Transplant immunology, Immunosuppression

PO-001 THE BALANCE BETWEEN EFFECTOR AND REGULATORY CELL POPULATIONS IN KIDNEY TRANSPLANT RECIPIENTS WITH OPERATIONAL TOLERANCE

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Introduction: Donor-reactive memory cells represent a barrier to long-term kidney graft survival. A better understanding of regulatory mechanisms that counterbalance alloreactive memory responses may help to identify patients with operational tolerance.
Methods: The prospective, bicentric BALANCE study investigated the equilibrium between memory T cell subsets and regulatory T or B cells (Tregs, Bregs) in peripheral blood of kidney transplant recipients with operational tolerance ($N = 8$), chronic rejection ($N = 8$), and different immunosuppressive treatment regimens ($N = 81$). Patients on hemodialysis and healthy individuals served as controls ($N = 50$). In addition, the expression of Treg- and Breg-associated molecule genes was analyzed.
Results: Patients with chronic rejection showed a disrupted memory T cell composition with a significantly increased frequency of circulating $CD8^+$ terminally differentiated effector memory (TEMRA) T cells than in patients with operational tolerance, patients on hemodialysis, or healthy controls ($P < 0.001$). Compared to all other transplant recipients, the lowest ratios between $CD8^+$TEMRA and naïve or effector T cells and the highest frequency of Tregs and transitional Bregs were found in operationally tolerant patients (for all $P = 0.001$). Consequently, operationally tolerant patients showed, as compared to all other transplant recipients with different immunosuppressive regiments, the lowest ratios between $CD8^+$TEMRA T cells and Tregs or Bregs (for both $P < 0.001$). A specific peripheral blood transcription pattern was found in operationally tolerant patients with an increased expression of Breg- and Treg-associated genes *CD22* and *FoxP3* and a decreased *FcγRIIA/FcγRIIB* transcript ratio (for all $P < 0.001$, as compared to all other transplant recipients).
Conclusion: Our study provides evidence in favor of regulatory mechanisms that counterbalance alloreactive immune responses and may encourage further investigations whether the ratio between $CD8^+$TEMRA T cells and Tregs or Bregs can help to safely guide minimization of immunosuppression in selected patients.

PO-002 RELEVANCE OF RECIPIENT-SPECIFIC HLA ANTIBODIES FOR GRAFT VERSUS HOST DISEASE IN SOLID ORGAN TRANSPLANTATION

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Introduction: Graft-versus-host-disease (GVHD) after liver, pancreas and bowel transplantation is a severe complication with very restricted data on risk factors, diagnosis and therapy. GVHD results from transplanted immunocompetent donor cells recognizing recipient alloantigens initiating a fulminant immune response. Allografts, especially liver, pancreas and bowel have been described to contain immunocompetent donor lymphocytes. Early post-transplant de novo HLA antibodies may be produced by donor lymphocytes and thus could reflect engraftment of reactive donor B lymphocytes. Recipient-specific HLA antibodies (RSA) could be a surrogate marker of GVHD following solid organ transplantation. Little is known on the incidence of HLA antibodies in organ donors and the relevance for promoting GvHD in solid organ transplantation.
Methods: Here, we report on early posttransplant occurrence of RSA in a 59 year old woman who received a liver transplant and experienced severe GVHD. Interestingly, these RSA have already been detected in the pre-transplant serum of the donor. To evaluate the incidence of HLA antibodies in deceased organ donors we screened sera of 306 liver donors by LABScreen Mixed (One Lambda Inc.). In the case of a positive screening we analyzed the specificity of HLA class I and II antibodies by LABScreen Single Antigen assay.
Results: Anti-HLA class I/II antibodies were detected in sera of 75 out of 306 donors (25%). Recipient-specific anti-HLA antibodies were found in 36 out of 75 anti-HLA class I/II antibody positive donors (48%). GvHD like symptomatology was found in seven patients received a RSA positive liver transplant (19%).
Conclusion: Our findings support the hypothesis of RSA as detected in the donor's serum as a risk factor for posttransplant GvHD in liver, pancreas and bowel but not kidney transplantation. Furthermore, these important findings might also have significant implications in the interpretation of post-transplant HLA antibody measurements, especially interpretation of early non-donor specific HLA antibodies.

PO-003 THE IMPACT OF NEPHRECTOMY AFTER ALLOGRAFT FAILURE ON CHRONIC INFLAMMATORY STATE, DSA AND OUTCOME OF RE-TRANSPLANTATION

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Introduction: Morbidity and mortality rates are high for patients returning to dialysis after renal graft failure. Keeping failed kidney transplants in situ with concomitant minimization or withdrawal of immunosuppression is standard of care in many transplant centers. It is unclear, however, whether the allospecific immune response may cause a microinflammatory milieu in this context. The present work investigates the impact of allograft nephrectomy on systemic inflammation, erythropoiesis, and donor-specific antibodies.
Methods: Retrospective analysis evaluating C-reactive protein (CRP), hemoglobin concentration (Hb), ferritin, iron dosages, erythropoietin dosages, and DSA in 92 transplant recipients with allograft failure, 43 of whom underwent transplant nephrectomy (Group B) and 49 did not (Group A). Blood samples were obtained 3 - 6 months after returning to dialysis respectively after nephrectomy. In a subgroup of 40 patients with DSA, we additionally assessed outcome of kidney re-transplantation in a 10-year follow.
Results: There was no significant difference in Hb concentrations, ferritin, CRP and EPO dosages between the two groups. Iron dosages were significantly higher in Group B ($P < 0.0001$). Patients undergoing allograft nephrectomy reveals a significantly higher rate of DSA (57.6 vs. 40.4%; $P = 0.0134$). In the 10-year follow up 2 patients of group B and none in group B suffered from allograft failure after primary successful re-transplantation.
Conclusion: Keeping a kidney graft in situ after returning to dialysis did not lead to an increase in microinflammation in terms of CRP or anemia. Although DSA may develop in more than 50% of patients after an allograft nephrectomy, outcome of a renal re-transplantation seems not to be affected. Thus, both strategies are feasible options in kidney transplant recipients after return to dialysis.

PO-004 INCREASED EFFECTOR/SUPPRESSOR T-CELL RATE IN LUNG TRANSPLANT RECIPIENTS WITH A HIGH DONOR-SPECIFIC IFNY T-CELL RESPONSE: PROTECTIVE AGAINST EARLY REJECTION?

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Introduction: Acute rejection (AR) after lung transplantation (LTX) displays a risk factor for chronic lung allograft dysfunction (CLAD) and hence long-

term survival. Thereby, donor-specific T-cell responses of the recipient are known to represent a key factor in the process of AR. By now, it is unknown whether an already preoperatively increased T-cell reactivity of the recipient against the donor is correlated with a worse graft outcome.
Methods: Preoperatively, donor-specific IFNy T-cell responses of 50 (age: 56 ± 1, LAS: 38 ± 1) LTX-recipients were detected with enzyme linked immune spot assay (ELISPOT). Thereby, recipients were stratified into a "low" (n = 13, lower quartile, ≤12.05% of positive control), "intermediate" (n = 24, 50% percentile) and "high" (n = 13, upper quartile, ≥27.33% of positive control) patient group. In addition, peripheral T-cell levels (T-helper, Th: $CD3^+CD4^+$; cytotoxic, CTL: $CD3^+CD8^+$; regulatory, Treg: $CD3^+CD4^+CD25^+FoxP3^+$) were measured via flow cytometry (FACS), pre- (day 0) and postoperatively (day 7, 14, 21, 90, 180, 270, 365). Positive histology (A≥1) was considered as acute rejection (AR), CLAD was defined according to Verleden (2014). Data were mean ± SEM, $*P < 0.05$.
Results: Preoperatively "high" LTX-recipients showed a worse conditional (day 21) AR-free survival (30.77%) when compared to "intermediate" (8.33%) and "low" (7.69%). In addition, the suppressor/effector T-cell rate was significantly increased in "high" patients (day 7, "high": 0.16 ± 0.01 vs. "intermediate": 0.11 ± 0.02 vs. "low": 0.09 ± 0.01) in the early postoperative period. CLAD-free survival showed no differences between the groups.
Conclusion: Recipients with a preoperatively "high" T-cell reactivity against the donor showed an increased early suppressor/effector T-cell rate in combination with a later incidence of AR. This indicates a possibly protective immunological profile and therefore no worse outcome after LTX.

PO-005 VIRO-IMMUNOLOGICAL MONITORING AS A PREDICTOR FOR COMPLICATIVE EVENTS IN THE FIRST YEAR AFTER KIDNEY TRANSPLANTATION: AN INTERIM ANALYSIS OF THE VIRENO STUDY

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Introduction: VIRENO is an interdisciplinary, multicenter study aiming to identify immunological parameters that predict major infectious and immunological adverse events after kidney transplantation (KTX).
Methods: Viro-immunological monitoring of the cohort was performed pre-KTX, 3 weeks and 6 months post-KTX. Concerning humoral immunity anti-Polyomavirus BK (BKPyV) IgGin living donor and recipient were assessed. Cellular immunity to CMV was assessed by QuantiFERON-CMV (Qiagen) and T-SPOT®CMV by Oxford Immunotec. In addition, Torque Teno Virus (TTV) viremia was surveyed in all recipients. Clinical parameters were recorded during follow-up 3 weeks, 6 months and 12 months after transplantation focusing on infection- and rejection-related outcomes.
Results: As part of first interim evaluation, 64 patients were followed up for one year after transplantation.
In a first step, we compared the median of reactive ELISPOT results in all CMV IgG positive recipients (R+) who had a CMV reactivation within the first year to patients without reactivation. Differences in median spot number for pp65 pre-KTX were significant (CMV-reactivation: 223 spots (Interquartile range (IQR): 414) vs. no CMV-reactivation: 506 spots (IQR: 584); $P = 0.04$).
BKPyV IgG levels after 6 months were significantly associated with the risk of BKPyV-Infection within the next 6 months ($P = 0.016$). In the group of patients with BKPyV-infection median IgG level was 91 (IQR: 20.1) IU/ml compared to 65 (IQR: 87.15) IU/ml in the group without BKPyV-infection.
Using the idea of TTV as an apathogenic indicator for the overall immunosuppressive burden, median TTV urine levels 3 weeks after transplantation were significantly higher in patients with BKPyV-Infection (5675 cop/ml BKPyV-Infection (IQR: 28410), 215 cop/ml No-BKPyV-Infection (IQR: 959,25); $P = 0.017$)).
Conclusion: The preliminary data indicate that viro-immunological monitoring is a promising tool to predict infectious complications after kidney transplantation and could become a useful tool for tailoring of immunosuppression.

PO-006 ATHENA: NON-HLA(ET_AR-& AT_1R-) ANTIBODIES AND THEIR EFFECT WITHIN 12 MONTHS AFTER KIDNEY TRANSPLANTATION

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Introduction: As previously shown in the ATHENA study, efficacy and safety are comparable in *de novo* kidney transplant [KTx] recipients with a regimen of everolimus plus tacrolimus [EVR/TAC] or plus cyclosporine A [EVR/CsA] vs. a regimen of mycophenolic acid and TAC [MPA/TAC]. As the role of non-HLA antibodies [Abs] for transplant outcomes is increasingly recognized this substudy analyzed the effect of non-HLA (ET_AR-& AT_1R-) Abs.
Methods: ATHENA, a randomized, open-label, 12-month [M] prospective, controlled trial enrolled 612 patients [pts] in Germany and France. Pts were randomized 1:1:1 at KTx to either EVR/TAC, EVR/CsA or MPA/TAC; all with steroids. Patient blood serum collection was performed at baseline [BL], M6 and M12 and non-HLA (ET_AR-& AT_1R-) Ab levels were analyzed using ELISA.
Results: Baseline non-HLA data were available for 478/612 pts (ITT). Here we report the per protocol [PP] results (n = 268; EVR/TAC n = 91, EVR/CsA n = 57 and MPA/TAC n = 120 pts), as ITT and PP analysis were comparable. At BL, 102 pts (38,1%) showed positivity for both ET_AR-and AT_1R-Abs, 34 pts (12,7%) were positive for ET_AR-Abs only, 16 pts (6%) were positive for AT_1R-Abs only and 116 pts (43,3%) showed absence of both non-HLA Abs (cutoff ≥ 10 U/l).
ET_AR-Ab concentration for ET_AR-Abs only pos pts at BL decreased at M6 and M12 below cutoff in all treatment arms (mean 11.3 U/l at BL). Titer decrease of ET_AR-Abs for ET_AR-& AT_1R-Abs positive pts differed between treatment groups at M12 compared to BL: (EVR/TAC - 6.3, EVR/CsA - 6,1 and MPA/TAC -1,9 U/l). Within 12M 13 BPAR events occurred (6 without non-HLA Abs, 4 with ET_AR- & AT_1R-Abs, 1 with ET_AR Abs and 2 with AT_1R Abs), two pts lost their graft (both without non-HLA Abs), and no death was observed. Lowest eGFR values at M12 were observed in pts with only positive AT_1R-Abs, but without significance.
Conclusion: Previous ATHENA results revealed comparable efficacy of the 3 treatment arms. Furthermore, this substudy indicates that preformed non-HLA Abs have no correlation on clinical outcome. However, EVR seemed to have a higher potential to reduce ET_AR-Ab titers than MPA/TAC at M12 compared to BL.

PO-007 INHIBITION OF CATHEPSIN S AND PROTEASE-ACTIVATED RECEPTOR-2 DEFICIENCY REDUCE ALLOGRAFT VASCULOPATHY IN A HETEROTOPIC MURINE AORTIC TRANSPLANTATION MODEL

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Introduction: Long-term graft survival following solid organ transplantation remains a challenge due to ongoing rejection processes. Cathepsin S (Cat-S) and Proteinase-activated receptor (PAR)-2[1] are essential for alloantigen presentation,[2][3] implicated in donor-specific antibody production[4] and involved in vascular wall degeneration and neointimal formation.[5] Thus, the aim of this study was to investigate the role of Cat-S/Par2 inhibition/deficiency for chronic rejection processes and CAV (chronic allograft vasculopathy) formation.
Methods: Heterotopic aortic murine transplantation was performed from C57BL/6 donors to C57BL/6 recipients (syngeneic control group), Balb/c to C57BL/6 without treatment (allogenic control group), Balb/c to C57BL/6 with twice daily treatment with an oral novel Cat-S inhibitor (allogenic treatment group) and Balb/c to *Par2-/-* C57BL/6 (allogenic knockout group). The grafts were harvested on day 28 for histological analysis and RT-qPCR to assess mRNA expression.
Results: On day 28, neointima formation and intima/media ratio were significantly decreased in the treatment and knockout group in comparison to the allogenic control group with decreased invasion of CD8+ T cells into the intima. Furthermore, treatment with the Cat-S inhibitor and PAR2-deficiency was associated with decreased mRNA-levels of interleukins and cytokines. The syngeneic control group exhibited virtually no allograft vasculopathy with highly significantly reduced mRNA expression of Cat S.
Conclusion: Our data suggest that Cat-S and its interaction with PAR-2 plays a notable role in allograft vasculopathy, with inhibition targeting this pathway reducing neointima formation and associated inflammation.

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PO-009 THE ATHENA TRIAL – IMPACT OF PRIMARY IMMUNOSUPPRESSION ON DEVELOPMENT OF *DE NOVO* HLA-DONOR-SPECIFIC ANTIBODIES WITHIN FIRST YEAR AFTER KIDNEY TRANSPLANTATION

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Introduction: The ATHENA study previously showed comparable safety and efficacy in *de novo* kidney transplant [KTx] recipients under regimen of everolimus+cyclosporine A [EVR/CsA] or +tacrolimus [EVR/TAC] *vs.* TAC+mycophenolic acid [MPA/TAC]. As human leukocyte antigen [HLA] antibodies [Abs] (donor-specific Abs [DSA]) are increasingly recognized for short- and long-term outcomes after KTx this substudy investigated the effect of HLA Abs within 1 year after KTx.
Methods: This 12 month [M] randomized, open-label, prospective, controlled clinical trial enrolled 612 patients [pts] in Germany and France. Pts were randomized 1:1:1 to either, EVR/TAC, EVR/CsA or MPA/TAC, all with steroids. Patient blood serum collection was carried out at baseline [BL], M6 and M12. HLA Abs were analyzed using Luminex-SAB technology.
Results: Baseline HLA data were available for 535 pts (intent to treat population [ITT]) and 294 pts (per protocol population [PP]). As results were comparable, here we report only PP results (EVR/TAC $n = 97$, EVR/CsA $n = 68$ and MPA/TAC $n = 129$ pts). 130 pts (44.2%) showed preformed HLA Abs at BL (EVR/TAC $n = 45$, EVR/CsA $n = 28$ and MPA/TAC $n = 57$; MFI≥500 independent of mismatch). 14 of those pts had preformed *critical* HLA Abs at BL (MFI≥500 although being a mismatch) but none of them had a clinical event. Only 8 pts of all three immunosuppressive regimen developed *de novo* DSA within 1 year after KTx (EVR/TAC $n = 1$, EVR/CsA $n = 4$, MPA/TAC $n = 3$ pts). In 2/8 pts BPAR was observed (EVR/CsA $n = 1$; MPA/TAC $n = 1$) and no graft loss or death occurred. eGFR change from M1 to M12 was comparable in pts with vs. without preformed HLA Abs (4.5 vs. 5.8 ml/min/1.73 m²) and in pts with vs. without *de novo* DSA (4.6 vs. 5.7 ml/min/1.73 m²). However, in pts with vs. without preformed *critical* HLA Abs, eGFR change from M1 to M12 differed (16.3 vs. 4.7 ml/min/1.73 m²).
Conclusion: The ATHENA substudy showed no immunosuppressive treatment impact on development of de novo DSA. Interestingly, the overall incidence of de novo DSA was extremely low under conditions of a controlled trial and DSA, at least in this setting, did not influence clinical outcome.

PO-010 SERUM IL-6 PREDICTS RISK OF ALLOGRAFT FAILURE INDEPENDENTLY OF IMMUNOLOGICAL RISK IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction: Interleukin-6 (IL-6) is an important mediator in immune responses and a target in novel antibody therapies. We aimed to determine whether serum IL-6 correlates with immunological risk stratification, allograft pathology and outcomes in kidney transplant patients.
Methods: We retrospectively analyzed 103 patients who received a kidney transplant at our center between 2011 – 2015 (median follow-up time of 62.8 mo post-transplant). Patients were divided into a high (PRA% 58.7 ± 20.4, $n = 35$) and a low (PRA% 1.81 ± 5.8, $n = 68$) risk group based on history of a previous transplant or PRA > 35% (high risk). IL-6 concentrations were measured before, 3 months, 12 months and 3 years after kidney transplantation, and were correlated with different types of rejection (ABMR, TCMR, ABMR + TCMR, none) and times of rejection (early, late, none). Lastly, survival data was analyzed for differences with regard to risk group and IL-6 levels.
Results: Although IL-6 levels did not differ significantly between immunological risk groups, patients with both ABMR and TCMR had significantly higher IL-6 levels than any other group at 3 mo ($P = 0.00008$) and patients with sole ABMR had significantly higher IL-6 levels at 3 yr post-transplant ($P = 0.001$). In addition, IL-6 was significantly higher in patients with late rejections (< 1yr post-transplant) than those with early or no rejections when measured at 3 yr post-transplant. Furthermore, above cut-off levels of IL-6 at 12 mo and 3 yr predicted death-censored graft failure regardless of immunological risk group ($P = 0.033$ at 12 mo; $P = 0.004$ at 3 yr). In 2 patients with allograft failure due to BK-nephropathy, IL-6 values were also elevated above predictive cut-off values.
Conclusion: Although IL-6 levels did not differ between immunological risk groups, elevated IL-6 was associated with ABMR, late rejection and was predictive of allograft failure when measured after 1 yr post-transplant. Determining IL-6 in patients with ABMR may identify patients potentially benefitting from therapeutic IL-6 receptor blockade. Furthermore, IL-6 may contribute to inflammatory allograft injury in other causes of graft failure such as BK-nephropathy.

PO-011 IMMUNOREGULATION AFTER RITUXIMAB INDUCTION IN BLOOD GROUP INCOMPATIBLE LIVING-DONOR RENAL TRANSPLANTATION – 2 YEAR DATA OF A PROSPECTIVE PILOT STUDY

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Introduction: An increased frequency of severe infectious diseases has been described in the first year after blood group incompatible renal transplantation. As rituximab induction may alter immunoregulation in these patients, we analyzed clinically relevant immune parameters in a prospective renal transplant study.
Methods: Mononuclear cell subsets (peripheral blood; lymph nodes taken during transplant surgery), intracellular cytokine responses, CD4 helper function and in-vitro B cell responses were assessed pretransplant and up to 2 years posttransplant in 85 renal transplant recipients (living donation (LD): $n = 25$ ABO incompatible (ABOi) and $n = 30$ ABO compatible (ABOc); deceased donation (DD): $n = 30$, all ABO compatible).
Results: Severe infectious diseases occurred more often in ABOi than ABOc LD recipients (11/24 (46%) versus 6/30 (20%), $P = 0.046$). After rituximab induction in ABOi recipients and 2 years of follow-up, B cell repopulation reached only 50% of the B cell counts observed in the blood of ABOc und DD recipients ($P = 0.001$; memory B cells, $P < 0.0005$). CD4+ T cell counts were significantly lower in ABOi compared to ABOc recipients at 3 and 6 months posttransplant ($P = 0.025$ and $P = 0.046$, respectively). In regional lymph nodes of ABOi patients, CD20+ B cell counts were vigorously downregulated at the time of transplantation ($P < 0.0005$) whereas counts of CD19+ B cells and CD4+ T cells were not altered. T-dependent B cell responses were significantly impaired in ABOi patients (2 years: $P = 0.01$; T-independent B cell responses $P = 0.137$).
Conclusion: An increased frequency of severe infectious diseases in ABOi renal transplant recipients may be explained by significantly downregulated CD4+ T cell counts and delayed B cell repopulation after rituximab induction, most pronounced with regard to memory B cells. Whether HLA antibody formation in ABOi recipients is suppressed by the impaired T-dependent B cell responses despite unaffected CD19+ B cell counts in regional lymph nodes at the time of transplantation, would be of considerable clinical interest.

PO-014 INTRAPATIENT TACROLIMUS VARIABILITY IN KIDNEY TRANSPLANTATION

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Introduction: Pitfalls in the use of tacrolimus after kidney transplantation (KTx) are mainly a narrow therapeutic range and a large intraindividual

variability of blood levels (IPV) [1]. It is well known that a high IPV is associated with unfavorable allograft and recipient outcomes [2].
This study aimed to identify risk factors, consequences and appropriate measures of high IPV to be able to prevent IPV-associated harms.
Methods: In this retrospective single-center study, 376 KTx recipients at the University Hospital of Münster, transplanted between 2007 and 2017 were evaluated for potential risk factors and consequences of high tacrolimus IPV. The three common IPV parameters variance, coefficient of variability (CV), and mean absolute deviation (MAD) [2,3], calculated based on at least three tacrolimus-trough levels, were used to classify patients into low and high IPV groups. Groups were characterized based on clinical data from medical electronic records.
Results: Patients with high IPV based on either variance or CV were significantly older (median age 58 years (interquartile range (IQR) 18 vs 51 (22) years, $P < 0.001$) and more obese (median BMI 26.5 (IQR 5.5 vs 25.1 (6.7) kg/m^2, $P = 0.025$) than those with low IPV. They showed an increased mortality ($P = 0.013$), a reduced allograft survival ($P = 0.032$) and a higher incidence of rejection episodes ($P = 0.034$), and cytomegalovirus (re-) activations ($P = 0.002$). The IPV parameters variance and CV could be evaluated as significant markers for IPV, alone or combined, whereas MAD failed to indicate adverse outcomes.
Conclusion: In contrast to MAD, CV and variance were appropriate parameters to represent IPV-associated outcome differences. Taken together with the risk factors age and obesity, they can be used to identify those patients who might benefit from e.g. a tacrolimus-free regimen.
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PO-015 COMPARISON OF RENAL FUNCTION BETWEEN FAST AND SLOW ER-TAC METABOLIZERS AFTER KIDNEY TRANSPLANTATION

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Introduction: Fast metabolism of immediate-release tacrolimus (IR-Tac) is associated with a decreased kidney function after renal transplantation (RTx) compared with slow metabolizers [1-3]. We hypothesized, by analogy, that fast metabolism of extended-release tacrolimus (ER-Tac) is associated with worse renal function.
Methods: We analyzed data from patients who underwent RTx at three different transplant centers (Münster and Cologne, Germany and Leuven, Belgium) between 2007 and 2016 and received an initial immunosuppressive regimen with ER-Tac, mycophenolate, and a corticosteroid. Three months after RTx, a Tac concentration to dose ratio (C/D ratio) <1.0 ng/ml*1/mL defined fast ER-Tac metabolism and ≥1.0 ng/ml*1/mL slow metabolism. Renal function (estimated glomerular filtration rate, eGFR), first acute rejection (AR), switch from ER-Tac, graft failure and patient survival were observed up to 60-months.
Results: 610 RTx patients were divided into 192 fast and 418 slow ER-Tac metabolizers. Fast metabolizers showed a decreased eGFR as early as 2 months after RTx until all subsequent time points compared with slow metabolizers. From 3 months after RTx, the combined event "switch from ER-Tac / graft failure / death" occurred earlier and more frequently in fast metabolizers ($P = 0.018$). While no difference was observed in the cumulative incidence of graft survival ($P = 0.562$), the fast metabolizer group included more patients who were switched from ER-Tac to another immunosuppression ($P < 0.001$) mainly due to calcineurin-inhibitor nephrotoxicity ($P < 0.001$). In addition, no difference was found in patient survival between the groups ($P = 0.320$) but the event "first AR" occurred more frequently in fast metabolizers ($P = 0.008$).
Conclusion: Analogous to previous studies on IR-Tac, fast ER-Tac metabolizer developed a decreased renal function and increased risk to develop an AR compared to slow metabolizer. Thus, calculation of the ER-Tac C/D ratio early after RTx may facilitate individualization of the immunosuppressive regimen and helps identify patients at risk for an unfavorable outcome.
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PO-016 PROMOTING IMMUNOSUPPRESSIVE THERAPY ADHERENCE: RESULTS FROM AN OBSERVATIONAL STUDY TO EVALUATE THE EFFICACY, SAFETY AND PATIENT ADHERENCE OF ONCE DAILY LCP-TACROLIMUS (ENVARSUS®) IN STABLE LIVER TRANSPLANT PATIENTS

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Introduction: Adherence to immunosuppressive therapy is a well-known factor influencing graft and patient survival after solid organ transplantation. The need to take multiple doses of a drug per day increases the risk for non-adherence. Hence, the aim of this 24 months monocenter observational study was to evaluate the adherence, efficacy and safety of LCP-tacrolimus (LCP-Tac) as a once daily formulation after conversion from a standard twice daily intermediate release tacrolimus (IR-Tac) regimen in stable liver transplant (LT) patients.
Methods: Between October 2016 and March 2018, 161 LT patients were switched from IR-Tac to LCP-Tac with laboratory parameters, Tac-trough levels, physical examinations and the BAASIS questionnaire for self-reported adherence serving as outcome parameters. Moreover, Tac-trough intrapatient variability (IPV) was calculated as an additional monitoring parameter.
Results: Following conversion, patient adherence significantly improved by 57% from 51% at baseline to 80% ($P = 0.001$) after 24 months. Patients on once daily co-medication showed the most prominent increase. In contrast, the IPV-coefficient of variation did not reveal significant changes when comparing pre and post conversion levels ($P = 0.57$). Tac-trough levels remained stable despite conducting a 0.7:1 LCP/IR conversion ratio, which underlines the higher LCP-Tac bioavailability. Although the mean Tac-trough level could be significantly decreased from 5.4±2.1 ng/ml at baseline to 4.1±1.9 ng/ml at month 24, no episode of graft loss or graft rejection was to be observed.
Conclusion: LCP-Tac can be considered as a safe alternative to IR-Tac, providing the opportunity for both a safe dose reduction and an increase in patient adherence. Future randomized controlled trials are needed to investigate potential positive long-term effects on patient and graft survival. The use of Tac-IPV is challenging in assessing immunosuppressive therapy adherence.

PO-017 STANDARDIZED, RISK-ADAPTED INDUCTION THERAPY IN KIDNEY TRANSPLANTATION – A SINGLE CENTER RETROSPECTIVE ANALYSIS

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Introduction: Choice of induction therapy in kidney transplantation is dependent on the immunological risk and usually consists of IL2-receptor antagonists or depleting antibodies, such as antithymocyte globulin (ATG) or the CD52-antibody alemtuzumab. Multiple trials have addressed the topic for optimized induction protocols, however heterogeneity on these protocols remain.
Methods: A retrospective analysis of renal transplant recipients since implementation of our standardized induction therapy protocol in 2017 until 05/2020 at the Tübingen Collaborative Transplant Center was performed. The protocol stratifies recipients according to immunologic risk into low-risk (LR, basiliximab 2 × 20 mg), intermediate-risk (IR, ATG 3 × 1.5 mg/kg) or high-risk-group (HR, alemtuzumab 1 × 20 mg). Intermediate risk comprises sensitized patients with re-transplantation or PRA < 15%, whereas high risk group comprises sensitized patients with PRA ≥ 15% or HLA-incompatibility in living donor kidney transplantation.

Results: 126 renal transplant recipients received induction therapy according to the protocol, of which 69 (55%) received basiliximab, 42 (33%) received ATG and 15 (12%) received alemtuzumab. After a median follow-up of 692 [IQR 376-952] days, allograft function was comparable between the different risk groups (47 vs. 58 vs. 44 ml/min/1.73m²; LR, IR, HR), yet with superior allograft function in the ATG-group. Patients receiving depleting antibodies showed lower rates of biopsy-proven acute rejection (TCMR: 10.1% vs. 7.1% vs. 0%; ABMR 0% vs 0% vs. 6.7%) with death-censored allograft loss favouring alemtuzumab induction (5.8% vs. 4.8% vs. 0%). The alemtuzumab group showed higher rates of severe opportunistic fungal and bacterial infections (4/15) compared to the basiliximab group (4/69) and the ATG-group (1/42). Although leukocytopenia occurred more often following depleting antibodies (60.3% vs. 74.4% vs. 93.3%) hardly any severe leukocytopenia was noted.
Conclusion: In conclusion, this risk-adapted induction therapy protocol allowed for comparable allograft function and allograft survival rates, even in sensitized patients, balancing the immunologic risk of rejection against the risk for infectious complications.

PO-018 EVEROLIMUS COMBINED WITH LOW-DOSE TACROLIMUS CONTROLS HISTOLOGICAL GRAFT INJURY AND LIVER FIBROSIS AS SUFFICIENTLY AS HIGH-DOSE TACROLIMUS COMBINED WITH MYCOPHENOLATE AFTER LIVER TRANSPLANTATION

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Introduction: The combination of everolimus (EVR) and low-dose tacrolimus prevents T cell-mediated rejection (TCMR) of liver grafts as sufficiently as the standard of care (SOC) with high-dose tacrolimus (highTAC) and mycophenolate, but is associated with a preserved kidney function within the first years after liver transplantation (LT). However, none of the available studies assessed the histological pattern of graft injury or liver graft fibrosis in surveillance biopsies (svLbx).
Methods: All svLbx taken under at least one month of stable immunosuppression with either EVR (aim 3-8 ng/ml) with lowTAC (aim 3-5 ng/ml) or SOC with highTAC (aim 5-8 ng/ml) and mycophenolate (500-1500 mg/day) within the first 3-4 years after LT at our center were included. Patients who were switched to EVR because of insufficient control of alloreactivity by SOC were excluded. Reasons for switches to EVR were malignancies before or after LT, chronic kidney injury, intolerance of SOC or CMV reactivations.
Results: We could include 16 svLbx with EVR/lowTAC and 30 svLbx with SOC. SvLbx of both groups were not significantly different regarding the patients' age and the biopsy time points after LT, but the EVR/lowTAC group exhibited lower TAC trough levels at svLbx (4.4 vs. 6.8 ng/ml; $P < 0.001$). Both groups had similar liver enzymes and similar kidney function. As expected, the EVR/lowTAC group had higher total cholesterol levels in comparison to SOC ($P = .002$).
Histological graft injury quantified by the rejection activity index and hepatitis activity index according to Ishak were not significantly different between the EVR/lowTAC and SOC groups. Similarly, liver graft fibrosis in all compartments (portal/periportal, sinusoidal, perivenular) was not significantly different between the groups. Likewise, patterns of TCMR, NAFLD/NASH and bile duct abnormalities exhibited similar frequencies in both treatment groups.
Conclusion: EVR/lowTAC seems to control alloreactivity and histological graft injury as sufficiently as SOC with highTAC within the first 3-4 years after LT. These histological safety data propose a broader application of this CNI-sparing regimen.

PO-019 DYSLIPIDEMIA AFTER RENAL TRANSPLANTATION - INDEPENDENT OF TACROLIMUS METABOLISM RATE - BUT STILL A RELEVANT PROBLEM

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Introduction: Tacrolimus (Tac) metabolism affects survival after renal transplantation (RTx) [1,2]. Because fast Tac metabolizers have higher mortality rates compared with slow metabolizers and dyslipidemia is one of the most important causes of cardiovascular death (the leading cause of death after RTx), we hypothesized that fast Tac metabolism is associated with increased dyslipidemia.
Methods: The study included patients who underwent RTx and received induction therapy with basiliximab, immediate-release tacrolimus (IR-Tac), mycophenolate, and prednisolone. Tac metabolism groups were defined by their Tac concentration-to-dose ratio (C/D ratio) 3 months after RTx [1,3]. Dyslipidemia parameters were analyzed at RTx, 3 months, and 12 months after RTx. Statin use and renal function were assessed at 12-month follow-up, and death at 60-month follow-up.
Results: Ninety-six RTx recipients were divided into 31 rapid Tac metabolizers (C/D ratio <1.05 ng/mL*1/mg) and 65 slow metabolizers (C/D ratio ≥1.05 ng/mL*1/mg). There were no differences in triglyceride and cholesterol levels between groups at the time points analyzed. According to ESC/EAS guidelines 2019, 93.5% of fast metabolizers and 95.4% of slow metabolizers did not reach target levels for low-density lipoprotein cholesterol (LDL-C) ($P = 0.657$) [4]. Fast metabolizers developed a lower estimated glomerular filtration rate 12 months after RTx compared to slow metabolizers ($P = 0.009$). Fast metabolizers showed a 60-month survival rate of 96.8%, similar to 94.7% in the slow metabolizer group ($P = 0.811$).
Conclusion: Poorly controlled dyslipidemia after NTx is very common. Since Tac metabolism is associated with renal function but not with dyslipidemia, individualized nutritional counseling and lipid-lowering therapy must be intensified.
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PO-020 EVALUATION OF THE IMPACT OF TACROLIMUS-BASED IMMUNOSUPPRESSION IN HEIDELBERG LIVER TRANSPLANT COHORT (HDTACRO STUDY)

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Introduction: Tacrolimus-based drugs are of the mostly used immunosuppressants after liver transplantation (LT). Therapy adherence and dose adjustment play a key role in achieving the desired blood level and therefore treatment success. This is the first study which prospectively evaluates the patients' therapy adherence as well as the need for adjustment of therapeutic doses of Tacrolimus after LT.
Methods: This is a pilot, prospective, exploratory, monocentric, noninterventional, and non-randomized investigator-initiated study (ClinicalTrials.gov: NCT04444817). Fifty consecutive patients receiving de novo LT who treated with oral Tacrolimus-based immunosuppressants were included. Patients' therapy adherence, number of required dose adjustments for achieving the target trough level, and efficacy and safety data were evaluated.
Results: Thirty patients received once daily Tacrolimus (Envarsus®), and in 20 patients, twice daily Tacrolimus (Prograf®). The mean age of the patients was 54±9.9 years, and 24 patients (48%) were males. The mean number of dose adjustments per patient was 5 times in both groups. Six-months after LT, the mean Tacrolimus trough level in Prograf® group (7.5 ± 7 μg/l) was 1.5-fold higher than the upper limit, whereas the mean Tacrolimus trough level in patients receiving Envarsus® (5.1±2 μg/l) was slightly higher than the therapeutic range. The rate of treatment conversion to cyclosporine (4 patients (13.3%) in Envarsus group and 2 patients (10%) in Prograf group) was not significantly different between two treatment regimens (P-value = 0.30). Except for serum levels of bilirubin, other markers including transaminases, liver function test, and renal function test did not differ between the two types of tacrolimus. During the study, there were no complaints or difficulties regarding adherence in either patient group and all patients adhered to immunosuppressant therapy. No significant difference was seen between two groups treated with Envarsus® (two deaths (4.5%)) and Prograf® (no death, P-value>0.05) regarding mortality.
Conclusion: There are no significant differences in patient adherence, number of dose adjustments and safety between once-daily or twice-daily Tacrolimus administration.
Acknowledgement: None.

LIVER AND VISCERAL TRANSPLANTS

PO-021 HYPOTHERMIC OXYGENATED MACHINE PERFUSION (HOPE) ENABLES PRESERVATION OF EXTENDED CRITERIA DONOR ALLOGRAFTS FOR UP TO 18 HOURS – IMPACT ON ORGAN REALLOCATION AND OPERATING ROOM LOGISTICS

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Introduction: Machine perfusion has redefined organ preservation and revolutionized high-risk allograft utilization. While clinical trials have demonstrated safety and feasibility of hypothermic oxygenated perfusion (HOPE), the potential safety limits regarding the duration of HOPE are yet to be explored. Besides marginal allograft quality, prolonged cold ischemia time (CIT) and organ logistics remain two of the most important factors for a high number of liver allografts being declined for transplantation.
Methods: Two allografts from brain dead extended criteria donors were each allocated to two recipients. The first allograft originated from a 50-year-old donor with liver transaminases >1000 U/l, 5% macro- and 20% microvesicular steatosis. The second allograft originated from a 68-year-old donor with chronic alcohol abuse and grade II liver fibrosis. CIT was 12 h 8 min and 10 h 50 min, respectively. Upon arrival at the transplant center, both recipients proved to be unsuitable to receive the assigned allograft. The organs were reallocated by Eurotransplant and accepted by our center for two different backup patients. During that time, HOPE was commenced and continued until recipient hepatectomy was completed. Liver transplantation was performed in a standard manner. Postoperative allograft function was assessed by serum levels of ALT, AST, bilirubin and INR. Incidence of early allograft dysfunction (EAD), postoperative complications and length of hospital stay were analyzed.
Results: HOPE was applied for 4 h 35 min and 4 h 20 min, resulting in total cold preservation time of 17 h 29 min and 15 h 20 min, respectively. Both recipients displayed decreasing serum transaminases and bilirubin levels postoperatively. No EAD or major postoperative complications (Clavien-Dindo > 3) occurred in either patient. Average hospital stay was 22 days. Serum ALT and AST levels were within normal range on discharge day.
Conclusion: Extended HOPE enables safe extension of preservation time for up to 18 hours in human liver transplantation. End-ischemic HOPE may significantly improve organ pool utilization, while simultaneously facilitating operating room logistics and preventing organ injury.
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PO-024 OUTCOME AND SAFETY OF A SURVEILLANCE BIOPSY GUIDED PERSONALIZED IMMUNOSUPPRESSION AFTER LIVER TRANSPLANTATION

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Introduction: Adverse effects of immunosuppression (IS) play a major role after liver transplantation (LT), although the liver is immunologically privileged with low rates of chronic rejection and the highest rates of operational tolerance. While surveillance biopsies (svLbx) can help to select patients for personalized IS approaches, only few LT centers perform svLbx.
Methods: This is an evaluation of outcome and safety of a single-center real-world individualized IS approach after LT, guided by baseline svLbx (293 biopsies (Lbx) including 211 svLbx). SvLbx and results of testing for donor-specific antibodies (DSA) were discussed in interdisciplinary conferences. Histological criteria for IS minimization was applied for the individual adjustment of IS according to our structured standard operating procedure, grouping the patients according to their rejection risk considering subclinical graft injury and DSA. Results were compared to a historical control group (HC; $n = 35$) which had undergone svLbx before the implementation of this structured assessment.
Results: 293 Lbx were performed without any procedural complications such as bleeding. Over 80% of svLbx had an impact on clinical management and 80% of IS adjustments were maintained during a follow-up of 8 to 22 months, available from 112 patients. In addition, 20% of Lbx triggered further medical, mostly nutritional, advice. While IS could be reduced in 62%, strength of IS had to be maintained or increased in 38% due to relevant subclinical graft injury which would have been missed without a svLbx. After IS reduction, 5% showed temporal elevation of liver enzymes and one patient had biopsy-proven acute rejection, both were not significantly increased as a combined endpoint compared to HC ($P = 1.0$) Besides this, a non-significant trend to ALT increase within normal range was observed in the group with reduced IS, while the reduction of calcineurin inhibitors led to a significantly preserved kidney function compared to HC ($P = 0.047$).
Conclusion: A biopsy-guided personalized IS after LT is not associated with relevant procedural risks. Personalized IS adjustment after a structured assessment can preserve kidney function without an elevated rejection risk.

PO-025 FEASIBILITY AND EFFICACY OF ADJUVANT CHEMOTHERAPY WITH GEMCITABINE AFTER LIVER TRANSPLANTATION FOR LOCALLY UNRESECTABLE PERIHILAR CHOLANGIOCARCINOMA - A MULTI-CENTER, RANDOMIZED, CONTROLLED TRIAL (PRO-DUCT 001)

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Introduction: Liver transplantation (LT) is an option for locally unresectable perihilar cholangiocarcinoma (PHC) within defined criteria. However, there is no evidence from prospective randomized trials for this therapeutic alternative. In particular, it remains uncertain whether patients can safely receive adjuvant chemotherapy after LT.
Methods: We performed a prospective, multi-center, randomized, non-blinded two-arm parallel group phase II trial (DRKS00000805). Patients after LT for unresectable PHC within defined criteria were randomized to adjuvant gemcitabine (LT-Gem group) and LT alone (LT alone group). The

primary objective was to investigate, if adjuvant chemotherapy is feasible in ≥ 85 % of patients after LT. Primary endpoint was the percentage of patients completing the 24 weeks course of adjuvant chemotherapy. Secondary endpoints were disease-free (DFS) and overall survival (OS), complication rate and the number of patients, which could not be randomized (due to perioperative complications, no detectable bile duct cancer in the explanted liver or other reasons).
Results: Twelve patients were included in the study, of which six (50%) were eligible for randomization (LT-Gem: three patients, LT alone: three patients). Two out of three patients discontinued adjuvant chemotherapy after LT due to intolerance. The study was prematurely terminated due to slow enrollment. One patient had underlying primary sclerosing cholangitis (PSC). Two third of all tumors were moderately differentiated (G2, 4 of 6, 67%) and lymph-node negative (N0 4 of 6, 67%). Tumor-free margins could be achieved in all patients. In both the LT-Gem and the LT alone group, the cumulative 1-, 3-, and 5-year OS and DFS rates were 100%, 100%, 67%, and 100%, 67% and 67%, respectively.
Conclusion: This prospective, multi-center study was terminated due to slow enrollment and a statement on the defined endpoints cannot be made. Nevertheless, long-term data are consistent with previously published retrospective data. Since the significance of LT *per se* for unresectable PHC within defined criteria remains uncertain, a prospective follow-up study (product 002) has been launched.

PO-026 EFFECTS OF MELD BASED ORGAN ALLOCATION ON PEDIATRIC LIVER TRANSPLANTATION – A COMPARISON BETWEEN THE USA AND GERMANY

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Introduction: Liver allocation systems for pediatric patients differ between countries. In the US, liver allocation for children <12 is based on the Pediatric End-Stage Liver Disease (PELD) score; children >12 qualify for Model of End-Stage Liver Disease (MELD) score. In Germany, a pediatric MELD score (pedMELD) applies to children <16, which does not depend on laboratory values but increases with time. In both countries high urgency (HU) status and PELD/MELD exceptions exist.
Methods: Using the UNOS and Eurotransplant data record, all pediatric and adult liver transplantations from 1999 to 2017 in the US and from 2004 to 2017 in Germany were analyzed retrospectively.
Results: In both countries, rates of pediatric liver transplantations were stable over the observed time period (USA 413/ Germany 97 per year). The amount of living liver donations decreased in the USA over time ($r = -0.651$, $P = 0.003$), while rising in Germany ($r = 0.633$, $P = 0.015$).
Focusing on deceased donor transplantations, time on waitlist in the US system was 6.5 days longer than in Germany in children <12 (⌀ 50 d vs. ⌀ 43.5 d, $P = 0.012$).
Since introduction in the US, PELD scores have been rising steadily (from 22 in 2002 to 33 in 2017). Allocation via PELD exception increased ($r = 0.944$, $P < 0.001$) reaching 42% in 2017 while standard allocation (SA) decreased to 14%. Diseases most affected by this decline in SA were non-cholestatic and cholestatic cirrhosis. In Germany, most organs were allocated via HU (⌀ 49%) and SA (⌀ 49%) while pedMELD exceptions remained neglectable. In both countries, MELD implementation increased the chance to receive liver transplantation for pediatric patients (USA: OR = 1.441, CI 1.283–1.619, $P < 0.001$; Germany: OR = 1.378, CI 0.938-2.025, $P = 0.102$). Favored diagnoses included acute hepatic necrosis and malignant neoplasms in both countries and biliary atresia in the USA.
Conclusion: Both systems led to elevated chances of liver transplantation for children. However, in the US, especially exceptional status pediatric liver transplant patients with the respective diagnoses were favored. In Germany, laboratory value-independent pedMELD allocation might prevent disadvantages for pediatric patients caused by PELD dependence.

PO-027 LONG TERM SURVIVAL OF PATIENTS WITH METASTATIC NEUROENDOCRINE TUMORS AFTER LIVER TRANSPLANTATION AND LIVER RESECTION

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Introduction: Most patients with metastatic neuroendocrine tumors (NET) develop liver metastases, but only a few of these can be treated by liver resection because in most cases metastases are bilateral, small, and diffuse. Liver transplantation (LT) could overcome this problem Patients with metastatic NETs often live for more than 5 years with conservative treatment. Therefore, we looked for 10-year results after surgical treatment of neuroendocrine liver metastases.
Methods: We analyzed long term survival of all patients who had an anatomical liver resection (LR) or LT in our hospital between 1995 and 2019. Survival time was evaluated from the date of liver surgery. Cumulative recurrence rates were calculated for macroscopically radical resected cases (R0-R1) from the date of liver surgery to the date of first recurrence or the date of last observation at the end of 2020. For all calculations Kaplan-Meier procedures were used.
Results: Analysis included 12 and 24 patients who underwent LT or LR, respectively. 29 tumors were grade 1-2, 7 grade 3. Bilateral metastases had 17 patients; 28 liver resections were macroscopically radical (R0/R1). The diameter of metastases ranged from 1 to 23 cm; median diameter was 4.5 cm. Primary NETs were symptomatic (functional NETs) in 7 patients. 11 primary NETs were in the pancreas, 14 in small bowel, 5 had unknown primaries, 3 colorectal, 2 in the lungs and one in the biliary tract. 25 and 11 patients lived for more than 5 or 10 years, respectively.
Overall 5- and 10-year survival rates (OS) after LT and LR were 82% and 36% and 57% and 40%, respectively. For grad 1-2 tumors the 10-year OS after LT and LR was 54% and 58%, respectively.
The cumulative 10-year recurrence rates (RR) after LT and LR were 83% and 69%, respectively. Median time to recurrence was 39 months and 50 months, respectively.
There was no statistically significant difference between OS rates or recurrence rates between LT and LR.
Conclusion: After liver transplantation patients with non resectable neuroendocrine liver metastases can reach OS survival and recurrence free survival like resectable patients after macroscopically radical liver resection.

PO-028 MACHINE PERFUSION OF THE LIVER IN SMALL ANIMALS: TECHNIQUES AND FUTURE

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Introduction: Donor liver machine perfusion (MP) is a promising novel strategy to enable the wider use of marginal grafts. However, ex-vivo "organ repair" of marginal organs ", eg steatotic livers, requiring eventually longer ex-vivo perfusion times, eg for defatting steatotic grafts, is not yet achieved. This study aims for generating a normothermic ex-vivo machine perfusion (NEVLP) system of the mouse liver based on the reported experiences.
Methods: We performed a literature review covering the last 10 years to get an insight into the machine perfusion of the rodent liver. Then we built a system consisting of a perfusate reservoir, an autoclavable organ chamber, an oxygenator, a peristaltic pump, a bubble trap, and a thermostat.
Results: Current studies (n = 31) regarding MP in rodent livers are limited to the use of rat livers. However, mouse livers are of special interest due to the large availability of transgenic animals facilitating the exploration of defined molecular pathways. Rat livers were perfused with medium (DMEM or Williams E) supplemented with fetal bovine serum in hypothermic and subnormothermic systems. Rat erythrocytes were added up to a hematocrit of 20% in normothermic systems. The maximum reported perfusion time was not longer than 8h. The main purpose was the alleviation of severe ischemic injury due to procurement from non-heart-beating donors. Based on this background, we aim for generating a miniaturized normothermic ex-vivo liver perfusion (NEVLP) system for mouse liver grafts.
We are currently able to preserve a mouse liver for 24 hours using a simple normothermic ex-vivo liver perfusion (NEVLP) system with oxygenated medium (DMEM) supplemented with fetal bovine serum. Histology showed signs of moderate damage with centroacinar necrosis. HMGB1-staining revealed moderate translocation.
Conclusion: As a next step, we are planning to add human erythrocytes as oxygen carriers to improve long-term organ preservation. If successful, we will have a tool suitable for investigating molecular strategies in ex-vivo "organ repair".

PO-029 TRANSPLANTATION OF EXTENDED RIGHT LOBE LIVER GRAFTS AFTER *EX SITU* SPLIT - A SINGLE CENTER ANALYSIS

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Introduction: Since the first description of successful extended right lobe (ERL) split liver transplantation (Tx) by Pichlmayr *et al.* in 1988, this

technical procedure has been optimized and experience of surgeons is growing steadily. Nevertheless, ERL-Tx still remains a challenging procedure with increased risk for certain complications such as vascular occlusion or bile leakage. Due to complex logistics, cold ischemic time often turns out to be longer than in allocation of whole grafts, especially when the ERL is transferred to a distant transplant center after completion of the splitting procedure. In addition, vascular reconstruction is usually far more challenging due to altered anatomy.
Methods: All liver transplantations performed at our center between January 2009 and December 2020 were screened for ERL-Tx and evaluated regarding clinical outcomes including perioperative complications, graft and patient survival.
Results: During the indicated time period 1008 liver transplantations were performed with 35 (3.5%) cases representing ERL-Tx after *ex situ* split. In 11 cases (31.4%), biliary reconstruction was performed by biliodigestive anastomosis. Three (3.8%) arterial reconstructions by aortal anastomosis were necessary. Main complications were bile-leakage (12 cases / 34%) and postoperative bleeding leading to re-operation (8 cases / 22.8%). Arterial thrombosis was found in two cases (5.7%). Graft loss leading to retransplantation occurred in eight cases (22.8%).
Conclusion: ERL-Tx after *ex situ* split remains to be a challenging procedure. Selection of recipients for ERL-Tx and matching of suitable grafts is a difficult task. In times of organ shortage, ERL-Tx continues to represent a suitable procedure to increase the number of liver transplantations.

PO-030 MACHINE BREAKDOWN DURING NORMOTHERMIC LIVER PERFUSION PRIOR TO SUCCESSFUL TRANSPLANTATION – A CASE REPORT

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Introduction: Normothermic machine perfusion (NMP) has evolved to be a promising tool in organ preservation and assessment. While grafts are perfused in near-physiological conditions, NMP offers the opportunity of recovering extended criteria liver grafts. Utilization of NMP involves the risk of graft loss due to machine malfunction. To date reports of NMP malfunction with consecutive successful liver transplant are rare.
Methods: We report a 57 minute machine breakdown during normothermic liver perfusion followed by successful liver transplant.
Results: Case: A liver graft from a 63 year old brain death donor with a donor risk index of 2.06 was allocated to a 45 year old female recipient suffering from alcoholic liver disease. The liver was connected to NMP after cold ischemia time of 6 hours and 42 minutes. A technical error undermining the power supply of the OrganOx metra machine, NMP ceased following 2 hours and 27 minutes. NMP was restarted following a perfusion stop for 57 minutes. At this point of time the graft temperature decreased to 27° C. Restarting NMP was uneventful and the liver graft showed regular flow parameters (arterial inflow 500 ml/min), sufficient lactate clearance (lactate $\leq$ 2.1 mmol/l), viscous bile production and moderate raise of transaminases. Based on favourable performance following NMP restart liver transplant was carried out following a total of 27 hours and 33 minutes NMP period. Postreperfusion liver biopsy showed regular liver parenchyma without evidence for hepatic necrosis. Postoperative ICU stay was 6 days and hospital stay was 15 days. The recipient was discharged in good clinical condition and liver function was normal. A postoperative acute kidney injury KDIGO stage 3 recovered spontaneously. Six month follow up showed neither laboratory liver dysfunction nor radiological evidence of bile duct complication.
Conclusion: Since the implementation of NMP in liver transplantation one major concern is allograft loss due to machine malfunction. Our case provides affirmation that successful liver transplant is possible despite a 57 minute full cessation of perfusion.

PO-031 IMPACT OF METABOLIC INDICES OF ^{18}F-FDG PET/CT ON SURVIVAL AND POST TRANSPLANTATION RECURRENCE OF HEPATOCELLULAR CARCINOMA

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Introduction: Tumor recurrence is the leading cause of death after liver transplantation (LT) in patients with hepatocellular carcinoma (HCC). There is an ongoing debate as to whether metabolic Indices like tumor to liver SUV ratio (TLR) in ^{18}F-FDG PET/CT of the primary tumor could identify patients outside the Milan criteria with as low recurrence rates as patients inside Milan and therefore should be added to the established prognostic factors.
Methods: This retrospective study analyzes consecutive patients who underwent ^{18}F-FDG PET/CT before liver transplantation for HCC using data of the clinical tumor registry of the clinic. Primary endpoints were overall survival (OS) and 10-year cumulative recurrence rates.
Results: Tumor to liver SUV ratio (TLR) of the primary tumor was statistically significant higher in Milan out tumors, UTS out tumors, Grade 3 tumors, AFP level >400 ng/ml and lesions of a diameter of 5cm and more. Factors with statistically significant influence on 10-year overall survival in univariate analysis were Milan, UTS, number of lesions and pT-category. COX regression analysis did not show independently statistically significant factors for 10-year overall survival. Milan, UTS, Grade, pV, Number of lesions, Size of lesion, pT-category, Tumor to liver SUV ratio influenced 10-year cumulative recurrence rates statistically significant. Tumor to liver SUV ratio, Grade and pT-category proved to be independently statistically significant factors for 10-year cumulative recurrence rates.
Conclusion: Our study suggests that Tumor to liver SUV ratio in ^{18}F-FDG PET/CT is an independent prognostic factor in transplanted patients with Hepatocellular Carcinoma and might be helpful in estimating the risk of recurrence for patients scheduled for liver transplantation.

PO-033 LIVER TRANSPLANTATION AFTER ORGAN DONATION DUE TO HYDROGEN SULFATE INTOXICATION – A CASE REPORT

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Introduction: The discrepancy of patients on the waiting list and the availability of suitable organ donors continues to represent a relevant problem in transplantation medicine. Regarding liver transplantation, the increasing use of organs from donors with extended criteria meanwhile has become daily practice. Every donor reported thus carefully is evaluated for suitability of organ donation. Being offered a liver from a brain dead donor after hydrogen sulfate (H2S) intoxication for a high-urgency listed patient, we did not find any literature, which could help for decision making in organ allocation. Herewith we want to share our experience following the successful use of the liver for transplantation.
Methods: A case report about a liver transplant retrieved from a donor with H2S- intoxication is presented.
Results: A 60-year old patient with acute liver failure caused by an autoimmune hepatitis was listed for high-urgency liver transplantation following biopsy proven diagnosis and due to rapid worsening of the clinical condition despite thorough intensive medical treatment. Within 5-hours we got offered a liver from a 19-year old brain dead donor following H2S-intoxication in suicidal intent. H2S in higher concentrations is toxic and eventually led to cardiac arrest in this patient. Following a short period of resuscitation, the patient was transferred to an ICU and eventually diagnosed brain dead. Within 24 hours severe lung oedema and subsequently respiratory failure developed. Regarding the liver, apart from an initial peak of transaminases the laboratory findings were unremarkable, and due to the severe condition of our recipient we thus accepted the organ. Subsequent liver transplantation was uneventful. The patient´s clinical condition improved rapidly with discharge at day 16 after transplantation.
Conclusion: To our knowledge, this is the first report of a liver transplant from a brain dead donor after hydrogen sulphate intoxication. Based on this single case experience, potential donors after hydrogen sulfate intoxication should be considered and eventually evaluated for organ donation.

PO-035 MULTICENTRE, OPEN-LABEL, RANDOMISED, TWO-ARM, SUPERIORITY STUDY ASSESSING BIOAVAILABILITY AND PRACTICABILITY OF ENVARSUS® VERSUS ADVAGRAF® IN LIVER TRANSPLANT RECIPIENTS – ENGRAFT STUDY PROTOCOL

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Introduction: Graft rejection and chronic CNI toxicity remain obstacles to organ transplant success. Currently formulations of tacrolimus, such as Prograf® and Advagraf®, exhibit limitations in terms of pharmacokinetics and tolerability, related in part to suboptimal bioavailability. As dosing non-

compliance can result in graft rejection, the once daily formulation of tacrolimus, Advagraf®, was developed (vs 2x/day Prograf®). Benefits of Advagraf® are counterbalanced by delayed achievement of therapeutic trough levels and need for up to 50% higher doses to maintain Prograf®-equivalent troughs. Envarsus® is also a prolonged-release once-daily tacrolimus formulation, developed using MeltDose™ drug-delivery technology to increase drug bioavailability; improved bioavailability results in low patient drug absorption variability and reduced peak-to-trough fluctuations. In phase III *de novo* kidney transplant studies, Envarsus® proved non-inferior to twice-daily tacrolimus; however, no phase IV studies show superiority of Envarsus® vs Advagraf®.
Methods: In EnGraft, we compare bioavailability and test superiority of Envarsus® (test arm) vs Advagraf® (comparator arm) in *de novo* liver transplant (LTx) recipients. A total of 268 patients from up to 14 German transplant centres will be randomised 1:1 within 14 days post-LTx. The primary endpoint is dose-normalised trough level (C/D ratio) measured 12 weeks after randomisation. Secondary endpoints include the number of dose adjustments, time to reach first defined trough level and incidence of graft rejections. Additionally, clinical and laboratory parameters will be assessed over a 3 year period.
Results: .
Conclusion: C/D ratio is an estimate for tacrolimus bioavailability. Improving bioavailability and increasing C/D ratio using Envarsus could reduce renal dysfunction and other tacrolimus-related toxicities; earlier trials have shown that a higher C/D ratio (i.e. slower tacrolimus metabolism) is not only associated with improved renal function, but also linked to reduced neurotoxic side-effects. A higher C/D ratio could improve clinical outcomes for LTx recipients; EnGraft has begun, with over 10% of patients already recruited.

PO-037 SCREENING IN PATIENTS AFTER LIVER TRANSPLANTATION FOR LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D) BY ANALYSIS OF DRIED BLOOD SAMPLES

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Introduction: Lysosomal acid lipase deficiency (LAL-D) is a rare autosomal recessive lysosomal storage disease caused by a mutation in the LIPA gene with high mortality if untreated [1]. The clinically affected patients develop elevated liver enzymes, hepatomegaly, liver steatosis and cirrhosis, dyslipidaemia, and atherosclerosis [2, 3]. Lately, there has been increasing evidence that LAL-D could be significantly underdiagnosed [3]. In liver transplant patients, probability for possible undiagnosed LAL-D is comparatively high, as patients might be misdiagnosed with NASH or cryptogenic liver disease. Therefore, in this study, a screening programme for patients after liver transplantation was implemented.
Methods: In this prospective study, adult patients in follow-up care after liver transplantation who visited the outpatient clinic at the University hospital of Tuebingen between June 2018 and September 2020 were screened for LAL-D by use of dried blood samples (Alexion). The samples were sent to the laboratory for metabolic diagnostics at the University hospital Hamburg-Eppendorf. Low LAL activity was classified as enzyme activity < 0.2 nmol/spot*3h, and normal > 0.2 nmol/spot*3h.
Results: In total, 307 consecutive patients (118 female, 189 male) in follow-up care after liver transplantation were included. Median age at screening was 60 years (IQR 49–67, range 18–81), median time after liver transplantation was 7.2 years (IQR 2–12, range 14 days - 31 years). 1.3% were transplanted for NASH, 8.1% were transplanted for cryptogenic liver disease. Mean LAL activity was 0.73 nmol/spot*3h (SD 3.34/ range 0.13–2.57). 302 patients (98.3%) displayed normal values, while five patients (1.6%) showed enzyme activity <0.2 mol/spot*3h. However, in these five patients, second testing for verification showed normal enzyme levels (> 0.2 mol/spot*3h).
Conclusion: After screening 307 patients after liver transplantation, no patient was diagnosed with LAL-D at our transplant centre. Thus, although possibly underdiagnosed, LAL-D still seems to be a very rare condition and other measures need to be implemented in order to detect this orphan disease.
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PO-038 LIVER TRANSPLANTATION IN MALIGNANCIES – A COMPREHENSIVE AND SYSTEMATIC REVIEW ON ONCOLOGICAL OUTCOME

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Introduction: Liver transplantation (LT) is the today's standard treatment for both end stage liver disease and tumors; however, suitable grafts for LT is a scarce resource and outcome after LT is highly dependent on its underlying indication. Thus, patients must be carefully selected to optimize the number of life years gained per graft. This comprehensive and systematic review critically reflects the most recently published oncological outcome data after LT in malignancies based on the preoperative radiological findings.
Methods: A systematic literature search was conducted to detect preferentially most recent high-volume series or large database analysis on oncological outcomes after LT for both primary liver cancer and liver metastases between 2019, January 1st to 2020, November 14th. A comprehensive review on the radiological assessment of the reviewed liver malignancies is included and its preoperative value for an outcome driven indication reflected.
Results: Twenty most recent high-volume or relevant studies including a total number of 2521 patients were identified including 4, 4, 4, 4, 3 and 1 publications on oncological outcome after LT for hepatocellular carcinoma (HCC), cholangiocellular carcinoma (CCC), hepatic epitheloid haemangioendothelioma (HEHE), hepatoblastoma and both metastatic neuroendocrine tumors (NELM), and colorectal cancer, respectively. Overall survival is comparable to patients without tumors if patients with malignancies are well selected for LT; however, this is highly dependent on tumor entity, tumor stage and both neoadjuvant and concomitant treatment.
Conclusion: LT is a promising option for better survival in patients with malignant liver tumors in selected patients; however, the indication must be critically discussed prior to LT in every single case in the context of organ shortage.

INFECTIONS/ COMPLICATIONS AFTER TRANSPLANTATION

PO-040 POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AFTER LUNG TRANSPLANTATION: RISK FACTORS AND MANAGEMENT

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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a rare syndrome characterized by neurological symptoms including headache, seizure, altered level of consciousness and visual abnormalities, which can occur under immunosuppressive therapy with tacrolimus after organ transplantation. It is diagnosed with MRI of the brain that shows vasogenic edema of the white matter, typically located in the occipital and parietal lobes supplied by posterior circulation.
Methods: We retrospectively reviewed the medical records of 545 patients, who have undergone lung transplantation between 2012 and 2019. All patients with PRES typical neurological symptoms ($n = 30$) were divided into two groups based on the diagnostic results, patients with ($n = 11$) and without ($n = 19$) PRES, and compared with each other.
Results: The incidence of PRES was 2%. Notably, 73% of patients with PRES were female with the average age of 39. It was more often diagnosed in patients with cystic fibrosis (64%, $P = 0.002$) compared to other diseases. Seizure (82% vs. 21%, $P = 0.004$) was the most common neurological presentation. Maximum creatinine level (1.9 vs. 1.1 mg/dl, $P = 0.0038$) and maximum tacrolimus level (19.4 vs. 16.5 ng/ml, $P = 0.048$) within one week prior to neurological symptoms were significantly higher in the patients with PRES. Furthermore, hypomagnesaemia (55% vs. 16%), hypertension (73% vs. 11%) and vasospasm of the brain vessels (36% vs. 11%) were much often observed without reflecting statistical significance. After the change of immunosuppression to Cyclosporine, a notable increase in the number of cellular (6.3% vs. 37.5%) and humoral (12.5% vs. 56.3%) rejection was detected.
Conclusion: Renal insufficiency and high tacrolimus level are risk factors for developing PRES after lung transplantation. Female patients under 40

with cystic fibrosis are at higher risk. Hypertension, hypomagnesemia and vasospasm of the brain vessels may play a significant role in the dysfunction of cerebrovascular autoregulation. A change of immunosuppressive drug should be applied after secured PRES diagnosis to minimize the risk of early allograft rejection.
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PO-041 PROSPECTIVE COMPARISON OF TWO LIVER STIFFNESS MEASUREMENT METHODS AFTER LIVER TRANSPLANTATION IN THE DAA ERA

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Introduction: Liver stiffness measurement (LSM) has invaluable clinical benefit for the non-invasive detection of liver fibrosis. However, most studies that established cut-off values after liver transplantation (LT) were performed in cohorts predominated by hepatitis C in the pre-DAA era, and SVR is associated with a reduction of liver stiffness. Our aim was to prospectively head-to-head evaluate two LSM methods in our LT biopsy program in the DAA era.
Methods: Over a time period of 18 months, liver biopsies (bx) were paired with two LSM methods in the right liver (ARFI and FibroScan(FiSc)) within one week prior to liver biopsy. We included only LSM with at least 10 valid measurements and a success rate of >60% as well as an interquartile range-to-median ratio <30%. 83% of bx were protocol bx.
Results: Valid LSM by FiSc were available for 101 patients (success rate 86%) and by ARFI for 93 patients (success rate 57%) with 73 patients having two paired LSM. FiSc had a more stringent correlation with graft fibrosis (≥Ishak F2) (AUC 0.868, CI 0.773-0.963) than ARFI (AUC 0.761, CI 0.576-0.946). Cut-off values for fibrosis ≥F2 were determined in the training cohort at 6.9 kPa for FiSc and at 1.37 m/s for ARFI. Both LSM showed good sensitivities (SEN) and moderate specificities (SPE) in training (t) and validation (v) cohorts (FiSc: t (n = 62)/v (n = 39): SEN 0.85 and 0.82, SPE 0.57 and 0.75; ARFI: t (n = 52)/v (n = 41): SEN 0.70 and 0.90, SPE 0.76 and 0.62). Correlation analysis showed LSM to be associated not only with fibrosis but also with graft inflammation. LSM were similarly associated with graft fibrosis both in patients undergoing protocol bx with normal or marginally elevated liver enzymes (< 2-fold elevation) and in patients with elevated enzymes: FiSc: AUC 0.832, (enzymes < 2-fold), CI 0.728-0.937 and 0.73 (enzyme elevated), CI 0.522-0.938; ARFI: AUC 0.733, CI 0.585-0.882 and 0.80, CI 0.602-0.998.
Conclusion: The study demonstrated a lower cut-off value for FiSc and a comparable cut-off for ARFI compared to a similar head-to-head study in the HCV era.[1] Overall, FiSc was more stringently associated with graft fibrosis in histology than ARFI but tended to be more susceptible to bias by graft inflammation.
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PO-042 PROTEOME ANALYSIS OF POLYOMA VIRUS INFECTED HUMAN TUBULAR CELLS

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Introduction: Human polyoma virus 1 (HPyV1, BK virus) infection is one of the important complications after renal transplantation. Uncontrolled infection results in polyomavirus-associated nephropathy and graft failure. There are currently no approved drug- or vaccine-based treatment strategies. Here we present detailed analysis of HPyV1-induced proteome changes at 8 different time points after infection, revealing potential treatment targets.
Methods: Renal tissue was obtained with ethics board approval and primary TEC isolated and maintained according to [1]. TEC were infected with HPyV1 strain ATCC-VR837 at a MOI of 4 and lysed at defined time points. Mass spectrometry was done according to [2] and bioinformatic analysis was based on R scripts (ge-lab.org/idep) as well as DisGeNET data (disgenet.org). Next TEC were infected in the presence of "substance A" (2,5- and 5 μM) and immunostaining performed for HPyV1's major capsid antigen VP1 after 96 hrs.
Results: HPyV1 infection of primary TEC induced specific, time-dependent changes. By k-means clustering (Fig. 1A) they can be divided into an early (0-36h), intermediate (48-60h) and late (72-96h) group. A major shift takes place after 48-60h, showing cluster A with increasing loss of "anatomical structure morphogenesis", progressive "cell cycle" up-regulation in cluster B and up-regulation of "mitochondrial organization" in cluster C (as most significant pathways). The comparison with the DisGeNET data set revealed a significant overlap to CKD at late time points (Fig. 1C), represented by factors known to be relevant in fibrosis. Importantly, testing of "substance A" (Fig. 1 D-G) resulted in a significant reduction of HPyV1 replication at 2,5 μM (Fig. 1F) and more pronounced at 5 μM (Fig. 2G) compared to virus control (Fig. 2E; uninfected TEC are shown in Fig. 1D).
Conclusion: HPyV1 infection of human primary TEC induces marked alterations, like in pathways relevant for tissue morphogenesis and cell cycle as well as induction of factors known to be important in fibrosis. Furthermore, there is a significant overlap to DisGeNET CKD data. Importantly testing of "substance A" resulted in a very significant inhibition of HPyV1 replication in TEC.
References: [1] Baer *et al.* 1997, Isolation of proximal and distal tubule cells from human kidney by immunomagnetic separation, Kidney International, 52, 1321–1331, Amsterdam, Elsevier. [2] Klann *et al.* 2020, Functional Translatome Proteomics Reveal Converging and Dose-Dependent Regulation by mTORC1 and eIF2α, Mol Cell 77,1-13, Cambridge, Cell Press.

PO-043 KIDNEY TRANSPLANT PATIENTS ARE ABLE TO GENERATE AND MOUNT VARICELLA ZOSTER-REACTIVE T CELL AND HUMORAL IMMUNITY FOLLOWING VARICELLA ZOSTER VACCINATION

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Introduction: Reactivation of the latent varicella zoster virus (VZV) can lead to serious complications including cerebellar ataxia and encephalitis leading to death especially among immunocompromised patients. To improve VZV protection, vaccination is recommended for individuals with impaired immunity such as immunosuppressed transplant patients. This study aimed to characterize long-term humoral and cellular immunity following VZV vaccination in kidney transplant patients (KTx).
Methods: In a cross sectional study, 39 immunosuppressed KTx were vaccinated with Shingrix®. To evaluate long-term humoral responses, VZV specific IgG titers were analyzed one year after the second VZV vaccination. In 23% of patients, pre-vaccination titers were also available. VZV-reactive T cell immunity was characterized by flow cytometry. To elaborate T cell assays for clinical utility, VZV-reactive T cells were compered in whole blood and peripheral blood mononuclear cells (PBMC) after VZV vaccine stimulation.
Results: VZV-specific IgG titers were detected in all vaccinated patients. In patients with available pre-vaccination titer, we observed a 2.1 ± 1.5 fold titer increase, indicating humoral responsiveness. Both protocols used for the detection of VZV specific T cells allowed the characterization of CD4 and CD8 T cell responses. In 67 % of the vaccinated KTx, we observed a $CD4^+$ VZV-specific T cell response in the PBMC and whole blood assay. Interestingly, $CD8^+$ VZV-reactive T cells were observed in 47% and 60% of PBMC- and whole blood assay, respectively. Neither the amounts of VZV-reactive CD4+ nor CD8+ T cells correlated with the amount of VZV IgG titers.
Conclusion: Despite the immune suppression, the majority of KTx patients develop measurable humoral and T cells response after VZV vaccination. Whether the detected CD8+ T cells result from previous convalescent VZV infection or from vaccine cross-presentation should be addressed in the future studies.

PO-044 VIRAL INFECTIOUS DISEASES IN THE TRANSPLANT COHORT OF THE GERMAN CENTER OF INFECTIOUS DISEASES (DZIF)

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Introduction: Viral infections are among the most common and most severe infections for renal allograft recipients under immunosuppression. However, to this date incidence-rates and timelines of posttransplant viral infections have not been comprehensively documented in a German transplant cohort.
Methods: In this prospective multicenter study of the German Center of Infectious Diseases (DZIF), all viral infectious events observed during first year after renal transplantation were evaluated, focusing on microbial etiology, incidence-rate, timing, frequency and duration. Our cohort comprised all adult renal transplant recipients included in DZIF-Cohort from January 2012 to November 2019 ($n = 804$).
Results: 804 renal transplant recipients (64.1% male, 35.9% female, mean age: 51±14) were enrolled. Nearly all received the present standard immunosuppression consisting of an CNI, MPA and low-dose steroids and induction with basiliximab. Within the first 12 months posttransplantation, 201 patients suffered 281 viral infectious events, demonstrating a first-year-incidence rate of 25.1% (201/804). Among 281 viral infections, herpesviruses predominated (53.7%). Cytomegalovirus (CMV) accounted for the largest proportion of all detected viral agents (44.1% [124/281]), affecting 98 patients (12.1%), some despite prophylaxis. CMV replication mainly occurred between 3 and 6 months after transplantation.
BKV was the second most frequently isolated viral agent, being responsible for 41.6% (117/281) of all viral infections. All other viral pathogens were documented rarely. Viral agents affecting the respiratory tract included Influenza A and B ($n = 8$), RSV ($n = 6$) and Rhinovirus ($n = 1$). The gastrointestinal site was scarcely affected by viral agents like Norovirus ($n = 6$) and Hepatitis E ($n = 2$).
Conclusion: In the current era of immunosuppression and prophylaxis, renal allograft recipients in Germany experience a high burden of viral infections throughout the first year posttransplantation, with CMV as main opportunistic pathogen, despite prophylaxis.

PO-045 ACUTE KIDNEY INJURY AFTER LUNG TRANSPLANTATION: LONG-TERM MORTALITY PREDICTED BY POST-OPERATIVE DAY-7 SERUM CREATININE AND FEW CLINICAL FACTORS

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Introduction: Acute kidney injury (AKI) after lung transplantation (LuTx) is associated with increased mortality. However, AKI-definitions vary substantially. The aim of this prospective observational study was to compare commonly used AKI-definitions with post-transplant day 7 serum creatinine (sCr-d7) regarding long-term mortality prediction after LuTx and to explore clinical and laboratory predictors of AKI.
Methods: 185 patients with LuTx at Hannover Medical School, Germany, were prospectively enrolled from 2013 - 2014. AKI was assessed by: (1) the Kidney Disease Improving Global Outcomes criteria (KDIGO-AKI), (2) the Acute Disease Quality Initiative 16 Workgroup classification (ADQI-AKI) and (3), by sCr-d7. Prediction of all-cause mortality was examined by uni- and multivariable cox regression analysis and clinical and laboratory factors were examined as predictors of sCr-d7 by linear regression analysis.
Results: AKI according to KDIGO occurred in 114 patients (61.6%). Persistent ADQI-AKI, KDIGO-AKI stage 3 and higher sCr-d7 were associated with higher mortality in the univariable analysis (HR 2.251, $P = 0.018$; HR 4.258, $P = 0.001$ and HR 1.011, $P = <0.001$). In the multivariable cox analysis, sCr-d7 in combination with body weight (HR 1.030, $P = 0.024$), intra- (HR 2.131, $P = 0.036$) and postoperative platelet transfusions (HR 2.248, $P = 0.020$) predicted mortality after LuTx with similar performance as models using KDIGO-AKI and ADQI-AKI (concordance index of 0.75 for sCr-d7 vs., 0.74 and 0.73, respectively) and required fewer additional clinical variables for the prediction. Pre-transplant renal function, diabetes, high BMI, and intraoperative ECMO predicted sCr-d7 ($r^2 = 0.354$, $P < 0.001$).
Conclusion: SCr-d7 is pragmatic and allows equal prediction of long-term mortality compared with categorical AKI-definitions by KDIGO and ADQI. Impaired renal function, higher BMI, diabetes before transplantation and intraoperative ECMO identify patients at higher risk for post-transplant AKI.
Acknowledgement: This work is dedicated to Prof. Dr. Faikah Güler, who initiated this study and unfortunately passed away far too early in her life.

PO-047 IMMUNOMODULATION OF NK CELL FUNCTION BY RIBAVIRIN IS DRIVEN BY TYK-2 ACTIVATION AND SUBSEQUENT INCREASED IFN-γ SECRETION IN THE CONTEXT OF HEV INFECTION

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Introduction: Hepatitis E virus (HEV) is one of the most common causes of acute hepatitis worldwide. In a majority of cases, the infection is asymptomatic and self-limiting. However, severe courses are observed in patient groups such as immunosuppressed patients, especially after SOT. Natural killer (NK) cells are an important part of the innate immune response. Through the production of IFN-γ and direct cytotoxicity, they are essential after viral infection.
Methods: HepaRG, a human hepatoma cell line, was inoculated with a full-length HEV (MOI 0.5). The infected cells then were co-cultured one week after with PBMCs for another day at an E:T ratio of 1:1. The concentration of RBV used was 500 μM. NK cells were analyzed by flow cytometry and PCR, HEV replication and antigen release were assessed by PCR and ELISA.
Results: Co-culture with PBMCs and treatment with RBV both resulted in a decrease of viral replication, demonstrating a synergistic effect when combined. NK cells simulated by RBV showed an increased expression of the activation marker CD38 ($P < 0.0001$) and the activatory receptors NKp46 ($P = 0.0139$), NKp80 ($P = 0.0005$) and NKG2C ($P = 0.0332$). An analysis of NK cell functions showed that cytotoxicity was reduced, as indicated by a decrease in TRAIL ($P = 0.0087$) and CD107a degranulation ($P = 0.0002$). Simultaneously, IFN-γ production was significantly elevated ($P < 0.0001$). To further understand the underlying mechanism, different stimulations were tested. It was shown that after RBV treatment, stimulation with IL-12 ($P = 0.0127$) led to significantly increased IFN-γ production, especially in combination with IL-15 ($P = 0.0082$). This indicates that RBV has a primary effect on the IL-12R pathway. There was no direct effect on the IL12R subunits, but downstream events were upregulated. Most notably TYK-2 ($P < 0.0001$), with subsequent upregulation of pSTAT4 ($P = 0.0004$). The inhibition of TYK-2 diminished the effect of RBV on IFN-γ production ($P = 0.0219$).
Conclusion: RBV exerts its immunomodulatory effect on NK cells via TYK-2, an essential part of the IL12R pathway. This subsequently results in an increased IFN-γ response, leading to a synergistic effect on viral replication in the context of an in-vitro HEV infection.

PO-048 INCIDENCES OF INFECTIOUS EVENTS IN THE TRANSPLANT COHORT OF THE GERMAN CENTER OF INFECTIOUS DISEASES (DZIF)

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Introduction: The burden of infectious diseases under immunosuppression is one of the major causes of morbidity and mortality after kidney transplantation. However, the occurrence and timeline of posttransplantation infections has not been comprehensively studied within a German transplant cohort.
Methods: In this prospective multicenter study of the German Center of Infectious Diseases (DZIF), all infectious events observed during first year after renal transplantation were evaluated, focusing on microbial etiology, incidence-rate, timing, frequency and duration. Our cohort comprised all adult renal transplant recipients included in the DZIF-Cohort from January 2012 to November 2019 ($n = 804$).

Results: 804 renal transplant recipients (64.1% male, 35.9% female, mean age: 51±14 years) were enrolled in the present analysis. Among 804 renal allograft recipients; 439 patients (54.6%) suffered 972 posttransplant infections during the first year at a median time of 55 days (IQR = 15-123). Almost half of the infections (464/972 [47.8%]) occurred within the first three months. Bacteria were identified as most common pathogen group, being responsible for 66.4% (645/972) of all posttransplant infectious events, followed by viral (28.1% [281/972]) and fungal (4.7% [46/972]) pathogens. The urinary tract was the most common site of infection posttransplant. Among bacterial infections Enterococcus, E.coli and Klebsiella species accounted for the vast majority of detections (61%), with Enterococcus being the most common isolated etiological agent (25%), followed by E.coli (21.1%) and Klebsiella (14.9%). Other frequently isolated bacterial pathogens were Pseudomonas aeruginosa and Staphylococcus sp. Coagulase negative. In 46 fungal infections, Candida spp (40.8%) predominated as pathogen in renal transplant recipients. Opportunistic pathogens, including Aspergillus fumigatus (1.5%) were rare. Viral infectious events occurred in 201 renal allograft recipients (25.1%).
Conclusion: Renal allograft recipients in Germany experience a high burden of infectious events including bacterial, fungal and viral pathogens throughout the first posttransplant year.

PO-050 LATE ONSET CEREBRAL NOCARDIOSIS IN A SENSITIZED RENAL TRANSPLANT RECIPIENT FOLLOWING ALEMTUZUMAB INDUCTION

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Introduction: Balancing immunosuppressive regimen to prevent rejection yet avoiding severe infectious complications remains a key challenge following renal transplantation, especially in HLA-sensitized patients. We herein report a late onset opportunistic infection with nocardia in a sensitized renal transplant recipient.
Methods: A 65-year-old renal transplant recipient presented with headache, dizziness and homonymous hemianopia. Kidney transplantation had been performed three years earlier with low-dose alemtuzumab induction due to HLA-sensitization. A cerebral magnetic resonance imaging showed a right parieto-occipital brain abscess. The patient underwent abscess drainage via craniotomy and was referred to our nephrology department.
Results: Microbiology detected *Nocardia paucivorans* in the abscess fluid- via mass spectrometry. We started antibiotic therapy according to published data with high-dose trimethoprim/sulfamethoxazole (TMP-SMX) and imipenem/cilastatin. Furthermore, immunosuppression was adapted with discontinuation of mycophenolate. Laboratory results showed persistently reduced lymphocyte and T-cell counts three years after transplantation. After a total of seven weeks of intravenous antibiotic therapy, the patient was switched to an oral antibiotic regimen with amoxicillin/ clavulanic acid and minocycline. In the follow up MR imaging, cerebral lesions were substantially reduced, initial symptoms completely disappeared and allograft function remained stable.
Conclusion: Induction therapy with the CD52-antibody alemtuzumab enables transplantation in highly sensitized patients but leads to B- and T-lymphocyte depletion for several weeks. Our patient presented with prolonged chronic lymphopenia and a significantly reduced T cell count three years after transplantation. To our knowledge, our case is the first to describe a late-onset nocardia infection three years after alemtuzumab induction in a renal transplant recipient. It underlines the importance of considering this rare disease in transplant patients, especially after induction therapy with depleting antibodies.

PO-051 SYMPTOMS AND OCCURRENCE OF HEPATITIS E IN SOLID ORGAN RECIPIENTS, A SINGLE CENTER EXPERIENCE OF THE LAST FIVE YEARS

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Introduction: The Hepatitis E virus (HEV) can be found worldwide and the transmission is mainly fecal-oral from contaminated water or food. In Germany, transfection occurs especially from pork or beef, where genotype 3 is predominant. While most infections are asymptomatic, under immunosuppression a chronic (and fetal) course of hepatitis E is possible. Regular testing is often missing due to lack of experience.
Methods: Retrospective analysis of all solid organ recipients with a positive HEV-RNA replication in blood in the last 5 years in our tertiary care center regarding disease manifestation, immunosuppressive therapy and course of HEV infection. HEV-IgG or IgM alone were not sufficient for diagnosis.
Results: From 2015 to 2020 14 patients after solid organ transplantation (4x kidney, 5x heart, 4x liver, 1x lung) were diagnosed with HEV in our center.
All patients showed elevated transaminases before diagnosis. In total 3 patients experienced clinical symptoms with abdominal pain, two presented which acute liver failure.
HEV infection occurred overall after a median of 8.6 years after transplantation, whereas 3 patients developed HEV within the first year after transplantation.
The transmission route remained uncertain in all cases. Most likely contaminated pork or deer – not cooked „well done" were suspected to be the most likely cause, especially as neither of them was vegetarian.
Regarding immunosuppression 92% ($N = 13$) had a tacrolimus based regime with mostly either mycophenolic acid or m-Tor inhibitor. No significant differences regarding the two could be detected. Further 10 out of 14 were treated with ribavirin because of either persistent HEV-RNA replication in stool or blood or because of the severe course of the disease. In 4 Patients HEV infection dissolved without specific treatment due to reduction of immunosuppressive therapy.
One patient developed a chronic HEV, which resolved after Ribavirin therapy.
Conclusion: HEV is a common reason of elevated transaminases in solid organ recipients and should be considered for differential diagnosis. Therefore, we suggest a more precise instruction – even years after transplantation – regarding cooking rules.

PO-052 SIROLIMUS VS. EVEROLIMUS ON CMV-INFECTIONS AFTER KIDNEY TRANSPLANTATION – A NETWORK META-ANALYSIS

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Introduction: Following renal transplantation, infection with cytomegalovirus (CMV) is a common and feared complication, causing increased morbidity, mortality, and reduced allograft survival. mTOR-inhibitor (mTOR-I) treatment either alone or in combination with Calcineurin inhibitors (CNIs) reduces significantly the CMV incidence after organ transplantation. As of yet, there is no information which mTOR-I, Sirolimus (SIR) or Everolimus (ERL), has a stronger anti-CMV effect.
Methods: The current literature was searched for prospective randomized controlled trials in renal transplantation. There were 1.164 trials screened of which 27 could be included (11.655 pts.). We performed a network meta-analysis to analyze the relative risk of different types of mTOR-I treatment on CMV-infection 12 months after transplantation compared to CNI treatment.
Results: Four different types of mTOR-I treatment were analyzed in network meta-analyses – SIR mono, ERL mono, SIR with CNI, ERL with CNI. The mTOR-I treatment with the strongest anti-CMV effect compared to a regular CNI-treatment was ERL in combination with a CNI (RR 0.27, CI 0.22–0.32, $P < 0.0001$). The other mTOR-I therapy groups showed slightly decreased anti-CMV efficacy (SIR mono: RR 0.35, CI 0.22–0.57, $P < 0.001$; SIR with CNI: RR 0.43, CI 0.29–0.64, $P < 0.0001$; ERL mono: RR 0.46, CI 0.22-0.93, $P = 0.031$).
Conclusion: It is well known that a mTOR-I based treatment in transplant patients significantly reduces the risk of a CMV infection in comparison to CNI treatment. A combination of ERL and CNI seems to be the most potent mTOR-I therapy against the CMV.

PO-057 BKV-ASSOCIATED UROTHELIAL CARCINOMA IN PATIENTS AFTER RENAL AND EXTRARENAL TRANSPLANTATION

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Purpose: Polyomavirus BK (BKV) reactivation or transmission is a well-known problem in renal transplant (TX) patients with BKV nephropathy and

interstitial cystitis. The role of BKV-associated urothelial carcinoma is still debated.
Methods: We reviewed the clinical data of six patients with BKV-associated urothelial carcinoma to understand the difference of this severe late complication compared to usual BKV-related problems in Tx patients.
Results: Between 2014 and 2021, we saw 6 patients (4 men and 2 women aged 51±16 yrs at TX) with urothelial carcinoma after renal ($n = 2$) and extrarenal TX (heart 2, combined heart-kidney 1, lung 1). Basal immunosuppression consisted in tacrolimus/ MMF/ prednisolone (pre) in 3, everolimus/ MMF/ pre in 2, and cyclosporine/ pre in 1 patient. Five patients had high viremia (maximum 596286±444272 copies/mL) and 4 also high viruria (maximum 7.5±5 billion copies/mL) 4 to 7 years before diagnosis of urothelial carcinoma. Four of 6 patients had had BKV nephropathy 3 to 58 months after TX. Urothelial carcinoma was diagnosed 96±26 (65-144) months after TX. Five tumors were located mainly in the bladder and multifocal, one in the TX ureter. Four patients had tumor recurrence or metastases. Tumor histology was lowly differentiated, grade 3 in all cases and showed distinct nuclear SV40 staining of the tumor cells. Cystectomy was performed in 5 cases, TX-ureterectomy in one case. Three patients died by metastatic tumor 7, 26 and 43 months after tumor diagnosis. Three patients are alive 36 (1) and 6 months (2 patients) after tumor diagnosis, 1 of these with metastasis.
Conclusion: BKV-associated urothelial carcinoma is a late phenomenon after renal and extrarenal TX. Diagnosis occurs often at an advanced stage, since BKV problems mostly happen up to two years after renal and only rarely after extrarenal TX. Routine BKV testing is done early after renal and only rarely at all after extrarenal TX. Prognosis is poor. Diagnosis may be suspected in cases of persisting high viruria, especially after preceding BKV nephropathy earlier. - Up to now, 26 cases in the literature have been reported.

KIDNEY TRANSPLANTATION I

PO-058 SEX DIFFERENCES IN KIDNEY TRANSPLANTATION: AUSTRIA AND THE UNITED STATES, 1978 TO 2018

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Introduction: Systematic analyses about sex differences in wait-listing and kidney transplantation after dialysis initiation are scarce. We aimed at identifying sex-specific disparities along this path (including death), comparing two countries with distinctive health care systems, the US and Austria, over time.
Methods: In this observational cohort study we analysed subjects who initiated dialysis, from the US Renal Data System or the Austrian Dialysis and Transplant Registry plus Eurotransplant datasets, from 1978 to 2018. The predoctors sex and age at dialysis initiation were used to model time to event from starting to end point of the consecutive states: dialysis initiation, wait-listing, kidney transplantation and death. We used cox regression to model male-to-female cause-specific hazard ratios (csHRs, 95% confidence intervals) for transitions along treatment states, adjusted for age and stratified by country and decade of dialysis initiation.
Results: Among 3,053,206 US and 36,608 Austrian patients starting dialysis, men had higher chances to enter the wait-list, which however decreased over time (male-to-female csHRs for wait-listing, 1978-1987: US 1.94[1.71,2.20], AUT 1.61[1.20,2.17]; 2008-2018: US 1.35[1.32,1.38], AUT 1.11[0.94,1.32]). Once wait-listed, the advantage of the men became smaller, but persisted in the US (male-to-female csHR for transplantation after wait-listing, 2008-2018: 1.08 [1.05,1.11]). The greatest disparity between men and women occurred in older age groups in both countries (male-to-female csHR for wait-listing after dialysis, adjusted to 75% age quantile, 2008-2018: US 1.83[1.74,1.92], AUT 1.48 [1.02,2.13]). Male-to-female csHRs for death were close to one, but higher after transplantation than after dialysis.
Conclusion: We found evidence for gender disparities in both countries, although the gender gaps are decreasing over time. Historically, men in the US and Austria had 90%, respectively 60% higher chances of being wait-listed for kidney transplantation. Efforts should be continued to render kidney transplantation equally accessible for both sexes, especially for older women.
Acknowledgement: We would like to thank the patients and the staff of the dialysis and transplant units for contributing the data via to the ADTR. We also acknowledge support from the Austrian Science Fund (grant No. KL754-B).

PO-059 RISK OF CELLULAR AND/OR ANTIBODY-MEDIATED TRANSPLANT REJECTION IN PAEDIATRIC KIDNEY TRANSPLANT RECIPIENTS WITH BK POLYOMAVIRUS REPLICATION - A MULTICENTRE CERTAIN ANALYSIS

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Introduction: To determine the risk of alloimmune responses (T cell-mediated rejection (TCMR) including borderline changes and *de novo* HLA donor-specific antibodies (dnDSA) and/or antibody-mediated rejection (ABMR)) as a consequence of reduced immunosuppression for BK polyomavirus (BKPyV) replication management in paediatric kidney transplant recipients
Methods: In the framework of the Cooperative European Paediatric Renal Transplant Initiative (CERTAIN), we studied 195 paediatric kidney transplant recipients (10.5 ± 5.5 years) in whom plasma BKPyV viral load and dnDSA were measured regularly over a period of up to 5 years post-transplant. Risk factors for the development of dnDSA and transplant rejection were analysed using univariate and multivariable Cox regression.
Results: BKPyV replication was observed in 65 (33.3%), and biopsy-proven BKPyV associated nephropathy in 13 (6.7%) patients. Ninety (46.2%) patients developed TCMR/borderline rejection, and 56 (28.7%) recipients developed dnDSA/ABMR during the 5-year period. The overall TCMR/borderline rate was comparable in patients with (20 (37.0%)) or without BKPyV replication (70 (49.3%), $P = 0.150$) but recipients with BKPyV replication developed TCMR/borderline rejection significantly ($P = 0.040$) later than those without, presumably due to reduced immunosuppression for BKPyV management. Independent risk factors for TCMR/borderline rejection were cold ischemia time >24 hrs (OR 3.0, $P = 0.024$), delayed graft function (OR 3.1, $P = 0.011$) and desensitisation at transplant (OR 2.5, $P = 0.031$).
The overall dnDSA/ABMR rate was also similar in patients with (16 (28.1%)) or without BKPyV replication (40 (29.0%), $P = 0.898$). Independent risk factors for dnDSA/ABMR development were re-transplantation (OR 5.8, $P = 0.000$), HLA-DR mismatch (OR 1.8, $P = 0.005$) and preformed DSA (OR 3.5, $P = 0.002$). In patients with BKPyV replication, independent risk factors for dnDSA/ABMR were re-transplantation (OR 8.1, $P = 0.011$) and an immunosuppressive regimen consisting of CSA/EVR vs. TAC/MMF (OR 3.9, $P = 0.034$).
Conclusion: Reduced immunosuppression as BKPyV management is not significantly associated with an increased risk of TCMR/borderline rejection and/or dnDSA/ABMR in paediatric kidney transplant recipients.

PO-060 BKPYV-SPECIFIC T CELLS REDUCE VIRAL LOAD IN A PRIMARY TUBULAR CELL MODEL

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Introduction: BK virus (BKPyV) infection is a major threat to kidney transplantation (KTx), occurring in up to 20% of KTx patients. To date, no specific antiviral treatment is available. Reactivation of BKPyV occurs in immunocompromised hosts, presumably as the lack of functioning T cells leads to a loss of control of viral replication.
Thus, application of BKPyV-specific T cells provides an interesting new therapeutic option. To our knowledge, a patient derived cell culture model to study viral replication and the effects of BKPyV-specific T cells in tubular kidney cells is lacking.

In this study, we established and analysed a co-culture model of human urinary Primary Tubular Cells (huPTC) of patients with BKPyV-associated nephropathy (BKVAN) and *ex vivo* stimulated BKPyV specific T cells.
Methods: Cell culture of huPTC and BKPyV-specific T cells, immunocytochemistry (ICC), qPCR, BKPyV-specific T-cell stimulation, FACS, ELISpot
Results: huPTC derived from the urine of patients with BKVAN or BK viremia were cultured and analysed for BKPyV infection with PCR and ICC staining. Infection of huPTC could be shown by SV40 positive nuclei. Cells showed typical morphological features of BKPyV infection (large nucleus, vesicular inclusions).
PBMCs were derived from healthy volunteers. Using BKPyV peptide pools (VP1/LT) CD8+ and CD4+ T cells were expanded over 9 days. FACS analysis showed an increased portion of activated T cells, ELISpot analysis demonstrated BKPyV specificity. BKPyV positive huPTC were co-cultured with stimulated T cells, unstimulated T cells or no T cells, as controls. Viral load in the supernatant was compared using qPCR, showing a significant reduction in cultures treated with stimulated T cells. This effect translated to a higher rate of viable cells, already visible by light microscopy.
Conclusion: Kidney cells infected with BKPyV can be derived from individual patients and passaged multiple times, providing a new and individualized tool for studying BKPyV infection. BKPyV specific T cells can be rapidly generated *ex vivo* and show a convincing reduction of BK viral load in co-culture experiments. This model enables assessment of the efficacy and safety of treatment with BKPyV-specific T cells.

PO-061 ANEW RISE IN DONOR-DERIVED CELL-FREE DNA (DD-CFDNA) IN A PATIENT WITH RELAPSE OF SEVERE TCMR - A CASE REPORT

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Introduction: Donor-derived cell-free DNA (dd-cfDNA) has been proposed as a noninvasive biomarker in monitoring allograft injury and rejection in kidney transplantation. Recently, the possibility of evaluating response to therapy by quantifying dd-cfDNA in patients receiving anti-rejection treatment has been discussed.
Methods: We present a case report of a patient with histopathologically diagnosed TCMR showing anew rise in dd-cfDNA after initial response to therapy. The case is part of an ongoing prospective single-center study to evaluate the diagnostic benefit of dd-cfDNA in detection of graft rejection.
Results: The 19-year-old woman received a kidney transplant in September 2020 from an ABO-compatible living donor. The patient's S-Creatinine decreased to 0.9 mg/dl 2 months after transplantation.
In December 2020, the patient presented with impairment of renal function (S-Creatinine 1.55). Biopsy revealed acute TCMR IIA with intimal arteritis (v1), severe interstitial inflammation (i3) and tubulitis (t3). No donor-specific antibodies (DSA) were detected. The patient was treated with steroid pulse therapy and ATG.
In April 2021, the patient presented with hydropic decompensation and S-Creatinine of 19.93. After recompensation, re-biopsy was performed, showing TCMR IA with severe interstitial inflammation (i3) and tubulitis (t2). De novo DSA against 3 different HLA alleles with maximum MFI 6,951 were detected. Despite immediate initiation of corticosteroid pulse therapy, ATG and immunoadsorption, kidney allograft function could not be restored.
dd-cfDNA was obtained at four occasions, namely at presentation for initial biopsy and a week as well as 1 and 3 months after initial treatment. dd-cfDNA levels decreased after initial treatment from 12% to 0.87% and increased again 1 and 3 months after initial treatment from 1.5% to 5.6%. S-Creatinine levels first decreased and subsequently plateaued (1.55; 1.14; 1.38; 1.18).
Conclusion: Decreasing levels of dd-cfDNA appear to indicate response to therapy in patients with allograft rejection. Our case report suggests that a new increase in dd-cfDNA levels after initial anti-rejection treatment may predict subclinical rejection even at stable S-Creatinine levels.

PO-063 IDENTIFYING INTERPERSONAL DIFFERENCES IN GUT MICROBIOTA METABOLISM OF TRANSPLANTATION AND CHRONIC KIDNEY DISEASE DRUGS

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Introduction: The outcome of kidney transplantation (KTx) and chronic kidney disease (CKD) depends on many therapeutic factors. We investigated how interpersonal differences in gut microbiome composition impact interpersonal variability in drug metabolism and prodrug activation. We focused on immunosuppressants, including tacrolimus and mycophenolate mofetil, which are challenging to dose due to their narrow therapeutic index and large interpersonal variability in drug response.
Methods: We constructed an *in vitro* system mimicking the intestinal environment and tested 10 human bacterial communities for the metabolism of 27 drugs, comprising four different classes of immunosuppressants and relevant non-immunosuppressive drugs. To link the metabolic activity of complex microbial communities to their composition, we additionally screened our drug panel against 44 highly abundant and prevalent gut bacterial strains.
Results: Our analysis revealed donor and compound-specific differences in bacterial drug metabolism. While more than 75% of the immunosuppressants were metabolized by at least one bacterial community, less than 30% of the non-immunosuppressive drugs were metabolized. Strikingly, bacterial communities differed in compound spectrum and kinetics of drug metabolism, indicating pronounced donor-specific differences. Further, we observed marked differences in metabolism between individual bacterial strains. Over 90% of the drug community metabolism was reproduced with single species, indicating a causal link between microbiome composition and metabolic activity.
Conclusion: We identified large interpersonal variability in gut bacterial metabolism of common immunosuppressive and non-immunosuppressive drugs used in KTx and CKD. Donor and drug-specific differences were particularly pronounced for immunosuppressants. Given the challenges associated with the dosage of immunosuppressants, we suggest that further studies should focus on how bacterial metabolism impacts immunosuppressive drug response in kidney disease patients. This may open new opportunities to establish microbial biomarkers for personalised drug selection and dosing.

PO-065 LONG-TERM KIDNEY GRAFT SURVIVAL: RELIABLE PROGNOSTICATION AND PATIENT STRATIFICATION WITH FACTORS FROM THE FIRST TRANSPLANT YEAR – ISSUE ON REJECTION LARGELY UNSOLVED

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Introduction: Kidney transplantation is the optimal treatment of end-stage renal disease. Long-term graft survival of kidney grafts has steadily improved. Therefore, re-assessment of graft outcomes and risks for premature graft failure is timely.
Methods: In this single-center analysis of 1753 patients with long-term follow-up of up to 17 years, random survival forests analysis was employed to train and validate a prediction model for death-censored graft survival. Similar to comprehensive medical judgment, a multitude of clinical and laboratory parameters from the first transplant year, including data from protocol biopsies were incorporated in the modeling.
Results: Death censored graft survival was 71% at 15 years in the training cohort. The final prediction model had good performance (concordance index 0.79) and calibration, was stable over time and was confirmed by an independent validation cohort (concordance index 0.74). Important factors for graft survival were graft function at one year, body weight, acute T cell- and antibody-mediated rejection, urinary tract and other infections, and recurrent or de novo glomer-ulonephritis, besides donor and recipient age. Rejections diagnosed in biopsies for cause had greater importance than rejections in protocol biopsies. Treated rejections as well as rejections left untreated were predic-tive. Post-hoc analyses after the first year demonstrated increasing frequency of T cell- and anti-body-mediated rejection in patients assigned with higher risk by the model.
Conclusion: The model reliably and early on identifies patients with virtually no risk of graft failure in the long-term, as well as patients at risk for premature graft failure and their individual risk factors. It can help to stratify patients into specific monitoring strategies and therapy protocols. Of concern is that both untreated and treated rejections are important, suggesting lack of sufficiently efficacious and specific therapies.

PO-066 NORMOTHERMIC EX VIVO KIDNEY PERFUSION FOR HUMAN KIDNEY TRANSPLANTATION: FIRST NORTH AMERICAN RESULTS

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Introduction: Normothermic ex-vivo kidney perfusion (NEVKP) has shown promising results for preservation, assessment, and reconditioning of kidney allografts in preclinical studies. Here, we report the first North American safety and feasibility trial of deceased donor kidneys grafts transplanted following preservation with NEVKP.
Methods: Outcomes of 13 human kidney grafts that received 1 to 3 hours of NEVKP after being transported in an anoxic hypothermic machine perfusion (HMP) device were compared with a matched control group of 39 grafts which were preserved with anoxic HMP alone.
Results: Grafts were perfused for a median of 171 minutes (range 44-275 minutes). The delayed graft function rate in NEVKP vs. control patients was 30.8% vs. 46.2% ($P = 0.51$). During the one-year follow-up no differences in postoperative graft function, measured by serum creatinine, necessity for dialysis, and urine production were found between the study group and the control group. There were no differences in one-year post-transplantation graft or patient survival between the two groups.
Conclusion: Our study demonstrates the safety and feasibility of NEVKP for human deceased donor kidney transplantation. Future trials need to investigate how this technology can minimize cold ischemia, improve post-transplant graft function, and assess and repair expanded criteria kidney grafts.
Acknowledgement: This work has been supported by grants from the Deutsche Forschungsgemeinschaft (DFG) (MA 8516/1-1 to L.I.M.).
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PO-067 USE OF HYPERSPECTRAL IMAGING (HSI) TO PREDICT DELAYED GRAFT FUNCTION IN KIDNEY TRANSPLANTATION FOLLOWING HYPOTHERMIC MACHINE PERFUSION -A PILOT STUDY

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Introduction: Hyperspectral Imaging (HSI) represents a promising optical non-invasive approach to evaluate kidney allografts by providing information regarding tissue oxygenation (StO_2), near infrared perfusion (NIR), hemoglobin (THI) and water concentration (TWI). While HSI is able to predict delayed graft function (DGF) following static cold storage, its ability in assessing kidney allogarfts following end ischaemic hypothermic machine perfusion (eHMP) remains unknown. Aim of this pilot study was to assess viability of kidney allografts preserved with and without HMP by HSI.
Methods: Twenty-one kidney allografts, nine of them after eHMP, were analyzed. HSI was performed before and after HMP as well as 10 and 30 minutes after reperfusion. DGF was defined as need for dialysis within the first week after transplantation.
Results: Duration of eHMP was 363 $\pm$ 301.3 min and warm ischemia time was 35.3 $\pm$ 8.1 min. Nine kidney allografts (42.8%) developed DGF. Patients with DGF showed reduced StO_2 ($P = 0.007$) and lower NIR ($P = 0.02$) at 10 and 30 min after reperfusion. The TWI after HMP was also reduced, but the trend did not reach statistical significance. In four cases, both allografts from the same donor were transplanted; one with one without eHMP due to logistic reasons. In these paired analyses, eHMP organs had better StO_2-levels 10 and 30 min after reperfusion. In addition, creatinine clearance was more improved after eHMP.
Conclusion: A study demonstrates that HSI is capable to predict DGF in kidney transplantation following eHMP. Intraoperative perfusion and especially quantification of oxygenation, hemoglobin as well as water concentration in the parenchyma can be monitored. Our data provides first evidence that HMP could reduce tissue water concentration. This diminution of reperfusion induced edema is to be further investigated and could be a reason for a better creatinine clearance. Therefore, further HSI studies are recommended to introduce and describe the potential of this promising imaging technique.

PO-068 MORPHSET: DIAGNOSING ANTIBODY-MEDIATED REJECTION THROUGH LEARNED DIAGNOSTIC VECTORS

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Introduction: Computer-aided diagnostic systems hold great promise for improving the accuracy and reproducibility of renal transplant pathology diagnostics. Common approaches for training Deep Neural Networks (DNNs) to predict Antibody-Mediated Rejection (AMR) in glomeruli currently involves the replication of costly expert nephropathologists assessment of a large number of individual glomeruli samples. We chose to explore an alternative approach.
Methods: This approach, called MorphSet, is a DNN architecture inspired by set transformers that processes encoded representations of Monte Carlo (MC)-sampled glomerular compartment crops to produce biopsy-level predictions (AMR or no-AMR). This method bypasses the need for costly fine-grained expert annotations. We tested this approach on a set of $n = 89$ randomly selected biopsies from our archive ($n = 51$ chronic-active, chronic or active AMR; and $n = 38$ without AMR). All 1,655 open glomeruli on two PAS level sections were included as manual crops from micrographs taken with a x40 objective. As a baseline we trained an EfficientNet-B3 encoder using a consensus-label approach, and comparisons were done using ROC curve metrics.
Results: The EfficientNet-B3 baseline yielded an AUC of 0.962, MorphSet outperforming it with 0.999 on case level predictions. In addition, MorphSet displayed higher confidence and point estimates in its AMR diagnoses in the confidence visualizations.
Conclusion: MorphSet outperformed a state-of-the-art DNN architecture on our dataset for the diagnosis of AMR. We note that MorphSet does not require fine-grained assessments, instead relying on learned understandings of discriminative features in its predictions. MorphSet-based diagnostic systems for AMR could be easily expanded with additional training sets from trusted institutions.

PO-069 C-TERMINAL AND INTACT FGF23 IN KIDNEY TRANSPLANT RECIPIENTS AND THEIR ASSOCIATIONS WITH OVERALL GRAFT SURVIVAL

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Introduction: Increased fibroblast growth factor 23 (FGF23) is a risk factor for mortality, cardiovascular disease, and progression of chronic kidney disease. Limited data exist comparing the association of either c-terminal FGF23 (cFGF23) or intact FGF23 (iFGF23) in kidney transplant recipients (KTRs) with overall (all-cause) graft loss.
Methods: We conducted a prospective observational cohort study in 562 stable kidney transplant recipients. Patients were followed for graft loss and all-cause mortality for a median follow-up of 48 months.
Results: During a median follow-up of 48 months, 94 patients had overall graft loss (primary graft loss or death with functioning graft). Both cFGF23 and iFGF23 concentrations were significantly higher in patients with overall graft loss than those without (24.59 [11.43-87.82] versus 10.67 [5.99-22.73] pg/ml; $P < 0.0001$ and 45.24 [18.63-159.0] versus 29.04 [15.23-60.65] pg/ml; $P = 0.002$ for cFGF23 and iFGF23, respectively). Time-dependent ROC analysis showed that cFGF23 concentrations had a better discriminatory ability than iFGF23 concentrations in predicting overall (all-cause) graft loss.

Cox regression analyses adjusted for risk factors showed that cFGF23 (HR for one unit increase of log-transformed cFGF23: 1.35; 95% CI, 1.01-1.79; $P = 0.043$) but not iFGF23 (HR for one unit increase of log-transformed iFGF23: 0.97; 95% CI, 0.75-1.25; $P = 0.794$) was associated with the overall graft loss.
Conclusion: Elevated cFGF23 concentrations at baseline are independently associated with an increased risk of overall graft loss. iFGF23 measurements were not independently associated with overall graft loss. The cFGF23 ELISA might detect bioactive FGF23 fragments that are not detected by the iFGF23 ELISA.
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PO-070 THE SUITABILITY OF THE CLASSICAL KIDNEY INJURY MARKERS NGAL, KIM-1 AND NAG AS EARLY MARKERS OF REPERFUSION INJURY IN PORCINE KIDNEYS DURING NORMOTHERMIC WHOLE-BLOOD PERFUSION

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Introduction: Normothermic machine perfusion (NMP) using oxygenated whole-blood is a currently investigated tool to combat the scarcity of usable kidneys for transplantation by assessing marginal organs under physiological conditions. The tubule damage-markers kidney injury marker 1 (KIM-1), N-Acetyl-β-D-glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin (NGAL) are well-known markers for kidney injury. Their suitability to contribute to a score assessing the transplantability of a kidney within NMP is yet to be elucidated.
Methods: Kidneys obtained from slaughterhouse pigs were perfused for 4 h. They were grouped based on their morphology after NMP into "good" (group A: $n = 7$) and "poor" (group B: $n = 3$). Urine and plasma samples were taken before starting the perfusion and after 1 h, 2 h and 4 h of NMP. KIM-1, NAG and NGAL were quantified by ELISA. Obtained concentrations were normalized to total protein-concentration.
Results: Preliminary data suggested a constant plasma concentration of KIM-1 and NAG in group A, but showed an increase within 1 h and reached maximum concentration after 2 h NMP in group B, with the 2 h-concentrations having been double compared to the group A kidneys. Plasma-NGAL was only slightly increased in group B. Urinary KIM-1 and NAG both increased continuously over the 4 h in group A whereas concentrations increased to their maxima already after 2 h in group B. Urinary NGAL-concentration however was almost constant in group B kidneys whereas its excretion rose sharply in group A after 2 h.
Conclusion: NAG and KIM-1 might be eligible markers to predict the outcome of NMP after only 2 h both in blood and urine samples. They appear to be sensitive and early markers of otherwise invisible tubule injury. NGAL is thought to have anti-apoptotic properties, which may explain the higher urinary excretion in good kidneys. It is possible that it acts as rescue factor aimed at limiting the extent of reperfusion injury. Due to the currently small sample size, results are not yet robust. Still, NAG and KIM-1 show potential to increase the informative value of a predictive score.
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Allocation of marginal organs, Surgical options for organ transplantation, Psychosocial aspects of organ transplantation

PO-074 PATIENT AND GRAFT SURVIVAL AFTER DUAL KIDNEY TRANSPLANTATION WITH MARGINAL DONORS IN COMPARISON TO MATCHED CONTROL GROUPS

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Introduction: Postmortal organ donor rates remain low in Germany. As a consequence of low donation rates older and more marginal donor kidneys are accepted for transplantation. However, procured kidneys from very old a/o marginal donors may be considered as not suitable for transplantation as a single organ and subsequently be discarded. However, dual transplantation of both kidneys (DKT) from such donors may provide an opportunity to nevertheless use these organs for renal transplantation, thereby providing the twofold nephron mass than a single kidney transplantation (SKT).
Methods: We compared in this retrospective analysis the outcome of 10 recipients of a DKT with 40 matched recipients of a SKT. Recipients were matched for donor and recipient age, i.e. a maximum age difference of ±10 years in a ratio of 1:4 for DKT versus SKT recipients. In addition, a second SKT control group of 10 SKT recipients being transplanted immediately before each DKT recipient with a kidney from a donor aged ≥65 years was used for comparison. All renal transplant recipients were followed for up to 3 years or until July 31, 2020.
Results: Mean donor and recipient age was 77.2±4.6/75.1±6.6/82.1±7.9, and 66.4±5.8/66.1±6.0/64.8±8.4 for SKT group 1/SKT group 2/DKT, respectively. Procurement serum creatinine concentrations were significantly higher in the DKT group in comparison to the SKT control group 1 ($P = 0.019$) as was the rate of transplant artery atherosclerosis ($p = 0.021$). KDPI (Kidney Donor Profile Index) and KDRI (Kidney Donor Risk Index) were significantly higher ($P = 0.0138$/$P = 0.064$, and $P < 0.001$/$P = 0.038$) in the DKT group than in the SKT group 1 and 2. Rates of acute rejection and DGF were not significantly different between groups, though BPAR was numerically higher in the SKT groups. Patient survival, overall and death-censored graft survival rates were also not significantly different between groups, though they tended to be higher after DKT.
Conclusion: DKT provides an opportunity to successfully use postmortal kidneys even from donors with an age >80 years and a KDPI≥95% for renal transplantation. DKT may thereby increase the available pool of donors to better serve end-stage renal disease patients on the waiting-list.

PO-075 MACHINE LEARNING ALGORITHM IN LIVER ALLOCATION – A PROMISING APPROACH?

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Introduction: Most liver allocation systems worldwide are urgency depended, defined by the "Model for End-stage Liver Disease" (MELD) score. These MELD-based liver allocation systems have several disadvantages, as MELD allocation i) is not equally fair for all transplant indications ii) is disadvantages for women iii) may lead to excess mortality in minority candidates iiii) is negatively correlated with post transplantation outcome.
The aim of this project is to generate a potent liver transplantation outcome score via machine learning algorithms in 2 different cohorts (Germany and US).
Methods: The datasets used for this analysis were obtain from United Network for Organ Sharing (UNOS) and eurotransplant cooperation (ET). The observation period was 2002-2017 for the US and 2006-2017 for Germany. Exclusion criteria were age below 18 years and missing follow-up. As machine learning method we chose "random forests" and compared that to logistic regression and well established outcome scores like the BAR- and a modified SOFT- score. Primary outcome was 3 month survival of the transplant recipients.
Results: A total of 104799 liver transplant recipients were included in this analysis. In both countries the cohorts were split in training sets (80% of all included patients; US: $n = 75411$; Germany: $n = 8429$) and test sets (20% of all patients). Applying machine learning achieved a prediction of 3 month survival with an area under the curve (AUC) of 0.68 in Germany and the US. This forecasting was comparable with logistic regression (Germany: 0.67; US: 0.69). In the US cohort, where more variable were available, the AUC of SOFT (0.67) and BAR (0.62) were calculated as well, showing no or minimal benefit of the "random forests" method. In general, all predictions showed relatively low accuracy with AUC below 0.7.
Conclusion: Machine learning methods as well as conventional outcome predictions show yet insufficient precision if the data sets are from real-life data registries. This may hinder implementation of such result-oriented scores in the process of organ allocation.

PO-076 LIVER GRAFTS WITH EXTENDED DONOR CRITERIA: SINGLE-CENTER EXPERIENCE

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Introduction: Die Transplantation ist die Therapie der Wahl bei End-stage Liver Disease (ESLD) und ausgewählten hepatischen Tumoren. Aufgrund des Spendermangels werden zunehmend Organe mit Extended Donor Criteria (EDC) akzeptiert. Zu den majorEDC zählen makrovesiculäre Steatosis >40%, Spender-Alter >65 Jahre und eine kalte Ischämiezeit (CIT) >14h. Die mEDC haben einen Einfluss auf Morbidität und Mortalität und damit auf das Outcome nach Lebertransplantation
Methods: In einer retrospektiven Datenerfassung wurden 90 Lebertransplantationen im Zeitraum 2014-2021 ausgewertet. Recipient- und Donordaten, perioperative Parameter und das Outcome wurden analysiert.
Results: Das mittlere Empfängeralter lag bei 55.8±11.03 (23-73) Jahren und 64.4% waren Männer. In 7.8% erfolgte eine Re-Transplantation. Grunderkrankungen waren in 36.0% äthyltoxische LZ, in 14.6% NASH, in 10.1% Hepatitiden bzw. cholestatische Erkrankungen und in 29.2% andere. In 42.2% lag ein HCC vor. Der mittl. DRI 1.867±0.347 (1.093-2.484) und der mittl. ET-DRI 1.933±0.357 (1.14-3.24) waren ohne signifikanten Einfluss auf das Overall Survival ($P = 0.402$, $P = 0.539$). Die einzelnen Spenderparameter (kalte Ischämiezeit $P = 0.973$; D-Alter $P = 0.213$; D-BMI $P = 0.147$; D-IST Zeit $P = 0.297$) hatten keinen signifikanten Einfluss auf das Outcome. Zwei oder mehr mEDC verschlechterten jedoch das Outcome signifikant ($P = 0.020$). Bei Spendern mit mEDC trat eine Early Allograft Dysfunction nicht signifikant häufiger auf ($P = 0.638$). Das gesamte 1-, 3- und 5-Jahres OS war 82,2%, 77,5% bzw. 72.1% bei einer mttl. Nachbeobachtungszeit von 34.1±27.98 (0-90) Monaten.
Conclusion: Spender- und Empfängerparameter bestimmen das Outcome nach Lebertransplantation. Das begrenze Spenderangebot schränkt jedoch die Möglichkeit der passenden Organauswahl ein. Spenderorgane mit major Extended Donor Criteria zeigen keine höhere Rate an EAD und können daher mit sehr guten Ergebnissen transplantiert werden.

PO-077 EX SITU ARTERIAL RECONSTRUCTION PRIOR NORMOTHERMIC MACHINE PERFUSION OF LIVER GRAFTS- FEASIBLE, SAFE, AND EFFECTIVE IN ALLOWING SIMULTANEOUS REPERFUSION -

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Introduction: Normothermic machine perfusion (NMP) is an evolving technology preserving and assessing liver grafts prior transplantation. Since arterial perfusion is normally conducted via single vessel cannulation of the common hepatic artery (CHA), atypical (accessory (a), replaced (r) HAs) arterial anatomy is a technical challenge for NMP. To perform just one singular arterial anastomosis in the recipient, arterial reconstruction can be performed prior, during or following NMP. While the first prolongs cold ischemia time (CIT), the second compromises arterial perfusion during NMP and the third prolongs time to arterial perfusion in the recipient. We report our experience with HA reconstruction prior NMP, which preserves the ability to alter the reconstruction in case of problems resulting from reconstruction itself.
Methods: Between 10/2019 and 05/2021 52 livers were perfused using the OrganOx Metra device and 9 livers showed HA variations: 3 right rHA, 3 left rHA, 2 left and right rHA and 1 left aHA. Reconstruction was performed by using either the CHA or gastroduodenal artery (GDA) for right rHA, right HA or GDA for left rHA and aHA as well as GDA and right gastric artery when both HAs required reconstruction.
Results: Livers were perfused following a CIT of 7.7 ± 2.6h and showed regular flow parameters (arterial inflow 422 ± 132 ml/min) and sufficient lactate clearance (76% drop after 1h) during NMP. Anastomotic patency and macroscopic appearance of the graft was visually checked during NMP and showed no irregularity. All grafts were successfully transplanted, and simultaneous reperfusion was carried out in 6 livers (67%). No hepatic artery thrombosis at the side of reconstruction was observed. None of the cases developed late hepatic artery thrombosis nor stenosis.
Conclusion: Our data provides evidence that atypical HA anatomy is not an obstacle for successful NMP and that reconstruction prior to NMP is allowing functional evaluation prior transplantation. Our approach inevitably prolongs CIT but distinguishes itself by the ability to perform simultaneous reperfusion, which has been shown to be associated with superior long-term outcome.

PO-079 DEVELOPMENT FOLLOWING PAEDIATRIC KIDNEY TRANSPLANTATION

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Introduction: The aim of this research is to assess quality of life, mental health, motor development, executive functioning and medication adherence in paediatric patients following kidney transplantation.
Methods: In a cross-sectional study we used standardised tools (FABEL, KINDL, PedsQL, CBCL, M-ABC, WISC-V, BAASIS) to assess the target parameters and analyse them against the background of selected medical data.
Results: We included 53 patients age 0-18 (♂32 ♀21). Parents reported increased financial burden and fear of the future. Half of the patients showed some symptoms of mental distress. 13/40 (32.5%) patients fulfilled DSM-criteria for mental health problems. Most frequent symptoms linked to depression and anxiety. Participants who started renal replacement therapy in their first three years of life mainly expressed symptoms of the externalising spectrum.
Motor-development could be assessed in 47 patients. Developmental deficits could manly be observed in the field of fine motor skills and dexterity as well as body-balance. In total 11/47 (23.4) patients had fine-motor-skills below the 2nd percentile, 14/47 (29.9%) had deficits in body-balance scoring below the 2nd percentile.
Processing speed was assessed in a subgroup of 36 patients without cognitive developmental delay. Mean score was 84 (45-112; sd 16.0). 5/36 (13.9%) patients had results below the 2nd percentile.
Conclusion: Even after successful transplantation chronic kidney disease seams to impact on the overall health and development of the affected child. While nowadays allograft survival is considered to be acceptable, it is time to shift focus on quality of survival and non-renal consequences of a renal disease. Besides further research clinical programs are needed to offer tailored assessments and support.

PO-087 ROBOT-ASSISTED (RDN) VS. OPEN LIVING DONOR NEPHRECTOMY (ODN):A RETROSPECTIVE ANALYSIS OF SURGICAL DONOR OUTCOMES

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Introduction: High demands are placed on the selected surgical procedure to ensure the greatest possible safety for the kidney donor. We aimed to assess the results of our first series of RDN versus ODN.
Methods: In a retrospective study, we compared the outcome of 28 RDN and 38 ODN kidney donors operated between 01/2010 and 09/2018. Following characteristics were analyzed: extraction side, BMI, numbers of vessels, ischemia times, duration of the operation, conversion rate, length of hospital stay, 30-day postoperative surgical complications according to Dindo-Clavien, laboratory chemistry (CRP, leukocytes, haemoglobin, creatinine) and initial graft function.
Results: Baseline characteristics were comparable between both groups. Outcome was not significant different for warm ischemia time, surgical complications, haemoglobin, leukocytes and creatinine. Significant differences were found for operation time, cold ischemia time, length of hospital stay and CRP (Table 1).

Parameter	RDN ($n = 28$)	ODN ($n = 38$)	P
operation time (min)	221.5 ± 50.4	148 ± 31.2	<0.001
cold ischemia time (min)	190.6 ± 50.7	140.0 ± 37.2	<0.001
length of hospital stay (d)	4.3 ± 1.6	5.5 ± 1.6	0.007
CRP (mg/l) day 2	71.4 ± 27.8	111.1 ± 60.9	0.001
conversion rate (%)	0	0	

Conclusion: In our experience, RDN appears to be a safe procedure. Hospitalization and CRP values were significantly lower in the RDN group, while the operation time was significantly higher compared to ODN. This might be a learning curve effect. However, the results encourage to continue and further implement RDN.

Pediatric transplantation, Pancreas transplantation, Thoracic organ transplantation, Basic science

PO-090 MATERNAL VERSUS PATERNAL LIVING KIDNEY TRANSPLANT DONATION IS ASSOCIATED WITH LOWER REJECTION IN YOUNG PEDIATRIC RECIPIENTS – A COLLABORATIVE TRANSPLANT STUDY REPORT

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Introduction: Approximately 1,700 children per year with end-stage kidney disease undergo kidney transplantation in Europe and the United States of America; 30–50% are living-donor kidney transplantations. There may be immunological differences between paternal and maternal donors due to the transplacental exchange of cells between the mother and fetus during pregnancy leading to microchimerism. We therefore investigated whether the outcome of living-related kidney transplantation in young children is different after maternal compared to paternal organ donation.
Methods: Using the international Collaborative Transplant Study (CTS) database, we analyzed the epidemiological data of 7,247 children and adolescents aged <18 years who had received a kidney transplant either from their mother or father. Risks of treated rejection episodes and death-censored graft failure were computed using the Kaplan-Meier method and multivariable Cox regression.
Results: In the recipient age group 1–4 years, the risk of treated rejection episodes in kidneys from maternal donors ($N = 195$) during the first 2 years post-transplant was significantly lower (hazard ratio HR = 0.47, $P = 0.004$) than in kidneys from paternal donors ($N = 179$). This association between donor sex and risk of treated rejections was not observed in children aged 5–9 years. The 5-year death-censored graft survival in children aged 1–4 years with a maternal or paternal donor was comparable.
Conclusion: Maternal kidney donation in young pediatric renal transplant recipients is associated with an approximately 50% lower rate of treated rejection than paternal kidney donation. Whether this phenomenon is due to maternal microchimerism-induced donor-specific hyporesponsiveness must be evaluated in prospective mechanistic studies.

PO-093 THERE IS NO TOO SMALL - SIMULTANEOUS KIDNEY AND "PIGGY BACK" PANCREAS TRANSPLANTATION OF INFANT DONOR ORGANS FOR ADULT RECIPIENTS

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Introduction: Simultaneous pancreas and kidney transplantation (SPK) provides the optimal therapy for patients with type I diabetes and associated end-stage renal disease (ESRD). Due to a discrepancy of wait list candidates and suitable grafts, optimization of donor utilisation is necessary. Utilisation of pediatric donor organs has been proposed to increase the organ donor pool. We report a case series of 4 patients, who received SPK of infant donors offered within rescue allocation track for as there were no other recipients identified nationwide.
Methods: All recipients suffered of ESRD secondary to type I diabetes. Recipients 1, 2 and 4 were female (Age 30, 40, 30 years). Recipient 3 was a 66 year old male with chronic cardiac insufficiency and three-vessel disease. Donors were 24, 7, 24 and 3 months old weighing 11, 8, 15 and 6 kg. All transplants were performed as en-bloc kidney and pancreas "piggy-back" transplant. Ureteric reconstruction was done by ureterocystostomy or by cystocystostomy using a bladder patch if possible. Exocrine drainage of the donor pancreas was achieved by side-to-side duodeno-duodenostomy.
Results: All patients showed immediate kidney function with increasing diuresis and were off insulin support at 7-10 days posttransplant despite pancreas allografts weighing as little as 16 grams. CCI score was 28.8. Median hospital stay was 18 days. Median increase of kidney size was 1 cm (range 0.5-1.9 cm) within 6 weeks. With a mean follow-up of 5 months all recipients are off dialysis (mean creatinine 0.9 mg/dl, GFR 79) without evidence for proteinuria. At the given follow-up all recipients were still off insulin with a mean HbA1c of 5.2%.
Conclusion: Pancreas and kidney allografts from infant donors are rarely used, reflecting unnecessary fear of surgical complications and impaired function secondary to a reduced islet cell and nephron mass. This series supports that infant allografts represent a viable source with good short-term and promising long-term outcome.

PO-094 HIGH MORTALITY RATE AFTER SIMULTANEOUS PANCREAS KIDNEY RETRANSPLANTATION

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Introduction: After simultaneous pancreas/kidney transplantation loss of graft function may occur due to rejection, bleeding or thrombosis. For this patient population retransplantation is an option. However, pancreas/kidney retransplantation in particular is a rare procedure for which only few case numbers are available in the literature.
Methods: A total of 56 patients underwent pancreas retransplantation at our transplant center between 01/1994 and 03/2021. This is a retrospective, monocentric evaluation of the outcome of 24 patients who underwent simultaneous pancreas/kidney retransplantation after receiving simultaneous pancreas/kidney transplantation before.
Results: In this patient population 16 were female and 8 were male with a mean age of 44.4 years. Nineteen patients underwent graft nephrectomy and 11 patients underwent graft pancreatectomy prior to or during retransplantation. Placement of the new anastomoses was challenging intraoperatively because of the prior surgery. Postoperatively 13 patients were indicated for relaparotomy due to bleeding complication or graft pancreatitis. Of these patients 20.8% ($n = 5$) died within the first 3 months after retransplantation. The 1-year mortality rate was 25% ($n = 6$). Cause of death was arterial hemorrhage in 3 patients, septic multiorgan failure in 2 patients and unknown in 1 patient. Seventeen patients (70.8%) were discharged with good pancreatic function and 16 patients (66.7%) with good renal function after a median hospital stay of 23.5 days. Patient survival was 75% ($n = 18$) at 1 year and 66.7% ($n = 16$) at 5 years after retransplantation.
Conclusion: Simultaneous pancreas/kidney retransplantation after previously performed simultaneous pancreas/kidney transplantation is a technical and immunological challenge. Due to the complexity of the procedure there is an increased complication rate associated with a high 1-year mortality rate. For this reason detailed preoperative planning with careful patient selection prior to retransplantation is essential.

PO-095 NORMOTHERMIC EX VIVO PANCREAS PERFUSION FOR THE PRESERVATION OF PORCINE PANCREAS GRAFTS

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Introduction: Pancreas transplantation (Tx) improves the life of patients with insulin dependent diabetes and reduces the risk of long-term cardiovascular disease. The shortness of suitable donors limit the pool of available grafts for Tx. This has lead to the increased usage of organs from expanded criteria donors and donors after cardiac death, which results in poorer outcomes after Tx. To decrease preservation injury and better assess grafts before Tx, research studies have focused their attention on ex-vivo machine perfusion. The first experimental and clinical trials for ex vivo lung, liver, and kidney perfusions demonstrated favorable outcomes. Normothermic ex vivo pancreas perfusion (NEVPP) can keep grafts metabolically active, allowing for better assessment and reconditioning, and has the potential to decrease preservation injury.
Methods: Pancreata were removed from 30 kg Yorkshire pigs in a model of heart-beating donation and subjected to 6 hours of NEVPP (n = 7). Perfusion parameters, potential assessment markers and graft injury were evaluated.
Results: During NEVPP, physiologic perfusion conditions were maintained with normal electrolyte and pH parameters. Arterial pressure was maintained at 25mmHg, which resulted in an arterial flow of 120 ± 21 mL/min at baseline and of 101± 15 mL/min at the end of perfusion. Oxygen consumption was constant over the course of perfusion, suggesting metabolic activity of the pancreas. Perfusate lactate levels decreased from baseline until the last hour of NEVPP (9.97 ± 1.06 mmol/L vs 2.1 ± 0.4 mmol/L). Amylase and lipase increased over the course of perfusion and were recorded as markers of organ injury. Histology at the end of perfusion showed intact islet cells with predominantly mild signs of tissue necrosis. Dialysis inclusion resulted in less graft edema, which allowed for a better graft perfusion. Anti-

inflammatory cytokines increased in the perfusate over the course of perfusion, while pro-inflammatory cytokines were dialysed off.
Conclusion: This study demonstrates that NEVPP is feasible for the preservation of heart-beating donor porcine pancreas grafts. Future studies need to explore the potential of NEVPP for graft assessment and reconditioning.
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PO-096 CYTOMEGALOVIRUS INFECTIONS FOLLOWING HEART TRANSPLANTATION: COMPARISON OF EARLY AND DELAYED DNAEMIA

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Introduction: Cytomegalovirus (CMV) infections are a risk factor for complications and impaired outcome following heart transplantation (HTx). Current literature vastly focuses on the impact of serologic CMV matching of recipients and donors as well as pharmacological prophylaxis schemes. However, impact of CMV infections after termination of the prophylaxis still remains unclear.
Methods: We retrospectively reviewed all patients undergoing HTx between 2010 and 2021 (n = 201) in our department. Of those, n = 125 (62.2%) patients passed 1-year follow-up and were divided in regard to their CMV status (Group 1 = no observed CMV-DNAemia during 1-year follow-up: n = 97 (77.6%); Group 2 = only CMV-DNAemia during initial HTx hospital stay: n = 10 (8.0%); Group 3 = only CMV-DNAemia after initial HTx hospital stay: n = 15 (12.0%); Group 4: CMV-DNAemia during and after initial hospital stay: n = 3 (2.4%). All patients underwent the same 90-day CMV prophylaxis scheme.
Results: Preoperative CMV serologic matching of donors (D+/-) and recipients (R+/-) significantly differed (P = 0.04) between the four groups with predominance of D+/R+ (33.3%) in Group 1, D-/R+ (66.7%) in Group 2, D+/R- and D-/R+ (40.0% each) in Group 3 and D+/R+ (66.7%) in Group 4. No association was found between postoperative primary graft dysfunction, kidney function and acute graft rejection and the on-set of CMV-DNAemia after HTx. In contrast to that, postoperative infections were observed significantly more often (P = 0.05) in patients with CMV-DNAemia (Group 2 = 30.0%, Group 3 = 26.7%, Group 4 = 66.7%) than in in those without (Group 1 = 14.4%). Furthermore, Kaplan-Meier survival analyses indicated by trend (P = 0.36) best survival for patients of Group 2 (estimated mean survival = 8.0±0.4 years) and Group 1 (8.3±0.9 years) compared to Group 3 (5.3±0.7 years) and Group 4 (1.6±0.1 years).
Conclusion: Although group sizes are small and results are only preliminary, our data suggest negative impact of CMV-DNAema after the termination of regular postoperative CMV prophylaxes on the survival after HTx. Therefore, prolongation or repetition of CMV prophylaxes might be considered in certain patients, especially in risk configurations and if early CMV-DNAema has already been observed.

PO-097 PULMONARY HYPERTENSION IN LONG-TERM FOLLOW-UP AFTER HEART TRANSPLANTATION

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Introduction: Pulmonary hypertension (PH) is a prognosis limiting condition in heart failure, but the evidence on the mortality relevance of PH in a long-term follow-up after HTx is still sparse. Therefore the aim of our study is to assess the prevalence and the prognostic implications of PH in a long-term follow-up after heart transplantation.
Methods: Retrospective analysis of the demographic data as well as the hemodynamic results derived from the last right heart catheterization (RHC).
Results: We identified 185 patients who were routinely monitored in our outpatient clinic, of which 161 (87 %) had undergone invasive haemodynamic assessment. The mean follow-up in these patients was 15.1 ± 6.7 years and the mean age at the time of HTx 46.8 ± 13.3 years. 133 patients were male (82.6 %). The last RHC was performed in 8.2 ± 6.3 years after HTx. Mean pulmonary artery pressure (mPAP) was on the upper limit of normal (20.0 ± 6.5 mmHg). All other mean hemodynamic values were in the normal range: pulmonary capillary wedge pressure (PCWP) - 13.3 ± 5.2 mmHg, calculated cardiac output - 6.7 ± 2.1 L/min, cardiac index - 3.5 ± 1.1 L/min/m^2, and pulmonary vascular resistance (PVR) – 1.3 ± 0.84 WU. A closer look at the data revealed that mPAP values > 20 mmHg were obtained in 63 patients (39.1 %). Of these, 25 patients (42.9 %) had PCWP values < 15 mmHg and consequently precapillary PH. The remaining 36 patients (57.1 %) presented with PCWP values > 15 mmHg as a sign of postcapillary PH. In almost all cases the latter was isolated postcapillary PH (PVR ≤ 3, n = 35, 97.2 % vs. PVR > 3, n = 1, 2.8 %). We observed no significant differences in the left ventricular systolic function between the patients with postcapillary PH vs. without or precapillary PH (LVEF 54.7 ± 9.3 % vs. 56.2 ± 8.4 %, P = 0.38) and no significant differences in the diastolic ventricular function (P = 0.095). PH was not a relevant prognostic factor in a univariate model (HR 1.2, 95% CI 0.7–2.2, P = 0.46).
Conclusion: Based on the haemodynamic data almost 40 % of our patients presented with PH in long-term follow-up, mostly postcapillary in origin. Additionally, our analysis showed no prognostic relevance of PH in long-term follow-up.

PO-098 EXPLANTATION OF ELECTROPHYSIOLOGICAL DEVICES IN THE CONTEXT OF HEART TRANSPLANTATION: COMPARISON OF COMBINED AND STAGED PROCEDURES

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Introduction: Cardiac implantable electrophysiological devices (CIEPD) such as resynchronization or cardioverter defibrillator devices are common in heart failure patients. During heart transplantation (HTx), tip of leads have to be cut when resecting the native heart. Optimal timing of the explantation of the remaining device and leads is still discussed controversially. Combined device explantation at HTx can prolong the transplant procedure and increase the risk for perioperative bleeding due to impaired haemostasis. Staged procedures require a second operation and carry certain risk of early endocarditis of the remaining device.
Methods: Between 2010 and 2021 a total of n = 201 patients underwent HTx in our department, of those n = 124 (62%) with a present CIEPD. These patients could be divided into two groups, depending on the time of complete device explantation (Group 1: combined procedure with HTx, n = 40 or Group 2: staged procedure, n = 83). The remaining patient (n = 1) was excluded due to incomplete data set. The groups were comparable regarding recipient and donor variables as well as allograft ischemic time.
Results: Postoperative hospital stay (Group 1 = 45±32 d, Group 2 = 48±38, P = 0.73) as well as ICU stay was comparable between both groups. Furthermore, we did not observed differences regarding perioperative transfusions of packed red blood cells (Group 1 = 2977±3752 ml, Group 2 = 4086±4364 ml, P = 0.17) and postoperative infections (Group 1: n = 10 (25.0%), Group 2: n = 22 (27.5%), P = 0.83). Acute graft rejection (P = 1.00), postoperative acute kidney injury requiring haemodialysis (P = 0.44), neurological adverse events (P = 0.23) as well as 30-day- (P = 1.00) and 1-year-survival (P = 0.81) were also affected by the CIEPD explantation strategy.
Conclusion: Presence of CIEPD is common in HTx patients. However, the explantation strategy of CIEPD did not affect postoperative morbidity and mortality. Especially, blood transfusions and infective complications are not correlated to the timing of CIEPD explantation.

PO-099 THE IMPACT OF DE-NOVO DONOR SPECIFIC AND – NONSPECIFIC ANTIBODIES ON OUTCOME AFTER HTX

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Introduction: Studies have shown that donor specific antibodies (DSA) have great impact on the clinical course and overall survival of patients after heart transplantation (HTx). De-novo non-DSA (NSA) were associated with graft loss after kidney transplantation, but it remains unclear to what extent NSA play a role in rejection, graft function and overall mortality after HTx. Thus, we analyze the impact of DSA and NSA on outcome after HTx.
Methods: Endomyocardial biopsies were taken after 1, 3, 6 months and yearly for 5 years after HTX, and cardiac allograft vasculopathy (CAV) was evaluated via coronary angiography. Serum HLA-class I and II antibodies were collected for analysis of donor specificity twice yearly. The antibody mean fluorescence intensity (MFI) cut-off values were set at >1000. Study data was collected retrospectively from internal medical records. End points of the study were death of any cause, primary graft failure (PGF), biopsy proven acute cellular rejection (BPACR) ≥2R ISHLT, antibody mediated rejection (AMR), and CAV. Complete data was obtained only from patients with a survival of 12 months or greater.
Results: 69 patients with a follow-up time of 18 months to 6 years after HTx were divided into two groups (G1: no DSA or NSA present, $n = 41$, G2: DSA and / or NSA present, $n = 27$). G2 was further divided into two subgroups, patients with both DSA+NSA ($n = 9$) and only NSA($n = 26$) status.
All-cause mortality was $n = 21$ (30.9%), with significant difference amongst the groups (G1: $n = 17$ (41.5%), G2: $n = 4$(18.4%)). This trend was also seen amongst cardiovascular mortality (G1: $n = 7$ (17.1%), G2: $n = 0$). No statistically significant difference was seen regarding CAV (G1: $n = 3$ (7.3%), G2: $n = 2$ (7.4%)), BPACR (G1: $n = 19$ (27.9%) or G2: $n = 9$ (22%)). Surprisingly, AMR was seen in patients in G1 $n = 3$ (4.4%), but not in G2 ($n = 0$), however, without statistically relevant difference.
Conclusion: Our study shows that a closer monitoring and early adjustment of immunosuppressive therapy including specific antibody treatments are important to preserve graft function in patients with DSA and NSA. The extension of the current study to an even larger and preferably prospective transplant series is clearly required.

PO-100 RISK FACTORS, TREATMENT AND PROGNOSIS OF PATIENTS WITH LUNG CANCER AFTER HEART TRANSPLANTATION

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Introduction: Long-term survival after heart transplantation (HTX) is impacted by adverse effects of immunosuppressive pharmacotherapy. Lung cancer is a common occurrence after HTX. This study aimed to examine the risk factors, treatment, and prognosis of patients with lung cancer after HTX.
Methods: This registry study included 625 adult patients who received HTX at Heidelberg Heart Center between 1989 and 2018. Patients were stratified by diagnosis and staging of lung cancer after HTX. Analysis comprised donor and recipient characteristics, medication including immunosuppressive drugs, and survival after diagnosis of lung cancer.
Results: 41 patients (6.6%) were diagnosed with lung cancer after HTX, 13 patients received curative care and 28 patients had palliative care. Mean time from HTX until diagnosis of lung cancer was 3132.5 ± 1449.4 days and 656.8 ± 970.5 days from diagnosis of lung cancer until last follow-up. Multivariate analysis showed recipient age (HR: 1.05; CI: 1.01–1.10.13; $P = 0.02$), COPD (HR: 3.72; CI: 1.88–7.37.13; $P < 0.01$), and history of smoking (HR: 20.39; CI: 2.73–152.13; $P < 0.01$) as risk factor for lung cancer after HTX. 24 patients (58.5%) were switched to mTOR-inhibitors after diagnosis of lung cancer. Patients in stage I+II had a significantly better 1-year (100.0% versus 3.6%), 2-year (69.2% versus 0.0%) and 5-year survival (53.8% versus 0.0%) than patients in stage III+IV ($P < 0.01$).
Conclusion: Early-stage lung cancer after HTX is associated with a 5-year survival rate of more than fifty percent, while late-stage lung cancer after HTX shows an infaust prognosis.
Acknowledgement: This work was supported by the Physician-Scientist-Program of the Faculty of Medicine, University of Heidelberg (FFD and RR) and the German Heart Foundation/German Foundation of Heart Research (RR).

PO-101 GENETIC VARIANTS IN THE HIF-PATHWAY IN PATIENTS WITH END-STAGE LUNG DISEASE AWAITING LUNG TRANSPLANTATION

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Introduction: Genetic variants in the HIF-pathway are associated with improved adaptation to hypoxia, reduced 30-day mortality in ARDS and the development of pulmonary hypertension (PH)[1,2]. Whether these genotypes should be determined in patients with end-stage lung disease regarding patients' prognosis or treatment is unclear. We tested the hypotheses that 1) SNPs in the HIF-1α or PHD2 genes are common in patients listed for lung transplantation (LTx) and 2) the genetic variants are associated with altered tolerance towards chronic hypoxia.
Methods: 262 patients undergoing LTx were analysed using pretransplant acquired biosamples. Patients' perioperative characteristics, genotypes (Taqman-Genotyping-Assay) and mortality were determined.
Results: *The Hypoxia inducible factor-1α (C/T rs11549465) Polymorphism* is a common genetic variant in patients listed for LTx, with 23.3% T-allel carriers (TT 3.1%, CT 20.2%, CC 76.7%). Patients' clinical characteristics did not differ between groups. There was no impact of this genetic variant on hypoxia-tolerance (mPAP, $P = 0.841$; paO_2, $P = 0.124$; Horowitz, $P = 0.905$) and 90-day-mortality after LTx ($P = 0.859$).
The Prolylhydroxlase 2 (C/T; rs516651) Polymorphism is a common genetic variant in patients listed for LTx, with 23.3% T-allel carriers (TT 0.4%, CT 22.9%, CC 76.7%). In contrast to ARDS patients, there was no impact of this genetic variant on hypoxia-tolerance (mPAP, $P = 0.212$; paO_2, $P = 0.536$; Horowitz, $P = 0.923$) and 90-day mortality after LTx ($P = 0.669$).
The Prolylhydroxylase 2 (T/C; rs480902) Polymorphism is a common genetic variant in patients listed for LTx, with 37.0% T-allel carriers (TT 6.5%, CT 30.5%, CC 63.0%). There was no significant influence of the genetic variation on the tolerance to hypoxia (mPAP, $P = 0.321$; paO_2, $P = 0.662$; Horowitz, $P = 0.467$).Kaplan-Meier analysis showed no influence of this genetic variation on 90-day mortality after LTx ($P = 0.56$).
Conclusion: Genetic variants in the HIF-pathway are common in patients suffering from end-stage lung disease. However, there was no impact on PH, oxygenation and 90-day mortality. LTx represents a complex surgical procedure and thus perioperative outcome parameters may overshadow the impact of genetic variants.
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PO-102 A NEW DRUG DISCOVERY PIPELINE TO OPTIMIZE KIDNEY NORMOTHERMIC MACHINE PERFUSION

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Introduction: Kidney transplantation is the best available therapy for end-stage renal disease. Shortage of organs for transplantation is the main limitation of this life-saving treatment. Normothermic machine perfusion (NMP) is a preservation technique with the potential to increase the number of transplantable organs via reduction of delayed graft function, testing- and inclusion of marginal organs. To date, the cellular effects of machine perfusion are incompletely understood, mostly due to technical drawbacks and limited access to tissue.
Methods: We established a mouse model of kidney NMP showing comparable physiologic- and molecular parameters to human NMP. Investigation of the molecular mechanisms via single-nucleus, bulk RNA sequencing, phosphoprotein analysis, and a combination of imaging techniques showed mitochondrial- and endoplasmic reticulum stress (ER stress) and subsequent initiation of apoptotic, necroptotic, and pyroptotic signaling, mainly in

proximal tubules. Next, we implemented a 3D-printed, high throughput *ex-vivo* mouse kidney slice incubator that mimics mouse kidney NMP by working under closely resembling conditions. Comparison of the incubator to mouse NMP showed similar cellular stress responses and signaling pathway activation.
Results: Testing of drugs predicted to alleviate the identified cellular stress responses in the kidney slice incubator returned two successful candidates, isoproterenol and salubrinal. The most promising drug, the nonselective β-sympathomimetic isoproterenol, was tested in the NMP model. Here, it ameliorated both ER stress and delayed the associated cell death.
Conclusion: In conclusion, we developed a mouse NMP model closely mimicking human kidney NMP, in which we identified cellular maladaptations leading to apoptosis, necroptosis, and pyroptosis. We started testing a drug library in a high-throughput approach aided by a novel kidney slice incubator and identified isoproterenol as a promising drug candidate to delay cell death during NMP. Our findings provide the foundation for future studies aiming to optimize the conditions of kidney NMP, which can in turn increase the number of available organs for transplantation.

PO-103 INSTANT CONTROLLED OXYGENATED REWARMING FOR KIDNEY GRAFTS RECONDITIONING

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Introduction: The possibility for functional improvement of the quality of extended criteria donor (ECD) grafts is essential attainment of the ex-vivo organ machine perfusion. The controlled oxygenated rewarming (COR) has been shown to achieve exceptional results in reconditioning of ECD kidney grafts after static cold-storage as well as demonstrated clear advantage against hypothermic machine perfusion and post-ischemic normothermic machine perfusion
Methods: Controlled oxygenated rewarming has three phases - pre-warming hypothermic perfusion, followed by logarithmic shaped controlled rewarming phase with parallel increase of the perfusion pressure and plateau-reaching phase with constant high temperature and high perfusion pressure. Considering the fact that mitochondria and mitochondrial uncoupling are the major player in the ischemic-reperfusion injury and that abrupt rewarming produce higher degree of such damage we hypothesize that the controlled rewarming have beneficial and protective effect upon mitochondria and mitochondrial function.
Results: We have investigated the importance of the hypothermic prewarming perfusion phase of the COR machine perfusion protocol and mitochondrial function. Through abrogation of pre-rewarming hypothermic perfusion phase we began instantly with the controlled rewarming phase and afterwards the protocol was same as described. The new protocol was named instant controlled oxygenated rewarming or iCOR. The new protocol is 30 minutes shorter compared to COR machine perfusion protocol. iCOR was not inferior compared to COR in energising the cell, protecting from cellular injury at re-perfusion and achieved functional capacity. The mitochondrial coupling was similar between iCOR and COR group. Both iCOR and COR reconditioned grafts had significantly better mitochondrial coupling compared to kidneys been subject to CS.
Conclusion: iCOR is not inferior to COR in energising the cell and prevention reperfusion injury.

PO-104 M1 AND M2 MACROPHAGES FUNCTIONALLY DIFFER WHEN INTERACTING WITH ALLOREACTIVE T-CELLS

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Introduction: Renal allograft rejection is amongst others influenced by the number of allograft infiltrating monocytes. Within the graft, infiltrating monocytes differentiate into macrophages that either have proinflammatory (M1 cells) or anti-inflammatory/ fibrogenic properties (M2 cells). In the present study we assessed if M1 and M2 cells functionally differ in their ability to stimulated alloreactive T-cells.
Methods: To this end, monocytes were cultured in the presence of CSF1 and IFNγ or CSF1 and IL-4 for polarization towards M1 and M2 cells respectively. At day 6 the cells were stimulated by LPS for 24 hrs and hereafter used in mixed leucocyte cultures (MLC) using CytoTell Green (CTG) labelled T-cells obtained from a different donor as responder cells. T-cell proliferation was assessed by CTG dilution as read-out parameter. For cytokine production in MLC supernatants a FACS based multiplex cytokine assays was used.
Results: While proliferation of alloreactive T-cells in MLC was poorly stimulated by M1 cells, a strong production of IL-17A and IFNγ by T-cells was observed. In contrast, M2 cells strongly supported T-cell proliferation but these T-cells produced lower (absolute and relative) amounts of IFNγ and IL-17A. The behaviour of M1 cells in MLC was likely attributed to adenosine signalling as they expressed high levels of CD39 and CD73. Moreover, the conversion of adenosine to inosine by addition of adenosine deaminase mitigated the effect of M1 on proliferation and IL-17A/IFNγ production. T-cell proliferation in MLC, but not anti-CD3 mediated T-cell proliferation, was inhibited by acetylsalicylic acid (ASA). ASA did not affect HLA-DR or CD86 expression on M1 or M2 cells. Supernatants of LPS stimulated M2 -, but not that of M1 cells, could overcome ASA mediated inhibition in MLC.
Conclusion: In conclusion our study demonstrates different functionalities of M1 and M2 cells when interacting with alloreactive T-cells. It also suggests that M1 cells may favour Th subset polarisation towards Th17 or Th1 cells.

KIDNEY TRANSPLANTATION II

PO-106 MONITORING OF SPECIFIC METABOLITES IN PLASMA BY NMR SPECTROSCOPY UNDER NORMOTHERMIC MACHINE PERFUSION (NMP) OF PORCINE KIDNEYS WITH WHOLE BLOOD

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Introduction: Due to the shortage of donor kidneys, the use of so-called "marginal organs" is steadily gaining importance. To assess the transplantability of such organs, it is essential to obtain additional information besides the available routine parameter data. Not only NMP can contribute to this, but also the measurement of certain metabolites in blood and urine.
Methods: Within the framework of the project "ASYS-Transplant", porcine kidneys were examined under NMP with whole blood. Several parameters for the assessment of the organ condition were investigated in order to be able to predict their transplantability.
In parallel, first plasma samples of organs macroscopically assessed as "transplantable" under perfusion for 4 hours were compared with those of organs classified as “unusable” by metabolomics using NMR spectroscopy in order to derive possible biomarkers and metabolic signatures for kidney injury.
Results: To date, 52 blood samples from a total of 12 machine-perfused porcine kidneys have been examined and evaluated. 7 of these kidneys were clinically assessed as "transplantable" and 5 as "unusable". Statistical analysis of metabolic profiles showed significant differences between the two groups. Glutamine for example increased in unusable kidneys during NMP whereas it decreased in transplantable ones. Even at the time of kidney collection, metabolites such as lactate, pyruvate and glutamine could already distinguish between "transplantable" and "unusable" kidneys.
Conclusion: The initial investigations to date suggest that early indications of the functionality of a donor organ may already be found when examining plasma from the organ donor by NMR spectroscopy. When transferred into a human setting, this could generate a tool that might be used to classify marginal donor organs at an early stage. Hopefully further studies in the field of NMP of kidneys in large animal models will confirm the initial results obtained.
Acknowledgement: The project "ASYS-Transplant" is funded by the European Union and the European Regional Development Fund (EFRE) and the Free State of Saxony (SAB; project no. 100382963).

PO-108 HLA-DERIVED EPITOPE MISMATCHING MAY PROVE USEFUL AS A PREDICTIVE BIOMARKER AMONG KIDNEY TRANSPLANT RECIPIENTS WITH REJECTION: AN ANALYSIS OF INDICATION AND FOLLOW-UP BIOPSIES

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Introduction: Indication biopsies due to a deterioration of kidney allograft function often require follow-up biopsies to assess treatment response or lack of improvement. Immune-mediated injury, namely borderline rejection,

T-cell mediated rejection (TCMR), or antibody-mediated rejection (ABMR), results from preformed or de novo alloreactivity due to donor and recipient HLA mismatches. The impact of HLA mismatches on alloreactivity is determined by the total HLA-epitope load that can be calculated using the Predicted Indirectly Recognizable HLA Epitopes (PIRCHE) algorithm.
Methods: We analyzed 123 kidney transplant recipients (KTRs) from 2009-2019 who underwent a first indication biopsy and a follow-up biopsy performed within a median of 3 months. We divided the KTRs into three groups according to the first biopsy: (1) No rejection/borderline (n = 68); (2) TCMR (n = 21); (3) ABMR (n = 34). KTRs with ABMR were subdivided into three groups according to the microvascular inflammation score (MVI). The HLA-derived epitope-mismatches were calculated using the PIRCHE algorithm.
Results: Group 1 (no rejection/borderline): KTRs with higher total PIRCHE scores were more likely to develop TCMR in the follow-up biopsy (P = 0.024). Interestingly, these differences were significant for both, HLA-class 1 (P = 0.015), and HLA-class 2 (P = 0.013). No differences were observed for those KTRs developing ABMR in the follow-up biopsy. Group 2 (TCMR): KTRs with ongoing TCMR in the follow-up biopsy were more likely to show higher total PIRCHE scores (median 101.50 vs 74.00). Group 3 (ABMR): KTRs with higher total PIRCHE scores were more likely to show an increase of the MVI score in the follow-up biopsy. This difference was more pronounced for the HLA-class II (median 70.00 vs. 31.76; P = 0.086).
Conclusion: PIRCHE scores may prove useful as a biomarker to predict the histopathological changes of immune-related injury from a first indication biopsy to a follow-up biopsy. This immunological risk stratification may contribute to individualized treatment strategies.

PO-109 AFTERCARE BY EXTERNAL NEPHROLOGISTS SUGGESTS EXCELLENT OUTCOMES REGARDING GFR DECLINE AND PROTEINURIA, WHEREAS AFTERCARE BY THE TRANSPLANT CENTER ENSURES PROMPT BIOPSY-CONFIRMED DIAGNOSES OF ALLOGRAFT DYSFUNCTION

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Introduction: Despite substantial medical progress, median kidney allograft survival remains stable at 13 to 15 years. However, whether and to what extent the transplant center's follow-up of kidney transplant recipients (KTRs) influences long-term outcomes, compared to external aftercare, is still unclear.
Methods: We analyzed 586 KTRs from 2009 to 2019, showing kidney allograft survival of at least 24 months and not developing rejection within the first year post-transplant. All KTRs underwent aftercare in the transplant center for at least 12 months. After that, KTRs were either followed three-monthly in the transplant center (n = 224) or three-monthly by external nephrologists, thus only yearly in our center (n = 362). We analyzed kidney allograft outcomes regarding allograft survival, kidney function, GFR decline, proteinuria, de novo DSA, and rejection.
Results: No differences in pre- and post-transplant characteristics were observed at 12 months post-transplant. Particularly, baseline GFR and proteinuria were comparable at 12 months post-transplant. Interestingly, GFR decline was -0.9ml/min/year among KTRs followed in the transplant center compared to -0.3ml/min/year among KTRs followed by external nephrologists (P = 0.043). In addition, proteinuria was lower among KTRs followed by external nephrologists over a 5-year period (P < 0.05). While no differences were observed for the development of de novo DSA (P = 0.704), KTRs followed in the transplant center were more likely to undergo indication biopsies to evaluate any cause of kidney allograft dysfunction (P < 0.001).
Conclusion: Our findings suggest that the quality of medical follow-up is independent of the caregiver. The observed better progression of renal function with external follow-up suggests more individualized care due to greater familiarity between patient and physician. For patients with complications, care by the transplant center is crucial, as prompt biopsies may lead to immediate treatment adjustment and prevent more severe courses.

PO-110 VASCULAR ANASTOMOSES AND ARTERIAL RECONSTRUCTIONS IN KIDNEY TRANSPLANTATION

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Introduction: Kidney transplantation (KT) is the therapy of choice for end-stage renal disease (ESRD). Multiple donor arteries and vascular reconstructions may be challenging in KT. We analyzed the effects of vascular reconstructions and different arterial insertion sites with regard to postoperative complications, patient and graft survival.
Methods: Between 2010 and 2016 a total of 612 KTs were performed at the Department of Surgery of the Charité University Hospital, Berlin, Germany. Of these, 336 post-mortem KTs were included in the analysis. Anatomical variants, insertion sites and vascular reconstructions were examined for the occurrence of complications, and 1-year patient and graft survival.
Results: The type of graft anastomosis [to the common iliac artery (AIC, n = 126) and to the external iliac artery (AIE, n = 208)] showed no significant influence on graft survival. Postoperative bleeding occurred 2.5 times more often in anastomoses to the AIC than to the AIE. Complex arterial reconstructions (reinsertion of the superior/inferior pole vessels; fusion of the renal arteries on the aortic patch; anastomosis on a vascular prosthesis, usage of a bovine pericardium neopatch or a vascular conduit) showed no negative effects on patient and graft survival in the univariate survival analysis (p = 0.806). In the multivariate survival time analysis, a body mass index (BMI) ≥30 kg/m2 of the recipient (p = 0.031) and the presence of atherosclerosis in the recipient (p = 0.026) were found to be significant predictors of reduced graft survival.
Conclusion: Vascular reconstruction in KT is safe even in very complex vascular anatomies. Anastomoses of the graft artery to the AIC were associated with an increased risk of bleeding. Recipient´s age ≥ 65 years of age was associated with a higher likelihood for vascular reconstruction.

PO-111 PREDICTORS OF DELAYED GRAFT FUNCTION IN RENAL TRANSPLANTATION

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Introduction: Delayed graft function (DGF) is a frequent occurrence in renal transplantation. The reasons for DGF are poorly understood but it is clear that these are likely to be multifactorial. There is no valid treatment for DGF and clinically, there is no real alternative to being patient.
This study was undertaken to analyze factors associated with DGF in our center in order to avoid identifiable risk factors for DGF as far as possible.
Methods: This is a retrospective case-control study of all patients transplanted in our center over a period of 11 years (January 1, 2003 to December 31, 2014) comparing patients with immediate graft function (n = 332) to those with delayed graft function (n = 165). DGF was defined as the need for hemodialysis within the first seven days after transplantation. Donor and recipient characteristics as well as procedural factors were compared by univariate and multivariate logistic regression analyses.
Results: Overall, 33% patients had DGF. The rate of DGF declined from 2003 to 2011. In cases with DGF, donors and recipients were significantly older (P = 0.004 and P = 0.005, respectively), had longer cold ischemia times (P = 0.039), more revision surgeries (P < 0.001) and more HLA mismatches (P = 0.001), especially in the DR locus (P = 0.002). Neither donor nor recipient gender, waiting time nor CMV status had any influence. In multivariable analysis, significant risk factors were ischemia time and mismatches at the HLA-DR loci.
Conclusion: DGF is a common complication in renal transplantation which occurred in 33% of our cases. Important factors identified were donor and recipient age, ischemia time, HLA mismatching and revision surgery.
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PO-112 DIFFERENTIAL EFFECTS OF *CYP3A4*22* AND *POR*28* ON TACROLIMUS METABOLISM AND ALLOIMMUNIZATION AFTER KIDNEY TRANSPLANTATION IN CONTRAST TO *CYP3A5* GENOTYPE

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Introduction: In our previous work we saw a significant effect of *CYP3A5* expresser status on the development of *de novo* donor-specific antibodies (DSAs) and antibody-mediated rejection (ABMR). Besides CYP3A5, other enzymes such as CYP3A4 and POR are involved in the tacrolimus metabolism. The impact of single nucleotide polymorphism (SNPs) in the genes of CYP3A4 and POR on alloimmunization after kidney transplantation is less understood. .
Methods: We retrospectively studied 400 kidney transplant recipients treated with a tacrolimus-based immunosuppression regimen to detect *CYP3A4*22* and *POR*28* and to analyze the association of the two SNPs with clinical outcome up to 5 years after transplant.
Results: In 38 (10%) recipients expressing *CYP3A4*22* significantly higher concentration-to-dose ratios of tacrolimus than in nonexpressers were observed in the first six months posttransplant. Concentration-to-dose ratios of tacrolimus were comparable in 35 (9%) homozygous expressers of *POR*28*, 158 (40%) heterozygous expressers and nonexpressers. *CYP3A4* and *POR* genotypes had no impact on the development of *de novo* DSAs, allograft failure and rejection. Indeed, *de novo* anti-HLA antibodies occurred more frequently and *de novo* anti-HLA antibody free-survival rates were significantly decreased in homozygous carriers of *POR*28*. Coexpression of *CYP3A4*22* with *CYP3A5* genotype was detected in only 4 (1%) recipients. Coexpression of *POR*28* with *CYP3A4* in 23 (6%) recipients and with *CYP3A5* genotype in 31 (8%) recipients, respectively, was not associated with significant changes in concentration-to-dose ratios of tacrolimus. *CYP3A5* expressers with *POR*28* showed similar rates of *de novo* DSAs, *de novo* anti-HLAs and rejection as recipients having only the *CYP3A5* genotype. Regarding separately the subgroup of *CYP3A5* nonexpressers, a significantly increased number of patients with *de novo* DSAs and *de novo* anti-HLAs was found among recipients homozygous for *POR*28* compared to *POR*28* nonexpressers.
Conclusion: Our results indicate a little effect of the SNPs, *CYP3A4*22* and *POR*28* on alloimmunization and occurrence of ABMR compared to *CYP3A5* genotype. Coexpression of *POR*28* had no synergistic effect on *CYP3A5* genotype.

PO-115 ESTIMATING THE EXPECTED SERUM CREATININE RANGE MAY IDENTIFY KIDNEY TRANSPLANT RECIPIENTS WITH ALLOGRAFT DYSFUNCTION

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Introduction: Many clinicians struggle to assess the expected kidney allograft function. While falling creatinine levels usually rule out allograft dysfunction, stable creatinine levels may represent a state of allograft dysfunction that requires histopathologic evaluation.
Methods: Al-Sehli *et al.* created a formula predicting the expected creatinine range, considering recipient and donor criteria and the adaptability of a single kidney. This formula was applied to 250 living donor (LD) and 390 deceased donor (DD) kidney transplant recipients (KTRs) from 2009 to 2019. KTRs were classified as falling below, within, or above the expected range.
Results: 222 LD KTRs (88.8%) and 292 DD KTRs (74.87%) fell below or within the expected range, while 28 LD (11.2%) and 98 DD (25.13%) KTRs exceeded it ($P < 0.001$). KTRs exceeding the expected range had a lower donor to recipient body weight ratio ($P < 0.001$) and more likely received a DCD kidney allograft ($P = 0.0025$). Post-transplant complications like DGF, vascular or urological complications, TCMR/ABMR, CMV, EBV, or BKV infection did not explain the classification of KTRs above the expected range ($p>0.05$). The lowest observed serum creatinine of DD KTRs falling below or within the expected range was 93 μmol/l (median, range 24-202μmol/l) and 104μmol/l (46-264μmol/l) for DD KTRs falling above the expected range ($P < 0.05$). Interestingly, the number of DD KTRs with baseline proteinuria >200mg/mmol*10 was higher among KTRs exceeding the expected range (19.6% vs. 9.00%; $P = 0.0095$). GFR decline was lowest among DD KTRs falling below the expected range (0.6ml/min/year vs. 0.9ml/min/year).
Conclusion: The greater number of DD KTRs exceeding the expected range may be explained by more ischemia-reperfusion injury and susceptibility to immune-related injury compared to LD KTRs. The observed higher baseline proteinuria and faster GFR decline in a subgroup of DD KTRs exceeding the expected range suggests an underlying pathology. If the expected range is not reached, an indication biopsy may clarify if this classification is meaningful.

PO-116 OSTEOPROTEGERIN IS AN INDEPENDENT RISK FACTOR PREDICTING DEATH IN STABLE RENAL TRANSPLANT RECIPIENTS

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Introduction: Vascular calcification is common in chronic kidney disease and is associated with significant cardiovascular morbidity and mortality. One of the important factors regulating vascular calcification is osteoprotegerin (OPG). There are, however, limited data on the impact of OPG on all-cause mortality and graft loss in kidney transplant recipients so far. Given its impact on vascular calcification, the aim of our study is to analyze whether OPG was a risk factor of all-cause mortality and graft loss in 600 stable kidney transplant recipients.
Methods: 600 stable renal transplant recipients (367 women, 233 men) were followed for all-cause mortality and graft loss for 3 years. Blood and urine samples for analysis and clinical data were collected at study entry. We performed Kaplan-Meier survival analysis and Cox regression models considering confounding factors such as age, estimated glomerular filtration rate (eGFR), cold ischemia time, HbA1c, phosphorus, calcium, and albumin.
Results: 65 patients died, and 38 patients had graft loss during the observation period. The OPG baseline concentrations had no effect on graft loss, whereas Kaplan-Meier survival curve showed that baseline plasma OPG concentrations were associated with all-cause mortality in stable kidney transplant recipients ($p < 0.0001$, log-rank test). After multiple Cox regression analysis assisting for age, eGFR, cold ischemia time, HbA1c, phosphorus, calcium, and albumin, plasma levels of OPG remained an independent predictor of all-cause mortality (HR, 1.181; 95% CI 1.035 – 1.347; $p = 0.014$).
Conclusion: Baseline plasma OPG is an independent risk factor for all-cause mortality but not graft loss in patients after kidney transplantation.
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COVID-19 AND TRANSPLANTATION

PO-119 AFTER FULL (TWO TIMES) VACCINATION WITH COMIRNATY®, 28% OF LIVER OR KIDNEY TRANSPLANTED PATIENTS HAD NO T-CELL-REACTIVITY AGAINST SARS-COV-2 SPECIFIC ANTIGENS

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Introduction: Patients after organ transplantation are exposed to a higher risk of infections. Therefore, patients under immunosuppressive medication were prioritized for SARS-CoV-2 vaccination in spring 2021. Antibody data suggests that the immune response to SARS-CoV-2 vaccination under immunosuppression is low. Therefore, we evaluated the cellular immune response in a cohort of kidney (KTX) and liver (LTX) transplant patients.
Methods: Until now, we included 17 patients four weeks after first vaccination (10 LTX, 7 KTX) and 18 patients (2 LTX and 16 KTX) four weeks after second vaccination with COMIRNATY®. T-cell-reactivity was investigated with an IL-2 and IFN-γ ELISpot against SARS-CoV-2 antigens (AID CoV-iSpot SARS-CoV-2 EliSpot Assay).

Results: After first vaccination, 10/17 patients revealed no T-cell reactivity. After the second vaccination, 5/18 patients did not show any T-cell reactivity against SARS-COV-2 antigens, three patients developed IL-2 response only and ten patients were positive for IL-2 and INF-γ producing T-cells.
Conclusion: After the first vaccination with COMIRNATY®, more than half of the kidney and liver transplanted patients evaluated did not show any T-cell response against SARS-CoV-2 antigens, whereas after the second vaccination, 28 % of the patients still did not develop a T-cell response. Our data might lead to the assumption that about 1/3 of our transplant patients are not sufficiently protected against SARS-CoV-2 after full vaccination with COMIRNATY®. Antibody data on these patients is under preparation.

PO-120 CELLULAR IMMUNITY PREDOMINATES OVER HUMORAL IMMUNITY AFTER THE FIRST DOSE OF COVID-19 VACCINES IN SOLID ORGAN TRANSPLANT RECIPIENTS

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Introduction: Knowledge on the vaccine-induced cellular and humoral immunity and on immunogenicity of vector-based and mRNA vaccines against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in solid organ transplant recipients is limited.
Methods: Therefore, SARS-CoV-2 specific T-cells and antibodies were analyzed in 40 transplant recipients and 70 age-matched controls after the first dose of vector-based (ChAdOx1) or mRNA vaccines (BNT162b2 or mRNA-127). Plasmablasts and SARS-CoV-2 specific CD4 and CD8 T-cells were quantified using flow-cytometry. Specific antibodies were analyzed by ELISA and neutralization assay.
Results: SARS-CoV-2 specific antibodies and T-cells were induced in both groups with significantly lower levels in transplant recipients. While antibodies were detected in 80% of controls and 5.3% of patients, specific CD4 and/or CD8 T-cells were more frequently found in both controls (84.3%) and patients (23.7%). The two vaccine types showed notable differences, as IgG and neutralizing activity were more pronounced after mRNA vaccination ($P < 0.0001$ each), whereas CD4 and CD8 T-cell levels were higher after vector vaccination ($P = 0.009$; $P < 0.0001$). Plasmablast numbers were significantly higher in controls and correlated with SARS-CoV-2 specific IgG- and CD4 T-cell levels.
Conclusion: In conclusion, assessment of antibodies is not sufficient to identify COVID-19-vaccine responders. Together with differences in immunogenicity among vaccines, this necessitates combined analysis of humoral and cellular immunity to reliably assess responders among immunocompetent and immunocompromised individuals.

PO-121 ASSESSING HUMORAL AND CELLULAR SARS-COV-2 SPECIFIC IMMUNE RESPONSE IN TRANSPLANT RECIPIENTS TREATED WITH CASIRIVIMAB/IMDEVIMAB FOR ACUTE SARS-COV-2 INFECTION

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Introduction: Neutralizing monoclonal antibodies directed against the spike protein of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) are promising in the treatment of risk patients with mild to moderate Coronavirus disease-2019 (COVID-19). However, clinical experience in the treatment of organ transplant recipients is limited. Moreover, it remains unclear how antibody administration influences adaptive immunity towards SARS-CoV-2 and how it can be characterized after passive immunization.
Methods: Two transplant recipients suffering from mild COVID-19 were treated with Casirivimab/Imdevimab in our transplant center. SARS-CoV-2 specific antibodies were detected by ELISA and chemiluminescence microparticle immunoassay (CMIA). Plasmablasts and SARS-CoV-2-specific CD4 and CD8 T-cells were quantified using flow-cytometry. SARS-CoV-2 infection was proven by RT-PCR from nasopharyngeal swabs. Viral load was estimated with cycling time of RT-PCR.
Results: Standard serologic testing detecting anti-spike protein IgG was impaired by antibody treatment. But SARS-CoV-2-specific T cells could readily be detected recognizing spike antigen (CD4 T cells) as well as NCAP (CD8 T cells) which is expressed by virus-infected human cells. Plasmablasts which indicate plasma cell differentiation, were detectable in one patient. He had higher initial viral load at diagnosis and progressed to severe COVID-19. The other patient with low initial viral load and less risk factors for progression recovered quickly without development of plasmablasts.
Conclusion: To conclude, after monoclonal antibody treatment adaptive immunity towards SARS-CoV-2 can be assessed by detection of SARS-CoV-2 specific T cells. Detection of SARS-CoV-2-specific cellular immune response in combination with differences in plasma cell differentiation indicated by plasmablasts may influence long term immunity towards SARS-CoV-2 and consequently vaccination policy of immunocompromised individuals passively immunized with monoclonal antibodies.

PO-122 INCREASING DIAGNOSTIC ACCURACY IN RENAL TRANSPLANT PATIENT WITH ACUTE COVID-19 AND GRAFT FAILURE BY T CELL ANALYSIS IN PERIPHERAL BLOOD AND BIOPSY

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Introduction: Several lines of evidence suggest that the novel coronavirus SARS-CoV-2 can infect the human kidney and induce acute renal or renal transplant (RTx) injury. Due to the focal occurrence within the RTx, the histology can miss the infected area providing thereby false negative results. Here, we present an application of two modern diagnostic technologies in a case of a living-related RTx patient hospitalized due to COVID-19 induced pneumonia followed by acute transplant failure.
Methods: SARS-CoV-2- and donor-reactive T-cells were evaluated in peripheral blood after stimulation with SARS-CoV-2 peptides and lysates of donor PBMCs. In parallel, kidney infiltrating T-cells were evaluated in a biopsy by multiparametric flow cytometry after stimulation with SARS-CoV-2 peptides. In addition, T-cell receptor (TCR) sequences of the SARS-CoV-2 and allograft-specific T-cells in peripheral blood were extracted by means of next generation sequencing. These were compared to the TCRs of the graft infiltrating T-cells to identify the clonal specificity of these T cells.
Results: A large degree of CD3+ T cell infiltration was found in the biopsy, however acute rejection was ruled out by pathological findings. Furthermore, in situ hybridization showed no SARS-CoV-2 indicating no renal SARS-CoV-2 infection. Flow cytometric analyses showed that in contrast to the substantial level of SARS-CoV-2 specific T-cells in the peripheral blood, none were observed in the biopsy. In addition, there were no measurable levels of allograft-reactive T-cells either in the peripheral blood or in the biopsy.
Conclusion: The applied technologies ruled out transplant rejection and SARS-CoV-2-related graft function deterioration suggesting unspecific T cell infiltration due to bystander activation. Analyzing SARS-CoV-2-reactive and donor-reactive T cells in peripheral blood and in kidney transplant biopsy can improve diagnostic accuracy enabling differential diagnosis and personalized therapy.

PO-123 INITIAL EXPERIENCE WITH SARS-COV-2-NEUTRALIZING MONOCLONAL ANTIBODIES IN KIDNEY OR COMBINED KIDNEY-PANCREAS TRANSPLANT RECIPIENTS

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Introduction: In contrast to convalescent plasma for treatment of COVID-19, "off-the-shelf" epitope-specific monoclonal antibodies (moAbs) are readily used and might exert more reliable efficacy. Two compounds have

received an FDA emergency-use authorization: Bamlanivimab (BAM) is a neutralizing IgG1 moAb targeting the receptor binding domain (RBD) of the spike protein. Casivirimab and imdevimab (CA/IM) are two moAbs directed against two different RBD epitopes. Solid organ transplant (SOT) recipients are at high risk to develop severe COVID-19 due to their immunosuppression.
Methods: We queried our electronic patient database "Tbase" up to April 30, 2021, for SOT recipients with a positive SARS-CoV-2 PCR who received moAbs (700mg BAM or 1200mg CA/IM). We collected clinical outcomes, medication history, lab values, and anti-SARS-CoV-2 antibodies (IgA + IgG). The co-primary endpoints were hospitalization rate and viral response
Results: We identified 11 SOT recipients with a median age of 55 (range, 30-64 years). They were diagnosed with SARS-CoV-2 at a median of 64 (range, 15-276) months since SOT. At that time, 8 (72.3%) pts were on triple while 3 (27.3%) had a steroid-free immunosuppression regimen. Median interval from diagnosis to treatment was 1 (range, 1- 30) days and median follow-up 43 (range, 14-67) days. Three pts were already hospitalized at rescue moAb dosing. Dialysis was required for 2 (18.2%) pts. BAM was administered to the first 8 (including all 3 hospitalized) and CA/IM to 3 pts. Neither infusion-related reactions nor renal-connoted events were seen. SARS-CoV-2 PCR became negative in 5/7 evaluable patients after a median of 20 days (range, 18-35). One patient with initial viral clearance relapsed later on and died due to COVID-19. Two further BAM pts died (COVID-19, refractory PTLD+COVID-19). The eight remaining pts had early diagnosis and mild symptoms with no hospitalizations.
Conclusion: Our initial experience with moABs in SOT recipients with COVID-19 suggests good efficacy and excellent tolerability. In contrast to rescue treatment, early administration was efficacious in prevention of severe COVID-19 and only 1/8 pts with early negative PCR developed fatal COVID.

PO-125 KIDNEY TRANSPLANTATIONS DURING COVID-19 PANDEMIC WITH INCREASED REJECTION RATES

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Introduction: The potential risk of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection and adverse courses for recently transplanted recipients led to adaptions of kidney transplantation programs in many transplant centers during the coronavirus disease-19 (COVID-19) pandemic. First reports indicate similar outcomes of kidney transplantations in countries with extensive decreases in transplantation numbers, but modification and consequences in countries with a rather stable volume of transplant procedures remain unclear.
Methods: This retrospective cohort study investigates activity, handling and outcomes of kidney transplantations performed during early COVID-19 pandemic, from March 15th to September 30th, in Germany based on insurance data of the Allgemeine Ortskrankenkassen (AOK). Data was compared to the corresponding period in 2019.
Results: 317 patients with a kidney transplantation performed during early COVID-19 pandemic were identified, translating into a 10.7% decline in transplant activity compared to 2019. No change in age, sex or comorbidities of recipients nor in the proportion of living donor, blood type incompatible or multiorgan transplantations occurred. Usage of rabbit antithymocyte globulin (rATG) remained stable (8.2% in 2020 vs. 6.5% in 2019, $p = 0.391$). Transplant hospital stay was 2.1 days shorter in 2020 and steroid use in early maintenance therapy decreased (86.1% vs. 93.5%, $p = 0.001$). Rates of delayed graft function remained stable, but re-admissions and early allograft rejections increased (65.6% vs. 55.8% for re-admissions and 22.7% vs. 14.4% for rejections). There was a nonsignificant trend to increased re-dialysis rates after transplantation (7.3% vs. 5.9%, $p = 0.483$). Admissions for cardiovascular diseases and all-cause mortality were unchanged. There was only one confirmed SARS-CoV-2 infection.
Conclusion: Activity, and management of kidney transplantations during the COVID-19 pandemic remained virtually stable. This perpetuation was overall safe and did not increase SARS-CoV-2 infection risk. Higher re-admission and rejection rates raise concern that transplant care was not yet balanced between COVID-19 avoidance and maintaining graft care.

PO-127 PSYCHOSOCIAL SITUATION, ADHERENCE, AND UTILIZATION OF VIDEO CONSULTATION IN YOUNG ADULT LONG-TERM PEDIATRIC LIVER TRANSPLANT RECIPIENTS DURING COVID-19 PANDEMIC

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Introduction: Young adults who underwent liver transplantation in childhood (YALTs) are highly vulnerable to non-adherent behavior and psychosocial problems. During the Covid-19 pandemic, special efforts may be necessary to maintain contact with these patients and to offer support. This can be achieved through the use of telemedicine. The study's objective was to assess adherence and the psychosocial situation of YALTs during the Covid-19 pandemic in Germany and to evaluate the utilization of video consultations.
Methods: In May 2020, a questionnaire was sent to 98 YALTs treated at the Hamburg University Transplant Center, accompanied by the offer of video appointments with the attending physician. The questionnaire included the Generalized Anxiety Disorder Scale 7, the Patient Health Questionnaire 2, and questions compiled by the authors.
Results: Of the 98 YALTs, 65% used in-person appointments only, and 12% accepted the video consultation offer. The 56 patients who completed the questionnaire did not report reduced medication adherence during the pandemic, but 40% missed follow-up visits with their primary care physician or check-up laboratory tests. About 70% of YALTs were afraid to visit their physician and the transplant center, and 34% were afraid of a SARS-CoV-2 infection. Overall mental health and well-being were unimpaired.
Conclusion: During the Covid-19 pandemic, YALTs in our study did not show an increased need for psychosocial support, but a majority were afraid to attend to medical visits and reported low appointment adherence. Nevertheless, acceptance of video consultations was lower than expected. The reasons for this need to be further investigated in order to optimize care.

PO-128 REDUCED HOSPITAL ADMISSIONS AND IMMUNOSUPPRESSION IN KIDNEY TRANSPLANT RECIPIENTS DURING COVID-19 WITHOUT ADVERSE CONSEQUENCES

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Introduction: The coronavirus disease 19 (COVID-19) pandemic was associated with substantial changes in medical care and supply. Declines in hospital admissions for cardiovascular diseases as well as redemption of cardiovascular drugs in the general population raise concern regarding medical care of kidney transplant recipients.
Methods: This retrospective cohort study constitutes of nationwide claim data of the Allgemeine Ortskrankenkassen (AOK). Kidney transplant recipients with transplantation at least 12 months earlier and functioning graft were investigated for hospitalization, in-patient treatment and redeemed outpatient prescriptions from March 15th to September 30th, 2020 and compared to the corresponding period in 2019.
Results: 7.503 kidney transplant recipients were identified in 2020 and compared to a randomly chosen similar-sized subset of 7.725 patients for 2019. Hospital admissions declined in 2020 by 16.8% with a main dip during a 3-month lockdown and without subsequent rebound. Hospital stay length, rates of intensive care treatment, ventilation, or dialysis were similar between years and did not increase during or after lockdown. Incidences of pulmonary infections declined (2.1% for 2019, 1.5% for 2020, $P < 0.001$), but no change in cardiovascular diseases or allograft rejections occurred. In-hospital mortality increased (2.1% vs. 3.0% $P = 0.026$), but this was driven by COVID-19 (13 of 92 deaths). Overall mortality remained unchanged. Redemption of angiotensin converting enzyme-inhibitors, tacrolimus, cyclosporine and steroids doses declined in 2020 (-5.7%, $P = 0.024$, -5.3%, $P < 0.001$; -4.0%, $P = 0.008$ and -2.3%, $P = 0.012$).
Conclusion: Hospital admissions decreased, and immunosuppression was slightly reduced in kidney transplant recipients during COVID-19 pandemic without serious adverse consequences. Overall short-term risk is mainly governed by COVID-19 rather than collateral effects of the pandemic.

PO-129 LIVER TRANSPLANTATION IN A CASE OF SCLEROSING CHOLANGITIS SECONDARY TO COVID-19

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Introduction: Transplant programs worldwide have been seriously affected by Coronavirus disease 2019 (COVID-19) as a global pandemic with unprecedented extent. Liver injury has been reported in patients with COVID-19 especially in those suffering of severe courses. Herein, we report a case of sclerosing cholangitis (SSC) secondary to Sars-Cov-2 infection, who underwent successful liver transplant.
Methods: The recipient was a 49 yoa male (BMI: 38) with the medical history of type II diabetes, arterial hypertension and COPD. He presented with severe ARDS due to Sars-Cov-2 infection. Being admitted to ICU in November 2020 and developing multi-organ-failure due to pulmonal sepsis he required ventilation for 40 days and intermittent dialysis. Developing persistent hyperbilirubinemia he was diagnosed with SSC two months after initial diagnosis of COVID-19. Within 8 weeks liver biopsies detected a progress of liver fibrosis and constant cholangitis. The patient was listed for liver transplant (lab-MELD 30). A DBD graft was allocated (43 years, DRI 1.47). Liver transplant was performed following normothermic machine perfusion for 20 hours and 35 minutes with subsequent simultaneous reperfusion.
Results: Besides a suspected rejection successfully treated with a steroid pulse, there was no sign of COVID-19 related graft dysfunction. At 2 months follow up the patient showed recovering constitution, normal transaminases and bilirubin with good liver function and no suspicion of rejection. Repeated Sars-COV-2-PCRs were negative.
Conclusion: COVID-19 is a pandemic virus with enormous impact on healthcare systems worldwide including transplant medicine. The perioperative care of solid organ transplant recipients after severe Sars-CoV-2 infection poses challenges and the long-term effect of immunosuppression on recovered COVID-19 patients has yet to be observed. Our present data supports, that despite these challenges solid organ transplantation in recovered COVID-19 patients is possible and shows promising results. The risk of Sars-COV-2 re-infection in immunosuppressed patients remains uncertain.

PO-130 SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS TYPE 2 (SARS-COV-2-) SPECIFIC CELLULAR AND HUMORAL IMMUNITY IN CORONAVIRUS DISEASE-2019 (COVID-19) CONVALESCENCE AFTER LIVER TRANSPLANTATION

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Introduction: Mortality due to COVID-19 is not increased in immunosuppressed individuals after orthotopic liver transplantation (OLT) compared to individuals without immunosuppression. Data on protective immunity against SARS-CoV-2 in immunosuppressed convalescents, especially after mild COVID-19, are limited. The aim of the study was to assess the immune response in COVID-19 OLT convalescents with ongoing immunosuppressive therapy.
Methods: Immune responses were measured prospectively in 23 OLT convalescents at the first outpatient visit after COVID-19, in comparison to matched non-immunosuppressed convalescents (non-IS-Con, $n = 24$ for cellular and $n = 11$ for humoral immunity). SARS-CoV-2-specific T cell reactivity was detected by IFN-γ ELISPOT. SARS-CoV-2-specific antibodies (IgG/A/M) were detected against four different SARS-CoV-2 antigens (S1/2, RBD, nucleocapsid).
The majority of OLT patients (22/23) had a mild or moderate COVID-19 and were managed as outpatients (18/23). At the first outpatient visit liver function tests and liver stiffness measurements were not suggestive for increased alloreactivity.
Results: Anti-SARS-CoV-2 IgA and IgG antibodies were detectable in 62-100%, IgM in 31-100% of OLT convalescents. Anti-SARS-CoV-2 IgG antibodies of OLT convalescents were not reduced, neither in frequency nor in concentration, compared to non-IS-Con. None of these OLT recipients with available pre-pandemic samples ($n = 12$) had preexisting anti-SARS-CoV-2 IgG, but some had preexisting IgA with cross-reactivity against antigens. OLT convalescents had no reduced IFN-γ production, normalized to numbers of PBMCs and T cells against SARS-CoV-2 compared to non-IS-Con. No T cell reactivity could be detected in pre-pandemic samples.
Conclusion: The study complements the data sets on cellular and humoral immunity of immunosuppressed COVID-19 convalescents by showing a robust and indistinguishable cellular and humoral immunity against SARS-CoV-2 also after mild/moderate infections without hints for a decline of cellular immunity. The development of a robust immunity without triggered rejection might justifies the continuation of immunosuppression during infection.

PO-133 COVID-19: CHALLENGE AND CHANCE - HIGHER APPROVAL RATES AND EFFICIENCY IN ORGANISATION ENCOURAGE CORNEAL TISSUE DONATION AND TRANSPLANTATION EVEN IN A PANDEMIC

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Introduction: SARS-CoV-2 (corona virus) presents the world with new kinds of challenges. The crisis mode that persisted in many countries also put a strain on the German health system: on the one hand, through the treatment of patients infected with corona, but on the other hand also through the cancellation and postponement of elective operations. This had a corresponding impact on tissue donation and transplantation.
Methods: The effects of the pandemic-related restrictions can be reflected by the rate of corneal donation in the DGFG network: With the beginning of the first closure, donations and transplants decreased by almost 25% from March to April 2020. After a recovery during summer, the activities were again restricted from October onwards due to increasing infection numbers.
The already careful screening of potential tissue donors was expanded in accordance with the guidelines of the Paul-Ehrlich-Institute. However, this important measure led to an increase in discontinued donations due to medical contraindications from 44% in 2019 to 52% in 2020. At the same time, there is an ongoing discussion whether the virus could be transmitted from donor to recipient through corneal transplantation and what risk is associated with it.
Results: Nevertheless, the donation and transplantation result from 2019 was exceeded and DGFG was able to maintain patient care on stable level compared to other European countries. This positive result is mainly due to an increased consent rate of 41% in 2020 due to a higher sensitivity in the population to health issues during the pandemic. According to current scientific knowledge and official guidelines, there is no evidence of viable virus in ocular tissues, and no cases of transmission of SARS-CoV-2 via tissue preparations have been reported.
Conclusion: Although a transmission of SARS-Cov-2 virus cannot be completely eliminated, the risk of transmission through corneal tissue seems very unlikely. Efficient donation programs, resilient network structures, awareness of population for tissue donation and effective precautionary measures ensure a safe patient care with corneal transplants also in pandemic times.

