LECTURES

KIDNEY II

V024 HLA-E ALLELIC GENOTYPE IMPACTS ON OCCURRENCE OF CMV INFECTION AFTER LIVING RENAL TRANSPLANTATION

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Introduction and Background: The non-classical HLA-E molecule is involved in a variety of immune functions ranging from inhibiting NK-cell activity till presenting allo-antigens to T-cells. HLA-E function is partly dependent on the presented peptide repertoire mostly derived from signal peptides of other HLA molecules or viruses (e.g. CMV immune evasion protein UL40). CMV infection (CMVi) is a major cause of severe complications after transplantation (Tx). Though HLA-E displays limited allelic variation, substantial functional differences (in terms of peptide affinity, cell surface expression, lytic activity) have been attributed to the 2 main alleles observed (HLA-E*01:01; HLA-E*01:03). Thus, the question emerged whether HLA-E allelic variation affects CMVi after renalTx (RTx) and may be useful for further identification of patients at risk.
Methods: 192 living kidney recipient (R) and donor (D) pairs were enrolled in this study. HLA-E typing was performed using PCR method. Clinical data (focusing on CMVi during 1st year after RTx) were assessed and associated with typing results.
Results and Conclusions: 20 R exhibited CMVi during the 1st year after RTx, regardless of CMV risk status. The median time from RTx to CMVi was 165 day (range, 21–365 day). With regard to R HLA-E allelic genotype, we found a significantly increased incidence of CMVi among HLA-E*01:03 carriers (homo- or heterozygote) compared to HLA-E*01:03 negative R ($p = 0.0086$; OR = 9.66 95% CI: 1.62–102.6). This is valid even for the CMV high-risk population ($n = 14$; $p = 0.036$; OR = 8.412 95% CI: 1.29–96.8). Kaplan-Meier and Cox analysis confirmed a noticeably increased risk for productive CMVi in HLA-E*01:03 allele carrying R (overall group $p = 0.009$ and high-risk $p = 0.036$, respectively). No association was observed between D HLA-E allelic variant and CMVi.

The strong HLA-E*01:03 R allele association with CMVi indicates that application of HLA-E typing may be useful for additional characterizing and monitoring R at risk of CMV infection.

V025 CLINICAL VALIDATION OF A NOVEL ELISPOT-BASED *IN VITRO* DIAGNOSTIC ASSAY TO MONITOR CMV-SPECIFIC CELL-MEDIATED IMMUNITY IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction and Background: Impaired cytomegalovirus (CMV)-specific cell-mediated immunity (CMV-CMI) is a major cause of CMV reactivation and associated complications in solid-organ transplantation. Reliably assessing CMV-CMI is desirable to individually adjust antiviral and immunosuppressive therapy. This study aimed to evaluate the suitability of T-Track® CMV, a novel IFN-γ ELISpot assay based on the stimulation of peripheral blood mononuclear cells with pp65 and IE-I CMV proteins, to monitor CMV-CMI following kidney transplantation.
Methods: A prospective, longitudinal, observational, multicenter study was conducted in 96 intermediate risk (D-/R+, D+R+) renal transplant recipients. Patients underwent pre-emptive antiviral therapy. CMV-CMI, CMV viral load (qPCR- or pp65-antigenemia-based) and clinical complications (CMV disease, opportunistic infections and graft dysfunction) were monitored over six months post-transplantation.
Results and conclusions: IFN-γ ELISpot assays showed a sensitivity of 95% pre-transplantation and of 88–92% post-transplantation. CMV-specific response was reduced following immunosuppressive treatment and increased in patients with graft rejection, indicating the ability of the ELISpot assay to monitor the patients" immunosuppressive state. Interestingly, median pp65-specific response was 9-fold higher in patients with self-clearing viral load compared to antivirally-treated patients prior to first viral load detection ($p < 0.001$), suggesting that reactivity to pp65 represents a potential immunocompetence marker. Altogether, T-Track® CMV is a highly sensitive IFN-γ ELISpot assay, suitable for the immunomonitoring of renal transplant recipients, and with a potential use for the risk assessment of CMV-related clinical complications.

V026 PEPTIDE VACCINATION AGAINST CYTOMEGALOVIRUS (CMV) INDUCES CELLULAR IMMUNE RESPONSES IN CMV SERONEGATIVE ENDSTAGE RENAL DISEASE PATIENTS

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Introduction and Background: Cytomegalovirus (CMV) reactivation occurs particularly in patients after solid organ transplantation (SOT) from seropositive donors. CMV reactivation is associated with a high risk of disease and mortality. The nonamer peptide NLVPMVATV derived from CMV phosphoprotein 65 (CMVpp65) is highly immunogenic. Here we report on a clinical phase I peptide vaccination trial with this peptide in a water-in-oil emulsion (Montanide™) plus administration of or imiquimod (Aldara™) as adjuvant.
Methods: Four vaccines were administered subcutaneously at a biweekly interval to ten CMV seronegative endstage renal disease patients waiting for kidney transplantation. The clinical course, CMVpp65 antigenemia and CMV replication were monitored. CMV-specific CD8+ T cells were characterized by multi-color flow cytometry and Enzyme Linked Immuno Spot Assay (ELISPOT).
Results and Conclusions: Peptide vaccination was well tolerated and no drug-related serious adverse events were detected except from local skin reactions. In four patients, specific CD8+ T cell responses against CMV could be elicited by prophylactic vaccinations. In responders an increase of CMV-tetramer positive CD8+ T cells and interferon gamma secretion was detected. Interestingly a shift from CCR7+ CD45+ naïve T cells toward CCR7-CD45RA+ effector T cells could be observed suggesting an effective immune response against the virus. TCR sequencing revealed a predominant TCR in patients with CMV specific T cells.

In ten CMV seronegative endstage renal disease patients on the waiting-list for kidney transplantation we demonstrated that administration of CMVpp65 peptide vaccination was safe, well tolerated and clinically encouraging. Imiquimod can serve as an adjuvant with a similar efficacy.

LIVER II

V031 RETROSPECTIVE ANALYSIS OF THE CURRENT SITUATION OF LIVER TRANSPLANTATION FOR HCC IN GERMANY WITH SPECIAL REGARD TO PRE- AND POSTTRANSPLANT TUMOUR STAGING

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Introduction and Background: In selected patients, the best curative treatment for hepatocellular carcinoma (HCC) in cirrhosis consists in liver transplantation (LTX). In most countries, due to existing organ shortage, only patients within the Milan criteria are preferred for LTX. However, classification is based on pretransplant imaging diagnostic, bearing the risk of incorrect diagnosis.
Methods: We performed a retrospective multicentre analysis in all German liver transplant centres including patients with primary LTX for HCC (2007–2013). Data were collected based on Eurotransplant database and surveys send to all German LTX centres.
Results and Conclusions: 1168 primary LTX for HCC were performed (age 57.9 ± 8.4 year, 78% male). Patients pretransplant inside the Milan, UCSF and up-to-seven criteria were misclassified with histological result in 18/15/11%, whereas patients outside the Milan, UCSF and up-to-seven criteria were otherwise misclassified in 34/43/41%. There was a significant better patient/recurrence free survival inside versus outside the Milan, UCSF and up-to-seven criteria (without impact of kind of criteria) for patients classified by histological report (all $p = 0.000$), whereas the difference was almost not evident if classification was based on imaging diagnostic ($p = 0.03$–0.255). Univariate analysis revealed primary tumour size, vascular invasion and grading as significant to outcome, whereas only tumour grading remained significant by multivariate testing.

About 15–40% of patients were misclassified by imaging diagnostic with impact to the LTX allocation resulting in possible preference or discrimination. Likewise, outcome analysis revealed a better correlation of histological compared to imaging diagnostic suggesting a reconsideration of the HCC allocation policy.

V032 RADIOEMBOLIZATION VERSUS TRANSARTERIAL CHEMOEMBOLIZATION BRIDGING TREATMENT PRIOR TO LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

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Introduction and Background: Locoregional treatments are commonly employed in hepatocellular carcinoma (HCC) patients as a bridge to liver transplantation to prevent tumor progression during waiting time. Transarterial chemoembolization (TACE) is the most widely utilized treatment while radioembolization has been emerging as a viable strategy. Objective of this study was to compare outcomes after liver transplantation for HCC after radioembolization and TACE bridging treatment.
Methods: A retrospective review of 127 consecutive HCC patients who underwent liver transplantation between January 2007 and December 2016 at our transplant center was performed. Possible risk factors associated with tumor recurrence were evaluated using simple and multivariable logistic regression.
Results and Conclusions: Radioembolization bridging treatment was applied in 44 patients while 83 patients underwent TACE. Both groups were comparable with regards to age and gender. Milan criteria for HCC were met significantly less frequently in the radioembolization group (20.5% vs. 66.3%, $p < 0.0001$). The number of treatments was significantly lower in the radioembolization group (1 [1–2] vs. 1 [1–7], $p = 0.0013$). Tumor differentiation, presence of microvascular invasion and rate of tumor necrosis on explant specimen were comparable between the groups. Median overall survival and rate of tumor recurrence were comparable between the groups. Median time from liver transplantation to diagnosis of tumor recurrence was 15 [4–56] months. Multivariable analysis detected age, male gender, complete tumor necrosis on explant specimen and the absence of microvascular invasion being independently significantly associated with decreased odds for tumor recurrence.

Successful bridging treatment leading to complete necrosis on explant specimen may enable successful liver transplantation in HCC patients. Patients with microvascular invasion are high at risk for tumor recurrence.

V033 IMMUNOPHENOTYPING OF HEPATOCELLULAR CARCINOMA PATIENTS

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Introduction and Background: Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer death worldwide. Liver transplantation and liver resection are curative options for early HCC. In some cases liver resection can achieve similar results as liver transplantation. The outcome is in part depended on the immunologic response to the malignancy. In this study we aimed to identify immunologic profiles of HCC patients.
Methods: Peripheral blood of HCC patients were analyzed with FACS before operation. Patients with prior intervention or hepatitis were excluded. Peripheral blood of healthy donors served as control group. Multicolor flow cytometry was used to analyze these blood samples. Detailed immunophenotyping characterized 39 immune cell subsets including T cells and its subsets, B cells and its subsets, natural killer cells (NK) and natural killer T cells (NKT), dendritic cells(DC), neutrophils, monocytes and myeloid-derived suppressor cells (MDSC).
Results and Conclusions: To date 10 healthy donors and 10 HCC patients have been recruited. Peripheral blood from HCC patients showed higher frequency of effector memory CD4+ lymphocytes, regulatory cells (Tregs), effector-memory Tregs, neutrophils and higher neutrophil-to-lymphocyte ratio than healthy donors($p < 0.05$), while the frequency of whole population of T cells, naive CD4+ lymphocytes, naive Tregs, NK, NKT and DC in HCC group were lower than Healthy donors($p < 0.05$).

This study shows that HCC provokes the distinct response not only with tumor infiltrating leukocytes but also in the peripheral blood. Judging by the subsets of cells, HCC exerts an immunosuppressive state presumably due to accumulation of effector-memory Tregs to negatively impact outcome. It remains to be seen what distinctive immunophenotypes prefer resection or transplantation.

THORACIC ORGANS I

V037 SIMPLIFICATION OF CYCLOSPORINE A DOSING STRATEGY TO IMPROVE MEDICATION ADHERENCE

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Introduction and Background: The pill amount is crucial for medical adherence of patients after heart transplantation (HTx). Thus, we investigated whether a simplification and systematic adjustment of CsA pill intake, could help to reduce the daily pill count.
Methods: From all patients, who underwent HTx at our heart center from 2009 to 2015, receiving CsA, the daily drug dosage was analyzed and the daily pill amount was counted. The data was compared to the available dosages of CsA (10, 25, 50 and 100 mg). In our mathematical model (model A), we reduced the daily pill count by systematic and targeted adjustment of partial Csa dosages, without changing the cumulative daily dose of CsA. In a second mathematical model (model B), we reduced the daily pill count furthermore, by allowing a change of the cumulative daily dose of <5%.
Results and Conclusions: 26/63 HTx patients (41.3%) were treated with CsA. 2/26 patients (7.7%) were female and mean age was 51.9 ± 13.2 years. The average CsA dosage was 148.9 ± 42.6 mg/day; the daily pill count was 4.3 ± 1.1, respectively. For example, a cumulative daily dose of 140 mg, led to a daily pill count of six (2 × 50 + 4 × 10 mg). By using model A, the daily pill count was reduced to five (1 × 100 + 4 × 10 mg) and by using model B (change of daily dosage of 3.57%), the daily pill count was 3 (1 × 100 + 1 × 10 + 1 × 25 mg). In general, by using model A, a 28% reduction of daily pill intake could be achieved. Allowing an average change of the cumulative daily dose of 0.6 ± 2.0% (model B), a 45% reduction of daily pill count of CsA.

A simplification of CsA dosing adjustment would lead to a significantly reduction of the daily pill count, and therefore, would increase medication adherence. Good adherence of immunosuppressive therapy is crucial to avoid acute allograft rejection, and furthermore, will help to reduce the burden of health costs to treat the non-adherent patients.

V038 DEVELOPMENT OF RENAL FUNCTION IN PATIENTS RECEIVING CNI-FREE THERAPY WITH SIROLIMUS COMPARED TO CNI-FREE THERAPY WITH EVEROLIMUS

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Introduction and Background: It is currently not known whether CNI-free-therapy with sirolimus (mTOR-inhibitors ± MMF ± prednisolone) is superior to the calcineurin inhibitor free therapy with everolimus (mTOR-inhibitors ± MMF ± prednisolone).
Methods: We compared 2-year clinical outcomes in 22 patients receiving CNI free immunosuppressive therapy with sirolimus ± MMF / ± prednisolone from 2002 to 2010 (SRL-group) with 22 patients receiving everolimus ± MMF / ± prednisolone from 2004 to 2010 (EVL-group).
Results and Conclusions: Groups were comparable regarding baseline characteristics such as age, primary diagnosis, body mass index (BMI), creatinine values and GFR. Glomerular filtration rate (GFR) increased from 35.8 mL/min at baseline to 45.8 mL/min after 24 months in the SRL group and increased from 31.9 mL/min to 36.6 mL/min in the EVL – group. Blood urea nitrogen (BUN) value decreased from 92 mg/dL at baseline to 78 mg/dL after 24 months in the SRL – group and decreased from 114 mg/dL to 79 mg/dL in the EVL– group ($p < 0.05$). In both groups GFR and BUN increased significantly ($p < 0.05$) but a difference between the groups was not seen ($p > 0.05$). Two-year survival did not differ significantly between the groups ($p > 0.05$). Laboratory parameters such as liver values, cholesterol values, triglycerides and blood count (erythrocytes, thrombocytes, leucocytes) did not differ significantly between the groups during two year follow up ($p > 0.05$).

We conclude that CNI free therapy with everolimus and sirolimus could be an option in patients with progressive renal failure, due to CNI – nephrotoxicity. Nevertheless, a significant difference between SRL and EVL was not seen. In our opinion, further randomized prospective investigations are required to evaluate the optimal CNI-free immunosuppressive therapy (SRL vs. EVL).

V039 IMPACT OF DENDRITIC CELL SUBSETS ON TOLERANCE INDUCTION FOLLOWING HEART TRANSPLANTATION

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Introduction and Background: Tolerance-inducing cell subsets which support the organ acceptance following heart transplantation (HTx) can be found among dendritic cells (DCs) and regulatory T cells (Tregs). At present, it is unknown which cell subsets change during tolerance induction and maintenance. Therefore, pre-HTx and long-term HTx (LT-HTx; HTx longer than 5 years ago) patients were investigated for their immunologic tolerance-inducing profile.
Methods: Heparinized whole blood samples of n = 20 patients with end-stage heart failure (pre-HTx) and n = 20 LT-HTx patients without rejection episodes were analyzed for DC cell subsets expressing BDCA1, 2, 3, 4 and for the Treg subsets expressing CD39, CD62L, CD120b and CD147. Percentages and mean fluorescence intensities (MFIs) of the cell subsets were documented. The cytokine profile of IL2, IL4, IL10, IFNg, IL17A, IL34 and IL35 was detected by multiplexing.
Results and Conclusions: Single DC subsets showed changes between pre-HTx and LT-HTx patients: BDCA2+ and 4+ plasmacytoid DCs were increased (%BDCA-2+ $p = 0.029$; %BDCA4+ $p = 0.017$) in LT-HTx patients compared to pre-HTx patients. The percentage of total Tregs and the highly suppressive CD62L+ subset was higher in pre-HTx patients compared to LT-HTx patients (%Tregs $p = 0.003$, %CD62L+ $p = 0.014$). LT-HTx patients showed a more balanced cytokine level. The tolerance-mediating cytokine IL34 plasma level was higher in LT-HTx patients (36.9 ± 25.8 pg/mL) compared to pre-HTx patients (21.0 ± 21.0 pg/mL). Principle component analysis and its visualization by heatmap analysis exhibited a high impact of BDCA1+, BDCA2+ and BDCA4+ DCs to discriminate between pre-HTx und LT-HTx patients. Consequently, BDCA1+, BDCA-2+ and -4+ plasmacytoid DCs seem to be important adjustment screws to maintain transplant tolerance and will serve as targets for the development of new tolerance-inducing strategies.

V040 MTOR-INHIBITION INDUCES DIFFERENCES IN THE TOLERANCE-INDUCTION PROFILE FOLLOWING HEART TRANSPLANTATION

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Introduction and Background: Tolerance-inducing properties have been attributed to the immunosuppression based on inhibitors of the mammalian target of rapamycin (mTORI). The present study investigated the differences in regulatory T cell (Treg) and dendritic cell (DC) subsets as well as on the immune balance in comparison to CNI-based immunotherapy following heart transplantation (HTx).
Methods: HTx patients with either mTORI- (n = 20) or CNI-based immunotherapy (n = 20) were included. Flow cytometric analyses for the DC subsets expressing BDCA-1, -2, -3, -4 and for the Treg subsets expressing CD39, CD62L, CD120b and CD147 were performed. The immune balance (IL-2, IL-4, IL-10, IFN-g) and IL-34 levels were multiplexed.
Results and Conclusions: Age at HTx (mTORI: 54.7 ± 9.9 years, CNI: 53.3 ± 8.9 years) and at study begin (mTORI: 59.7 ± 10.2 years, CNI: 57.0 ± 9.0 years) were comparable in both groups. BDCA-1+ und -3+ myeloid DCs were higher and BDCA-2+ and -4+ plasmacytoid DCs were lower in mTORI-treated HTx patients. The total percentage of Tregs (mTORI: 11.4% ± 3.4%, CNI: 8.7% ± 2.4%, $p = 0.006$) as well as the percentage of the CD39+ Treg subset (mTORI: 35.4% ± 15.9%, CNI: 27.1% ± 10.8%, $p = 0.060$) was increased in HTx patients with mTORI-based immunosuppression compared to CNI-based immunosuppression. Serum levels of the pro- and anti-inflammatory cytokines as well as the Treg-specific cytokine IL-34 were higher in patients treated with CNI-based immunosuppression suggesting that these patients suffer from an immune imbalance. Furthermore, principle component analysis identified as suitable markers to distinguish between both groups and between rejectors and non-rejectors in the mTORI group. Inhibition of mTOR following HTx promotes changes of distinct tolerance-inducing cell subsets of Tregs and DCs, an immune imbalance and a lower rate of rejections compared to CNI-treated patients. Future studies will show, if the immunological monitoring of DC subsets and Tregs will predict rejection.

IMMUNOLOGY I

V046 PREDICTED INDIRECTLY RECOGNIZABLE HLA EPITOPES FROM EPLET MISMATCHES CORRELATE WITH *DE NOVO* DONOR-SPECIFIC HLA ANTIBODIES AFTER KIDNEY TRANSPLANTATION

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Introduction and Background: Previous studies demonstrated that both the HLAMatchmaker and the Predicted Indirectly Recognizable HLA Epitope algorithm (PIRCHE-II) independently identify epitope mismatches as risk factors *de novo* donor-specific HLA antibodies (dnDSA). We aimed to combine both algorithms to increase the power of prediction.
Methods: To develop a combined score PIRCHE-II-LR and evaluate its performance we performed a retrospective analysis, including 2725 consecutive kidney transplants performed after 1995, which had no DSA prior to transplantation as detected by solid-phase immunoassays. Posttransplant *dn*DSA were detected by the single antigen assay. HLA epitope mismatches were determined by HLAMatchmaker and PIRCHE and combined to the PIRCHE-II-LR score. The combined PIRCHE-II-LR considers only HLA-derived PIRCHE-II peptides of eplet-mismatched HLA.
Results and Conclusions: Multivariate analysis (MVA) adjusted for ABCDRDQ-mismatches confirmed that both individual scores are independent predictors of dnDSA ($p < 0.001$). The discriminative ability (AUC) and calibration (R2) of the combined PIRCHE-II-LR score to predict dnDSA was assessed with different IC50 thresholds and cutoffs of HLAMatchmaker per allele. Best prediction of *de novo* DSA within 15 years after transplantation was achieved using a cutoff of 5 epitope MM per HLA predicted by Matchmaker and an IC50 threshold of 1250 nM with PIRCHE-II (ln(PIRCHE-II-LR) C-statistic (AUC): 0.659, R2 Nagelkerke: 0.041). Correspondent MVA of the combined ln (PIRCHE-II-LR) confirmed the prediction of dnDSA independently from classical ABCDRDQ-mismatches (HR: 1.43, $p < 0.001$). Kaplan–Meier analysis of terciles showed, that lower values of ln(PIRCHE-II-LR) correlate with decreased incidence of dnDSA after 15 years (19.5%, 33.5%, 42.7%; $p < 0.001$).

The PIRCHE-II-LR effectively joins the two metrics of direct and indirect allorecognition and showed a better predictive value for dnDSA than the individual algorithms.

PANCREAS

V051 INFLUENCE OF COMPLICATIONS ON THE OUTCOME AFTER PANCREAS TRANSPLANTATION

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Introduction and Background: Pancreas transplantation (PT) shows a higher rate of complications compared with other organ transplantations. Graft thrombosis and intraabdominal infections are the most common causes for relaparatomy. We analyzed the influence of complications on the organ function after PT.
Methods: 145 pancreas grafts were transplanted between 01/2010 and 12/2015 at the Knappschaftskrankenhaus Bochum with 132 SPK, 5 PTA and 8 PAK. Out of this, 16 were retransplantations. A further analyzation was done for 132 of these transplants.
Results and Conclusions: Complications occurred in 72 of 132 patients. Pancreatitis (n = 53), pancreatic fistulas (n = 33) and postoperative bleeding (n = 24) were most commonly observed. A relaparatomy was required for every 3 patient, mainly because of infectious reasons as abscess and pancreatitis. 22 pancreas transplants and 14 kidney transplants lost their function shortly after transplant. Until 05/2017 68.18% of the pancreas and 78.03% of the kidney transplants are full functional. Complications had an significant influence on the organ function after PT (p = 7.046e-05). Operative revision (p = 0.0009), pancreatitis (p = 0.0114), bleeding (p = 0.0045) and graft thrombosis (p = 0.0054) showed statistical significant influence on the pancreas graft function after transplantation. Rejection, pancreatic fistulas and CT-drain demonstrated no further influence. Our data showed no correlation between the occurrence of complications and donor or recipient variables. Neither had the ischemia time nor the operation duration or the presence of positive germ wraps a significant influence.

Complication rates are still high in PT and affect the function of the pancreas graft significant. Strategies to reduce postoperative pancreatitis and infections need to be further investigated

V052 SIMPLIFIED CLASSIFICATION OF PANCREAS TRANSPLANT INSUFFICIENCY

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Introduction and Background: To date, the definition of pancreas transplant (PTX) failure is based on the need for antidiabetic therapy. However, as even a marginal PTX function can improve blood glucose control, a more differentiated definition is needed. As the proposed definitions are complicated, the applicability is to be questioned. To better characterize PTX insufficiency, we analyzed the HbA1c and C-peptide values from 107 SPK patients and classified the patients based on HbA1c, antidiabetic therapy and C-peptide levels. The patients were assessed based on the lab testing at study entry (median 8.9 years after SPK) and followed up once a year. According to the tests used in our laboratory we used a HbA1c ≥6.0% as cut off for impaired glucose homeostasis.
Methods: Four groups of patients were identified:

1. Normal graft function: Patients without antidiabetic therapy and normal HbA1c (n = 71)
2. Impaired graft function: Patients without therapy with elevated HbA1c and detectable C-Peptide (n = 7)
3. Clinically manifest graft insufficiency: Patients with therapy, variable HbA1c but detectable C-Peptide (n = 14)
4. Terminal allograft failure: Patients with therapy, variable HbA1c but negative C-Peptide (n = 16)

Results and Conclusions: While Group 1 consists of normoglycemic patients and Group 4 consists of patients with complete loss of PTX function, it becomes evident from Groups 2 and 3 that "antidiabetic therapy " or "elevated HbA1c" as sole criterion is not sufficient to characterize PTX failure. Blood glucose and HbA1c levels were significantly higher in group 2-4 compared with group one. Renal transplant function was similar in all patient groups.

Our data show that a clinically relevant and easily applicable definition of PTX function can be made based on HbA1c, antidiabetic therapy and C-peptide secretion in PTX- patients. Important markers of glucose metabolism differ between the respective groups. This definition of PTX function could be the base for further studies on patient outcome and differentiated therapy.

V053 DONOR AND RECIPIENT CHARACTERISTICS INFLUENCE OUTCOME AFTER PANCREAS TRANSPLANTATION

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Introduction and Background: The Pre-procurement Pancreas Allocation Suitability Score (P-PASS) and the Pancreas Donor Risk Index (pDRI) are currently applied as predictive scores in pancreas transplantation. Regarding recent publications, some were affirmative, others unfavorable for the one or the other score. Therefore, the predictive value on outcome under today's conditions needs to be re-evaluated for cases involving simultaneous Pancreas and Kidney (SPK) or Pancreas after Kidney transplantation (PAK).
Methods: Hundred and eight consecutive transplants of 105 patients who underwent SPK or PAK for Diabetes mellitus Type 1 between 2000 and 2017 at the University Hospital Heidelberg were included in the study. Donor and recipient specific parameters and outcome after transplantation were analyzed retrospectively using the Kaplan-Meier method and Cox regression analysis.
Results and Conclusions: Hundred and four (96.3%) SPK and four (3.7%) PAK transplantations were performed. The mean 1- and 5-year overall/pancreas graft survival rates were 93.2%/78.7% and 90.0%/76.9%, respectively. The donor risk factors hypertension (p = 0.005) and smoking (p = 0.046) and the recipient risk factor coronary heart disease (CHD, p = 0.003) showed significant difference in pancreas graft survival. A P-PASS of less than 17 revealed no significant difference in postoperative outcome when compared to a score greater than 17. A high pDRI revealed no significant difference compared to low pDRI as well.

Neither P-PASS nor pDRI can reliably predict the outcome after pancreas transplantation. Donor and recipient specific characteristics must be taken into account.

BASIC SCIENCE I

V057 EFFECTS OF B CELL ACTIVATING FACTOR BAFF BLOCKADE ON *DE NOVO* DONOR-SPECIFIC ANTIBODIES, ALLOGRAFT FUNCTION AND MORPHOLOGY IN A RAT MODEL OF RENAL TRANSPLANTATION

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Introduction and Background: B cell activating factor (BAFF) has been associated with donor-specific antibodies (DSA) and antibody-mediated rejection (ABMR). The aim of this study was to test the effects of an anti-BAFF intervention on the development of *de novo* donor-specific antibodies (DSA), B cell populations, as well as allograft function and morphology in a rat renal transplant model.
Methods: A monoclonal anti-BAFF antibody was injected into rats after allogeneic renal transplantation (Brown Norway → Lewis) on days 3, 17, 31, and 45. Rats were treated with subtherapeutic doses of cyclosporine A (CyA 5 mg/KG every other day) in order to allow survival yet induce chronic allograft injury. *De novo* DSA were measured by flow crossmatch and complement-dependent cytotoxicity (CDC) assay. DSA IgG subclasses were also assessed. Changes in leukocyte and B cell subsets in spleen, peripheral blood and renal allografts were measured by flow cytometry. Fibrosis was quantified by trichrome staining. Proteinuria and serum creatinine were quantified by ELISA.
Results and Conclusion: In this model of allogeneic renal transplantation, anti-BAFF intervention post-Tx initially (d28) led to an increase in *de novo* DSA compared to control, but overtime (d56) DSA levels were reduced compared to control. DSA IgG subclasses were differentially affected, where anti-BAFF treatment led to a transient increase in complement-fixing and non-complement-fixing subclasses IgG1 and IgG2a in comparison to the non-intervention control. Analysis of B cell subpopulations showed a reduction in the absolute number of intra-splenic and intra-graft B cell numbers with specific shifts in B cell subset markers (CD38, CD27, IgM). These effects did not lead to significant functional or morphological allograft changes, such as fibrosis, proteinuria or changes in serum creatinine.

V058 DEVELOPMENT OF ORGANIZED INTRA-GRAFT LYMPHOCYTE CLUSTERS: INTERPLAY OF B CELLS AND LYMPHOID FOLLICLE PROMOTING FACTORS IN A RAT MODEL OF RENAL TRANSPLANTATION

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Introduction and Background: Chronic allograft rejection is a major cause of graft loss in solid organ transplantation. Intra-graft lymphoid follicles have been associated with worsened outcome, although their role remains controversial. We have established a rat model of renal transplantation demonstrating the development of organized clusters of lymphocytes after prolonged subtherapeutic calcineurin inhibition. Here, we study the factors known to promote the development of tertiary lymphoid organs (TLO) and demonstrate an interplay of B cells and TLO-promoting factors in the local intra-graft milieu.
Methods: We used a MHC-mismatched rat model of renal transplantation (Brown Norway → Lewis) with intermittent cyclosporine A administration (CyA 5 mg/KG every other day) to induce chronic allograft injury. Transplanted rats were sacrificed after 28 and 56 days. One group additionally received a BAFF-blocking antibody on days 3, 17, 31, and 45. Intra-graft leukocyte populations (CD11b/c, CD3, CD45R) and B cell subsets (CD38, CD27, IgM) were analyzed by flow cytometry. Factors of intra-graft leukocyte migration and homing were analyzed by qPCR. Leukocyte intra-graft spacial distribution was assessed by immunohistochemistry and immunofluorescence.
Results and conclusion: Intra-graft clusters of B cells were observed after prolonged and subtherapeutic CyA treatment. This was associated with chemokines and cytokines associated with TLO-formation, incl. CCL19, CCL21, lymphotoxin-β, BAFF, and Bcl-6, and intra-graft IgG production. Intervention by BAFF-blocking antibody led to a decrease in absolute numbers of intra-graft B cells. This was accompanied by a decrease in intra-graft transcription of all measured TLO-promoting factors and IgG. We conclude that local intra-graft B cells act to amplify TLO-promoting factors and advance local mechanisms of chronic inflammation. We therefore advocate further investigation into strategically targeting the intra-graft B cell niche.

THORACIC ORGANS II

V063 PRESERVATION SOLUTION AFFECTS THE IMMUNOLOGICAL MILIEU IN LUNG TRANSPLANTATION BY CHANGING THE INFLAMMATORY BALANCE AND RECRUITING DIFFERENT T AND NK CELL SUBSETS

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Introduction and Background: The pro-/ anti-inflammatory balance in lung transplantation is shaped by the pulmonary immune compartments, T and NK cell repertoire. At present, it is unknown, whether the perfusion solution may influence the microenvironment of the lung. Therefore, perfusion solutions Perfadex® (PER) and Celsior® (CEL) after transplantation and peripheral blood of lung transplant recipients were analysed for lymphocyte composition and the cytokine, chemokine profile.
Methods: Lymphocytes from peripheral blood and perfusates of 42 lung transplant recipients (PER n = 19 and CEL n = 23), were isolated and T and NK cell subsets were analysed by FACS; 96 cytokines, chemokines were quantified by protein multiplex analyses.
Results and Conclusions: Compared to the blood, lymphocytes obtained from perfusates showed increased frequencies of NK cells, CD69+ CD8+ and CD4+ T cells and KIR+ T and NK cells. In CEL perfusates, increased numbers of CD8+ T cells ($p = 0.023$) and reduced CD4+ T cell numbers with an altered CD4/CD8 ratio ($p = 0.045$) were observed compared to PER perfusates which correlated with increased CD8+ T cells, KIR+ T cells in blood postop in CEL recipients vs. PER recipients ($p = 0.0071$). Moreover, higher CD69+ T and NK cells were detected in perfusates ($p < 0.01$) indicating their lung tissue origin. Regarding the protein microenvironment, IL-6, Ang-2 and VEGF-C levels were elevated in PER vs. CEL perfusates ($p < 0.05$) which correlated postoperatively with significantly higher IL-6 levels in PER compared to CEL recipients ($p = 0.003$).

Here, we unravel a novel mechanism of immune alterations subsequent to the application of perfusion solutions by changing composition of pulmonary T and NK cell subsets. In summary, lymphocyte subsets and cytokine release may be influenced by the perfusion solutions and potentially affect the pro-/anti-inflammatory balance of the preserved organ. This impact on ischaemia/reperfusion injury may be relevant for clinical outcome of the recipient.

V064 ANTIBODY-MEDIATED REJECTION IN LUNG TRANSPLANT RECIPIENTS TREATED WITH PLASMAPHERESIS

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Introduction and Background: Antibody-mediated rejection (AMR) after lung transplantation remains an unsolved and acutely life-threatening complication with poor outcome. Treatment options are discussed controversially. Plasma exchange (TPE) and immunoadsorption (IA) for plasmapheretic removal of anti-HLA and anti-non-HLA antibodies have been suggested as treatment of AMR based on a few small series (≤5 patients). We report our experience with plasmapheresis in patients with AMR after lung transplantation.
Methods: In all lung transplant recipients (n = 122) we assessed the incidence of AMR between 2006 and 2016 and the outcome after therapy with plasmapheresis. According to our protocol, all patients with deterioration of lung function were treated with high-dose corticosteroids for acute rejection after ruling out an infection by bronchoscopy. In all patients with new-onset or significant increase of anti-HLA and non-HLA antibodies, AMR was suspected and additional treatment with TPE or IA was initiated.
Results and Conclusions: In 14 patients (11.5%), we identified a total of 19 episodes of AMR as described above. Significant deterioration of FEV1 was observed (before AMR: 2.2 ± 0.7 l vs AMR: 1.4 ± 0.4 l; $p < 0.05$). 15 of the 19 episodes were treated with TPE (3.7 ± 2.5), in 2 episodes IA was added and 2 AMRs were treated only with IA. In 89.5% of cases, the identified antibodies could be eliminated or significantly reduced though treatment. In 15 AMR episodes (79.0%) complete recovery of clinical status could be observed. FEV1 was significantly improved (AMR: 1.4 ± 0.4 L vs after plasmapheresis: 1.9 ± 0.6 L; $p < 0.05$). Survival was 92.9% at 30 days and 71.4% at 1 year after rejection.

Our experience suggests that plasmapheresis represents a promising therapy in patients with AMR after lung transplantation. Complete recovery of pulmonary function is achievable in up to 80% of patients with favorable one year survival. Prospective randomized evaluation is required.

V065 CREATING IMMUNOLOGICALLY INVISIBLE ORGANS: SILENCING MHC EXPRESSION IN AN ENTIRE PORCINE LUNG DURING NORMOTHERMIC *EX VIVO* PERFUSION

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Introduction and Background: Lung transplantation is a successful therapy; however, it is hampered by development of chronic rejection and opportunistic infections. Disparities at the HLA loci are the main cause for rejection and the need for immunosuppression.
Methods: We evaluated the capacity to silence MHC class I and II expression in the porcine lung. Lentiviral vectors encoding for short hairpin RNAs targeting β2-microglobulin (shβ2m) or the class II transactivator (shCIITA) were produced to target SLA class I or class II, respectively, and to express NanoLuc as reporter gene. Lungs were connected to an *ex vivo* lung perfusion system and perfused for 2 h with the shRNAs encoding vectors. After perfusion, tissue of different lung regions was enzymatically digested and endothelial cells (ECs) were isolated. ECs were cultured and analysed for NanoLuc expression in bioluminescence assays. Transcript levels of β2-microglobulin, CIITA or SLA-DR in ECs were measured by real-time PCR. Tissue histological analyses were performed.
Results and Conclusions: Expression of NanoLuc was already detectable 24 h after perfusion in all regions of the lungs. ECs of lungs perfused with shβ2 m encoding vectors showed a downregulation of β2-microglobulin by up to 80%. Similarly, lungs perfused with the vector encoding for shCIITA showed a knockdown of CIITA, SLA-DR and SLA-DQ by up to 70%. In presence of IFN-γ, ECs from non-perfused lungs were able to up-regulate CIITA expression up to 15-fold. In contrast, levels of CIITA transcripts remained unaffected or even decreased upon IFN-γ stimulation on ECs of lungs perfused with shCIITA-encoding vectors. Vector integration was detected in the cell genome, which is essential to achieve a permanent MHC suppression. The integrity of the pulmonary tissue remained unaffected. MHC downregulation in an organ creates a status of immunological invisibility and represents a promising approach to combat the burden of rejection and immunosuppression.

IMMUNOLOGY II

V085 KIDNEY TRANSPLANT SURVIVAL IN PATIENTS WITH PREFORMED DONOR-SPECIFIC HLA ANTIBODIES IN SOLID-PHASE ASSAYS

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Introduction and Background: The prognostic value of preformed DSA detected by solid-phase assays, especially those with low reactivity, is still debated controversially. This multicenter study aims to elucidate the effect of DSA detected during routine antibody screening prior to transplantation on outcome of kidney allografts in Germany.
Methods: 3297 patients from 15 German centers transplanted between 2012 and 2015 have been included in this study so far. Data on preformed DSA, clinical outcome and possible covariates were collected retrospectively. Outcome of kidney allografts was analyzed in the prespecified groups of patients (i) without DSA, (ii) with DSA <3000 medium fluorescence intensities (MFI), and (iii) with DSA ≥3000 MFI.
Results and Conclusions: In the preliminary analysis, 140 patients (3.3%) had preformed DSA ≥3000 MFI. 175 patients (3.7%) had DSA <3000 MFI. Mean follow-up was two years. Both, patients with DSA <3000 MFI and patients with stronger DSA had decreased graft survival compared to patients without DSA in the univariate Kaplan-Meier-analysis ($p < 0.001$). This difference remained significant in the multivariate Cox regression analysis for DSA ≥3000 MFI (1.9-fold risk for graft failure, $p = 0.006$), but not for weaker DSA ($p = 0.13$). Graft survival during the first two months, however, was significantly reduced for weak DSA only (2.5-fold risk for graft failure, $p = 0.002$ in the multivariate analysis).

The observed effect of DSA on graft survival differs according to their reaction intensity. As the antibody tests evaluated in this study were already performed prior to transplantation, different clinical consequences according to the reported strength of DSA (e.g. immunosuppression) may have influenced the outcome.

PSYCHOSOMATICS II

V095 FATIGUE AND QUALITY OF LIFE AND THEIR CORRELATES IN LIVING KIDNEY DONORS

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Introduction and background: In addition to health-related quality of life (HRQOL), fatigue is evolving as an important outcome parameter after living kidney donation (LKD). Research is esp. needed on possible correlates, e.g. sex, age, depression, kidney function, and recipient outcome. This study aimed to assess HRQOL and fatigue in LKD and identify correlates of increased fatigue and decreased HRQOL.
Methods: Donors were prospectively assessed before and 1 year after LKD. HRQOL was evaluated with the *Short-Form 36-Item Health Survey* (*SF-36*), anxiety and depression with the *Hospital Anxiety and Depression Scale* (*HADS*), and fatigue with the *Multidimensional Fatigue Inventory* (*MFI-20*).
Results and conclusions: Of 82 German-speaking donors (LKD 2/2012–3/2016), pre- and postoperative data were available from 58 donors (71%). Mean age at LKD was 53.4 years (SD = 10.6), 67% were female. Of the recipients, 90% were adults; 43% were the donor's child, 41% spouse/partner, 9% sibling, 7% other.

While the "physical component summary" of the SF-36 showed no significant HRQOL changes, a significant HRQOL decrease was observed in the "mental component summary" ($p = 0.01$, $d_z = 0.4$), esp. the subscale "vitality" ($p < 0.001$, $d_z = 0.6$). The MFI-20 showed corresponding increases in "general fatigue" ($p = 0.02$, $d_z = 0.3$) and "physical fatigue" ($p = 0.05$, $d_z = 0.4$). In the affected domains, the preoperative score was superior to the general population, whereas the postoperative score was similar to the general population. No significant pre to post changes were noted in the HADS, but 4 donors showed clinically relevant depression scores 1 year after LKD.

HRQOL and fatigue were not significantly correlated with sex, age, or serum creatinine/GFR. Regarding recipient outcome, moderate correlations ($r = 0.3$–0.5) were observed between donor-rated well-being of the recipient and changes in donors' mental HRQOL and fatigue. Attention should be focused on affected donors and factors predicting a negative outcome.

V096 PSYCHOSOCIAL BURDEN OF RELATIVES OF PATIENTS IN TRANSPLANTATION PROCESS

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Introduction and Background: Relatives and partners are an important resource for transplantation patients. Although they have to deal with comparable challenges as the patients there is only little knowledge about the burden they have to carry over years.
Methods: We conducted two seminars of 90 min each, the first for relatives/partners who want to become living kidney donors or who had donated (1), the second for relatives/partners of patients on waiting list or after kidney transplantation (2). After a brief introduction the participants could share their experiences, questions etc. with the group supported by a Psychosomatic doctor. At the end the participants were asked to write down the most important remarks on 4 topics as narratives.

Group 1 (n = 21) was asked for needs and challenges concerning to living donation and the time after and for wishes they want to address to doctors and caregivers. Group 2 (n = 26) was asked similarly with the focus on being the next person for a patient on the waiting list or after kidney transplantation.
Results and Conclusions: Group 1 was dominated by wishes of complete and early information about the organ removal and results and enough time for decision making. Second was the significant double burden of being the familiar caretaker for many years and the organ donor in one person. Many of them expressed their thanks for the support they received so far. Group 2 named many problems and challenges during the waiting time of the patient and the restrictions in life quality and freedom they share with the patient. They feel to be too little involved in therapy decisions which would have many consequences for them and gave advice for consequent self-care to other relatives.

This qualitative exploration gives 1. a first orientation of these special challenges for relatives/partners of transplantation patients and 2. shows how they can be supported by the medical system.

LIVER III

V104 REPEATED ANTIBODY MISMATCH – A RISK FACTOR IN LIVER RETRANSPLANTATION?

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Introduction and Background: Donor specific antibodies seem to be associated with inferior outcome after liver transplantation. Especially patients with a failing liver allograft are prone to develop anti HLA-antibodies. A modified liver allocation-algorithm for liver retransplantation (reLT) recipients could avoid repeated allo-antibody-mismatch (RAM). Since there is no evidence and almost no experience available for RAM in reLT, we reviewed all reLT with known allo-antibody status at our center.
Methods: The prospective LT-database at the Munich Transplant Center was screened for all reLT between October 2014 and March 2017. Patients with known allo-antibody status before reLT were included in the analysis. Parameters of interest were mortality and graft-survival, vascular- and infectious complications, ICU-stay and hospitalization after reLT.
Results and Conclusions: In the studied period 27 reLT were performed in 25 patients. Allo-antibody-status before reLT was obtained in 20 cases. We found RAM before reLT in 7 cases. A standard immunosuppressive regimen without induction therapy was used in all cases. Mortality after reLT was 43% vs. 15% in RAM- vs. non-RAM patients. Generally RAM was associated with complications after reLT. Interestingly the rate of biliary- and vascular complications and severe peritonitis after reLT was strikingly higher in RAM patients compared with non-RAM reLT recipients. Due to this small sample size, the results did not reach statistical significance.

Patients in need for a reLT are at increased risk for a complicated post transplant course. We found an increased mortality and morbidity in patients after reLT with RAM compared with non-RAM patients. These results have to be confirmed with a higher sample size, preferably in a multicenter cohort to evaluate the relevance of RAM for the allocation of grafts for reLT-recipients.

V105 MELD BASED ALLOCATION DETERIORATES PATIENT SURVIVAL WITHOUT IMPROVING WAITING LIST MORTALITY IN GERMANY

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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 patient survival. Purpose of this study is to evaluate post transplant results and waiting list mortality since the introduction of MELD-based allocation.
Methods: Liver transplant patients were assessed retrospectively from 2005 to 2015 using our own center as well as open access 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 median Match-MELD at time of transplantation increased from 16 to 26 (Pearson $r = 0.69$, $p = 0.019$). Concomitantly, 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 decreased from 78% to 70%. In these years on average 57 percent of all liver transplantations were performed in Germany. During this time period donor age increased from 48 to 54 to overcome organ shortage. Simultaneously the number of transplantations per year dramatically decreased from 158 in 2005 to 79 in 2015 at our center. At the same time the ratio of waiting list mortality/active-listed patients increased significantly from 2007 to 2016 (Pearson $r = 0.69$, $p = 0.019$), indicating an increased waiting list mortality.

The combination of increasing organ scarcity and MELD based allocation may require reconsideration of the current allocation policy and the inclusion of prognostic outcome factors should be discussed.

V106 IMPACT OF DONOR SPECIFIC ANTIBODIES FOLLOWING LIVER TRANSPLANTATION

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Introduction and Background: There is an ongoing controverse about the importance of donor specific antibodies (DSA) after liver transplantation (LT), their prevalence and consequences for graft and patient survival. Furthermore, monitoring of DSAs is not standardized, neither is the therapeutic procedure in case of humoral graft damage. This analysis wants to elucidate the association of DSAs with complications after LT.
Methods: Clinical and demographic data of 430 LT recipients were collected who are registered for aftercare at the LT unit of the university hospital Essen. Detection of antibodies (AB) was performed by Luminex single antigen beats. A cumulative mean fluorescence intensity (MFI) of more than 500 was considered positive. For statistical analysis SPSS software was used. A p-value less than 0.05 was considered statistically significant.
Results and Conclusions: Among all patients, 19.1% (82/430) were positive for DSA. Of these were 83.9% (68/82) HLA class II AB and 18.5% (15/82) HLA class I AB. HLA class II AB show a higher MFI (median: 4900, range: 600-20600) compared to HLA class I AB (median: 500, range: 1–20200). Patients who developed DSA experienced more often complications after LT (30.5%, 25/82) compared to DSA negative patients (16.5%, 56/349, $p = 0.07$). Of the DSA positive patients 10% (8/82) developed *de novo* autoimmune hepatitis (dnAIH) while in DSA negative patients dnAIH occurred in only 4.3% (15/349, $p = 0.053$). Acute rejections (AR) were experienced by 22% (18/82) of the DSA positive patients compared to 16.6% (58/349, $p = 0.14$) of the DSA negative. With regard to other complication (CMV infection, graft fibrosis, cirrhosis) no difference in DSA status could be detected.

Thus, patients who develop DSA after LT have a higher risk to experience complications with dnAIH, AR and CMV infection being the most relevant. Those patients should receive a prolonged monitoring. Regular monitoring of DSAs after LT may be important for an individualized risk management.

ETHICS AND ECONOMY

V115 ON THE ETHICAL COMMITMENT TO REDUCE THE TENSION BETWEEN ORGAN DEFICIENCY AND TRANSPLANTATIONS IN GERMANY

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Organ shortage limits the use of transplantation medicine, especially in Germany. Many patients cannot be treated in time, have long periods of suffering and die before transplantation can take place or shortly after. Allocation rules are very complex, always represent an ethical challenge and sometimes a dilemma and are only approximately fair. The larger the shortage of organs the more problematic is the organ distribution.

Political and legal requirements, the structure of medical care, disincentives and the retention on taboos fix the Status quo in organ donation and transplantation in Germany. In this area we only go “half way” often leaving our patients alone.

1. Postmortal organ donation: Concerning to the decision to organ donation we avoid the systematic and scientific discussion about the opt in or opt out-solution and the legitimacy of organ donation after cardiac and circulatory death. Up to now, the rejection is based largely on intuitive motivation.
2. Significant improvement of a systematic and professionally structured aftercare following every organ transplantation to avoid organ loss due to non adherence, medication errors etc. It would be necessary to include well-trained doctors, therapist and nurses and include new techniques like Telemedicine etc.
3. Significant improvement of preventive medicine (Primary – and especially secondary and tertiary prevention) to reduce the cases, which develop disease, which need transplantation. That includes especially Disease associated with alcohol misuse and smoking.
4. Systematic review and evaluation of incentives and disincentives in the medical system, which increase problems in transplantation system including the reimbursement system.

V116 CONCERNS OVER DEATH DETERMINATION PRACTICE IN EXECUTION BY LETHAL INJECTION IN CHINA

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Since 1997, execution in China has been increasingly performed by lethal injection. The current death determination criteria (cessation of heartbeat, cessation of respiration and dilated pupils) for execution by lethal injection neither conform to current medical science nor to any standard of medical ethics. Practically, death is pronounced in China within tens of seconds after starting lethal injection. At this stage, however, neither the common criteria for cardiopulmonary death (irreversible cessation of heartbeat and breathing) nor that of brain death (irreversible cessation of brain functions) are met. To declare a still-living person dead is incompatible with human dignity regardless the processes following death pronouncement. The ethic concern is further aggravated, if organs are procured from the prisoners. Analysis of postmortem blood thiopental level data from the US indicates that thiopental, as used, may not provide sufficient surgical anesthesia. The dose of thiopental used in China is kept secret. If similar doses are applied in China as those used in the US, it cannot be excluded that some of the explantation surgeries from prisoners subjected to lethal injection are performed under insufficient anesthesia in China. In such cases, the inmate may potentially experience asphyxiation and pain. Yet this can be easily overlooked by the medical professionals performing the explantation surgery because pancuronium prevents muscle responses to pain, resulting in an extremely inhuman situation. Therefore, we call for an immediate revision of the death determination criteria in execution by lethal injection in China. Biologic death must be ensured before death pronouncement regardless whether organ procurement is involved or not.

V118 LIVER TRANSPLANTATION IN PATIENTS WITH A HISTORY OF MIGRATION – A GERMAN SINGLE CENTER COMPARATIVE ANALYSIS

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Introduction and Background: Liver transplant (LT) programs in Germany increasingly face a multiethnic patient population. To date no outcome data for LT in patients with migration background is available for Germany. We conducted a single-center cohort analysis to investigate differences in the clinical course of LT recipients, stratified for their history of migration.
Methods: We included all primary LT between April 2007 and December 2015. Patients were assigned a categorized migration status. We compared demographic, epidemiological data and migration-related factors by Chi^2 and Student’s t tests. Patient survival was determined by Kaplan-Meier curves (KMC), risk factors for mortality were analyzed by multivariate Cox regression.
Results and Conclusions: Of 358 primary LT, 67 recipients (19%) had a migration background. Significant differences were found concerning age at LT, prevalence of viral hepatitis and alcoholic cirrhosis leading to LT and viral hepatitis leading to HCC. Other standard demographic, epidemiologic and allocation-relevant indicators were not different. Re-Transplant rates, overall survival, also after stratification for viral hepatitis, sex, ethnicity or presence of a language barrier showed no statistical differences. The multivariate analysis showed no migration-related covariate associated with the outcome.

In the region served by our transplant center 18.6% of the population have a history of migration. Prima vista the similar transplant rates and comparable outcomes imply the absence of inequalities in access to LT and to high-quality post-transplant care. However, social, ethnic and economic factors can influence the access to the transplant-waitlist and affect waitlist mortality. Therefore, these conclusions have to be drawn with caution and an intention-to-treat analysis is needed.

KIDNEY III

V127 TUMOR RECURRENCE IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction and Background: Compelling evidence indicates that kidney transplant recipients (KTR) are at high risk to develop malignancies after transplantation. However, it is currently unknown if the same risk accounts for tumor recurrence in KTR with pre-transplant malignancies and whether this affects graft and patient survival.
Methods: We retrospectively analyzed data of 1217 KTR (January 2000 to May 2012) for pre-transplant malignancies at our center. We assessed one- and five-year patient and graft (overall and death-censored) survival and incidence of post-transplant tumor recurrence as well as post-transplant incidence of *de novo* malignancies. To compare the results, we used a matched control group from the same time period similar in age, sex and time under immunosuppressive therapy.
Results and Conclusions: We identified 82 KTR patients with pre-transplant malignancies; the most common one being tumors of the urinary system (21.9%). The median time from tumor diagnosis to kidney transplantation (72 brain dead donors, ten living kidney donations) was 96.5 months (range 6-301). From 82 patients with pre-transplant malignancy, four (4.9%) experienced tumor recurrence, with one patient dying from recurrent metastatic urothelial carcinoma. After transplantation, tumor reoccurred in average after 33.5 months (range 23–47). Fifteen (18.3%) patients with pre-transplant malignancies developed a *de novo* malignancy, which was a significant increase compared to the control group ($n = 6$, 7.3%, $p = 0.036$). One- and five-year patient survival was 91.5% and 80.5%, respectively and similar to the control group ($p = 0.9$). When comparing five-year overall and death censored graft survival we found no differences between patients with pre-transplant malignancy (68.3%, 78.0%) and the control group (72.0%, 86.6%). In conclusion, we found a higher incidence of *de novo* carcinoma in KTR with pre-transplant malignancies; however, this had no effect on five-year patient and graft survival.

V128 REDUCED INCIDENCE OF CMV-EVENTS WITH MODERN EVEROLIMUS-BASED VS CONSERVATIVE TACROLIMUS-MPA-BASED REGIMEN IN *DE NOVO* RENAL TRANSPLANT RECIPIENTS: 12 MONTHS DATA ON INFECTIONS FROM ATHENA STUDY

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Introduction and Background: The ATHENA trial was designed to compare everolimus[EVR] in combination with tacrolimus [TAC] or cyclosporine A [CyA] vs. a standard treatment protocol of mycophenolic acid [MPA] and TAC in *de novo* kidney transplant recipients[KTxR].
Methods: In this 12 months [M], prospective, open-label, randomized, controlled multi-center study with 15 German and 12 French sites, 612 patients [pts] were randomized 1:1:1 at time of Tx to either (a) EVR (target: 3–8 ng/mL M1-M12) +TAC (4–8 ng/mL M1-M3; 3–5 ng/mL M3-M12), (b) EVR (3–8 ng/mL M1-M12) +CyA (75–125 ng/mL M1-M3; 50–100 ng/mL M3-M12) or (c) control TAC (4–8 ng/mL M1-M3; 3-5 ng/mL M3-M12) +MPA. All pts continued on steroids. Herein we report M12 outcomes on infections and CMV events from ITT full analysis set with 208 EVR+TAC pts vs 199 EVR+CyA pts vs 205 TAC+MPA pts.
Results and Conclusions: From randomization to M12 total incidences of infections were 73% in EVR+TAC and 72% in EVR+CyA treated pts vs 82% in TAC+MPA pts. While incidences of bacterial infections were similar between the three treatment groups (44% EVR+TAC, 43% EVR+CyA, 42% TAC+MPA) major differences were seen for viral infections with incidences of 41% in TAC+MPA vs only 26% in EVR+TAC and 12% in EVR+CyA groups. Incidence of BKV events was 23% in TAC+MPA vs 17% in EVR+TAC vs 9% in EVR+CyA pts ($p < 0.01$). CMV events occurred two thirds less in EVR treated pts compared to TAC+MPA control group with an incidence of 21% in TAC+MPA vs 6% for EVR+TAC and 3% for EVR+CyA treatment pts ($p < 0.001$).

ATHENA as largest European KTx study confirmed comparable efficacy and safety together with less viral infections for EVR-based treatment groups compared to TAC+MPA. In addition a significant protective effect of EVR-based regimens vs CMV/BKV events was robustly confirmed.

BASIC SCIENCE II

V138 HOSPITALIZATION BEFORE LIVER TRANSPLANTATION – AN EASILY AVAILABLE PREDICTOR OF POST-TRANSPLANT PATIENT SURVIVAL

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Introduction and Background: According to the German law of transplantation (Tx) organ allocation should be based on urgency and prospect of success. Unfortunately, no outcome predictors have been implemented for liver allocation to date. Aim of this study was to analyze whether hospitalization before transplantation and the duration thereof is a prognostic factor for transplant outcome.
Methods: The electronic record system of the Charité, Berlin was analyzed for all patients who underwent liver transplantation from 2004 to 2015 for hospitalization before transplantation.
Results and Conclusions: From 1169 liver transplant recipients in this era, 249 underwent transplantation coming from an intensive care unit (ICU) (group 1), 167 patients from a regular ward (group 2) and 753 from home (group 3). Patients coming from the ICU were significantly younger but sicker according to their higher labMELD at day of transplantation. Not surprisingly these patients had a significant lower 3 month, 1 year and 3 year survival compared to patients coming from home (ICU vs. home; 77.5% vs. 94.7% and 67.1% vs. 87.5% and 65.5% vs. 81.9%; all $p = 0.000$).

Significant differences between patients from group 1 and 2 was limited to short term survival (3 month: 77.5% vs. 86.2%; $p = 0{,}027$) and did not have an influence on 1- and 3 year survival (1 year: 67.1% vs. 74.3; $p = 0.09$; 3 year: 65.5% vs. 66.5%; $p = 0.545$). Comparing patients who spent >14 days on ICU with patients who spent >14 days on a regular ward, patients with ICU stay did not show inferior outcome (1 year $p = 0.442$; 3 year $p = 0.816$).

Subgroup analysis revealed that the length of ICU stay prior to Tx had a significant impact on patient survival if longer than 6 days (1–6 days vs. 7–14 days; 1 year $p = 0.023$). Remarkably no changes between 7 and 14 days or >14 days could be noticed.

Hospitalization status before transplantation is a valuable predictor for patient survival following liver transplantation and should be considered for prognostic scores.

V139 SURGICAL CHALLENGES IN THE LONGTERM FOLLOW-UP OF INTESTINAL TRANSPLANTATION

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Introduction and Background: Intestinal- (ITX) and multivisceral (MVTX) transplant-recipients have undergone multiple operations prior to and early after transplantation. Furthermore, they are prone to rejection and infection due to the high immunosuppression they receive.

Thus abdominal surgery at a later stage posttransplant may be challenging and may increase patients' morbidity and mortality.
Methods: Sixty-nine patients had undergone intestine-including transplantations in the two large European transplant centers Oxford, United Kingdom and Berlin, Germany between 2000 and 2015. Maintenance immunosuppression consisted of tacrolimus monotherapy or a double combination of tacrolimus/MMF, tacrolimus/sirolimus or tacrolimus/everolimus. We recorded all intraabdominal surgical interventions which were performed after discharge from the initial hospital stay following transplantation and subdivided them into two groups depending on whether or not they were directly related to the intestinal graft.
Results and Conclusions: A total of 18 patients (nine female, nine male, mean age 38 ± 10) who had received ITX ($n = 13$), mMVTX ($n = 2$) or MVTX ($n = 3$) underwent 22 intraabdominal surgical interventions after a median of two years posttransplant. The median follow-up time posttransplant was eight years [1;15]. 82% were emergency operations, 18% elective. Graft-related surgery was required in ten patients: partial-graft resection was performed in five and total graft resection in four. Two patients died after graft loss. Graft-unrelated operations were performed in 12 patients and did not affect graft function or patient/graft survival.

Abdominal surgery in ITX and (m)MVTX-recipients is challenging but feasible. Especially graft-related surgery was accompanied with an increased morbidity and higher risk of graft-resection or graft-loss. Graft-unrelated surgery did not affect graft function or longterm survival.

V140 PREVENTION OF ALLOGRAFT REJECTION BY USE OF REGULATORY T CELLS WITH A MHC-SPECIFIC CHIMERIC ANTIGEN RECEPTOR

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Introduction and Background: Regulatory T cells (Tregs) play an important role in controlling donor reactive immune responses after transplantation. As opposed to lymphopenic settings a variety of animal studies had shown that the impact of polyclonal Tregs in organ transplantation is small, indicating that graft-specific Tregs are required.
Methods: We have generated a highly specific chimeric antigen receptor (CAR) recognizing the HLA molecule A*02 (A2-CAR) that enables us to obtain large numbers of stable, donor-reactive Tregs with long-term survival after adoptive transfer.
Results and Conclusions: Transduction of the CAR into nTregs changes the specificity of the Tregs without alteration of their regulatory phenotype. Moreover, activation of nTregs via the A2-CAR induced proliferation and enhanced the suppressor function of modified nTregs. Compared to nTregs, A2-CAR Tregs inhibited an allo-MLR in a donor-specific way and were more potent in controlling an allospecific immune response in humanized mouse models. Further, they completely prevented the rejection of allogeneic targets – cells and tissues - in immune reconstituted humanized mice in the absence of immunosuppression.

A technical benefit is the generation via a short *in vitro* transduction protocol without the need for prolonged *in vitro* expansion. As A2-CAR Tregs can induce graft-specific tolerance without perturbation of the general immune competence of the recipient, these modified cells have great potential for incorporation into clinical trials of Treg supported weaning in HLA-A*02- recipients receiving an HLA-A*02 + graft.

V141 IGG SUBTYPES IDENTIFIED BY A FLOW CROSSMATCH ASSAY INCREASES SUCCESSFUL TRANSPLANTS IN SENSITIZED RECIPIENTS

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Introduction and Background: A flow cytometric crossmatch (FCXM) is the final test determining donor-recipient compatibility. We have developed a new FCXM assay that distinguishes between harmful complement-activating (IgG1 and IgG3) and non-complement activating (IgG2 and IgG4) antibodies using donor cells and recipient sera. Our new FCXM assay has led to successful heart and kidney transplants in adult and pediatric cases.
Methods: PBMCs isolated from the donor samples were incubated with the pre-transplant sera from 8 heart, and 10 kidney recipients with appropriate controls. The cells were then incubated in the lyophilized custom cocktail of antibodies that specifically recognize the various IgG subtypes bound to the cells, followed by FCXM analysis. C1q testing was carried out on all sera.
Results and Conclusions: *Heart:* Most of the heart transplant cases studied had a positive crossmatch due to IgG2 or IgG4 antibodies (non-complement activating), correlating with C1q results. Two cases were positive for C1q; probably due to prozone effect of HLA-specific IgM antibodies. All cases had positive 30-day and 90-day survival post-transplant with no PGD or >2R rejection. Two cases with documented AMR continued to have normal graft function. *Kidney:* There was almost complete agreement between the IgG subtype assay and C1q assay results in most of the cases studied. A positive FCXM was due to presence of non-complement activating IgG 2 or IgG4 antibodies. Only one case showed the presence of IgG3 antibodies with a negative C1q; probably the result of denatured antibodies. Our new FCXM assay has also helped 2 pediatric kidney recipients who have no rejection episodes reported.

The assay is highly accurate in detecting the IgG subtype/s causing a positive flow crossmatch. Clinical implementation of our IgG subtypes assay would have a great impact on increasing the number of successful transplants carried out, especially in sensitized recipients.