ORAL PRESENTATIONS

LIVER I (INCL. PAEDIATRICS)

V001 PERCUTANEOUS PRERECOVERY LIVER BIOPSY IN BRAIN DEAD DONORS – IMPACT ON ORGAN ALLOCATION AND ECONOMICS IN LIVER TRANSPLANTATION

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Introduction: The valueand safety of percutaneous prerecovery liver biopsy (PLB) at intensive care unit (ICU) and its impact on allocation of liver transplantation (LT) are still unclear, as is the influence on economic aspects.
Methods: Part 1, donor evaluation and safety of PLB: percutaneous ultrasound-guided PLB was performed in 36 brain death donors (BDD). Complications of the procedure, results of ultrasonography, macroscopic evaluation and histological results of PLB and donor characteristics were analysed.

Part 2, survey: a survey was conducted with participation of 11 liver transplant experts, resulting in 396 virtual cases. The demand of PLB and its influence on liver allocation was evaluated.

Part 3, economic analysis: a calculation of possible cost savings, based on the survey results, was carried out.
Results: No complications resulted from the ultrasound guided PLB. The PLB partly showed good results in livers which were macroscopically and sonographically defined as marginal. The survey revealed that the PLB significantly influences the allocation process of all liver grafts with the EDC grafts in particular.

Cost calculation based on survey results revealed an enormous potential for cost savings (transportation, personnel and materials) due to an optimized organ allocation and avoidance of futile organ procurements.
Conclusion: PLB is a safe procedure and has the potential for improving the outcome in liver transplantation, optimizing the allocation process before procurement, and thereby reducing cold ischemia time, avoiding falsely discards of organ grafts, and cost saving. Thus we propose PLB as a per-protocol procedure in liver transplantation of Brain Death Donors (BDD) with EDC.

V002 HIGHER PRE-TRANSPLANT KDIGO STAGES INCREASE THE RISK FOR EARLY GRAFT REJECTION EPISODES AFTER LIVER TRANSPLANTATION

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Introduction: Compromised renal function prior to liver transplantation is a known risk factor for post-transplant patient survival which is especially relevant in MELD-based allocation systems. However, the impact of higher pre-transplant KDIGO stages on post-transplant rejection-free graft survival remains to be determined.
Methods: Patients with primary liver transplantation at Medical University Graz between the 1.1.2007 and the 31.12.2018 were included. Patients with additional kidney transplantation were excluded from analysis leading to a cohort of 211 patients for investigation of independent risk factors for rejection free graft survival using multivariable Cox regression analysis.
Results: Kaplan-Meier analysis demonstrated a significant influence of the number of rejection episodes on long-term patient survival ($p < 0.001$, log rank test). Multivariable Cox regression revealed that higher KDIGO stages increased the risk for early graft rejection independently and significantly in the long-term (HR = 1.273, p = 0.025), whereas a D+/R- CMV mismatch was a protective factor for rejection-free graft survival (HR = 0.427, p = 0.027). Low dose ATG induction (0.5–1.0 mg/kg/d for 3–4 days) did not have an influence on both study end-points.
Conclusion: ATG induction with higher dosages (>1.0 mg/kg/d for 3–4 days) may be able to reduce the increased risk for rejection-free graft survival in patients with higher pre-transplant KDIGO stages. D+/R- CMV mismatch reduces the risk of early rejection as has been reported before (Dogan et al., 2018).
References: Dogan N, Hüsing-Kabar A, Schmidt HH, Cicinnati VR, Beckebaum S, Kabar I (2018). Acute allograft rejection in liver transplant recipients: Incidence, risk factors, treatment success, and impact on graft failure. J Int Med Res. 2018 Sep;46(9):3979–3990. https://doi.org/10.1177/0300060518785543. Epub 2018 Jul 12.

V003 HEPATIC ARTERY RECONSTRUCTION UNDER THE MICROSCOPE IN PEDIATRIC LIVER TRANSPLANTATION – IS IT WORTH THE EFFORT?

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Introduction: The incidence of hepatic artery thrombosis (HAT) after pediatric liver transplantation (PLT) is described up to 28.1%. Depending on the graft type, the hepatic artery (HA) diameter being anastomosed is very small. If thrombectomy is unsuccessful, retransplantation is the only option. We herein describe our experience with HA reconstruction under the microscope.
Methods: Single center retrospective analysis of all pediatric liver transplantations (age < 16 years) carried out between 01/2011 and 05/2019. Since 01/2015, in cases of living donation or left lateral or extended right splits with the artery cut at the level of the right/left HA, reconstruction is carried out under the microscope using 10/0 or 11/0 silk interrupted sutures. In all other cases, HA reconstruction was either carried out using lupes and 7-0/8-0 prolene running/interrupted sutures. 1-year graft and patient survival was assessed by Kaplan Meier analysis. Primary endpoint was hepatic artery thrombosis.
Results: 51 PLTs – 12 living donor PLTs (23.5%, 11 left lateral segments, 1 left hemiliver) and 39 livers from brain dead donors (76.5%, 25 left lateral segments, 11 full size organs and 3 extended right lobes) – have been carried out in the period observed. Overall one year survival was 92.16%. In 14 cases (27.45%), the HA was reconstructed under the microscope. HAT occurred in 0 patients (0%) in the microscope group and in 7 patients (18.92%) in the lupe group.
Conclusion: Based on our results we highly recommend hepatic artery reconstruction in pediatric liver transplantation under the microscope.

V004 CONTRAIL I STUDY RATIONALE AND DESIGN: EVALUATION OF PHARMACOKINETICS, PHARMACODYNAMICS, EFFICACY AND SAFETY OF ISCALIMAB (CFZ533) – AN ANTI-CD40 MONOCLONAL ANTIBODY IN *DE NOVO* LIVER TRANSPLANTATION

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Introduction: To date, one major unmet medical need in liver transplantation (LT) is the successful development of calcineurin inhibitor (CNI)-free regimens able to preserve antirejection efficacy while providing patients with long-term renal and other benefits. In preclinical models and humans, the fully human anti-CD40 monoclonal antibody CFZ533 (iscalimab) has yielded excellent patient/graft survival, as well as fully blocked *de novo* antibody responses, respectively. Here, we introduce the rationale and design of the phase 2 study CONTRAIL I, in which pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of two CFZ533 dosing regimens (high and low) as CNI-free arms are evaluated and compared to a standard tacrolimus (TAC) arm in *de novo* LT recipients (LTRs).
Methods: CONTRAIL I (NCT03781414) is an open-label, multi-center, 12 months (M) study with a 12M follow-up period. Patients must be 18–70 years old with an estimated glomerular filtration rate (eGRF [MDRD-4]]) ≥ 30 mL/min/1.73 m. Grafts will be received from deceased donors only. Upon successful LT, LTRs will be randomized (2:3:3) on Day 8 ± 1 post-LT to i) TAC control arm, ii) low dose CFZ533 arm, or iii) high dose CFZ533 arm. Moreover, from LT to M24, all patients will be given mycophenolate mofetil and corticosteroids. The primary objective is to assess the number of subjects with composite efficacy failure (biopsy-proven acute rejection [BPAR; rejection

activity index ≥3], graft loss, or death after 12 M. Key secondary objectives entail PK and PD of CFZ533 (soluble CD40 in plasma), efficacy event rates, renal function (evolution of eGFR), as well as safety and tolerability (incidence of [serious] adverse events and study/treatment discontinuation) over 12 M and 24 M.
Results: Randomization of ≥128 LTRs will be rolled out at multiple centers (>45) throughout Europe and North America with first patient first visit planned for Q3 2019 and completion of study expected by Q4 2022.
Conclusion: Results of the study will reveal suitable CFZ533 dosing for further clinical development, as well as important information regarding PK/PD, efficacy and safety of CFZ533 as a CNI-free therapy in LTRs.

V005 INFECTION SAFETY OF LOW-DOSE ATG INDUCTION IN LIVER TRANSPLANTATION

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Introduction: CMV PCR positive episodes, as well as urinary tract and bronchopulmonary infections are typical complications of immunosuppression and are associated with increased mortality after liver transplantation. Systematic analyses of the effects of routine low-dose ATG induction therapy on infectious complications after liver transplantation are lacking. This study analyses the influence of low-dose ATG induction (0.5–1.0 mg/kg/d for 3–4 days) on CMV PCR positive episodes as well as urinary tract and/or bronchopulmonary infections within the first month after liver transplantation.
Methods: Patients with primary liver transplantation performed at Medical University Graz between the 1.1.2007 and the 31.12.2018 were included. Patients with additional kidney transplantation within the first year after liver transplantation were excluded leading to a cohort of 211 patients for the investigation of independent influences of ATG on urinary tract and/or bronchopulmonary infections and CMV PCR positive episodes within the first month after liver transplantation.
Results: 131 patients received ATG induction (62.1%). Multivariable binary logistic regression revealed that ATG induction had no independent, significant influence on urinary tract and/or bronchopulmonary infections (OR = 1.052, $p = 0.890$) while it independently and significantly increased the risk of CMV PCR positive episodes (OR = 4.648, $p < 0.001$) within the first month. A D-/R-CMV match was revealed as an independent and significant protective factor for CMV PCR positive episodes within the first month after transplantation (OR = 0.070, $p < 0.001$). Obese patients with a BMI > 25 kg/m^2 were identified to be exposed to an independently and significantly increased risk of urinary tract and bronchopulmonary infection within 1 month after transplantation.
Conclusion: Low-dose ATG induction is safe regarding the risk of early urinary tract and bronchopulmonary infections but is an independent and significant risk factor for CMV PCR positive episodes within the first month after liver transplantation. Patients with low-dose ATG induction should therefore receive routine CMV prophylaxis, which is even more important in patients with a BMI > 25 kg/m^2.

V006 LIVERS WITH MAJOR EXTENDED DONOR CRITERIA MIGHT EXPAND THE ORGAN POOL FOR PATIENTS WITH LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

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Introduction: The major extended donor criteria (maEDC; steatosis >40%, age >65 years, and cold ischemia time >14 hours) impact graft and patient survival after liver transplantation (LT). Because of this, and despite organ shortage, maEDC grafts are often discarded because they are considered unsuitable for transplantation. This study focuses on patients with liver cirrhosis (LC) and hepatocellular carcinoma (HCC) and examines the outcomes of maEDC organ LT in these recipients.
Methods: After exclusion of recipients under 18 years of age, living donation LTs, split liver LTs, combined LTs, high-urgency LTs, and re-transplantations (re-LT), 264 HCC LT patients were eligible for analysis. Risk factor analysis was performed for early allograft dysfunction, primary non-function, 30-day and 90-day graft failure, and 30-day, 90-day and 1-year patient mortality. Survival rates were analyzed with the Kaplan–Meier method. Cox regression analysis was used to calculate the multivariate hazard ratio (HR) and 95% confidence intervals (95% CI).
Results: One-year graft survival was higher in recipients of no-maEDC grafts (89.5% vs. 75.3%, $p = 0.003$). One-year patient survival did not differ between the recipients of no-maEDC and maEDC organs. Also, 1-year patient survival after censoring for mortality secondary to reasons other than graft failure-related complications did not differ between the recipients of no-maEDC and maEDC organs (95.5% vs. 90.5%; $p = 0.118$). Furthermore, the univariate and multivariate analyses revealed no association between maEDC grafts and 1-year patient mortality. Graft survival differed between the recipients of no-maEDC and maEDC organs after correcting for a labMELD score with a cut-off value of 20, but patient survival did not. Also, patient survival did not differ between recipients who did and did not meet the Milan criteria and who received grafts with and without maEDC ($p = 0.836$ and $p = 0.75$, respectively).
Conclusion: Major EDC grafts do not impair patient survival after LT. Instead of being discarded, maEDC grafts may expand the organ pool for patients with HCC who are waiting for a LT and reduce drop-out from the waiting list because of disease progression.

HEART

V007 THE COMPOSITION OF T AND NK CELLS CHANGES IMMEDIATELY FOLLOWING HEART TRANSPLANTATION AND CYTOKINE RELEASE LEADS TO A PRO-INFLAMMATORY MILIEU IN RECIPIENT BLOOD

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Introduction: Multiple cardiac diseases ultimately lead to end stage heart failure for which there is no curative treatment other than heart transplantation (HTx). An association of a pro-inflammatory milieu and migration of multiple lymphocytes upon the ischemia-reperfusion injury (IRI) has been described in the development of organ rejection. Therefore, changes in the composition of T/NK cell subsets in the early post-operative phase might be clinically relevant for graft survival. Hence, it is necessary to gain a better understanding of the immunological mechanisms taking place after HTx.
Methods: T/NK cell subsets from 31 HTx recipients were analyzed at different time points pre-HTx, T0 and T24 after HTx with respect to naïve, central memory, effector memory and terminally differentiated CD4$^+$ T helper and CD8$^+$ cytotoxic T cell subsets using flow cytometry of CD45RO and CCR7. In order to investigate cytokine responses in parallel to the changing in T/NK cell subsets after HTx, blood plasma of 11 HTx recipient patients was analysed at these time points using multiplex assays. Clinical parameters will be correlated in order to define their relevance and influence in clinical outcome.
Results: In all patients, we observed a relative increase of CD56^{dim} NK cells within recipient blood directly after HTx ($p < 0.001$). Elevated NK cells were accompanied by distinct changes in the composition of T cells with decrease in CD4$^+$ T cells ($p < 0.001$), primarily in CD45RO$^+$ CCR7$^+$ central memory (CM) CD4$^+$ T cells ($p < 0.0001$). Simultaneously, we measured a significant increase of relevant pro- but also anti-inflammatory cytokines like IL-6 and chemokines like CXCL8-10 directly after HTx ($p < 0.0001$) with the increase being independent from the cold ischemic time (CIT) of the donor heart.
Conclusion: The composition of both T/NK cell compartments in recipient blood is severely altered by decreased CD4$^+$ CM T cell subsets. Clinical correlation analyses indicate that processes taking place are rather due to regulated processes in the recipient rather than the organ and CIT after explantation. These analyses will contribute to a better understanding of the immunological mechanisms involved in induction of tolerance vs. rejection.

V008 SINGLE-CENTER EXPERIENCE WITH FREQUENT USE OF ORGANS AFTER RESCUE ALLOCATION FOR HEART TRANSPLANTATION

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Introduction: The number of patients on the heart waiting list in the ET-region is almost threefold higher than the number of patients who will actually undergo heart transplantation (htx). Consequently waiting times continue to increase and can be beyond a year even for high-urgent (HU)-listed patients. One possible solution for an increased donor pool is the acceptance of so-called marginal organs.

This analysis deals with the effect of frequently using organs after rescue allocation for cardiac transplant in our department.
Methods: Between 10/2010 and 5/2018 129 patients underwent htx in our department. 75 of the 129 transplant recipients (58.1%) were transplanted with HU-allocations (group HU), the remaining patients received organs after rescue

allocation (gr. T). These organs had been rejected by at least 3 consecutive transplant centers due to medical reasons.

Perioperative parameters of donor and recipient and posttransplant outcomes were compared between these 2 groups.

Results: Mean donor age was higher in group T ($p < 0.05$), whereas donor ejection fraction was slightly lower ($p > 0.05$). All other donor parameters (CMV status, time of ischemia as well as sex) were comparable between the groups.

30-day mortality was higher in HU-patients (13.3%) compared to 11.1% after rescue allocation, $p > 0.05$.

Primary graft dysfunction (PGD) with extracorporeal life support occurred in 36% after HU-transplantation and in 18.5% of gr. T ($p < 0.05$).

We did not find significant differences between the groups regarding incidence of rejection and of postoperative renal failure. Duration of mechanical ventilation, stay on intensive care unit and in hospital were significantly prolonged in group HU.

1-year-follow up revealed a comparable morbidity and mortality between the groups (1-y-survival in group HU: 72.3%, group T: 70.5%, $p > 0.05$).

Conclusion: Our data support the use of hearts after rescue allocation. Probably as a consequence of the impaired clinical status of HU-recipients, early mortality was lower in patients after receiving rescue organs. However, one-year survival was comparable again, indicating a yet remarkable mortality in those patients beyond the first postoperative month.

V009 IMPROVED OUTCOME OF EXTRACORPORAL LIFE SUPPORT (ECLS) IN CARDIOGENIC SHOCK (CS)

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Introduction: Outcome of CS is fatal with survival rates of 8–15%. ECLS is a new tool for stabilization weaning or bridging to further therapy. After establishment of a regional 24/7/365 ECLS service at our institution with introduction of a protocol for acute, interim and long term support, it was the aim of this study to assess the results of the use of this staged ECLS strategy and outcome for these critically ill patients.

Methods: In a retrospective single center study, data from 164 consecutive ECLS implantations for severe CS from 2012 until 2018 were analyzed. Due to unclear neurology or complicated ECLS 28 patients were bridged with a surgical interim assist device allowing further evaluation and stabilization. 45 patients were implanted with a permanent left ventricular assist device (LVAD). In hospital mortality (30d), survival, major cardiovascular events as well as further therapeutic measures were analyzed.

Results: 51 patients died on ECLS within 10 days due to progressing multi organ failure and/or sepsis. 31 patients were weaned from ECLS and referred to ambulatory heart failure clinic for intensified follow up. Out of 28 patients with interim assist device, 12 received a permanent LVAD. Respectively 33 patients received a permanent LVAD implantation directly from ECLS. In total, 45 patients (27.4%) needed permanent LVAD support with an 1 year survival rate after LVAD implantation of 53.3%. 3 months overall survival was at 36.6% and respectively 1 year survival 33.5%. Overall survival conditional on 3 months survival was 81.7%. To date 3 patients could be weaned from LVAD therapy, 1 patient was successfully heart transplanted and 15 patients are listed or in the process for listing for heart transplantation.

Conclusion: Use of ECLS in CS improves survival compared to the numbers reported in the literature. Patients weaned from ECLS have a favorable outcome, especially for patients in need for a long term support survival benefit is high as shown in the survival rate conditional on 3 months survival. These data support the need of specialized heart failure centers offering a wide choice of individual support strategies.

V010 PREDICTION OF SURVIVAL ON THE WAITING LIST FOR HEART TRANSPLANTATION AND OF POSTTRANSPLANT NONADHERENCE – RESULTS OF A PROSPECTIVE LONGITUDINAL STUDY

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Introduction: Only a few previous studies have focused on the interaction between pretransplant psychological variables, survival on the waiting list and adherence to therapy after heart transplantation (HTx).

Methods: This work combined two studies: Study one monitored survival of patients on a HTx waiting list ($n = 50$) and study two examined barriers to adherence after HTx (subgroup of $n = 20$). All patients were evaluated immediately after listing for HTx (T0). Those in study two were also evaluated immediately after HTx (T1) and after six months (T2). Psychosocial functioning was measured by the Transplant Evaluation Rating Scale (TERS), depression and anxiety by Patient Health Questionnaire and Hospital Anxiety and Depression Scale. Barriers to immunosuppressive adherence post-HTx were measured by the Medication Experience Scale for Immunosuppressants (MESI).

Results: According to the TERS classification of Rothenhäusler et al., patients were divided into three groups in study one. Compared with inconspicuous patients ($n = 23$) and risk patients ($n = 21$), high risk patients ($n = 6$) demonstrated a higher mortality (log rank test of trend, $p = 0.002$). In study two, there was a strong correlation between the TERS (T0) and the MESI (T2) ($r = 0.84$, $p = 0.001$).

Conclusion: The TERS may serve as a predictor of survival on the waiting list. There is need for further longitudinal data with larger sample sizes.

Acknowledgement: The Clinical Trials Center Cologne was supported by the German Federal Ministry of Research and Education (BMBF grant 01KN1106).

Reference: 1. Vitinius F, Reklat A, Hellmich M, Klask E, Wahlers T, Rahmanian PB, Pfister R, Müller-Ehmsen J, Albus C. Prediction of survival on the waiting list for heart transplantation and of posttransplant nonadherence – results of a prospective longitudinal study. Clin Transplant. 2019 May 28: e13616. https://doi.org/10.1111/ctr.13616. [Epub ahead of print] PubMed PMID: 31136011.

V011 THE PROGNOSTIC VALUE OF SARCOPENIA ON DEATH OR EMERGENCY VAD IMPLANTATION IN HOSPITALIZED PATIENTS AWAITING HEART TRANSPLANTATION

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Introduction: Donor organ shortage and prolonged waiting times are a major concern in heart transplantation. Since patients' clinical status often further deteriorates while waiting, deciding between a ventricular assist device (VAD) implantation and further waiting time is difficult.

The impact of frailty and sarcopenia on outcomes after cardiac surgery has been recently investigated. However, data about their influence on survival during the waiting time remains scarce.

Methods: We analyzed the area of the erector spinae muscle (ESM) on level Th12 and the iliopsoas muscle (IPM) on level L4 from computed tomography (CT) scans as a surrogate for sarcopenia/frailty in hospitalized patients awaiting heart transplantation. Fifty-eight patients with advanced heart failure due to dilated cardiomyopathy (38 (66%)), ischemic heart disease (8 (14%)) or other causes (12 (20%)) waited with a "high urgency" status (43 (74%) male; 15 (26%) female).

Three (5%) patients died during the waiting time and 24 (42%) patients underwent emergency VAD implantation. These 27 (47%) patients were pooled into a group "no transplantation" and compared to 31 (53%) patients, who reached transplantation.

Results: Shapiro-Wilk test was used to test for Gaussian distribution. Depending on the result, we tested with Mann-Whitney-U- or Student T-Test.

Both groups did not differ significantly in their baseline characteristics of age, body constitution or commonly used parameters to evaluate heart failure ($p > 0.05$ in all), especially not in NT-proBNP adjusted for eGFR.

ESM area, adjusted for body surface, was significantly lower in the group "no transplantation", compared with patients, who reached transplantation, analyzed with Mann-Whitney-U-Test ($U = 286$, $Z = -2.065$, $p = 0.039$). No significant difference in IPM area was recognized in this cohort.

Conclusion: In this small cohort, patients who underwent emergency VAD implantation or died while waiting for an organ, had a significantly smaller MES area, adjusted for body surface. Frailty and sarcopenia may impact the prognosis of patients on the waiting list and should be further explored.

V012 IMPROVED KIDNEY FUNCTION BY ADMINISTRATION OF INOTROPES IN TYPE 1 CARDIORENAL SYNDROME PRIOR TO HIGH-URGENT HEART TRANSPLANTATION

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Introduction: A 47-y-old female patient with DCM and recurrent small complex tachycardia experienced first decompensation in 02/2019. Myocardial

biopsy 03/2019 ruled out myocarditis. Shortly after discharge emergency re-admission was necessary. Recompensation followed over 4 weeks with inotropic therapy including Levosimendan, cardioversions and dialysis therapy. A LifeVest was provided.

The patient was admitted to our center with onset of arrhythmias and a second episode of cardiac decompensation for further evaluation.

The patient was initially evaluated for high urgency heart transplantation (HTx) listing due to severely impaired cardiac index. Due to a type 1 cardio-renal syndrome, listing for combined heart and renal transplantation was considered. The patient was initially listed "T".

Methods: The clinical and laboratory course throughout a period of 4.5 weeks under intermediate care surveillance were observed and changes in dosing of inotropic medication were documented.

Results: Initial recovery using inotropes and i.v. diuretics was achieved after stabilization of heart rhythm (AVNRT). GFR increased from 13 initially (Creatinine 3.01 mg/dl; without Milrinone) to 35 ml/min/BSA (Creatinine 1.7 mg/dl; 0.5 mcg/kg bw Milrinone), dialysis was avoided. Weaning of inotropes failed initially due to worsening GFR (19 ml/min/BSA; Creatinine 2.88 mg/dl; after Milrinone weaning) and zvSO2 (down to 45%). Two further attempts to wean inotropes also failed.

After reimplementation of Milrinone (0.55 mcg/kg bw) GFR recovered to 67 ml/min/BSA (Creatinine 1.01 mg/dl). Right heart catheterization was performed again and high urgent status for heart transplantation was granted for end-organ function depending on inotropes. GFR remained stable at 49 – 53 ml/min/BSA (Creatinine 1.29 – 1.21 mg/dl) during the further course.

Conclusion: Re-establishment of stable kidney function after type 1 cardio-renal syndrome is possible by carefully balancing diuretic and inotropic therapy and hemofiltration. In this case combined Heart-Kidney-transplantation was avoided.

IMMUNOLOGY I –TOLERANCE AND CHIMERISM

V013 MHC CLASS-I DEFICIENCY BY TARGETING B2M IN PIGS – PHENOTYPICAL AND FUNCTIONAL CHARACTERISATION FOR XENOTRANSPLANTATION

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Introduction: Foreign MHC molecules are the main inducers of anti-graft responses and targets of cytotoxic effector cells during rejection. The interaction between porcine MHC (SLA, swine leucocyte antigen) molecules and the human T cell receptor is functional across the species-barrier. The absence of SLA class-I molecules should lead to a decreased immunogenicity of porcine cells and tissues. Therefore, SLA class-I deficient pigs were generated. The immune status of the animals and the stimulatory potential of their cells and tissues were characterised.

Methods: For expression of SLA class-I molecules, the non-polymorphic beta2-microglobulin (b2m) is regarded to be essential. SLA class-I deficient pigs were generated by targeting the b2m gene using CRISPR/Cas9 following somatic cell nuclear transfer (SCNT). Resulting b2m "knock-out" (b2m-ko) pigs were characterised phenotypically and cells from these animals were tested for their potential to stimulate proliferative responses and cytotoxic activity of human cells in comparison to wildtype (wt) porcine cells.

Results: Histological staining of transplantation relevant organs and FACS analyses of PBMC and fibroblasts revealed a strongly decreased b2m and SLA class-I expression. SLA class-I deficiency was also reflected by the total absence of $CD8^+$ T cells in peripheral blood. Piglets showed reduced cytokine and IgG levels. In xenogeneic MLR assays we observed significantly reduced proliferation of human $CD8^+$ T cells to stimulation with PBMC from b2m-ko pigs. Despite this, cytotoxic effector cells (generated in 6d MLRs) lysed SLA class-I negative targets as effectively as targets from SLA class-I positive wt pigs. Experiments are ongoing to clarify whether this lysis reflects the activity of NK cells or killing mediated by human $CD4^+$ T cells via the CD95/CD95L pathway.

Conclusion: Targeting b2m is an appropriate strategy to generate pigs expressing significantly reduced levels of SLA class-I. The functional data indicate a low immunogenic status of cells from SLA class-I deficient pigs, mainly by preventing the induction phase of human anti-pig T cell reactivity. Additional strategies should be introduced to protect porcine cells from cytotoxic effector cells.

Acknowledgement: Supported by the DFG (SFB-TRR 127 "Xenotransplantation").

V014 DE NOVO GENERATED TCRS DOMINATE THE REPERTOIRE IN PEDIATRIC HSCT PATIENTS

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Introduction: Immune reconstitution after hematopoietic stem cell transplantation (HSCT) mitigate infection and cancer relapse and promote long-term survival. The role of the pre-transplant T cell receptor (TCR) repertoire of the donor and recipient in post-transplant TCR reconstitution remains unclear. In particular, it is not known whether the post-transplant replenished TCR repertoire is of donor origin or de novo generated.

Methods: To address this, we assessed TCR repertories in 14 pediatric donor-recipient pairs pre-HSCT and in recipients 2.2–5.1 years post-HSCT by next-generation sequencing. TCRβ clonotypes were identified in PBMCs and pairwise clonotype overlap analysis was performed. In addition, we inferred the antigen-specificity of the obtained TCR repertoires from similarity to TCRs in recently published curated databases.

Results: Despite long-term follow-up, we identified overlapping clonotypes in thirteen donor-recipient pairs (92.9%) which accounted for up to 20.6% of the post-HSTC repertoire. Persisting clonotypes from the pre-transplant recipient repertoire were more prevalent after reduced-intensity conditioning regimens but also observed in patients following myeloablative conditioning with complete donor chimerism. The specificity of the TCR as assessed by comparison to curated databases of TCRs with known specificity. We found a dominance of CMV- and influenza-specific clonotypes of the donor derived TCRs, suggesting a transferred protection.

Conclusion: This study contributes to the understanding of TCR reconstitution mechanisms and provides new insights in antigenic specificity in follow up of HSCT.

V015 CORRELATION BETWEEN CLAD DEVELOPMENT AND PGD 24 H AFTER LUNG TRANSPLANTATION WITH RESPECT TO EARLY OCCURRENCE OF B- AND NK-CELLS

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Introduction: An important cause of early morbidity and mortality after lung transplantation is primary graft dysfunction (PGD). The involvement of B and NK cells in the immune response after lung transplantation is not yet fully understood. The involvement of the innate immune response in the development of PGD after lung transplantation has not yet been fully investigated. It is known that natural killer cells (NK cells) are important components of innate immunity and that activated B cells regulate the activity of naturally occurring cells. In this study, we wanted to investigate the relationship between early peripheral B and NK cell frequencies and the development of CLAD and PGD 24 h.

Methods: The frequencies of circulating peripheral cell subsets were detected by flow cytometry at 3 weeks after transplantation in 178 lung TX patients. We analyzed B cells by CD19, CD27, IgM and IgG expressions, as well as the main NK cell subsets, CD56dimCD16+ vs. CD56bright CD16-. And correlated all measured cell types with CLAD development and PGD 24 h.

Results: The cohort was divided into two groups based on CLAD development after 2 years of lung transplantation and without CLAD development. Patients in the non-cCLAD group showed a higher percentage of CD56+ CD16+ NK cells (73.09 ± 20.4% vs. 63.78 ± 22.3) 3 weeks after lung transplantation compared to the CLAD group. Three weeks after lung transplantation, the B-cell population was significantly higher in the CLAD group (8.06 ± 5.8% vs. 4.05 ± 4.6; $p = 0.0009$) than in the non-CLAD group. In PGD24h, B cell populations were similar (3.62 ± 3.9% vs. 4.34 ± 4.7). Patients in PGD2/3 at 24h group showed significantly higher proportions of CD56+ CD16+ NK cells (5.33 ± 4.6% vs. 3.19 ± 2.4) at 3 weeks after lung transplantation compared to PGD0/1 at 24 h group.

Conclusion: It appears that the primary dysfunction of the graft is correlated with the activation of innate immunity, especially with CD56bright CD16 NK cells in the periphery. Three weeks after lung transplantation, CLAD patients showed increased frequencies of CD56dimCD16+ NK cells and CD19+ B cells, suggesting that possible activation of the innate immune response may contribute to the development of CLAD.

V016 EXTRACORPOREAL PHOTOPHERESIS TREATMENT TO TRIGGER A SPECIFIC IMMUNE TOLERANCE RESPONSE AFTER HEART TRANSPLANTATION

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Introduction: Extracorporeal photopheresis (ECP) treatment following heart transplantation (HTx) may induce transplant tolerance. A monitoring tool for successful ECP-treatment would allow determination of patient-specific duration and frequency of ECP therapy. This study established a monitoring tool and identified the immunological changes induced by ECP.
Methods: Blood samples were analyzed from HTx patients treated by ECP 3 mos after HTx ($n = 19$). ECP treatment included a total of 5 ECP cycles, each on 2 consecutive days every 4–8 wks over a period of 8.4 ± 0.4 mos. Subsets of both dendritic cells (DCs) and regulatory T cells (T_{regs}) were quantified by flow cytometry prior to ECP (baseline), before each ECP cycle and 4 mos after the last ECP cycle.
Results: Compared to baseline, ECP-treatment reduced $CD4^+$ T cells (baseline: 23.2 ± 9.2%, ECP cycle 5: 23.6 ± 3.4%, after ECP: 16.3 ± 7.4%, $p < 0.01$) and increased total T_{regs} (baseline: 9.8 ± 2.4%, ECP cycle 5: 12.5 ± 1.4%, after ECP: 17.5 ± 4.0%, $p < 0.01$). While $CD120b^+$, $CD147^+$ and $CD39^+$ T_{regs} were unaffected by ECP, $CD62L^+$ T_{regs} were downregulated (baseline: 78.9 ± 12.9%, ECP cycle 5: 55.9 ± 13.6%, after ECP: 81.0 ± 11.7%, $p > 0.01$). DC subsets expressing blood dendritic cell antigen (BDCA) 1, 2, 3 or 4 increased during ECP but returned to baseline levels 4 mos after ECP ($BDCA1_{prior\ ECP}$: 42.1 ± 13.4%, $BDCA1_{ECP\ cycle\ 5}$: 53.4 ± 3.7%, $BDCA1_{after\ ECP}$: 43.6 ± 8.7%, $BDCA2_{prior\ ECP}$: 20.2 ± 9.1%, $BDCA2_{ECP\ cycle\ 5}$: 32.6 ± 3.2%, $BDCA2_{after\ ECP}$: 24.0 ± 6.0%, $BDCA3_{prior\ ECP}$: 73.2 ± 17.8%, $BDCA3_{ECP\ cycle\ 5}$: 90.4 ± 5.0%, $BDCA3_{after\ ECP}$: 75.4 ± 12.4%, $BDCA4_{prior\ ECP}$: 21.6 ± 10.0%, $BDCA4_{ECP\ cycle\ 5}$: 31.7 ± 3.9%, $BDCA4_{after\ ECP}$: 21.4 ± 5.9%, all $p \leq 0.01$).
Conclusion: Our results show that ECP treatment could be a useful tool to stimulate specific immune tolerance responses in patients after HTx. A combined increase of $BDCA1^+$, 2^+, 3^+ and 4^+ DCs, total T_{regs} and the highly suppressive $CD39^+$ T_{reg} subset may indicate successful ECP treatment. Furthermore, these data will help to further elucidate the ECP-specific mechanism of action.

V017 MODULATION OF THE HUMAN IMMUNE RESPONSE USING VIRAL CD45 LIGANDS

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Introduction: The protein tyrosine phosphatase CD45 is a key molecule in T cell receptor (TcR)-mediated signal transduction. CD45 activity can be modulated by binding of anti-CD45 antibodies or viral ligands. The human cytomegalovirus (CMV) protein UL11 is such a viral ligand. Interaction of UL11 fusion proteins with CD45 reduces TcR signaling and T cell proliferation[1]. In this study, we asked whether UL11 can be stably expressed on human and porcine cell lines and if membrane bound transgenic UL11 binds to CD45 on T cells, which functional consequences can be observed.
Methods: Human embryonic kidney 293 cells and the porcine B cell line L23 were transfected with the pcDNA3 vector containing the CMV protein UL11. Stable transfectants (293-UL11, L23-UL11) were established and used in co-cultivation experiments with human peripheral blood mononuclear cells (PBMCs) as responders.
Results: Flow cytometry experiments revealed significant expression of UL11 in both, human 293 and porcine L23 cells after transfection with pcDNA3-UL11 vector. Expression was slightly higher in 293 (MFI ~100) than L23 cells (MFI ~30). Triggering of CD45 by antibodies is known to alter the adhesion properties of CD45-expressing T cells. To study whether binding of membrane bound UL11 to CD45 has similar effects 293-mock or 293-UL11 cells were incubated with PBMCs. Aggregation of PBMCs around UL11 expressing cells but not around mock cells could be seen. We were also interested in whether the surface expressed UL11 can alter the proliferative response of PBMCs. Therefore, L23-mock or L23-UL11 cells were incubated with PBMCs and proliferation was measured after different time points. Preliminary data indicate that human PBMCs responded with reduced proliferation to L23-UL11 cells as compared to stimulation with mock-transfected L23 cells.
Conclusion: The human CMV protein UL11 can be stably expressed on the cell surface of porcine cells. Interaction of human T cells with L23-UL11 transfectants is associated with altered cellular functions. It remains to be established whether UL11-mediated triggering of CD45 could be an approach to reduce human anti-pig T-cell responses after xenotransplantation.
Acknowledgement: Supported by SFB-TRR 127 ("Xenotransplantation").
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V019 mTOR INHIBITOR-BASED IMMUNOSUPPRESSION IS ASSOCIATED WITH A HIGHER FREQUENCY OF IFNγ-PRODUCING EBV-SPECIFIC $CD4^+$ T CELLS AS COMPARED TO mTOR INHIBITOR-FREE THERAPY IN KIDNEY TRANSPLANT PATIENTS

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Introduction: About 80–90% of adults are infected with Epstein-Barr-Virus (EBV), which persists in a latent stage. The immunosuppressive regime after organ transplantations can cause reactivation of EBV and thereby complications such as Post-transplant lymphoproliferative disorder (PTLD), a life-threatening malignant lymphoma. Cellular immunity is known to control viral proliferation and reconstitution of EBV-specific T cell immunity under immunosuppression (IS) is crucial for prevention of EBV replication. IS drugs are known to impact the functionality of cellular immunity at different extent. Previously, we demonstrated advantageous effect of mTORi on the efficacy of BKV-specific T-cell immunity as compared to other IS drugs. However, the effect of mTORi on EBV-specific cellular immunity has been not analysed in details. The aim of this study is to elicit the effect of mTORi on the quantity and functionality of EBV-specific T-cell response in kidney transplant patients.
Methods: We conducted an explorative cross-sectional analysis on characterisation of EBV-specific T-cells in patients treated with mTORi-based triple IS; $n = 20$) in comparison to pair-matched controls treated by mTORi-free triple IS ($n = 20$). PBMCs were challenged with EBV overlapping peptides and EBV-specific T cells were analysed by multi-parameter flow cytometry.
Results: Our data revealed a significantly higher number of EBV-specific T cells in patients treated with mTORi as compared to mTORi-free group. Within EBV-specific T cells, the number of $CD4^+CD154^+IFN\gamma^+$ T cells was significantly higher in mTORi therapy group as compared to mTORi-free regimen.
Conclusion: Our study provides evident for advantageous impact of mTORi therapy on the magnitude and functionality of EBV-specific $CD4^+$ T cells. This might lead to a better EBV control and prevention of EBV-associated complications in transplant patients. Further studies are required to confirm our observation.

KIDNEY I/PANCREAS

V020 B CELL DENSITY IN RENAL GRAFTS CORRELATES WITH REJECTION, FIBROSIS, POLYOMA NEPHROPATHY AND DONOR CHARACTERISTICS

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Introduction: The relevance of B cell infiltrates for the long-term function of kidney allografts is controversial. Precise quantification and localization of immune cells by eye is challenging and time-consuming. Digital morphological approaches may improve the diagnostic accuracy.
Methods: A total of 766 renal allograft biopsies (patient age ranging from 2 to 78 years, 40.8% from female recipients), including both biopsies for clinical cause (57.8%) and surveillance biopsies from the Hannover Protocol Biopsy Program (42.2%), were stained in an automated manner (Ventana) for B cells using a monoclonal CD20 (clone L26) antibody and scanned (Leica). Whole Slide Images (WSI) were subsequently analyzed for immunopositively stained area (%/region of interest) using a pixel-based digital approach. Results were obtained for cortical, medullary and extrarenal area, respectively. The spatial distribution of B cells was evaluated in a subgroup of 160 biopsies (nodular, diffuse and mixed patterns).
Results: B cell abundancies in the biopsies differed between patients with vs. without rejection: The highest B cell abundancy was observed in biopsies with T cell-mediated rejection (TCMR), compared with biopsies without rejection or Borderline rejection ($p < 0.05$). Borderline rejection showed a slight increase in comparison to rejection-free samples ($p < 0.05$). B cell numbers in humoral rejection (ABMR) were not increased, whereas mixed TCMR/ABMR cases had higher numbers ($p < 0.05$) in comparison to biopsies without rejection. Cortical B cell densities correlated with fibrosis grade according to Banff category 5 and

coding for tubular atrophy (ct), interstitial fibrosis (ci), and with (interstitial) inflammation (i, ti), tubulitis (t), vasculitis (v), peritubular capillary cell margination (ptc), i-IFTA and polyoma nephropathy ($p < 0.05$). Grafts from brain dead donors had higher cortical B cell densities compared to living donation ($p < 0.01$) and standard transplantations less than Eurotransplant Senior Program ($p < 0.05$). Donor age positively associated with nodular infiltrates ($p < 0.05$).
Conclusion: Our results suggest an important role of B cell infiltration in TCMR and IFTA (i-IFTA, Polyoma) and thus long-term graft survival.

V021 ACCELERATED GRAFT LOSS IN KIDNEY TRANSPLANT PATIENTS WITH HIGH SCD30 LEVELS AND DSA WITH HIGH MFI – IMPLICATIONS FOR THE DEFINITION OF UNACCEPTABLE ANTIGENS

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Introduction: Defining all HLA as unacceptable (UAG) against which waiting list patients have antibodies with MFI > 5000 determined by single antigen bead assays (SAB) prevents many graft losses at the expense of a high false positive rate. It was suggested that antibodies directed against the donor with MFI > 5000 (SAB-DSA^{high}) do not increase the risk of early graft loss in patients with low sCD30 levels. We asked whether considering both biomarkers would improve the accuracy of a purely MFI-based UAG algorithm.
Methods: Pretransplant sera from 170 CDC crossmatch-negative patients following deceased donor kidney transplantation were retrospectively analyzed for the presence of DSA (MFI cutoff 1000) using SAB and sCD30 (cutoff 80 U/ml) using ELISA. The incidence of AMR and death-censored graft survival – excluding losses due to technical failure ($n = 1$) or primary non-function without evidence of rejection on biopsy ($n = 7$) – was assessed.
Results: 5-year graft survival was lower in sCD30$^+$ DSA$^+$ patients (72%, 5 graft losses after 5 years/19 patients) compared to sCD30$^-$ DSA$^+$ (93%, 2/29), sCD30$^+$ DSA$^-$ (94%, 2/43) and sCD30$^-$ DSA$^-$ patients (90.5%, 7/79). During a median follow up of 5.2 years, there were 11 graft losses in 48 DSA-positive patients, 9/11 losses occurring in those with MFI > 5000 ($n = 29$). In this patient population, 5-year graft survival was inferior in sCD30$^+$ (67%, 4/12) compared to sCD30$^-$ patients (93%, 1/17). However, the incidence of early AMR (4/12 vs. 6/17) and the cumulative incidence of graft loss during follow up (4/12 vs. 5/17) were comparable between these two groups.
Conclusion: Analysis of 5-year graft survival argues in favor of implementing sCD30 in MFI-based UAG algorithms as graft survival in patients with SAB-DSA^{high} who have low sCD30 levels was comparable to DSA-negative patients. Whether these findings are only a reflection of an accelerated graft loss in sCD30-positive as compared to sCD30-negative patients deserves further investigation.

V022 HYPERSPECTRAL IMAGING – FIRST APPLICATION IN HUMAN KIDNEY TRANSPLANTATION

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Introduction: Medical Hyperspectral Imaging (MHIS) is capable to offer quantitative diagnostic information about tissue pathology, morphology and composition based on the spectral characteristics of different tissue. To date it has not been applied to human solid organ transplantation.
Methods: Acquisition of hyperspectral images of different components (parenchyma, ureter) of human kidney allografts was taken early after reperfusion and after ureteroneocystostomy using the TIVITA® camera device. Images were recorded and analyzed using HSI acquisition software generating oxygen saturation levels (StO_2), near infrared perfusion indices (NIR), organ hemoglobin indices (OHI) and tissue water indices (TWI) of explored tissues.
Results: Four consecutive kidney allografts were assessed in this pilot trial. Assessed Parameters were as follows: (StO_2: 76.5%; range: (67.2%–80.0%)) (NIR: 0.69; range: (0.48 – 0.79)) (OHI: 0.67; range: (0.45 – 0.85)) and (TWI: 0.65; range: (0.56 – 0.74)). A fifth patient was assessed 3-month post-transplant suffering from ureter necrosis. Intraoperative TIVITA® imaging displayed marked differences in NIR, OHI and TWI parameters allowing to distinguish viable from necrotic tissue. This assessment had a trend-setting impact on operative strategy. A sixth scheduled for transplant nephrectomy due to chronic rejection also displayed considerable differences in all assessed parameters when compared to vital organs recorded early after reperfusion.
Conclusion: Hyperspectral imaging is a novel tool suitable for non-invasive assessment of kidney allografts early after reperfusion. It allows to identify areas with reduced oxygen supply and perfusion deficits. Further clinical application might allow prediction of early and future organ performance.

V023 IMPACT OF DONOR CARDIOPULMONARY RESUSCITATION ON THE OUTCOME OF SIMULTANEOUS PANCREAS KIDNEY TRANSPLANTATION (SPK)

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Introduction: Pancreas allograft acceptance is distinctly more selective than other solid organs. Previous cardiac arrest in brain death donors has been discussed as a potential risk factor in pancreas transplantation (PT) and leads to a higher rate of organ refusal. The aim of the study was to assess the impact of cardiopulmonary resuscitation (CPR) in brain death donors on pancreas transplant outcome.
Methods: A total of 518 type-1 diabetics underwent primary SPK at our centre between 1994 and 2018. We divided these patients into two groups, depending on whether their donor was resuscitated or not and retrospectively analysed the outcome after PT.
Results: A total of 91 (17.6%) donors after CPR were accepted for transplantation (mean duration of cardiac arrest 19.4 ± 15.6 min). Donors with CPR were younger ($p < 0.001$), had a lower PDRI ($p = 0.003$) but a higher serum-creatinine ($p = 0.021$). No differences were found regarding all other donor characteristics. With a mean follow-up of 131.2 ± 81.1 months, both groups demonstrated comparable short and long-term patient- and graft survival. Investigation whether resuscitation time (< 20 min vs. ≥ 20 min) had an impact, also showed similar survival rates. Multivariate analysis did not suggest an association between donor CPR and early graft failure, patient- or graft survival.
Conclusion: In this study, brain death donors after CPR are suitable for pancreas transplantation without increasing the risk of complications. Duration of resuscitation did not affect the results. A possible protective role of CPR against ischemia/reperfusion injury, like ischemic preconditioning, should be furthermore investigated.

V024 IMMUNOSUPPRESSION RELATED NEGATIVE EFFECTS ON ISLET GRAFTS CAN BE MITIGATED BY GROWTH HORMONE RELEASING HORMONE (GHRH) AGONIST

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Introduction: Islet transplantation is a valid therapy for type 1 diabetic patients. However, a progressive islet dysfunction is often seen over time. This is in part the result of adverse effects of immunosuppressive agents (IS). The current protocols include a combination most commonly based on calcineurin-inhibitors, mTOR-inhibitors and Mycophenolate. In this study we aim to investigate the impact of MMF and Everolimus on islet proliferation and functional capacity. In addition, we combined IS with a growth hormone releasing hormone (GHRH) agonist that potentially can reduce negative effects of IS.
Methods: Islets from female Wistar rats were isolated and purified according to standard protocols. The culture media (RPMI 1640) was supplemented with 10% FBS alone (control) or with Mycophenolate or Everolimus at clinically accepted trough levels. Subsequently, GHRH agonist was added at a previously established concentration. Islets were analysed for viability, islet function, apoptosis and proliferation.
Results: The viability after islet isolation was > 90% and maintained in the control group during the five day culture period with only minor loss of islet numbers. In contrast, the addition of either MMF or Everolimus caused a significant and progressive decrease in viability and function. This effect of IS was also reflected in a significantly increased percentage of apoptotic cells. The addition of GHRH agonist was able to abrogate these negative effects to nearly the level of control islets.
Conclusion: Progressive islet graft dysfunction following islet transplantation results in part from immunosuppressive agents. Within this study we wanted to elucidate this effect by direct exposure of isolated islets to two commonly used immunosuppressive drugs and determine their effect on islet integrity. We could show that these agents negatively impact on viability and function and this effect can be limited by the combination with a potent GHRH agonist. This study emphasizes the potential of this substance class for improving islet viability, function and long term survival.

V025 EXPANDING PANCREAS DONOR POOL BY EVALUATION OF UNALLOCATED ORGANS AFTER BRAIN DEATH – EXPLORE STUDY

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Introduction: Data from Eurotransplant indicate that only 27% of donor pancreases are transplanted, either as whole pancreas grafts or as islet grafts. In this multicenter study we will assess the histopathological quality of unallocated pancreas organs from brain-dead donors in Baden-Württemberg, Germany. Our aim is to determine how many of these unallocated organs are suitable for transplantation based on a histopathologic evaluation of organ quality.
Methods: This is a multicenter cross-sectional explorative study. All pancreas organs from brain-dead donors, which have been reported to Eurotransplant Foundation (ET) by the DSO region of Baden-Württemberg without being allocated or transplanted will be included in this study. All donor organs will meet the requirements of the German law on organ donation and transplantation (Gesetz über die Spende, Entnahme und Übertragung von Organen und Geweben; TPG) the corresponding guidelines of the German Doctors Association (Richtlinien der Bundesärztekammer gemäß §16 TPG) as well as the procedural instructions of the German Organ Transplantation Foundation (Verfahrensanweisungen der Deutschen Stiftung Organtransplantation, DSO, gemäß §11 TPG).
Results: The pancreases of all included donors will be explanted and sent to the Department of General Pathology of the University of Heidelberg after primary assessment by the explant surgeon. Finally, a complete macroscopic and microscopic assessment of the organs will be performed by two transplant surgeons and two pathologists in Heidelberg.
Conclusion: Pancreas graft pool to overcome organ shortage in the field of pancreas transplantation. Due to shortage donor organ, we focused on macroscopic and microscopic histopathological aspects of unallocated donor pancreas in this study for the first time. To achieve this goal, unallocated pancreas wants to be evaluated by two expert surgeons macroscopically and then wants to be the expert pathologist to evaluate microscopically.

BASIC SCIENCE I – ISCHEMIA/REPERFUSION

V026 GENERATION OF IMMUNOLOGICALLY INVISIBLE TRANSGENIC PORCINE PANCREATIC ISLET CELL CLUSTERS AFTER SINGLE CELL ENGINEERING AND ISLET REASSEMBLING TO SUPPORT XENOGRAFT SURVIVAL

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Introduction: Xenotransplantation of transgenic porcine pancreatic islets offers a promising alternative source to circumvent current limitations posed by the scarcity of allogeneic donors. To decrease xenogeneic immune responses, we have investigated the feasibility to generate tissue engineered SLA silenced islet cell clusters (ICC) from alpha-Gal knock out, CD46, CD55 and CD59 transgenic pigs.
Methods: Pancreatic islets single cell suspensions were generated by enzymatic digestion of porcine ICCs. The single cells were silenced for SLA class I and II by lentiviral vectors encoding for Nanoluciferase as reporter gene and for short hairpin RNAs targeting beta2-microglobulin (shb2m) or class II transactivator (shCIITA), respectively. SLA transcripts were evaluated by real-time PCR and protein levels by flow cytometry and fluorescence microscopy analyses. Cell death was evaluated by Annexin V and Propidium Iodide staining. The effect of SLA class I silencing was evaluated in human T and NK cell cytotoxicity assays. SLA-silenced pancreatic beta-cells were then used to form new ICCs in stirred bioreactors.
Results: SLA class I silencing was designed to reach a level of up to 84% and class II by up to 50% on pancreatic islet cell monolayers. Silencing SLA expression did not affect cell viability and the insulin-producing beta-cell phenotype as indicated by Dithizone staining and levels of insulin production. Xenogeneic T-cell immune responses ($p < 0.05$) as well as antibody-mediated cellular-dependent immune responses ($p < 0.01$) were significantly decreased. Silencing SLA class I expression did not increase susceptibility to NK-cell cytotoxicity. In stirred bioreactors, tissue engineered islets showing the typical 3D-structure and morphology of ICC were assembled from SLA-silenced pancreatic cell suspensions to be used for transplantation in humanized mice as a first model.
Conclusion: These data shows the feasibility to generate low immunogenic porcine ICC from transgenic pigs after single cell engineering and post-transduction islet reassembling that might serve as a robust alternative to allogeneic pancreatic islet cell transplantation.
Acknowledgement: This study was supported by the DFG grant TRR127/A1

V028 CALCINEURIN INHIBITORS CAUSE FUNCTIONAL ALTERATIONS AND INFLAMMATORY REACTIONS OF ENDOTHELIAL PROGENITOR CELLS IN VITRO

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Introduction: Immunosuppressants, e.g. calcineurin inhibitors are a mandatory therapy for transplant patients to avoid rejection of the transplanted organ by the immune system. However, there are several known side effects including alterations of the vasculature which involve a higher occurrence of cardiovascular events. While the effects of calcineurin inhibitors on mature endothelial cells have been addressed in several studies, we focused our research on the effect of calcineurin inhibitors on endothelial colony forming cells (ECFCs), a subgroup of endothelial progenitor cells, which play an important role in vascular repair and angiogenesis.
Methods: ECFCs were isolated from cord blood of healthy pregnancies and incubated with different doses (0.01 μM – 10 μM) of Tacrolimus and Cyclosporine A. ECFC function was determined using in vitro models and mRNA expression of inflammatory cytokines and adhesion molecules was explored by real time PCR and NFKB translocation by immunofluorescence.
Results: Calcineurin inhibitors significantly impaired ECFC function, including proliferation, migration, chemotaxis and angiogenesis. Calcineurin inhibitors lead to an increase of TNFalpha, IL6, VCAM and ICAM mRNA expression as well as NFKB nuclear translocation. Addition of Parthenolide, a NFKB-activation-inhibitor, counteracted calcineurin inhibitor mediated proinflammatory cytokine mRNA expression. There was no increase of LDH release excluding a cell toxic effect of the treatment.
Conclusion: Functional impairment of ECFCs may contribute to higher cardiovascular risk in transplant patients under calcineurin inhibitor therapy.
Acknowledgement: This project was supported by the German Ministry of Research and Education (Reference Number 01EO1302).

V029 THE ISOTHIOCYANATE SULFORAPHANE ELICITS PROTECTION IN A MURINE MODEL OF INTESTINAL ISCHEMIA REPERFUSION INJURY BY REDUCING LEUCOCYTE ADHESION

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Introduction: Intestinal ischemia reperfusion injury (IRI) is an inherent event following small bowel transplantation, resulting in an inflammatory state, with the hallmark event of leukocyte adhesion at the vascular endothelium. One compound known to affect the crosstalk between leukocytes, platelets and the endothelium is the naturally occurring isothiocyanate sulforaphane (SFN). This project aimed to study protective effects of SFN in a murine model of intestinal IRI coupled with real-time imaging using intravital fluorescence microscopy (IVM).
Methods: Male C57BL/6 mice were treated intraperitoneally with SFN (50 mg/kg) or vehicle and subjected to 30 minutes of occlusion of the superior mesenteric artery to create total ischemia of the small bowel. After

2 hours reperfusion, IVM was used to study cellular interactions and samples were collected for histological assessment (Park/Chiu Score). Intestinal mucosal permeability was assessed by measuring translocation from the gut into the bloodstream of exogenously administered ovalbumin and qPCR was used to quantify changes in gene expression of cellular adhesion molecules.
Results: Intestinal IRI elicited a robust inflammatory response with histological signs of disintegration of the lamina propria and crypt layer injury in vehicle treated animals (5.8 $\pm$ 0.2). This was significantly ameliorated in SFN treated animals (3.2 $\pm$ 0.7, $p < 0.05$). IVM revealed a significant reduction in leucocyte rolling and adhesion as well as leucocyte-platelet interactions coupled with a reduction in the expression of ICAM-1 and VCAM-1. No changes were noted in platelet adhesion. SFN also elicited an improvement in intestinal barrier integrity measured by a reduced trans-epithelial ovalbumin translocation.
Conclusion: The naturally occurring isothiocyanate SFN is a promising agent to ameliorate intestinal IRI by reducing leukocyte adhesion as the key feature of IRI-elicited inflammation resulting in reduced immune-mediated enterocyte destruction and preservation of epithelial barrier function.

V030 ROLE OF FERROPTOSIS AND ISCHEMIA REPERFUSION INJURY IN LIVER TRANSPLANTATIONS

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Introduction: Ischemia reperfusion injury (IRI) remains an important problem in liver transplantations especially in the use of marginal organs. Ferroptosis, a regulated cell death (RCD) event, plays a key role in hepatic IRI. Today, there are still some unknown steps within the ferroptosis pathway.
Methods: In a clinical trial we discover a correlation between IRI and marginal organ transplantation. We investigate the expression of ferroptosis linked proteins in human pre- and post-transplant liver samples via western blots. Differences between pre- and post-transplant samples, general outcomes and patient characteristics are in the focus of the analysis.
Results: We can detect different ferroptosis linked proteins and their up respectively down regulation due to warm and cold ischemia in human transplant samples. Furthermore, steatosis is an important factor for IRI. Especially, livers with macrosteatosis and IRI have a significant worse outcome in allograft function and long-term survival.
Conclusion: Ferroptosis events and steatosis appear to be a main factor in IRI in liver transplantations and therefore as well in the general outcome and patient survival.

V031 URINARY BIOMARKERS FOR CELL CYCLE ARREST TIMP-2 AND IGFBP7 ARE PREDICTIVE FOR RECOVERY FROM ISCHEMIA-REPERFUSION-INJURY AFTER KIDNEY TRANSPLANTATION

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Introduction: Conventional clinical markers often fail to predict recovery from ischemia-reperfusion injury in the early phase after kidney transplantation (KTx). Urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor 7 (IGFBP7), markers for G1 cell cycle arrest, have been identified and validated for the early detection of renal injury in critical ill patients, but data on recovery of allograft function after KTx are scarce. We evaluated whether post-transplant urinary [TIMP-2]*[IGFBP7] can predict recovery early after KTx.
Methods: In a prospective observational multicenter cohort study of renal transplant recipients, urinary [TIMP-2]*[IGFBP7] (NephroCheck®; Astute Medical, San Diego, CA, USA) was evaluated daily from day 1–7 after KTx. Different stages of early graft function were defined: immediate graft function (IGF) (decrease $\geq$ 10% in serum creatinine (s-crea) within 24 hours post KTx); slow graft function (SGF) (decrease in s-crea less than 10% within 24 hours post-Tx) and delayed-graft function (DGF)(any dialysis needed within the first week after KTx). Clinical and routine laboratory parameter as well as transplant outcome were documented.
Results: A total of 186 KTx patients were analyzed, 138 (74%) with a deceased donor and 48 (26%) with a living donor KTx. IGF was observed in 58.6%, SGF in 23.1% and DGF in 18.3% of the cohort. [TIMP-2]*[IGFBP7] were significantly elevated in patients with DGF compared to other groups during first week of transplant starting at day 1. Renal function parameters were not able to differentiate between DGF and SGF early after Ktx. ROC-Analysis of [TIMP-2]*[IGFBP7] at day1 posttransplant for event "Non-DGF" revealed a cut-off value of 0.9 $(ng/ml)^2/1000$ with a sensitivity of 87% and a specificity of 71%. Positive predictive value for non-DGF was 93%.
Conclusion: Early[TIMP-2]*[IGFBP7] post KTx measurement (day 1) can predict recovery from ischemia-reperfusion-injury. [TIMP-2]*[IGFBP7] is a promising biomarker for clinical decision-making in patients with KTx.

V032 THE SEVERITY OF LPS INDUCED INFLAMMATORY INJURY IS NEGATIVELY ASSOCIATED WITH THE FUNCTIONAL LIVER MASS AFTER LPS INJECTION IN RAT MODEL

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Introduction: High levels of serum lipopolysaccharide (LPS) were observed in sepsis patients with liver injury and high mortality. However, the role of liver in modulation LPS induced inflammatory injury was ill investigated. In the present study, the severity of LPS induced inflammatory response was observed after liver resection or portal branch occlusion to decreasing functional liver mass. The local and systemic damage was observed to investigate the role of liver in modulation inflammatory injury.
Methods: First, 30%, 70%, and 90% partial hepatectomy (PH) were performed, and serum TNF-α, survival rate, and hepatic LPS uptake was observed. Second, LPS-exposure of the functional liver mass was decreased by selectively blocking the RL prior to LPS-injection, which was given 30 min before a 70% PH, and the inflammatory response was compared in the occluded and the non-occluded liver. The control group was subjected to LPS injection 30 min prior to liver resection without blocking the RL transiently. The serum TNF-α, ALT, AST, creatinine levels, survival rate, hepatic LPS uptake, and hepatic inflammatory cytokines were observed.
Results: The decreasing of functional liver mass after 90%, 70%, and 30% PH was associated with decreased serum TNF-α, survival rate, and increased hepatic LPS uptake after LPS injection. Occluding the right lobes (RL) prior to LPS administration reversed the liver injury caused by 70% PH, indicated by 100% survival rate and decreased liver and kidney injury, and systemic inflammatory response. The induction of inflammatory response in occluding liver lobes were lower than un-occluding liver lobes.
Conclusion: The severity of the LPS-induced systemic inflammatory injury is determined by functional liver volume. This observation suggests that the liver is the central organ for the initiation of the inflammatory response, and is involved in causing a severe SIRS with systemic damage and death.

LIVER II

V035 MOLECULAR FINGERPRINT OF T CELL-MEDIATED AND ANTIBODY-MEDIATED REJECTION AFTER LIVER TRANSPLANTATION

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Introduction: The long-term outcome of patients after liver transplantation (LTx) has not been improved over the past three decades. Up to 50% of patients show refibrosis in 5-year biopsies and side effects of chronic immunosuppression determine the morbidity and quality of life after LTx. The long-term histology is less precise in distinguishing between harmful and non-harmful findings, we employed molecular analysis to better characterize various rejection types.
Methods: We conducted next generation sequencing of mRNA isolated from 71 cryo-conserved liver allograft biopsies with no histological rejection (NHR; $n = 20$), subclinical TCMR (subTCMR; $n = 25$), clinical TCMR (cTCMR; $n = 10$) or possible cAMR (pcAMR; $n = 16$). Pathway analysis was performed with Ingenuity Pathway Analysis (QIAGEN) for transcripts with $p < 0.05$, false discovery rate < 0.05 and with $>$ 2fold change in expression.
Results: In the principal component analysis NHR and subTCMR exhibited quite similar intrahepatic gene expression pattern indicating no major inflammation in the graft. In contrast cTCMR and pcAMR were molecular different from NHR. Each rejection type (subTCMR, cTCMR, pcAMR) was compared to NHR and the overlap of these three comparisons was determined. Only two transcripts (PRDM1, RGCC) were consistently regulated in all three rejection types. Furthermore cTCMR and pcAMR were significantly different from NHR. Both types shared 200 transcripts mostly involved in regulation of the T cell compartment and cell cycle control including proliferation and DNA repair. 516

pcAMR specific transcripts were mostly involved in similar pathways as those shared by cTCMR. 341 cTCMR specific transcripts were mostly involved in cell cycle control, potentially reflecting tissue response to more severe and acute tissue damage during cTCMR compared to subTCMR and pcAMR.
Conclusion: On the molecular level subTCMR is nearly indistinguishable from NHR ruling out any relevant graft inflammation. In contrast pcAMR is rather a resembling TCMR thereby showing substantial graft injury and tissue repair. Molecular profiling will help to identify patients with relevant graft inflammation thereby potentially providing a chance for individualized immunosuppression.

V036 EXTENDED RIGHT LOBE VERSUS WHOLE ORGAN LIVER TRANSPLANTATION – GERMAN MULTICENTRE MATCHED-PAIR ANALYSIS

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Introduction: Split liver transplantation allows expansion of the limited organ pool. Available data suggest a comparable outcome between extended right lobes liver transplantation (ERLT) and whole organs. However, excellent liver graft quality in ERLT in contrast to largely marginal donors used for whole organ LT in the recent transplant era, makes conclusions not reliable.
Methods: Retrospective multicentre study of 7 large transplant centres in Germany between 2007 and 2015. We performed a 1:1 matched-pairs analysis of 121 patients with ERLT and whole organ LT each, using the matching criteria recipient and donor age and recipient MELD score.
Results: Patients with ERLT and whole organ LT were comparable concerning recipient age (40.3 ± 19.9 vs. 41.8 ± 20.7y), BMI (23.6 ± 6.9 vs. 23.3 ± 5.2), MELD score (both 19 ± 11points) and donor age (29.1 ± 14.5 vs. 31.2 ± 15.5y). We found a significant ($p = 0.000$) longer cold ischemic time in the ERLT group (779 ± 149 min versus 640 ± 143 min). Graft survival was significant reduced in patients after ERLT in contrast to whole organ LT (1-/5-/10-y graft survival rates 74%/66.2%/53% vs. 89%/75%/70.7%; $p = 0.046$), whereas patient survival was comparable. In the ERLT group 27.3% biliary complications occurred, including 16 biliary leakages, 10 biliary stenoses and 7 ITBL. 25.6% of the patients following whole organ LT suffered from biliary complications (biliary leakages $n = 7$, biliary stenoses $n = 17$, ITBL $n = 8$) without significant difference ($p = 0.884$). Likewise overall vascular complications were comparable between the ERLT group ($n = 8$) and the whole organ group ($n = 6$; $p = 0.784$).
Conclusion: In patients undergoing LT from comparable high-quality donors we found an elevated risk for graft failure after ERLT compared to whole organ LT. In an otherwise matched cohort, this appears to be most likely due to the significantly longer cold ischemic time. Consequently, efforts should be made to reduce cold ischemic time by improved allocation and reduced transportation time.

V037 MOLECULAR CLASSIFIER FOR T CELL-MEDIATED AND ANTIBODY-MEDIATED REJECTION AFTER LIVER TRANSPLANTATION

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Introduction: Long-term management after liver transplantation (LTx) is complicated by low sensitivity of liver enzymes for subclinical graft injuries, atypical histological features of T cell-mediated rejection (TCMR) and limited knowledge on antibody-mediated rejection (AMR). Graft gene expression analysis showed superiority over conventional histopathological assessment after kidney transplantation. The aim was to generate a molecular classifier for various rejection entities after LTx.
Methods: Liver allograft biopsies were prospectively collected since 2008. Three cohorts were used throughout this study: 1) A screening cohort of 71 biopsies with no histological rejection (NHR), subclinical (subTCMR) and clinical TCMR (cTCMR) and possible chronic AMR (pcAMR) for mRNA sequencing. 2) An identification cohort of 101 biopsies with the same four entities. This identification cohort was used for qPCR analysis of candidates from sequencing and designing of classifier. 3) An application cohort of 97 liver biopsies with ambiguous histological findings for the application of the rejection classifier.
Results: For the distinction of the four entities (NHR, subTCMR, cTCMR, pcAMR), 88 transcript candidates were identified by mRNA sequencing. These candidates were tested with qPCR in the identification cohort consisting of the same four entities. Finally, a rejection classifier consisting of 40 transcripts (RC40) was designed and validated based on this qPCR data set. Thereby, RC40 reached low sensitivities (33–62%), but moderate to high specificities (70–93%) for the identification of the four entities. When applied with qPCR in the application cohort, RC40 identified about 80% of subTCMR as well as of cTCMR features within these ambiguous cohort correctly. Graft hepatitis with elevated liver enzymes mostly had molecular phenotype of cTCMR (80%) or pcAMR (10%), while subclinical graft hepatitis mostly had a molecular phenotype of subTCMR (80%) or NHR (10%).
Conclusion: This is the first gene expression classifier after LTx incorporating more than TCMR. After further validation such a rejection classifier could help to retrieve more information from allograft biopsies and facilitate individualized immunosuppression.

V038 HOSPITALIZATION BEFORE LIVER TRANSPLANTATION PREDICTS POST-TRANSPLANT PATIENT SURVIVAL – A PROPENSITY-SCORE MATCHED ANALYSIS

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Introduction: In contrast to donor factors predicting outcomes of liver transplantation (LT), few suitable recipient parameters have been identified. To this end we performed an in-depth analysis of hospitalization status and duration prior to LT as a potential risk factor for post-transplant outcome.
Methods: The pre-transplant hospitalization status of all patients undergoing LT between 2005 and 2016 at the Charité-Berlin was analyzed retrospectively. To minimize the influence of known risk factors Propensity Score Matching by recipient age, laboratory MELD Score, donor age and cold ischemic time was conducted.
Results: At the time of organ acceptance 226 (19.9%) of 1134 recipients were hospitalized on an intensive care unit (ICU), 146 (12.9%) on a regular ward and 762 patients (67.2%) were at home. Hospitalized patients (regular ward and ICU) showed a dramatically shorter 3-month, 1- and 3-year survival compared to patients from home (78.7% vs. 94.4%; 66.3% vs. 87.3%; 61.7% vs. 81.7%; all $p < 0.001$) while no significant difference was detected between ICU and regular ward patients (3-year survival: 61.5% vs. 62.3%; $p = 0.598$) After Propensity Score Matching survival in the hospitalized groups remained significantly worse compared to non-hospitalized patients (82.1% vs. 91.0%; 69.2% vs. 83.3%; 60.3% vs. 82.1%, $p = 0.019$, $p = 0.003$, $p < 0.001$). Again, there was no significant survival benefit of regular ward compared to ICU patients. (56.5% vs. 63.8%, $p = 0.290$). Furthermore, in ICU patients, but not in patients on a regular ward, survival correlated with days spent on ICU before LT (3-year survival: 1–6 days vs. 7–14 days vs. > 14 days: 71.0% vs. 53.3% vs. 45.2%; $p = 0.012$; $p = 0.004$). These results were independent of recipient age, laboratory MELD Score, donor age and cold ischemia time as shown by Propensity Score Matching.
Conclusion: Hospitalization status before transplantation is a valuable predictor of patient survival following LT.

V039 PRESENCE OF CLASS II DSAS IS ASSOCIATED WITH DEVELOPMENT OF FIBROSIS, CHRONIC REJECTION AND GRAFT LOSS MORE THAN 10 YEARS AFTER LIVER TRANSPLANTATION

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Introduction: Recent studies have suggested a negative impact of DSA class II (DSA c II) on short term outcome of OLT recipients. Aim of this study was to

assess the prevalence of DSA c II in long-term pediatric and adult OLT recipients and their impact on graft outcome.
Methods: OLT recipients presenting to the transplant outpatient clinic of the UKE between 2013 and 2019 with a 10–21 years post op follow-up were included in the retrospective study. Patients with HCV infection and incomplete set of data were excluded. Luminex single antigen beads (LABScreen®) were used to detect anti-HLA-DR and DQ antibodies (Cut-off: MFI > 1500 U). Liver function was assessed by liver tests, ultrasound, elastography and biopsies.
Results: Altogether 156 patients (112 adults, 44 children) were analysed. 46% of patients were DSA c II positive after a median follow-up of 15 years. Of note, DSA c II positive (+) patients were significantly younger (25y vs 46y; $p < 0.001$) and had a significantly longer follow-up than DSA c II negative (-) patients (16y vs 14.y; $p < 0.002$). Most importantly, the mean liver stiffness on elastography of DSA c II + patients was significantly higher than of DSA c II- patients (9.4 ± 9.0 kPa vs 6.5 ± 6.3 kPa; $p < 0.002$). Also, DSA c II+ patients showed more often relevant parenchymal damage on ultrasound ($p = 0.069$) and had significantly higher fibrosis stages on the performed liver biopsies $n = 49$; $p = 0.002$). Also, a significant higher incidence of chronic rejections (11% vs 2%; $p = 0.045$) and graft losses (6% vs 0%; $p = 0.043$) were found in DSA c II+ patients. But there was no significant difference between DSA c II+ and DSA c II- patients with regard to early or late acute rejection episodes and biliary complications. On multivariate analysis including patients' age, time of follow-up, the use of mTOR inhibitor for at least 6 months and presence of DSA c II, the only significant risk factor for development of liver on elastography was DSA positivity (odd ratio: 5.2; $p = 0.003$).
Conclusion: In this study of long-term pediatric and adult OLT recipients, positivity of DSA c II was significantly associated with development of graft fibrosis, a higher incidence of chronic rejection and graft loss.

HEART/LUNG (INCL. PAEDIATRICS)

V040 PERSISTENCE OF DE NOVO DSA IS ASSOCIATED WITH CHRONIC LUNG ALLOGRAFT DYSFUNCTION AFTER LUNG TRANSPLANTATION

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Introduction: De novo donor-specific anti-HLA-antibodies (dnDSA) appear frequently after lung transplantation. The impact of dnDSA on chronic lung allograft dysfunction and survival is still a matter of debate. In recent studies there was a growing interest in the course over time of dnDSA after transplantation. So far, there is no standardized therapeutic approach.
Methods: We investigated the clinical relevance of dnDSA on lung allograft outcome prospectively in 133 recipients transplanted between 2013 and 2016. The median follow-up time was 36 months with a minimum follow-up time of 3 years per patient. The presence of HLA-antibodies was analyzed by Luminex Single Antigen Bead assay prior and after transplantation
Results: After transplantation 38% of the patients ($n = 51$) developed dnDSA. In 25 of these patients (49%) dnDSA persisted throughout the surveillance period whereas in 26 of these patients (51%) dnDSA disappeared early after transplantation. In one patient transient DSA turned up again. Interestingly, 78% of dnDSA appeared within the first year after transplantation. Patients with persistent DSA had a reduced survival compared to patients with transient DSA (1y-survival 72% versus 96%; $p = 0.024$ and 3y-survival 60% versus 77%; $p = 0.237$).

Bronchiolitis obliterans syndrome (BOS) occurred in 24% of dnDSA negative patients and in 42% of dnDSA positive patients ($p = 0.046$). BOS free survival is significantly shorter in patients with de novo DSA (log-rank, $p = 0.014$).

Eight patients with persistent dnDSA suffering from severe graft dysfunction were treated with plasmapheresis, IVIG and in some cases additionally with rituximab. Only in one patient DSA permanently removed. The treatment did not improve lung function in any of the patients and five patients died due to rapidly progressive graft failure.
Conclusion: Persistence of dnDSA after lung transplantation is an important risk factor for dismal survival and is associated with a higher incidence of CLAD after lung transplantation. We could demonstrate that in case of beginning transplant deterioration the treatment of dnDSA was not successfull. So now we start to treat dnDSA independently of allograft dysfunction.

V041 FURTHER STEPS TOWARDS THE DEVELOPMENT OF A BIOHYBRID LUNGE

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Introduction: The only curative therapy option for patients suffering from end stage lung diseases is lung transplantation. However, due to the shortage of suitable organs it is only available for a limited number of selected patients. Furthermore, the procedure is still associated with high risks. In order to provide an alternative treatment option, this project aims for the development of an implantable biohybrid lung (BL), based on hollow fibre membrane (HFM) technology used in extracorporeal membrane oxygenators (ECMO). Therefore, a crucial requirement to achieve long-lasting durability is the optimized bio- and haemocompatibility of all blood contacting surfaces, which can be achieved by endothelialisation.
Methods: In vitro test were carried out to compare the eligibility of Albumin/Heparin (A/H) and Fibronectin (FN) coated HFM to mediate the establishment of a viable, confluent and non-thrombogenic EC-monolayer. The activation status of seeded ECs was analysed in Leukocyte- and thrombocyte adhesion assays. In order to assess the behaviour of the HFM-seeded ECs under workload conditions, i.e. fluid flow and oxidative stress exposure, experiments in a customized flow chamber were carried out. To identify a clinically relevant EC source, comparative studies including human cord blood derived endothelial cells (hCBECs,) induced pluripotent stem cell derived endothelial cells (iPSC-EC) and immunotolerable HLA-silenced hCBECs were conducted.
Results: A viable, confluent and physiologic monolayer, could be sustained under both, static and flow dynamic culture conditions. All tested EC types preserved their non-thrombogenic and non-inflammatory status on all tested HMF coatings. Exposure to relevant levels of hyperoxia or hypoxia did not affect the physiological function of the ECs. However, FN coated HFMs demonstrated an improved EC-monolayer resistance towards flow conditions.
Conclusion: These results are the first promising steps towards the development of a BL. HLA-silenced ECs could be considered as suitable cell source, escaping the recipients immune response, while being used for sufficient endothelialisation of the FN coated HFM.

V042 EVOLUTION OF PULMONARY HYPERTENSION IN TERMINAL LUNG FAILURE

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Introduction: Hemodynamic parameters are an important diagnostic tool for patients awaiting Lung Transplantation (LTX), not only concerning prognosis and further therapeutic options but also during the procedure considering the evaluation for extracorporeal membrane oxygenation. However, hemodynamic parameters are initially conducted at time of wait listing, but there is no guideline assessing the time point of reevaluation of hemodynamic parameters. The present study aimed to assess the hemodynamic changes in patients undergoing lung transplantation between time of wait listing and LTX.
Methods: All patients undergoing LTX between 12/2011 and 12/2017 were retrospectively analysed ($n = 351$). Patients were screened for their right heart catheterization at time of listing and hemodynamic parameters during lung transplantation.
Results: There was a significant change in mPAP values from wait listing to first measured value by use of a pulmonary artery catheter at the beginning of LTX in all patients (Fig. 1). Divided by diagnosis, patients with COPD had the lowest increase in mPAP values and ILD patients showed the highest rise in mPAP values (+11.8 ± 9.9 vs 19.3 ± 13.5; $p = 0.264$; Table1). There were no differences in survival probabilities after LTX between patients divided by mPAP value at time of wait listing ($p = 0.87$ by log-rank test).
Conclusion: The is the first study assessing the changes in mPAP values from time of listing to intraoperatively measured values during transplantation. Our data suggest closer monitoring of hemodynamic changes between time of listing and lung transplantation, especially in patients with ILD.

V043 ALVEOLAR FIBROELASTOSIS IN CHRONIC LUNG ALLOGRAFT DYSFUNCTION

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Introduction: Alveolar fibroelastosis (AFE) is an increasingly recognized histological pattern of interstitial lung disease found in different life-threatening conditions after lung transplantation, but also following immune reactions after bone marrow transplantation and in idiopathic pleuroparenchymal fibroelastosis (iPPFE). However, it can also be found in clinically indolent fibrotic remodelling of the lung such as the so-called "apical cap". If fully developed it is easily distinguished from other typical patterns of tissue remodelling. However, in practice histological diagnosis can be challenging due to sampling bias, if some features are missing or if fibrotic areas are only partially represented in a biopsy specimen.

Similar problems have led to the comprehensive guidelines for the diagnosis of idiopathic pulmonary fibrosis (IPF) provided by ATS/ERS/JRS/ALAT which includes a systematic approach for histologic workup and reporting of the usual interstitial pneumonia (UIP) pattern with special consideration of partial and not fully developed changes.

We want to investigate morphological and molecular features shared between and discriminating fibroelastic remodeling of the lung.

Methods: We have evaluated over 100 lung specimens including explanted lung transplants from the archives of the Institute for Pathology (MHH) to identify morphological properties of fibroelastic remodelling of the lung.

Results: Our results indicate that fibroelastic remodeling in life threatening conditions – such as in restrictive allograft dysfunction after lung transplantation – has different morphological features compared to indolent forms.

Conclusion: We propose histologic criteria and a classification scheme for the reporting of the AFE pattern analogous to the reporting criteria for the UIP pattern. These criteria were established by systematic assessment of pathomorphological changes in surgical lung resections and explanted recipient lungs after lung transplantation with definitive AFE pattern. The proposed system helps to distinguish AFE from its histological mimics and establishes a reporting system for the histological diagnosis.

ORGAN PROCUREMENT/TISSUE DONATION

V045 0-BIOPSY & KIDNEY TRANSPLANT FUNCTION OF DONOR KIDNEYS FROM ACCELERATED ORGAN ALLOCATION PROCEDURE (AOAP): REAL, RESCUE, CENTRE OFFER, COMPARED TO STANDARD EUROTRANSPLANT KIDNEY ALLOCATION SYSTEM (ETKAS) – SINGLE CENTRE ANALYSIS

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Introduction: In December 2013, only in Germany AOAP were supplemented by a web-based system "recipient oriented extended allocation" (REAL). AOAP accounts 19% of ET kidney allocation. Donor kidney that is repeatedly rejected as non-transplantable in standard ET allocation process go into AOAP. ET offers donor kidney concurrently to several transplant centers, according to the motto "first come, first served". Hence, donor kidney may be judged being of inferior quality due to previous offer rejections.

Methods: 1. Is there a potential quality difference in pre-implant biopsy (0-Bx) of AOAP versus ETKAS kidney?

2. Is there a possible quality difference in primary function (<2 dialyses post transplant (ktx)), creatinine at discharge, at month (mo) 6, 12, 24.

12/2013–12/2017, $n = 216$ ET realised ktx at our center, 50 (23%) AOAP/166 ETKAS. In 211 cases (97.7%) 0-Bx was obtained, 23% AOAP ($n = 48$).

Results: AOAP/ETKAS: Interstitial fibrosis, tubular atrophy (IFTA): 66.7/58.9%. Arterial hyalinosis (AAH): 50.0%/35.0%. Glomerulosclerosis (gs): 45.8/44.8%. Acute tubular necrosis (ATN): 93.8/97.5%. Delayed graft function (DGF, >1 dialysis post ktx): 48.2/26.0%. Mean creatinine (mg/dl) at discharge: 2.94/1.88; 6th mo: 1.75/1.49; 12th mo: 1.67/1.45; 24th mo: 1.68/1.5.

Conclusion: Our analysis shows that kidneys of AOAP perform poorer compared to ETKAS in preimplantation phase as well as in early phase of ktx, given clearly higher proportion of IFTA, AAH in 0-Bx and higher risk for DGF. These early quality differences level out with 6th month after ktx. 2-year observation does not show significant functional difference between AOAP and ETKAS. This effect may be due to free choice of recipients that transplant center can make in AOAP. Then, donor-recipient match is independent of ET allocation criteria and allows to use center-specific matching criteria (biometric, immunologic, age-related). Our analysis calls for a multicenter study to confirm our results in general and also in longterm monitoring.

V046 DECEASED DONOR HEART CHARACTERIZATION: WHEN SHOULD WE PERFORM CORONARY ANGIOGRAPHY IN TIMES OF SCARCE RESOURCES IN DONOR HOSPITALS?

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Introduction: In donation after brain death (DBD) coronary angiography (CORO) is helpful to assess heart graft suitability. Unfortunately, the indication for CORO is not standardized within Eurotransplant countries. This results in a variety of specific demands for CORO by individual centres, implicating some challenges in donor hospitals.

In a pilot study, we applied a multivariate logistic regression to assess the effect of donor factors on the result of CORO and to evaluate whether guidance can be derived from such data for the indication of CORO.

Methods: In a research database with data collected for DBD characterization (Germany, 2006–2010, $n = 6426$) results of 797 CORO performed are available. We compared age, sex, history of arterial hypertension and smoking with reference to the impact in predicting an abnormal CORO defined as any kind of wall irregularity or stenosis ($n = 357$, 45%). Further risk factors (e.g. diabetes) could not be included due to their low frequency in the population. Reference point for odds ratios (OR) is a DBD ≥ 55 years. (vs. 45–54 years. & <45 years.), male, smoker and history of arterial hypertension (significance: $p < 0.05$).

Results: The risk decreases for obtaining an abnormal finding at the CORO in younger DBD (45–54 years.: OR 0.69, 95%CI 0.51–0.95, $p = 0.022$; <45 years.: OR 0.42, 95%CI 0.25–0.69 $p = 0.001$), DBD without history of smoking (OR 0.53, 95%CI 0.39–0.71, $p < 0.001$), DBD without arterial hypertension (OR 0.53, 95%CI 0.46–0.83, $p = 0.002$) or female DBD (OR 0.42, 95%CI 0.32–0.57, $p < 0.001$) [c-statistics = 0.64, 95%CI 0.60–0.67, $p < 0.001$].

303 hearts were transplanted from 440 DBD with normal CORO (69%) vs. 104 hearts from 211 DBD without stenosis > 50% at CORO (49%) vs. 11 hearts in 146 DBD with stenosis > 50% at CORO (8%).

Conclusion: A significant correlation exists between cumulating traditional cardiovascular risk factors and the results of CORO. Still the indication for CORO should be individualized in DBD because no predictive algorithm can be provided without further research. A limitation of the study is that data are extracted from a real DBD population exposed to some pre-test selection bias.

V047 INCREASING ORGAN DONATION: EXPERT OPINION FROM AUSTRIA, GERMANY, SPAIN AND THE UK

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Introduction: Post-mortal organ donation rates and organizational approaches to organ donation differ drastically between countries at a similar level of health care. Expert opinions from Austria, Germany, Spain and the UK on the respective system and practice of organ donation can help to improve organ donation.

Methods: Opinions from intensive care nurses, physicians, transplant coordinators and transplant surgeons in the four countries were obtained in semi-structured interviews followed by qualitative analysis.

Results: Interviews show that a variety of factors can have a beneficial effect on organ donation rates, e.g. standardized screening for potential donors, family approach and mandatory training for family approach teams. The role of ICU doctors is crucial, but they need to be supported by full-time in-house special nurses for organ donation who organize donor evaluation, transport

logistics and coordination and by pastoral workers if required. Failure to report potential organ donors should have consequences, but incentives are not effective. Awareness campaigns should encourage families to discuss organ donation. An opt-out system is likely to stimulate family discussions. Public trust can be achieved by full transparency in organ donation and transplantation and by prevention of scandals. Broad public consensus on the concept of brain death and donation after cardiac death is a sound basis for organ donation. Standards and best-practice procedures need to be regulated and supervised by state authorities.
Conclusion: A consensus between experts from four different countries and health care systems within Europe can be achieved easily on how to improve organ donation systems and organ donation rates. This advice should be used to reform organ donation systems that lack efficiency and effectiveness as well as transparency resulting on low realized organ donation rates per capita with drastic consequences for patients in need of organ transplantation.

PSYCHOSOMATICS

V048 MULTILEVEL INTERPROFESSIONAL INTERVENTION PROGRAMME FOR PATIENTS AFTER KIDNEY AND LIVER TRANSPLANTATION – A WAY TO IMPROVE MEDICATION ADHERENCE?

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Introduction: Medication adherence is a key element for a good transplant outcome. Nonetheless around 20–70% of all patients post transplant are not adherent about taking their immunosuppression. There are several factors which have impact on the adherence like previous nonadherence, side-effects, relationship to the doctor, interruption of daily routine, depressive symptomatology and lack of adherence assessment and support. Therefore a multilevel approach is necessary to manage those factors (Neuberger, 2017, p. 8).
Methods: To improve the adherence to immunosuppressive medications we developed a trans-theoretical model with the challenge of having a clinical impact, cost-effectiveness and scalability. Through an interprofessional cooperation between an advanced practice nurse and a psychiatrist a multilevel intervention programme is implemented since October 2018 at the transplant unit. The programme contains adherence assessment, a group session with behavioural and psychodynamic elements to improve the knowledge about medication, lifestyle and immune system. Before the transplantation and during their outpatient follow up medication adherence is self-reported through the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) and the tacrolimus level variability. Patients who are identified as non-adherent get outpatient follow-up with the psychiatrist.
Results: Effectiveness of this multilevel interprofessional intervention programme is getting surveyed through a randomized controlled trial starting in autumn 2019. Through the training from the nursing team beforehand awareness of the importance of this topic increased widely. The multidisciplinary concern leads to a common goal between professions and patients. Progress and implementation of the programme is discussed and evaluated every three to four months during a team meeting.
Conclusion: To implement patient education during the inpatient stay a nurse with scientific background is necessary to prepare and train the nursing team and to provide support during the implementation. To focus on the psychological aspects of adherence psychotherapeutic support is needed for the success of the programme.
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KIDNEY II

V053 IMMUNOLOGICAL CHARACTERISTICS OF PREIMPLANTATION BIOPSIES DETECT RENAL ALLOGRAFTS AT RISK FOR FUNCTIONAL IMPAIRMENT

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Introduction: Antibody mediated rejection (ABMR) in kidney allografts is the main reason for loss of graft and long term function. Macrophages contribute to ABMR. Knowledge about immunological characteristics of preimplantation biopsies (0-Bx) and their relation to future graft function is poor.
Methods: Kidney transplant biopsies ($n = 198$) from 37 patients (from two university hospitals, 57% male, 43% female, average age at time of transplantation 49.6 $\pm$ 14.9 years) including the 0-Bx were re-evaluated according to actual Banff criteria and stained for macrophages (Pan: CD68, M2: CD163, CD163L1, CD206), dendritic cells (DCs; CD209), T cells (CD3) and B cells (CD20). The biopsies were analyzed digitally as whole slide images for immunopositively stained area (pixel based approach; % per region of interest; QuPath). Renal cortex, medulla and extrarenal tissue were evaluated separately.
Results: Cortical M2 macrophages (CD163 and CD206) showed higher densities in 0-Bx of grafts with delayed function ($p < 0.05$). Neither donors' age nor cold ischemia time (CIT) revealed an association with initial graft function. Renal cortical B cells and medullary B cells and M2 macrophages (CD206 and CD163L1) in 0-Bx correlated with donors' age ($p < 0.05$). Medullary macrophages (CD68) correlated with creatinine of donors ($p < 0.05$).

In follow-up biopsies, ABMR was associated with a higher density of cortical $CD68^+$ and $CD163^+$ macrophages ($p < 0.01$) and also medullary T cells and $CD68^+$ macrophages ($p < 0.05$) compared to biopsies without rejection. Medullary DCs were less dense in ABMR than in T cell-mediated rejection ($p < 0.05$). Combined rejections revealed higher densities of cortical DCs (CD209) and $CD163^+$ macrophages than rejection-free biopsies ($p < 0.05$). Assessing the clinical parameters, we found that renal cortical CD163 inversely correlated with estimated glomerular filtration (eGFR; $p < 0.05$).
Conclusion: In conclusion, immunological analysis of 0-Bx can detect grafts with higher risk for future functional impairment: M2 macrophages in 0-Bx might predict initial graft function. In follow-up samples, ABMR is associated with high macrophage density and high numbers of M2 macrophages are connected with impaired graft function.

V054 IMPACT OF DE NOVO ANTI-HLA DSA IN A COHORT OF 88 LIVING-DONOR RENAL TRANSPLANT RECIPIENTS: A FOLLOW-UP OF A RETROSPECTIVE STUDY

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Introduction: Our previously reported retrospective analysis showed inferior allograft outcome in patients with de novo donor-specific anti-HLA antibodies (DSA) in a cohort of 88 consecutive living-donor renal transplantations. Aim of the current study was, by focusing on the group of DSA positive patients to closely follow the course of DSA and to determine risk factors for DSA persistence. Furthermore, we compared the long-term outcome of patients with DSA persistence to patients with transient or without DSA positivity.
Methods: Patients underwent HLA IgG antibody testing by Luminex solid phase assay pre-transplant and post-transplant. All patients were DSA negative at time of transplantation. Post-transplant testing was performed at least twice, first to determine DSA status and second to determine the course of DSA. Graft survival was assessed up to 128 months post-transplant
Results: The DSA course was followed in all thirty-one DSA positive patients (35%). Seventeen patients (55%) showed DSA persistence. Patients with DSA persistence showed a higher rate of class II antibodies (primarily DQ, 59%, $p = 0.02$) and higher initial and follow-up MFIs (mean 4747, $p = 0.03$). In

contrast all patients with transient DSA positivity showed in general low initial MFIs, which became negative during the follow-up. Developing DSA persistence in our cohort meant inferior allograft function (mean creatinine: 1.9 mg/dl, $p = 0.079$), allograft survival (log-rank $p = 0.001$) and a higher rate of acute rejection episodes ($p = 0.073$) during long-term follow up.
Conclusion: In our cohort of living donor transplant recipients, the course of DSA was highly diverse after its onset. We identified antibody-based factors for persistent and transient DSA positivity. This is of great importance, given the varying outcome in patients of these two groups. This finding emphasizes that the appropriate clinical management of DSA positive patients after living donor renal transplantation should include evaluating the strength of the antibody (initial MFI) and following the course of DSA with additional antibody testing.

V055 EUROTRANSPLANT SENIOR PROGRAM (ESP): RISK FACTORS, GRAFT AND PATIENT SURVIVAL

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Introduction: In 1999 Eurotransplant started the European Senior Program (ESP), a special kidney allocation program for recipients and donors older than 65 years.
Methods: In our retrospective study we analysed 125 ESP patients transplanted in the university clinic Frankfurt between 2005 and 2014. The aim of our study was to identify risk factors for patient and graft survival. In addition, infectious complications during the first year after transplantation were analysed.
Results: 1-year patient survival rate was 93% and 3-year survival rate was 83%. Delayed graft function (DGF) ($p < 0.001$) as well as rejections ($p = 0.016$) were identified as risk factors for patient survival. Risk of graft loss was associated with cold ischaemia time (CIT > 10 h: 3-fold higher risk, $p = 0.024$), incidence of delayed graft function (DGF, 3.15 higher risk; $p < 0.001$) and episodes of rejection (5.4-fold higher risk, $p < 0.001$). Moreover DGF was correlated with a prolonged warm ischaemia time ($p < 0.001$) and significantly lower GFR at discharge from hospital ($p < 0.001$). Patients who received HLA class II (DR locus) mismatched grafts had a higher incidence of DGF ($p = 0.032$) and rejections ($p = 0.025$). Patients who received their graft from 2010 to 2014 suffered fewer infections ($p < 0.001$) during the entire first year after kidney transplantation, especially fewer CMV infections due to a CMV prophylaxis with valganciclovir after 2010. Interestingly recipients suffering from infectious complications during their hospital stay after transplantation had significantly lower $CD4^+$ T cell counts during the first week after transplantation.
Conclusion: Patient survival was reduced by the occurrence of DGF and/or rejection and as DGF and rejection rates were correlated with HLA-DR mismatches, DR-matching in the ESP might improve graft and patient survival. In addition a lower infection rate may be achieved by a determination of $CD4^+$ cell count especially in the first weeks after kidney transplantation and by the use of CMV prophylaxis.

LUNG

V056 DONOR T AND NK CELLS ARE DERIVED FROM THE DONOR LUNG PARENCHYMA AND REPRESENT A SUBSET OF TISSUE-RESIDENT MEMORY CELLS

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Introduction: In previous studies, we identified donor lymphocytes in peripheral blood of recipients directly after transplantation that expressed the retention marker CD69. In this study we aimed to determine the origin of those cells and to analyze whether they have a tissue-resident memory phenotype.
Methods: Donor lymphocytes in recipient blood were determined in 27 lung transplant patients at T0, T24, 3 weeks by staining of donor HLA class I molecules in combination with lineage- and tissue-specific markers using multicolor flow cytometry. The phenotype of T and NK cells in perfusates, donor trachea and recipient explanted parenchyma was compared to circulating cells.
Results: In peripheral blood of all lung transplant recipients, donor derived T and NK cells were detected and had higher CD69 expression compared to recipient cells and were mostly $CD25^-$. T cells from trachea and parenchyma also showed high CD69 expression and a significant enrichment of effector memory ($CCR7^-$ $CD45RO^+$) T cells. In these compartments, $CD69^+$ T cells showed coexpression of other tissue residency markers such as CD103, CD49a and PD-1, while these were not found in perfusates, highlighting the differences between these compartments.
Conclusion: Our results suggest that donor T and NK cells found in the periphery of lung transplant recipients are derived from lung parenchyma and represent a subset of tissue-resident memory cells. These cells might be clinically relevant for tolerance induction after transplantation.

V057 TOLERANCE INDUCTION BY DELAYED NON-MYELOABLATIVE IRRADIATION IN A LARGE ANIMAL LUNG TRANSPLANTATION MODEL

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Introduction: We induced longterm allograft acceptance in our allogeneic lung transplantation (LTx) model in miniature swine. Animals underwent perioperative non-myeloablative irradiation combined with the infusion of donor specific alloantigen. To improve clinical applicability, we delayed induction with IRR
Methods: Left sided single LTx from MHC mismatched male donors was performed in 22 female minipigs. Group1 (preOP, SpTx POD0; $n = 7$) received non-myeloablative IRR (7 Gy thymus +1.5 Gy whole body IRR) 12 h before LTx and a perioperative donor specific splenocyte infusion (SpTx). Group2 (SpTx POD0, IRR POD3; $n = 3$) received perioperative SpTx and delayed IRR on POD3. Group3 (IRR POD3; $n = 8$) was exposed to delayed IRR without SpTx. Group4 (Control; $n = 4$) underwent no induction therapy at all. Immunosuppression was maintained for 28 days with tacrolimus and methylprednisolone in all groups. Graft survival was monitored by bronchoscopy and chest x-rays. Frequencies of $CD4^+CD25^{high+}$ $Foxp3^+$ Treg were monitored by flow cytometry. Peripheral blood leukocyte chimerism was quantified by qPCR
Results: Whereas 4 out of 7 animals from group1 never rejected their grafts and were electively sacrificed on POD 600+, 3 out of 8 animals from group IRR POD3 turned into longterm survivors. All animals from group2 rejected their grafts until POD108. In group4, only 1 out of 4 animals did survive longterm. In all groups, donor cell chimerism peaked up to 20% after reperfusion of the lung. Whereas levels in groups 2–4 constantly decreased thereafter, chimerism in group1 started rising again from POD7 onwards. Relative putative Treg cell counts were significantly higher in group3 compared to group 4
Conclusion: Delayed IRR has the potential to improve longterm graft survival compared to untreated controls, as long as no SpTx is administered before IRR. Even though survival in group preOP, SpTx POD0 is superior to group IRR POD3, we could again prove that IRR spares the proregulatory $CD4^+CD25^{high+}$ $Foxp3^+$ T cell subtype, resulting in a favorable immunological state. The lacking establishment of longterm donor cell coexistence in the delayed IRR group indicates, however, that long term stability of tolerance might be compromised

V058 LETERMOVIR FOR DIFFICULT TO TREAT CYTOMEGALOVIRUS INFECTION IN LUNG TRANSPLANT RECIPIENTS

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Introduction: Cytomegalovirus (CMV)-infection remains a major cause of morbidity and mortality after lung transplantation. Treatment with currently available drugs poses treatment difficulties in some patients due to drug resistance or intolerability.
Methods: We report a series of seven lung transplant recipients with CMV-infection (6x high risk D+/R- and 1x intermediate risk D+/R+) and treatment failure upon standard care due to antiviral drug resistance and treatment limiting side effects. Genotypic testing for ganciclovir (GCV)- and foscarnet (FOS)-resistance using sequencing of sections of UL97-gene and UL54-gene revealed a GCV-associated resistance in six cases. One patient developed an allergic reaction after initiation of ganciclovir. As rescue therapy letermovir, recently approved for the prophylaxis of CMV-infection in patients after hematopoietic stem cell transplantation was initiated. Patients received 480 mg per day for a follow up of 29.7 ± 17.8 weeks. Efficacy and tolerability

was assessed retrospectively. CMV-specific immunity was measured by use of T-Track® CMV (Lophius Biosciences GmbH, Regensburg, Germany). Immunity and resistance testing was performed on request of the treating physician.
Results: Mild nausea, vomiting and diarrhea were the only side effects of letermovir reported by a single patient. None of the patients developed atrial fibrillation or flutter. Myelotoxic and nephrotoxic events did not occur or were not aggravated, respectively. Organ biopsies revealed CMV gastritis in two cases and CMV pneumonia/colitis in one case. A small adjustment of the tacrolimus dose was mandatory upon treatment initiation with letermovir. In two cases immunosuppression was switched to quadruple immunosuppression regimen. CMV-viral load could be decreased and cleared subsequently in all patients. CMV clearance was observed after 14.4 ± 13.7 weeks despite lack of CMV-immunity.
Conclusion: CMV-infection and –disease were successfully managed with letermovir. Letermovir was well tolerated and effective in treating CMV-infections in lung transplant recipients failing on currently available antiviral agents.

IMMUNOLOGY II

V059 FORMATION OF ALLOANTIBODIES AGAINST NK CELL ANTIGENS IN PATIENTS AFTER SOLID ORGAN TRANSPLANTATION

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Introduction: Chronic antibody-mediated rejection (ABMR) is known to play a key role in graft survival, dysfunction or rejection and is still a major obstacle in transplantation success. Recent studies have shown the importance of non-HLA antigens in the formation of donor-specific antibodies (DSA) in graft rejection. Previous experiments revealed the presence of allospecific antibodies against antigens encoded in the NK cell gene complex (NKC) and leukocyte receptor gene complex (LRC) in 23% of plasma samples from liver and kidney recipients ($n = 92$).

The current study further investigates the frequency and relevance of these alloantibodies and their role in transplantation outcome in patients after solid organ transplantation of kidney, lung and liver.
Methods: The extracellular domain gene sequences of NKG2C, KIR2DL2, KIR2DS2, KIR2DS1, KIR2DL1 and LILRB3 followed by a V5/His-tag were cloned into a lentiviral vector. HEK293 cells were transduced with the vector encoding for the different vectors for the mass production of soluble proteins and expanded in the CELLine bioreactor flasks. Proteins were isolated from 500 mL cell culture supernatants using affinity chromatography. The recombinant proteins were coupled to differentially colored-multiplex beads which were then used to screen patient plasma for the presence of antibodies using FACSCanto II flow cytometer.
Results: Overall, antigen-allospecific antibodies against various NKC- and LRC-encoded receptors such as NKG2C, KIR2DL2/DS2, KIR2DS1/DL1 and LILRB3 were found in 20% of Kidney recipient patents ($n = 15$), 19% of liver recipient patients ($n = 42$) and 17% of lung recipient patients ($n = 41$).
Conclusion: The data indicate a high degree of potential mismatch in NK cell diversity between donor and recipient in the case of solid organ transplantation. Further analysis is being performed to evaluate the functional consequences and clinical relevance of these antibodies in transplantation outcome.
Acknowledgement: Supported by DFG grant SFB738/A5
The last two authors contributed equally to this study.

V060 RECIPIENT NATURAL KILLER CELLS ALTER THE COURSE OF REJECTION OF ALLOGENEIC HEART GRAFTS IN RATS

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Introduction: Rejection of solid organ grafts is regarded to be dependent on T cell responses. Nonetheless, numerous studies have focused on the contribution of NK cells in this process, resulting in contradictory theories. While some conclude that there is no participation of NK cells, others found an inflammatory or regulative role of NK cells. The aim of the present study was to evaluate the hypothesis that NK cells react to allogeneic grafts and upon activation interfere with T cells in a suppressive manner.
Methods: We performed heterotopic heart transplantation (HTx) in congeneic Lewis rat strains, selecting one donor-recipient-combination leading to a fast (Lew.1a → Lew wt) and a second leading to a prolonged course (Lew.1u7B → Lew.1a) of graft rejection. We intervened in the rejection process, by depletion of recipient NK cells and by injection of activated NK cells syngeneic to the recipient, respectively.
Results: The fast course of organ graft rejection could not be influenced by the NK cell manipulative treatments. However, the more prolonged course of rejection was highly susceptible to depletion of NK cells, resulting in significant acceleration of rejection. Injection of NK cells on the other hand, induced acceptance of the grafts and led to significantly diminished fractions of graft infiltrating activated T cells, monocytes and macrophages.
Conclusion: In this study, we provide evidence that NK cells are regulative agents, able to control T cell activity during rejection of completely MHC-disparate grafts. This observation however, was dependent on the chosen strain combination.
Acknowledgement: This abstract along with the corresponding data was submitted to the journal of the Public Library of Science (PLOS ONE) and is currently under review.

V061 EFFECT OF RITUXIMAB AND BORTEZOMIB TREATMENT ON THE CELLULAR IMMUNITY IN KIDNEY TRANSPLANT PATIENTS WITH HUMORAL REJECTION

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Introduction: Humoral rejection is an important cause of early and late graft loss triggered mainly by B cell immunity. Different therapeutic approaches modulating the immune system have been applied so far without a clear preference for one of the strategies or for their effects on the immune system.
Methods: Here, we performed a small single center prospective study using Rituximab or Bortezomib to counteract B cell immunity. The aim of this study is to compare the effect of Rituximab or Bortezomib treatment on the immune system in patients with humoral rejection. The immune phenotype of patients with humoral rejection after renal transplantation were analysed before the therapy initiation, and 6 months thereafter. We measured the main immune cell types and performed an in-depth characterization of B cell, dendritic cell (DC) and regulatory T cell (Treg) phenotypes.
Results: The immune phenotype of patients with humoral rejection was similar in both therapy groups before therapy initiation. We found no differences in the frequency of the main immune cell types or any B cell-, DC- or Treg subpopulations. 6 month follow up analysis demonstrated a significant decrease of B cell number in the Bortezomib group and nearly non-existent B-cell count in the Rituximab group. Furthermore, we found a significantly increased frequency of $BDCA3^+$ myeloid DCs type 2 (mDC2) in patients with Rituximab therapy compared to Bortezomib treated patients. Additionally, we found significant differences in developmental stage of Treg subpopulations in patients with Bortezomib therapy. Thus effector memory $CD4^+$T reg cells were significantly reduced, whereas the frequency of naïve $CD4^+$T cells was significantly increased compared to pretreatment values and to the Rituximab therapy group.
Conclusion: We demonstrate first insights into the immune system changes occurred under rituximab and bortezomib therapy in patients with humoral rejection. Further studies are required to evaluate clinical and immunological long-term effects.

ORGAN DONATION

V062 TRANSMISSION OF INFECTIONS FROM ORGAN DONOR TO RECIPIENT – GERMAN DATA/EXPERIENCES

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Introduction: Vigilance monitoring after organ transplant includes Serious Adverse Events (SAE) and Serious Adverse Reactions (SAR). All SAE/SAR

related to deceased organ donors from German and recipients in Germany have to be reported to the German Foundation for Organtransplantation (DSO).

SAE describe delayed findings in the donor or in donor substances after transplant that pose a certain *risk of harm* to the already transplanted recipients of this specific donor.

SAR refer to *harm that has occurred* to one or more recipients of the same donor and that is suspicious of being associated with the donor organ.

Methods: Analysis of total reported SAE/SAR regarding infections from 1/2016 to 12/2017.

Results: 52 donor-associated pathogens (SAE) were detected in different samples: donor blood (5), swabs (6), BAL (14), not-transplanted organs (2) or organ transport fluid (25). The pathogens were bacterial (43 incl. 6 multidrug resistant (MDR) and one Mycobacterium), fungal (7), viral (1 (HCV)) and 1 unidentifiable. 1 donor with occult HCV-infection transmitted HCV to all 5 recipients. These recipients were cured by immediate therapy. In addition 1 VRE was found and 1 C. albicans in a kidney recipient. None of the other pathogens have been shown to be transmitted.

From donors outside Germany, 30 donor pathogens have been reported as SAE: bacterial (25 incl. 5 A. baumannii and one M. tuberculosis), fungal (3), viral (2) without transmission.

Regarding SAR, 17 pathogens were described to cause suspected donor-transmitted infections: bacterial (5), viral (5), fungal (4) and undetermined sepsis (2). 3 of those were confirmed/probable to be of donor origin (Bornavirus/3 recipients/2 deceased; 2 Candida species/2 recipients/alive), 4 were possibly of donor origin, 7 unlikely and in 2 cases donor origin was excluded.

Conclusion: Previously undetected and transmissible donor infections may be the cause of fulminant and life-threatening infections in recipients. Therefore, detailed reporting and national and international analysis of SAE/SAR is crucial to learn more about the risk of donor-derived infections and possible consequences on organ acceptance.

V063 COMPREHENSIVE ANALYSIS OF THE GERMAN DONOR POPULATION: STEATOSIS HEPATIS AND OTHER CHALLENGES

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Introduction: Despite recent efforts to increase the number of donors for organ transplantation, there is still a substantial mismatch between supply and demand of suitable allografts. In Germany, the outcome of liver transplantation is increasingly limited by graft quality. The future development of strategies to deal with organ scarcity requires an update on the key reasons for non-acceptance of liver allografts.

Methods: We therefore analyzed the characteristics of all 6848 reported liver donors in Germany between 2010 and 2016 and the histopathological report of liver biopsies, which were present in 2699 cases (41.6%).

Results: Of all 6848 donors, 966 (14.1%) were not transplanted and 475 (49.17%) not procured at all. Throughout this time period, the overall number of liver transplantations in Germany dropped by 34.2% from 1072 in 2010 to 705 in 2016. Additionally, there was a trend towards a more frequent demand for histopathological reports, from 34.3% in 2010 to 47.9% in 2016 ($p < 0.001$), indicating cases of unclear donor characteristics or macroscopic appearance. Donors from livers not transplanted were significantly older (61 vs. 54 years; $p < 0.001$), presented with higher grades of steatosis hepatis (30% vs. 7.5%; $p < 0.001$), higher aspartate aminotransferase levels (91U/l vs. 64U/l; $p < 0.001$) and more alcohol abuse (29.9% vs. 15.6%, $p < 0.001$).

Conclusion: Future concepts to counteract organ scarcity will need to address the aforementioned characteristics of the current donor pool, since age, steatosis hepatis and elevated liver enzymes can all lead to early allograft dysfunction. An update of the pre-transplant assessment and acceptance policies might be necessary to optimally use the available organ pool.

ETHICS

V065 PUBLIC CONFIDENCE OR PUBLIC ACCEPTANCE? REFLECTING THE ROLE OF TRUST IN BODILY DONATIONS FROM AN ETHICAL PERSPECTIVE

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Introduction: When the organ allocation scandal in Germany made headlines in 2012, transplantation medicine attracted attention in academic and political discourse. Both media and researchers claimed that "public mistrust" significantly caused a decline in organ donations. Even though the absolute number of post-mortem donors had started to decrease before this scandal, it was only after this disruptive event that new control and monitoring bodies have been set up with the intent to increase trust.

Methods: Our contribution reconstructs the concept of trust from an ethical perspective. Thereby, we unfold the complex interdependencies of trust, mistrust, and the willingness to donate. We distinguish morally loaded references to trust from primarily strategically motivated uses.

Results: Conventional wisdom holds that corrective measures will promote people's willingness to donate organs. However, this understanding tends to ignore two important things, which we want to illustrate by looking at organ donation for transplantation and tissue donation for research. First, more factors than trust are at work in determining the (un)willingness of donors. Second, trust is not only a rational belief that a person or institution will behave in a certain way but also an emotional attitude. A trusting person (trustor) assumes that another person or institution (trustee) is acting in her interest. Mistrust arises when the trustor expects or has already experienced that the trustee disregards her values and interests. For bodily donations, these aspects of trust and mistrust are of great relevance: Tissue donors must trust that research will achieve its promised goals. Organ donors must trust that both the medical community and their relatives will respect their preferences at the end of life. In both cases, relevant medical actors and institutions are gatekeepers to trust. Moreover, medical professionals, recipients, and donors' relatives also need to trust the system.

Conclusion: We conclude that corrective measures need to take the emotional dimension of trust into account and to strengthen the commitment of medical professionals. Not least, a critical discourse needs to reflect the multiple addressees of appeals for "more trust."

V067 PUBLIC PREFERENCES FOR THE ALLOCATION OF DONOR ORGANS FOR TRANSPLANTATION: PRINCIPLES OF DISTRIBUTIVE JUSTICE

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Introduction: Deceased donor organs are a scarce resource because of a large mismatch between supply and demand. This scarcity leads to an ethical dilemma, forcing priority-setting of how these organs should be allocated and who should be considered to receive a suitable organ. A systematic review and focus groups were performed to determine public preferences in regard to ethical aspects of distributive justice.

Methods: For the systematic review, the databases PubMed, Web of Science, EBSCO and PsycINFO were searched for literature published between January 2000 and December 2018. Only original studies were selected. For the focus groups discussions, participants were recruited via Hannover Medical School event series "Patientenuniversität" and online advertising. Transcripts were analyzed thematically. All identified and discussed criteria were grouped into a self-developed matrix according to the principles of distributive justice.

Results: Overall, 9,645 references were identified, and 15 studies represented in 16 publications were included. In total, 27 criteria clustered in seven theory-guided groups could be identified: "equality", "effectiveness/benefit", "medical urgency", "own fault", "value for society", "medical background" and "sociodemographic status". It was shown that not only a single principle but rather a combination of principles are relevant for the allocation. Six focus groups with 31 participants were conducted. Four major themes emerged: fairness and opportunity to get an organ, saving and improving most lives, lowering the risk of lost opportunities and own fault. Important considerations were compatibility, high chance for a successful transplantation and favoring those with a positive lifestyle and compliance.

Conclusion: The public not only wanted to allocate organs mainly to those with a good probability of having a successful transplantation but also wanted to consider those who need an organ most urgently. Clear trade-offs between effectiveness/benefit and medical urgency were important, but are still lacking. These preliminary studies result in a discrete choice experiment to elucidate public preferences in organ allocation.

MACHINE PERFUSION

V069 SHORT-TERM REWARMING KIDNEY PERFUSION AFTER COLD STORAGE – ROLE OF ERYTHROCYTES

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Introduction: Preservation/reperfusion injury still represents a notable issue after kidney transplantation. Short term (1–2 hours) normothermic reconditioning by machine perfusion after cold storage has shown beneficial effects in renal transplantation models. Best results were obtained using controlled increase in temperature. Systematic investigations concerning the inclusion of washed erythrocytes as oxygen carriers are lacking in this context.
Methods: Porcine kidneys were subjected to 20 h of static cold storage. Prior to reperfusion, grafts were put on a machine for 2 h of oxygenated (95% O_2; 5% CO_2) rewarming perfusion with gentle elevation of the perfusion temperature from 10°C to 35°C during the first 90 min. In one group ($n = 6$) washed erythrocytes were added to the perfusate after temperature has reached 20°C; the other group ($n = 6$) run without additives. Control kidneys ($n = 6$) were reperfused without treatment after cold storage.
Results: Upon reperfusion *in vitro*, a huge functional benefit of the machine perfusion was documented by more than twofold improvement of renal clearance of creatinine, urinary protein loss, fractional excretion of sodium, efficiency of oxygen utilization (TNa/VO_2) and a significant reduction of innate immune activation (HMGB1, tenascin C, expression of TLR4) compared with the controls. However, no advantage could be obtained by the addition of erythrocytes and inner cortical tissue pO2 always remained above normal values upon cell free machine perfusion.
Conclusion: In conclusion, our data strongly argue in favor of a rewarming perfusion of cold stored donor kidneys but do not substantiate an indication for adding oxygen carriers in this particular setting.

V070 USE OF EX VIVO LUNG PERFUSION FOR LUNG TRANSPLANTATION – MID-TERM RESULTS FROM A SINGLE CENTER

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Introduction: Ex vivo lung perfusion (EVLP) offers a unique potential in evaluation, optimization and transplantation of lungs that would otherwise rejected. Between 2016 and 2019 140 lung transplants (LTx) were performed and 18 donor lungs were evaluated by EVLP. Aim of the study was to compare mid-term results in LTx recipients with or without the use of EVLP.
Methods: In a retrospective single-centre analysis data from a prospectively collected database were analysed. The EVLP group ($n = 14$) consisted donor lungs classified as marginal, that were evaluated by EVLP. The non EVLP group ($n = 14$) consisted of conventional LTx recipients matched for age and pulmonary disease. Both groups were compared for the endpoints survival, primary graft dysfunction, rejection episodes and chronic allograft dysfunction.
Results: Recipient age was 55 ± 6 years in EVLP group and 56 ± 5 years non EVLP group (n.s.). The rate PGD grade 1 at 72 h post-LTx was 14% in both groups (each2/14). In the non-EVLP group, 7% (1/14) developed PGD2 and in the EVLP group 14% (2/14) PGD3 at 72 h post-LTx (n.s.).

At last visit, post-LTx, forced expiratory volume in 1 s (FEV1%) as percentage of predicted best was similar in the EVLP and non-EVLP group (78% and 80%) (n.s.). Chronic lung allograft dysfunction was diagnosed in 2 non EVLP patients during follow up post-LTx. In EVLP group 2 patients had rejection episodes and 5 patients in the non EVLP group (n.s.). Overall survival was 79% (3/14) in both groups (n.s.).
Conclusion: These results show that recipients transplanted with donor lungs that were evaluated by EVLP can be transplanted with similar outcome as in conventional LTx regarding rate of primary graft dysfunction, lung function parameters, rejections and survival.

V071 NORMOTHERMIC EX-VIVO KIDNEY PERFUSION IMPROVES FUNCTION OF KIDNEY GRAFTS DONATED AFTER CARDIAC DEATH COMPARED TO COLD STORAGE PRESERVATION TECHNIQUES

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Introduction: To increase the donor pool, better preservation strategies for the storage of marginal kidney grafts are crucial. Currently, kidney grafts are either stored on ice (SCS) or perfused at 4 degrees Celsius without oxygen (HMP). Various recent studies showed evidence for improved graft function after transplantation when oxygen is provided during machine perfusion. Moreover, over the last years, a novel technique, normothermic ex vivo kidney perfusion (NEVKP), was developed with promising results regarding graft function and survival. We compared NEVKP with oxygenated HMP (HMPox) and static cold storage (SCS) in a porcine kidney autotransplantation model.
Methods: After 30 minutes of warm ischemia, porcine kidneys were removed and either stored on ice or preserved with HMPox or NEVKP for 16 hours, followed by autotransplantation ($n = 5$ per group). Animals were followed for 8 days and graft function was assessed.
Results: Postoperative graft assessment demonstrated improved graft function with more rapid recovery for the NEVKP preserved grafts compared to HMPox and SCS groups (mean peak serum creatinine: 3.66+/-1.33 mg/dl on POD1, 8.625+/-2.74 mg/dl on POD2, and 12.9+/-2.19 mg/dl on POD3), respectively. Differences in daily serum creatinine levels are significant between NEVKP and HMPox on day 1 and 2 ($p = 0.004$, $p = 0.021$), between HMPox and SCS on day 3 ($p = 0.03$) and between NEVKP and SCS on days 1 to 4 ($p = 0.004$, $p < 0.001$, $p < 0.001$, $p = 0.022$). Moreover, on postoperative day 3, creatinine clearance was increased in the NEVKP group.
Conclusion: In a DCD model of renal autotransplantation, grafts preserved with NEVKP demonstrated significantly better function compared to both static and oxygenated machine cold storage. However, grafts preserved with oxygenated HMP showed improvement over SCS. NEVKP appears to offer better preservation in DCD grafts compared to cold preservation techniques.

V072 FIRST EXPERIENCE USING THE ORGAN CARE SYSTEM IN HIGH/RISK HEART TRANSPLANTATION

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Introduction: Heart transplantation today meets new challenges. Due to organ shortage, extended donor criteria organs are used and surgeons are faced with an increasing number of high risk recipients under mechanical support. Donor organ machine perfusion allows continuous perfusion of the heart, thus reducing time of ischemia as well as allowing for evaluation of the organ. Aim of this study was to evaluate results of the introduction of the Organ Care System (OCS).
Methods: In a retrospective single-center study data from a prospectively collected database were analysed. From July 2018 to April 2019 three patients were transplanted after organ retrieval using the OCS. The system was used based on 1) high risk donor constellation: estimated ischemic time > 4 hours, cardiac arrest, catecholamine therapy > 0.25 µg/kg/min, LV-EF < 45%, coronary vessel disease, LV hypertrophy, evaluation of retrieval surgeon 2) on recipient constellation: mechanical circulatory support, pulmonary hypertension. In-hospital survival, major adverse events, graft function after 7 days, rejection episodes and overall survival were analyzed.
Results: All patients survived up to day. One patient needed A/V ECMO for 6 days. Graft function after 7 days was good, endomyocardial biopsies showed no rejection or mild rejection 1R (1 patient at 3 months surveillance biopsy. One patient needed laparotomy due to ischemic colitis.
Conclusion: Use of the OCS in heart transplantation is a safe method to allow for optimal settings in high risk constellations. Reduction of cold ischemia time and the possibility to assess organ function should increase the number of acceptable donor hearts via utilization of extended organs, reduction of distance limitations and more relaxed surgical preparation of patients on mechanical circulatory support.

QUALITY ASSURANCE & ECONOMY

V073 ORGAN SHORTAGE, PATIENT SURVIVAL AND WAITING LIST MORTALITY – DEVELOPMENTS SINCE IMPLEMENTATION OF MELD-BASED LIVER ALLOCATION IN GERMANY

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Introduction: The Model for End-stage liver disease (MELD) based allocation system has been implemented in Germany in 2006 in order to reduce waiting list mortality. Purpose of this study is to evaluate post-transplant outcome and waiting list mortality – especially under the aspect of increasing organ shortage in Germany.
Methods: All patients undergoing liver transplantation (LT) in Germany from 2004 to 2015 were assessed retrospectively using the electronic record system of Eurotransplant (ET). The study period was divided into three time sections (A: Pre-MELD 2004–2006; B: post-MELD low donor 2007–2010; C: post-MELD high donor 2011–2012). During this period 21444 patients were registered patients on the waiting list for liver transplantation in Germany.
Results: From 2004 to 2015 a total of 12762 LTs were performed in Germany. After MELD implementation, the median matchMELD at time of LT increased from 17 to 28 in 2015. Donation rate increased after 2004 and remained stable from 2006 to 2011 (around 14 per million inhabitants), but decreased afterwards considerably to 10.4 organ donors/million in 2015. Compensatory, during this period, median donor age increased from 44 to 53 years ($p < 0.001$) and the percentage extended donors (age $\geq$ 65 years) increased from 11.1% to 25.4%. The ratio of used liver donors to reported donors was found to be notably higher in Germany (around 85% since MELD implementation) compared to other ET countries (around 77%). Comparing the different time periods 3-year patient survival in group A was 72.2%, 67.4% group B in group B and then remained constant at 69.1% in group C 2011–2012 (A vs. B, $p < 0.001$; B vs. C, $p = 0.282$). When analyzing patients who died on waiting list or were removed due to poor health status (=mortality), the absolute number was constant over the years (median 388; IQR 334–470; $p = 0.63$). However, the quotient of mortality and actively listed patients increased noticeably from 0.16 to 0.26 ($p = 0.0045$).
Conclusion: Organ shortage lead to looser acceptance of marginal organs since MELD implementation. Despite an initial increase of organ donors survival declined after MELD implementation in Germany with no benefit for waiting list mortality.

IMPROVED IMMUNOSUPPRESSION AND TOLERANCE

V076 INCREASED POPULATION OF CMV-SPECIFIC CD4$^+$ T-CELLS IN DE NOVO KIDNEY TRANSPLANT PATIENTS YIELDING CMV PROTECTION: RESULTS OF EVEROLIMUS VS STANDARD TACROLIMUS-MPA TREATMENT IN 12 MONTHS ATHENA STUDY

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Introduction: After *de novo* kidney transplantation [KTx], many recipients undergo CMV (re)activation resulting in CMV infections. Clinical evidence showed that mTOR inhibitors such as everolimus [EVR] can decrease CMV reactivation rates, though the mechanism is not yet fully understood. In the 12M ATHENA trial and designated CMV-substudy, differences in CMV-specific T-cells and CMV-replication were evaluated for EVR-based therapy vs standard tacrolimus-mycophenolic acid [TAC-MPA] treatment.
Methods: For ATHENA, the largest European prospective, open-label KTx study, 612 patients (pts) were randomized 1:1:1 at the time of KTx to TAC+MPA, EVR+TAC, and EVR+CyA (Cyclosporine A) arms. Across the groups, CMV-donor[D]/recipient[R] status at baseline was well balanced and for D+/R- and D+/R+ pts, a 3M valganciclovir prophylaxis was mandatory. In the CMV-substudy, samples from 121 pts were taken prospectively for CMV-specific stimulation assays. For all on-treatment pts at M12, cytokine profiling and expression of functional anergy markers (CTLA-4; PD-1) was done on stimulated CMV-specific CD4$^+$ T-cells by flow-cytometry.
Results: In ATHENA, significantly less KTx pts receiving EVR-based therapy acquired CMV infections compared to TAC+MPA pts (21%TAC+MPA, 6% EVR+TAC, 3%EVR+CyA; $p < 0.01$). Moreover, stimulated CMV-specific CD4$^+$ T-cell analysis showed: median CTLA-4 & PD-1 expression was significantly lower in EVR+CyA and EVR+TAC pts samples as opposed to TAC+MPA pts (median CTLA-4 MFI: 463 ($n = 8$), 744 ($n = 16$), 1282 ($n = 28$); $p = 0.02$ and $p = 0.05$, respectively) (median PD-1 MFI: 320 ($n = 8$) 227 ($n = 15$), 351 ($n = 28$); $p = 0.59$ and $p = 0.02$, respectively). Further, the proportion of multifunctional IL-2, IFNγ, and TNFα triple-positive CMV-specific CD4$^+$ T-cells was higher in samples from EVR+CyA and EVR+TAC pts than in samples from TAC+MPA pts (median: 27% ($n = 8$), 28% ($n = 16$), 14% ($n = 28$); $p = 0.13$ and $p = 0.02$, respectively).
Conclusion: ATHENA confirmed significant reduction of CMV infections in KTx pts receiving EVR-based therapy. In addition, the CMV-substudy gave novel insights about enhanced functionality of CMV-specific T-cells in pts treated with EVR, potentially yielding enhanced protection against CMV.

V077 EVEROLIMUS IN COMBINATION WITH REDUCED TACROLIMUS IMPROVES KIDNEY FUNCTION VS STANDARD TACROLIMUS IN *DE NOVO* LIVER TRANSPLANT RECIPIENTS: HEPHAISTOS STUDY 12 MONTHS DATA

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Introduction: Kidney failure due to nephrotoxic calcineurin inhibitors [CNI] like tacrolimus [TAC] remains the main cause for morbidity after liver transplantation [LTx]. Therefore, innovative therapeutic strategies aim to minimize the use of TAC. In the HEPHAISTOS study the renal benefits of a combination therapy with everolimus [EVR] and reduced TAC [rTAC] vs a standard TAC regime [TAC-C] was investigated in *de novo* LTx recipients.
Methods: In this 12 months [M] prospective, open-label German study 333 patients [pts] in 15 centers were randomized 1:1 between day 7 to 21 after LTx to receive either EVR (3–8 ng/ml) + rTAC (<5 ng/ml) or TAC-C (6–10 ng/ml), all with steroids until M6. Renal function after M12 was assessed in the full analysis [FAS] and per protocol [PP] set.
Results: In the FAS set 169 and 164 pts were treated with EVR+rTAC and TAC-C, respectively. Randomization occurred on average 15 days after LTx. At M12 mean eGFR (MDRD4) was numerically higher with EVR+rTAC (adjusted mean difference of 4.09 mL/min/1.73 m^2; $p = 0.0970$). However, analysis of TAC trough concentrations showed that in the EVR+rTAC group mean TAC trough levels exceeded target range until M3 and remained close to the upper limit of the target range thereafter. Among pts in the PP set (110 EVR+rTAC, 101 TAC-C), mean eGFR was significantly higher in the EVR+rTAC compared to the TAC-C group (+7.79 mL/min/1.73 m^2 vs TAC-C; $p = 0.0085$). Most importantly, efficacy profiles in both groups were comparable.
Conclusion: Early use of EVR in combination with rTAC leads to a sustainably improved renal function 12M after LTx compared to TAC-C, without compromising efficacy. HEPHAISTOS confirms that an early CNI reduction after LTx is safe and feasible and offers renal benefits in *de novo* LTx recipients.

V078 LOW-DOSE ATG HAS NO INFLUENCE ON PATIENT SURVIVAL, GRAFT SURVIVAL AND CANCER-FREE SURVIVAL AND IMPROVES RENAL OUTCOME IN PATIENTS WITH COMPROMISED KIDNEY FUNCTION AFTER LIVER TRANSPLANTATION

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Introduction: The current indication for ATG induction in liver transplantation is highly controversial. Data on the effects of low-dose ATG induction are lacking. This study therefore investigates retrospectively the safety and benefits of low-dose ATG induction (0.5 to 1.0 mg/kg/d for 3–4 days) in liver transplantation.
Methods: Patients with primary liver transplantation at Medical University Graz between the 1.1.2007 and the 31.12.2018 were included. Patients with additional kidney transplantation were excluded from analysis leading to a cohort of 211 patients for the investigation of independent influences of ATG on patient survival, graft survival and cancer-free survival using multivariable Cox regression analysis. The independent influence of ATG on KDIGO-stage improvement of renal function at 6 months after transplantation was investigated using multivariable logistic regression analysis after further exclusion of 31 patients with lack of data for postoperative renal function classified in KDIGO-stages at 6 months after transplant.
Results: 131 patients received ATG induction (62.1%). Significant differences between patients with ATG induction versus without ATG induction were identified for the distribution of the indication hepatocellular carcinoma (16.0%, 28.8%, respectively). The distribution of all other pre-transplant variables was not significantly different. Multivariable Cox regression revealed that ATG induction did not have an independent statistically significant influence on patient survival, graft survival and cancer-free survival ($p > 0.050$). Multivariable logistic regression revealed that a body-mass index (BMI) > 25 kg/m^2 (OR = 0.297, $p = 0.036$), pre-transplant KDIGO-stages (OR = 3.746, $p < 0.001$) and low-dose ATG induction (OR = 3.636, $p = 0.043$) had

independent significant influences on KDIGO-stage improvement at 6 months after liver transplantation.
Conclusion: Low-dose ATG induction is safe in regard to patient, graft and cancer-free survival. Low-dose ATG induction improves renal function after liver transplantation which is more pronounced in patients with compromised renal function prior to liver transplantation and in those patients with a BMI < 25 kg/m^2.

V079 SAFETY AND EFFICACY OF EARLY USE OF EVEROLIMUS IN COMBINATION WITH REDUCED TACROLIMUS VS STANDARD TACROLIMUS IN *DE NOVO* LIVER TRANSPLANT RECIPIENTS: HEPHAISTOS STUDY 12 MONTHS DATA

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Introduction: Current immunosuppressive strategies after liver transplantation [LTx] aim to preserve kidney function by reduction of tacrolimus [TAC]. HEPHAISTOS investigated efficacy and safety of early use of reduced TAC [rTAC] in combination with everolimus [EVR] in *de novo* LTx recipients.
Methods: In this 12 months [M] prospective, open-label, multi-center study 333 patients [pts] were randomized 1:1 to receive EVR (3–8 ng/ml) + rTAC (<5 ng/ml), or TAC-C (6–10 ng/ml), all with steroids until M6. Here we report M12 safety and efficacy results.
Results: 169 and 164 pts were randomized to EVR+rTAC or TAC-C, respectively. Both groups showed a similar safety and efficacy profile: i) Incidences of adverse events leading to study drug discontinuation were 23.7% [EVR+rTAC] vs 23.2% [TAC-C]. Renal and urinary disorders (1.2% vs 7.3%) and leukopenia (2.4% vs 0.0%) were the main reasons for discontinuation. No new safety signals were identified. ii) Incidence of biopsy-proven acute rejection (BPAR) until M12 was 8.3% in the EVR+rTAC and 6.7% in the TAC-C group and there were no differences in BPAR severity (mild: 9 vs 7; moderate/severe: 8 vs 7). Under treatment, no vs 3 graft losses and 2 vs 3 deaths occurred in the EVR+rTAC or TAC-C arm, respectively.
Conclusion: HEPHAISTOS confirmed that early use of EVR in combination with rTAC in *de novo* LTx recipients is feasible and safe with good efficacy outcomes.

LIVER III

V080 IS DETERMINATION OF THE ETHYL GLUCURONIDE CONCENTRATION IN A HAIR STRAIN RELIABLE IN PATIENTS WITH RENAL DYSFUNCTION TO PROVE ABSTINENCE?

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Introduction: Due to the high renal excretion of ethyl glucuronide (EtG) it is conceivable that hair ethyl glucuronide (hEtG) levels are influenced by renal dysfunction. Therefore, aim of this study is to evaluate the impact of renal impairment on hEtG-results.
Methods: Patients presenting to the outpatient liver and kidney transplant clinic of the UKE were prospectively included. According to the GFR (MDRD) patients were divided into 3 groups: GFR1: > 60 ml/min, GFR2: 60–30 ml/min and GFR3: < 30 ml/min. Alcohol consumption was evaluated by a questionnaire and by determination of the EtG concentration in a 3 cm long hair strain. Diagnostic performance of hEtG was calculated, considering a hEtG result above 7 pg/mg as true positive if patients reported alcohol consumption > 10 g ethanol/die over the last 3 months.
Results: 94 patients (GFR1,2,3 n = 47, n = 29, n = 18) were included in the study. 25.5% of patients tested positive for hEtG (> 7 pg/mg). Patients in group GFR3 had significantly more often positive hEtGs results compared to the other patients (GFR1,2,3: 19%, 28%, 39%), although they reported less alcohol consumption. So, the percentage of false positive hEtGs increased markedly with deterioration of the kidney function (GFR1,2,3: 44%, 50%, 100%), the PPV decreased accordingly (GFR1,2,3: 0.56, 0.5, 0). Thus, the specificity (GFR1,2,3: 0.89, 0.84, 0.61) was the lowest in GFR3, since patients drinking <10 g/d were less often correctly identified as teetotalers. Also, despite less alcohol consumption the mean hEtG concentration (pg/mg) was highest in patients in group GFR3 (GFR1,2,3: 91, 59, 135).
Conclusion: Our data show, that the determination of the hEtG concentration to evaluate the amount of alcohol consumed within the last 3 months is not reliable in patients with advanced renal dysfunction. Future studies are needed to evaluate, if hEtG can be used to prove abstinence more reliably in case of different cut-off values for the hEtG concentration, or definition of longer detection periods of alcohol consumption.

V083 INFLUENCE OF METABOLIC PARAMETERS ON THE HISTOPATHOLOGY OF THE GRAFT AFTER LIVER TRANSPLANTATION

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Introduction: Non-alcoholic steatohepatitis (NASH) became one of the leading causes for liver transplantation. The development of steatosis and NASH relapse after liver transplantation remain poorly understood. This study evaluates metabolic parameters and histopathological changes of the graft after liver transplantation during long-term follow up.
Methods: 1494 longitudinal liver biopsies of 414 recipients were analyzed during a follow up period of 5 to 10 years. Clinical and laboratory parameters as well as histopathological categories of steatosis, inflammation, fibrosis, and hemosiderosis were explored.
Results: The BMI was higher in men than women. A significant weight gain occurred after liver transplantation ($p < 0.01$). Percentage of patients with diabetes mellitus was 27.5% after one year and 33.1% after 5 years ($p < 0.01$). The BMI, diabetes mellitus, triglycerides and fasting glucose were significantly related to the degree of steatosis of the graft. Inflammation was a precursor of fibrosis and fibrosis increased over the first 5 years ($p < 0.01$). Steatosis and fibrosis were not significantly associated. Severe graft dysfunction was not observed.
Conclusion: High BMI, postoperative weight gain and diabetes mellitus correlate with relapse of and de-novo non-alcoholic fatty liver disease (NAFLD) after liver transplantation. Similar processes as in the original organ seem to lead to steatosis and NAFLD in the graft. Metabolic syndrome has to be considered as a serious complication after liver transplantation forwarding severe histopathological alteration of the graft.

V084 IMPACT OF GLUCOSE METABOLISM ON KIDNEY FUNCTION AFTER LIVER TRANSPLANTATION

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Introduction: Posttransplant diabetes mellitus (PTDM) is a common complication after liver transplantation with substantial impact on patient and graft survival. Here we analyze the effect of different states of glucose metabolism after liver transplantation on kidney function in long-term follow-up.
Methods: In this retrospective study, data of all consecutive adult patients (n = 429) who underwent liver transplantation at the University Hospital of Tuebingen between 2007 and 2017 were collected. Parameters for longitudinal follow-up included fasting plasma glucose and glycated hemoglobin (HbA1c), data on kidney and allograft function, as well as immune-suppression.
Results: Median follow-up time was 37 (IQR 9–64) months. 102 patients (24%) had pre-existing diabetes prior to transplantation. Median prevalence of PTDM throughout follow-up was 9% (IQR 8–12%) and of prediabetes 43% (IQR 40–44%). Patients with pre-existing diabetes had a significantly lower eGFR (CKD-EPI) at time of transplantation compared to patients without (67 ml/min/1.73 m^2 vs. 82 ml/min/1.73 m^2, p = 0.001), persisting throughout follow-up. Stratifying patients according to glucose metabolism at 9–12 months after liver transplantation, eGFR trajectories revealed a negative slope in patients with PTDM in long-term follow-up, whereas in patients with prediabetes, eGFR decreased only minimally. In patients with normal glucose regulation, renal function stabilized over time.
Conclusion: The glucose metabolism at time of liver transplantation and during follow-up impacts kidney function in long-term follow-up. The magnitude of the problem as well as the clinical implications require transplant physicians to increase awareness and to implement strategies for effective screening and prevention, in order to improve long-term outcome after liver transplantation.

V086 RE-ENTERING THE CHALLENGE FOR INTESTINAL AND MULTIVISCERAL TRANSPLANTATION: A CASE SERIES AND SINGLE-CENTER EXPERIENCE

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Introduction: Intestinal transplantation is the only curative treatment for selected patients with irreversible intestinal failure. Since these patients often suffer from various comorbidities (e.g. end-stage liver or renal failure), different techniques and combinations of intestinal grafts are necessary ranging from isolated intestinal (ITX) to multivisceral transplantations (MVTx). Already being a procedure with acceptable long-term survival, ITx remains rare for patients in Germany. Upon reintroduction of ITx at University Hospital Muenster, we discuss our very early experiences with four cases.
Methods: Four intestinal transplants were performed between 11/2018 and 05/2019. Indications for MVTx or ITx were mesenteric ischemia, slow transit obstipation, and intestinal failure-associated liver disease. The median recipient age was 34 years (patients ranged from 22–55 years of age).
Results: A total of two MVTxs, including small bowel, right hemicolon, liver, pancreas, stomach, and spleen were performed by transplanting the liver in a piggyback technique with Belghiti side-to-side cavo-cavostomies. The spleen was removed 4 hours after transplantation to prime a natural resistance against graft versus host disease. Proximal gastrointestinal reconstruction was done via gastro-gastrostomy or esophago-gastronomy. One combined ITx included the small bowel, right hemicolon and liver; another ITx combined small bowel and kidney transplantation. Each abdominal wall closure was supported by transplantation of non-vascularized fascia. Immunosuppressive therapy included antithymocyte globulin, cortisone, and tacrolimus with early conversion to a dual calcineurin inhibitor (CNI) and mToR maintenance at 6 weeks post-transplant. Endoscopic intestinal graft surveillance occurred regularly with mucosal biopsies.
Conclusion: MVTx and ITx are challenging surgical treatments. Patients require individual surgical solutions due to different anatomical circumstances. An ongoing follow-up needs to be conducted for long-term outcome.
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KIDNEY III (INCL. PAEDIATRICS)

V087 RISK FACTORS, PREDICTION AND OUTCOMES OF DELAYED GRAFT FUNCTION (DGF). AN ANALYSIS FROM A GERMAN COHORT OF EXTENDED CRITERIA DONOR KIDNEYS WITH POST-EXPLANTATION BIOPSIES

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Introduction: DGF occurs frequently after transplantation and is associated with worse short- and long-term outcomes and associated with higher rejection rates. Risk factors include both donor and recipient characteristics, although their prediction is imprecise. Therefore, we tested known risk factors of DGF and validated the performance of existing risk scores in predicting DGF in recipients of extended criteria donor kidneys with procurement biopsies.
Methods: We retrospectively evaluated the records of 223 consecutive adult cadaver renal transplant recipients with donor evaluation biopsies. 135 patients developed DGF (defined as the need for hemodialysis during the first week after transplantation). Clinical donor and recipient characteristics as well as histological features of the biopsy were compared between the two groups and the following risk scores were evaluated regarding their association with observed DGF: Navarro (2011), Ortiz (2004), Balaz (2013), Lopes (2004), Snoeijs (2008), Remuzzi (1999), Nyberg (2003), Rao (2009), Foucher (2009), Schold (2005), Port (2002), Anglicheau (2008), Leuven (2013) Irish (2010), KDRI/KDPI and EPTS.
Results: Severity of acute kidney injury (similar to AKIN Classification) at ICU stay, last creatinine, proteinuria, macroscopic organ quality, microthrombi by histology, prolonged warm ischemia time, recipient body mass index, and recipient duration of dialysis were significant risk factors for the development of DGF in the recipient in univariable analysis. None of the evaluated scores could accurately predict DGF. In multivariable analysis only severity of acute kidney injury and microthrombi by biopsy remained statistically significant (OR 1.89 95%CI 1.26–2.84, p = 0.002; OR 3.06, 95%CI 1.00–9.34, p = 0.049, respectively).
Conclusion: None of the established clinical, histological or combined scores for quality assessment of deceased donor kidneys appeared sufficiently prognostic for DGF in our cohort. We are currently working on a novel combined clinicopathological score better suited for clinical application in the Eurotransplant network.

V090 IMMUNE CELL INFILTRATION IN PEDIATRIC RENAL ALLOGRAFTS CORRELATES WITH REJECTION, RE-TRANSPLANTATION, FIBROSIS AND GRAFT FUNCTION IN A RETROSPECTIVE STUDY

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Introduction: Standardized evaluation of immune cell infiltration in kidney transplantation (KTx) may improve diagnostics. To date, no larger study investigating the types and roles of immune cells in renal pediatric allografts exists and their impact on long-term outcome is poorly understood.
Methods: All available KTx samples (n = 202) from 59 pediatric patients (63% male, mean age 10 years) transplanted 2000–2017 at our center were re-evaluated according to recent Banff criteria and stained for macrophages, dendritic cells (DC), B-cells and T-cells (CD68, CD206, CD163L1, CD209, CD20, CD3). Quantification of immune cells was performed in whole slide images (WSI) using an image analysis software (QuPath). Results were obtained separately for cortex, medulla and extrarenal tissue and displayed as percentages (%) of positively stained area.
Results: Protocol biopsies had lower cortical and medullary macrophage, DC, T cell and B cell numbers than indication biopsies ($p < 0.05$; Kruskal-Wallis test). In TCMR (cellular), ABMR (humoral rejection) and combined TCMR/ABMR cortical macrophages (CD68, CD206) were more frequent than in samples without rejection ($p < 0.05$); B and T cells were more abundant in borderline, TCMR and combined TCMR/ABMR than in non-rejection samples ($p < 0.05$). TCMR revealed highest densities of B cells and combined rejection of T cells. All immune cells correlated with fibrosis at time of biopsy (% IFTA; Spearman's $r > 0.25$–0.5, $p < 0.01$). Infiltration of B and T cells and macrophages had higher densities in i-IFTA2 and i-IFTA3 compared to i-IFTA0 ($p < 0.05$) in cortex. High creatinine levels were associated with high macrophage abundance (CD68: $r = 0.27$; CD206: $r = 0.34$, $p < 0.01$).
Conclusion: B cells within KTx do not correlate with ABMR. Infiltrating immune cells, especially mononuclear phagocytes, are highly abundant in pediatric renal transplants in rejection, re-transplantation and fibrosis, correlate with creatinine levels and influence long-term graft function.

V091 THE TRANSFORM STUDY: 24-MONTHS ANALYSIS OF CARDIOMETABOLIC EVENTS IN RENAL TRANSPLANT RECIPIENTS RECEIVING EVEROLIMUS WITH REDUCED-EXPOSURE CALCINEURIN INHIBITOR REGIMEN

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Introduction: M-TOR inhibitors (eg, everolimus [EVR]), are thought to increase the risk of post-transplant (Tx) proteinuria (PU) as well as post-transplant lipid abnormalities are considered to increase the risk of cardiovascular (CV) events in renal transplant recipients (RTxRs). Here, we evaluate PU onset and outcomes, lipid profiles, cumulative incidences of dyslipidaemia (DL), major adverse cardiac events (MACE) at month (M) 24 in de novo RTxRs receiving EVR+reduced-exposure calcineurin inhibitor (EVR+rCNI) or mycophenolic acid+standard CNI (MPA+sCNI) regimen from the TRANSFORM study.
Methods: In this 24M, multicenter, open-label study, RTxRs were randomised to EVR+rCNI (N = 1022) or MPA+sCNI (N = 1015) + induction and steroids. Dyslipidaemia (various parameters) and MACE were reported by investigators as adverse events (AEs) or serious AEs. Lipid profiles and MACE were examined in the overall population and in the dyslipidaemia cohort, by treatment arms. EVR trough level (C_0), urine protein:creatinine ratio (UPCR), antihypertensive medication use and onset time in patients with PU AEs were assessed.
Results: 384/1014 and 217/1012 RTxRs had dyslipidaemia in the EVR+rCNI and MPA+sCNI arms, respectively. In the overall population, M24 lipid levels

and mean changes from baseline were higher in the EVR+rCNI vs MPA+sCNI arm. Incidence of MACE was low in the study and, in particular, was lower in the EVR+rCNI arm among patients with DL. Proportion of patients in both arms was similar across UPCR categories (<500 mg/g: >85% in both; 500-<3000 mg/g: 13.3% [EVR+rCNI] and 8.07% [MPA+sCNI]; and > 3000 mg/g: ~1% in both). PU as an AE was reported in 14.1% (EVR+rCNI) and 7.0% (MPA+sCNI) of patients. Median time to PU onset was 76 vs 63 days with EVR+rCNI vs MPA+sCNI. Difference in median UPCR up to M24 was 2.5-fold higher in EVR+rCNI vs MPA+sCNI arm among patients with PU.
Conclusion: Despite a higher incidence of DL, MACE-incidence was lower in the EVR+rCNI vs MPA+sCNI arm up to 24M. EVR+rCNI-associated DL appears to be manageable and did not confer increased CV risk up to M24. Although EVR+rCNI regimen was associated with a high incidence of PU AEs, this rarely led to drug discontinuation.

V092 GRAFT SURVIVAL AFTER REPEAT RENAL TRANSPLANTATION

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Introduction: There is an increasing number of patients listed for renal transplantation (RT) awaiting a re-transplantation after an initial graft failure. While it has been demonstrated that results are superior for primary RT, data on subsequent graft survival are still limited. This study aimed to analyze graft survival in a cohort of patients stratified for their second (RT2), third (RT3) or fourth (RT4) transplantation.
Methods: In-center registry data for 2578 RT recipients (1971 to 2012) at the University Münster was retrospectively analyzed and stratified for patients with a repeat RT. Medium follow-up time (starting from the primary RT) was 279 months (interquartile range 201–363) and medium follow-up time from the last RT was 178 months (interquartile range 84–270). Baseline donor and recipient characteristics as well as five-year graft survival were assessed. Factors associated graft survival were identified using a multivariable Cox proportional hazards model.
Results: A total of 400 RT recipients with a repeat kidney transplantation were identified, this group consisted of 335 RT2, 55 RT3 and 10 RT4 patients. Patients were only counted in one respective group. RT2 patients had a 5-year graft survival of 40.9% for the first and 79.9% for the second transplantation. RT3 patients had a 5-year graft survival of 21.8% for the first, 38.2% for the second and 65.5% for the third transplantation. RT4 had a 5-year graft survival of 0% for the first, 30.0% for the second, 20.0% for the third and 60.0% for the fourth transplantation. Recipient-related risk factors associated with graft loss were age, waiting time and immunization.
Conclusion: We found an acceptable graft survival for final kidney grafts in patients with repeated RT. While sensitization, surgical challenges and increasing co-morbidities complicate repeated RT, our data reinforced the concept that RT is a safe and successful in patients with a history of renal graft failure.

V093 CRADLE STUDY: THREE-YEAR RESULTS OF GROWTH AND SEXUAL MATURATION IN PEDIATRIC KIDNEY TRANSPLANT PATIENTS RECEIVING EVEROLIMUS WITH REDUCED TACROLIMUS AND EARLY STEROID WITHDRAWAL

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Introduction: The CRADLE study compares efficacy and safety outcomes (36-month [M]) of everolimus with reduced tacrolimus (EVR+rTAC) and early corticosteroid (CS) withdrawal regimen vs mycophenolate mofetil+standard TAC (MMF+sTAC) + CS in pediatric kidney transplant recipients (pKTxRs).
Methods: In this 12M core + 24M multicenter follow-up study, 106 pKTxRs (≥1-<18 years) on MMF+ sTAC+CS were randomized (1:1) at 4–6 weeks post transplantation (Tx) to either EVR+rTAC (N = 52) with CS withdrawal at 6M post-Tx (EVR trough levels [C_0]:3–8 ng/mL; TAC C_0: randomization [RND] to M3: 4–6 ng/mL; after M4: 2–4 ng/mL) or MMF+sTAC and CS (N = 54) regimen (TAC C_0: RND to M3: 7–10 ng/mL; from M4 to 5–8 ng/mL). Here we report results with primary focus on body growth (height, weight, and BMI) and sexual maturation as well acute rejections and renal function at 3 years post-transplant.
Results: Overall, 98 (92.5%) patients completed M36 (EVR+rTAC, *n* = 47; MMF+sTAC, *n* = 51). Baseline and demographic characteristics were comparable between both arms. The mean height and weight increased in both treatment groups from RND to M36. Mean change in height from randomization to month 36 was comparable with EVR+rTAC versus MMF+sTAC in all age subgroups. In EVR+rTAC group, KTRs with limited use of steroids tended to have better longitudinal growth followed by KTRs with no steroids. Mean change in BMI from RND to M36 was numerically lower in the EVR+rTAC compared to MMF+sTAC group (0.02 vs. 0.47; p = 0.0916). Pubertal development of male and females was similar in both treatment groups. Serum testosterone levels (measured in male KTRs only) increased in both treatment groups. The Kaplan-Meier incidence of composite efficacy failure (BPAR, graft loss, or death) was comparable between EVR+rTAC and MMF+sTAC (9.8% [5/52] vs. 9.6% [5/54].
Conclusion: In conclusion, these 36M long-term results are in line with the 12M findings and uphold the benefit-risk assessment that EVR+rTAC with an early steroid withdrawal regimen does not impact growth and development in pediatric KTRs. This regimen could be an alternative treatment option that enables withdrawal of steroids as well as reduction of CNIs for pediatric KTRs.

BASIC SCIENCE II – CELL DEATH

V095 HLA CLASS II ANTIBODIES INDUCE NECROTIC CELL DEATH IN HUMAN ENDOTHELIAL CELLS VIA A LYSOSOMAL MEMBRANE PERMEABILIZATION-MEDIATED PATHWAY

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Introduction: Antibody-mediated rejection (AMR) is the major cause of allograft loss after solid organ transplantation. Circulating donor-specific antibodies against human leukocyte antigen (HLA), in particular HLA class II antibodies, are critical for the pathogenesis of AMR via interactions with endothelial cells (ECs).
Methods: After pretreatment with human interferon-gamma cell cultures of human umbilical vein ECs (HUVECs), human aortic ECs, human dermal and pulmonary microvascular ECs were treated with the pan HLA class II monoclonal antibody L243 or with sera from allo-immunized patients. Knockdown of HLA-DR was performed with a lentiviral vector-based approach. Cell death in ECs was determined with various experimental and pharmacological strategies.
Results: Antibody ligation of HLA class II molecules in interferon-gamma-treated ECs caused necrotic cell death without complement via a pathway that was independent of apoptosis and necroptosis. HLA-DR-mediated cell death was blocked by specific neutralization of antibody ligation with recombinant HLA class II protein and by lentiviral knockdown of HLA-DR in ECs. Importantly, HLA class II-mediated cytotoxicity was also induced by relevant native allele-specific antibodies from human allosera. Necrosis of ECs in response to HLA-DR ligation was mediated via hyperactivation of lysosomes, lysosomal membrane permeabilization (LMP) and release of cathepsins. Notably, LMP was caused by rearrangements of the actin cytoskeleton. This was indicated by the finding that LMP and F actin stress fiber formation by HLA-DR antibodies were both down-regulated by the actin polymerization inhibitor cytochalasin D and inhibition of Rho GTPases, respectively. Finally, HLA-DR-dependent F actin stress fiber formation and LMP led to mitochondrial stress, which was revealed by decreased mitochondrial membrane potential and release of reactive oxygen species in ECs.
Conclusion: Ligation of HLA class II antibodies to ECs induces necrotic cell death independent of apoptosis and necroptosis via a LMP-mediated pathway. These findings may enable novel therapeutic approaches for the treatment of AMR in solid organ transplantation.

V098 EFFICACY OF WNT PATHWAY INHIBITORS FOR THE PREVENTION OF CARDIAC ALLOGRAFT VASCULOPATHY IN A MOUSE MODEL

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Introduction: The wnt pathway is involved in tissue homeostasis in the adult and its dysregulation is associated with many diseases, including pathologies of the cardiovascular system. Chronic rejection, detectable as cardiac allograft vasculopathy (CAV), is among the major causes of death after heart transplantation. CAV is histologically characterized by the development of a

neointima consisting primarily of smooth muscle cells (SMCs). Wnt antagonists are known to inhibit SMC proliferation and therefore might be able to prevent CAV manifestation.
Methods: Human (hu) und murine (mu) SMCs were treated with different concentrations of three wnt inhibitors: XAV-939, ICG-001 and PKF118-310. Proliferation of SMCs was measured *in vitro* as the extent of PrestoBlue™ metabolism. XAV-939 and ICG-001 were also used to treat mice after aortic transplantation and neointimal area was analyzed as the indicator for CAV. Expression of β-Catenin, the central signaling molecule of the wnt pathway, was examined in transplanted aortas as well as expression of several cytokines. Influence of the wnt antagonists on expression of wnt target genes is currently assessed.
Results: XAV-939 and especially ICG-001 caused a reproducible dose-dependent inhibition of the proliferation of huSMC and muSMC *in vitro*. Preliminary results for PKF118-310 suggest a similar effect. However, treatment with XAV-939 or ICG-001 *in vivo* could not prevent CAV development in mice after allogeneic aortic transplantation ($p = 0.63$ for XAV-939 and $p = 0.19$ for ICG-001). Expression of β-Catenin in the neointima, though, was reduced after treatment with the wnt antagonists ($p = 0.0067$ for XAV-939 and $p = 0.022$ for ICG-001). Expression of inflammatory cytokines was almost unimpaired by XAV-939 treatment, while ICG-001 reduced levels of INFγ, TNFα and IL-6.
Conclusion: SMC proliferation is the central patho-mechanism in CAV development and Wnt inhibitors could effectively suppress this proliferation *in vitro*. However, neointima formation *in vivo* was not reduced after treatment with XAV-939 or ICG-001. *In vitro* and *in vivo* experiments with PKF118-310 are currently in progress as are analyses of the expression of wnt target genes.

V099 BKV-SPECIFIC CELLULAR IMMUNITY DEMONSTRATES A CD4+ T CELL RESTRICTION THAT IS NOT DUE TO LIMITATIONS IN CD8+ T CELL DETECTION ASSAY

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Introduction: BKV-associated nephropathy (BKVAN) represents a serious complication of the post-transplant period in kidney recipients leading to organ loss in up 50% of all cases. There is no specific anti-viral therapy. Reduction of immunosuppression to improve antiviral immunity represents the cornerstone in the therapy. Analysis of BKV-specific immunity is therefore crucial for monitoring antiviral response and guiding immunosuppressive therapy. Our previous data demonstrated that $CD4^+$ but not $CD8^+$ BKV-specific T cells are associated with BKV clearance. However, it was not finally clear, whether the low detection level of $CD8^+$ T was due to the use of BKV-specific 15-mer peptides. While 15-mer peptides are known to fit to $CD4^+$ T cell activating MHCII grooves, 9-mer are the optimal size for $CD8^+$ T cell activating MHCI.
Methods: Here, we evaluate the effect of the BKV peptide library size on its stimulatory capacity and clarify the role of BKV-specific $CD8^+$ T cells in BKV-specific immunity. For this, analysis of BKV-specific T cells was performed using BKV-overlapping 9-mer and 15-mer peptides. PBMC from 17 healthy blood donors were stimulated with 9-mer or 15-mer BKV peptides for 16 h, subsequently stained and analysed by multi-parameter flow cytometry.
Results: Both stimulation approaches were able to elicit T cell response and the data on BKV-specific $CD8^+$ T cells were comparable for 9- and 15-mer peptide stimulation. We also did not see any differences in phenotype of $CD8^+$ T cells using 9- or 15-mer peptides. Comparing $CD4^+$ and $CD8^+$ BKV immunity, we demonstrated the dominance of $CD4^+$ T cells including single, double cytokine producers and polyfunctional T cells
Conclusion: We demonstrated, that 15-mer BKV peptide library does not underestimate $CD8^+$ immunity and elicit similar $CD8^+$ T cell response as compared to 9-mer peptides. Furthermore, $CD4^+$ T cells showed significantly higher frequencies as compared to $CD8^+$ T cells demonstrating their dominance in BKV-specific cellular immunity.