essen, Germany;* [4]*Royal Brompton & Harefield NHS Trust Foundation, Cardiology, Transplant medicine and Circulatory Support, Harefield, United Kingdom*

Introduction and Background: Left ventricular assist devices (LVAD) are standard of care for patients with advanced heart failure as a bridge to heart transplantation (HTx). Though, LVAD therapy is known to increase functional status prior and outcome after HTx, transplanting these patients is challenging and a risk factor for increased early mortality. Despite hypothermic cardioplegic arrest (HCA), the use of ex-vivo normothermic preservation (Transmedics Organ Care System, OCS) drastically minimizes cold ischaemic time and optimizes logistics and meticulous recipients' preparation. The purpose of this study was to compare the influence of OCS on outcome in LVAD patients bridged to HTx (BTT).
Methods: A retrospective study of all LVAD patients bridged to HTx at a single centre from July 2007 to March 2015 was performed. Donor data and outcomes in the patients transplanted with HCA vs. OCS preserved grafts were compared.

Results and Conclusions: 236 patients underwent LVAD implantation. 39 (16.5%) patients were successfully bridged to HTx. 15 (38.5%) patients received grafts from HCA (2007–12) vs. 24 (61.5%; 2013–15) using OCS. Considering donor risk factors, there was a trend towards higher donor age in the OCS group (40 ± 10 vs. 34 ± 11 years; $P = 0.08$) with donor smoking history significantly more prevalent (75% OCS vs. 40%; $P = 0.029$) and a trend towards prolonged transport time (>150 min; 41.7% vs. 13.3%; $P = 0.083$). The incidence of primary graft failure requiring mechanical circulatory support was higher for the HCA group (66.7% vs. 25%; $P = 0.01$) as wells as duration of inotropic support, mechanical ventilation, blood loss in 24 h and need for blood products. There was a trend towards beneficial overall cumulative survival at 1 year for OCS (74.8% vs. 53.3%; $P = 0.069$). The use of OCS in LVAD patients (BTT) results in substantially beneficial procedural logistics and significantly improves the short-term outcome. We have increased the number of patients transplanted on long term LVAD while this strategy has become the standard of care at our institution.

V043 CONTINUOUS-FLOW LEFT VENTRICULAR ASSIST DEVICE FOR ENDSTAGE HEART FAILURE: MIDTERM RESULTS FROM A SINGLE-CENTRE

N. Pizanis[*,1], H. Carstens[1], K. Kreikemeier[1], A. Koch[1], P. Lüdike[2], T. Rassaf[2], M. Kamler[1]

[1]*Universitätsklinikum Essen, Thorakale Transplantation und Unterstützungssysteme, Essen, Germany;* [2]*Universitätsklinikum Essen, Kardiologie, Essen, Germany*

Introduction and Background: Left ventricular assist devices (LVADs) have progressed to an established therapy of advanced heart failure due to heart transplant scarcity. The aim of this study was to present our institutional experience and mid-term outcomes after implantation of 130 continuous-flow (CF) LVADs.
Methods: One hundred and thirty consecutive HeartWare® left ventricular assist device (HVAD®) implantations were performed between 12/2010 and 05/2016. 65 patients suffered from nonischaemic- and 57 from ischaemic cardiomyopathy, with eight patients suffering from other diseases. Mean age was 58 ± 13 years. 66% of patients were on inotropic support or more (86 patients; Intermacs 1–3), with 20 (15%) on preoperative mechanical support (ECLS) and 21 (16%) on IABP.
Results and Conclusions: Mean support duration was 491 ± 509 days, with longest support duration of 1880 days (ongoing). The overall cumulative survival rate was 81% at 30 days, 60% at 1 year and 55% at 2 years. Hospital discharge occurred after a mean of 38 ± 28 days. Two patients were successfully weaned from the device. Postoperatively, 30 day mortality occurred mainly in the Intermacs 1–3 collective (20 from 25 patients, 80%). Adverse events in the following were pump thrombosis (6%), neurological events (5%), gastrointestinal bleeding (12%) and driveline infections (28%). Pump exchange due to technical problems occurred in 1 patient (<1%).

Current CF-LVADs can be used successfully and reliably for endstage heart failure. Survival rates are good when considering the high number of Intermacs 1–3 patients in the study cohort. Further investigations are needed in order to improve survival by selection and timing of implantation. Adverse events remain an important issue, requiring interdisciplinary approaches. Finally, due to the increasing number of LVAD patients, improved support services for outpatient care are required.

V044 SUPPLEMENTAL CARDIOPLEGIA BEFORE GRAFT IMPLANTATION: DOES IT CREATE MORE HARM THAN GOOD FOR DONOR HEARTS?

U. Boeken[*,1], A. Albert[1], A. Mehdiani[1], G. Petrov[1], B. Sowinski[1], R. Westenfeld[2], D. Saeed[1], P. Akhyari[1], A. Lichtenberg[1]

[1]*Uni-Klinik, Kardiovaskuläre Chirurgie, Düsseldorf, Germany;* [2]*Uni-Klinik, Kardiologie, Düsseldorf, Germany*

Introduction and Background: In times of prolonged ischemic times myocardial protection for donor hearts is a prerequisite to improve the outcome after heart transplantation (htx). The preservation of cardiac grafts is not standardized, the majority of centers prefer a single application of cardioplegic solution. However, the benefit of an additional dose of cardioplegia prior to warm ischemic time is still discussed controversially.
Methods: Between 10/2010 and 04/2016 60 patients underwent htx in our department. The patients could retrospectively be divided into two groups with regard to the cardioplegic preservation of donor hearts: 20 patients with one single cardioplegia during donation (cp1) and 40 patients with additional cardioplegia immediately before implantation (cp2).
Results and Conclusions: We found a slightly prolonged allograft cold ischemic time in group cp2. Grafts of cp2-patients received additional antegrade cardioplegia immediately before implantation.

The incidence of perioperative graft dysfunction (PGD) and low cardiac output was comparable between the groups. Likewise we did not find significant differences regarding postoperative markers of myocardial ischemia and regarding clinical course.

However, significant differences could be found in patients with ischemic graft times > 210 min for: PGD: cp1: 21.4% (3/14), cp2: 9.7% (3/31), postoperative peak hs-cTnT: 4865 pg/ml vs. 2980 pg/ml, ITN: 59.9 ± 22.6 h vs. 40.9 ± 13.2 h), and stay on intensive care unit.

1-year-follow up ($n = 50$) revealed a comparable survival rate for the total groups (cp1: 70.6% (12/17), cp2: 75.8% (25/33)), as well as for patients with prolonged graft ischemia.
Conclusions: In our patients an additional application of cardioplegic solution did not positively influence the outcome after htx. However, as we observed reduced myocardial damage and improved clinical course in patients with prolonged graft ischemia and supplemental cardioplegia, this approach may be useful in selected patients.

IMMUNOLOGY I (DSA)

V048 THE IMPACT OF DONOR-SPECIFIC ANTI-HLA ANTIBODY MEDIATED REJECTION IN LIVER TRANSPLANTATION

S. Ünlü[*,1,2], T. Dziodzio[1], N. Lachmann[2], S. Weiss[1], S. Gül[1], U. Gerlach[1], C. Denecke[1], M. Biebl[1], C. Schönemann[2], J. Pratschke[1], R. Öllinger[1]

[1]*Charité – Universitätsmedizin Berlin, Chirurgische Klinik, Campus Virchow-Klinikum, Berlin, Germany;* [2]*Charité – Universitätsmedizin Berlin, Institut für Transfusionsmedizin, Gewebetypisierung, Berlin, Germany*

Introduction and Background: The clinical role of donor-specific anti-HLA antibodies (DSAs) in liver transplantation (LT) is not clearly established. We investigated the impact of antibody-mediated rejection (AMR) on the clinical course, morbidity and mortality of LT recipients.
Methods: Between 2008 and 2015 649 LTs were performed at our institute. DSAs were determined by the Luminex® assay for all patients. Patients with more than two positive DSA results were included in the study. The mean fluorescence intensity (MFI) was used to quantify DSAs and was correlated with the patient courses and the success of AMR therapy.
Results and Conclusions: Thirty-three patients with class-I and/or class-II DSAs were identified. Of those, 19 patients (57.6%) showed clinical signs of AMR. In 17 patients (51.5%) an additional cellular rejection was observed. Sixteen patients (48.5%) were treated with steroids, 11 (33.3%) with plasmapheresis and immunoglobulins and six patients (18.2%) received antithymocyte globulin. Six patients (18.2%) showed a decay of rejection (MFI value reduction of >84%) and improvement of clinical parameters. Six patients needed a re-transplantation. Overall mortality was 21.2% with sepsis being the leading cause of death (five patients). Fourteen patients (12.1%) with persistent elevated MFI values showed no clinical signs of AMR.
Conclusion: AMR after LT is relatively rare, however DSAs can cause fulminant rejections with fatal courses. Current therapy concepts were only successful in a quarter of patients. Interestingly, sepsis was the leading cause of death. Further, nearly half of the patients with positive DSAs showed no signs of AMR. Thus, future investigations need to focus on the balancing of AMR treatment and its side-effects, as well as the causes of heterogeneous susceptibility of LT recipients to AMR.

V049 REDUCED INCIDENCE AND LEVEL OF *DE NOVO* DONOR-SPECIFIC ANTIBODIES IN BELATACEPT-TREATED VS. CYCLOSPORINE-TREATED PATIENTS: FINAL RESULTS FROM BENEFIT

R. Bray[1], H. Gebel[1], R. Townsend[2], M. Polinsky[2], L. Yang[2], U. Meier-Kriesche[*,2], C. Larsen[1]

[1]*Emory University, Atlanta, United States of America;* [2]*Bristol-Myers Squibb, Lawrenceville, United States of America*

Introduction and Background: The presence of donor-specific antibodies (DSA) has been associated with an increased risk of antibody-mediated rejection and graft failure. Mean fluorescence intensity (MFI) is a semi-quantitative measure of the level of DSAs in a recipient's circulation. The level of MFI in the subset of BENEFIT study participants who developed de novo DSAs was examined.
Methods: Recipients of a living or standard criteria deceased donor kidney were randomized to receive belatacept more intense (MI)-based, belatacept less intense (LI)-based, or cyclosporine A (CsA)-based immunosuppression. In all randomized, transplanted patients, the presence of pre-existing DSAs was assessed at baseline; the development of *de novo* DSAs was assessed at months 6, 12, 24, 36, 48, 60, 84 and at the time of any clinically suspected episodes of acute rejection. Antibody screening was performed centrally at Emory University using solid phase flow cytometry (FlowPRA™). Samples from all DSA-positive patients were further tested with Luminex® single antigen bead assays (One Lambda, Inc). Patients were scored as follows: MFI > 2000 was considered positive and MFI < 2000 as negative.
Results and Conclusions: At 5 years post-transplant, MFI in de novo DSA-positive belatacept-treated patients was lower than that of de novo DSA-

positive CsA-treated patients. By 7 years post-transplant, 1.4% (3/219) of belatacept MI-treated, 3.5% (8/226) of belatacept LI-treated, and 12.6% (27/215) of CsA-treated patients had developed de novo DSAs. Updated 7-year MFI results will be presented at the meeting. In conclusion, belatacept-based immunosuppression seems to be associated with a lower incidence of de novo DSAs and, in those who develop de novo DSAs, lower MFI vs. CsA-based immunosuppression.

V050 LOSS OF REGULATORY ANTI-ANGIOGENIC PROTEASE ACTIVATED RECEPTOR-1 (PAR-1) ANTIBODIES ASSOCIATE WITH THE DEVELOPMENT OF METASTATIC CANCER POST RENAL TRANSPLANTATION AND PATIENT DEATH

R. Catar[*,1], R. Carroll[2], I. Schramm[1], M. Simon[1], O. Wischnewski[1], A. Kusch[1], T. Coates[2], A. Philippe[1], D. Dragun[1,3]

[1]*Charite, Medizinische Klinik m.S. Nephrologie und Internistische Intensivmedizin, Berlin, Germany;* [2]*Royal Adelaide Hospital, Centre for Experimental Transplantation, Adelaide, Australia;* [3]*Berliner Institut für Gesundheitsforschung, Berlin, Germany*

Introduction and Background: Activated angiogenesis and impaired host immune response contribute to cancers in renal transplant recipients. Induction of VEGF is crucial for neoangiogenesis in tumors. Functional autoantibodies targeting GPCRs are able to induce endothelial dysfunction. We hypothesized that autoimmune GPCR targeting process may disturb VEGF induced angiogenesis. We identified in an *in vitro* model PAR-1 as a novel activating autoantibody target and assessed the presence of this naturally occurring blocking antibodies in 20 Kidney Transplant Recipients (KTR) with and 29 KTR without metastatic cancer.
Methods: Human endothelial cells were stimulated with IgG isolated from sera of kidney transplant recipients (KTx-IgG). Transcriptional regulation of VEGF was studied by promoter deletion assay. Transcription factor activation and binding was assessed by qRT-PCR, western blot, EMSA and cFOS knockdown. VEGF secretion was determined by ELISA. Tube formation on matrigel served to study endothelial neoangiogenic response. All 49 patients enrolled had sera for assessment of PARab via ELISA in 2014 and at the time of transplantation.
Results and Conclusions: Treatment with KTx-IgG reduced ERK1/2 dependent VEGF secretion and tube formation. VEGF secretion and endothelial tube formation could be only normalized by pretreatment with specific PAR-1 inhibitor. KTx-IgG contributed to deregulated neoangiogenesis via reduced VEGF-promoter activity and increased cFos protein expression via its binding to the VEGF promoter. PARab levels were lower at the time of transplant in KTR who developed cancer after transplant compared to those who did not. Levels were also different at the time of cancer diagnosis compared to those who had not developed cancer when assessed in 2014.

We identified the PAR-1 receptor as a new target for functional antibodies in the context of kidney transplantation and tumor angiogenesis. PAR-1 regulated angiogenesis could offer new possibilities for treatment of kidney transplants obviate tumor angiogenesis.

V051 CLINICAL UTILITY OF LUMINEX-BASED ANALYSIS OF PRETRANSPLANT ANTI-HLA ANTIBODIES FOR THE DEFINITION OF UNACCEPTABLE HLA ANTIGEN MISMATCHES IN RENAL TRANSPLANTATION

D. Zecher[*,1], C. Bach[2], C. Staudner[1], B. Banas[1], B. Spriewald[2], C. Böger[1]

[1]*Universitätsklinikum Regensburg, Nephrologie, Regensburg, Germany;* [2]*Universitätsklinikum Erlangen, Medizinische Kliniken 3/5 (Rheumatologie/Hämatologie-Onkologie), Labor für Immungenetik, Erlangen, Germany*

Introduction and Background: The German Society for Immunogenetics (DGI) recently published recommendations on the definition of unacceptable HLA antigen mismatches (UAM) in patients awaiting kidney transplantation (NTX). Potential donor HLA antigens were classified as UAM if pretransplant Luminex analysis of recipient sera revealed anti-HLA-specific antibodies (HSA) with mean fluorescence intensity (MFI) values >3000 in patients without prior NTX having HSA against HLA class I and II or in previously transplanted patients with HSA against HLA class I or II (high risk). Also, HSA with MFI >5000 were defined as UAM in patients without prior NTX and HSA against class I or II (intermediate risk). The consequences of this new allocation algorithm for sensitized patients have not yet been investigated.
Methods: We retrospectively applied the UAM criteria to a cohort of 174 CDC-cross-match-negative NTX patients and studied the incidence of antibody-mediated rejection (AMR) and allograft loss. To define UAM, day of transplant sera were retrospectively analyzed for the presence of HSA using Luminex single antigen bead technology. Donor-specificity of HSA was determined based on available donor HLA typing.
Results and Conclusions: 101/174 patients (58%) had HSA with a median MFI of 5822 (range 525–24432). 51/101 (50.5%) had HSA against HLA class I and II and 36/101 (35.6%) awaited retransplantation. We identified UAM in 54/101 patients of which 42 had donor-specific HSA (DSA). 3/42 patients were identified as intermediate risk and had an uneventful follow-up. 13/39 (33.3%) classified as high risk experienced AMR and 8/39 (20.5%) lost their grafts. If the proposed UAM criteria had been applied, 8/9 allograft losses would have been prevented in patients with DSA. However, 29/42 (69%) patients were free from AMR and 34/42 (81%) did not experience graft loss during a median follow-up of 5.4 years.

The favorable clinical outcome in the majority of patients indicates limited clinical utility of the DGI's algorithm for the definition of UAM.

PANCREAS

V055 PRECLINICAL STUDIES ON PORCINE ISLET MACROENCAPSULATION IN NON-HUMAN PRIMATES

B. Ludwig[*,1,2], S. Ludwig[3], A. Steffen[1,2], B. Zimerman[4], F.-J. Kaup[5], U. Barkai[4], J. Weitz[3], S. Bornstein[1,6]

[1]*University Hospital Carl Gustav Carus of TU Dresden, Department of Medicine III, Dresden, Germany;* [2]*Paul Langerhans Institute Dresden of Helmholtz Centre Munich at University Clinic Carl Gustav Carus of TU Dresden, DZD- German Centre for Diabetes Research, Dresden, Germany;* [3]*University Hospital Carl Gustav Carus of TU Dresden, Department of Visceral-, Thorax- and Vascular Surgery, Dresden, Germany;* [4]*Beta-O2 Technologies, Rosh-Ha'ain, Israel;* [5]*German Primate Center Göttingen, Leibniz Institute for Primate Research, Göttingen, Germany;* [6]*Kings College London, Division of Diabetes & Nutritional Sciences, London, United Kingdom*

Introduction and Background: Pancreatic islet transplantation is currently restricted to patients with critical metabolic lability due to the need for immunosuppression and shortage of donor organs. To overcome these obstacles we have developed a strategy for islet macroencapsulation using the Beta O2 device that provides sufficient immune-isolation whereas regulated islet graft function is maintained. This concept was successfully tested in various animal models, and a first clinical case. Here we present the first results using the Beta O2 device on safety and efficacy for macro-encapsulated porcine islets in diabetic non-human primates.
Methods: Isolated porcine islets from Gottingen minipigs were immobilized in alginate and integrated into the Beta O2 device. For safety assessment, healthy cynomolgus monkeys were implanted at a preperitoneal site with encapsulated porcine islets and followed for up to 12 months. For assessment of microbiological transmission, a list of 52 pathogens was tested. For efficacy assessments rhesus macaques underwent surgical subtotal pancreatectomy followed by streptozotocin injection in order to induce complete insulin-deficiency. Animals were transplanted with 20 000 islets/kgBW and followed for 6 months. The study was carried out without immunosuppression. For metabolic assessment, blood glucose (BG) was closely monitored and ivGTT were conducted.
Results and Conclusions: Regarding safety issues, we saw no transmission of any pathogens to the recipients. Upon transplantation of diabetic animals we saw steadily improving glycemic control while insulin demand could be decreased. Upon glucose challenge, we observed BG kinetics comparable to healthy control animals and adequate c-peptide secretion.

In conclusion, we demonstrated a comprehensive safety profile of the xenograft in the Beta O2 device and persistent graft function with regulated insulin secretion without any immunosuppression. These results may pave the way for a first clinical trial on macroencapsulated porcine islets in man.

V056 PDRI AND P-PASS IN PANCREAS TRANSPLANTATION – WHICH IS SCORING MORE?

M.S. Ayami[*,1], T. Klein[2], S. Kykalos[1], R. Viebahn[1], P. Schenker[1]

[1]*University Hospital Knappschaftskrankenhaus Bochum, Department of Surgery, Bochum, Germany;* [2]*Marienhospital Herne, Department of Medicine I, Herne, Germany*

Introduction and Background: Pancreas donor risk index (PDRI) and preprocurement pancreas suitability score (P-PASS) are controversial in clinical pancreas transplantation.
Methods: In this retrospective study PDRI and P-PASS were evaluated in 322 patients, who underwent pancreas transplantation between 2002 and 2015 at a single-center (SPK = 292, PAK = 12, PTA = 18). Both indices were compared and correlated to pancreas graft survival. Patients were divided into three groups for PDRI analysis (PDRI < 1; PDRI 1–1.5; PDRI > 1.5) and in two groups for P-PASS analysis (P-PASS < 17; P-PASS ≥ 17).
Results and Conclusions: The mean P-PASS and mean PDRI were 17 ± 2.5 and 1.31 ± 0.4. Pancreas graft survival rates for 1, 5 and 10 years were 84%, 73%, and 65% among P-PASS < 17 (n = 115) and 74%, 67%, and 58% among P-PASS ≥ 17 groups (n = 207) (P = 0.081). In the PDRI < 1 group (n = 87) 1, 5, and 10 years graft survival were 79%, 75%, and 68%, in

the group PDRI 1–1.5 (n = 130) 83%, 75%, and 64% and in the PDRI > 1.5-group (n = 105) 69%, 57%, and 50%.

In this analysis, PDRI > 1.5 was associated with a significant poorer pancreas graft survival (P = 0.016). No differences were found between the PDRI group <1 and PDRI group 1–1.5 (P = 0.885). The P-PASS of 17 or higher was associated with a slightly worse graft survival, although this difference was not statistically significant. Concerning Eurotransplant donor reports, the already mentioned P-PASS should be replaced by the PDRI.

V058 ROLE OF ENDOVASCULAR PROCEDURES IN THE MANAGEMENT OF ARTERIAL COMPLICATIONS FOLLOWING PANCREAS TRANSPLANTATION

A. Wunsch*[1], M. Bialobrzecka[1], L. Berger[1], P. Schenker[1], A. Tischert[2], R. Viebahn[1]

[1]Knappschaftskrankenhaus Bochum, Chirurgische Klinik, Bochum, Germany; [2]Knappschaftskrankenhaus Bochum, Institut für Radiologie, Bochum, Germany

Introduction and Background: Endovascular medicine is one of the most rapidly expanding fields in medicine today. Vascular complications after pancreatic transplantation carry a high rate of graft loss. It is therefore obvious that efforts have been made to utilize endovascular techniques to treat the challenges of pancreas transplantation.
Methods: We reviewed all pancreas transplant procedures in our centre since 1994 (n = 556). All endovascular procedures performed for arterial complications in our hospital related to the pancreas graft were collected. We confined our search to arterial problems since interventions on the veinous side were less homogenous and much more diverse. We also did not consider procedures carried out for improvement of inflow in the pelvic vessels or for problems related to PAD because the indication for these intervention does not differ from the indications in not transplanted patients.
Results and Conclusions: In our series endovascular techniques were used in the following settings:

- Stenosis of the Y-graft: n = 6
- Pseudoaneurysm: n = 1
- Av fistula: n = 1
- Consolidation of the vessel wall after bleeding due to arrosion: n = 7

In all cases the procedure could be carried out successfully thus minimizing the need for surgery. The implantation of covered stent grafts following a bleeding episode due to arrosion originating from the pancreas graft seemed also superior to open surgery because we did not observe any episodes of rebleeding. Especially in these cases the covered stent offers a valuable bail out option in patient not fit for further surgery.

None of the procedures had to be carried out in the first month following transplantation, but all were treatment options in the long run (range 41–4012 days after the transplant operation).

BASIC SCIENCE I

V062 NK CELLS PROMOTE KIDNEY GRAFT REJECTION THROUGH EVASION OF CYCLOSPORINE-A THERAPY

M.I. Ashraf*[1], T. Resch[2], C. Fabritius[2], S. Ebner[2], P. Ritschl[1], V. Mellitzer[2], J. Günther[2], F. Aigner[1], J. Pratschke[1], K. Kotsch[1]

[1]Charité – Universitätsmedizin, Campus Virchow-Klinikum, Visceral, and Transplantation Surgery, Berlin, Germany; [2]Medical University of Innsbruck, Department of General, Visceral, and Transplantation Surgery, Innsbruck, Austria

Introduction and Background: Despite advances in immunosuppressive regimens having significantly increased short-term graft outcome, overall long-term graft survival has not dramatically changed. Frequently used immunosuppressive drugs e.g. cyclosporine A (CsA) or tacrolimus (Tac) primarily target T cells, whereas their influence on other immune subsets such as NK cells might be limited. As NK cells have recently been recognized as key players in chronic allograft failure comprehensive studies are required to address whether NK cells can escape conventional immunosuppressants and play a role in recurrence of allograft rejection.
Methods: We characterized the effects of CsA on murine NK cells and further assessed its influence on NK cells during transplantation using a murine model of allogenic KTX (Balb/C to C57Bl/6). Immunophenotyping of NK cells and other graft infiltrating lymphocytes was performed by flow cytometry. Allograft function was assessed by measuring serum creatinine and urea levels. Histology of the HE stained tissue sections were performed following Banff criteria. Expression of cytokines was performed by RT-qPCR.
Results and Conclusions: NK cells isolated from CsA treated C57Bl/6 mice (10 mg/kg) revealed normal function regarding degranulation and IFNγ production, whereas $CD8^+$ T cells were functionally impaired. *In vivo,* application of CsA to C57Bl/6 recipients of fully allogeneic Balb/C kidneys resulted in a significant reduction of creatinine levels at day 7. Flow cytometric analysis revealed a CsA mediated reduction of intragraft $CD4^+$ and $CD8^+$ T cells by half, whereas intragraft NK cell frequencies significantly increased and remained unaffected within the spleen or liver. Importantly, the additional depletion of NK cells resulted in a further improvement of kidney function, associated with reduced intragraft and splenic IFNγ expression. Taken together, CsA insufficiently targets murine NK cells and their depletion combined with CsA synergistically improves graft function in an acute transplantation setting.

V063 PHENOTYPICAL CHARACTERIZATION OF HUMAN CD49A+ LIVER-RESIDENT NK CELLS

G. Martrus[1], M. Altfeld[1], H. Goebels*[1], B. Nashan[2]

[1]Heinrich-Pette-Institut, Leibniz-Institut für Experimentelle Virologie, Virus Immunologie, Hamburg, Germany; [2]Universitätsklinikum Hamburg-Eppendorf, Klinik für Hepatobiliäre Chirurgie und Transplantationschirurgie, Hamburg, Germany

Introduction and Background: Natural Killer (NK) cells play a crucial role during infections and inflammatory processes. NK cells represent an enriched population within the intrahepatic lymphocytes (IHLs) by constituting up to 40% of this population. In animal models, specific hepatic NK cells have shown to confer hapten- or virus-specific responses. While data obtained in mice have defined a subset of liver-resident NK (lr-NK) cells, human lr-NKs remain poorly characterized.

The main objective of this study was to characterize lr-NK cells using IHLs and compare their phenotype and function to conventional peripheral blood NK cells from 15 matched donors.
Methods: Matched liver tissues and blood samples were obtained from patients undergoing a liver transplantation, signed written consent according to the ethical guidelines of the Universitäts-Klinikum Hamburg. Liver samples were processed through hashing and filtering protocols, PBMCs were obtained by Ficoll-gradient purification. Recovered cells were immediately stained, fixed and measured with an LRS Fortessa.
Results and Conclusions: Using Principal Component Analysis as an untargeted approach, we observed that NK cells derived from IHLs possessed a distinct phenotypic signature when compared to conventional NK (cNK) cells. $CD56^{bright}$ NK cells were more frequent in IHLs compared to peripheral blood (P < 0.001). NK cells from IHLs exhibited a less activated and a more immature phenotype, with lower expression of CD57 (P < 0.001), DNAM-1 (P = 0.002) and higher expression of CD34 (P = 0.002). CD49a was exclusively expressed on IHL NK cells (P < 0.001), as previously reported for mice lr-NK cells. These human $CD49a^+$ NK cells showed higher expression levels of CD25 (P = 0.002), CD34 (P = 0.002) and CXCR3 (P = 0.002).

Taken together, intrahepatic NK cells differ phenotypically from blood NK cells derived from matched sample individuals, and include liver-specific $CD49a^+CD25^+$ and $CD49a^+CD34^+$ NK cell populations, suggesting different functional features including self-renewal and persistence.

V064 KIDNEY-SPECIFIC IMMUNOSUPPRESSION IN A RAT MODEL OF RENAL TRANSPLANTATION

D. Kentrup*[1], K. Schütte-Nütgen[1], H. Pawelski[1], E. Schlatter[1], H. Pavenstädt[1], S. Hermann[2], M. Schäfers[2], G. Larbig[3], A. Kübelbeck[3], S. Reuter[1]

[1]University Hospital Münster, Department of Medicine D, Experimental Nephrology, Münster, Germany; [2]University Hospital Münster, European Institute for Molecular Imaging – EIMI, Münster, Germany; [3]Merck KGaA, Darmstadt, Germany

Introduction and Background: Renal transplantation is the best available renal replacement therapy for the treatment of patients with end stage renal disease although the necessary immunosuppressive therapy can result in severe side effects, mostly caused by systemic effects of the drugs.

Aim of this study was the evaluation of a modified version of the immunosuppressive drug prednisolone in a rat model of allogeneic kidney transplantation. Coupled to a polypeptide the compound is selectively taken up by the kidney where the prednisolone is released, avoiding systemic effects.
Methods: Six groups of animals were used (N = 5–6): syngeneically (Lewis Brown Norway F1 to Lewis Brown Norway F1) and allogeneically (Lewis Brown Norway F1 to Lewis) transplanted rats without immunosuppressive therapy, as well as allogeneically transplanted animals receiving either systemically acting or kidney-specific prednisolone at two different concentrations (4 mg/kg/12 h or 16 mg/kg/12 h, i.p). Treatment efficiency was evaluated at day 4 post-surgery by ^{18}F-FDG positron emission tomography and histological analysis. Blood glucose levels were measured to assess possible systemic effects.
Results and Conclusions: Compared with allogeneically transplanted animals receiving no immunosuppressive drugs, high-dose treatment with systemically acting prednisolone significantly reduced renal ^{18}F-FDG accumulation and histological signs of rejection, low dose treatment had no effect. Animals treated with kidney-specific prednisolone showed significant

amelioration of graft rejection already at low dose treatment, high dose treatment resulted in further improvement. Elevated blood glucose levels were only observed after administration of systemically acting prednisolone.

We conclude that kidney-specific prednisolone can effectively prevent graft rejection and partially even outperform systemically acting prednisolone. Because we did not find systemic effects on blood glucose further evaluations seem to be promising.

V065 AGEING PACKED RED BLOOD CELLS AGGRAVATE RENAL ISCHEMIA REPERFUSION INJURY (IRI)

L. Wang[1], K. Hüper[2], R. Chen[1], A. Thorenz[1], M. Gutberlet[2], H. Haller[1], K. Madyaningrana[3], V. Vijayan[3], M. Meier[4], J.-H. Bräsen[5], B. Akerstrom[6], M. Gram[6], S. Immenschuh[3], F. Güler*[,1]

[1]Medizinische Hochschule Hannover, Klinik für Nieren- und Hochdruckerkrankungen, Hannover, Germany; [2]Medizinische Hochschule Hannover, Radiologie, Hannover, Germany; [3]Medizinische Hochschule Hannover, Transfusionsmedizin, Hannover, Germany; [4]Medizinische Hochschule Hannover, Zentrales Tierlabor, Hannover, Germany; [5]Medizinische Hochschule Hannover, Pathologie, Hannover, Germany; [6]University Lund, Division of Infection Medicine, Lund, Sweden

Introduction and Background: Acute kidney injury (AKI) is a frequent complication after solid organ transplantation. Especially, lung, heart and liver transplantation are associated with substantial blood loss and the need of packed red blood cell (pRBC) transfusions. Although pRBC are beneficial and in many cases lifesaving, blood products also have adverse effects. Release of toxic extracellular hemoglobin (hb) and heme has been shown to contribute to acute organ (especially lung) injury. In this study, the effect of free hb / heme on ischemia-induced subclinical AKI was investigated in a mouse model.
Methods: Renal ischemia reperfusion injury (IRI) was induced by bilateral 15 min renal pedicle clamping in mice. Mice after sham surgery served as controls. Afterward, free hb, free heme or vehicle was infused. Clinical chemistry for renal function parameters and functional magnetic resonance imaging (fMRI) was done to quantify creatinine elevation, renal perfusion impairment and tissue edema. qPCR for cytokine expression, histology and immunohistochemistry for acute kidney injury and inflammation were done.
Results and Conclusions: Free hb/heme infusion resulted in marked aggravation of AKI with elevated s-creatinine and BUN whereas vehicle treatment did not cause a relevant impairment in renal function. By fMRI significant decrease of renal perfusion was measured due to heme injection after IRI but not after sham surgery. Inflammation and acute tubular injury were more prominent in mice after free hb/heme infusion than in those given vehicle. Tissue levels of pro-inflammatory cytokines were significantly higher in free hb/heme-treated mice than in vehicle treated animals.

Taken together, transfusion of aged pRBC is pro-inflammatory and aggravates AKI in an experimental mouse model of mild renal IRI.

THORACIC ORGANS II (LUNG)

V069 PRELIMINARY RESULTS ON THE USE OF *EX-VIVO*-LUNG-PERFUSION IN GERMANY

A. Koch*[,1], N. Pizanis[1], H. Carstens[1], O. Abou-Issa[1], J. Heckmann[1], M. Brumhard[2], E. Altinöz[1], A. Slama[3], C. Aigner[3], M. Kamler[1]

[1]Universitätsklinik Essen, Thorakale Organtransplantation, Essen, Germany; [2]Universitätsklinik Essen, Kardiotechnik, Essen, Germany; [3]Ruhrlandklinik, Thoraxchirurgie, Essen, Germany

Introduction and Background: Ex vivo lung perfusion (EVLP) offers the possibility to re-evaluate donor lungs that previously were deemed untransplantable. According to the Toronto protocol the lungs were reconditioned for 4 h.
Methods: We started the EVLP program in our institution in April 2016. So far 4 donor lungs were evaluated by use of EVLP. All four lungs were allocated according to Eurotransplant extended allocation criteria. Donor mean pO2 at FiO2 1.0/PEEP 5 was 313 $\pm$ 61 mmHg, mean donor age 63 $\pm$ 9 years. The donors were ventilated before retrieval for a mean of 8 $\pm$ 4 days.
Results and Conclusions: Two lungs improved during processing in the Xvivo system to a Δ pO_2 higher than 350 mmHg and were transplanted. The third donor lung also reached the threshold of Δ pO_2 above 350 mmHg but had significant localized edema and pneumonia of the left lower lobe. Thus, only the right lung was transplanted. The fourth lung kept a Δ pO_2 higher than 350 mmHg for 3 h. During the fourth hour suddenly significant fluid loss over the ventilation tube occurred and the Δ pO_2 drop. Thus, the lung was declined for transplantation. The lungs were transplanted with a mean total ischemic time of 468 $\pm$ 52 min. Mean ventilation time was 120 $\pm$ 60 h and the recipients remained on intensive care unit for 4.7 $\pm$ 1.7 days.

The first results from the use of Xvivo EVLP show a significant potential to increase the number and quality of lungs otherwise unsuitable for lung transplantation. In a first series we were able to transplant three patients. The use of this technique potentially results in a reduction of waiting list mortality.

V070 INFLUENCE OF DONOR AGE ON RECIPIENT SURVIVAL POST-LUNG TRANSPLANT: A STUDY OF THE INTERNATIONAL SOCIETY OF HEART AND LUNG TRANSPLANTATION DATABASE

A. Bernhardt*[,1], A.P. Levin[2], J. Stehlik[3], C. Benden[4], L. Edwards[5], H. Reichenspurner[1], F. Wagner[1]

[1]University Heart Center Hamburg, Hamburg, Germany; [2]Columbia University Medical Center, New York City, United States of America; [3]University of Utah Hospital and the Salt Lake City Veterans Affairs Medical Center, Utah, United States of America; [4]University Hospital Zurich, Zürich, Switzerland; [5]United Network for Organ Sharing, Richmond, United States of America

Introduction and Background: Lung transplantation is an established treatment strategy for patients with advanced lung disease. Currently, guidelines for donor selection recommend the use of donors <55 years of age, which markedly limits the available donor pool. In this study, we assessed how outcomes in recipients from older donors differ from those of donors <55 years.
Methods: The Registry of the International Society for Heart and Lung Transplantation (ISHLT) was queried. All adult primary lung transplants performed between 1988 and 2012 were included. All recipients were divided into three groups based on donor age <55, 55–64, and >64 years.
Results and Conclusions: During the study period, 41 738 adult primary lung transplants were performed. In this cohort, 36 630 donors were <55 years, 4362 were 55–64 years, and 736 donors were >65 years old. The one-year post-transplant survival rate from donors <55, 55–64 and >64 was 81.1%, 79.0% and 79.0%, respectively. The 5-year survival rate was 68.0%, 63.8% and 51.7%, respectively. As compared to recipients of lungs from donors <55, the hazard ratio for recipients from donors aged 55–64 and donors over 64 years of age were 1.15 (95% CI: 1.08–1.21, $P < 0.001$), and 1.67 (95% CI: 1.51–1.84, $P < 0.001$). Subgroup analyses revealed no significant differences in survival for patients with pulmonary hypertension or α1-antitrypsin deficiency. Further, these findings were similar after adjustment for pertinent recipient characteristics.
Conclusion: In the largest international lung transplant registry to date, donor age of 55–65 years conveys only a relatively small increase in mortality hazard compared to donors <55 years. However, outcomes among recipients with donors >64 years of age had clinically relevant reductions in long-term survival. In light of these data, it should be further investigated whether and how the acceptable donor age can be safely increased to 64 years, which would have the potential to significantly expand the pool of donor lungs.

V071 PERSISTENCE OF *DE NOVO* DONOR SPECIFIC HLA-ANTIBODIES INCREASES THE RISK OF LUNG ALLOGRAFT DYSFUNCTION

M. Schmitzer[1], N. Kneidinger[2], A. Dick[3], C. Neurohr[2], V. von Dossow[4], R. Schramm[5], H. Winter[1], T. Kauke*[,1]

[1]Klinikum der Universität München, Thoraxchirurgie, München, Germany; [2]Klinikum der Universität München, Innere Medizin, München, Germany; [3]Klinikum der Universität München, Labor für Immungenetik, München, Germany; [4]Klinikum der Universität München, Anaesthesiologie, München, Germany; [5]Klinikum der Universität München, Herzchirurgie, München, Germany

Introduction and Background: The impact of donor-specific (DSA) anti-HLA antibodies diagnosed by solid-phase assays on outcome in patients after lung transplantation is still a matter of debate. We hypothesize that persistent as opposed to transient appearance of de novo DSA are associated with a dismal prognosis for survival following lung transplantation.
Methods: We investigated the clinical relevance of HLA-antibodies on lung allograft outcome prospectively in 72 recipients who were transplanted between 2013 and 2015. The presence of HLA-antibodies was analyzed regularly prior and after (3 weeks, 3, 6, 9, 12 and 18 months) transplantation and in case of graft dysfunction. Lung function, survival of patients and risk factors for the development of DSA were assessed within a median follow-up of 21 months.
Results and Conclusions: Two patients (3%) were transplanted with preformed weak DSA. Twenty-three patients (32%) developed de novo DSA. In 13 out of 23 patients (56%) DSA disappeared after a median of 114 days. Forty-four % (10/23) of the patients had persistent DSA post-transplant. Time to first DSA appearance was earlier in the case of transient DSA compared to persistent DSA (51.9 $\pm$ 62.1 vs. 177.3 $\pm$ 156.2 days, $P = 0.035$). Risk factors for DSA development seem to be the concurrent existence of nDSA ($P = 0.001$) and change in the immunosuppressive regime from Tacrolimus

to Cyclosporine A in the first 3 months after transplantation ($P = 0.03$). DSA impaired patient survival in comparison to controls (1-year patient survival 83% vs. 97%; $P = 0.078$). Remarkably 1-year survival of patients with persistent antibodies was only 60%. Patients with persistent DSA had significantly reduced survival compared to those without DSA or with transient DSA ($P = 0.001$).

De novo DSA are associated with an increased risk for impaired graft function. Persistence of DSA in the first year after transplantation seems to be more harmful for lung allograft dysfunction than temporary DSA at an early stage.

V072 UP TO SIX YEARS EXPERIENCE OF LOBAR LUNG TRANSPLANTATION

D. Reichart[*,1], *B. Sill*[1], *C. Oelschner*[1], *M. Oldigs*[2], *H. Klose*[3], *M.J. Barten*[1], *H. Reichenspurner*[1], *T. Deuse*[4]

[1]*Universitäres Herzzentrum Hamburg, Herzchirurgie, Hamburg, Germany;* [2]*Lungenklinik Großhansdorf, Großhansdorf, Germany;* [3]*Universitätsklinik Hamburg-Eppendorf, Hamburg, Germany;* [4]*University of California, San Francisco, United States of America*

Introduction and Background: The shortage of suitable donor organs is a problem in lung transplantation. This dilemma is even worse in recipients with small chest cavities. To exploit a larger donor pool, we electively accepted bigger organs and performed lobar lung transplants.
Methods: 10 patients (eight women and two men, 47.3 ± 10.5 years old) received elective lobar lung transplantation between May 2010 and August 2014 with a mean waiting time of 227 ± 163 days. The underlying diseases were IPF ($n = 7$), CF ($n = 2$) and PHT ($n = 1$). The mean recipient height was 165 ± 8 cm and their calculated total lung capacity (TLC) was 5.3 ± 1.0 l.
Results and Conclusions: Donor lungs from nine males and one female with a calculated TLC of 7.4 ± 0.9 l and a donor height of 183 ± 7 cm were accepted. Mean donor age was 46.0 ± 7.2 years. In 5 cases, we transplanted a right upper (RUL) + right middle lobe (RML) and a left upper lobe (LUL). The remaining patients received RUL and LUL ($n = 2$), RLL and LLL ($n = 2$), and RML + RLL and LLL ($n = 1$). There postoperative complications regarding bronchus insufficiency ($n = 1$), bleeding ($n = 1$), kinking of pulmonary artery ($n = 1$) and lung edema ($n = 1$) needing further interventions. The one year survival was 70%. All other patients are still alive in 04/2016 at 32.5 months (range 1–68). The Kaplan–Meier curve is slightly better compared to our patients, who received regular bilateral lung transplantation ($n = 52$). Cause of death ($n = 3$) during the first year were graft failure (day 11), encephalopathy (day 77) and sepsis (day 134). Further complications have been BOS at stage III in one patient and 10 hospitalizations due to infections at some point. All survivors are followed in an outpatient clinic. Their last measured VC and FEV1 was 64.7 ± 18.7% and 58.3 ± 11.3%, respectively. This is again comparable to our regular lung transplants. In this study it is shown that elective lobar lung transplantation can be performed safely with similar overall results as regular lung transplants. It is an option for patients, mainly female with small thoraces.

IMMUNOLOGY II (HLA, GENETICS)

V088 CELLULAR IMMUNE FUNCTION AFTER POLYCLONAL STIMULATION DIFFERS BETWEEN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED INDIVIDUALS AND IS DOSE-DEPENDENTLY INHIBITED BY IMMUNOSUPPRESSIVE DRUGS

S. Marx[*,1], *C. Adam*[2], *S. Leyking*[2], *U. Sester*[2], *M. Sester*[1]

[1]*Saarland University, Transplant and Infection Immunology, Homburg/Saar, Germany;* [2]*Saarland University, Internal Medicine IV, Homburg/Saar, Germany*

Introduction and Background: Dosage of immunosuppressive drugs must be balanced to prevent graft rejection and to minimize infectious complications. At present pharmacodynamic monitoring of drug effects is not available in clinical routine. We characterized variability in cell function among healthy controls and immunocompromised patients after stimulation of blood samples with anti-CD3 and the TLR7/8 agonist R848 (QuantiFERON Monitor (QFM) assay, Qiagen). Susceptibility towards different immunosuppressive drugs and their dosages was assessed in vitro and in vivo.
Methods: Whole blood from 35 controls, 31 dialysis patients, and 35 transplant patients were recruited cross-sectionally and longitudinally. Samples were stimulated for 20 h and IFNγ secretion was measured by ELISA. Intracellular staining of different cytokines was performed among T-, B-, and NK cells using flow-cytometry.
Results and Conclusions: IFNγ secretion was mainly observed in CD4, CD8 and NK cells. Blood sampling from controls over 24 h revealed diurnal variations and these inversely correlated with endogenous cortisol levels. Calcineurin inhibitors or steroids alone dose-dependently reduced IFNγ secretion, and reactivity was further reduced when these drugs were combined. In general, intra-assay variability of cell-reactivity was low (CV = 8.0 ± 6.7%), whereas interassay variability from longitudinal analyses was rather high despite absence of clinical events (CV = 64.1 ± 38.6%). Nevertheless, median IFNγ levels were significantly different between controls, dialysis and transplant patients ($P < 0.001$). Among transplant patients, lowest IFNγ levels were observed in the early period after transplantation.

In conclusion, cell-reactivity after polyclonal stimulation differs between immunocompetent and immunocompromised individuals and is dose-dependently inhibited by immunosuppressive drugs. The assay may have potential for assessing loss of immunocompetence and for pharmacodynamic monitoring of immunosuppressive drugs in transplant patients.

V089 INTRA-RENAL B CELL POPULATIONS, B CELL PROLIFERATION FACTORS AND ANTIBODY FORMATION IN A MODEL OF NON-ADHERENCE

*L. Kühne**, *B. Jung*, *H. Reinfrank*, *A. Schuster*, *B. Banas*, *T. Bergler*

Klinikum der Universität Regensburg, Abteilung für Nephrologie, Regensburg, Germany

Introduction and Background: *De novo* donor-specific antibodies (DSA) are associated with reduced graft survival. Nonadherence to immunosuppressive therapy is a major cause of DSA formation. In this context, B cells have gained increasing interest due to their role as antibody producing cells. Furthermore, B cells are not specifically targeted by current standard induction or maintenance immunosuppressive protocols. The aim of this study was to phenotypically characterize the intrarenal B cell population, and to compare intrarenal and serological antibody production in the setting of nonadherence to therapy.
Methods: We used a full MHC-mismatch model of allogeneic kidney transplantation in the rat (Brown-Norway rat = donor, Lewis rat = recipient). Standard immunosuppression consisted of daily administration of Cyclosporine A (5 mg/kg). Nonadherence to therapy was simulated by administering Cyclosporine A on alternating days only. Intrarenal B cells were analysed by flow cytometry and RT-PCR regarding expression of maturation/activation markers. Intrarenal and peripheral blood levels of B cell activating factors BAFF and APRIL were determined using flow cytometry and RT-PCR. Intrarenal antibody production, as well as serological levels of DSA (flow cytometry, RT-PCR) were compared in groups with standard immunosuppression and nonadherence.
Results and Conclusions: Although, nonadherence lead to elevated levels of the B cell activating factors BAFF and APRIL, this did not lead to a significant change in B cell markers. However, intrarenal transcription of the plasma cell specific transcription marker BLIMP-1 and IgG were significantly increased. Furthermore, a short period of nonadherence resulted in a marked increase of serum levels of DSA.

V090 ASSESSMENT OF DONOR-REACTIVE T-CELL IMMUNITY BY THE NOVEL URINE CELL-DERIVED ALLOANTIGEN ASSAY ALLOWS PREDICTION OF ACUTE REJECTION IN RENAL TRANSPLANT PATIENTS

C. Thieme[*,1], *B. Weist*[1], *A. Müskes*[1], *P. Reinke*[1,2], *T. Westhoff*[3], *N. Babel*[1,3]

[1]*BCRT, Berlin, Germany;* [2]*Charité - Universitätsmedizin Berlin, Berlin, Germany;* [3]*Ruhr Universität, Bochum, Germany*

Introduction and Background: Presensitization and donor-specific immunity play a major role in acute and chronic rejection of kidney transplant patients. While assessment of humoral sensitization is well standardized by the measurement of donor-specific antibodies, analyses of donor-specific T-cells is not applied in clinical routine. Here, the major obstacle is either low quantity (limited amount of donor spleen cells) or quality (lack of sufficient matching between HLA-bank and donor HLA) of stimulator cells. To overcome this shortage we established a method utilizing exfoliated allograft cells from the urine as stimulator cells in a short term stimulation assay and analysed patients with/without acute rejection in post-transplant follow-up.
Methods: Donor-derived stimulator cells were generated from urine of kidney-transplant patients with acute rejection (AR) and with an uncomplicated clinical course as controls (Co). Peripheral blood mononuclear cells (PBMCs) were obtained at days 0, 5–7, 11–17 and 60–81 in both groups and incubated with the urinary cells for 16 h. Multiparameter flow cytometry was used to assess the frequency and functionality of donor-specific T-cells using activation markers, cytokines and effector molecules in patients with AR and Co.
Results and Conclusions: Applying the novel assay we were able to demonstrate increased frequencies of donor-reactive CD4+ T-cells at the time point of AR. Even more, increased frequencies of donor-reactive CD4+ and CD8+ T-cells were observed already before transplantation in AR group. In contrast, donor-reactive T-cells were hardly detectable in Co patients before transplantation and during follow-up. Characterization of donor-reactive CD4+ cells revealed higher frequencies of CD161+ cells respectively Th17 and/or Th22 cells producing IL17A and IL22 in AR patients. Hereby we demonstrate the clinical utility of the newly established flow cytometry-based alloantigen-assay allowing quantification as well as functional and phenotypic characterization of donor-reactive T-cells.

V091 RENAL TRANSPLANT PATIENTS WITH DONOR SPECIFIC ANTIBODIES HARBOUR AN INCREASED FRACTION OF ALLOSPECIFIC T-CELLS AND FOLLICULAR T-HELPER-CELLS

J. Subburayalu[*,1], *S. Dolff*[1,2], *J.W. Cohen Tervaert*[3], *U. Eisenberger*[1], *M. Lindemann*[4], *A. Kribben*[1], *O. Witzke*[2], *B. Wilde*[1]

[1]*Universität Duisburg-Essen, Universitätsklinikum Essen, Klinik für Nephrologie, Essen, Germany;* [2]*Universität Duisburg-Essen, Universitätsklinikum Essen, Klinik für Infektiologie, Essen, Germany;* [3]*Maastricht University, Immunology, Maastricht, Netherlands;* [4]*Universität Duisburg-Essen, Universitätsklinikum Essen, Institut für Transfusionsmedizin, Essen, Germany*

Introduction and Background: Renal transplantation (RTX) is the treatment of choice for patients with end-stage renal disease. Despite immunosuppressive therapy, some patients develop donor-specific antibodies (DSA) and are at risk for humoral antibody-mediated rejection (AMR). Recently, a distinct T-cell subset, so called follicular T-helper-cells (TfH), is thought to exert a key role in inducing humoral immune responses and DSA. Thus, it was the aim of this study to characterize Tfh in RTX patients with DSA.
Methods: 70 RTX patients with stable renal allograft function for at least six months and 21 healthy controls (HC) were recruited. 31 RTX patients had DSA and in 39 RTX patients DSA were not detectable. Renal function was not significantly different between RTX with and without DSA. Peripheral blood mononuclear cells (PBMC) were isolated by Ficoll gradient isolation. TfH were analysed by flow cytometry and were defined as being $CXCR5^{pos}$ or being $IL\text{-}21^{pos}$. In addition, allospecific T-cells were detected by CFSE-based tracking of recipient T-cells proliferation in presence of irradiated donor PBMC.
Results and Conclusions: $IL21^+$ TFH were increased in RTX patients with DSA as compared to HC ($IL21^+$, % of $CD3^+CD8^-$: 13.55 ± 6.0% vs. 9.5 ± 2.4%, $P = 0.007$). RTX without DSA did not show a higher frequency of $IL21^+$ TfH as compared to HC ($IL21^+$, % of $CD3^+CD8^-$: 10.8 ± 6.5%, vs. 9.5 ± 2.4%, $P = 0.57$). Patients with DSA and history of antibody mediated rejection showed a significant correlation of serum creatinine and $IL\text{-}21^+$ TfH ($n = 14$, $r = 0.56$, $P < 0.05$). RTX patients with DSA had an enhanced allospecific proliferation of CFSE-labelled T-cells compared to RTX without DSA.
Conclusion: Circulating $IL21^+$ TfH and allospecific T-cells were expanded in RTX patients with DSA. Higher serum creatinine, i.e. worse renal function, was associated with an expansion of $IL\text{-}21^+$ TfH in patients with DSA and previous allograft rejection. TfH may drive formation of DSA and could have a key role in AMR.

ETHICS AND ECONOMY

V099 DIFFERENT TYPES OF HUMAN RIGHTS VIOLATIONS IN ORGAN PROCUREMENT PRACTICE IN CHINA

H. Li[*,1], *N.W. Paul*[2]

[1]*Universitätsmedizin der Johannes Gutenberg-Universität, Institut für Pharmakologie, Mainz, Germany;* [2]*Universitätsmedizin der Johannes Gutenberg-Universität, Institut für Geschichte, Theorie und Ethik der Medizin, Mainz, Germany*

Introduction and Background: Over 90% of the 120 000 transplanted organs in China before 2010 were procured from executed prisoners. Although China announced in December 2014 to cease the use of prisoner organs, the announcement is not followed by any changes to China's organ donation laws. As a result, the use of prisoner organs remains legal in China, if "consent" is obtained.
Methods: We have collected and analyzed available evidence on human rights violations in the organ procurement practice in China.
Results and Conclusions: The practice of organ procurement from prisoners in China not only violates international ethics standard, it is also associated with a large scale of human rights abuses. This includes organ procurement without consent of the prisoners or their families, procurement of organs from incompletely executed, still-living prisoners, as well as from prisoners of conscience without death sentence. To end the unethical practice and the abuse associated with it, China should enact new legislations prohibiting the use of organs from prisoners.

IMMUNOLOGY III (BENCH TO BEDSIDE)

V106 LOW CD4 CELL COUNT ARE ASSOCIATED WITH WORSE OUTCOME AFTER PNEUMOCYSTIS INFECTION AMONG KIDNEY TRANSPLANT PATIENTS

T. Freiwald[*,1], *S. Büttner*[1], *S. Martin*[2], *A. Asbe-Vollkopf*[1], *R.U. Pliquett*[3], *H. Geiger*[1], *V. Jacobi*[2], *I. Hauser*[1]

[1]*Uniklinikum Frankfurt, Nephrologie, Frankfurt, Germany;* [2]*Uniklinikum Frankfurt, Radiologie, Frankfurt, Germany;* [3]*Martin Luther University Halle-Wittenberg, Nephrologie, Halle (Saale), Germany*

Introduction and Background: Pneumocystis jiroveci pneumonia (PJP) is a life-threatening opportunistic infection after solid organ transplantation even in the era of pneumocystis prophylaxis. Recently lymphopenia has been discussed as a risk factor for the development of PJP. CD4 cells are pivotal for transplant rejection but also for host defense against infection. We investigated in a retrospective analysis whether the CD4 cell count might be a biomarker to estimate the risk for a severe PJP.
Methods: We performed a retrospective analysis of all kidney transplant patients in our center who had a Pneumocystis infection in the years 2005–2015 ($n = 46$). We correlated clinical and demographic data with the outcome of the disease.
Results and Conclusions: Median age at time of infection was 58.5 years. There were 13 (28.3%) women and 33 (71.7%) men. Immunosuppressive therapy consisted of steroids, mycophenolate mofetil and a Calcineurin inhibitor. Median CD4 cell count at diagnosis was low with 284 /µl. Median CRP was 16.2 mg/dl. Median hospitalization was 26.5 days. 7/46 (15.2%) patients died during hospital stay and 10/46 (22.2%) patients required mechanical ventilation.

Lower CD4 cell count was associated with a higher mortality ($P = 0.01$) and also with a higher risk for mechanical ventilation ($P < 0.001$). A higher CRP also was associated with higher rates of mortality and mechanical ventilation. No significant correlation was found for mortality or mechanical ventilation with CD8 cell count, LDH, arterial pCO2 and pO2 or symptoms of fever and dyspnoea. A higher age only correlated significantly with higher rates of mechanical ventilation.

The CD4 cell count of renal transplant patients should be further evaluated not only as a risk factor for PJP development but also as a possible biomarker for disease severity to guide immunosuppression, anti-infective therapy and referral to intensive care units.

V107 HUMORAL AND CELLULAR RESPONSES TO A SINGLE DOSE OF FENDRIX IN KIDNEY TRANSPLANT RECIPIENTS WITH NON-RESPONSE TO CONVENTIONAL HEPATITIS B VACCINES

M. Zaslavskaya[1,2], *M. Fiedler*[3], *B. Wilde*[4], *F.M. Heinemann*[1], *A. Heinold*[1], *P.A. Horn*[1], *O. Witzke*[2,4], *M. Lindemann*[*,1]

[1]*University Hospital, Institute for Transfusion Medicine, Essen, Germany;* [2]*University Hospital, Department of Infectious Disease, Essen, Germany;* [3]*University Hospital, Institute of Virology, Essen, Germany;* [4]*University Hospital, Department of Nephrology, Essen, Germany*

Introduction and Background: In kidney transplant recipients the risk for nonresponsiveness to conventional hepatitis B virus (HBV) vaccines is increased to approximately 60%, pointing to the need for better vaccines. Highly potent third generation HBV vaccines, which contain the PreS1 and PreS2 antigens in addition to the small S antigen (e.g., Sci-B-Vac™ or Hepimmune™), are not licensed in Germany. But there could be an alternative, the second generation HBV vaccine Fendrix™, containing 3-O-desacyl-4′-monophosphoryl lipid A (MPL) as adjuvant. It was examined in kidney transplant recipients whether Fendrix™ could induce humoral and cellular HBV immunity. Their vaccination efficacy was compared with the efficacy in other cohorts tested by the same assays (nonresponders receiving Sci-B-Vac™ and nonvaccinated young, healthy controls receiving either Hepimmune™ or HBVaxPro™, respectively).
Methods: We selected clinically stable kidney transplant recipients who had been vaccinated at least three times against HBV but had never displayed anti-HBs antibodies. Twenty-nine transplant recipients fulfilled these criteria and we re-assessed anti-HBs antibody titers and further determined cellular HBV immunity by proliferation assay and interferon (IFN)-γ ELISpot.
Results and Conclusions: Eleven of the 29 recipients did neither display humoral nor cellular immunity and could be tested prior to and at month 1 after vaccination. In four out of them we detected anti-HBs antibodies ≥ 10 IU/l (21–264), in three HBV specific lymphocyte proliferation (stimulation index of 2.6 - 5.5) and in one specific IFN-γ responses (12 spots increment) at month 1 (Figure). This vaccination response was even higher than the response after a single vaccination with HBVaxPro™ in young healthy controls. In conclusion, the results show that a single vaccination with Fendrix™ can already induce HBV specific humoral and/or cellular responses in six out of eleven kidney transplant patients.

V108 TIE2-EXPRESSING MONOCYTES CORRELATE WITH ANGIOGENESIS AND PREDICT OUTCOME AFTER LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

G. Atanasov[*,1], C. Benzing[1], F. Krenzien[1], A. Brandl[1], K. Schierle[2], A. Reutzel-Selke[1], M. Bartels[3], A. Pascher[1], J. Pratschke[1], M. Schmelzle[1], H.M. Hau[3]*

[1]Charite - Universitätsmedizin Berlin, Chirurgische Klinik, Berlin, Germany; [2]Uniklinik Leipzig, Institut für Pathologie, Leipzig, Germany; [3]Uniklinik Leipzig, Klinik für Chirurgie II, Leipzig, Germany

Introduction and Background: Tie2-expressing monocytes (TEMs) promote tumor progression and have an effect on survival in human cancer. However, little is known regarding their influence on tumor progression, angiogenesis and prognosis after orthotopic liver transplantation for hepatocellular carcinoma (HCC).
Methods: We analyzed tumor specimens of HCC ($n = 33$) in hepatectomy specimens for distribution and localization of TEMs, as defined by co-expression of CD14 and Tie2. Abundance of TEMs was correlated with clinicopathologic characteristics, angiogenesis and patients' survival after liver transplantation. None of the patients received neoadjuvant radio- and/or chemotherapy prior to transplantation. Statistical analysis was performed using SPSS software.
Results and Conclusions: Patients with high prevalence of TEMs in tumor invasive front (TIF) of hepatectomy specimen showed significantly reduced survival following liver transplantation ($\rho < 0.05$). Furthermore, high expression of TEMs in hepatectomy specimen was associated with enhanced tumor angiogenesis, as defined by CD31 expression ($\rho < 0.05$). TEMs were confirmed as independent prognostic variable in the multivariate survival analysis ($\rho < 0.05$).

Our study provides first evidence that TEMs associate with patient outcome following liver transplantation for HCC. Patient survival after transplantation was significantly reduced in patients with high expressions of TEMs in HCC of hepatectomy specimen. TEMs might serve as a potential biomarker in HCC in the setting of liver transplantation, whereas further studies are needed to elucidate their functional role.

V109 KIDNEY RECIPIENTS WITH 10 YEAR BELATACEPT-TREATMENT DISPLAY AN ALTERED T CELL SUBSET COMPOSITION AND LOW PLASMA CYTOKINE LEVELS COMPARED TO MATCHED PATIENTS WITH CNI-BASED IMMUNOSUPPRESSION

C. Neudörfl[*,1], A. Scherf[1], K. Daemen[1], J. Keil[1], J. Klempnauer[2], F. Lehner[2], C. Falk[1], G. Grannas[2]*

[1]Hannover Medical School, Inst. of Transplant immunology, Hannover, Germany; [2]Hannover Medical School, Department of General, Visceral, and Transplantation Surgery, Hannover, Germany

Introduction and Background: More than 10 years ago, Belatacept (Bela)-based immunosuppression was investigated in the BENEFIT trial of kidney transplantation (KTx) compared to CNI-based immunosuppression. Bela inhibits T cell costimulation by blocking the binding of CD28 to CD80/CD86. This specific interaction is supposed to affect CD28-dependent de novo T cell responses and, thus, may have less side effects in contrast to calcineurin inhibitors (CNI). Therefore, we investigated the long-term effects of Bela on lymphocyte subset composition and plasma cytokine/chemokine levels compared to the CNI group.
Methods: Peripheral blood samples of five kidney recipients with Bela- and 10 matched recipients with CNI-treatment were collected, PBMCs were analysed by flow cytometry for lymphocyte subsets using a newly developed Lyotube panel and plasma by multiplex technology for cytokine/ chemokine levels.
Results and Conclusions: In the T cell compartment, Bela-treated patients show some differences to CNI-treated patients: Frequencies of $CD56^+CD4^+$ T cells and $HLA^-DR^+CD45RO^+$ memory T_{regs} were significantly lower ($P < 0.03$) in the Bela than in the CNI group. Naïve, central, effector memory and T_{EMRA} T cell subsets showed no differences between the two groups. Neither $CD27^-CD28^-$ "virus-specific" memory T cells nor $CCR7^-CD57^+CD4^+$ "senescent" T cells, discussed to be responsible for early rejection upon Bela-treatment, are altered. Slightly reduced plasma levels were detected for many cytokines like IFN-g, TNF-a, IL-1, 4, 10, IL-17 and chemokines like CCL2-4, CXCL8-12. Only MIF was significantly lower in plasma of Bela-treated patients. Importantly, the creatinine levels in both groups were equal. Taken together, long-term treatment of KTx patients with Bela is associated with lower frequencies of activated effector and memory T_{reg} subsets accompanied by low levels of cytokines/chemokines indicating that systemic immunosuppression with equal kidney function can be achieved by a CNI-free regimen.

LIVING DONATION

V115 INITIAL EXPERIENCE WITH ROBOTIC DONOR NEPHRECTOMY

S. Dralle, F. Braun, J.-H. Egberts, T. Feldkamp, T. Becker, H. Aselmann*

UKSH, Klinik für Allgemeine, Viszeral-, Thorax-, Transplantations- und Kinderchirurgie, Kiel, Germany

Introduction and Background: To report the first 12 successful robotic living donor nephrectomies and to assess its feasibility using the da Vinci Surgical System (Intuitive Surgical, Mountain View, CA).
Methods: Since 2015 we performed all our living-donor nephrectomies ($n = 12$) in a robotic technique. Medical records were used to make retrospective investigations in the Donors.
Results and Conclusions: Median intraoperative bleeding was 42 ml (range, 0–150) but no patient needed intraoperative transfusion with blood cells. The median warm ischemia time was 7.5 min (range, 4–13). There was no case of conversion to an open procedure. The median operative time was 223 min (range, 175–340). The median creatinine before surgery was 68 μmol/l and after nephrectomy was from 104 μmol/l in the donors. No complications occurred. Our initial experience has shown that the robotic approach allows the performance of donor nephrectomy in a safe and accurate fashion. Donor mortality and morbidity rates as well as donor outcome are comparable to the open approach. Furthermore, the procedure is associated with reduced donor discomfort, faster recovery, and improved cosmetic results. Future studies to prove organ function and patient condition in the recipient should examine if this approach is feasible for the future.

V116 LIFE WITHOUT IMMUNOSUPPRESSION AFTER PEDIATRIC IDENTICAL LIVING-DONOR LIVER AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

S. Hartleif[*,1], P. Lang[2], R. Handgretinger[2], T. Feuchtinger[2], J. Fuchs[3], A. Königsrainer[4], S. Nadalin[4], E. Sturm[1]*

[1]Universitätsklinik für Kinder und Jugendliche, Pädiatrische Gastroenterologie und Hepatologie, Tübingen, Germany; [2]Universitätsklinik für Kinder und Jugendliche, Pädiatrische Hämatologie und Onkologie, Tübingen, Germany; [3]Universitätsklinik für Kinder und Jugendliche, Kinderchirurgie und Kinderurologie, Tübingen, Germany; [4]Universitätsklinik für Allgemeine, Viszeral- und Transplantationschirurgie, Tübingen, Germany

Introduction and Background: Chronic immunosuppression (IS) is associated with significant morbidity in liver transplant (LT) recipients. Moreover, IS does not prevent chronic graft failure frequently. Allograft immune tolerance in LT can be induced by complete donor chimerism through allogenic hematopoietic stem cell transplantation (HSCT) combined with identical living-donor liver transplantation (LDLT). This approach may exempt patients from chronic lifelong IS. However, it is unclear whether its benefits justify its risks.
Methods: We performed a retrospective study on clinical outcome of identical living-donor LT and HSCT in children. We analyzed three cases from our institution and seven published cases identified in the literature for indication for HSCT/LDLT, donor type, HSCT conditioning regimen, manipulation of stem cell graft, T-cell chimerism, IS, complications, and clinical outcome.
Results and Conclusions: Indications for LDLT were veno-occlusive disease or graft-vs.-host disease (GvHD) after HSCT ($n = 5$), acute liver failure ($n = 3$), and liver malignancy ($n = 2$). All patients received HSCT due to hemato-oncological disease indications. In 8 of 10 cases, donor macrochimerism resulted in allograft tolerance and IS withdrawal was successful. Complications were bone marrow rejection, GvHD and infections. One patient died due to fulminant adenovirus infection. Nine patients survived.

These cases demonstrate that donor-specific allograft tolerance and life without immunosuppression can be achieved by identical-donor HSCT/LDLT. In children with isolated liver failure in need for LT, however, the significant risks for complications of myeloablative conditioning HSCT do not outweigh the benefit of tolerance at present. Novel toxicity-reduced conditioning protocols for HSCT/LDLT may prove to be a sufficiently safe approach for inducing graft tolerance in children receiving a LDLT in the future. This concept can reduce the burden of lifelong IS.

ECONOMY AND (POLITICS)

V121 DISTRIBUTION OF DONOR ORGANS TO NON-RESIDENTS IN GERMANY: RESIDENCY CANNOT BE AN EXCLUSIVE CRITERION

*W. Safi**

Universität Erlangen-Nürnberg, Klinik für Nephrologie und Hypertensiologie, Erlangen, Germany

Introduction and Background: In 2015 the number of available donor organs has reached an all-time low in Germany. Allocation criteria and justified discriminations of organ recipients have been discussed thoroughly in the Eurotransplant area, except for the group of nonresident refugees and migrants (NRMs). However, the continuously increasing number of NRMs calls for discussing their case and possibly adapting ethical frameworks. There is no legal settlement on this question available, yet. However, centers across Germany used to transplant organs by an unofficial, self-imposed 5%-rule to NRMs. Due to the increasing scarcity of organs this rule has been abandoned a few months ago.

We discuss the ethical question on how residency as a disqualifying allocation criterion can be compatible with the ethical framework defined in the extensive ethical and philosophical work concerning allocative justice in transplantation medicine.

Methods: Methodologically, we summarize main ethical arguments for existing allocation criteria in the Eurotransplant area and examine their compatibility with the disqualifying allocation criterion „residency". We pay particular attention to arguments as established for the criterion of urgency and utility but also for arguments that should be taken into consideration, for example the universal duty to assist or the obligation of mutual aid.

Results and Conclusions: Our analysis shows that a supposedly universal ethical framework is currently (un/consciously) only applicable at a national-European level. At the same time, based on the arguing of Eurotransplant "residency" is an utilitarian-only criterion that does not take the established deontological arguments into account. In order to establish a 0% rule based on general ethical principles, every argument against utility as an exclusive allocation criterion and every argument for deontological criteria have to be dismantled. This would lead to a collapse of the established ethical framework.

BASIC SCIENCE II

V138 PROLONGED NORMOTHERMIC *EX VIVO* KIDNEY PERFUSION IS SUPERIOR TO BRIEF NORMOTHERMIC PERFUSION FOLLOWING STATIC COLD STORAGE IN DONATION AFTER CIRCULATORY DEATH PIG KIDNEY TRANSPLANTATION

J.M. Kaths[*,1,2], J. Echeverri[1], I. Linares[1], M. Hamar[1], J.Y. Cen[2], S. Ganesh[1], P.M. Yip[3], R. John[3], D. Bagli[4], I. Mucsi[5], A. Ghanekar[1], D. Grant[1], L. Robinson[2], M. Selzner[1]*

[1]Toronto General Hospital, Department of Surgery, Multi Organ Transplant Program, Toronto, Canada; [2]The Hospital for Sick Children, Division of Nephrology, Toronto, Canada; [3]Toronto General Hospital, Laboratory Medicine & Pathobiology, Toronto, Canada; [4]The Hospital for Sick Children, Department of Surgery, Toronto, Canada; [5]Toronto General Hospital, Department of Medicine, Multi Organ Transplant Program, Toronto, Canada

Introduction and Background: Hypothermic preservation in donation after circulatory death (DCD) kidney transplantation causes graft injury. Normothermic ex vivo kidney perfusion (NEVKP) represents a promising alternative preservation technique. It is unclear whether the duration of NEVKP affects graft function.

Methods: We investigated the impact of cold storage (SCS) vs. short periods of NEVKP after SCS vs. prolonged, continuous NEVKP with near avoidance of SCS on kidney injury and function after transplantation. Following 30 min of warm ischemia, right kidneys were removed from 30 kg Yorkshire pigs and preserved for 16 h with four different combinations of SCS and NEVKP: A) 16 h SCS, B) 15 h SCS + 1 h NEVKP, C) 8 h SCS + 8 h NEVKP, D) 16 h NEVKP. After contralateral kidney resection, grafts were autotransplanted heterotopically and pigs followed up for 8 days.

Results and Conclusions: Throughout NEVKP, electrolytes and pH values were maintained. Intrarenal resistance at initiation of NEVKP decreased significantly until the end of perfusion in all groups ($P < 0.05$). Injury markers aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) remained low. Perfusate lactate decreased significantly until the end of perfusion in groups C and D ($P < 0.001$ and $P < 0.01$). Following renal autotransplantation, group D demonstrated significantly lower serum creatinine peak values when compared to all other groups ($P < 0.001$). 24-h creatinine clearance at day 3 after surgery was significantly higher in group D (63.4 ± 19.0 ml/min) ($P < 0.001$). Serum NGAL demonstrated significant differences in between all groups at day 3 after transplant ($P < 0.001$), significantly lower values were found for group D (1103 ± 485 ng/ml) vs. B (7437 ± 1941 ng/ml). Histological assessment on day 8 demonstrated significantly fewer apoptotic cells in group D ($P = 0.008$).

Conclusion: Prolonged NEVKP provides superior short-term outcomes following DCD kidney transplantation vs. SCS or short additional NEVKP following SCS.

V139 INFLUENCE OF SEROTONIN (5-HT) RECEPTOR TYPE 2 ANTAGONISTS ON THE DEVELOPMENT OF TRANSPLANT VASCULOPATHY IN A MODEL OF MURINE AORTIC TRANSPLANTATION

A. Gocht[*,1], J. Distler[2], S. Ensminger[3], B. Spriewald[2], M. Ramsperger-Gleixner[1], M. Weyand[1], C. Heim[1]*

[1]Universitätsklinikum Erlangen, Herzchirurgie, Erlangen, Germany; [2]Universitätsklinikum Erlangen, Erlangen, Germany; [3]Herz- und Diabeteszentrum NRW, Bad Oeynhausen, Germany

Introduction and Background: Serotonin promotes platelet activation and smooth muscle cell proliferation – key factors for the development of transplant vasculopathy (TV). Receptors potentially involved are 5-HT_{2A} and 5-HT_{2B}. We aimed to identify the influence of these receptors on the development of TV.

Methods: A fully allogeneic murine aortic transplant model was used with C57Bl/6 ($H2^b$) as donor and CBA ($H2^k$) as recipient mice. Recipients were treated with: 1) sarpogrelate (5-HT_{2A} antagonist); 2) SB 204741 (5-HT_{2B} antagonist) or 3) terguride (5-HT_{2A+B} antagonist). Treatment continued until sacrifice on day 14 (gene expression analysis by quantitative RT-PCR) or day 30 (morphometry and immunohistology).

Results and Conclusions: Most prominent finding is a marked reduction of intimal proliferation after sarpogrelate treatment while SB 204741 had fewer effects and terguride surprisingly had no inhibitory effect on neointima development.

All treated groups showed significantly reduced infiltration of macrophages in the graft media and sarpogrelate additionally in the intima. These results come along with significantly reduced intragraft expression of monocyte chemoattractant protein 1 after treatment with sarpogrelate as well as pro-inflammatory cytokines like platelet derived growth-factor, CD40 ligand and intercellular adhesion molecule 1.

We conclude that 5-HT_2 receptors, especially the 5-HT_{2A} receptor, are of significance in the development of TV in murine vessel transplants and sarpogrelate is a promising substance for further research in this area.

V140 MOLECULAR ARCHITECTURE OF AT1R ACTIVATION MEDIATED BY ANGIOTENSIN II AND AT1R-AGONISTIC ANTIBODIES

J.J. Gruner[*,1], R. Catar[1,2], P. Scheerer[3], P. Hildebrand[3], M. Szczepek[3], D. Dragun[1,2], A. Philippe[1]*

[1]Charité Universitätsmedizin Berlin, Nephrologie, Berlin, Germany; [2]Berliner Institut für Gesundheitsforschung, Berlin, Germany; [3]Charité Universitätsmedizin Berlin, Institut für Medizinische Physik und Biophysik, Berlin, Germany

Introduction and Background: Angiotensin II type 1 receptor (AT_1R) exhibits multiligand binding abilities and signals upon endogenous Angiotensin II (Ang II)-mediated and AT_1R-agonistic IgG (AT_1R-Abs)-mediated stimulation. Development of high resolution methods allows for structural-functional relationship studies of specific receptor modules, including the extracellular domains, in the receptor activation. Elucidation of AT_1R activation mechanisms could have broad clinical relevance for transplantation and autoimmune diseases.

Methods: To distinguish the AT_1R endogenous and immune-mediated activation, we developed a yeast model where human AT_1R expression is coupled to the yeast's growth response. The human AT_1R cDNA was cloned in a yeast expression plasmid. AT_1R activation was induced by addition of Ang II or AT_1R-IgG isolated from patients with associated transplant pathology.

Results and Conclusions: Both, Ang II and AT_1R-IgG triggered a dose-dependent increase in yeasts' growth. AT_1R-Abs stimulation induced stronger and more sustainable activation of the receptor than Ang II. Targeted mutagenesis was performed in order to identify which receptor regions govern the activation. Mutating the cysteins contained in the disulfide bridge connecting third transmembrane domain and second extracellular loop (ECL2) abolished receptor activation, irrespective of the stimulus. Point mutations introduced into ECL2 led to the same result, emphasizing the importance of this structural module in AT_1R activation via Ang II and AT1R-IgG. Mutation of ECL1 precluded AT_1R-IgG, but not Ang II-mediated activation. ECL3 had no effect in receptor activation irrespective of the stimulus. We successfully created a model allowing for structural and functional studies of molecular architecture modules appreciating AT_1R receptor plasticity which helped us to define the role of the specific extracellular domains. Better understanding of the molecular mechanisms responsible for AT_1R activation holds great potential for design of more specific AT1R blockers.