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Abstracts of the 23rd Annual Meeting of the German Transplantation Society
Mannheim, Germany
16–18 October 2014

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WELCOME ADDRESS

Dear ladies and gentlemen, dear DTG members

We would like to welcome you to the 23rd Annual Meeting of the German Transplantation Society (Deutsche Transplantationsgesellschaft, DTG). It is a great pleasure for us to host this year's conference in Mannheim – especially because the Transplantation Centre Mannheim is celebrating its 25th anniversary.

Although transplantation medicine has made tremendous progress during the past 60 years, unsolved issues remain, which we will focus on during the DTG's Annual Meeting:

- Shortage of organs, management of donors and patients
- allocation of organs: novel concepts, ethical issues concerning distributive justice
- Living donation: morbidity and long-term effects
- Long-term survival of patients and grafts
- Immunisation: diagnostics and treatment
- Psycho-social support, adherence
- Immunosuppression: mechanisms and novel agents

In the opening session Prof. Jochen Taupitz, Hochschule Mannheim, will give a lecture dealing with the most interesting topic "Law and ethics in research with embryonal stem cells". In our plenary session I on October 17, 2014 lectures from Prof. Volker Nickeleit, Chapel Hill, dealing with polyomavirus nephropathy after renal transplantation from Prof. Edward Geissler, Regensburg, dealing with cellular approaches to achieve transplant tolerance and from Dr. Gregor Warnecke, Hannover discussing the use of OCS in lung transplantation will be congress highlights. The plenary session II on October 18, 2014 will deal with the most important topic of "ethics in transplantation medicine".

The high number and excellent quality of scientific abstracts presented at the 23rd Annual Meeting of the German Transplantation Society as depicted in this issue of Transplantation International demonstrate the good scientific standing and lively exchange of ideas within the German Transplantation Society.

Special emphasis will be placed on creating a platform for young transplant physicians from surgery, internal medicine, immunology, psychosomatic medicine, pathology and others by providing a framework of open lectures, poster sessions and events for young professionals (Master Classes).

As in previous years, the 18th Symposium of associated health professionals (AKTx Pflege e. V.) will be held simultaneously.

The 'city of the squares' Mannheim is lively and cosmopolitan. With the National Theatre, known as Schiller's stage (inaugural performance of Friedrich Schiller's The Robbers 'Die Räuber' in 1782), the Kunsthalle Mannheim and the Technoseum, Mannheim is an important theatre and museum centre. The Popakademie Baden-Wuerttemberg (since 2003) and an active music and cabaret scene make Mannheim a cultural landmark. The former residence of the Elector Palatine is the economic and cultural centre of the densely populated Rhine-Neckar Metropolitan Region, which has a population of 2.4 Million inhabitants. Important inventions were made in Mannheim: the first two-wheeler by Karl Drais in 1817, the world's first electric elevator by Werner von Siemens in 1880, the first automobile by Carl Benz in 1886, the Lanz Bulldog in 1921.

We are looking forward to a successful as well as interesting conference and to your participation in the 23rd DTG Annual Meeting in Mannheim.

Prof. Bernhard K. Krämer, Prof. Stefan Post
Conference presidents

Prof. Bernd Krüger, Prof. Kai Nowak
Conference secretaries

Wednesday, 15 October 2014

13:00–15:30	DTG Pre-Meeting	
16:00–18:00	DTG Board Meeting	
18:00–19:30	Committee Meeting: Immunology	Committee Meeting: Liver

Thursday, 16 October 2014

09:00–10:30	Committee Meeting: Pancreas	Committee Meeting: Ethics & Psychosomatics	Committee Meeting: Thoracic Organs	
10:30–12:00	Committee Meeting: Kidney	Committee Meeting: Organ Donation and Procurement	Master Class I: Living Donation	
12:00–13:00	Industry Lunch Symposium	Industry Lunch Symposium	Lunch Break	
13:00–14:00				Poster Session I
14:00–14:45	Session: Kidney	Session: Thoracic Organs I	Session: Basic Science I	
15:00–16:15	Opening Ceremony			
16:15–16:45	Coffee Break			
16:45–17:45	Session: Liver	Session: Immunology and HLA	Session: Economy	Session: Paediatric Transplantation
18:00–20:00	DTG General Meeting			
20:00–21:00	Get-together			

Friday, 17 October 2014

08:30–10:00	Session: Kidney/ Pancreas I	Session: Thoracic Organs II	Session: Basic Science II	Master Class II: Law and Transplantation Medicine
10:00–10:30	Coffee Break			
10:30–11:30	Poster Session II			
11:30–12:30	Industry Lunch Symposium	Industry Lunch Symposium	Industry Lunch Symposium	Industry Lunch Symposium
12:30–13:00	Lunch Break			
13:00–15:00	Plenary Session I			
15:00–15:30	Coffee Break			
15:30–16:45	Session: Liver/Small Intestine	Session: "Hot Topics"	Session: Psychosomatics	Report on Development of Guidelines
17:00–18:00	Session: Kidney/ Pancreas II	Session: Infections and Complications	Session: Organ Donation/ Marginal Organs	Session: Long-term Complications
from 19:30	Banquet			

Saturday, 18 October 2014

08:30–10:00	Session: Immunosuppression/ Novel Studies	Session: Living Donation	Session: Miscellaneous	Master Class III: Lessons to Learn from Allogeneic Hematopoietic Cell Transplantation
10:15–11:30	Presentation of Best Posters	Reports of DTG Committees		
11:45–13:45	Plenary Session II: Ethical Issues in Transplantation Medicine			
13:45–14:15	Closing Session			

LECTURES

KIDNEY

V01 PRETRANSPLANT DSA BUT NOT COMPLEMENT FIXING HLA ANTIBODIES ARE ASSOCIATED WITH INCREASED RISK FOR ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

U. Eisenberger[1], *D. Keles*[2], *A. Heinold*[2], *O. Witzke*[1], *A. Kribben*[1], *A. Paul*[3], *H.A. Baba*[4], *J.U. Becker*[5], *P.A. Horn*[2], **F.M. Heinemann*[2]

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It is still not fully elucidated whether kidney transplant recipients with preformed donor-specific human leukocyte antigen (HLA) antibodies (DSA) detectable by Luminex Single Antigen Beads (SAB) are at increased risk of reduced allograft function early after transplantation. Especially the effect of complement fixing DSA detected by the C1q SAB assay remains unclear. Regarding the C1q assay recent studies indicated controversial results, possibly related to centre effects or the size of the patient cohorts analyzed.

The aim of our retrospective analysis was to evaluate the early impact of C1q fixing DSA in a large single centre study. We included a cohort of 255/289 renal transplant recipients transplanted in a short period between January 2011 and December 2012 at the local kidney transplantation program in this analysis. All transplantations were performed with a CDC negative crossmatch. For living donation also flow cytometric crossmatches were performed. The pretransplant HLA antibody status determined by Luminex SAB was not systematically considered for transplant decisions. Indication biopsies performed in more than 50 % of all patients within the first one to two years of follow-up for were analysed for histological signs of antibody mediated rejection (AMR).

Pretransplant SAB DSA were present in 40 patients (25 with anti-HLA-class I, 11 with class II, and 4 with class I+II specificities, respectively). In total 27/255 patients showed signs of AMR, 14 of 215 patients without DSA (5.5%, RR 0.2) compared to 13/40 patients with DSA (32.5%, RR 5.2). The C1q fixing capacity was positive in 6/40 patients with DSA, but only in 1/27 patients with AMR. Follow-up data for graft survival and function are pending.

Although still preliminary, our study could clearly confirm pretransplant Luminex DSA as a significant risk factor for the occurrence of early AMR after renal transplantation. C1q-binding capacity of DSA at the time of transplantation seems to be not predictive for the occurrence of AMR during early follow-up.

V03 EFFECTS OF TREATMENT OF ASYMPTOMATIC HYPERURICEMIA AFTER RENAL TRANSPLANTATION ON MORTALITY AND GRAFT LOSS

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Background: Hyperuricemia is very common after renal transplantation. It is associated with increased risk of cardiovascular events and chronic allograft nephropathy. However, no data exist about any benefit of a medical treatment of asymptomatic hyperuriceamia in patients after renal transplantation.
Methods: Adult patients who underwent kidney transplantation at the Charité-Universitätsmedizin Berlin between 1996 and 2011 were retrospectively included in the study. Patients were identified from our outpatient charts and the hospital's electronic database by searching with the keywords: hyperuricemia, allopurinol, benzbromaron. Patients were followed-up for a maximal period of 120 months.
Results: Of 503 kidney transplant patients were identified and included in the trial. From these, 211 patients with uric acid >7 mg/dl one month after transplantation (no treatment of hyperuricemia at this time) were considered for further analysis. 126 patients were treated with allopurinol ($n = 61$) or benzbromaron ($n = 65$) and 85 did not receive any of these medications in the follow-up period and served as control group. Baseline characteristics did not differ between groups. In the mean follow-up of 78 ± 35 months 21 patients of the control group and 12 patient in the treatment group had graft loss and returned to hemodialysis ($P < 0.001$). 17 patients in the control group and 29 patients in the treatment group died during follow-up ($P = 0.49$). The combined endpoint graft loss or death was significant lower in the treatment group, even when adjusted for age, gender and eGFR (estimated Glomerular Filtration Rate) at one month after transplantation. Survival rates did not differ between patients treated with allopurinol or benzbromaron.
Conclusions: Renal transplant patients with asymptomatic hyperuricemia defined as an uric acid level >7 mg/dl had a longer overall- and graft-survival when treated with allopurinol or benzbromaron in the current trial. To the best of our knowledge, this retrospective analysis constitutes the first study on the effect of treatment of asymptomatic hyperuricemia on mortality and graft loss.

THORACIC ORGANS I

V04 COMBINED HEART-LIVER TRANSPLANTATIONS WITHIN EUROPE – RESULTS OF A ELTR-WIDE SURVEY

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Introduction: Combined heart-liver transplantations (CHLT) are rarely performed procedures. European experiences are limited to occasional case reports or case series. Therefore, we conducted, in close collaboration with the European Liver Transplant Registry (ELTR), a survey to acquire the current status of CHLT within Europe.
Methods: The survey included an enquiry for recipient and donor demographics, operation data and follow-up data including the immunosuppressive regime after CHLT. The questionnaires were sent to all centres having performed CHLT, which were registered by the ELTR.
Results: We obtained data from 57 CHLT. The 1-year- and 5-year-survival in our cohort is 68.4 and 57.9 %. In most cases (52.6 %), indication for CHLT was familial amyloid polyneuropathy (FAP). The operation mode differed widely, but mostly either implantations of the liver were performed after weaning of the cardiopulmonary bypass and without use of a veno-venous bypass ($n = 14$; 31.1 %) or liver transplantation with the recipients still on cardiopulmonary bypass ($n = 13$; 28.9 %). The time period of cardio-pulmonary bypass time was significantly shorter in patients who were liver transplanted after cardio-pulmonary bypass weaning (121 vs. 240 min, $P < 0.000$). The cardio-pulmonary bypass duration was an outcome determining variable: patients with a fastly weaned bypass had a significant better outcome than patients whose liver transplantation was performed while being on cardio-pulmonary bypass ($P = 0.009$). For immunosuppression, most centres used the usual liver protocol (71.4 %) of their centre, followed by the use of the usual heart protocol (24.5 %).
Discussion: This series represents by far the largest European cohort of CHLT recipients. Furthermore, it is the largest series describing the operation technique and the immunosuppressive strategies in CHLT patients. Main indication was familial amyloid polyneuropathy. The duration of the cardiopulmonary bypass played an important role in the survival of the recipient and should be taken in account when planning this procedure.

V05 THE MUNICH LUNG TRANSPLANT GROUP: WAITING LIST DURING THE FIRST 9 MONTHS OF THE LUNG ALLOCATION SCORE ERA

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The Eurotransplant Foundation introduced the lung allocation score (LAS) in Germany on December 10th, 2011. We analyzed characteristics of the Munich Lung Transplant Group (MLTG) waiting list during the first 9 month after the introduction of the LAS.

A mean number of 39 + 1 patients were constantly listed for lung transplantation and 60 transplants were performed by the MLTG during the observation period. While the majority (42 + 0%) of patients waiting for transplant comprised of chronic obstructive pulmonary disease (COPD)/emphysema patients, only 26% of transplanted patients suffered from COPD/emphysema. Instead, the majority (42%) of transplanted patients suffered from interstitial lung disease. Wainting times did not markedly change in the LAS era. Notably, patients with interstitial lung disease had shorter wainting times when compared to patients suffering from COPD/emphysem and cystic fibrosis, both on the waiting list and at the time of transplant.

The MLTG lung transplant waiting list has not markedly changed during the first 9 months after introduction of the LAS. Our data indicate that the LAS accomodates disease-specific patient statuses well. Although patients with interstitial lung disease are preferably transplanted, the LAS system provides a very reasonable basis to also list and transplant COPD/emphysema patients.

V06 MODULATION OF IMMUNE-MEDIATORS FROM DONOR LUNGS USING THE ORGAN CARE SYSTEM® – A POTENTIAL MECHANISM FOR IMPROVED OUTCOME

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Objectives: Release of donor-derived immune mediators (IM), triggering allorecognition and inflammation after transplantation (Tx), may impinge on clinical outcome using warm perfusion of donor lungs (Organ-Care-System®, OCS) or standard cold preservation (SOC). IM were analysed in preservation solutions (PS) and peripheral blood (PB), also clinical outcomes monitored.
Methods: IM were quantified in perfusion solutions (PS) and plasma at protein level by multiplex-technology at the end of warm preservation ($n = 12$) or cold storage ($n = 9$) and in PB. Donor and recipient demographics and midterm outcomes were analysed.
Results: In PS, concentrations of IL-6, IL-10, IL-16, IFN-g CXCL8, CCL4, Ang-2, PECAM-1 and PDGF-b were significantly higher in OCS than SOC ($P < 0.0001$). Inverse distribution was observed for FGF-b ($P = 0.005$). High concentrations in PS following OCS preservation correlated with lower concentrations of several IM in recipient plasma after Tx. OCS vs. SOC median donor age was 44.5 vs. 46 years. Median recipient age was 54.5 vs. 56 years, underlying diagnoses: idiopathic fibrosis ($n = 6$ vs. $n = 5$), cystic fibrosis ($n = 3$ vs. $n = 2$), idiopathic pulmonary hypertension ($n = 0$ vs. $n = 1$) and emphysema ($n = 3$ vs. $n = 1$). No significant differences of the median cross clamp times (minutes) for the right lung (430 vs. 505) and left lung (568.5 vs. 641) were seen. Shorter median ICU-stay was observed in the OCS group (3585 vs. 3750 min), as well shorter mechanical ventilation times (795 vs. 1051 min). Significantly higher %predicted FEV1 at discharge (FEV1) was seen in the OCS group (71% vs. 55%, $P = 0.04$). PGD-scores were lower at T24 in the OCS group ($P = 0.28$). Six-month-survival was not different in this small cohort. Correlations between Ang-2 as well as IL-6 concentrations and FEV1, mechanical ventilation time, paO2/FiO2 and ICU-stay were identified.
Conclusion: IM remained low in PS using SOC probably due to reduced metabolic activity in lung tissue during cold ischemia. During OCS preservation, significantly higher amounts of IM were released into PS which may potentially represent depletion from the organ by accumulation in PS. This 'dialysis' effect was associated with reduced inflammatory conditions in the recipient after Tx which, at least in our still limited experience, had a positive impact on the clinical outcome in the OCS group, in particular a tendency towards shorter mechanical ventilation, ICU-stay and lower PGD-scores and significantly higher early FEV1.

BASIC SCIENCE I

V07 INDUCTION OF AN IMMUNOSUPPRESSIVE MECHANISM BY PRETREATMENT OF RECIPIENTS WITH MITOMYCIN-INCUBATED DONOR BLOOOD CELLS IN A RAT HEART ALLOTRANSPLANT MODEL

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Purpose: Dendritic cells are immunomodulatory cells that can be transformed into suppressive cells by ex vivo treatment with mitomycin C (MMC). We applied the same treatment to peripheral blood mononuclear cells (PBMCs) or blood, and studied their mechanism of action in a rat heart allograft model.
Methods/Materials: Donor blood or PBMCs were incubated with MMC, washed and injected i.v. into recipients prior to heterotopic allogeneic heart transplantation. Further, PBMCs were depleted of monocytes and used in the same way. Grafts were analyzed for infiltrating cells, antibody-mediated and chronic rejection. Recipient PBMCs and spleen cells were characterised by flow cytometry and tested in vivo for their regulatory properties.
Results: Of 10^8 MMC-PBMCs significantly prolonged graft survival (65 $\pm$ 17 vs. 9 $\pm$ 0.3 days in untreated and 7 $\pm$ 1 days in PBMC-pretreated controls). MMC-blood treated animals showed a graft survival of 35 $\pm$ 4 days. Depletion of monocytes from MMC-PBMCs abrogated the graft-prolonging action. Suppression was donor- specific since third-party heart allograft survival showed no prolongation.

Analysis of graft infiltrating cells showed a significant increase of Treg-number in tolerated hearts when compared to naïve and rejected hearts (6.4 $\pm$ 3.8 vs. 0.2 vs. 1.1 $\pm$ 0.6 cells/field). Complement activation significantly decreased seven days after transplantation in comparison to rejected hearts. A non-significant narrowing of the vascular lumen of tolerated grafts was observed.

Tolerant recipients had an increased number of Tregs ($CD4^+CD25^+Foxp3^+$) in their blood (6.1 $\pm$ 1% vs. rejected 5.5 $\pm$ 0.3 %) and spleen (8.3 $\pm$ 1.1 % vs. rejected 6.7 $\pm$ 0.1 %). When adoptively transferred into syngeneic recipients these cells induced immunotolerance in contrast to cells from rejecting animals (PBMCs: 133.7 $\pm$ 100.2 vs. 15.2 $\pm$ 3.2; spleen cells: 120 $\pm$ 80 vs. 8 $\pm$ 1.3 days).
Conclusion: A single infusion of MMC-treated donor blood cells prior to transplantation strongly prolongs heart allograft survival. This effect might be mediated by MMC-induced regulatory mechanisms including an increase of Treg-number, and inhibition of antibody-mediated rejection.

V08 $CD27^{low}$ NK CELLS PROLONG ALLOGRAFT SURVIVAL IN MICE BY CONTROLLING ALLOREACTIVE $CD8^+$ T-CELLS IN A T-BET DEPENDENT MANNER

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Aim: We investigated the role of functionally distinct NK cell subsets in alloimmunity. We hypothesized that the dichotomous role of NK cells in transplantation can be explained by the functional heterogeneity of NK cell subsets.
Methods: Since T-bet controls the maturation of NK cells from $CD27^{high}$ NK cells to terminally-differentiated $CD27^{low}$ NK cells, we used $Rag^{-/-}T\text{-}bet^{-/-}$ mice (lack $CD27^{low}$ NK cells) to study the roles of $CD27^{low}$ versus $CD27^{high}$ NK cells in a model of T-cell-mediated allograft rejection under co-stimulatory blockade conditions (MR1 + CTLA4Ig).
Results: We found that T-cell-reconstituted $Rag1^{-/-}$ recipients (possessing $CD27^{low}$ NK cells) show significantly prolonged allograft survival (7 days MST) upon co-stimulatory blockade when compared to $Rag1^{-/-}T\text{-}bet^{-/-}$ mice (35 $\pm$ 3.4 versus 28 $\pm$ 1.2 days MST), indicating that $CD27^{low}$ NK cells can promote allograft survival. Critically, $Rag1^{-/-}T\text{-}bet^{-/-}$ recipients had strikingly elevated alloreactive memory $CD8^+$ T-cell responses, as indicated by high $CD8^+IFN\text{-}\gamma^+$ T-cell proliferation (1.4-fold). Furthermore, adoptive transfer experiments of $CD27^{low}$ NK cells into $Rag1^{-/-}T\text{-}bet^{-/-}$ STx recipients confirm that $CD27^{low}$ NK cells directly regulate $CD8^+$ T-cell responses by inhibiting the proliferation of alloreactive $IFN\text{-}\gamma^+CD8^+$ T-cells and controlling the availability of donor-derived-IL-15.
Conclusion: In summary, mature $CD27^{low}$ NK cells promote allograft survival under co-stimulatory blockade conditions by regulating alloreactive memory $CD8^+$ T-cell responses.

V09 STRUCTURAL AND FUNCTIONAL BASIS OF ANGIOTENSIN II AND PATHOGENIC IGG MEDIATED AT_1R ACTIVATION

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Angiotensin II type 1 (AT_1R) receptor signals stimuli provided by its natural ligand angiotensin II (Ang II) and pathogenic IgG antibodies (AT_1R-IgG) in severe transplant and autoimmune vasculopathies. AT_1R is well established pharmacologic target for several inverse agonists. Our new findings show differences in strength of activation and signalling effectors between Ang II and AT_1R-IgG. Elucidation of mechanisms governing AT_1R activation could have broad clinical relevance in renal and cardiovascular medicine.

To study differences in activation between Ang II and AT_1R-IgG, we developed a yeast model where the expression of a single human AT_1R is coupled to yeast's growth response in absence of Histidine. First, the human AT_1R cDNA was cloned in a yeast expression plasmid and expressed in the appropriate strain. AT_1R activation was induced by addition Ang II or AT_1R-IgG isolated from patients with associated renal pathology.

Both, Ang II and AT_1R-IgG triggered a dose-dependent increase in yeasts' growth. AT_1R-IgG stimulation induced stronger and more sustainable activation of the receptor than Ang II. Targeted mutagenesis was performed in order to identify which receptor regions govern the activation. Mutating of one cystein contained in the disulfide bridge connecting first (1ECL) and second extracellular loops (2ECL) of the protein impressively decreased activation in response to AT_1R-IgG, yet less to Ang II. Random mutations of 2ECL increased both AT_1R-IgG and Ang II mediated yeast growth. Finally, an introduction of point mutations associated with receptor activation stressed that specific amino acid changes in the 2ECL of the AT_1R triggered a highest activation of the receptor irrespective of the nature of the stimulus.

We successfully created a model allowing for structural and functional studies of AT_1R receptor plasticity. They provided us with new insights in similarities and differences of binding of AT_1R agonists. Better understanding of the molecular mechanisms responsible for AT_1R activation holds great potential for enhancing renal and cardiovascular health.

LIVER

V10 ENDOSCOPIC ULTRASOUND FOR THE DIAGNOSIS OF BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION

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Background: Biliary complications after liver transplantation (LT) are still common and are an important cause of mortality and morbidity. Until now, endoscopic retrograde cholangiopancreatography (ERCP) has been considered the gold standard for diagnosing such complications. The aim of this study was to evaluate the diagnostic yield and therapeutic impact of endoscopic ultrasound (EUS) in the management of biliary complications after LT.
Methods: Thirty-seven liver transplant patients who presented with clinical, biochemical, sonographic and / or histological evidence of biliary complications, and who first received EUS followed by ERCP, were enrolled into this prospective observational study. Subsequently, we evaluated the value of EUS in detecting and classifying biliary complications after LT.
Results: Thirty-seven biliary complications were detected in 32 patients. Endoscopic ultrasound showed an overall sensitivity and accuracy of 94.6% each. In cases of biliary cast and ischemic cholangiopathy, EUS was found to be diagnostically superior to ERCP and has had, in these cases, a significant impact on clinical decision-making. However, EUS was less reliable when diagnosing anastomotic strictures.
Conclusion: EUS can complement ERCP to improve diagnosis of biliary complications after LT and help guide treatment strategies to address these complications.

V11 CONTRAST ENHANCED ULTRASOUND CHOLANGIOGRAPHY VIA T-TUBE FOLLOWING LIVER TRANSPLANTATION

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The objective was to evaluate contrast enhanced ultrasound (CEUS) based cholangiography compared to conventional radiography as a reference method in patients after liver transplantation. Contrast agents were administered through T-tubes, which were placed during the operation. Twelve patients with side-to-side choledocho-choledochostomy and standardized intraoperative T-tube placement were investigated on the 5th postoperative day (POD 5) with both techniques. All images were digitally acquired and assessed in consensus by two investigators regarding complete anatomic visualization, depiction of pathology (e.g. delayed contrast outflow, stenosis, leakage) and general image quality. CEUS cholangiography showed comparable results in the detection of biliary pathology and overall image quality. Regarding the visualization of the extrahepatic bile duct CEUS produced limited results in six patients. In conclusion, CEUS cholangiography via T-tube represents a potential bedside test for visualization of intrahepatic bile ducts of transplanted livers; it's diagnostic value remains to be determined in further studies.

V12 COMPLICATIONS REQUIRING REOPERATION AFFECT THE OUTCOME AFTER LIVER TRANSPLANTATION

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Introduction: Surgical complications may have not only immediate, but also long term effects on postoperative outcomes. Here, we analyzed the effect of surgical (grade 3b) complications requiring an early reoperation on patients'- and graft survival following liver transplantation.
Methods: Graft and patient survival in relation to donor and recipient variables and the need for reoperation for complications of 277 consecutive liver transplants performed from January 2007 to December 2012 were analyzed.
Results: Of 277 liver transplants were performed in 252 patients. 47% (n = 118) required a reoperation in the early course after transplantation. Overall patient and graft survival at 1, 2 and 3 years was significantly reduced in patients requiring a reoperation. The major impact was found to be within the first 3 months after transplantation. Kaplan-Meier curves showed a similar course thereafter. In the multivariate analysis the need of reoperation, the MELD-score and the cold ischemia time correlated with the overall survival.
Conclusion: These data suggest that surgical complications after liver transplantation have a significant impact especially in the early phase after liver transplantation. Therefore, factors that determine the early postoperative course and surgical complication rates are most critical for the outcomes after liver transplantation.

PAEDIATRIC TRANSPLANTATION

V13 C1Q-FIXING DONOR-SPECIFIC HLA ANTIBODIES AT THE TIME OF KIDNEY TRANSPLANT BIOPSY ASSOCIATE WITH LATE GRAFT FAILURE IN PEDIATRIC RENAL TRANSPLANT RECIPIENTS

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Purpose: The role of antibody-mediated rejection (AMR) for late graft failure in pediatric renal transplant (RTx) recipients is poorly defined.
Methods: We therefore investigated 54 patients undergoing a late biopsy taken for clinical indications (>1 year post-transplant). Patients were tested for DSA and C1q-fixing DSA using the LABScreen Luminex kit (One Lambda) at the time of biopsy.
Results: Of 21/54 (39%) of the tested sera were DSA positive. In 20/21 (95%) patients with DSA the DSA were directed against HLA-class-II-antigens and 8/21 (38%) sera were C1q-fixing DSA positive. The 4-year graft survival post biopsy was significantly inferior in the DSA^+ (42%) compared to the DSA^- cohort (89%; $P = 0.002$). Furthermore graft survival for patients with C1q-fixing DSAs (12%) was significantly worse compared to DSA^- ($P < 0.001$) or C1q-negative DSA^+ patients (77%, $P = 0.04$). Overall 13 grafts failed: 10/13 (77%) patients were DSA positive, 2/13 (15%) were DSA negative, but C4d positive. Cox regression analysis revealed C1q-fixing DSA (HR 6.5) as a significant risk factor associated with graft loss.
Conclusions: In pediatric RTx recipients C1q-fixing DSAs at the time of a late graft biopsy for clinical indication associate with subsequent graft failure. In this cohort as many as 92% of the graft failures could be attributed to AMR.

V14 EPIDEMIOLOGY OF CYTOMEGALOVIRUS (CMV) INFECTION IN PAEDIATRIC RENAL TRANSPLANTATION AND PROPHYLAXIS WITH (VAL-)GANCICLOVIR: AN ANALYSIS OF THE CERTAIN REGISTRY

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Purpose: Controlled studies on (val-)ganciclovir (VGCV) prophylaxis for CMV prevention in paediatric renal transplantation are lacking.
Methods: In the framework of the Cooperative European Paediatric Renal Transplant Initiative (CERTAIN) Registry, we hence analysed the efficacy and safety of VGCV prophylaxis according to a standardised protocol among 242 paediatric kidney allograft recipients on a CNI-based regimen. 99 patients received VGCV for 3 months post-transplant (prophylaxis group), 143 patients without VGCV serving as controls.
Results: CMV high-risk (D+/R-) patients in the prophylaxis group experienced significantly less CMV events (infections and/or diseases) (12/48, 25%) than controls (10/15, 67%, $P = 0.003$). VGCV was generally well tolerated, but associated with a higher rate of anaemia (18% *vs.* 8% in controls; $P = 0.023$), leukopenia (23% *vs.* 10%; $P = 0.002$) and agranulocytosis (13% *vs.* 1%, $P = 0.001$). Patients suffering CMV events had a significantly lower eGFR than CMV-free patients, both 2 years and 3 years post-transplant (54.7 $\pm$ 20.3 vs. 66.4 $\pm$ 21.6 ml/min·1.73 m²; $P = 0.014$).
Conclusions: This is the largest study on the efficacy and safety of VGCV in this patient population. VGCV prophylaxis is effective against CMV in paediatric CMV high-risk renal transplant recipients with an acceptable safety profile. CMV infections are associated with a by 17% decreased graft function 3 years post-transplant.

V15 ABDOMINAL CLOSURE USING AN INTERIM MESH IN SIZE-MISMATCH PEDIATRIC LIVER TRANSPLANTATION – TECHNIQUE DESCRIPTION AND OUTCOME ANALYSIS

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Introduction: Based on a lack of size matched donors most children undergoing liver transplantation (LTX) receive a technical variant graft from adult donors, resulting in a large-for-size situation especially in smaller children. To avoid complications of further graft reduction (e.g. monosegmental LTX) or complications of an oversized liver graft (e.g. reduced graft perfusion, elevated intraabdominal pressure) we use an interim mesh. Here we describe our technique of step wise abdominal closure by a silastic mesh.
Methods: Retrospective analysis of our prospective LTX database with review of all surgical reports from 2003–2012. Transplantations were divided based on primary abdominal closure versus usage of a silastic mesh.
Results: Overall 298 pediatric LTX were performed, thereof 23 LTX were excluded from the study (1 intraoperative death; 22 combined liver-kidney transplantations). Primary closure was possible after 187/275(68%) LTX, whereas after 88/275(32%) LTX closure was performed using a patch. Decision about usage and size oft the patch (size trimmed) was guided by doppler ultrasound (DU) (single investigator; DU after reperfusion and abdominal closure, guided by systolic peak flow, resistance index, maximum portal flow). DU-guided operative reduction of the patch was performed every 3–4 days. Successful patch removal with definitive closure could be achieved in all children after a median of two revisions (range 1–14), after median 6 days (range 1–67 days) with no abdominal hernia development long-term (median follow-up 89 month). Children with patch were significantly younger 0.7(0–14.9) versus 2.8(0–15.9)years and lighter 7(2–35) versus 12(3–62)kg and had higher GRWR 4.4(1–12.5) versus 2.8(0.7–12)% compared to children with primary closure (all $P < 0.001$). Comparing donor age, weight, height, graft weight or kind of graft there was no significant difference. There was no significant difference in the graft (1-/5-y 78.3/71.5% versus 86.2/68.4%) or patient survival (1-/5-y 94.6/90.5% versus 95.1/90%) between children with or without patch ($P = 0.449/1$).
Conclusion: Successful abdominal closure in pediatric LTX using a silastic mesh with step-wise reduction could be achieved without further graft modifying surgery even in children with very large-for-size grafts.

KIDNEY/PANCREAS I

V16 ACTIVATION OF TRANSIENT RECEPTOR POTENTIAL VANILLOID TYPE 1 CHANNELS BY N-OCTANOYL DOPAMINE IMPROVES RENAL FUNCTION AFTER WARM ISCHEMIA BUT NOT AFTER PROLONGED COLD PRESERVATION

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Aim: N-octanoyl dopamine (NOD) improves renal function, when applied shortly before induction of acute kidney injury (AKI). It remains to be assessed how NOD convey its renoprotective properties, if NOD also protects after AKI induction, and if renal allograft recipients also benefit from NOD treatment.
Methods: AKI was induced by clamping the left renal artery (45 min) in unilateral nephrectomized Lewis or Spaque Dawley (SD), wild type (WT) and TRPV1$^{-/-}$ rats. Transplantations were performed in the Fisher to Lewis model using a standardized cold ischemia time of 20 h. Treatment was installed directly after restoration of organ perfusion. Renal function, histology and perfusion were assessed by serum creatinine, microscopy and magnetic resonance imaging (MRI) using arterial spin labeling (ASL).
Results: NOD significantly improved renal function in AKI WT Lewis and SD rats, but not in TRPV1$^{-/-}$ SD rats. Improved renal function was paralleled by reduced renal inflammation, yet no differences were found in the expression of inflammatory mediators (adhesion molecules and cytokines). Although MRI-ASL, showed a significant lower cortical perfusion in ischemic as compared to non-ischemic kidneys, no influence of NOD was observed. Even though prolonged cold storage did not abrogate TRPV1 activation by NOD, treatment of renal allograft recipients did not show a salutary effect.
Conclusions: While NOD treatment improves renal function after warm ischemia induced AKI, it does not so after prolonged cold ischemia. Since the renoprotective effect of NOD depends on TRPV1 activation, it remains to be assessed why its salutary effect is lost after prolonged cold ischemia.

V17 AGE-RELATED CHANGES IN RAT DONOR KIDNEYS RELEVANT FOR ORGAN QUALITY AND FUNCTION

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Background: Since the need of deceased donor kidneys for transplantation is much higher than organs available, the acceptance of allografts retrieved from older donors in or beyond their seventh decade has been markedly increased. Higher donor age is known to be associated with reduced allograft survival. However, acceptance of elder organs is not standardized yet since the underlying processes in physiological organ aging are not known so far.
Methods: Using a well-defined rat model we were interested to analyze functional and histomorphological changes in aging kidneys, age-dependent regulation of the TGF system (as key player of fibrosis), of Toll-like receptors (TLR, as part of the innate immune system) and of chemokines (as prototypic signaling molecules). Furthermore we were interested to find age-specific markers in the urine by NMR-spectroscopy.
Results: 3 and 24 months old male Sprague Dawley rats were investigated. Comparing rats 3 months of age with 24 months old rats no changes in blood pressure and heart rate could be detected. Old rats showed significantly increased proteinuria. Computer-aided morphometry of glomeruli demonstrated significantly increased accumulation of matrix, collagen and desmin, a marker for podocyte damage, in old rat kidneys. KI 67 staining revealed a significantly reduced cell proliferation in older rat kidneys. Electron microscopy confirmed structural changes of glomerular cells, membranes and matrix. TGFß1, TGFß2, Smad2, CCL5 and most TLR investigated (except TLR2,3 and 9) showed a significant higher mRNA expression in 24 months old rat kidneys. The numbers of T cells present in peritubular and periglomerular compartments and around vessels were much higher in older rats. Using NMR spectroscopy significant differences could be seen for 6 of the analyzed metabolites.
Conclusion: Healthy 24 months old rat kidneys show significant structural changes compared to younger kidneys. Locally expressed markers of fibrosis and immune activation were associated with kidney aging and infiltration of immune cells was observed. Regarding these results increasing knowledge about kidney aging will lead to novel methods and biomarkers for classifying pre-transplant organ quality. An adequate selection, combination and dosing of immunosuppressive drugs should help to increase the long-term function of allografts accepted from donors with advanced biological age.

V18 COMPLEMENT RECEPTOR (C5AR & C5L2) DEFICIENCY IN ACUTE KIDNEY INJURY (AKI)

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Background: Acute kidney injury (AKI) and is a relevant complication after in solid organ transplantation: incidence after lung tx: ~50–75 % and 40–70% after liver tx. AKI increases early post-operative morbidity and mortality. Rapid activation of the complement cascade with binding of C5a to C5aR and the orphan receptor C5a like 2 (C5L2) mediates inflammation and modulates the innate and adaptive immune response. So far, little is known about the differences between the C5aR and the C5L2 receptor mediated downstream signaling in ischemia reperfusion injury (IRI).
Methods: AKI by ischemia reperfusion injury (IRI) was induced in C5aR and C5L2 deficient and wild type control mice (WT; C57Bl/6) by transient unilateral clipping of the right renal pedicle for 45 min. The renal morphology, the glomerular filtration rate (GFR), renal blood flow (RBF) and expression of pro-fibrotic and pro-inflammatory markers and infiltrating leukocytes were analyzed three weeks after injury induction. Functional magnetic resonance imaging (MRI) was performed to further analyze renal perfusion and kidney volume.
Results: Complement receptor deficiency attenuated inflammation and macrophage infiltration due to IRI. In addition, fibrosis and collagen deposition were attenuated compared to WT mice. The protective effects in C5L2 deficient mice were clearly more pronounced than in C5aR deficient mice. By functional MRI we could show that IRI caused severe impairment of renal perfusion with a maximum at d7 and only little recovery after 3 weeks. In addition WT mice showed severe kidney volume loss correlating with progressive renal fibrosis. C5L2 deficient mice had a similar impairment of renal perfusion at d1 but less further decrease towards d7 and totally recovered to normal renal perfusion at 3 weeks. In line with the better renal perfusion, kidney volume loss was significantly less in C5L2 deficient mice at 3 weeks after IRI.
Conclusion: The study points towards a distinct role of C5L2 and C5aR signalling in inflammation and AKI. Complement modulating therapies might be promising therapeutic targets in treatment of AKI and also delayed graft function.

V19 ASSOCIATIONS OF SMOKING WITH ALTERATIONS IN RENAL HEMODYNAMICS MAY DEPEND ON SEX – INVESTIGATIONS IN POTENTIAL KIDNEY DONORS

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Problem: Cigarette smoking is a risk factor for renal damage, but little is known about subclinical effects of smoking on renal hemodynamics and parameters of renal function in humans. We examined the associations of smoking with systemic and renal hemodynamics and renal function parameters in healthy individuals.
Methods: Data from 196 potential living kidney donors were analysed retrospectively. Mean arterial blood pressure (MAP), effective renal plasma flow (ERPF) and creatinine clearance had been measured. We additionally calculated parameters of renal hemodynamics. Data were analyzed for the effects of smoking and sex dependent on age and MAP.
Results: Systemic and renal hemodynamic parameters did not differ between smokers and non-smokers. In non-smokers of both sexes MAP was negatively correlated with ERPF, and higher MAP was associated with increased renal vascular resistance and afferent arteriolar resistance, with glomerular pressure (P_G) remaining constant. However, in male, but not in female smokers, ERPF and P_G increased with MAP. A correlation of age with a steeper decline in ERPF in male smokers was lost in multiple regression analysis.
Conclusions: As compared to women, smoking men may exhibit an increased glomerular hydrostatic pressure, which is a known promoter of kidney damage.

V20 CORRELATION BETWEEN GLOMERULAR FILTRATION RATE (GFR) AND DIFFERENT MOLECULAR FORMS OF PSA

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Introduction: In patients with kidney insufficiency serological cancer markers should be interpreted with caution, because some markers are affected by reduced renal elimination. Several studies showed there is no significant effect of terminal renal failure on total PSA (t-PSA). This is different from free PSA (f-PSA): renal insufficiency leads to increased serum levels of this low molecular weight PSA form and causes a shift of the f/t-PSA ratio to higher values. Little data exists concerning the behaviour of complexed PSA (c-PSA) under the conditions of renal failure.
Materials and Methods: Blood samples have been analyzed for t-PSA, f-PSA and c-PSA in 104 patients (37 dialysis patients, 29 after renal transplantation and 38 with normal renal function). The correlation to the GFR (according to MDRD formula) was calculated. There is no significant difference in regards to age and prostate volume between the study groups. There are statistically significant differences between the GFR of the three patient groups ($P < 0.000$).
Results: The GFR has no influence on the serum values of t-PSA and c-PSA (correlation coefficients according to Pearson, 0.009 respectively 0.017). In contrast, f/t-PSA ratio is negatively correlated with renal function (correlation coefficient according to Pearson −0.415).
Conclusion: It seems that t-PSA and c-PSA are not affected by renal function. The ratio f/t-PSA shifts with decreasing GFR to higher values. Therefore, the decision limit of f/t-PSA ratio of men with normal kidney function is non-applicable to men with reduced GFR. Especially in transplant recipients the renal function should be taken into account when interpreting the f/t-PSA.

V21 DURATION OF IN HOUSE MACHINE PERFUSION AFTER COLD STORAGE AND ITS IMPACT ON EARLY REPERFUSION PARAMETERS IN PORCINE KIDNEYS

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Background: In house machine perfusion after cold storage (hypothermic reconditioning) has been proposed as convenient tool to improve kidney graft function. The present study aimed to investigate the influence of the duration of machine perfusion for early reperfusion parameters in porcine kidneys.
Methods: Kidney function after cold preservation (4°C, 18 h) and subsequent reconditioning by one or 4 h of pulsatile machine perfusion (HMP) was studied in an isolated kidney perfusion model in pigs ($n = 6$, resp.) and compared with simply cold stored grafts (CS).
Results: Compared to CS alone, 1 h of subsequent HMP significantly reduced perfusate concentrations of endothelin-1 and increased vascular release of nitric oxide upon warm reperfusion. Renal flow and kidney function (clearance and sodium reabsorption) were also significantly improved. The beneficial effect of HMP was not altered by extension of the HMP time to 4 h. Molecular effects of HMP comprised a significant (vs CS) mRNA elevation of the endothelial transcription factor KLF2 along with significantly lower expression of endothelin that were observed already at the end of 1 h HMP after CS.
Conclusion: Reconditioning of cold stored kidneys is possible, even if clinical logistics allow for as little as 1 h of therapy, while limited extension of the overall cold storage time by in house machine perfusion might also allow for postponing of the transplantation from night to early day work.

THORACIC ORGANS II

V22 MIDTERM CLINICAL OUTCOME IN HEART TRANSPLANT RECIPIENTS RECEIVING THYMOGLOBIN FOR INDUCTION THERAPY

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We have recently presented data showing that heart transplant recipients who require induction therapy with thymoglobin (THY) have a higher 1-year mortality than heart transplant recipients with standard therapy, especially when those patients were major histocompatibility complex (MHC) antibody positive. Here we present data on midterm mortality in HTx patients receiving calcineurin inhibitor-free induction therapy. We followed for up to five years a group of 55 patients who received THY (39 MHC positive patients and 16 patients with chronic kidney disease stages III-IV) and a control group ($n = 55$) who received standard immunosuppressive therapy. Age, sex, and diagnosis were comparable between the two groups ($P > 0.05$), whereas body mass index was significantly higher in the THY group compared with the control group (26.4 $\pm$ 3.8 kg/m^2 vs. 24.1 $\pm$ 4.1 kg/m^2; $P = 0.006$). Median follow up was 43.1 months (IQR:5.0–50.4 months) in the THY group and 45.6 months (IQR:36.8–51.7 months) in the controls. Unadjusted mortality tended to be higher in the THY group compared with the controls (34.5% vs. 18.2%; $P = 0.051$). However, the multivariable-adjusted hazard ratio (HR) of mortality did not differ between groups (HR for the THY group=1.69 (95%CI:0.78–3.68; $P = 0.187$). In the surviving patients, postoperative CRP levels remained longer elevated and postoperative platelets and white blood cell counts showed a more pronounced transient decrease in the THY group compared with the controls ($P = 0.001$–0.046). Compared with HTx patients receiving standard immunosuppressive therapy, our data indicate an acceptable midterm survival in the group of high-risk patients who require CNI-free induction therapy.

V23 CLINICAL OUTCOME IN HEART TRANSPLANT RECIPIENTS RECEIVING EVEROLIMUS PLUS DOSAGE REDUCTION OF TACROLIMUS

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It is currently not known whether in heart transplant (HTx) recipients the combination of everolimus (EVL) plus dosage reduction of tacrolimus (TAC) is superior to the regular TAC dosage regimen regarding clinical outcomes. We compared 5-year survival and kidney function in 67 maintenance HTx patients receiving EVL plus dosage reduction of TAC (EVL group) with 67 patients matched for age, sex and transplantation date receiving the regular TAC regimen (TAC group). Statistical analyses were performed using Kaplan-Meier survival estimates and 2-factor ANOVA. Initial estimated glomerular filtration rate (eGFR) was significantly lower and blood leucocyte counts were significantly higher in the EVL group compared with the TAC group (GFR: 38.5 $\pm$ 13.2 vs. 67.3 $\pm$ 29.5 ml/min/1.73^2;respectively, $P < 0.001$, blood leucocyte counts: 8.4 $\pm$ 2.9 vs. 7.0 $\pm$ 2.110^9/l, respectively, $P = 0.002$). Five-year mortality did not differ between groups (19.4% vs. 17.9%; $P = 0.766$). There were however significant time x treatment effects with respect to eGFR values ($P < 0.001$). In detail, eGFR decreased on average by 10 ml/min/1.73 m^2 during follow up in the TAC group but increased by 8 ml/min/1.73 m^2 in the EVL group. Blood leucocyte counts improved significantly in the EVL group but not in the TAC group ($P = 0.008$). Parameters of liver function did not change significantly, either in the EVL group or in the TAC group. EVL plus dosage reduction of TAC improved kidney function compared with the regular TAC dosage regimen. Despite poorer initial kidney function and higher blood leucocyte counts in the EVL group, 5-year survival was comparable between the two groups.

V24 INFLUENCE OF MITRAL REGURGITATION AT TIME OF IMPLANTATION ON OUTCOME IN PATIENTS WITH VENTRICULAR ASSIST DEVICES

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Objectives: Mitral regurgitation (MR) of any degree is a common finding in failing hearts and often due to left ventricular dilatation. However, the impact of MR at the time of left ventricular assist device (LVAD) implantation on outcome still remains unclear. The aim of this study was to evaluate changes in left ventricular geometry and MR grade during follow-up and the influence of pre-implant MR on long-term outcome.
Methods: Thirty-five consecutive patients, mean age 57.6 $\pm$ 11.5 years, underwent HeartWare HVAD implantation without concomitant mitral valve repair. Mean follow-up was 9.9 $\pm$ 7.1 months. Prospectively compiled trans-thoracic echocardiography data (baseline and follow-up) were retrospectively analyzed. Endpoints were death, stroke, thrombembolism, major bleeding and right heart failure during follow-up. Follow-up was complete in all patients.
Results: Left ventricular (LV) enddiastolic diameter decreased from 73.61 $\pm$ 12.13 mm to 64.36 $\pm$ 13.04 mm ($P = 0.04$). At the time of implantation, 27 patients (77.1%) had MR of any degree and in 17 patients (48.6%), MR was graded moderate to severe. At 3 months follow-up, only one patient (2.8%) had moderate MR and 12 patients had mild MR (34.3%); thus, the degree of MR decreased in a significant portion of patients. One-year survival in patients without MR at implant was 80% compared to 52% in patients with moderate to severe MR ($P = 0.156$). One-year event-free survival was 72% in patients without MR vs. 33% in patients with moderate to severe MR ($P = 0.035$).
Conclusions: The LV diameters and MR grades decreased during LVAD support. Although survival was not significantly different, event-free survival was significantly more common in patients that did not present moderate to severe MR at time of LVAD implantation.

V25 THE USE OF ROUTINE ENDOMYOCARDIAL BIOPSY FOR DIAGNOSIS OF CELLULAR REJECTION BEYOND 2 YEARS AFTER CARDIAC TRANSPLANTATION

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Introduction: Endomyocardial biopsy (EMB) is widely used for routine surveillance of cardiac allograft rejection. The need for continued EMB beyond the first year after cardiac transplantation is controversial. EMB is performed through the jugular or femoral veins and is associated with a complication rate of less than 1%. The aim of this study was to investigate the use of EMB in monitoring long term surviving heart transplant recipients.
Methods: We conducted a retrospective chart review of all patients at our center 2 years or more after heart transplantation.97 long-term survivors after HTx between 2000 and 2011 were included in this study. Significant cellular rejection was defined as grade 2R or 3R using ISHLT nomenclature. Patients were analyzed assessing immunosuppressive regimen and procedural related complications.
Results: Out of 97 long-term survivors of cardiac transplantation, 17 patients developed at least 1 episode of significant late (>2 years after Tx) cellular rejection (17.5%). Analyzing the respective immunosuppressive regimen showed increased number of calcineurin inhibitor (CNI)-free regimen (64.7%) in patients rejecting late after heart transplantation. Only 35.3% of late cellular rejections occurred in patients treated with Ciclosporin A or Tacrolimus. The overall incidence of procedural related complications was low (1.0%) and none was life threatening.
Conclusion: The above data demonstrates that endomyocardial biopsies continue to detect clinically significant rejection beyond 2 years after cardiac transplantation. Late rejection was not depending on previous episodes of early cellular rejections. Therefore, we recommend routine endomyocardial biopsies in cardiac transplant recipients even though late after transplantation.

V26 CLOPIDOGREL PRESERVES MICROVASCULAR VASCULAR INTEGRITY IN ORTHOTOPIC TRACHEAL TRANSPLANTS AFFECTED BY OBLITERATIVE BRONCHIOLITIS

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Introduction: Survival after lung transplantation is mainly limited by the development of chronic lung allograft dysfunction (CLAD). The aim of this study was to investigate if platelet inhibition by clopidogrel has an influence on the microvascular integrity of orthotopic tracheal allografts and the formation of obliterative bronchiolitis, present in the majority of patients suffering from CLAD.
Methods: C57Bl/6 ($H2^b$) donor tracheas were orthotopically transplanted into CBA.J ($H2^k$) recipients. Mice received clopidogrel alone or in combination with everolimus. Grafts were analyzed by serial tissue PO2 monitoring by a fluorescence quenching technique. Blood flow monitoring was performed by laser Doppler flowmetry and a Lectin-binding assay to analyze the function of the microvasculature on postoperative days 4, 10 and 30.
Results: Isografts showed a stable tissue PO2 and blood flow during the initial timepoints after transplantations. In contrast, allografts showed a steady decline in tissue PO2 and blood flow in rejecting airway allografts until the PO2 nadirs 10–12 days after transplantation. Continous administration of clopidogrel (Clopi) or Everolimus (Evero) alone and in combination (EC) significantly improved tissue oxygenation, limited microvascular leakiness, and prevented airway ischemia. (Fig. 1)
Conclusions: These data demonstrate that clopidogrel alone and in combination with everolimus ameliorates microvascular injury during acute airway rejection and subsequently reduces post-transplant obliterative bronchiolitis.

V27 HVAD CONTINUOUS FLOW VENTRICULAR ASSIST DEVICE FOR ISCHEMIC VENTRICULAR SEPTAL RUPTURE – NO NEED FOR A TOTAL ARTIFICIAL HEART!

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Background: Ventricular septal defect after myocardial infarction (post-MI-VSD) is a severe complication and associated with high mortality. Surgical closure is necessary for all hemodynamically-relevant shunts, but surgery has a high risk of postoperative right or left heart failure. Total artificial heart implantation is a classical indication for patients in cardiogenic shock from post-MI-VSD.
Methods: Three patients with post-MI-VSD (age 46, 47 and 67 years old) emergently underwent HeartWare ventricular assist devices (HVAD) implantation. The patients were in INTERMACS class 1 to 2. In two patients, an occluded LAD was the reason for acute LV failure and the post-MI-VSD. The patients had surgical patch closure of the VSD with concomitant LVAD implantation. In these patients, the VSD patch was extended around the LV apex like a modified Dor plasty and had the HeartWare sewing ring attached to it. In another patient, an occluded RCA led to post-MI-VSD and caused predominant RV failure. He had VSD patch closure and the HVAD was implanted into the RV. Procedural and clinical outcomes were analysed.
Results: All three patients survived the first 30 days and could be discharged. The first patient had an uneventful follow-up of six months. The second patient had a pump thrombosis of the RVAD and the device was explanted with partially recovered RV function after 3 months. Due to a recurrence of RV failure, however, the patient required heart transplanted six months later and recovered completely. The third patient died of a fatal device mishandling six months after LVAD implantation.
Conclusion: Surgical closure of post-MI-VSD with concomitant continuous flow LVAD or RVAD implantation is feasible and might obviate the need for a total artificial heart in these specific patients.

BASIC SCIENCE II

V28 COSTIMULATION BLOCKADE BY BELATACEPT INHIBITS ALLO-SPECIFIC DE NOVO T CELL RESPONSES AND PRESERVES VIRUS-SPECIFIC MEMORY T CELL RESPONSES IN HEALTHY DONORS AND KIDNEY TRANSPLANTED PATIENTS

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Purpose: Belatacept (Bela) inhibits T cell activation at the interaction between costimulatory CD28 and its ligands CD80/CD86. Side effects are minimal compared to calcineurin or mTOR inhibitors. However, patients with Belatacept-based immunosuppression showed increased acute T cell mediated rejections (TCMRs) early after kidney transplantation (KTx) and more frequently EBV or CMV reactivation. EBV-derived virus like particles (VLPs) are currently discussed as vaccination strategy for Ktx candidates. Our project was designed to compare inhibitory capacities of Bela, CNI, mTORi regarding allogeneic de novo and memory virus-specific T cell responses in healthy donors and kidney recipients.
Methods: IFNg-ELISpots and intracellular cytokine staining were performed with PBMCs of healthy donors (HD) ($n = 9$) or KTx patients ($n = 7$) with or without Bela, CTLA-4-Ig or CNI/mTORi. Supernatants were tested for cytokines by multiplex assays. T cells were stimulated with CMV, EBV or flu peptides (CEF), allogeneic LCL, EBV-VLPs or PHA as control. Binding of Bela to CD80/CD86$^+$ immune cells was compared to CTLA-4-Ig.
Results: While CNI completely blocked both virus- and allospecific T cell responses, Bela was unable to inhibit virus-specific IFNg production of memory T cells. In contrast, IFNg and IL-2 but not IL-10 and IL-17 production by de novo allo-specific T cells was inhibited by Bela and CTLA-4-Ig in HD and KTx patients. Bela displayed stronger binding than CTLA-4-Ig to CD80/CD86 + immune cells. Compared to CNI, mTORi were less efficient in inhibiting T cell responses. EBV-VLPs induced weak IFNg production in CD4 + T cells in HD whereas significantly weaker responses were seen in KTx patients.
Conclusions: In contrast to CNI, virus-specific memory T cell responses were not impaired in HD and kidney Tx patients by costimulation blockade. Allo-specific IFN-g and IL-2 production was impaired by costimulation blockade while other cytokines remained unaffected which may be responsible for the increased TCMR frequency early after KTx. EBV-specific VLPs may represent vaccination strategy for KTx patients despite their limited capacity to induce T cell responses. Our studies argue for individual variability of the sensitivity towards Bela among HD and KTx recipients which implies that predisposition of the immune response determines susceptibility to costimulation blockade.

V29 COSTIMULATORY BLOCKADE SUPPRESSES TH1- BUT NOT TH2- AND TH17-MEDIATED ALLOIMMUNE RESPONSES

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Background: Costimulatory blockade resistant allograft rejection remains an understudied obstacle of this promising strategy for tolerance induction in transplantation. Therefore, the purpose of this study was to evaluate the responsiveness of distinct T helper cell subsets to treatment with costimulatory blockade.
Methods: We transferred purified T cells from B6.RORγt knockout (KO), B6.T-bet KO, and B6.RORγt-T-bet double KO (DKO) mice into B6.Rag-common-γc DKO recipients of fully mismatched Balb/c skin allografts +/- treatment with CTLA4Ig and anti-CD154.
Results: Untreated controls from all used mouse strains promptly rejected their skin allografts with similar kinetics. However, immunological analyses (histology, flow cytometry, ELISA) revealed that RORγt KO T cell recipients showed a Th1-mediated allograft rejection while T-bet KO recipients featured a Th17/Th2-driven rejection. Moreover, DKO T cells rejected early with a Th2 phenotype (high IL-4 levels and eosinophilic allograft infiltration). Importantly, under treatment with costimulatory blockade RORγt KO T cells showed a significantly prolonged allograft survival (MST 76.2 days+/−24.3 days), whereas T-bet KO (MST 22.25 days+/−8.5 days) or DKO recipients rejected promptly (MST 27.5 days+/−10.1 days) with a mixed Th2/Th17 and Th2 phenotype, respectively (as indicated by IL4, IL-17 and IFN-γ levels in FACS and ELISA).
Conclusion: These results indicate that costimulatory blockade differentially affects Th2 and Th17 versus Th1 alloresponses, resulting in allograft rejection.

V30 ACUTE REJECTION IN MURINE RENAL TRANSPLANTATION IS ALLEVIATED BY A NOVEL INHIBITOR OF THE MCP1/CCR2 SIGNALING PATHWAY

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Introduction: Biopsies are often required to detect acute rejection after renal transplantation. Here, we tested a novel substance which inhibits the MCP1/CCR2 pathway via oligonucleotides in a murine renal Tx model. The aim was 1.) to detect potential effects of this drug on acute rejection processes and 2.) show that new imaging techniques may be helpful for a non-invasive monitoring.
Methods: Kidneys of Balb/c mice were transplanted onto B6. Mice were either treated with the anti-MCP1-Spiegelmer in monotherapy or in combination with subtherapeutic CsA (10 mg/kgBW). Transplant function was assessed by MRI on d 10. The outcome was compared with results from histology, immunohistochemistry, doppler ultrasound and RT-PCR.
Results: The number of F4/80$^+$ cells was significantly suppressed and kidney cortex perfusion measurements improved under combination therapy. IFN-g and TNFa were significantly suppressed under mono- and combination therapy. Similar results were found for BAFF. The apparent diffusion coefficient (ADC) of native kidneys and syngenic allografts did not show significant differences. Allogenic allografts without treatment showed significantly lower ADC ($P < 0.001$). Under combination therapy the ADC significantly improved ($P = 0.002$).
Conclusion: The novel drug based on oligonucleotide technology inhibiting the MCP1 alleviates acute rejection especially as an adjunct. Diffusion-weighted MRI may serve as new tool to non-invasively detect rejection processes.

V31 ISOLATED TRANSFER OF HUMAN PLATELETS RESULTS IN FORMATION OF TRANSPLANT ARTERIOSCLEROSIS IN A RAG2$^{-/-}$γ-CHAIN$^{-/-}$ MOUSE AORTIC XENOGRAFT MODEL

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Background: Platelets play an important role in the formation of vascular lesions. The aim of this study was to investigate the interaction of isolated human platelets (hPlts) with human endothelium in a Rag2$^{-/-}$γc$^{-/-}$ mouse model of human arterial xenotransplantation.
Methods: Inactivated and TRAP6-stimulated hPlts were phenotyped for surface markers (CD62p,CD63) by flow cytometry. Recovery of 2'–7'-dichlorofluorescein-labeled hPlts was detected with an in vivo fluorescence imager and by flow cytometry. Side branches of human mammary artery were implanted into the infrarenal aorta of Rag2$^{-/-}$γc$^{-/-}$ recipients, followed by daily application of 4×10^8 inactivated or activated hPlts. Arterial grafts were analyzed by histology on day 30 after transplantation.
Results: Inactivated hPlts showed low levels of CD62p and CD63 [17.32 ± 2.20% / 3.75 ± 0.84% ($n = 6$)]. After TRAP6 stimulation (activated hPlts), expression of CD62p and CD63 was markedly increased [89.03 ± 3.70% / 79.79 ± 4.13% ($n = 6$, $P < 0.001$)]. Circulating DCF-labeled hPlts were detected within the lung, liver, kidney, spleen and arteries of recipients. Activated platelets had lower in vivo recoveries compared to inactivated platelets after 60 min [4.53 ± 0.32%/36.71 ± 3.04% ($n = 5$, $P < 0.001$)]. Daily intravenous injection of inactivated or activated hPlts both groups showed intimal proliferation 30 days after transplantation [Rag2$^{-/-}$γc$^{-/-}$ + inactivated hPlts: 59.37 ± 4.91% ($n = 5$, $P < 0.001$ vs. control) and Rag2$^{-/-}$γc$^{-/-}$ + activated hPlts: 70.42 ± 19.55% ($n = 3$)].
Conclusion: Here we can show that isolated application of inactivated or activated hPlts in the absence of T-, B- and NK-cells results in the significant amounts of transplant arteriosclerosis.

V32 OPTIMISATION OF HEPATOCYTE TRANSPLANTATION USING REGULATORY T CELLS – AN *IN VITRO* MODEL USING PRIMARY HUMAN HEPATOCYTES

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Background: The liver is generally considered an immunoprivileged organ with comparatively low risk of rejection regarding solid organ transplantation. In accordance with this, tolerant liver transplanted patients show a higher percentage of regulatory T cells (T_{reg}) within the grafts. As key players of tolerance, they are capable of suppressing T cell mediated immune responses, but also may regulate effectors of innate immunity. Concerning human hepatocytes, only limited data is available on immunological processes involved following cell transplantation. Hence, this project's objectives were characterisation of hepatocyte-induced T cell responses as well as evaluation of the immunomodulatory potential of T_{reg} in this setting.

Methods: Hepatocyte isolation was carried out in a 2-step perfusion technique from partially resected livers and then cultured as monolayers. T_{reg} were sorted for a $CD4^+CD25^{high}$ phenotype from human peripheral blood lymphocytes and expanded with CD3/CD28-expanderbeads and high doses of interleukin-2. Using flow-cytometry, cell proliferation in mixed lymphocyte cultures (MLC) and mixed lymphocyte hepatocyte cultures (MLHC) was detected by labelling responder cells with PKH-26. Furthermore, multi-colour flow-cytometry was applied for characterisation of T cell subpopulations. Cytokine profiles from culture supernatants were determined by Bio-Plex technology.

Results: In comparison to conventional MLC, the T cell response to allogeneic stimulation with hepatocytes (MLHC) was distinctly reduced and showed a delayed onset. The reaction appeared to be especially $CD4^+$ T cell mediated, whereas the $CD8^+$ -subpopulation only proliferated slightly. However, an early up-regulation of the CD69-expression could be observed in this subgroup. T cell activation was efficiently suppressed by adding T_{reg}, whose immunomodulatory effect could be verified not only in the proliferative response but also in the cytokine profiles.

Conclusion: Primary human hepatocytes induce an especially $CD4^+$ T cell mediated immune response when co-cultured with allogeneic lymphocytes. Regulatory T cells have shown a promising potential for the modulation of these immune reactions.

LIVER/SMALL INTESTINE

V34 OPERATIONAL TOLERANCE CAUSES A LONG LASTING ACTIVE IMMUNOREGULATION WITHIN THE GRAFT

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Aims: Immunosuppression (IS) can be discontinued from selected, stable patients after liver transplantation resulting in operational tolerance (OT). While biomarkers can predict the outcome of IS withdrawal, the mechanisms mediating OT remain elusive.
Methods: In the current study, we analyzed serial liver biopsies obtained from adult liver recipients enrolled in a prospective multi-center IS withdrawal trial employing immunophenotyping and transcriptional profiling. Liver samples were collected before the initiation of IS withdrawal, at the time of rejection, or 1 and 3 years after complete drug discontinuation. In parallel immune cells from peripheral blood were analysed by flow analysis.
Results: Out of the 102 recipients participating in the trial, IS withdrawal was successful in 41 recipients. We analyzed mechanisms of tolerance in 15 patients with serial biopsies. The number of liver infiltrating T cell subsets did not differ at baseline between patients who rejected and those who successfully discontinued IS, However, to our surprise the tolerated grafts exhibited portal tract expansion with increased T cell infiltration despite normal transaminases and no signs of rejection one year after IS withdrawal. This was associated with preferential accumulation of CD4 + Foxp3 + T cells, a shift in the CD4/CD8 T cell ratio and a trend towards up-regulation of immune activation and regulatory genes. At three years after induction of operational tolerance the grafts had still large inflammatory infiltrates, but with reduced CD8 + T cells leading to an increased CD4/CD8 ratio suggestive of additional deletional mechanisms. The inflammatory gene signature returned to baseline 3 years after IS withdrawal. Changes within the graft were not paralleled by analysis of PBMCs.
Conclusion: We report here for the first time data suggesting that in human liver transplant recipients OT is an active, long-lasting phenomenon in which IS withdrawal elicits dominant immunoregulatory mechanisms that restrain effector alloimmune responses. The results will need to be taken into account when designing future diagnostic and therapeutic clinical studies aiming at achieving allograft tolerance in clinical organ transplantation.

V35 TUMOR DNA-INDEX AND α-FETOPROTEIN LEVEL DEFINE OUTCOME FOLLOWING LIVER TRANSPLANTATION FOR ADVANCED HEPATOCELLULAR CARCINOMA

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Background: Patients with hepatocellular carcinoma (HCC) beyond the Milan criteria (MC) are expected to have an inferior outcome after liver transplantation (LT) and are therefore currently not considered for LT in many countries. The purpose of this study was to identify predictive factors for overall survival (OS) following LT for HCC that may support MC in the selection of appropriate transplant candidates.
Patients and Methods: Clinicopathological data of 364 patients with HCC who underwent LT in a high-volume transplant center between 1989 and 2010 were retrospectively evaluated. Predictors of overall survival in the entire cohort as well as in subsets of patients within (n = 214) and beyond (n = 150) the MC were analyzed.
Results: After a median follow-up time of 78 months the median survival (MS) was 100 months. Factors associated with OS in univariate analysis included recipient age, tumor DNA-index, α-fetoprotein level (AFP), MC, bilobar lesions, microvascular invasion, tumor differentiation, and hepatitis C. In multivariate analysis, DNA-index>1.5 ($P < 0.0001$), AFP>200 ng/ml ($P = 0.009$), and HCC beyond MC ($P = 0.003$) independently predicted worse OS. In patients within the MC (MS = 170 months), DNA-index>1.5 ($P < 0.0001$) was the only predictive factor for OS in multivariate analysis. In patients beyond the MC (MS = 44 months), DNA-index>1.5, AFP>200 ng/ml, microvascular invasion, patient age > 60 years and DNA-index>1.5 concomitant with AFP>200 ng/ml were associated with worse OS in univariate analysis. Multivariate analysis identified DNA-index>1.5 concomitant with AFP>200 ng/ml ($P < 0.0001$) as the only independent predictor of worse OS.
Conclusions: DNA-index and AFP level predict OS following LT in patients with advanced HCC beyond the MC. Combined assessment of these markers during the evaluation of transplant candidates can contribute to the selection of patients with HCC who may benefit from LT independently of their tumor burden.

V36 REEVALUATION OF RATS' HEPATIC VASCULAR ANATOMY – GETTING READY FOR ALLPS MODEL

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Background: Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS) is a surgical strategy which induces a rapid regeneration of the future liver remnant (FLR). Regeneration seems to be faster than after classical PVL. However, the underlying mechanism is not yet investigated. Therefore we did a detailed anatomical study to clarify the anatomy of the portal vein and median hepatic vein of rats as a prerequisite to develop a surgical model.
Method: Reevaluation of the detailed vascular anatomy of ML was performed. 10 explanted livers were subjected to imaging techniques after microfil injection. 3D reconstruction was performed in order to visualize the spatial distribution of the vascular branches of portal vein and hepatic vein.
Result: Similar to the human liver, the ML was supplied by the right median and left median portal branches (RMPB and LMPB) and the parallel hepatic arterial branches. The ML was drained by 3 main branches: right median, middle median and left median hepatic vein (RMHV, MMHV and LMHV). The main bifurcation of MMHV was located in RML, draining not only the middle portion of ML, but also the anterior portion of LML. However, the spatial distribution of the branching pattern was subject to some variations potentially influencing the size of the territory at risk of outflow obstruction.
Conclusion: According to our anatomical study, it seems better to perform transection along the umbilical fissure in rats, although it can cause outflow obstruction of anterior portion of LML. In this case, a resection of the anterior portion of LML could be discussed.

V37 PREDICTIVE VALUE OF EARLY POSTOPERATIVE MELD SCORES ON PATIENT AND GRAFT SURVIVAL AFTER LIVER TRANSPLANTATION

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Early allograft dysfunction after liver transplantation is not well defined. The aim of this study was to evaluate predictive value of early postoperative MELD scores on 3- and 12-months survival.

In this single center retrospective study, 362 consecutive patients after liver transplantation were included. MELD scores at 7, 14, and 21 postoperative days (POD) were calculated from primary lab values.

About 89% of patients survived 3 months and 84% one year after transplantation. The graft survival rate was 84% after 3 months and 69% after one year. The MELD scores were on POD-7 21 ± 7 and 18 ± 8 (dead vs. alive patients, respectively), on POD-14: 20 ± 8 vs. 15 ± 7, at POD-21: 19 ± 8 vs. 15 ± 7 As shown by ROC analysis, the best cutoff of MELD score predicting the one-year patient survival was on POD-14 (17 for one-year survival and 19 for 3 months-survival, p

In conclusion, MELD scores early after liver transplantation are predictive for 3 and 12 months outcome. The postoperative MELD score on POD-14 is a good predictor for the patient survival and on POD-7 for the graft survival after liver transplantation.

V38 DEVELOPMENT OF A MODEL FOR ESTIMATION OF SUBCUTANEOUS HEPATITIS B IMMUNOGLOBULIN DOSE REQUIREMENT AFTER LIVER TRANSPLANTATION

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Subcutaneous HBIG dosing according to summary of product characteristics (SPC) which is based solely on a cutoff value of 75 kg body weight to categorize patients in those requiring a single (<75 kg, 500 IU/week) or a double shot (≥75 kg, 1000 IU/week) may not be sufficient to reliably estimate HBIG requirement. High interindividual variability of anti-HBs consumption may be of multifactorial etiology including distinct HBIG distribution and clearance. In our HBV transplant study, we aimed to identify predictive parameters for sc HBIG consumption. Laboratory parameters and bioelectrical impedance analysis were determined over 12 months from liver transplant (LT) HBV recipients ($n = 43$) who were converted from 2–3 monthly iv HBIG± nucleos (t) ide analogues (NUC) to weekly sc HBIG±NUC to identify additional factors that may impact anti-HBs titers. Pearson correlation analysis showed that anti-HBs titers were negatively associated with estimated glomerular filtration rate, total protein, total body water, fat-free mass and muscle mass and positively associated with serum creatinine, body weight, body mass index, body waist and fat mass. These results suggest that body composition may impact HBIG levels through distinct HBIG distribution. For a drug eliminated primarily via renal excretory mechanisms, renal dysfunction may also alter pharmacokinetics and pharmacodynamics. Moreover, we developed a model including "easy-to-apply" predictors for HBIG dose requirement that avoids excess titers and reduces the economic burden of passive immunoprophylaxis.

HOT TOPICS

V39 ORGAN ALLOCATION: CAN WE JUSTIFY THE PRIORITY GIVEN TO CHILDREN?

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In Germany as well as in the whole Eurotransplant region organ allocation rules give priority to children. Paediatricians refer to impending developmental disorders, and thus to the ethical principle of prevention of harm. They hereby imply that the medical urgency of adult patients has not the same ethical importance. Opponents of this priority rule argue that adults should not be discriminated against and all patients be given equal opportunity of their life being saved. Moreover, opponents object that in times of extreme organ shortage for example women of small height and weight do not have the chance to get a liver transplant. Rather, they have to accept a split-liver which involves several disadvantages in regard to complication and success rates.

Strong moral intuitions militate in favour of children's priority. At first sight, deontological theories seem to claim equality of chance and respect of dignity of every human being, regardless of their age or stage of life. Several promising arguments in favor of such a prioritization will be discussed, for example the idea to allow children a "normal life-span" or the idea of strengthening children as beings with no blame in the causation of their organ failure.

V40 CHINA'S ORGAN HARVESTING FROM PRISONERS: A NEVER ENDING STORY?

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Medical organizations worldwide condemn the use of organs from executed prisoners. China is the only country in the world that still systematically takes organs from executed prisoners for transplantation. Recently, Chinese officials announced the plan to integrate organs from executed prisoners into the public voluntary organ donation and allocation system. Huang Jiefu, director of the China Organ Donation Committee and former vice-minister of health, told Beijing Times on March 04 that "once the organs from willing death-row prisoners are enrolled into our unified allocation system, they are then counted as voluntary donation from citizens; the so called death-row donation doesn't exist any longer." If this plan is accepted by the international community, China will continue using prisoner organs and the unethical practice would officially bypass international standards. In addition to the acknowledged organ source of executed prisoners, there is accumulating evidence that China also harvests organs from political prisoners without consent. A recent piece of evidence came from the case of Wang Lijun, former police chief of Jinzhou City, who referred to several thousand cases in his transplantation research from 2004 to 2006. Transplantation professionals in the world must respond actively to stop this barbaric practice immediately.

V41 VALIDATION OF THE SUITABILITY OF LOPHIUS BIOSCIENCES T-TRACK® CMV TO ASSESS THE FUNCTIONALITY OF CELL-MEDIATED IMMUNITY (CMI) IN HEMODIALYSIS PATIENTS

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Objective: Impairment of cytomegalovirus (CMV)- specific cell-mediated immunity (CMI) by immunosuppressive therapy is a major cause for CMV reactivations and associated complications in solid organ transplantation. Thus, assessing the function ofCMV- specific CMI may help to predict the onset of complications and to individually adjust immunosuppressive as well as antiviral therapy. The novel diagnostic tool T-Track® CMV allows the simultaneous detection of CMV- reactive T-helper- and cytotoxic T-cells as well as NK- and NKT-cells using *activated* pp65 and IE-1 proteins for *in-vitro* restimulation of PBMC and a highly standardized IFN-gELISpot assay. The aim of this cross sectional multicenter study was to evaluate the suitability of the novel tool T-Track® CMV for assessing the functionality of CMV-specific CMI in a clinically relevant pre-transplant patient population.
Methods: Test sensitivity and specificity of T-Track® CMV were examined in a cohort of 124 hemodialysis patients of whom 67 (54%) revealed a CMV positive serostatus. Moreover the results of T-Track® CMV were compared with Quantiferon®-CMV and a cocktailof 6 preselected CMV tetramers as reference tests.
Results: Positive T-Track® CMV results were obtained in 60/67 (sensitivity 89.6%) of CMV- seropositive hemodialysis patients. Low, however significant numbers of IE-1- but not pp65- reactive cellswere observed in12 of 57 CMV-seronegative dialysis patients confirming data from other groups showing IE-1 specific T-cell responses in seronegative individuals.

For comparison, the reference tests Quantiferon®-CMV and CMV tetramer cocktail revealed sensitivities of 72.6% (45/62) and 76.9% (40/52), respectively.
Conclusion: T-Track® CMV can be used in a broad population of hemodialysis patients independent of their HLA-type. Thus, T-Track® CMV assay may also represent a valuable tool to assess functionality of CMV-specific CMI in transplant recipients and help to guide personalized antiviral and immunosuppressive therapy.

PSYCHOSOMATICS

V44 FREQUENCY OF SYMPTOMS OF DEPRESSION AND ANXIETY IN DIALYSIS AND LIVER CIRRHOSIS PATIENTS BEFORE AND AFTER ADMISSION TO THE WAITING LIST

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Introduction: Symptoms of depression and anxiety are known in patients with end stage kidney or liver disease who are potential candidates for organ transplantation. The aim of this study was to evaluate the frequency of symptoms of depression and anxiety in transplant candidates before and after admission to the waiting list.
Methods: Patients on dialysis or suffering from liver cirrhosis were evaluated by the Hospital Anxiety and Depression Scale (HADS) questionnaire. Results were stratified according to the underlying disease and age (<60; ≥60 years).
Results: In total, 41 dialysis and 42 liver cirrhosis patients were evaluated. In patients ≥60 years, 45% of the dialysis and 27% of liver cirrhosis patients and in patients <60 years, 25% of dialysis and 57% of liver cirrhosis patients indicated symptoms of depression. Symptoms of anxiety were observed in 30% of the dialysis patients, independent from age. In liver cirrhosis patients 52% of patients <60 years and 36%of patients ≥60 years showed symptoms of anxiety.
Conclusion: Patients with chronic liver and kidney disease show significant differences in the frequency of symptoms of depression or anxiety depending on the type of disease and age. These results have to be further analyzed in the context of quality of life and medication adherence.

V45 DELISTING AND "INACTIVE STATUS": SURVEY ON ETHICAL ASPECTS OF MANAGING A WAITING LIST IN TIMES OF DECREASING ORGAN DONATION

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The German „transplant scandal" had a severe impact on all aspects of organ transplantation in Germany. Mainly the donor rates dropped by almost 30% causing longer waiting times and an increase of death on the waiting list. The cause of manipulation in German liver transplant programs may have been the fact that only patients with a MELD>35 were transplanted with the consequence of accelerated postoperative morbidity and mortality. Thus the question of access to and removal from the waiting list has to be discussed: Should patients inappropriate for transplantation be listed and should patients be delisted after getting too sick for transplantation?

By surveying „google" (g) and „pubmed" (p) the dimension of discussion was quantified. Subsequently the retrieved articles on pubmed were analyzed concerning the decision criteria and their coverage of ethical dimensions.

The following number of hits was retrieved: „delisting and kidney transplantation": g: 104.000, p:3, „delisting and cardiac transplantation": g:21.900, P:15, „delisting and liver transplantation": G:1.150.000, p: 15, „delisting and lung transplantation": g:41.100, p:4. Almost every publication retrieved in p gave clear cut medical criteria for listing and delisting, however delisting was ony a small chapter. Only three publications touched ethical aspects. Several papers compared the prognosis after delisting with remaining on the list and transplantation. Delisting does not seem to have a definite beneficial effect on the waiting list as well as the consequences of „inactivating" a candidate. In heart transplant programs patients may be delisted because they recovered by medical treatment and became „too good for transplantation".

The high number of retrievals in google demonstrates that delisting and inactivating are of great interest in the waiting list management of liver transplantation. Obviously the guidelines in the other fields of transplantation are clear enough. The ethical aspects of „adequacy for transplantation" remain poorly assessed.

V46 WHICH RULES FOR ORGAN DONATION AND ALLOCATION ARE ETHICALLY ACCEPTABLE AND EFFECTIVE IN RELIEVING THE SHORTAGE OF TRANPLANTABLE ORGANS?

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Objectives: The paper aims at defining formal and informal rules of organ donation and allocation which are politically and ethically acceptable and would contribute to relieving the global shortage of transplantable organs.
Material and Methods: 1. The literature of medical, health economics and ethics on organ shortage is assessed with respect to existing and possible new rules for organ donation and allocation.

2. 80 empirical surveys in rich and poor countries on the preference of people for alternative rules of organ donation and allocation are assessed.
Results: The literature shows that reciprocity rules would contribute to relieving the organ shortage. From empirical surveys one can conclude that many people consider a system of organ donation and allocation as a fair system if it is based on reciprocity. The paper shows how reciprocity rules could be implemented in national and international legislation on organ donation and allocation.
Conclusions: The national and global shortage of transplantable organs leads transplant physicians and politicians to reconsider the current rules of organ donation and allocation. Additional elements of reciprocity to the current rules should be a guidepost for further reforms.

KIDNEY/PANCREAS II

V47 DUODENAL LEAKS AFTER PANCREAS TRANSPLANTATION WITH ENTERIC DRAINAGE – CHARACTERISTICS AND RISK FACTORS

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Background: Simultaneous pancreas-kidney (SPK) and pancreas after kidney (PAK) transplantation with enteric drainage has become a standard treatment in diabetic patients with renal failure. Leaks of the graft duodenum are a common complication after transplantation. We studied causes and predisposing factors of duodenal leaks in both SPK and PAK transplantation.
Method: Between January 2002 and April 2013 284 pancreas transplantations with enteric drainage were performed at our institution including 191 SPK (67.3%) and 93 PAK (32.7%). We analyzed the occurrence of duodenal leaks, anamnestic risk factors, leak etiology, and graft survival.
Results: Out of 18 duodenal leaks (incidence 6.3%), 12 cumulated over the first 100 days after transplantation. 6 pancreas grafts with duodenal leak were rescued by duodenal segment resection. PAK transplantation sequence (odds ratio 3.526, $P = 0.008$) and preoperative immunosuppression (odds ratio 3.328, $P = 0.012$) were significant risk factors for duodenal leaks. In the SPK subgroup, postoperative peak amylase as marker of reperfusion injury was associated with an increased incidence of duodenal leaks. No anamnestic donor or recipient aspect showed a significant influence on duodenal leak occurrence.
Conclusion: Long-term immunosuppression in PAK transplantation is a risk factor for duodenal leaks. Early surgical revision offers the chance of pancreatic graft rescue.

V48 COMPARISON OF HISTIDINE-TRYPTOPHAN-KETOGLUTARATE (HTK) SOLUTION AND UNIVERSITY OF WISCONSIN (UW) SOLUTION IN PANCREAS TRANSPLANTATION

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Backround: HTK solution is currently the most common used solution for pancreas transplantation (PT) in Germany. The use of HTK is controversial, particular in pancreas grafts with longer ischemia times.
Methods: A total of 240 PT (218 SPK, 16 PAK, 6 PTA) procedures were performed in our centre between 2002 and 2012. HTK was used in 133 patients, and UW in 107 patients. We retrospectively compared our experience with these two types of preservation solutions, focusing on graft and patient survivals, as well as postoperative complications.
Results: Demographic data of donors and recipients showed no significant difference.

With a mean follow-up of 75.2 $\pm$ 39.9 months, both groups demonstrated comparable patient survivals after 1, 3 and 5 years (HTK 96.2, 94.7 and 92.0%; UW 95.3, 91.7 and 90.7%, $P = 0.451$). Pancreas graft survival rates after 1.3 and 5 years were significant better in the HTK-group (84.2, 82.6, 80.0%) vs. the UW-group (74.9, 71.1, 67.3%) $P = 0.013$. Relaparotomy-rate within the first three postoperative months was not significant different for both the groups (HTK 44.36% versus UW 43.93%). Serum amylase and lipase values did not differ between both groups.

In a subgroup analysis of 98 pancreas grafts (UW 44 / HTK 54) with a cold ischemic time > 12 h (mean CIT UW: 14.2 $\pm$ 1.7; HTK: 14.1 $\pm$ 1.6) UW and HTK were similar.
Conclusion: In our study, we demonstrate equal results for patient survival, and a better pancreas graft survival using HTK in pancreas transplantation. No increased incidence of allograft pancreatitis or graft loss was observed, especially in PT with longer ischemic time. However, this study has some limitations (single center, retrospective), and the comparison of both solutions was an analysis of two different time points as well (UW-group historically older). Therefore, the results should be interpreted with caution.

V49 ELUCIDATING ISCHEMIA REPERFUSION INJURY IN HUMAN RENAL TRANSPLANTS BY MICRORNA PROFILING USING NEXT GENERATION SEQUENCING

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Small noncoding RNA fragments of 20–24 bp, so called microRNAs, are important gene regulators in various (patho-) physiological processes. To date, pre-perfusion kidney biopsies fail to predict post-transplant pathologies, especially delayed graft function) as a consequence of ischemia reperfusion injury (I/R-injury). Profiling of microRNA, obtained by next generation sequencing, might offer the ability to generate specific molecular patterns to elucidate pathways in I/R -njury and predicting clinical outcome.

Formalin-fixed paraffin embedded (FFPE) pre perfusion biopsies of different clinical graft injuries were used to perform microRNA profiling. The next generation sequencing platform “Ion Torrent” was used to assess microRNA profiles. Data were analyzed by Geneious Pro

In all biopsies with different clinical graft injuries robust and reproducible microRNA profiles, even if only small amounts of tissue could be used, were obtained. Different microRNA profiles with differential expression could be shown in an unsupervised hierarchical clustering which revealed specific microRNA expression patterns related to clinical outcome and graft injury.

This work proved the ability of microRNA profiles to offer the potential of revealing specific pathways which are involved in graft injury after renal transplantation. Further research is needed to clarify the interaction between specific microRNAs, gene expression, graft injury and clinical outcome.

INFECTIONS AND COMPLICATIONS

V51 HIGH SVR AFTER TELAPREVIR BASED ANTIVIRAL TRIPLE THERAPY FOR HCV-REINFECTION AFTER ORTHOTOPIC LIVER TRANSPLANTATION

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Background: The development of graft cirrhosis due to HCV-reinfection remains a major problem after orthotopic liver transplantation (OLT). Protease inhibitors have extended the antiviral treatment options especially in genotype-1 infected HCV relapsers and non-responders to Pegylated Interferon/Ribavirin therapy. The aim of this study was to analyze the significance of telaprevir based triple therapy for patients with HCV-reinfection after OLT.
Methods: We included 12 patients with histologically confirmed graft fibrosis due to HCV-reinfection. Treatment duration was scheduled for 12 weeks of telaprevir based antiviral triple therapy followed by 36 weeks of consecutive dual therapy with Pegylated Interferon/Ribavirin.
Results: Of 6/12 patients (50%) completed the full 48 weeks of antiviral treatment. Triple therapy had to be discontinued in one patient due to non-response and in one patient due to severe hematological side effects. Four patients did not complete dual therapy due to hematological and/or renal side effects. One year after begin of antiviral treatment 8/12 patients (66%) showed a sustained virological response (SVR).
Conclusion: Telaprevir based triple therapy may be an effective treatment option for individual patients with HCV graft hepatitis. However treatment management is complex and patients need to be carefully monitored for drug-drug interactions and possibly severe treatment-related side effects.

V52 DACLATASVIR, SIMEPREVIR AND RIBAVIRIN AS A NEW IFN-FREE TRIPLE REGIMEN FOR HCV RECURRENCE AFTER LIVER TRANSPLANTATION: FIRST RESULTS OF SAFETY AND EFFICACY IN 6 PATIENTS

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Background: Recurrent HCV infection following liver transplantation leads to accelerated allograft injury and is associated with reduced graft and patient survival. Therapeutic intervention with interferon is difficult due to poor efficacy and tolerability. The application of first generation PIs is limited due to drug-drug interactions with immunosuppressants (IS). The introduction of new IFN-free therapeutic options with DAA-combinations are in the prospect to substantially improve the outcome for LT patients with HCV.
Methods: Daclatasvir 60 mg/daily, simeprevir 150 mg/daily and ribavirin 600 mg /daily were administered as an all oral triple regimen to 6 LT patients with recurrent HCV infection, one with genotype 1a and 5 with genotype 1b. All patients were treated for 24 weeks and monitored closely concerning trough levels of IS (one received everolimus and five tacrolimus), laboratory parameters and potential side effects.
Results: One patient experienced a viral breakthrough at treatment week (tw) 8 which was associated with emergence of resistance-associated mutations in the NS3 protease domain as well as a NS5A deletion. Antiviral regimen was successfully swiched to sofosbuvir / RBV in this case. The remaining five patients cleared viral load between tw 4 and 8 and achieved end of treatment response (EOT), three patients have a SVR4 at that stage. Clinical parameters (ALT, AST, bilirubin, fibrosis stage) improved in all patients except a moderate transient increase of bilirubin in one. All patients tolerated the medication very well. Adverse events were hardly observed and limited to moderate anemia due to RBV. Uptake of IS and trough levels were constant during therapy, the dose of IS did not have to be adjusted.
Conclusions: Our observations suggest the described regime as safe and efficient for LT patients and provide great promise for the use of this all-oral antiviral regimen in other immunosuppressed and IFN-intolerant HCV patients.

ORGAN DONATION/MARGINAL ORGANS

V53 BEGGARS CAN'T BE CHOOSERS: THE FATE OF DECLINED LIVER ORGAN OFFERS

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Background: In a scenario of severe organ shortage the decline of potentially transplantable livers has to be critically analyzed. With the intention to evaluate our clinical decision-making within the organ acceptance process, we have followed the fate of liver organ offers, that were declined by our transplant team.
Methods: Declined organ offers from primary MELD-based allocation and rescue allocation from 2012 to 2014 were analyzed. Primary outcome data were provided by the Eurotransplant registry. The compound endpoint "successful transplant" included: 1) 90-days patient survival without 2) a retransplant for primary graft dysfunction or 3) an indication for relisting within 90 days after transplant.
Results: From 2012 to 2014 $n = 325$ liver organ offers were handled by our team. The organ refusal rate (ORR) was similar for different surgeons (ORR 57–68%) A trend towards higher ORR was found for early-hour offers (12 pm – 8 am 74%). Reasons for refusal were size (22%), elevated liver enzymes (14%), organ quality (13%), recipient readiness (8%), BMI (6%) and age (5%). However, no significant differences were found between declined and accepted liver offers with respect to age (56.2 vs. 53.3 years), male gender (56 vs. 56%), BMI (27 vs. 26), cause of death, BAR-Score (12.8 vs. 9.9) and DRI (1.8 vs. 1.6).

125 of 201 (62%) liver organ offers, that were declined by our team, were transplanted elsewhere after a total of 13.2 offers per donor. Relisting or death
Conclusion: These findings suggest that the majority of declined organs could be successfully transplanted. A poor donor-recipient match may be a component of the high rate of declined organs. However, we cannot exclude that a proportion of wait list mortality results from declined, rather than lack of opportunity, for transplantation. Therefore, decision making whether to accept or not an offered organ has to be critically appraised in the context of severe organ shortage.

LONG-TERM COMPLICATIONS

V56 PREVALENCE OF DIABETES AND PREDIABETES AMONG KIDNEY TRANSPLANT WAITING LIST CANDIDATES

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Purpose: Diabetes mellitus (DM), the most common cause of ESRD, limits access to transplantation and impairs patient and allograft outcome. Prediabetes is an independent risk factor for progression to overt DM, as well as post-transplant DM. Albeit a modifiable risk factor, a paucity of data exists on the prevalence on kidney transplantat waiting list.
Methods: The active kidney transplant waiting list of a large European university hospital transplant center was metabolically phenotyped using oral glucose tolerance test. Indices for insulin sensitivity and secretion were calculated.
Results: Of the 138 patients investigated, 30 (22%) had known diabetes mellitus, 14 with type 1 DM and 16 with type 2 DM. 4 patients (3%) were newly diagnosed with diabetes mellitus, 39 patients (28%) were detected to have prediabetes. Overall, more than half of patients on active waitlist (53%) showed disturbances in glucose metabolism.
Conclusion: We demonstrate the prevalence of DM or prediabetes on kidney transplant waitlist to be as high as 53%, with more than 30 % of patients previously undiagnosed. Considering prognostic implications, strategies to reduce patient risk prior to and following transplantation are warranted. Our data provide a basis for early risk stratification and intervention to improve patient and allograft outcome.

IMMUNOSUPPRESSION/NOVEL STUDIES

V59 IMMUNOGLOBULIN INDUCTION THERAPY IN RENAL TRANSPLANT RECIPIENTS – FIVE YEAR DATA OF A PROSPECTIVE RANDOMIZED PILOT STUDY

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Intravenous immunoglobulin (IVIG) administration provides an established treatment modality to reverse steroid resistant rejection and to suppress alloantibody formation in sensitized recipients. To analyze graft protective effects of IVIG induction therapy, we performed a prospective randomized study in 50 renal transplant recipients who were randomly assigned to receive 7 × 10 g IVIG and 7 × 10 g iv albumin infusions, respectively.

IVIG induction therapy did not affect sCD30 and sIL1-RA levels, but regulatory autoantibody levels were increased on day 10 (IgG anti-Fab and anti-$F(ab)_2$: $P \leq 0.005$; IgA anti-Fab, anti-$F(ab)_2$ and anti-hinge: $P < 0.05$). IVIG patients showed an enhanced monocyte IL-10 production early post-transplant (day 30: $P = 0.011$, unstimulated; $P = 0.049$, LPS), followed by downregulated monocyte activation ($P = 0.024$, 4-month neopterin) and profoundly suppressed 1-year CD4 helper activity compared to non-IVIG patients ($P = 0.003$; logistic regression: $P = 0.001$). However, IVIG induction had no impact on 5-year patient and graft survival, graft function, incidence of acute rejections, chronic graft dysfunction and severe infectious diseases.

Our data show that IVIG induction is associated with potentially graft protective immunological effects (regulatory autoantibody levels, monocyte IL-10 production and activation, profoundly decreased CD4 helper activity at 1 year). However, no improved clinical outcome was found up to 5 years posttransplant in this cohort of immunologically low-risk patients.

V60 FINAL RESULTS FROM THE LONG-TERM EXTENSION (LTE) OF THE BELATACEPT PHASE 2 STUDY IN KIDNEY TRANSPLANTATION

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Background: At 5 years post-transplant, data from the Phase 2 IM103-100 LTE study of belatacept in kidney transplantation demonstrated a favorable safety profile and improved renal function vs. cyclosporine (CsA) (Vincenti F et al, *JASN* 2010;21(9):1587–96). The safety and efficacy of belatacept up to study closure (9–11 years follow-up) is reported herein.
Methods: Of 218 patients were randomized to receive a more or less intensive regimen of bela ($n = 145$) or CsA ($n = 73$), with bela patients receiving treatment at 4- or 8-week intervals (5 mg/kg after 6 months). Here we focus on the results of the 44 bela patients who remained in the LTE cohort until study end; too few CsA patients ($n = 9$) remained at the end of the study to make comparisons between groups.
Results: The 44 patients remaining in the bela group at study end received treatment for a mean of 9.7 years. From randomization to end of study, 25% of patients missed no infusions, and 21% missed only 1 infusion. There were no deaths or graft losses in this cohort. From randomization to study end, 84% of bela patients had serious AEs, 36% had serious infections, and 23% had malignancies. There were no cases of PTLD in this cohort. In the pooled bela cohort, mean (SD) MDRD cGFR was 70 (21) ml/min/1.73 m^2 at Month 3 and 72 (17) ml/min/1.73 m^2 at the end of the study. From randomization to study end, there was 1 acute rejection episode (Banff grade IIA), occurring in Year 9 in a patient randomized to the 8-week dosing interval group.
Conclusions: Data suggest that the profile of belatacept is consistent over approximately 10 years of treatment: patients maintained renal function with no new safety findings and there was high treatment compliance. However, the sample sizes are limited in this self-selecting cohort, therefore results should be interpreted with caution.

V61 COMPARISON OF THE CALCINEURIN INHIBITORS TACROLIMUS AND CYCLOSPORINE IN COMBINATION WITH EVEROLIMUS IN HEART TRANSPLANT RECIPIENTS WHO SURVIVED 1 YEAR AND LONGER

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The mTOR inhibitor everolimus (EVL) is used for calcineurin inhibitor-sparing immunosuppression in heart transplantation (HTx). However, comparable data regarding clinical outcomes in HTx recipients receiving EVL either with dosage reduction of cyclosporine A (CSA) or with dosage reduction of tacrolimus (TAC) is lacking. In a retrospective data analysis, we compared 5-year clinical outcomes in 154 maintenance patients receiving EVL with CSA ($n = 106$) or TAC ($n = 48$). The primary endpoint was a composite of death, graft loss and EVL discontinuation (treatment failure). Secondary endpoints were kidney function, cardiac rejection, cytomegalovirus infection and biochemical safety parameters. In the CSA and TAC group, the primary endpoint was reached by 59.8% and 53.1%, respectively ($P = 0.716$). Five-year mortality was 30.4% (CSA group) and 23.13% (TAC group), respectively ($P = 0.371$), and freedom from EVL discontinuation was 53.3% and 59.6% ($P = 0.566$) in the respective groups. Covariate-adjusted relative risk of treatment failure was in the CSA group = 1.28 (95% CI:0.70–2.34; $P = 0.43$) compared with the TAC group. The course of covariate-adjusted estimated glomerular filtration rate and cytomegalovirus infection was similar in the two groups ($P = 0.502$), whereas freedom from rejection was lower in the CSA group compared with the TAC group ($P = 0.023$). Lipid status and blood cell counts were comparable between groups. In conclusion, data indicate that EVL plus reduced TAC is not superior to EVL plus reduced CSA regarding treatment failure and kidney function. Both study groups showed high EVL discontinuation rates.

V62 SUPERIOR RENAL FUNCTION IN AN EVEROLIMUS-BASED CALCINEURIN INHIBITOR FREE REGIMEN COMPARED TO STANDARD CYCLOSPORINE/MYCOPHENOLATE AND LOW CYCLOSPORINE/EVEROLIMUS: FOLLOW-UP OF THE HERAKLES STUDY AT MONTH 36

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Purpose: To follow up (FU) on renal function (RF) at month (Mo) 36 after kidney transplantation (Tx) in patients (pts) on immunosuppressive regimen with different calcineurin inhibitor (CNI) exposures.
Methods: Of 802 pts were included in a 1 year, prospective, open-label, randomized (RDZ), multi-center study. After induction with basiliximab all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3Mo post Tx 499 pts were RDZ 1:1:1 to either a) continue standard (STD) CsA (100–180 ng/ml) with EC-MPS ($n = 166$), b) convert to a CNI-free regimen with everolimus (EVR;5–10 ng/ml) +EC-MPS ($n = 171$) or c) convert to CNI-low regimen CsA (50–75 ng/ml) with EVR (3–8 ng/ml) ($n = 162$). Mo36 FU visit was performed by 123(89%) STD, 130(95%) CNI-free and 123(94%) CNI-low pts.
Results: Median trough levels: CsA 98 ng/ml in STD, 72 ng/ml in CNI-low pts; EVR 6.0 ng/ml in CNI-free, 5.4 ng/ml in CNI-low pts. RF (Nankivell) was similar at RDZ 3Mo post Tx and had significantly improved at Mo12 by +5.6 ml/min (95%CI:[+2.9;+8.3]; $P < 0.001$) and remained significantly improved by +7.0 ml/min in favor of CNI-free regimen at Mo36($P = 0.009$). 58% of CNI-free, 36% of CNI-low and 46% of STD pts had an improvement in RF at Mo36 ($P = 0.04$ CNI-free vs. STD). All 3 groups had similar rejection rate since RDZ (13%STD, 15%CNI-free, 14%CNI-low) and overall comparable safety profile.
Conclusion: CNI-free as well as reduced CNI in combination with EVR are both efficacious and safe regimen. The CsA trough levels in CNI-low group didn't fully meet reduction, that might have hampered to translate into better RF compared to STD. However, CNI-free regimen lead to better RF maintained for 3 years post Tx. The results of this large trial confirm previous reports of improved RF after CsA withdrawal with EVR in combination with EC-MPS.

V63 EVEROLIMUS, MTORC1 INHIBITION, AND IMPACT ON HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANTATION – 12, 24, AND 36 MONTHS DATA FROM 719 LTX RECIPIENTS

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Background: For patients with localized hepatocellular carcinoma (HCC) who don't qualify for surgical resection, LTx is an appropriate strategy for candidates with a single lesion ≤5 cm, up to three separate nodules, none larger than 3 cm (Milan criteria), no evidence of gross vascular invasion, and no regional nodal or extrahepatic distant metastases. Because immunosuppression to reduce the incidence of acute rejection is associated with higher tumor recurrence, efforts have been underway to reduce doses and to evaluate new treatment options to reduce this risk.
Methods: Data were retrieved from study H2304 (NCT00622869) and its extension, a 3-year RCT in 719 de novo LTx recipients comparing everolimus (EVR, C0 3–8 ng/ml) plus reduced tacrolimus (rTAC, C0 3–5 ng/ml), or EVR (C0 6–10 ng/ml) with TAC Withdrawal (TAC-WD) at M4 to standard TAC (TAC-C, C0 6–10 ng/ml). Here, we present HCC recurrence, patient outcome and impact of everolimus treatment and exposure in 203 HCC patients at 12, 24, and 36 months after LTx.
Results: Baseline demographics and HCC characteristics were comparable: $n = 67$, 76, 60 patients with HCC; mean age 58.4, 58.6, 58.4 years; male gender 53 (79.1%), 56 (73.7%), 52 (86.7%); average weight 75.1, 74.3, 74.1 kg; prior tumor treatment 33/67, 41/76, 27/60; within Milan criteria 60 (89.6%), 65 (85.5%), 51 (85.9%); average number of lesions 1.6, 1.6, 1.6; largest diameter (mean) 2.7, 4.0, 5.4 cm; total tumor diameter (mean) 4.1, 4.4, 4.2 cm; AFP positive 46 (68.7%), 52 (68.4%), 47 (78.3%); mean AFP level 99.7, 53.9, 34.0 ng/ml in the EVR/rTAC, TAC-WD, and TAC-C arm, respectively.

HCC recurrence was observed in 2, 12, and 14 patients at M12, 24 and 36. HCC recurrence was lower in patients treated with everolimus. Detailed data by treatment, exposure and risk factor analyses will be presented.
Conclusion: Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR inhibitor), may offer an alternative immunosuppressive agent with intriguing prospects in patients transplanted for HCC.

V64 THE INFLUENCE OF IMMUNOSUPPRESSIVE DRUGS ON THE EPITHELIAL MICROENVIRONMENT IN SOLID ORGAN TRANSPLANTATION

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Background: In the context of kidney and liver transplantation, NK cells play an important role by recognizing the allogeneic organ. The specific interaction with the allogeneic tissue can activate NK cell function and mediate allograft rejection. Here, we investigated the effect of immunosuppressive drugs on proliferation and chemokine production of epithelial cells.
Methods: Renal and liver cells were incubated with Cyclosporin A, Tacrolimus, Rapamycin, Everolimus, Mycophenolate mofetil (MMF) and Mycophenolic Acid (MPA) for 48 h. Surface expression of T/NK cell ligands by FACS and production of chemokines and phosphorylation of Akt/mTOR pathway components were analyzed by the Bioplex technique.
Results: CNI and mTORi down modulate CD166, CD155 and HLA class I surface expression on HEK293, HepG2 and Huh7 cells and CD166 expression on RCC26. mTORi inhibited significantly kinases of the PI3K/Akt pathway in renal cell lines, while CNI had no effect. In liver cell lines Rapa and Ever inhibited the PI3K/Akt pathway. In contrast CsA and MMF induced activation of the mTOR pathway in Huh7. Chemokine secretion was also influenced by immunosuppressive drugs. In HEK293 cells, CXCL12 was suppressed by Rapa and CsA. MIF was significantly suppressed by Rapa, Ever, CsA, Tac, MMF and MPA. In RCC26 cells, CXCL8 was suppressed by CsA, Tac and MMF. In Hep3B cells, CXCL8 and VEGF were suppressed by Rapa, CsA, MMF and MPA. In contrast, in HepG2 and Huh7 cells, Follistatin and Leptin were induced by Ever and Tac.
Conclusion: Our results demonstrate that CNI as well as mTORi are able to modulate the microenvironment and surface expression of T and NK cell ligands on kidney and liver cells. However, mTORi, but not CNI inhibit the PI3K/Akt pathway in renal cell lines. In liver cell lines, both mTORi and CNI suppressed the mTOR pathway. Chemokine secretion was impaired upon immunosuppressive treatment, which may be important for the prevention from graft rejection. Taken together, it may be important to suppress the chemokine secretion by epithelial cells, so that the immune system would not be able to respond against the transplanted organ and starts a graft rejection.

LIVING DONATION

V65 OUTCOME ON RENAL FUNCTION, EFFICACY AND SAFETY IN LIVING-DONOR KIDNEY TRANSPLANT RECIPIENTS AFTER CONVERSION FROM A CALCINEURIN INHIBITOR TO AN EVEROLIMUS BASED REGIMEN: A POST HOC SUBGROUP ANALYSIS OF ZEUS

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Aim: To study renal function and patient outcome in living donation subgroup of kidney de novo transplant recipients after conversion to an everolimus (EVR) based regimen and withdrawal of calcineurin inhibitor (CNI) therapy. Methods: Post hoc subgroup analysis from the prospective, open-label, controlled, multicenter study ZEUS. 300 renal transplant (Tx) patients (pts) were randomized (rdz) at month (Mo) 4.5 post Tx to either EVR plus enteric coated-mycophenolate sodium (EC-MPS) or cyclosporine (CsA) plus EC-MPS regimen, among them 80 living donor recipients (EVR $n = 42$; CsA $n = 38$).
Results: In liv.donor recipients subpopulation, adjusted estimated GFR (Nankivell) at Mo12 (primary endpoint) was 74.3 (95%CI [70.7, 77.9]) ml/min/1.73 m^2 in EVR vs. 63.8 (95%CI [60.0, 67.7]) ml/min/1.73 m^2) in CsA group, i.e. 10.5 ml/min/1.73 m^2 difference in favor of EVR ($P < 0.001$). From rdz to Mo12, mean adj.estimated GFR was +9.8 (95%CI [6.2, 13.4]) ml/min/1.73 m^2 in the EVR subgroup, versus −0.7 (95%CI [−4.6, 3.1]) ml/min/1.73 m^2) ($P < 0.001$) within CsA group since rdz. Of 6 BPAR episodes in the EVR group, 5 were Banff I graded. Overall safety profile was similar between treatment groups. Discontinuation due to adverse events occurred in 3 EVR-treated (7.1%) and 5 CsA-treated pts (13.2%) between rdz and Mo12.
Conclusion: EVR-based regimen with early elimination of CNI therapy in living donor kidney transplant recipients is associated with a significant renal benefit at 12Mo post Tx without compromising safety and efficacy.

V68 A BODY MASS INDEX (BMI) GREATER THAN 30 IS NOT A CONTRAINDICATION FOR LIVE DONOR LIVER TRANSPLANTATION (LDLT)

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Obesity is dramatically increasing in Western countries, and accordingly, many potential donors interested in living liver donation are obese. We investigated if adult-to-adult living donor liver transplantation using living donors with a BMI>30 vs. <30 is safe for the donor and provides comparable recipient outcomes.
Methods: We investigated 320 adult-to-adult living liver transplantation performed in a single institution between December 2000 and December 2013. We compared donor and recipient outcome of 78 donors wit a BMI >30, with 242 donors with a BMI <30. Steatosis was <10% in all donor livers, as confirmed by imaging and biopsy.
Results: BMI of the obese (35 + 6) vs. lean donors (24 + 3) was significantly increased ($P < 0.01$). No difference existed between obese and lean donors regarding donor age, gender, and residual liver volume. Donor hepatectomy in lean vs. obese donors was associated with similar blood loss (898 + 346 cc vs. 1090 + 452 cc, $P = 02$), transfusion requirement (2% vs. 0%, p- = 0.6), and duration of surgery (7.3 + 1.3 h vs. 7.6 + 1.3 h, $P = 0.2$). No difference was observed between both donor groups regarding peak AST, ALT, INR or bilirubin after hepatectomy. 23%of lean vs. 27% of obese donors experienced a complication after surgery. Dindo-Clavien Grad 3b complications occurred in 3.8% of lean vs. 2.3% of obese donors ($P = 0.7$), no grad 4 or 5 complication was observed. Median hospital stay was 7 days in both donor groups. Recipient outcome was comparable with no difference regarding peak AST, ALT,INR and bilirubin levels within the first week after transplantation. Recipients of the lean vs. obese donor group had similar 5-year graft (71% vs. 76%, $P = 0.64$) and patient (76% vs. 79%, $P = 0.64$) survival.
Conclusion: Living liver donation of obese donors is safe in the absence of steatosis and provides similar donor and recipient outcomes in a carefully selected donor population.

MISCELLANEOUS

V69 ORGAN DONATION AND TRANSPLANTATION- ATTIDUDES OF MEDICAL PROFESSIONALS INVOLVED

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Objective: Attitudes of medical personnel are crucial in the process of organ donation. We conducted a survey to find out the attitudes of hospital staff towards organ donation and transplantation.
Methods: The medical staff in 50 Bavarian hospitals were asked to respond anonymously to a questionnaire.
Results: Of 2983 questionnaires could be evaluated. The majority of all respondents had a positive attitude towards organ donation; 71% were willing to donate their organs after brain death and 57% were willing to accept a transplant in case of organ failure. Rates of positive attitude were lower among nurses than among physicians. The majority of nurses and a large proportion of physicians considered themselves as not well informed.
Conclusion: Although the attitude of medical personnel to organ donation is more positive than it has been reported in the general population, the responses reflect concerns in a substantial proportion of health care professionals, which may represent important hurdles to organ donation, often caused by a lack of information. Therefore, it is necessary to improve the knowledge of the medical staff.

V70 TRANSPLANT SURGERY IN GERMANY: RESULTS OF A NATION-WIDE SURVEY

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We have conducted a nation-wide survey on demographics, training, position, individual case loads, center volumes, program structure, professional practice, grade of specialization, workload, working-hours, salary and career expectations of transplant surgeons in Germany.

Transplant surgeons of 32 German transplant centers were asked to participate on this survey. There were 85 respondents who were 43 ± 8 years of age and predominantly male (85%). Most transplant surgeons were fully trained general and visceral surgeons. Only, few surgeons have formal specialty training in transplantation. Clinical transplant practice included, kidney, liver and pancreas transplantation, living-donor procedures and pediatric transplantation. Overall, the grade of specialization was low. Transplantation was rated to be only 10–25% of the operative clinical practice and most surgeons considered themselves as hepatobilary surgeons and only second-line as transplant surgeons. The individual caseload per active surgeon was low (e.g. 16 deceased liver transplant procedures/a, 16 kidney transplant procedures/a and 3 pancreas transplant procedures/a). The majority of transplant surgeons reported working hours of 66 h/week and above, at least 7 days of transplant on-calls and a median of 8 (1–52) operative transplant cases a year. The majority of surgeons reported an annual salary between 80 and 125.000€. Only 60% of the transplant surgeons would recommend following a transplant surgeon career. This is the first study assessing the professional life of transplant surgeons in Germany. The results of this survey should be taken into account by the setup of current and new transplant positions in Germany.

V71 ABDOMINAL WALL TRANSPLANTATION: A SENTINEL MARKER FOR REJECTION?

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Abdominal wall transplantation (AWT) has revolutionized difficult abdominal closure after intestinal transplantation (ITX) in eligible patients. The pioneering immunological benefit is however to precociously detect and treat rejection (skin rash on AWT), before it manifests in the intestine thus avoiding severe bowel dysfunction; and the ability to distinguish it from infection (no skin rash before bowel dysfunction).

Between 2012 and 2014, twelve patients (mean age 42 ± 13 years) received AWT to complement ITX from the same donor at the Oxford Transplant Centre. Two doses of Alemtuzumab were used for induction therapy (30 mg, 6 and 24 after reperfusion) Tacrolimus (trough levels 8–12 ng/ml) was used for maintenance immunosuppression.

Three recipients had biopsy proven rejection of the skin on their AWT. These patients did not demonstrate concurrent intestinal graft rejection. In contrast, in one patient with bowel dysfunction (fever,diarrhoea), the skin of the AWT remained normal. Intestinal histology was reported as CMV disease.

The skin component of the AWT may serve as a sentinel marker for immunological activity in the host. This is a vital tool for timely prevention of intestinal graft rejection and more importantly the avoidance of overimmunosuppression in cases where bowel dysfunction manifests without the skin component being affected.

POSTERS

KIDNEY

P001 KYNURENINE AS AN EARLY MARKER FOR COMPLICATIONS AFTER RENAL TRANSPLANTATION

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Aim: By this largest study as yet we want to clarify the suitability of Kynurenine (KYN) – the primary degradation product of the amino acid tryptophan – to detect post-transplant complications.
Methods: The KYN serum levels were quantitatively measured [μmol/l] in 4083 blood samples from 355 kidney transplant recipients. Statistics: ANOVA.
Results: (i) In recipients with immediately functioning grafts ($n = 212$), the KYN levels dropped down from pre-Tx 13.3 ± 5.9 to 5.8 ± 3.0 at post-Tx day 5 with subsequently further reduction (normal value: 2.7 ± 0.6). In recipients with delayed graft function, the reduction of the KYN levels started only after the last hemodialysis. (ii) The increase of the KYN levels in connection with ARs depended on the severity of ARs. In hemodialysis-free recipients the KYN levels increased within one week pre-AR to 6.0 ± 6.1 in steroid-sensitive ARs, to 12.9 ± 7.1 in steroid-resistant ARs and to 16.9 ± 9.1 in vascular rejections. (iii) All infections evaluated were associated with significantly elevated KYN levels already before the final diagnosis (5.7 ± 3.4 in asymptomatic CMV infection; 7.5 ± 4.4 in CMV disease; 8.3 ± 3.3 in pneumonia and 10.4 ± 6.5 in sepsis).
Conclusion: The KYN serum level is an additional reliable marker for detection of a broad spectrum of complications and for monitoring the efficacy of therapeutic measurements.

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

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Rationale: Recurrence of atypical hemolytic uremic syndrome (aHUS) is frequent after kidney transplantation, limiting transplant options for these patients. The reported incidence of 15–90% is largely dependent upon the underlying dysfunction of the complement system. The complement C5-inhibitor eculizumab effectively blocks terminal complement activation, thereby providing a specific therapeutic option.
Methods: Clinical and outcome data is reported from a case series of patients with a HUS, who successfully underwent kidney transplantation under preemptive eculizumab therapy at our University Hospital between 2010 and 2014.
Results: A series of 5 patients, among them 2 children, is presented. Four patients received living donor kidney transplantation, one patient was transplanted via regular waiting list. Eculizumab was given immediately prior to transplantation and after one week. Subsequent dosing intervals were two to four weeks. Outcome of these patients is excellent, with excellent allograft function and no recurrence of aHUS after a median follow-up of 30 [1–51] months.
Summary: Preemptive eculizumab therapy is effective in preventing recurrence of aHUS after kidney transplantation, thereby allowing access to transplantation for these patients, both, via living donor kidney transplantation or regular waiting list.

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

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

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

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

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

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

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

Eight percent (141 patients) of the 1729 patients recorded along the period study met the TG biopsy proven criteria. More than 50% of this TG group had a value for AT1RAb and ETARAb >10 U/ml. Of the 89 TG patients tested for AT1RAb at transplantation, 38 were positive for AT1RAb. We showed a strong link between the value of AT1AbR and patient survival with a significant risk of death in the high value group (>17 U/ml). The presence of DSA did not correlate with AT1RAb and 8 of the 38 patients developed TG were positive for AT1RAb tested at transplantation without DSA or HLA antibodies, suggesting an independent role of AT1RAb in TG.

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

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

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Objectives: In immunocompetent individuals, Epstein-Barr virus (EBV) infections are effectively controlled by cell-mediated immunity (CMI). Impairment of CMI by immunosuppressive therapy after transplantation occasionally causes EBV-reactivation which can be associated with serious clinical complications i.e. PTLD. The aim of the pilot study in renal transplant recipients was to evaluate the suitability of *activated* (*a*) BZLF1 to assess the functionality of BZLF1-reactive effector cells in the course of immunosuppressive treatment. Herein, (*a*)BZLF1 reveals the unique property to stimulate a broad spectrum of antigen-reactive effector cells.
Methods: We performed a two year prospective observational study in a cohort of 83 renal transplant recipients, of whom 92.8% revealed a positive EBV serostatus. Heparinized blood of patients was collected pre- and at different time points post transplantation. Functional BZLF1-reactive T cells were quantified applying (*a*) BZLF1 as stimulator antigen combined with the sensitive IFN-γ ELISpot. EBV load was determined in serum samples using quantitative PCR.
Results: Prior to transplantation, a significant (*a*)BZLF1-reactive CMI was detected in 60.9% of EBV-seropositive patients followed by a substantial decrease in the first three weeks post transplantation. In some patients, (*a*) BZLF1-reactive cells started to recover in month 6–18 reaching in part maximum levels exceeding even those observed prior to immunosuppression. Transient and weak, clinically inapparent EBV-reactivation was observed in 53% of the patients. Importantly, analysis of individual patient courses revealed that EBV-reactivations occurred preferentially at times with low numbers of (*a*) BZLF1-reactive effector cells.
Conclusion: Monitoring of functional (*a*)BZLF1-reactive CMI may be an interesting novel strategy to assess the risk for EBV-reactivation in immunocompromised transplant recipients.

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

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Background: Ureteral stents are commonly used in kidney transplantation, but data on their use in elderly recipients are scarce. We sought to evaluate the impact of routine ureteral stenting in kidney transplant recipients over 65 years (ESP; Eurotransplant Senior Program) compared to younger recipients under 65 years.
Methods: In this retrospective, single-center study, data of 1247 patients transplanted between 1 January 2000 and 21 December 2010 in Innsbruck were evaluated. Complication rates, shortterm and longterm outcome of 193 elderly patients and 1054 younger patients were investigated.
Results: Elderly recipients (median age: 68.17 $\pm$ 2.75 years) had a lower patient (old vs. young: 5 years: 71.2% vs .89.1%, 10 years: 50.6% vs. 79.2%, $P < 0.001$) and graft survival (old vs. young: 5 year: 65.9% vs. 79.6%, 10 years: 44.8% vs.61.9%, $P < 0.001$) than younger patients (46.22 $\pm$ 12.13 years; $P < 0.0001$). However, both groups showed a comparable graft survival censored for patient death with a functioning graft (10 yearr graft survival 72.5% vs. 75.6%, P = n.s.). Elderly recipients suffered more frequently from urological complications than younger patients (old vs. young 25.39% vs. 17.84%, $P = 0.015$). Next, ureteroneocystostomy techniques (Lich-Gregoire, LG, vs. Leadbetter-Politano, LP) were analysed. While there were no differences in elderly patients, the LG-technique was associated with a lower rate of ureteral stenosis in younger patients (LG vs. LP: 1.59% vs. 6.67%, $P = 0.007$).

Overall, patients with ureteral stents had fewer ureteral complications (stenosis: 8.33% vs. 2.13%, $P < 0.0001$; urine leakage: 1.44% vs. 0.24%, $P = 0.049$). When comparing the impact of stents in both age groups, the use of stents was associated with lower complication rates in younger patients, whereas elderly patients with a splint suffered more frequently from ureteral reflux. However, ureteroneocystostomy techniques or the routine use of stents did not impact on graft or patient survival.
Conclusion: Aged recipients had a lower patient and graft survival, yet graft survival censored for patient death was comparable between the groups. Routine ureteral stenting should be recommended as it was associated with lower complications rates without impacting on graft survival.

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

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

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

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

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

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

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Introduction: In addition to other causes, the duration of cold ischemia is hold responsible for the extent of the ischemia-reperfusion injury of the graft. We investigated if there are parameters which are correlated with the cold ischemia time (CIT), and accordingly allow conclusions about the quality of the graft.
Materials and Methods: In 34 patients, who received a kidney transplant at our hospital, the pro-inflammatory urinary cytokines interleukin 6 (IL6), interleukin 8 (IL8) and the chemokine MIG were measured both before and after surgery. The CIT was <10 h in 20 patients (group 1) and longer than 10 h in 14 patients (group 2).
Results: The median values of the cytokine levels of the patients in group 2 (>10 h CIT) are higher than the ones in group 1 (<10 h CIT). The same conclusion applies the glomerular filtration rate, measured 3 months and 1 year following surgery.

These differences in the groups are only significant for MIG, measured in the first urine after transplantation ($P = 0.012$, Mann-Whitney U-Test). A significant positive correlation was detected between the duration of cold ischemia time and urinary MIG ($r = 0.449$, $P = 0.011$, Spearman rank correlation).
Conclusion: Urinary MIG is correlated with the duration of the CIT and could possibly help to provide information regarding the extent of ischemia-reperfusion injury.

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

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Microcirculatory changes, inflammation and scarring might be responsible for kidney failures. We hypothesized that investigating (early) inflammatory parameters like Kynurenine (Kyn), HMGB-1, IMPDH, CRP and C5b-9 could give predictive information about delayed graft function (DGF), rejection (AR) and long term survival (GS). Depleting anti-lymphocyte or-thymocyte polyclonal antibodies as induction treatment could have influence on this response and results.
Patients and Methods: In a consecutive group of patients transplanted between 10/1989 and 06/1992 ($n = 324$) treated either with quadruple drug induction (QDT, $n = 238$; ATG-F, CsA, AZA, MP) or triple drug (TDT, $n = 86$; CsA, AZA, MP) as immunosuppressive therapy.
Results: There was a significant difference between HMGB-1 in PF versus DGF. This was found even14 days after transplantation (correlation HMGB-1 and DGF $r^2 = 0.718$) HMGB-1 in ATG-treated patients at week 1 after transplantation was decreased by 82% whereas elevated by 24% in TDT patients. With Kyn we differentiated two groups of patients, all with no surgical failures, no delayed graft function, no rejection episode and no CMV-reactivation within the first 2 months: Gr.I ($n = 52$) involved patients showing

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

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

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

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

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

Method: Retrospective cohort analysis of $n = 369$ transplant recipients at Saxony-Anhalt Renal Transplant Unit. Respectively, overall waiting time, blood-group related waiting time, European senior program (ESP), acceptable mismatch program (AM), living kidney donation (LKD), full house or high urgent allocation (0MM/HU) and other allocation parameters were evaluated. Descriptive statistical analysis was done with SPSS 17.0.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

P016 ALPHA-1-MICROGLOBULIN AND HAPTOGLOBIN AS BIOMARKERS FOR DETECTION OF ACUTE ALLOGRAFT REJECTION FOLLOWING KIDNEY TRANSPLANTATION

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Introduction: Early diagnosis of acute rejection and effective immunosuppressive therapy lead to improvement in graft survival following kidney transplantation. In this study, we aimed to establish a urinary protein profile suitable to distinguish between patients with rejection and stable graft function and to predict acute rejection based on postoperative collected urine samples. A further objective was to identify candidate proteins for the use as biomarkers in clinical practice.
Material and Methods: Urine samples of 116 kidney recipients were included. Rejection was proven by biopsy ($n = 58$) and stable transplant function was monitored for at least 2 years ($n = 58$). Postoperative urine samples were collected between 3rd and 10th day following transplantation. Urinary protein profiles were obtained by SELDI-TOF-MS. Protein identification and validation were performed using Multiplex-Fluorescence-2DE, Peptide Mass Fingerprinting and ELISA.
Results: A protein profile including 4 mass peaks differentiated acute rejection from stable transplants at the time point of rejection and at the postoperative state with 73% sensitivity and 88% specificity. Alpha-1-microglobulin (A1MG) and Haptoglobin (Hp) were identified as putative biomarkers. Protein levels were significantly higher in postoperative urine from patients with rejection (A1MG: 29.13 μg/ml vs. 22.06 μg/ml, $P = 0.001$; Hp: 628.34 ng/ml vs. 248.57 ng/ml, $P = 0.003$). The combination of both proteins enabled the diagnosis of early rejection with 85% sensitivity and 80% specificity.
Conclusion: Protein profiling is suitable for non-invasive detection of rejection. A specific protein profile enables prediction of rejection in the immediate postoperative period. A1MG and Hp appear to be reliable rejection biomarkers.

P017 RELEVANCE OF URETERAL COMPLICATIONS IN KIDNEY TRANSPLANT PATIENTS

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Introduction: Ureteral complication may endanger the success of kidney transplantations.
Methods: We analyzed retrospectively whether the occurrence of such a complication led to an inferior outcome compared to transplant patients who had in this respect an uneventful transplantation.
Results: In our series of kidney transplants (total: 1218 patients) 50 patients underwent surgery for ureteral complications. The indications for the intervention were as follows: ureteral necrosis ($n = 5/10\%$), ureteral stenosis ($n = 26/52\%$), insufficiency of the ureteral anastomosis ($n = 11/22\%$), vesico-renal reflux ($n = 8/16\%$). Surgery for the complication was timed for ureteral necrosis 63.4 days (mean), for ureteral stenosis 367.16 days, for insufficiency 42.27 days and for vesico-renal reflux 718 days after the transplantation. Mean donor age was 53.18 years (28–72). Timing for surgery differed significantly and not surprisingly between correction of ureteral insufficiency/ necrosis and correction of ureteral stenosis and vesico-renal reflux (*t*-test, $P < 0.05$). Creatinine levels within one year following successful correction of the underlying pathology were comparable to those of patients who had received a kidney without ureteral complications: ureteral necrosis: 1.85 mg/dl/ ureteral stenosis: 2.53 mg/dl/ureteral insufficiency: 1.65 mg/dl/vesico-renal reflux: 2.43 mg/dl.
Discussion: The mean donor age in kidney transplants with ureteral complications showed no significant difference from kidneys without such drawbacks. The more favorable creatinine values following operations in ureteral necrosis and ureteral insufficiency in comparison to those in the later interventions because of other indications mirror the natural history of a kidney transplant. However, ureteral pathologies can be corrected without disadvantage to the transplant organ.

P018 TWO CASES OF ENTEROHEMORRHAGIC *ESCHERICHIA COLI* (EHEC) DETECTION IN SOLID-ORGAN TRANSPLANT RECIPIENTS

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

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

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

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

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

P019 DIFFERENT WAYS OF PROTECTING A KIDNEY TRANSPLANT DURING AORTIC OR AORTOILIAC RECONSTRUCTION

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Introduction: If an aortic or aorto-iliac reconstruction is necessary in a patient who previously received a kidney transplant, there are different ways of preserving the perfusion of the graft during surgery. We present three different methods of how circulation to the transplanted kidney might be maintained.
Patient: The first patient had a high grade distal stenosis of the aorta and both common iliac and femoral arteries. The transplant kidney showed a deteriorating function. An aorto-bifemoral reconstruction with renal graft protection (temporary axillo-renal bypass) and later the implantation of the distal segment of the temporary bypass into the right branch of the bifemoral prothesis was performed. After surgery the kidney function recovered and the patient had no more symptoms of claudication.

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

The third patient underwent a repair of a suprarenal aortic aneurysm with a reinsertion of the superior mesenteric artery and retrograde renal graft perfusion with a temporary axillo-femoral bypass. The intra- and postoperative kidney function was stable although the patient died on the second postoperative day due to a thrombosis oft the first branch of superior mesenteric artery.
Discussion: If the expected ischemia of the graft exceeds time 30 min a temporary bypass procedure should be taken into consideration. Well-planed, in the hands of an experienced surgeon all of the methods seem to be effective.

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

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Backround: Organ shortage has resulted in an increased use of older donors. We report the experience of our transplant center in the utilization of "very-old" (>80 years) donors in renal transplantation.
Methods: Between 2002 and 2013, 23 grafts from donors aged 80 years or older (mean age 83.4 ± 3.6 years, range 80–95 years) were used for 19 patients: 15 as single and 4 as double transplants (mean cold ischemic time 9.6 ± 2.9 h). Mean recipient age was 69.3 ± 3.7 years.
Results: Cumulative graft survival at 1, 3, and 5 years were 78%, 63%, and 42%, respectively. Patient survival was 100%, 93%, and 78% at the same time points. Eighteen grafts (95%) had posttransplant function with a mean serum-creatinine of 2.1 ± 0.7 at the time of discharge. The delayed graft function rate and one-year acute rejection rate were 42% and 26%. After a mean follow-up period of 38.8 ± 24.7 months, 16 (84%) patients were alive. 11 (58%) patients have a functioning graft with a mean serum creatinine of 2.3 ± 0.7 mg/dl. Two patients died with a functioning graft.
Conclusion: The results regarding graft survival and graft function are slightly worse than in our "old-for-old" program using donors aged 65–79 years, but still generally acceptable.

KIDNEY / PANCREAS

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

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

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

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

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

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

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

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Introduction: Different complications can lead to the loss of the pancreas graft. Retransplantation may be a therapeutic option.
Methods: Between 1994 and 2014 in total 517 pancreas-Tx were performed with 39 s and third Re-PTX. Graft and patient survival rate were compared in the primary transplant and the retransplant group between 1996 and 2014. Causes of primary and secondary graft loss were analyzed.
Results: Graft loss following the first transplantation was caused by thrombosis (38.9%), chronic rejection (30.6%), severe pancreatitis (8.3%) and unknown reasons (22.2%). Reasons for pancreas graft loss after the second transplantation were thrombosis (9.5%), acute and chronic rejection (14.3%), severe pancreatitis (14.3%), sepsis with bleeding and death of the patient (57.1%) and unknown (4.8%). The median time until pancreas graft loss was 908 days. The median time between graft loss and retransplantation was 586 days. The median time between first and second transplantation was 1463 days. Total pancreas graft survival rate was 79.7%, 77.4%, and 73.2% after one, three and five years respectively in the comparison group. After second SPK the graft survival was 68.4%, 50%, 43.8% after one, three and five years and after second PAK 52.9%, 42.9% and 42.9% respectively. Total patient survival rate was 96.1%, 93.1%, and 91.2% after one, three and five years in our comparison group. After Re-PTx the patient survival rate was 80.6%, 72%, and 72% respectively. In total 13 patients died, 3 of them during the hospital stay after Re-Tx and 3 of them more then 8 years after Re-Tx. After the second transplantation 15 of 36 pancreas grafts are still working.
Conclusion: Although the results of second pancreas transplantation are inferior to the first transplant, pancreas retransplantation is a valuable option for patients with type I diabetes who lost their first graft especially with regard to spontaneous course of the disease.

P025 RECONSTITUTION OF HYPOGLYCEAMIC COUNTERREGULATION AFTER ISLET TRANSPLANTATION

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

In this project we sought to study the changes in counter-regulatory mechanisms and hypoglycemia symptoms in patients with type 1 diabetes and determine the effect of intrahepatic islet transplantation on glucose counter-regulation and hypoglycemia symptoms.
Methods: Patients with long-standing type 1 diabetes and severe hypoglycemia ($n = 9$) underwent induced hypoglycemic clamp while awaiting islet transplantation and every 6 months after intrahepatic single islet transplantation up to 2 years post transplantation. During induced hypoglycemia ($\leq$3.0 mmol/l), plasma samples were taken for glucagon, insulin, pro-insulin, c-peptide, free fatty acids, cortisol, and catecholamines and autonomic symptoms were determined.
Results: Prior to transplantation, hypoglyceamia induced basically no changes in glucagon or catecholamine levels indicating a highly defective counterregulatory system in patients awaiting islet transplantation due to severe metabolic lability. After islet transplantation all enrolled patients showed a restoration of endogenous insulin secretion and remarkable stabilization of blood glucose control. Comparison of pre- and post-transplant levels during hypoglycemia showed a substantial reconstitution of glucagonergic and adrenergic counter-regulation following islet transplantation.
Conclusion: The transplantation of isolated islets can restore β-cell secretory capacity, improve glucose counter-regulation, and return hypoglycemia awareness, thus alleviating severe hypoglycemia. This beneficial effect of islet transplantation is independent of achieving insulin independence.

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

P026 EXTENDED INDICATIONS FOR ISLET AUTOTRANSPLANTATION – DRESDEN EXPERIENCE

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Objective: To assess metabolic outcomes of islet autotransplantation (IAT) in 12 patients undergoing pancreatic surgery for either benign or malignant disease.
Background: Traditionally islet autotransplantation is performed to improve glycemic control after extended pancreatectomy mainly in patients with chronic pancreatitis. Extending the indication for islet autotransplantation to patients with major complications following pancreas surgery for various reasons and to patients with pancreatic malignancies has been discussed controversially.
Methods: In addition to chronic pancreatitis, indications for islet autotransplantation were pancreatic anastomosis insufficiencies requiring completion pancreatectomy and distal/complete pancreatectomy for benign/borderline neoplasm of pancreatic body-neck including IPMN. Patients were followed metabolically by SMBG, glucose tolerance test and mixed meal test.
Results: 12 patients were autotransplanted with 150.000 $\pm$ 50.000 islet equivalents. The autotransplantation procedure was performed without complications. 2/12 patients died during hospital stay due to septic complications with functioning autografts. The remaining 10 patients showed good primary, 6 month and 1 year graft function with 50% of the patients off insulin. No graft failure was observed. HbA1c levels in all patients were normal after IAT. The mixed meal tolerance test showed similar results as the ivgt test with delayed c-peptide peak and slower return to baseline levels. No adverse events according to transfer of premalignant cells in to the liver was observed.
Conclusions: IAT results in a good glycemic control in all patients preventing overt pancreoprive diabetes with its complications. Although larger data and

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

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

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Objective: Retrospective analysis of long term results regarding patient and graft survival, graft function and major complications in two patients after combined pancreas 4th-kidney 3rd and pancreas 3rd-kidney 2nd transplantation performed at our center.
Methods: Patient 1: A 47 years old woman underwent a combined pancreas 4th-kidney 3rd transplantation (after explantation of 2 previous kidney- and 2 pancreas-grafts). Patient 2: A 51 years old men underwent a combined pancreas 3rd-kidney 2nd transplantation (after explantation of the kidney graft).

The transplantations were performed due to standard techniques. The induction therapy consisted of Alemtuzumab and the maintenance immunosuppression of steroids, Tacrolimus, CellCept. Both patients are on permanent anticoagulation.
Results: No immunological complication occurred apart from one early reversible acute kidney rejection. Both patients are currently well within a stable pancreas and kidney function (mean serum creatinine 1.45 mg/dl, blood glucose 80 mg/dl). Leucopenia, thrombocytopenia, bacterial sepsis and chronic hepatitis C as major complications were controllable.
Conclusion: Good results can be achieved in multiple pancreas- retransplantations in combination to a simultaneous renal transplantation. An explantation of previously non functioning grafts could be favorable. An exact immunosuppression and careful monitoring basing on an excellent patients adhaerance would contribute to good long term results.

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

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Purpose: Here we evaluate contrast-enhanced ultrasonography targeting T-lymphocytes with anti-CD3 antibody labeled microbubbles for diagnosis and differentiation of acute renal allograft rejection in different rodent models of renal disease.
Methods: Uninephrectomized, allogeneically kidney transplanted rats [Lewis-Brown Norway (LBN) to Lewis, aTX] were intravenously injected with microbubbles conjugated to an anti-CD3 antibody. Ultrasound measurements of the transplanted as well as the native kidney were performed. Syngeneically transplanted kidneys (LBN to LBN, sTX), kidneys exposed to ischemia/reperfusion injury (IRI, 45 min warm ischemia), and kidneys subjected to acute cyclosporine A toxicity (CSA, 50 mg/kg for 2 days i.p.) served as controls. Post mortem histological evaluation of CD3 expression and quantitative real time PCR for KIM-1 were performed.
Results: Renal allografts demonstrating AR showed a significantly increased ultrasound signal (3.90 $\pm$ 0.50 A.U., $P < 0.05$, $n = 5$–8 in all groups) when compared to their native control kidneys (0.24 $\pm$ 0.12 A.U.).

Moreover, evaluation of signal intensities allowed a clear differentiation of AR from syngeneically transplanted kidneys without AR (1.31 $\pm$ 0.37 A.U.), kidneys with CSA toxicity (0.67 $\pm$ 0.27 A.U.) and kidneys with IRI (0.99 $\pm$ 0.28 A.U.). Finally, quantification of ultrasound signals correlated well with immunohistochemical analysis for CD3, but not with KIM-1 mRNA expression.
Conclusion: Contrast enhanced ultrasonography using anti-CD3-antibody labeled microbubbles is a non-invasive method to detect and differentiate AR from acute tubule necrosis and acute calcineurin inhibitor toxicity in different rat models of renal disease. Since in daily clinical medicine, sonography is easily available, fast, inexpensive and reproducible, this approach has significant potential for future application in patients.

INFECTIONS / COMPLICATIONS

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

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Background: The clinical profile of belatacept (bela) was demonstrated in two phase 3 studies; BENEFIT enrolled recipients of living donor or SCD kidneys, and BENEFIT-EXT enrolled recipients of ECD kidneys defined by UNOS criteria, anticipated CIT >24 h, or NHB donor. Each assessed a more (MI) and less intensive (LI) bela regimen vs. cyclosporine (CsA) in adult kidney transplant recipients. The bela LI regimen is approved for use in EBV+ recipients. Here we present *post hoc* analyses of 3-year outcomes in EBV+ patients (pts) in Europe (EU) from BENEFIT and BENEFIT EXT by donor type.
Methods: EBV+ pts from EU were categorized by donor type: UNOS ECD in BENEFIT-EXT and deceased donors (DD, pooled from BENEFIT and BENEFIT-EXT). Endpoints evaluated at year 3 were death (D), graft loss (GL), cGFR, AR, and a composite endpoint (EP) of time to D, GL, or cGFR<30 ml/min/1.73 m^2.
Results: Among EU EBV+ patients in BENEFIT EXT, 67 MI, 69 LI, and 73 CsA received a UNOS ECD kidney. Of these, 54 (81%) MI, 60 (87%) LI, 59 (81%) CsA pts survived with a functioning graft; mean cGFR was 40 MI, 42 LI, 26 ml/min/1.73 m^2 CsA; AR was reported in 11 (16%) MI, 16 (23%) LI, 9 (12%) CsA pts. By 3 years, 26 MI, 21 LI, and 42 CsA pts met the composite EP.

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

The safety outcomes in the overall population of EBV+ pts were consistent to those of the ITT; the rates of serious adverse events in the cohorts presented here were similar between treatment arms.
Conclusions: Results of these analyses in EU EBV+ pts in BENEFIT and BENEFIT-EXT are consistent with those of the global ITT population and also demonstrate a lower rate of composite EP with both bela regimens vs. CsA.

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

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Introduction: A 53-year old female patient underwent liver transplantation (LT) for HCV-induced end-stage liver disease. 3 weeks following LT with good initial graft function using a Tacrolimus-based immunosuppressive regime, our patient developed severe HCV-recurrence with highly elevated aminotransferases and cholestasis. Viral load was 136.300.000 IU/ml, and recurrent hepatitis was confirmed histologically.
Methods: Due to imminent graft failure, Silibinin was administered intravenously as rescue therapy for 2 weeks (20 mg/kg of body weight), which resulted in a moderate decline of HCV copies to approximately 60.000.000 IU/ml. Treatment with the novel direct acting antiviral agent Sofosbuvir (400 mg od) in combination with Ribavirin (400 mg bid) was started.
Results: The combination of Sofosbuvir and Ribavirin resulted in a striking decline of HCV copies. Clinically, the patient improved markedly with resolution of HCV-related symptoms. Aminotransferases and cholestasis parameters normalized quickly. Sofosbuvir and Ribavirin showed no severe side effects or interaction with the immunosuppressive medication despite the early treatment period after LT. However, HCV viral load persisted at approximately 50 IU/ml.
Conclusion: Sofosbuvir and Ribavirin are applicable in the early course after LT and, in our case, resulted in good control of HCV replication with normalization of liver function. However, complete virus elimination was not achieved.

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

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Background: Urinary tract infections are the most common infectious complications after kidney transplantation. Increasing resistance to broad-spectrum antibiotics is a growing problem in the treatment of infections especially in kidney transplant recipients. Frequently colistin, a very effective polymyxin antibiotic, remains the last-resort antibiotic for treating of bacteria involved in those potentially life-threatening events. However, systemic and especially prolongued use of colistin bears the risk of nephro- and neurotoxicity.
Results: We describe the medical case of a 73 year old female kidney transplant recipient with chronic graft failure (serum creatinine: 2.45 mg/dl). Four weeks after an episode of successfully treated urosepsis with *E. coli*, a recurrent transplant pyelonephritis and cystitis with a multiresistant Pseudomonas aeruginosa (classified as to 4 MRGN) was diagnosed. Antibiotic treatment with fosfomycin was already started at our outpatient clinic, but failed to eradicate the germ. A systemic therapy with the combination of colistimethate sodium, fosfomycin and meropeneme was started after admission. Leukocyturia declined slightly, but urine cultures were still positive for Pseudomonas and resistance testing showed an increase in minimum inhibitory concentration for colistin and fosfomycin. Also, a preexisting diabetic polyneuropathy worsened dramatically during intravenous antibiotic therapy. Thus, we decided to deploy an intravesical treatment approach. Using a single-lumen urinary catheter we administered 100.000 IU of colistin in the subsequently blocked catheter over 90 min. This procedure was applied 3 times/day for 7 days. Additionally – to prevent endogenous reinfection – colistin sulfate was administered orally. Two days after completion the urine samples were sterile. Even 4 weeks after this phase the cultures were still sterile, with no signs of urinary tract infection.
Conclusion: Our case shows that urinary tract infections with multidrug-resistant Pseudomonas (susceptible to colistin only) can be successfully treated with intravesical instillation of colistin combined with selective decontamination of the bowel. Especially in kidney transplant recipients this could be a promising treatment option and should be considered in analogue situations.

P036 DIAGNOSIS AND MANAGEMENT OF POLYOMAVIRUS INFECTION AFTER PEDIATRIC KIDNEY TRANSPLANTATION

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Background: BK virus and John Cunningham virus (BKV an JCV) are viruses from the family of polyomaviridae. BKV-associated nephropathy is a severe complication after kidney transplantation. So far only little is known about relevance of JCV infections. We retrospectively analysed infections with BKV and JCV in a cohort of patients after pediatric kidney transplantation (pKTx).
Patients and Methods: 50 patients after pKTx in the age of 1–18 years were included, mean follow up was 4.9 years. In total 1764 BKV and 1689 JCV polymerase chain reaction (PCR)-measurements from urine and blood were analysed. Data on renal function, immunosuppressive and cidofovir treatment were recorded.
Results: 28/50 (56%) patients had evidence of polyomavirus infection. BKV-infections were more frequent than JCV-infections (BKV $n = 16$; BKV+JCV $n = 9$; JCV $n = 3$). Relevant viremia was only seen with BKV (14/25, 56%). Highest incidence of infections ($n = 10$) was during the first three months post transplant. Late infections (>3 months – ≤2 years after PKTX) were observed in eight and very late (>2 years) in ten patients. BKV copy number of >125.000 copies/ml urine was identified as prognostically relevant cut-off value for the development of a viremia (100% sensitivity, 93% specificity). Early reduction of immunosuppression was the main treatment approach, 12 patients received an additional 1–4 doses of cidofovir (0.5 mg/kg), which were well tolerated. Only one patient in our cohort developed BKV-associated nephropathy. Polyomavirus infection could not be identified as an independent risk factor worsening renal function. Treatment with tacrolimus and mycophenolate was not associated with a greater risk for BKV or JCV infection.

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

P037 NOSOCOMIAL INFECTIONS IN A KIDNEY TRANSPLANTATION CENTER

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Introduction: Posttransplant bacterial infections are important because of their impact on patient and graft-outcomes. Therefore, efforts on preventing these infections are of great interest.
Material and Methods: In this surveillance study all hospital-acquired bacterial infections occurring during one year (2009) in a kidney transplantation center were analyzed and risk factors, such as age, gender, BMI, length of hospitalization and immunosuppression were investigated. Furthermore the microbiological spectrum of urinary tract infections (UTI) including the antibiotic resistance pattern was surveyed.
Results: 496 patients with 770 inpatient treatments where included in this study. 105 nosocomial infections occurred, whereas the infection rate among transplant recipients was higher than in non-transplant patients.

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

Significant risk factors for the development of nosocomial infections were immunosuppression (especially immunosuppressive regimen with antithymocyte globulin) and BMI. Gender and age did not have a significant influence. The length of hospitalization was associated with higher rates of hospital acquired infections but also is extended by each infection in turn.
Conclusions: Reducing the time of long term catheterization (under surgical aspects as possible) and the duration of hospital treatment may prevent nosocomial infections in kidney transplant recipients.

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

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Objective: Monitoring the cellular immunity for Cytomegalovirus (CMV) in organ transplant recipients is a promising tool to support prevention strategies for posttransplant CMV infection or reactivation. Commercially available *in vitro* test systems differ substantially in their capacity to stimulate subpopulations of T-lymphocytes. We compared two assays for CMV immune monitoring in respect of their clinical practicability and significance.
Methods: Blood samples of 30 lung transplant recipients (LuTRs) were examined before transplantation and over a period of six months afterwards with T-Track® CMV (Lophius Biosciences GmbH, Regensburg) and QuantiFERON®-CMV (Cellestis GmbH, Darmstadt). The T-Track® CMV is based on ELISpot-technology, allowing quantification of interferon-gamma (IFNγ) secreting CD4+ and CD8+ T-cells after specific stimulation. Contrarily, the QuantiFERON®-CMV assay is restricted to detection of IFNγ secreted by CD8+ T-lymphocytes with ELISA. The data are evaluated in the context of transplant outcome and determination of viral load in plasma by qPCR.
Results and Conclusion: Both approaches provide similar results while exhibiting certain advantages and limitations. Early during immune suppressive therapy, QuantiFERON®-CMV generates often indeterminate results as depletion of T-cells is not taken into account. Although a comparatively large volume of blood is required, T-Track® CMV circumvents this drawback. In addition, T-Track® CMV reaches a higher sensitivity prior to LuTx and shortly after onset of immunosuppression.

ETHICS / PSYCHOSOMATICS

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

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Introduction: Due to long HU-waiting time some patients have to be supported by VAD instead of heart transplantation. These patients have to deal with an addition surgical procedure, the loss of the HU-status, the emotional coping of disappointment and new challenges with the device.
Method: We present case reports of two patients with terminal heart failure who were listed for transplantation. The necessity for inotropes justified the HU status on the waiting list. The hemodynamic status deteriorated further, that finally a LVAD had to be implanted.

The patients reacted with acute stress disorder but differently according to their premorbid personality, decision making process and symptoms. A 34 year old man (DCM) suffered from severe fears of death and delirium in spite of his own decision pro VAD. A 45 year old male patient (DCM) described first a negative attitude against VAD and refused to accept the device. Consequently, specific psychotherapeutic treatments were installed in both cases.
Results: At first both patients described the disappointment about the loss of HU waiting time, the burden of an additional surgery, new future fears and finally, an emotional acceptance of a machine instead of a new heart and a sufficient quality of life on device. No further psychological complications occurred during the implantation and follow up processes.
Conclusion: Patients cope differently switching from HU waiting list to VAD program. Communication emphasizes on the life rescuing demand. Psychological treatment should be added to support individual coping styles. Further investigation (predictors, intervention) is needed.

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

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Objective: For liver transplantation, patients with alcoholic liver disease are universally required to achieve a minimum of six months of sobriety prior to surgery. There is therefore a need to accurately measure the amount of alcohol consumption. Studies have found that self-report measures often underestimate the amount, as patients who abuse alcohol generally tend to minimize their drinking behavior.The present study investigates the influence of the setting on self-reported drinking behavior.
Methods: Patients prior to liver transplantation ($n = 40$) and patients in rehabilitation therapy ($n = 44$) were compared using the Munich Alcoholism Inventory, which consists of a self-report-scale and an expert-rating-scale.
Results: A significant difference in the MALT-self-report-scale and MALT-expert-rating-scale discrepancy was found between patients prior to liver transplantation and patients in rehabilitation therapy. Furthermore, patients in the rehabilitation therapy group reported higher alcoholism scores in the self-report questionnaire than patients prior to liver transplantation, but the groups did not differ in the expert evaluation value.
Conclusion: The transplantation setting seems to evoke minimizing in self-reports, in patients with alcohol abuse. Minimizing or denying alcohol consumption does not seem to be a specific characteristic of persons with alcohol abuse, as it is also caused by the circumstances. The results suggest the employment of biomarkers in addition to self-reports for a more precise appraisal of alcohol consumption and to relieve patients from the contradicting motivations of candor and self-protection.

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

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Objective: In type I diabetics depending on dialysis there usually is a markedly decreased quality of life. There is only limited data on long term quality of life in patients after a simultaneous pancreas-kidney transplantation (PNTx).
Methods: The health related quality of life was measured with the Short Form Health Survey (SF 36) in 350 patients after PNTx. In a preliminary evaluation, the quality of life of 30 patients (17 m:13f) after successfull PNTx and 30 patients on the waiting list (18 m:12f) were compared. The survey of the transplanted patients (mean duration of diabetes 29.38 $\pm$ 5.8 years) was conducted at a mean of 60 month after transplantation. The patients awaiting transplantation (mean duration of diabetes 28.97 $\pm$ 8.2 years) were listed for transplantation for a median of 622 days and were depending on dialysis for 1222 $\pm$ 899 days.
Results: Comparing the two groups there was a significant increase in physical functioning after PNTx ($P = 0.022$), general health perceptions ($P < 0.001$) as well as in mental health ($P = 0.007$). The psychological and social items showed a tendency towards improvement. There was no difference in emotional role functioning. The improvement of quality of life started being evident in the second year postoperatively. The subgroup analysis showed gender specific differences.
Conclusions: There is a significant increase in health related quality of life in patients after successfull PNTx. This improvement usually is reached two years after transplantation.

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

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

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

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

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

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

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Objective: Little is known about the perceived emotional stress of hospital staff involved in the organ donation process. We have conducted a large survey to assess attitudes and experiences of hospital staff with organ donation, including emotional stress in relation to professional experience.
Methods: In 50 Bavarian hospitals, medical professionals, who are involved in the organ donation process, were asked to respond anonymously to a questionnaire. Responses were stratified for physicians and care staff and for the duration of professional experience (<5 years vs. >5 years).
Results: 2983 questionnaires could be evaluated. The majority of respondents in all four categories do not feel emotionally stressed by the donation process (range of mean values 53.4–69.7%). 24.4–31.3%, depending on the particular subgroup of the respondents, indicated a certain stress and 4.6–18.4% were uncertain. Medical personnel with more than 5 years of professional experience reported significantly less uncertainty.
Conclusion: A considerable number of medical professionals stated that they are emotionally affected by the donation process. Strategies to identify and cope with emotional stress may improve the attitudes towards organ donation among health care professionals with special focus on those, who are uncertain.

ORGAN DONATION / MARGINAL ORGANS

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

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

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

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

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

P047 WHO SHOULD RECEIVE THE TTR DOMINO LIVER?

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

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

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Introduction: The shortage of organs has led to more people receiving organs from living donors. Whether donor age in itself constitutes a limitation to living donation or not remains unclear.
Methods: The outcome of 22 living kidney transplantations (LKTx) from donors older than 65 years (average age 68.9 year), been performed in our center since 1997 was evaluated. The results were compared to the rest of our LKTx- cohort (n = 164) regarding this period.
Results: The mean ischemia-time of senior transplants was 203 min (range: 127–291 min) vs. 199 min (range: 115–329 min.) in the rest cohort (CG). The primary function and recipient survival rates in the senior group (SG) were as high as 95.5%. The donor mortality was zero percent. The mean creatinine value of the recipients of the SG at discharge was equal to that of the CG (1.6 mg/dl, range 0.8–3.5). The average postoperative hospital stay was 26 days (vs. 24 days in CG). The 1- and 3-year organ survival in the SG was 95.5% and 91% respectively (vs. 97.5% and 92.5% in the CG). There were no statistically significant differences observed between the two groups.
Conclusion: The LKTx eliminates the long wait time on the deceased donor waiting list. The operation can be timed for the optimal health of the recipient and for donor convenience. People older than 65 years can be safely considered as eligible for kidney living donation.

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

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Introduction: The German transplantation system is in a crisis due to a lack of donor organs. One of the main approaches to increase organ donation rates are information campaigns. We raised the hypothesis: The willingness to sign a donor card rises by receiving information material due to the subsequent increase of specific knowledge.
Material and methods: We conducted an online survey. The hyperlink was distributed via Facebook groups and mailing lists of medical faculties in Germany. Five factual questions with different levels of difficulty were asked.
Results: A total of 2484 participants took part in our survey. Use of an online tool to conduct the survey and mode of distribution were associated with overrepresentation of academics, participants of the medical sector and younger participants. Putative organ acceptance rate was associated with specific knowledge score, but not with the general education level or with receiving information material. Holding a donor card was associated with specific knowledge, but not with the general education level. Receiving information material is not associated with an increase in specific knowledge, but with holding a donor card. Association between receiving information material of the health insurance funds and specific knowledge is very slight. However, receiving information material of the health insurance funds was correlated with holding an organ donor card. Reading the information material of the health insurance funds was also correlated with holding an organ donor card.
Discussion: Our study indicates a basic level of 46.9% organ donor card holders in our sample group. This is much more than in a representative previous study by Techniker Krankenkasse (21%). These different findings may be explained by the self-selection bias. It is possible that five factual questions were not sufficient to prove the effect of the information material on specific knowledge concerning organ donation.
Conclusions: The willingness to sign a donor card was higher in the group receiving information material. However, we did not observe that this effect was related to a subsequent increase of specific knowledge, but was apparently related to the combination of information and easy access to the organ donor card.

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

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

We investigated whether differences between the two surgical methods are detectable based on renal function parameters.
Materials and Methods: Between 1999 and 2008, 60 patients received kidney transplantations from living donors. Laparoscopic hand-assisted nephrectomy was performed in 28 donors, and 32 underwent open living-donor nephrectomy. Biochemical markers of glomerular filtration rate (serum creatinine, serum cystatin C) and glomerular and tubular renal function (high and low molecular weight urinary proteins and enzymes) were determined up to one year after transplantation.
Results: Neither in the first days after transplantation, nor after one year, the glomerular filtration rates differed significantly between the two patient groups. This is also true for most of the urinary proteins. After a temporary rise during the first weeks after surgery, the urinary protein concentrations fall continuously to the normal level. Only the tubular marker protein ß2-microglobulin and the urinary enzyme N-acetyl-ß-D-glucosaminidase indicate a difference between the two surgical methods. This difference is not statistically significant.

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

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

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Objectives: The major goal in living donation is to maximize donor safety while minimizing postoperative impairments. In 2011, we changed technique from open anterior mini-incision (MIDN) to retroperitoneoscopic donor nephrectomy (RPDN). We evaluated operation time, time to discharge, surgical complications, and health-related quality of life (QOL).
Methods: 38 MIDN and 45 RPDN donors were included. In a subsample ($N = 18$ MIDN; $N = 32$ RPDN), QOL was prospectively assessed with the WHOQOL Bref questionnaire.
Results: Age and BMI were not different between groups. Skin-to-skin time (169 vs. 116 min, $P < 0.001$) and hospitalisation (6.6 vs. 4.9 days, $P < 0.001$) were significantly shorter in RPDN. 10/38 (26%) MIDN patients and 6/45 (13%) RPDN patients developed postoperative complications ($P = 0.14$). Most complications were mild. No blood transfusions were necessary. While in MIDN, 3 of 5 QOL scales (physical: $P = 0.03$; psychological: $P = 0.03$; global: $P = 0.003$) were significantly reduced 3 months post donation compared to pre donation, no significant reduction was observed in RPDN. At 3 months, RPDN donors retrospectively reported significantly less pain ($P = 0.007$) and physical stress ($P = 0.05$) caused by the operation than MIDN donors.
Conclusion: We conclude that the change of procedure was safe for our patients, operation time and hospital stay were shortened, and QOL recovery was accelerated.

P055 LIVING KIDNEY DONATION: IMPORTANCE OF DONOR EDUCATION

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Background: The rising prevalence of end-stage renal disease and Germany's chronic organ shortage subsequently calls more people upon to consider living donation.
Methods: We performed a study on 312 living kidney donors at our transplant center in the last 15 years, and aimed to address the impact of donation on social determinants, mental and physical health. The questionnaire consisted of 5 questions about social, financial, and job-related consequences, and 12 questions about donation-related stress, and health changes.
Results: The response rate was 86.7%. Using a mulitvariate donation-related quality of living score, 51% of donors were in excellent health, while 34% reported of moderately, and 15% of severely compromised health. Severely compromised donors were more likely to be younger, unemployed (25%), or forced to change their job (16%; $P < 0.05$). Most donors would be willing to donate again (90%). However, siblings (16%), donors under 45 years (15%), and notably siblings under 45 years (37%), had negative attitudes towards donation ($P < 0.05$). While open-surgery correlated with compromised health, it didn't affect willigness to donate again.
Conclusions: For adequately informing potential donors, medical professionals must know possible long-term effects on physical and mental health in different subgroups. Reliable donor education is essential to improve society recognition of living donation.

LONG-TERM COMPLICATIONS

P059 SERUM CALCIFICATION PROPENSITY PREDICTS MORTALITY AFTER AENAL TRANSPLANTATION

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Aim: Death with a functioning graft due to cardiovascular disease is the one of the most important issues in renal transplantation. Medial arterial calcification is accelerated in patients with chronic kidney disease and closely associated with arterial stiffness and mortality. Recently, we developed a novel *in vitro* blood test that provides an overall measure of calcification propensity by monitoring the maturation time (T 50) of calciprotein particles in serum. The current study elucidates clinical and hemodynamic factors influencing calcification propensity and analyses the value of T50 measurements for prediction of mortality after renal transplantation.
Method: We measured T50 in a prospective single centre cohort of 198 renal transplant patients with a follow-up of 5 years. Mean time after transplantation at study inclusion was on average7 years. T 50 measurements were performed using a Nephelostar nephelometer (BMG Labtech, Offenurg, Germany) as previously described (Pasch et al. JASN 2012). Renal resistance index was measured by color-coded duplex ultrasound. All hemodynamic and laboratory measurements were performed at study inclusion.
Results: At baseline the major determinants for tertiles of T50 included higher serum phosphate ($P < 0.001$), lower transplant function ($P < 0.001$) and serum albumine ($P < 0.01$), higher HbA_1C ($P < 0.05$) and total cholesterol ($P < 0.01$), higher pulse pressure ($P < 0.05$), systolic blood pressure ($P < 0.05$) and renal resistance index ($P < 0.05$) as well as the use of Calcineurin inhibitors ($P = 0.02$).

In a multivariate analysis, increased serum calcification propensity was independently associated with higher serum phosphate ($P < 0.001$), lower serum albumine ($P < 0.005$), higher HbA_1C ($P < 0.05$), total cholesterol ($P < 0.05$) and interestingly with use of Calcineurin inhibitors ($P < 0.05$).

Mortality divided by tertiles of T50 is associated with highest calcification propensity corresponding to the lowest tertile of T50 (Kaplan-Meyer analysis, log rank $P = 0.01$). The lowest tertile of of T50 revealed a more than 3 times increased relative risk for mortality compared to the highest tertile.
Conclusion: Our results suggest that serum T 50 measurement may be a valuable biomarker to evaluate cardiovascular risk in renal transplantation and might guide adjusted therapy in the future.

P060 NEW ONSET OF DIABETES AFTER TRANSPLANTATION IS ASSOCIATED WITH IMPROVED PATIENT SURVIVAL AFTER LIVER TRANSPLANTATION

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

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

NODAT was diagnosed in 41 patients (16.1%). There was no difference in frequency of NODAT according to the etiology of liver cirrhosis. NODAT was associated with a higher body weight ($P = 0.004$) and BMI ($P = 0.002$) 5 years after LT, but not with weight gain ($P = 0.201$) or increase in BMI ($P = 0.335$) 5 years after LT. HbA1c 5 years after LT was significantly higher in patients with NODAT ($P = 0.001$), but mean HbA1c still remained lower than 6.5% (6.4 ($\pm$1.2)%). Patients with NODAT showed better survival rates (log rank: $P = 0.002$) compared to LT recipients without diabetes. This might be explained by recovery of metabolism in patients without complications after LT, while complications of NODAT will not appear during the relatively short postoperative time and observation period (mean follow up 6.08 ($\pm$2.67) years).
Conclusion: NODAT is frequently diagnosed in LT recipients and is associated with an improved 5 year survival after LT.

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

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Background: Only few data exists about the reason of death in patients, who underwent a simultaneous pancreas-kidney-transplantation more than two years ago.
Methods: We reviewed 517 consecutive pancreas transplantations since June 1994, including 36 patients with two pancreas-transplantations and three patients with three pancreas-transplantations.
Results: From the 475 patients, who underwent at least one pancreas-transplantation, 26 patients died within the first two years after transplantation and 65 died during the long-term follow-up after the second year. Among the 65 patients there are 15 patients (23.1%), who died because of cardiac reasons, 13 patients (20%) who died due to sepsis and 8 patients (12.3%) who died of cancer. The reason of death is unknown in 19 patients (29.2%), as most of them died suddenly without being in a hospital.
Conclusion: Cardiac diseases and sepsis are the most common reasons of death in patients,who underwent a simultaneous pancreas-kidney transplantation more than two years ago. Regular cardiac checks and early treatment of infections in transplant centers seem to be very important in the long-term care of patients after transplantation.

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

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Objective: Assessment of possible differences in the pattern of cardiac allograft vasculopathy (CAV) evaluated by optical coherence tomography (OCT) in short- versus long-term cardiac transplant recipients (CTR)
Methods: Forty consecutive CTR underwent routine surveillance coronary angiography during 2013 in Munich University Clinic, twelve patients underwent OCT and were included in this study. Patients were divided into two groups according to the mean length of time interval after heart transplantation, <13.9 years ($n = 6$, group 1) and $\geq$13.9 years ($n = 6$, group 2). Primary outcomes of interest were intima and media thickness in OCT.
Results: The two groups had comparable baseline characteristics, except a significantly higher HbA1c plasma level in group 2 (5.69 vs. 6.27%, $P = 0.01$). In 94.2% of all frames with distinct three layers intima hyperplasia could be diagnosed, defined as intima-media ratio >1. Significantly more frames with intima hyperplasia were detected in group 1 ($P = 0.048$). Mean intima thickness was similar in both groups while mean media thickness was significantly greater in group 2 (0.092 ± 0.04 vs. 0.101 ± 0.06; $P = 0.024$). Signs of atherosclerosis were present in all patients independently of the time since transplantation.
Conclusion: In long-term cardiac transplant recipients with CAV media hyperplasia develops in addition to intima hyperplasia.

LIVER

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

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

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

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

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

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

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Aim: Protein based biomarkers are emerging tools for diagnosis and prediction of allograft rejection. Identifying patients at lower risk of rejection could help to adjust immunosuppressive therapy and reduce long-term side effects which are crucial for long term outcome. The aim of our study was to investigate protein levels in the bile of liver transplantation (LTX) recipients in order to evaluate its usability for diagnostics of acute rejection.
Material and Methods: From August 2011 to December 2012, 120 patients received LTX at our institution. A total of 45 patients with external bile drainage and sufficient amount of bile for analysis were included in a prospective, non-interventional study. The study was approved by the local ethics committee and all participants gave their written informed consent. Bile samples were collected at consecutive time points after LTX (postoperative days/POD 1, 3, 5, 7) and when acute rejection was suspected. Primary endpoint of the study was histologically proven rejection within the first six months after transplantation. Patients were grouped into a *rejection group* ($n = 25$) and *control group* ($n = 20$). Protein levels were measured with ELISA.
Results: *Rejection* and *control group* showed no significant differences regarding Sex (male/female: 16/9 vs. 17/3; ns), BMI (26 vs. 27; ns), cold (519 vs. 551 min; ns) and warm ischemic time (48 vs. 51 min; ns), and labMELD score before LTX (19 vs. 16; ns). Only recipient age (50 vs. 56 years; $P = 0.0349$) and INR on the day before transplant (1.88 vs. 1.34; $P = 0.0163$) differed significantly between the groups.

CXCL9 as well as CD44 protein levels were significantly higher in bile of patients at time of acute rejection compared to controls (CXCL-9: $P = 0.0067$: CD44: $P = 0.0043$). CXCL9 did not show changes prior rejection, while CD44 was already increased on POD 1 and 5 in the *rejection group* (POD1: $P < 0.0001$; POD5: $P = 0.0059$). A significant higher level of CXCL9 in the *rejection group* was found on POD7 ($P = 0.0087$). IL-6 failed to distinguish between the groups (ns).
Conclusions: CXCL9 and CD44 in bile could be used as biomarkers to improve diagnosis after liver transplantation. Bile protein biomarkers could serve as prognostic markers to establish individualized immunosuppressive regimes and thereby reduce the long-term side effects of immunosuppression.

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

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Introduction: Portal vein thrombosis (PVT) in liver transplantation remains a serious condition. An absolute contraindication in the earlier times, PVT can nowadays be successfully managed in the majority of pts. The aim of this study was to analyze our data for the incidence of PVTs prior to LTx, describe the operative techniques and compare the outcome to the LTx patients without PVT.
Methods: We retrospectively screened our liver transplant data for portal vein thrombosis and evaluated transplant variables, the underlying condition and the outcome. Budd-Chiari syndrome was excluded.
Results: We performed $n = 277$ liver transplants in $n = 252$ pts. from 2007 to 2012. A total of $n = 33$ PVTs (11.9%) was detected, which were mostly located in the main portal vein (34%). Underlying conditions were alcoholic (39.4%), HCV (24.2%), cryptogenic (9.1%),HBV (6.1%), drug related (6.1%), secondary biliary liver cirrhosis (3%), PSC (9.1%) and echinococcosis (3%).The majority of the PVTs were managed by venous thrombectomies (84.9%). In $n = 3$ (9.1%) patients we used a venous jump graft and $n = 2$ pts. (6.1%) received anastomosis to varix.1-year-survival was similar to existing literature (76%) and showed no significant difference to survival of patients, who didn't suffer PVT (82%). PVT also had no significant effect on 1-year-graft survival (73% vs. 77%).
Conclusion: In our cohort of liver transplant patients we found a number of PVTs comparable to the existing literature. It remains a technically challenging situation. However, in most cases, PVT can be managed successfully.

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

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Background: A retrospective analysis of our liver transplant cohort has shown a reduction of I/R injury and superior graft survival rates in cava-sparing liver transplantation using a porto-caval shunt (PCS). In order evaluate the benefit of a PCS during hepatectomy we propose a randomized controlled trial.
Methods: Patients receiving their first liver transplant are eligible. A cava-sparing liver transplant technique will be used in both arms. In the SHUNT group an extracorporeal PCS will be established during hepatectomy. Hepatectomy in the CONTROL group will be performed without a shunt. The primary endpoint is the peak ALT within the first 48 h after surgery. Secondary endpoints include patient- and graft survival as well as markers of I/R injury and liver function. Porto-venous and systemic endotoxin levels along with other immunological markers (e.g. IL-6) will be determined intraoperatively and in the early postoperative phase after transplantation to elucidate the mechanisms of the shunt. The calculated sample size to prove superiority of one of the arms is 60 per arm.
Conclusions: This investigator-initiated trial examines a technical/physiologic modification of a standard transplant technique. As industry sponsorship is unlikely, funding application for the trial is in review at the BMBF.

P070 FLUPIRTIN INDUCED LIVER TOXICITY: INDICATION FOR TRANSPLANTATION

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

injury has rarely been reported. We report two cases comparing clinical course, paraclinical findings, therapy and outcome.
Methods: Retrospective review of two Caucasian male patients with severe liver injury due to flupirtin intake. This included RUCAM (Roussel Uclaf Causality Assessment Method) score calculation and comparison of clinical presentation and histology.
Results: RUCAM score (8 and 10) was probable and highly probable. Both patients received flupirtin for pseudoradicular pain, and jaundice and malaise led to admission. Case 1: 48 year old otherwise healthy man, intake 400 mg daily for 90 days. Case 2: 42 year old male with polyarthritis, intake 300 mg daily for 45 days. Case 1 became severely encephalopathic (NH_3 292 mg/dl) within 24 h and required urgent liver transplantation. Case 2 made an uneventful recovery under conservative therapy with steroids and intravenous N-acetylcysteine. Compared to case 1, alanine aminotransferase (ALT) levels on admission were >4-fold higher in case 2 (3528 U/l), whereas maximum total bilirubin was similar (21.4 and 19.3 mg/dl). Serological screening for viral hepatitis, autoimmune liver disease and infectious disease were negative. Explant histology in case 1 revealed panlobular necrosis and biopsy in case 2 bridging necrosis between portal fields.
Conclusion: Male cases in FILI are rarely reported and compared. In these two patients with severe FILI, there was no dose response pattern and the extent of ALT elevation was no predictor of outcome. Clinical deterioration is difficult to predict, but crucial for the indication of liver transplantation. Early liver biopsy in patients with suspected FILI provides additional diagnostic clues and potentially aids in outcome prediction and therapy.

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

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Background: An increasing life expectancy and decreasing birth rates result in an aging population. This demographic shift suggests that older donors, including donors over 80 years, may help alleviate organ shortage in liver transplantation. The aim of this analysis was to determine the percentage of octogenarian donors in the Eurotransplant zone.
Methods: The percentage of octogenarian donors and median donor age were analyzed in the Eurotransplant Database from 2004 to 2013.
Results: 318 livers from octogenarian donors were transplanted during the observation period (total liver donors: 15 080). The percentage of octogenarians increased significantly (2004: 0.8%, 2006: 1.1%, 2008: 1.6%, 2010: 2.9%, 2012: 3.0%, 2013 3.0%) ($P < 0.001$, Chi-Square-Test). The median age of liver donors increased numerically within the last decade (2004: 46 years, 2008: 50 years, 2013: 53 years), but this change did not reach statistical significance ($P > 0.05$).
Conclusions: Although the demographic change is aggravating, octogenarians account for only 3% of all liver donors in the Eurotransplant allocation system. A detailed analysis to assess the short- and long-term survival of these grafts is in process. Facing an ageing society and the current critical organ shortage, those results may facilitate the acceptance of octogenarian donors thereby extending the donor pool.

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

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Background and Methods: The subclinical rejection (SCR) of liver transplants constitutes a histological state of acute cellular rejection without any relevant biochemical abnormalities. In this prospective study we analysed the clinical course of 95 patients after liver transplantation being part of a protocol biopsy program (average follow up period of 21 months). Late SCR was a common event occurring in 32/95 patients. Furthermore protocol liver biopsies of 25 patients with SCR were stained for CD4, CD8, FOXP3 and DAPI with multicolour immunofluorescence and compared to patients with acute cellular rejection and normal protocol biopsies. In parallel PBMCs were analysed by FACs.
Results: Late SCR represents no risk factor for subsequent ACR, graft dysfunction, progressive liver fibrosis, graft loss or liver related death in our protocol biopsy program. This is despite the fact that liver biopsies of SCR and ACR are indistinguishable in terms of pathological diagnosis, size of portal infiltrates and the density of T lymphocytes (CD4 & CD8) within the infiltrated areas. Immunophenotyping of the infiltrated portal areas revealed a possible explanation. CD4+ T cells increase significantly in both SCR and ACR with higher levels of inflammation (measured by the rejection activity index – RAI). CD8+ T cells, on the other hand, only correlate with RAI in ACR and do not increase in SCR. This causes a positive correlation of portal CD4+/CD8+ ratio with RAI in SCR and a negative correlation in ACR.

The portal infiltration of Treg ($CD4^+FOXP3^+$) increases with RAI in both SCR and ACR. The ratio of Treg to cytotoxic $CD8^+$ T cells, the latter correlate with transaminases in ACR, only increases with RAI in SCR and remains steady in ACR. Compared to normal protocol biopsies without rejection Treg are significantly enriched in SCR and ratios of Treg to overall Teff, $CD4^+$ and $CD8^+$ cells are also significantly higher in SCR. These intragraft changes are not paralleled in the blood.
Conclusion: Late SCR have a benign clinical course. Immunophenotyping shows the signs of successful regulation by Treg within the allograft. These patterns of T cell immunoregulation in portal infiltrates may contribute to the unimpaired clinical outcome of SCR after liver transplantation and may represent one aspect of the liver as an immunological privileged organ.

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

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

P077 GENOTYPES AND PHENOTYPES OF A LARGE GERMAN ATTR COHORT

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Transthyretin amyloidosis (ATTR) is the most frequent cause of autosomal-dominant hereditary systemic amyloidosis worldwide. The genotype of a German cohort ($n = 89$; 56 males; 33 females; age 51.4 ± 17 years) was studied. ATTR diagnosis was confirmed by DNA sequence analysis. 13 different genotypes were recorded in altogether 50 families/index patients. The highest frequency was observed for mutation p.V30M (53.9%) followed by p.G47A (25.8%). Mutations p.V30M and p.G47A were observed in 29 (58.0%) and 5 (10.0%) of the families, respectively. The remaining 11 genotypes (84.6% of all genotypes) were found in 18 patients (20.2%) from 16 families (32.0% of index patients). Within this latter group, p.L58H represented the largest single mutation with 3 families affected (6.0% of index patients). Pedigree analysis was performed in 4 families with mutation p.V30.M, 3 families with p.G47A, and in one family each with mutation p.G53A, p.L58H and p.I107V. Whereas, a range of phenotypic expressions was observed, some unifying characteristics were noticed with individual genotypes. Onset of disease in patients having mutation p.V30M was observed relative late (>50 years) whereas onset in patients with p.G47A was earlier (<41 years). The highly progressive course of disease related to mutation p.G47A was demonstrated by the relative low time period between onset and fatal disease. Most patients died due to heart failure. One main phenomenon of this phenotype is the frequent involvement of failures in the autonomous nervous

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

P078 RISK OF POSTOPERATIVE INFECTIONS AFTER LTX RISES WITH MELD SCORE

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Aim: Identifying patients at higher risk of infection after liver transplantation could help to adjust treatment at large and anti-infective therapy and prophylaxis in particular. Known risk factors for postoperative infections after LTX are operation time, operation technique, blood volume replacement and episodes of acute rejection. Aim of this study was to evaluate and stratify the risk of postoperative infections after LTX. Although more critical ill patients receive liver transplantation (LTX) in the MELD era, a correlation between postoperative infections and MELD score has not yet been described.
Material and Methods: 748 consecutive liver transplantations after implementation of MELD score from December 2006 till December 2013 were included in a retrospective analysis. All transplantations were orthotropic liver transplantations from brain dead donors in adult recipients. Number of infections, infection-site andinfectiousagent during hospital stay after LTX were analyzed retrospectively and correlated to labMELD score resulting from lab values collected directly before transplantation. Statistical analysis was performed using Kruskal-Wallis-test and logistic regression analysis.
Results: At least one infection occurred in 166 of 748 cases during hospitalization after LTX. Pulmonary infections were the most common site of post-transplant infections ($n = 110$). Most infections were caused by enterobacteria. A higher MELD score correlated strongly with the risk of infection after LTX, the regression coefficient was highly significant (P-value
Conclusions: We identified MELD score as a strong predictor for infections after LTX. The risk of suffering from infection as well as number of infection rises with MELD score pre-transplant. Therefore, patients with high MELD score are at high risk for post-transplant infections. Subsequent analysis are necessary to identify risk factors for the location and type of infection to implement stratified measures for screening and prophylaxis.

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

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Background: Facing critical organ shortage the TOP-Study was initiated in November 2011 to reduce ischemia reperfusion injury (IRI) in extended donor criteria (EDC) liver grafts. Based on experimental data indicating protective effects of a Tacrolimus-Rinse on hepatic IRI, a prospective randomized multicenter-IIT was designed. Participating centers are Munich LMU, Berlin, Frankfurt, Heidelberg and Regensburg. Funding was received from Astellas.
Methods: Liver from donors exhibiting ≥2 EDC were flushed with Tacrolimus (20 ng/ml) in 1000 ml HTK (intervention) or with HTK before transplantation (control). Primary endpoint was the peak ALT level within 48 h following surgery, the observation period was 7 days. To analyze the effects of an organ-rinse in marginal liver grafts, study patients were compared to patients without a rinse treatment (placebo) utilizing the liver transplant data base of our hospital.
Results: 23 patients meeting the inclusion criteria had been enrolled in the trial until August 2013. An interim analysis revealed that tacrolimus rinse did not improve hepatic IRI indicated by similar maximum ALT levels in both groups: Tacrolimus-Rinse 768 vs. HTK-Rinse 610 (median, U/l, $P > 0.05$).
Conclusion: In contrast to experimental data, a tacrolimus Rinse is not advisable in EDC liver grafts. The rather low ALT levels in both groups may suggest beneficial effects of *ex vivo* organ rinsing prior to implantation.

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

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Introduction: MELD-based liver allocation led to reduced graft and patient survival. Organ shortage has led to increased use of marginal donor organs. Detailed analyses of donor-recipient-matching according to labMELD and Eurotransplant Donor-Risk-Index (ET-DRI) and their impact on long-term graft-survival after liver transplantation (LT) are missing.
Methods: In a retrospective single-center study of 1727 adult primary LTs (median follow-up: 89 months) long-term graft-survival was assessed according to recipient labMELD-score and in regard to donor quality measured by ET-DRI (Kaplan-Meier-estimates, Log-rank).
Results: Mean labMELD and ET-DRI were 17(±8.49) and 1.63(±0.43). One-, ten- and 15-year graft-survival was 84.1%, 63.7% and 55.1%. Long-term graft-survival was not significantly influenced by labMELD ($P = 0.058$), but ET-DRI (p35) and ET-DRI (E1:1–1.2; E2: >1.2–1.4; E3: >1.4–2 and E4: >2) categories were defined. Matching those categories revealed significant influences of ET-DRI on long-term graft-survival in labMELD categories M1(p1.4 causing markedly reduced long-term graft-survival. However, this marked difference was absent in patients of category M4 ($P = 0.172$). In these recipients 10-year graft survival was similar (E2:53.1%; E3:55.4%; E4:48.2%) for all donors with ET-DRIs >1.2.
Conclusion: For recipients with labMELD ≤ 35 superior long-term graft-survival may among others be achievable with organs from donors with ET-DRIs ≤ 1.4. Although our data have to be analyzed in more detail, the usefulness of a reverse matching of high MELD and low DRI seems not to be supported by the present data.

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

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Introduction: Organ shortage has led to increased use of marginal donor organs. Recently the Eurotransplant Donor Risk Index (ET-DRI) was developed for estimation of graft outcome after Liver Transplantation (LT). Long-term data on ET-DRI and its impact on different indications for LT are missing.
Methods: In a retrospective single-center study of 1767 adult primary LTs (median follow-up: 88 months) long-term graft-survival was assessed according to indication and in regard to donor quality measured by ET-DRI (Kaplan-Meier-estimates, Log-rank).
Results: Mean ET-DRI in our cohort was 1.63(±0.43). One-, ten- and 15-year graft survival was 83.5%, 63.3% and 54.8%. Long-term graft survival was significantly influenced by ET-DRI (p)
Conclusion: To achieve excellent long-term graft survival higher risk organs (ET-DRI > 1.4) should only be used restrictively for patients with CD/AIH or HCV. Their use in HCC, HBV, ALF and crypotogenic cirrhosis seems to be less problematic. If these results are confirmed in other analyses the ET-DRI may be a useful supportive tool in liver allocation.

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

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

(MELD) score. In 16 cases TIPSS could safely be placed in both patients with caval-replacement and piggy-back anastomosis of the V. cava.
Results: To our knowledge this is the largest case series of TIPSS placement after liver transplantation yet. The median labMELD score of patients at the time of intervention was 17 (range 8–24). The median atrial-portal gradient was 19 mmHg pre-interventionally and could significantly be reduced to a median of 7 mmHg in our patient collective, thus documenting technically successful TIPSS implantation. 4 patients were bridged to re-transplantation, 3 were re-listed and in 5 patients re-transplantation could be avoided. All TIPSS still in place were patent in patients alive at the time of analysis. No major, procedure-associated, complications occurred. Death within one year of TIPSS placement ($n = 7$) was associated with a significant higher MELD score (median= 20), whereas age, time since transplantation and hight of the atrial-portal gradient did not show a significant impact.
Conclusion: TIPSS placement in liver transplant recipients is feasible and safe irrespective of the applied transplant technique, effectively reducing portal hypertension. Still, the indication should be carefully considered and individualized as patients with a higher MELD score do not seem to profit from TIPSS implantation as a rescue measure. The ideal time-point of application and its limitations have to be defined further.

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

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Background: We developed a novel technique of subnormothermic *ex vivo* liver perfusion (SNEVLP) for the storage of liver grafts prior to transplantation. To test the safety of SNEVLP we compared it to a control group with minimal cold storage (CS) time.
Methods: Heart beating pig liver retrieval was performed and the liver grafts were either cold stored for 6 h (minimal injury) or preserved with a sequence of 2 h cold storage and 4 h SNEVLP (34 °C), followed by orthotopic liver transplantation. Liver function tests and histology were investigated.
Result: AST levels during SNEVLP remained stable within the normal range for pigs during *ex vivo* perfusion (42.2 + 5.6 U/l) with stable bile production. SNEVLP vs. CS livers had a trend towards decreased AST (297.3 vs. 1396.0 U/l, $P = 0.104$) and alkaline phosphatase (131.3 vs. 194.7 U/l, $P = 0.115$) levels at day 2 after transplantation, as well as peak bilirubin levels (3.3 vs. 7.3 μmol/l, $P = 0.123$). Peak INR was similar between SNEVLP and CS groups after transplantation (1.07 vs. 1.27, $P = 0.408$). Histology revealed minimal necrosis at the end of follow-up in both groups.
Conclusion: SNEVLP allows assessment of graft injury and function during organ preservation and is associated with comparable outcome even to grafts with minimal CS time.

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

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Background: It is unclear if patients with chronic liver disease and hepato-renal syndrome (HRS) have similar outcome after deceased donor (DD) and living donor (LD) liver transplantation (LT).
Methods: 30 adult patients with HRS receiving a LDLT and 90 adult HRS patients receiving a full graft DDLT were compared using a match pair study design.
Results: LDLT vs DDLT of patients with HRS was associated with decreased peak AST levels (339 ± 214 vs. 953 ± 1253 U/l; $P = 0.0001$), and similar 7-day bilirubin (8.42 ± 7.89 vs. 6.95 ± 7.13 mg/dl; $P = 0.35$), and INR levels (1.93 ± 0.62 vs. 1.78 ± 0.78; $P = 0.314$). LDLT vs. DDLT had a decreased ICU (2 (1–39) vs. 4 (0–93) days; $P = 0.004$) and hospital stay (17 (4–313) vs. 26 (0–126) days; $P = 0.016$) and a similar incidence of overall postoperative complications (20% vs. 27%; $P = 0.62$). No significant difference was detected between LDLT and DDLT patients regarding graft survival at 1- (80% vs. 82%), at 3- (69% vs. 76%), and 5-years (65% vs. 76%; $P = 0.63$). The incidence of chronic kidney disease post-liver transplantation (10% vs. 6%; $P = 0.4$) was similar between both groups.
Conclusion: LDLT results in comparable long-term outcome when compared with DDLT in patients with HRS.

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

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Introduction and Aim: Diaphragmatic hernias (DH) are a rare but life threatening complication following pediatric segmental liver transplantation (LT).
Case Report: Herein we present two cases of right-sided DH after left-lateral LT in 2 paediatric recipients: a 19 month-old boy who developed an early DH 3 months after left lateral split LT because of Alagille syndrome and a 3 years old girl with a late DH, 18 months after left lateral LDLT because of biliary atresia.

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

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

Both children underwent urgent explorative laparotomy. Intraoperative a subtotal herniation of small bowel through a right sided enlarged diaphragmatic caval opening (maximal diameter 3.5 cm) was detected in both cases. After reposition of intestine in the abdominal cavity the diaphragmatic opening was closed with prolene running suture and a chest tube was inserted. The further postoperative course was uneventful.
Discussion: From the present 2 cases and review of the literature (to date 19 cases of right sided DH after segmental pediatric LT have been reported) we can conclude that: (1) it is a rare but potentially life threatening complication which can occur early as well as lately after LT (2) the clinical manifestation is insidious (3) lipase values can be elevated probably due to pancreatic venous congestion (3) chest-x-ray and US are sufficient and specific diagnostic tools (4) a urgent laparotomy with reposition of intestine in abdominal cavity and closure of diaphragmatic opening is the treatment of choice (5) possible risk factors reported in the literature are represented by segmental liver graft, surgical trauma, malnourishment, elevated intra-abdominal pressures, and immunsuppression with mTor-i.

BASIC SCIENCE

P089 FRAGMENTS OF AT1R AND ETAR-ANTIBODIES INDUCE COMPLEMENT-INDEPENDENT ENDOTHELIAL ACTIVATION

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

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

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

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

P090 T-CELLS LICENCE IL-10$^+$ REGULATORY B-CELLS TO PRODUCE GRANZYME B AND CONFER CYTOTOXIC CAPACITY TO REGULATORY B-BELLS

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Objective: Regulatory B-cells (Breg) have recently been identified as a cell population with immunoregulatory capacity and play a role in solid organ transplantation by suppressing allograft rejection. Breg inhibit pro-inflammatory T-cell responses and promote Treg development. The exact mechanisms of Breg mediated T-cell inhibition are unknown. The aim of this study was to investigate possible mechanisms of Breg mediated immune regulation.
Methods: B-cells from 20 healthy blood donors were purified by magnetic bead isolation. Purified B-cells were then stimulated with CpG in presence of varying cytokines (without any exogenous cytokines, +IL-2, +IL-6, +IL-7, +IL-15, +IL-17A, +IFNγ). In some conditions, B-cells were co-cultured with autologous CD3$^+$ T-cells. After 24–72 h of culture, B-cells were analyzed for IL-10, granzyme A/B (GrA, GrB) and perforin (Per) expression.
Results: CpG stimulation without any additional exogenous cytokines induced IL-10 production in B-cells (B-cells: %IL-10$^+$ 14.4 $\pm$ 1.2%). IL-10$^+$ Breg and IL-10^{neg} B-cells did not produce GrA/GrB or Per. In contrast, CpG stimulation of B-cells in presence of IL-2, IL-15 or IFNg induced an additional, separate GrB$^+$IL-10^{neg} B-cell subset (B-cells: %GrB$^+$ 7.2 $\pm$ 0.8%, 7.0 $\pm$ 0.9%, 5.1 $\pm$ 1.5%). In these conditions, IL-10$^+$ Breg were lacking GrA/GrB or Per. However, IL-10$^+$ Breg acquired the ability to produce GrB upon coculture with autologous CD3$^+$ T-cells (IL-10$^+$ Breg: %GrB$^+$ 35 $\pm$ 9%).
Conclusion: Depending on the cytokine environment, a separate GrB producing B-cell population can be induced. GrB confers cytotoxic capacity to B-cells and may allow specific lysis of target immune cells. Thus, GrB$^+$ B-cells can be regarded as an additional Breg subpopulation. IL-10$^+$ Breg do not express GrA, GrB or Per. Interestingly, coculture with T-cells seems to licence IL-10$^+$ Breg to produce GrB. Thus, autologous T-cells promote the development of IL-10$^+$GrB$^+$ Breg. These Breg may have a pivotal in establishing immune tolerance.

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

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Aim: Chronic allograft rejection (CR) is the main risk factor after lung transplantation (LTx). The anti-inflammatory/anti-fibrotic properties of pirfenidone might reduce CR after experimental LTX alone or in combination with an inhibitor of mammalian target of rapamycin (everolimus).
Method: A rat model of left lung allo-transplantation (F344-to-WKY) was used to evaluate the anti-fibrotic effects of pirfenidone (InterMune, USA; 600 mg/kg/day; 0.85% in chow; day -3 to 60) alone (group 1; $n = 8$) or in combination with everolimus (Novartis, Swiss; 2.5 mg/kg/day; by gavage; day 7 to 60) (group 2; $n = 8$).
Results: Non-treated allografts showed severe acute (day 20, ISHLT A4/B2R) and chronic rejection (day 60, ISHLT C/D). Only the combination therapy reduced early acute rejection (ISHLT A3/B1R-B2R). Both treatment strategies significantly reduced chronic bronchiolar rejection (group 1, $P \leq 0.05$; group 2, $P \leq 0.01$). Additionally, group 2 demonstrated significantly less vascular damage ($P \leq 0.01$).
Conclusion: Early administration of pirfenidone in combination with everolimus retarded chronic rejection processes and might improve survival after experimental LTx.

P095 VARIABILITY OF INTRAHEPATIC VASCULAR ANATOMY IN RODENTS & THEIR SURGICAL IMPLICATIONS

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Background: The need for precise experimental surgical procedures parallels the development of clinical hepatobiliary surgery rising. The intra-hepatic vascular anatomy in rodents, its variations and corresponding supplying and draining territories in respect to the lobar structure of the liver have not been described. We performed a detailed anatomical imaging study in rats and mice to allow for further refinement of experimental-surgical approaches.
Methods: LEWIS-Rats & C57Bl/6N-Mice were subjected to ex-vivo & in-vivo imaging using CT & MRI. Underlying vascular anatomy was reconstructed, analysed and used for volume-determination of the dependent territories.
Results: Variations in hepatic vascular anatomy were observed in terms of branching pattern and of distance of branches to each other. Most liver lobes have their own portal supply and their hepatic drainage. In contrast the paracaval liver is supplied by various branches from other lobar portal vein and drains directly into the vena cava. Surgically relevant variations were primarily observed in portal venous supply of right lobe and the distance between branching in left median and left lateral portal vein in rats, but not in mice.

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

P096 IMPAIRED LIVER REGENERATION IN MICE LACKING NUCLEAR FACTOR I-C

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Introduction: Knockout studies of Nuclear Factor I-C (NFI-C) revealed effects on skin wound healing and on the growth of its appendages. The aim of this study was to assess a possible role in liver regeneration following partial hepatectomy (PH).
Methods: NFI-C knockout and C57/Bl6 mice underwent 60% PH. Liver regeneration, gene and protein expression [e.g. transforming growth factor-ß1

(TGF-ß1), plasminogen activator inhibitor-1 (PAI-1), urokinase plasminogen activator (uPA)] were assessed at specific time points.
Results: NFI-C knockout mice revealed decreased number of proliferating hepatocytes at the peak of regeneration and a delayed liver regeneration process in comparison to controls. Gene and protein expression analysis revealed that TGF-ß1 and PAI-1 were overexpressed in NFI-C knockout mice. Knockout mice displayed a blunted increase in uPA activity, a PAI-1-regulated early liver regeneration event mediating the breakdown of the extracellular matrix (ECM), and they did not abrogate PAI-1 expression at later phases of liver regeneration. In knockout mice, the decrease of HGF signaling was indicated by lower phosphorylation levels of its receptor cMET.
Conclusion: NFI-C acts as a regulator of TGF-ß1 and PAI-1 expression following PH, leading to decreased PAI-1 secretion and to an increase of uPA signaling, thereby activating hepatocyte proliferation and liver regeneration.

P098 MULTIDRUG-PRECONDITIONING ALLEVIATES IMMUNE RESPONSE IN RAT KIDNEY GRAFTS

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Background: Reduced ischemia reperfusion-injury by multidrug-preconditioning inhibiting Crosstalk between ROS and Innate Immunity was evaluated in a rat kidney transplant model.
Materials and methods: 70 orthotopic, life-sustaining rat kidney transplantants were performed using a fully mismatched allogenic model (Lewis-Brown-Norwayà Lewis). Rats were randomly assigned to either therapy or vehicle group. Donors were preconditioned with oxidase inhibitors (Allopurinol, Diphenyleneiodonium, Apocynin) and recipients received the radical scavenger Edaravone preoperatively and for 4 days after the operation. 6 h, 3, 7, 14 and 28 days after kidney transplantation biopsies and blood samples ($n = 7$ for each time point per group) were taken for analysis. Histological scoring of all tissue specimens was performed by two pathologists blinded to applied treatment. Expression of 84 genes relevant for innate immunity and adaptive immune response was studies by PCR-array.
Results: 28 day-survival was 100% vs. 71.4% (Therapy vs. Control). Histological scoring showed a lower ischemia-reperfusion injury at early time points [e.g. semiquantitative ATN-Score d3: 1.21 + 0.6 vs. 0 (Therapy vs. Control)] and a significantly lower cumulative Banff score (6 h, 3d, 7d, 28d, $P < 0.05$). PCR revealed significant regulation of >25 genes related to innate and adaptive immune response indicating an initially diminished innate immune response and a retarded activation of adaptive immunity.
Conclusion: Reduced damage during transplantation may lead to a lower activation of innate immunity and a delayed adaptive immune response.

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

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Aim: Due to their hydrophobicity and redox properties, N-acyl dopamines (NADD) may affect oxidative protein folding and thereby induce the unfolded protein response (UPR) This was tested in the present study.
Methods: Genome wide gene expression profiling, confirmatory qPCR and reporter assays were employed on human umbilical vein endothelial cells (HUVEC) to validate induction of UPR target genes and UPR sensor activation. Intracellular ATP, apoptosis and thermotolerance were used as functional parameters to assess adaptation of HUVEC.
Results: NOD, but not dopamine dose dependently induces the UPR. This was also found for other synthetic NADD. Induction of the UPR was dependent on the redox activity of NADD and was not caused by selective activation of a particular UPR sensor. UPR induction did not result in cell apoptosis, yet NOD strongly impaired cell proliferation by attenuation of cells in the S-G2/M phase. Long-term treatment of HUVEC with low NOD concentration showed decreased intracellular ATP concentration paralleled with activation of AMPK. These cells were significantly more resistant to cold inflicted injury.
Conclusions: We provide for the first time evidence that NADD induce the UPR *in vitro*. It remains to be assessed if UPR induction is causally associated with hypometabolism and thermotolerance. Further pharmacokinetic studies are warranted to address if the NADD concentrations used *in vitro* can be obtained *in vivo* and if this in turn shows therapeutic efficacy.

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

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Aim: Static cold preservation (CP) severely impairs endothelial barrier function in solid organ allografts. Although N-octanoyl dopamine (NOD) treatment can prevent cell damage suring CP, intercellular gap formation still occurs. We analyzed the effect of NOD treatment of EC in relation to barrier function.
Methods: Impedance was measured in NOD treated or untreated HUVEC during treatment and after CP and re-warming. Changes in F-actin and Paxillin (pax) staining were studied by immune-fluorescence and Western blotting.
Results: NOD strongly increased impedance when HUVEC were cultured at 37°C, paralleled by increased F-actin fibers, mostly associated with phosphorylated paxillin (pPax). This was completely abrogated in the presence of U0126 or Fasudil suggesting activation of p42/p44 and ROCK. Neither U0126 nor Fasudil impaired the propensity of NOD to protect EC against cold inflicted injury. While in untreated HUVEC subjected to CP impedance was strongly diminished, in NOD treated HUVEC impedance rapidly increased during re-warming. The expression of F-actin fibres and pPax increased in parallel to activation of p42/44. Phosphorylation of pax was strongly diminished in the presence of U0126.While inhibition of ROCK did not affect impedance; this was strongly abrogated in the presence of U0126.
Conclusions: NOD treatment of EC increase impedance suggesting improved endothelial barrier properties. This is mediated through the activation of ROCK and p42/44 and involves activation of focal adhesion contacts. During re-warming gap closure does not depend on ROCK activation but requires p42/p44.

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

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Background: Kidney transplantation in mice is challenging but offers good translational models to study mechanisms of disease. In this study allogenic and isogenic kidney transplantation in combination with different cold ischemia times (CIT) was performed and analysed by functional magnetic resonance imaging (MRI) and histological evaluation.
Methods: For the model of acute rejection C57Bl/6 male donor kidneys were transplanted to Balb/C recipients and prolonged CIT (60 min) was used resulting in acute T-cell mediated rejection. As comparison isogenic kidney transplantation (ktx) was done. For chronic allograft rejection Balb/C donor kidneys were transplanted into C57Bl/6 recipients (CIT: 30 min). Warm ischemia time was 30 min in all surgeries. During transplantation the left recipient kidney was nephrectomised. After 3 weeks in the acute rejection model and 7 weeks in the chronic rejection model FACS analysis for infiltrating leukocytes and histology was evaluated (PAS stain) and immunostaining for fibrosis (Sirius red) and inflammation (leukocytes) was done. Functional MRI was performed repetitively and analysed for renal perfusion.
Results: Isogenic ktx histology revealed normal renal morphology 3 weeks after surgery and stable renal perfusion in functional MRI. Allogenic ktx in the acute model resulted in acute rejection (Banff IIA, IIB, III) with severe inflammation. 75% of the allografts had local infarctions with vessel occlusion partially in areas of heavy inflammation suggesting that infarction was secondary to inflammation. Infarcted areas without any leukocyte are suggestive for surgical complications. Infarcts were characterized by MRI signal alterations and perfusion defects. Longitudinal functional MRI studies showed declining renal perfusion with ongoing rejection also when excluding areas of infarction. Perfusion defects occurred mainly after allogenic kidney transplantation. Prolonged CIT enhances inflammation and the incidence of infarction (75% with 60 min CIT, 25% with 30 min CIT in the allogenic model). In the direct vicinity of occluded vessels fibrosis was markedly enhanced.
Conclusion: The duration of cold ischemia time enhances the risk for partial infarction and accelerates rejection. Renal perfusion measurements by functional MRI correlate with rejection and offers non-invasive techniques to monitor inflammation and to assess graft pathologies.

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

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Introduction: Organs of brain dead donors are linked to compromised patient and graft survival. Hence interventions that counteract the negative effects of brain death and maintain organ quality are urgently needed. Retrospective studies suggest that donor desmopressin (DDAVP) treatment improves outcome after kidney transplantation. We hypothesized that DDAVP disarms the graft's endothelium from pro-inflammatory angiopoietin-2 (ang-2) containing Weibel-Palade bodies (WPB) in the donor; resulting in a reduced WPB release at the time of reperfusion in the recipient.
Methods: The influence of DDAVP treatment on the expression of vasopressin-2 receptors (V2R) and adhesion molecules was tested in brain dead donor rats. Furthermore, renal function was evaluated in an allogeneic transplantation model of brain dead rats.
Results: WPB were released upon rewarming in a static cold preservation model of cultured endothelial cells, but V2R expression was only scarcely found on the renal vasculature and down-regulated in BD rats by DDAVP. Nevertheless, donor expression of VCAM-1 and ICAM-1 were significantly reduced in DDAVP donor rats, but these benefits neither improved renal function nor histology in our allogeneic renal transplant model.
Conclusion: Our results do not support the hypothesis that the beneficial effect of DDAVP treatment is caused by the release of WPB in renal donor grafts.

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

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Background: MRI is a promising tool to non-invasively visualize renal posttransplant diseases. To assess if MRI enhanced by ultrasmall particles of iron oxide (USPIO) P904 can detect ischemic acute kidney injury (iAKI) and cyclosporine nephrotoxicity (CyA) in a rat model.
Methods: Of 30 Lewis-rats were studied in three groups: Nine animals were subjected to 45 min unilateral ischemia (iAKI). Eleven animals received daily cyclosporine A (CyA, 15 mg/kg s.c.) under low-salt diet (<0.03% sodium) and 10 Controls received daily sterile oil (50 mg/ml s.c.) for 28 days. MRI was performed 36 h after injection of P904 (516 μmol/kg, Guerbet) on a 3T scanner (Siemens TimTrio), spatial resolution 0.3 × 0.3 × 1.0 mm³. Signal-to-noise measurements (SNR) were performed in the cortex, medulla and pyelon, respectively. Histology was assessed as gold standard including Perl's Prussian blue staining to demonstrate iron (i.e. P904) and ED1-immunohistochemistry to detect rat macrophages.
Results: In the iAKI group a vast signal decay was seen mainly in the medulla. The SNR of the iAKI kidneys vs. Controls were: cortex 19.6 vs. 10.4, medulla 4.5 vs. 18.8, pyelon 14.6 vs. 33.7 ($P < 0.0001$, respectively) In CyA kidneys we observed a moderate decrease of signal intensity without compartment-specific predominance: The respective SNR in the cortex were 11.0 vs. 10.4 (n.s.), medulla 15.3 vs. 18.8 ($P < 0.01$) and pyelon 24.6 vs. 33.7 ($P < 0.0001$), CyA versus Controls, respectively. In kidneys with iAKI histology confirmed abundant Prussian blue- and ED1-positive macrophages predominantly in the outer medulla (ED1-labeling in iAKI versus Controls 49 vs. ≤1 cell(s) per field of view, $P < 0.0001$) in conjunction with typical changes of iAKI while being normal in the control group. Contrastingly, iron staining was completely negative in all compartments in CyA kidneys, whereas ED1-labeling detected moderate macrophage infiltration (CyA versus Controls: 20 vs. ≤1 cell(s), $P < 0.0001$) and light microscopy demonstated the typical features of calcineurin inhibitor toxicity.
Conclusions: USPIO-enhanced MRI with the novel contrast agent P904 seems to be a suitable tool to detect iAKI with excellent correlation to histology. In contrast, P904 alone fails to detect cyclosporine nephrotoxicity, probably due to its low-inflammatory histologic characteristics.

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

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Objectives: The number of marginal organs for transplantation increased in the last recent years. The transplantation of marginal organs leads to a raised risk of graft failure and DGF. Normothermic extracorporeal kidney perfusion provides the chance to assess the organ quality before transplantation. However, existing parameters for vitality assessment are discussed controversial. For this purpose we discuss a novel approach based on the characterization of autoregulation.
Methods: Porcine kidneys ($n = 18$, cold static storage: 1–14 h) were normothermic and pressure controlled perfused with autologous oxygenated blood, conditioned with heparin, glucose and sodium-bicarbonate. After 1 h of kidney conditioning the arterial pressure during the perfusion was changed every 5 min by 2 mmHg in a range of 60 mmHg to 110 mmHg and flow characteristics were recorded.
Results: Three different flow characteristics (FC) were detected: FC1 – typical autoregulation ($n = 5$); FC2 – restricted autoregulation ($n = 6$); FC3 – no autoregulation ($n = 7$). Those could be assigned to the times of ischemia as following (FC-$Q_{0,25}$,median,$Q_{0,75}$ in hh:mm:ss): FC1 – 01:05:02, 01:19:28, 01:52:00; FC2 – 02:51:38, 06:26:23, 08:09:13; FC3 – 08:12:17, 10:41:17, 13:00:52.
Conclusion: The results suggest that the autoregulatory behavior is highly correlated to the cold ischemia time. Accordingly, parameters describing autoregulation characteristics could be used as potential markers for kidney assessment during warm machine perfusion.

P106 RENAL TRANSPLANT RECIPIENTS LACK CIRCULATING CD19 + CD24HICD38HI INTERLEUKIN-10 PRODUCING REGULATORY B-LYMPHOCYTES

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Recent studies demonstrated that CD19 + CD24hiCD38hi regulatory B-Lymphocytes (Breg) appear to suppress immune mechanisms by cell-cell contact or production of IL-10. Here, we analyzed peripherally circulating Bregs by flow cytometry in healthy subjects ($n = 18$) and renal transplant recipients receiving a calcineurin inhibitor (CNI) based immunosuppression (Tacrolimus $n = 35$, CsA $n = 11$).

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

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

THORACIC ORGANS

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

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Background: There is growing evidence on the beneficial use of everolimus (EVR) in heart transplantation to support minimization or withdrawal of calcineurin inhibitor (CNI) therapy, mainly to spare renal function or avoid malignancy or to reduce progression of cardiac allograft vasculopathy. The MANDELA study (NCT00862979) aims to evaluate the benefit of either CNI-free or CNI-minimized EVR-based regimens after early conversion from standard treatment in de novo heart transplant recipients (HTxR).
Methods: MANDELA is a multi-center, randomized, controlled, open-label, 12 month study. Overall, 200 de novo HTxR (3 months post Tx) will be randomized (1:1) to receive either EVR (C0-h 5–10 ng/ml) + reduced CNI (TAC C0-h 3–8 ng/ml or CsA C0-h 50–150 ng/ml) + steroids (≤0.3 mg/kg) or to receive EVR (C0-h 5–10 ng/ml) + mycophenolic acid (EC-MPS max. 2880 mg/day or MMF max. 3 g/day) + steroids (≤0.3 mg/kg). The primary objective of MANDELA is to demonstrate superior renal function (assessed by eGFR, MDRD) 12 months post randomization in HTxR with a CNI-free regimen after tapering serum CNI-levels to the respective target ranges. Key secondary objectives include: non-inferior efficacy (composite endpoint of BPAR of ISHLT 1990 grade ≥3A/ISHLT 2004 grade ≥2R, acute rejection, episodes of hemodynamic compromise, graft loss/re-transplant, death or loss to follow-up) and safety outcomes (infections, hypertension, hyperlipidemia, diabetes).
Results: So far 138 patients at nine German heart transplantation centers have been randomized in the MANDELA study until April 2014. Continuation of the study was well supported by a neutral data safety monitoring board.
Conclusion: The Mandela study might help to evaluate benefit on renal function of an EVR-based CNI-free regimen in HTxR after early conversion.

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

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Objectives: The lack of donors for heart transplantation (HTX) is increasing while at once the waiting list increases even greater. This leads to high urgency (HU) listing ("sickest first") of the recipients and need of acceptance of extended donor criteria (EDC) resulting in allocation of donor hearts to HU recipients in more than 90%. The purpose of our study was to investigate the impact of donor profile and pre-implantation factors on postoperative outcome in Eurotransplant (ET) HU recipients.
Methods: We retrospectively analyzed data of 50 consecutively performed HTX procedures in our institution (07/2010-08/2012). Data were collected from medical records and outcome were calculated for perioperative factors. Main outcome parameters included survival, intensive care unit (ICU) stay, graft injury characterized by postop creatine kinase (CK-MB)-release and postop catecholamine dosage.
Results: Of all recipients, 47 (94%) were HU (35 m,70%), mean age was 51.16 ± 1.81 years. Mean follow-up was 20.18 ± 1.46 month. 1-year survival was 84%; overall survival was 80%. Donor factors like age (48.23 ± 1.68 years), age ≥55 years (n = 19;45.8%), sex (16 m;32%), organ ischemic time (273 ± 7.29 min) and body surface donor/recipient index (1.01 ± 0.15), brain death-to-explant time (BD2Ex-t;729.78 ± 42.88 min), cause of brain death (non-traumatic ICB (n = 26.52%), traumatic ICB (n = 10.20%), insult (n = 9.18%), other (n = 5.10%)) and postop CK-MB max (92.96 ± 5.85 U/l) did not show any association with the outcome measures. Early catecholamine therapy was need with a combination of nor-epinephrine (NE) and dobutamine (DBX) in 27 (54%), epinephrine+NE+DBX in 10 (20%), DBX+milrinone in 6 (12%) and other in 7 (14%) patients. Mean ICU stay (7.18 ± 1.31 days), ventilation time (50.5 ± 7.75 h), catecholamine dosage and CK-MB max was not influenced by BD2Ex-t, organ ischemic time, donor age or sex. Longer ICU-stay was associated with higher mortality (P = 0.021).
Conclusions: HU patients had a comparable survival as reported by the ISHLT. In our cohort, donor related factors did not have influence on the early and late outcome. Factors of success are more likely to be depending on recipient's condition rather then on the donor's. Our data support the use of EDC donors in ET HU recipients. However, discussion about the principles of organ allocation focusing the ideal recipient and time remains even more crucial.

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

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Aim: We report on a 45-year-old male patient with a ventricular septum defect (VSD) following myocardial infarction due to acute occlusion of right coronary artery. This patient underwent repair of ventricular septum defect, implantation of right ventricular assist device (RVAD), successful weaning and explantation of the VAD.
Method & Result: On admission this patient was hemodynamically highly unstable following an acute proximal occlusion of the right coronary artery and a relevant ruptured ventricular septum. A percutaneous intervention of the RCA was unsuccessful. We performed a repair of the VSD through the apex of the left ventricle using cardiopulmonary bypass. The VSD was mainly apical but the myocardial infarction involved most of the anterior septum. After repair, weaning off from bypass with support of IABP and catecholamines was not successful due to massively impaired right ventricular function. A continuous flow pump (HeartWare® ventricular assist device) was implanted in a RA-PA position and weaning from bypass was possible. An epicardial lead was placed to the RV and attached to an implantable pacing device due to complete AV block. Two months later the patient was admitted to the emergency room with a thrombus that partially occluded the RVAD. Despite systemic thrombolytic therapy the pump completely stopped. The device was successfully explanted during an emergency operation. With stable hemodynamics, highly impaired right ventricluar function and a small remnant VSD the patient was successfully heart transplanted within the next year.
Conclusions: Early repair of VSD during an unstable hemodynamic situation bears high risk for intra- and post operative lethal outcome. Implantation of HVAD for recovery or bridge is an adequate option for these patients.

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

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Objective: After cardiac transplantation treatment of sinus tachycardia with b-blockers may significantly impair cardiac function, particularly regarding right ventricle. A favorable response to Ivabradine after cardiac surgery was described in many studies. However, we wanted to evaluate effects and side-effects of ivabradine in the early period after heart transplantation (htx).
Methods: Between 10/2010 and 05/2014 44 patients underwent htx in our department. Ivabradine was administered in 23 patients immediately after htx (starting on POD 4-27), in addition to ß-blockers in 6 patients. Of the other 21 patients, 11 received ß-blockers due to sinus tachycardia.
Results: After ivabradine mean heart rate was reduced from 113.7 ± 15.2 bpm at baseline to 90.4 ± 11.0 bpm before hospital discharge (P < 0.05). Echocardiographic evaluation confirmed an improvement of cardiac function, correlating to substantial clinical advances. The heart reduction was less pronounced in patients with ß-blockers (P > 0.05).

There were no substantial adverse effects in all patients with ivabradine. We did not detect relevant interactions with immunosuppressants, except from a distinct increase of mycophenolate mofetil blood levels.
Conclusions: We could demonstrate that patients with sinus tachycardia after htx can be successfully treated with ivabradine, even compared to ß-blockers. Reducing the resting heart rate, it did not negatively influence cardiac contractility. Interactions with immunosuppressive medication or other adverse effects could not be detected.

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

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Background: Multifactorial anemia with impairment of renal function (CRF) is a common problem after heart transplantation (HTX). Erythropoiesis – stimulating agents (ESAs) are commonly used to improve hemoglobin levels in patients with anemia due to CRF. With CERA (Continuous Erythropoietin Receptor Activator) a new therapeutic agent with a larger serum half time is available. However, data in patients after HTX are extremely limited. This study retrospectively evaluated the effects of anemia therapy with CERA versus conventional ESAs (Erythropoietin beta) in patients after HTX with anemia due to CRF.
Patients and methods: A total of 20 ESA naive heart transplant recipients with anemia due to CRF were included. All patients had baseline hemoglobin levels below 11 g/dl. 10 patients (mean age 53.4 ± 10.2 years, mean time post HTX 0.71 ± 0.73 years, 9 male/1 female) were included in the CERA group and 10 patients (mean age 60.3 ± 12.9 years, mean time post HTX 5.5 ± 5.2 years, 7 male/3 female) in the conventional ESA group (Erythropoietin beta). The primary endpoint was the change in hemoglobin level from baseline to month four, eight, and twelve month post initiation of either CERA or conventional ESAs. Hemoglobin target level was 12 g/dl.
Results: After 12 months of CERA and ESA therapy a statistically significant increase in mean hemoglobin levels was observed (CERA group: 9.0 ± 1.0 g/dl vs. 11.8 ± 1.9 g/dl, $P = 0.005$ vs. baseline, ESA group 9.2 ± 1.1 g/dl vs. 11.0 ± 2.2 g/dl, $P = 0.02$ vs baseline). In CERA patients, a continuous increase in mean hemoglobin levels was observed throughout the study period, whereas mean hemoglobin level was more fluctuant in conventional ESA patients. However, CERA and ESA therapy was well tolerated and no adverse events occurred during the study period. Patient self-assessment questionnaire revealed a lower pain level during the study period. Longer dosing intervals were advantageous as ease of dosing was more pronounced in CERA patients and the rate of missed doses was lower in CERA patients indicating a better adherence.
Conclusions: During the study period CERA corrected anemia and maintained sustained and stable control of mean hemoglobin levels. Our results underline the importance of optimized patient adherence by longer dosing intervals in this selected patient population with a multitude of comedications.

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

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Background: The use of tacrolimus (TAC) in patients after heart transplantation (HTX) increased during the last years.
Aim: In this retrospective study we evaluated the effects of a TAC (conventional and extended release TAC) based immunosuppressive therapy regarding rejection profile in comparison to a Cyclosporine A (CSA) based regimen in patients after HTX.
Methods: The data of 233 patients who underwent HTX at the Heidelberg Heart Transplantation Center from May 1998 until November 2010 were retrospectively analyzed. Primary immunosuppressive therapy was changed from a CSA ($n = 114$) to a TAC ($n = 119$) based regimen in 2/2006 according to center routine. Follow-up period was two years post HTX. Primary end-point was time to first biopsy-proven rejection requiring therapy. In all patients routine follow-up at the Heidelberg HTX Center was mandatory.
Results: Risk factor analysis regarding time to first rejection episode showed no statistical significant differences regarding recipient age, donor age, recipient gender, donor gender, gender mismatch, ischemic time, and diagnosis leading to HTX between the two groups (all P = ns). Time to first biopsy proven rejection was significantly longer in the TAC group (intention to treat analysis (ITT), $n = 233$, log-rank-test $P < 0.0001$, per protocol analysis, $n = 150$, log-rank-test $P = 0.0003$). In patients who underwent a change of primary immunosuppression ($n = 49$), also a significant longer time to first biopsy proven rejection was found in the primary TAC subgroup (log-rank-test, $P = 0.0297$). Further subgroup analysis in the TAC subgroup showed a longer time to biopsy proven rejection under extended release TAC compared to conventional TAC, however the level of statistical significance was not met (ITT, log-rank analysis, $P = 0.1736$).
Conclusion: Our study demonstrated that a TAC based primary immunosuppressive therapy is superior to a CSA based immunosuppressive regimen in patients after HTX regarding time to first biopsy proven rejection.

P114 RISK FACTORS FOR ACUTE KIDNEY INJURY AFTER LUNG TRANSPLANTATION

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Background: Solid non-renal organ transplantations have an increased risk for acute kidney injury (AKI). Little is known about the peri-surgical risk factors for AKI. Identifying risk factors for AKI could help to modify the therapy towards reducing nephrotoxic medication. Therefore, we aimed to identify predictors to estimate the severity of AKI and to find new biomarkers for risk prediction.
Material and Methods: For risk factor identification we analysed 950 electronic patient files for type of surgery, blood transfusions, time on ICU, nephrotoxic medication and co-morbidities. AKI was defined according to the AKIN criteria into mild (AKIN-1), moderate (AKIN-2) and severe AKI (AKIN-3) based on by loss of eGFR, or increase of s-creatinine within the first 48 h after surgery. CART analysis for risk prediction was performed.

In addition, a prospective clinical trial to verify the risk factors was performed. Patient urine and blood samples were collected at different time points before and after surgery. Functional MRI (inculding 22 patients) was performed at day 12–16.
Results: AKI incidence was 50% after double lung-tx in the retrospective cohort (26% mild, 15% moderate, 9% severe). Relevant risk factors for aggravation of AKI was the transfusion of >2 red blood cells packages during surgery. Also pre-existing renal impairment increased the risk of AKI.

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

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

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Background: The outcome after orthotopic heart transplant (HTX) is most importantly dependent on a short cardiac arrest time. Here we present our single-center experience of patients who underwent HTX with need of a second cardioplegic cardiac arrest (CCA) due to intraoperative complication.
Methods: We analyzed perioperative and follow-up data of patients, who underwent HTX with need of concomitant secondary cardioplegic cardiac arrest between 1996 and 2014. Mean follow-up time was 63 ± 86 month (range 0–217).
Results: Nine patients (two female) with a mean age of 52 ± 14 years were identified who needed a concomitant second CCA due to intraoperative complications. Eight patients were in need of surgical intervention of the ascending aorta including overstitching or resection and replacement. One patient needed mitral valve reconstruction and mechanical aortic conduit. Average first cardiac arrest time was 263 ± 97 min (range 86–366) and second 117 ± 119 min (range 6–412). Actuarial survival displayed a 1-year and 5 years survival of 64 ± 17%. Six patients are currently still alive. Two patients died within hospital stay. One patient deceased after hospital discharge due to intra-cerebral bleeding. Two deceased patients received female and one male donor grafts. Mean donor age (seven female) was 47 ± 14 years.
Conclusion: Secondary cardioplegic cardiac arrest due to intraoperative complications after orthotopic heart transplant bears high mortality and morbidity risk, but can be performed with an acceptable short- and long-term survival.

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

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

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

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

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

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

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

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

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

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

IMMUNOLOGY AND HLA

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

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

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

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

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

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

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

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

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

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

P120 PREFORMED CELLULAR ALLOREACTIVITY IS ASSOCIATED WITH HUMAN LEUKOCYTE ANTIGEN MISMATCHES

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

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

Among the 1502 tests, a significant association was found between the frequency of alloreactive CD8 T-cells and the HLA-A/B/C-MM number ($P = 0.030$), and between respective CD4 T-cells with HLA-DR-MM number ($P < 0.0001$). Peak levels of alloreactive CD8 T-cells increased with HLA-A/B/C-MM numbers (0MM:0%; 1MM:0.041%; 2MM:2.752%; 3MM:4.118%; 4MM:7.001%; 5MM:8.549%; 6MM:6.864%), and CD4 T-cells with HLA-DR-MM numbers (0MM:0.078%; 1MM:0.578%; 2MM:0.780%). Dialysis-patients showed higher alloreactive CD4 ($P = 0.015$) and CD8 T-cell levels ($P < 0.0001$) as compared to controls.

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

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

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

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

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

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

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

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

IMMUNOSUPPRESSION

P123 CONVERSION FROM PROGRAF TO GENERIC TACROLIMUS IN GERMANY

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Introduction: Generic Tacrolimus HEXAL® was introduced in Germany in 2010. Despite overall exposure >287 000 patient-years worldwide and publications reporting >3000 transplant patients, clinical data in Germany is scarce. The present report retrospectively evaluates experience from two NHZM centers.
Methods: Of 18 stable patients (17 kidney/1 liver, mean age ± SD 44 ± 18 years) were switched from Prograf® to Tacrolimus HEXAL® on a mg:mg monitored basis at 69 ± 71 months after transplant. Serum creatinine and tacrolimus trough levels were recorded up to 32 ± 20 weeks post switch. Comparisons were based upon three visits post- versus three visits pre-conversion.
Results: Dose changes were not performed. The group mean tacrolimus dose remained unchanged vs. pre-conversion values. Similarly, trough levels 7.0 ± 1.8 vs. 6.6 ± 1.6 ng/ml ($P = 0.32$) and serum creatinine 1.8 ± 0.7 vs. 1.8 ± 0.6 mg/dl ($P = 0.37$) also remained stable. Some patients exhibited higher intra-patient variability in tacrolimus trough levels. This was unaffected by conversion and group mean variability was not significantly changed. Acute rejection was absent and conversion was well tolerated.
Conclusion: This initial experience confirms earlier reports that Tacrolimus HEXAL® has a similar therapeutic profile to Prograf®. Conversion is safe and feasible in a controlled setting under supervision from a transplant physician.

P125 USE OF PLASMA GCFDNA QUANTIFICATION TO GUIDE PERSONALIZED IMMUNOSUPPRESSION

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Objectives: A new graft-derived cell-free DNA (GcfDNA) method was used to monitor liver graft integrity in response to early post-transplant immunosuppression.
Methods: GcfDNA percent was measured as described (Beck et al. Clin Chem 2013). Total cfDNA was quantified by assays for single copy genes together with an artificial internal DNA standard in one droplet digital PCR. GcfDNA amount was calculated by multiplying GcfDNA (%) with total cfDNA (cp/mL); corrected for extraction efficiency of the internal standard. GcfDNA and trough blood tacrolimus were measured in 260 samples from 20 patients during 240 days post-transplant.
Results: There was good correlation ($r^2 = 0.66$; $P < 0.001$) between percent and amount GcfDNA, which is high after engraftment, rapidly declining during the first week. Subtherapeutic tacrolimus levels were associated with elevated GcfDNA percent and amount, with the latter showing better discrimination. Both, the cut-off value for GcfDNA and tacrolimus levels decreased with time post-transplant. Discrimination accuracy was 64% using GcfDNA amount versus tacrolimus with 3750 cp/ml and 7.8 μg/l during week 2 post-surgery, 3000 cp/ml and 7.0 μg/l (week 3 & 4) and 2000 cp/ml and 6.5 μg/l thereafter.
Conclusion: Both GcfDNA expressions appear useful to identify the minimal needed tacrolimus concentrations, whereas the amount GcfDNA has advantage early after transplantation, given its higher dynamic range.

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

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Purpose: To study renal function, safety and efficacy of an Everolimus (EVR) based regimen after Calcineurin-Inhibitor (CNI) withdrawal in maintenance kidney allograft recipients.
Methods: In an open-label, randomized,controlled,multi-center study 93 patients on stable immunosuppressive therapy consisting of CNI (CsA or Tac), Enteric-Coated Mycophenolate Sodium (EC-MPS) with or without steroids were randomized to either continue CNI/EC-MPS or convert to an EVR/EC-MPS based regimen. After completion of the 12-months core study patients were included in an observational 4 year follow-up.
Results: 93 maintenance kidney Tx patients with a mean time of 6.4 years since the most recent transplantation (Tx) were randomized to either EVR ($n = 46$) or CNI ($n = 47$) treatment. 78 patients completed the 12-month core study and 67 (72%) attended the final 60-month study visit. Mean trough levels were 81 ± 34 ng/ml in CsA, 5.2 ± 1.9 ng/ml in Tac and 6.1 ± 2.4 ng/ml in EVR treated patients. Mean time post-Tx at baseline was 82.6 months and 70.5 months in the EVR and CNI groups, respectively. At month 60, adjusted mean eGFR (Nankivell) was 63.0 (95% CI 57.8, 68.2) mL/min/1.73 m^2 in the EVR group versus 57.9 (95% CI 52.6, 63.1) mL/min/1.73 m^2 in the CNI group, a difference of 5.1 (95% CI −0.6, 10.8) mL/min/1.73 m^2 ($P = 0.076$). Among patients who remained on randomized study drug at month 60, mean eGFR (Nankivell) was 71.6 (95% CI 64.2, 79.0) mL/min/1.73 m^2 in EVR-treated patients ($n = 21$) versus 60.6 (95% CI 55.1, 66.1) mL/min/1.73 m^2 in CNI-treated patients ($n = 29$) (mean difference 11.0; 95% CI 3.6, 18.5 mL/min/1.73 m^2; $P = 0.005$). No cases of BPAR occurred from randomization to month 60 in either group. Graft loss occurred in three EVR-treated patients and one CNI-treated patient.Graft loss occurred in three EVR-treated patients and one CNI-treated patient. Until month 60 one death had occured in the EVR group, three deaths in the CNI group. No unexpected safety concerns were observed in either group.
Conclusion: The late conversion to an EVR/EC-MPS treatment in maintenance renal Tx patients after CNI withdrawal is safe and led to a sustained better renal function in EVR treated patients 5 years post Tx.

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

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Purpose: To compare incidence of new-onset diabetes mellitus (DM) after transplantation (Tx) (NODAT) and progression of pre-existing DM in de novo kidney (K) allograft recipients after conversion to everolimus (EVR) based regimen and withdrawal or reduction of cyclosporine A (CsA) combined with EVR.
Methods: Post hoc analysis from ZEUS and HERAKLES, 12 months (Mo), prospective, open-label, multicenter, randomized (rdz) trials. De novo KTx pts received standard-exposure CsA + EC-MPS +steroids since Tx and were rdz to i) either continue CsA regimen or convert to ii) EVR/EC-MPS (at Mo4.5 post Tx in ZEUS, at Mo3 post Tx in HERAKLES) or to iii) a third rdz arm with reduced CNI+EVR regimen (HERAKLES). Post hoc analysis was done on NODAT development or DM progression.
Results: Results from ZEUS: 8% (25/300) of pts had DM at Tx, until Mo12 NODAT had developed in 8% (22/275) of non-DM pts (EVR 14/142, CsA 8/133); among these 22 pts 7% (20/275) had developed NODAT already at randomization (EVR 13/142, CsA 7/133). Incidence of NODAT after randomization was similar between groups ($P = 0.97$). Mean blood glucose change from randomization to Mo12 was similar in NODAT and DM subpopulation between EVR and CsA pts. eGFR (Nankivell,[ml/min]) was similar at randomization and significantly higher at Mo12 for EVR versus CsA pts within all subpopulations (NODAT: EVR +14.0(11.4) vs. CsA −9.2(15.9); pre-existing DM: EVR +5.5(5.9) vs. +0.7 (10.0) CsA). Results from HERAKLES: At Mo12 NODAT occured in 6.8%(30/438) of all pts (EVR group 6.7%(10/149) vs. CsA group 8.3%(11/133) vs. reduced-CsA group 6.3%(9/143), thus the same incidence of NODAT was found between the 3 HERAKLES regimens ($P = 0.62$).
Conclusion: No difference in NODAT incidence or progression of DM after CNI withdrawal and conversion to EVR were found within 12 Mo post Tx by post hoc analysis of these two large randomized trials. The benefit on renal function of an early conversion to an EVR-based regimen was seen in the NODAT subpopulation similar to what was seen from total study population results.

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

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Background: Post-kidney transplant (KTx) long-term and full dose/standard calcineurin inhibitor (CNI) use is associated with an increased risk for malignancies, cardiovascular disease, and renal failure. Previous studies have shown that everolimus (EVR) allowed further CNI reduction and therefore helps to preserve renal function without affecting efficacy. ATHENA study is designed to evaluate the renal function comparing EVR-based regimens with reduced CNI exposure (tacrolimus [TAC] or cyclosporine A [CsA]) versus a standard treatment protocol with mycophenolic acid (MPA) and TAC in *de novo* KTx (day 0) recipients (KTxR).
Methods: This is a 12-month (M), multi-center, open-label, prospective, randomised, parallel group study in KTxR (≥18 years) receiving renal allografts from deceased or living donors. Eligible patients will be randomized prior to Tx to one of the three treatment arms (1:1:1): TAC MPA+steroids (n = 204) or EVR+TAC+steroids (n = 204) or EVR+CsA+steroids (n = 204) all with basiliximab induction. Patients with thrombocytopenia or leukopenia, uncontrolled hypercholesterolemia or hypertriglyceridemia, ABO incompatible Tx will be excluded. The primary objective is to demonstrate non-inferiority in renal function (eGFR by Nankivell formula) in one of the EVR arms compared to the TAC MPA+steroids arm at M12 post-KTx. The key secondary objective is to assess the incidence of treatment failure (BPAR, graft loss or death) at M12 post-KTx. Other objectives are to evaluate GFR by different formulae, assess the incidence of efficacy endpoints (BPAR, graft loss and death), the incidence and severity of viral infections (CMV, BKV), the incidence and duration of delayed graft function, to evaluate left ventricular hypertrophy (by LV mass index), and to compare HLA- and non-HLA-antibody evolution.
Study status: The study recruitment is currently ongoing and 371 patients were enrolled in Germany and 66 in France. The preliminary results of this ongoing trial are expected in 2016.
Conclusion: ATHENA is the largest bi-national/German/French renal transplant study and the first study evaluating the non-inferiority of renal function as a primary objective in a *de novo* EVR-based immunosuppressive protocol.

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

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

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

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Introduction and Aims: Acute rejection and poor graft function at one year post renal transplantation are important predictors for graft failure. TRANSFORM, is a phase IV study that is designed to evaluate the impact of two immunosuppressive regimens [everolimus (EVR)-facilitated reduced (r) calcineurin inhibitor (CNI) exposure versus mycophenolic acid (MPA) plus standard (s) CNI exposure] on these clinically relevant outcomes in a novel single composite endpoint.
Methods: TRANSFORM (NCT01950819) is a 24 M, multicentre, open-label study randomising *de novo* RTxR 1:1 to EVR+rCNI or MPA+sCNI arm with basiliximab or antithymocyte globulin induction and steroids. Each arm will be further stratified by donor type (living donors, deceased standard criteria donors, or deceased expanded criteria donors) and CNI usage (cyclosporine or tacrolimus). At M12 the primary endpoint will be a composite of treated biopsy-proven acute rejection (tBPAR) rate or proportion of RTxR with estimated glomerular filtration rate <50 ml/min/1.73 m^2 (eGFR; MDRD4). Key secondary endpoint will be composite efficacy failure rate (tBPAR, graft loss, or death). These endpoints will be also assessed at M24. In a subset of subjects, the incidence of donor-specific antibodies by treatment group in relation to acute rejection and development of chronic allograft nephropathy/interstitial fibrosis and tubular atrophy expression (renal protocol biopsy) will be explored. Patients completing 24 M of treatment will be eligible to participate in an extension study for a further 36 M with outcomes including eGFR, patient and graft survival, incidence of cardiovascular disease, malignancy, and infection analysed up to 5 years.
Results: TRANSFORM study will be conducted across 229 centres worldwide and approximately 2040 RTxR will be randomised. The study enrolment has started and first data are expected in 2017.
Conclusions: Using de novo CNI-reduction in an EVR-based regimen, the TRANSFORM study aims to address the unmet medical need of balancing immunologic efficacy and renal function preservation. As the largest clinical trial in RTx with extended follow-up to 5 years, TRANSFORM will provide critical data required to help improve long-term outcomes.

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

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Aim: To compare safety and efficacy of 3 different immunosuppressive (IS) regimens 3 years after renal transplantation (Tx).
Methods: Of 802 patients (pts) were included in this 1 year, prospective, open-label, randomized (rdz), controlled multi-center study. After induction therapy with basiliximab all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 months (Mo) post Tx 499pts were rdz 1:1:1 to either a) continue standard CsA(100–180 ng/ml)+EC-MPS (n = 166) (STD) or convert b) to a calcineurin inhibitor (CNI)-free regimen with everolimus (EVR)(5–10 ng/ml)+EC-MPS (n = 171) or c) to a CNI-low regimen with EVR(3–8 ng/ml) + reduced CsA(50–75 ng/ml) (n = 162). All pts continued on steroids. Mo36 follow-up(FU) visit was performed by 123(89%) STD,130 (95%) CNI-free and 123(94%) CNI-low treated pts of the FU population (pop).
Results: From rdz to Mo36 BPAR was reported in 19/151(13%)STD, 22/149 (15%)CNI-free and in 21/146(14%)CNI-low pts (ITT;p=ns). 3 deaths (2%) occurred in STD, 2(1%) in CNI-free and 5(3%) in the CNI-low group. 6(4%) graft losses were observed in the STD, 5(3%) in the CNI-free and 1(1%) in the CNI-low group. Composite failure (BPAR,death,graft loss,loss to FU) occured in 27 (19%) STD, 28(20%) CNI-free, 33(23%) CNI-low treated pts. Premature discontinuation due to AEs occurred in 4/154(3%) of STD, 4/150(3%) of CNI-free and 1/147(1%) of CNI-low pts (safety-pop) from Mo12 to 36. Renal function (cGFR, Nankivell) was significantly improved by +7.0 ml/min/1.73 m^2 in favor of the CNI-free regimen at Mo36 (ITT; P = 0.009).
Conclusion: Mo36 results from HERAKLES show that IS regimens using EVR with low-dose or without CNI-exposure reflect an efficacious and safe therapeutic approach offering the opportunity for an individualized IS.

P133 COMPARISON OF SIROLIMUS AND EVEROLIMUS IN THEIR EFFECTS ON KIDNEY FUNCTION AND SURVIVAL IN HEART TRANSPLANT RECIPIENTS

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The mammalian target of rapamycin (mTOR) inhibitors sirolimus (SRL) and everolimus (EVL) are potent immunosuppressive agents, which allow reducing the dose of nephrotoxic calcineurin (CNI) inhibitors in solid organ transplant recipients. However, comparative data of the two mTOR inhibitors concerning clinical outcome in heart transplant (HTx) recipients is scarce. We assessed 5-year mortality and kidney function in 212 maintenance HTx patients with poor kidney function (estimated glomeralur filtration rate [eGFR] <60 ml/min/1.73 m^2), who were switched over to SRL (n = 64) or EVL (n = 148) between 2000 and 2007. In both groups, the CNI inhibitor dose was reduced by 50%.
Results: Baseline characteristics differed significantly between the two groups with respect to body mass index, age, duration on regular CNI inhibitor dose and year of SRL or EVL introduction (P = 0.013–2 (P = 0.012). Results did not differ between the SRL and EVL group (P = 0.911).
Conclusions: Data indicate that in HTx patients with poor kidney function, the introduction of both SRL and EVL plus CNI dosage reduction is able to maintain kidney function. Nevertheless, results also suggest that regarding 5-year survival EVL may be superior to SRL.

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